Infectious Disease
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Stephen C. Piscitelli
Keith A. Rodvold
Manjunath P. Pai *Editors*

Drug Interactions in Infectious Diseases

Third Edition

Humana Press

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Foreword

Over the past decade, the prognosis for patients with many life threatening infections has improved dramatically. For patients with HIV infection, systemic fungal diseases, parasitic diseases, and highly resistant bacteria, we have new drugs and new strategies for eradicating infections even in our patients with the most devastating underlying morbidities. Thus, for patients who are receiving immunosuppressive therapy to combat cancer or transplant rejection or autoimmune disease, and for patients with multisystem injury due to trauma or cardiovascular disease or other processes, we can succeed in preventing or treating infections that most often had fatal consequences a decade ago.

Health care providers are well aware that drugs are only effective and safe if administered with tactical and strategic planning. The right dose, given at the right time, to the right patient is a foundation for safe, error free care. However, determining the right dose and the right time is not easy in complex patients who have fluctuating renal and hepatic function, rapidly changing volumes of distribution, and who are receiving multiple drugs. Safe and effective management of pharmacotherapy is also difficult because drugs may change from day to day, week to week, or month to month, depending on how stable the patient is and how successful the patient's regimen is in terms of efficacy and safety.

One of the promises of electronic ordering systems in hospitals and physician offices is that drug interactions, so complicated to understand and remember, will be managed by the computer. While computers are able to identify drug interactions that are programmed into their memory, health care providers who are not pharmacology experts are often baffled about how to respond to the warnings. Since these pharmacokinetic interactions clearly influence patient outcome in terms of efficacy and safety, providers must understand the bases of interactions. They must also have a reference source for looking up interactions so that they can understand how to manage these complex processes.

This 3rd edition of *Drug Interaction in Infectious Diseases* provides health care providers with a unique resource for both understanding basic principles, and for

finding important information. Section 1 on General Concepts, and Section 2 on Drug Classes are well organized for providers to quickly find practical information.

This book belongs on the shelf of infectious disease practitioners, pharmacists, and other health care providers who prescribe and manage infections in complex patients. The authors of this book are the best minds in their field. This book enables providers to understand how best to maximize safety and efficacy in terms of managing drug interactions successfully. Drs. Piscitelli, Rodvold, and Pai deserve enormous credit for expanding this valuable resource, now in its 3rd edition.

Bethesda, MD Henry Masur, MD

Preface

Drug-drug interactions are an under recognized source of medical errors that have major health related costs and consequences. Overriding drug interactions as 'inconsequential' is likely contributing to a silent epidemic. The association of sudden deaths as a consequence of antimicrobial drug-drug interactions speaks to this epidemic. The ever increasing foray of therapeutic agents will continue to reduce our ability as clinicians to predict the risk and implications of drug-drug interactions. Identification of new mechanistic pathways of drug interaction coupled with pharmacogenomic variation has also added new complexities to our design of predictive tools. We now recognize that acute infection and inflammation can also alter drug disposition, which can lead to direct and indirect effects on drug-drug interactions. To date, a comprehensive computer model that can integrate the effects of all known covariates of drug-drug interaction has not been developed. Hence, clinical intuition and vigilance remain key defenses against untoward drug-drug interactions. As the editors of the third edition of *Drug Interactions in Infectious Diseases* we are delighted to deliver a text that will enhance your clinical knowledge of the complex mechanisms, risks, and consequences of drug interactions associated with antimicrobials, infection, and inflammation.

One of the key strengths of this comprehensive textbook is the inclusion of unique chapters on issues that are difficult to find in the medical literature. Chapters on drug-cytokine interactions, food effects, and study design/data analysis remain noteworthy examples. The third edition includes several improvements and changes. The introductory chapter has been modified to encompass the regulatory guidance on the evaluation of drug-drug interactions in order to provide a broad but practical perspective on this topic. The book has been divided into three sections to provide a better organization and structure. Four new chapters have been added to describe interactions with a number of drug classes, which include, non-HIV antiviral agents, antimalarial, antiparasitic, and macrolides, azalides and ketolides. The antiparasitic and antimalarial chapters address key drug-drug interactions faced primarily by patients in underdeveloped countries, which was not addressed in previous editions of this book. There is also a novel chapter on probe cocktail studies, which serve as important research tools in drug development. We are confident that the information

provided in the detailed tables and text will provide new insights to the practicing clinician, the academic instructor and the infectious disease researcher.

As always the quantity and quality of the information provided would not be possible without the contributions of an excellent number of authors. We are indebted to our authors for their time and diligence to ensure that this textbook remains a premier reference for those engaged in the field of Infectious Diseases. Finally, we thank our families for their continued support and encouragement throughout this important and meticulous undertaking.

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Chapter 1
Introduction to Drug-Drug Interactions

David J. Greenblatt

Abstract Innovations in drug development have led to the introduction of many chemical entities in clinical practice over the past 60 years. This innovation coupled with the increasing use of polypharmacy has raised the potential for pharmacokinetic and pharmacodynamic drug interactions. The current chapter provides a basic overview of the mechanisms and preclinical prediction of drug interactions. The interpretation of the results of clinical drug studies and the necessity for continued review of primary literature on this topic are discussed.

1.1 Introduction

Drug-drug interactions (DDIs) have emerged as a topic of increasing importance for basic and clinical pharmacology, the drug development process, regulatory science, and clinical therapeutics. In the decades since World War II, innovations in drug development have led to the introduction of many new chemical entities into clinical practice [1]. Many infectious, cardiovascular, metabolic, immunologic, and neoplastic diseases that were essentially untreatable in the 1940s and 1950s now can be successfully managed or even cured. As a result, numerous patients with serious diseases have not only extended survival expectations, but survival with good quality of life.

A consequence of this striking success of pharmaceutical innovation and development is an increasing prevalence of polypharmacy—patients taking multiple drugs. Whenever two drugs are taken together, there is the theoretical possibility of a DDI. The more drugs coadministered, the greater the number of potential pairwise

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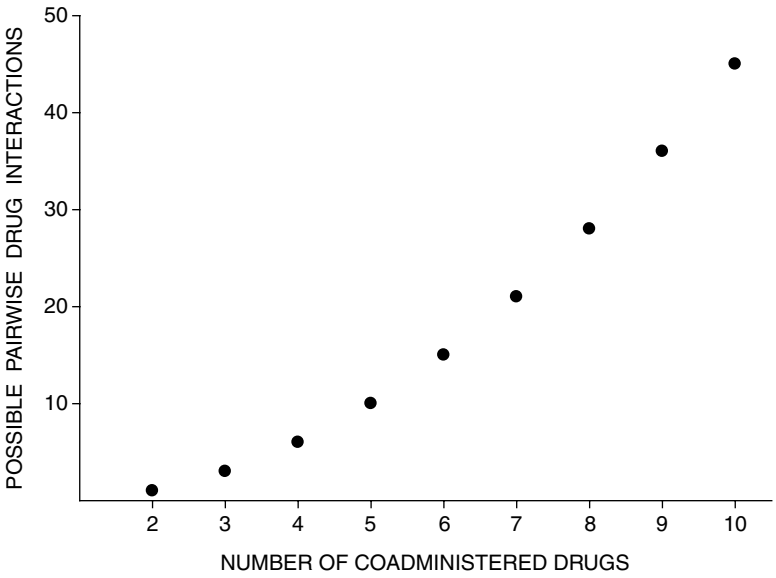

Fig. 1.1 Relation of number of drugs co-administered (x-axis) to the theoretical number of pairwise drug-drug interactions

interactions [2]. In a patient taking 10 drugs concurrently, there are 45 possible pairwise DDIs (Fig. 1.1). Given the extent of polypharmacy in contemporary clinical practice and the numerous potential DDIs, it is remarkable that so few clinically important DDIs actually occur [3–5].

The possible outcomes of drug coadministration, in decreasing order of probability, are:

1. No DDI of any kind.
2. A statistically significant DDI can be detected, but the interaction is of no clinical importance—either the magnitude of the interaction is small, or the therapeutic index of the substrate drug is large.
3. A clinically important DDI occurs, but it can be managed by monitoring the concentrations (or effects) of the substrate drug and making dose adjustments if necessary.
4. A clinically important DDI occurs, and is best managed by changing to an alternative substrate drug (also termed the "victim"—the drug being interacted with), or an alternative to the drug causing the interaction (also termed the "perpetrator") such that therapeutic objectives are maintained, but the DDI hazard is reduced or eliminated. As an example, a patient with a fungal infection (receiving ketoconazole) and a sleep disorder (receiving triazolam) could receive zolpidem instead of triazolam.
5. The DDI is hazardous, with the potential for causing serious or life-threatening adverse reactions.

Serious adverse events due to DDIs, though very rare, are extensively publicized when they occur, and inevitably are followed by finger-pointing and blame. Pharmaceutical manufacturers are blamed for marketing and promoting drugs with serious hazards; regulatory agencies are blamed for failing to protect the public against dangerous drugs; and practicing physicians are blamed for their non-understanding of the hazards of co-prescribing medications. The occurrence of serious or fatal cardiac arrhythmias attributable to terfenadine when co-prescribed with CYP3A inhibitors (such as ketoconazole or erythromycin) exemplifies this scenario of events, ultimately leading to the withdrawal of terfenadine from marketing in the United States [6–12].

1.2 Mechanisms of Drug Interactions

Pharmacodynamic DDIs involve the additive or opposing effects of two drugs on the same clinical endpoint [2, 13–16]. Many pharmacodynamic interactions are intuitively evident. For example, benzodiazepine agonists and ethanol, when administered separately, each produce clinical sedation. When co-administered, they produce additive sedation [17]. Conversely, caffeine—which produces alertness when administered by itself—can partly prevent or reverse sedation due to a benzodiazepine agonist [18, 19]. A variant type of pharmacodynamic DDI can involve the target receptor mediating pharmacodynamic action. Flumazenil, a high-affinity neutral ligand for the gamma-aminobutyric acid benzodiazepine receptor complex, can act as a functional benzodiazepine antagonist through competitive displacement of typical full-agonist ligands [20].

Pharmacokinetic DDIs are "indirect," in that the perpetrator either inhibits or induces the metabolic clearance of the substrate victim drug [2, 13–16]. As a result, the clinical effect of the victim is augmented or reduced due to a change in its systemic plasma concentrations. When the substrate victim's clearance is inhibited by the perpetrator, plasma levels of the substrate are increased, with excessive clinical effects or toxicity being the principal concern. When the substrate's clearance is induced, plasma levels fall and the principal clinical concern is loss of efficacy.

Inhibition and induction of metabolism reflect different biological mechanisms. *Inhibition* involves a direct effect of a perpetrator drug upon a metabolic enzyme. The onset of the inhibitory effect is rapid, as the inhibitor comes in contact with the enzyme; the offset of inhibitory action is also rapid when the inhibitor is discontinued, but the effect offset will be modified depending on the clearance of the inhibitor itself [21]. When inhibition is *mechanism-based* (or irreversible)—as opposed to reversible—it might be anticipated that the inhibitory effect would be sustained following discontinuation of the perpetrator [22–25]. However, recovery even from mechanism-based inhibition is relatively rapid following inhibitor removal, largely because of the continuous intrinsic regeneration and turnover of metabolic enzymes [26].

In contrast to metabolic inhibition, *induction* involves a signal to a nuclear receptor from an exogenous chemical, instructing the cellular protein-synthetic

mechanism to produce greater amounts of metabolic protein [27–29]. As an example, the metabolic inducer rifampin acts to increase expression of hepatic and enteric CYP3A enzyme (as well as a number of other metabolic enzymes and transport proteins) via the nuclear receptor termed the Pregnane-X Receptor (PXR) [30–33]. Unlike metabolic inhibition, the onset and offset of induced clearance of a victim substrate will be relatively slow following exposure to and discontinuation of the inducer [34–37].

1.3 Prediction of Drug Interactions

Controlled clinical DDI studies provide definitive information on whether a candidate perpetrator will alter the clearance of a candidate victim drug. However, the need for DDI information—either in the process of drug development, or to support rational therapeutic decisions—far exceeds the realistic capacity of the industrial and academic research community to provide such data. Clinical DDI studies are expensive, time-consuming, and involve low but non-zero risk to volunteer participants. It is simply not possible to execute a clinical DDI study to evaluate all DDIs that need evaluation. Consequently in vitro models are used to identify those drug combinations that should receive priority for clinical studies, such that resources available for in vivo studies can be allocated more wisely. The models can also identify drug pairs which are unlikely to interact, thereby excluding the need for an in vivo study.

Human liver microsomal preparations are most commonly used for in vitro studies of DDIs due to metabolic inhibition [38–40]. For any given substrate-inhibitor combination, an in vitro inhibition constant (K_i) can be generated relatively quickly and at low cost. What is more difficult is the *interpretation* of the K_i value in terms of prediction of a DDI during actual drug coadministration in humans. In a clinical pharmacokinetic DDI study, AUC_0 is the total area under the plasma concentration curve for the substrate victim drug in the control condition (without coadministration of the inhibitor) [2]. AUC_I is the corresponding area value when the substrate is given with the inhibitor. The ratio of the area values ($R_{AUC} = AUC_I/AUC_0$) is the quantitative magnitude of the DDI. It can be shown that the outcome of the clinical DDI study is theoretically related to the in vitro DDI results as follows:

$$R_{AUC} = 1 + [I]/K_i$$

where [I] is the in vivo concentration of the inhibitor to which the metabolic enzyme is exposed.

The validity of this in vitro-in vivo scaling relationship has been tested in numerous studies and data compilations over the last two decades [38–59]. It can be reasonably concluded that the overall predictive validity is weak. This can be attributed to many sources of variance and bias that cannot be fully accounted for.

Probably the most important of these limitations is the inability to determine [I], the enzyme-available inhibitor concentration. In any case, the current regulatory guidelines mandate that [I] is most straightforwardly estimated as the maximum total plasma inhibitor concentration produced by the maximum approved therapeutic dosage. From this, a value of $[I]/K_i$ less than 0.1 indicates that a clinical DDI is unlikely, whereas a value greater than 10.0 indicates a probable clinical DDI. For all values in between, a clinical DDI is "possible," and a clinical DDI study is needed. These regulatory boundaries are very conservative, and their application has compelled many DDI studies.

In vitro studies of induction are another matter altogether. While inhibition can be quantitated in vitro using inexpensive and readily available cell homogenates (liver microsomal preparations), the study of induction require live cells—namely, human hepatocytes in culture. There is no straightforward metric (analogous to an inhibition constant) established for quantitation of induction potency. Current guidelines mandate the conduct of a clinical DDI study if the in vitro data—based on cultured human hepatocytes—indicate that the candidate inducer has a potency exceeding 30% of that produced by the "index" inducer. In the case of inducers acting via the nuclear PXR receptor, the index inducer is rifampin.

1.4 Interpreting Clinical Drug Interaction Studies

A typical DDI study will yield an R_{AUC} value (AUC_I/AUC_0) for each subject that participates in the study. According to current regulatory guidelines, the R_{AUC} values are aggregated by calculation of the geometric mean value, and the 90% confidence interval about the geometric mean. We have contended that this approach yields a biased value, and that the arithmetic mean ratio provides the most appropriate metric for the magnitude of the DDI [2, 60]. In any case, the investigator is left to interpret the aggregate R_{AUC} value, however it is calculated.

Is the DDI—whether or not it is statistically significant—of clinical importance? That is—what is the boundary at which a value of R_{AUC} greater than 1.0 assumes clinical significance (for example, a modification in dosage of the substrate victim is needed)? Unless the pharmacokinetic DDI study includes well-defined pharmacodynamic endpoints, this question can only be answered with supplemental research information on the concentration-response relationship for the substrate drug [2, 60, 61]. Suppose a DDI study yields an aggregate R_{AUC} value of 1.5, which is significantly different from 1.0. This indicates, on average, that clearance of the substrate victim is reduced by 33% due to coadministration of the inhibitor, causing an average increase of 50% in steady-state levels of the substrate at any given dosing rate. This change might be of clinical importance if the substrate drug is warfarin or phenytoin, but is unlikely to be clinically important if the substrate is sertraline or omeprazole.

If concentration-response information on the substrate drug is not available, the FDA invokes "default" guidelines for interpretation, illustrated in the classification

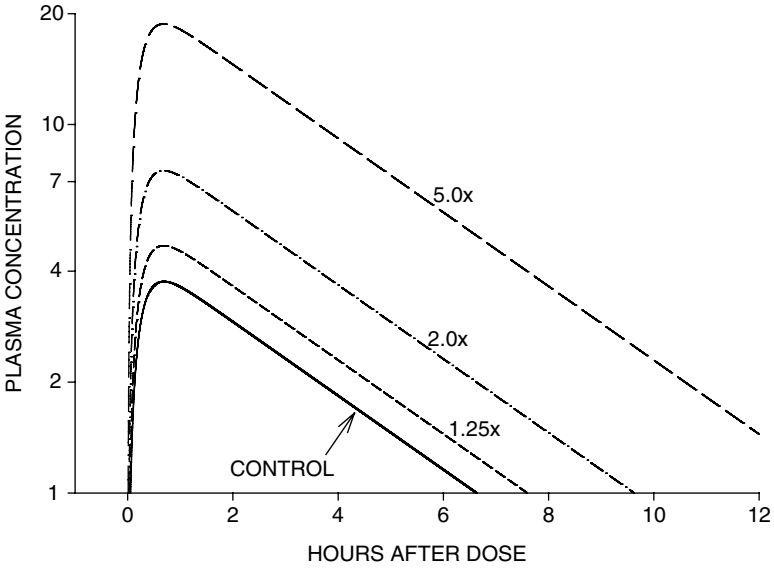

Fig. 1.2 Plasma concentrations of a hypothetical drug after oral dosage in the control condition without inhibitor (*solid line*), and with coadministration of inhibitors having different potencies, producing R_{AUC} values of 1.25, 2.0, and 5.0

of DDIs involving "sensitive" CYP3A substrates. If the upper boundary of the 90% confidence interval around the geometric mean R_{AUC} is below 1.25, a "no effect" conclusion is justified. If the upper boundary exceeds 1.25, the DDI is of potential clinical importance. The inhibitor is then classified as follows: "weak" if R_{AUC} is between 1.25 and 2.0; "moderate" if R_{AUC} is between 2.0 and 5.0; and "strong" if R_{AUC} exceeds 5.0 (Fig. 1.2). It is consistent with common sense that quantitatively large DDIs (very high values of R_{AUC} from inhibition, or very small values of R_{AUC} due to induction) are most likely to be clinically important. In the context of CYP3A substrate drugs as victims of DDIs, the most potent perpetrators of inhibition and induction are drugs used to treat infectious disease: ketoconazole and ritonavir as inhibitors [62–65], and rifampin as inducer.

1.5 Sources of Information on Drug-Drug Interactions

The vast literature database on DDIs has encouraged the development of many secondary and tertiary sources: books, review articles, pharmacy compendia, product labels, and websites. Many of these sources are comprehensive and useful, but the intrinsic limitations of secondary and tertiary sources should be recognized—they necessarily represent the author's filtration and interpretation of the original

data, and may or may not be updated with the most current original research. Of particular concern are product labels, which tend to be "etched in stone" until modification is initiated by the sponsor, or by the regulatory agency based on safety concerns. We recommend that secondary and tertiary sources be used as "gateway" documents, through which scientists and clinicians access primary research documents for definitive information on DDIs.

References

1. Greenblatt DJ. The maturation of clinical pharmacology: recognizing the contributions of Dr. Louis Lasagna. J Clin Pharmacol 1998;38:572–574.
2. Greenblatt DJ and von Moltke LL (2010). Clinical studies of drug-drug interactions: design and interpretation. In, Enzyme and Transporter-Based Drug-Drug Interactions: Progress and Future Challenges. Edited by K. S. Pang, A. D. Rodrigues and R. M. Peter. New York, Springer. 625–649.
3. Bergk V, Gasse C, Rothenbacher D, Loew M, Brenner H and Haefeli WE. Drug interactions in primary care: impact of a new algorithm on risk determination. Clin Pharmacol Ther 2004;76:85–96.
4. Glintborg B, Andersen SE and Dalhoff K. Drug-drug interactions among recently hospitalised patients--frequent but mostly clinically insignificant. Eur J Clin Pharmacol 2005;61: 675–681.
5. DeVane CL. Antidepressant-drug interactions are potentially but rarely clinically significant. Neuropsychopharmacology 2006;31:1594–1604; discussion 1614–1595.
6. von Moltke LL, Greenblatt DJ, Duan SX, Harmatz JS and Shader RI. In vitro prediction of the terfenadine-ketoconazole pharmacokinetic interaction. J Clin Pharmacol 1994;34: 1222–1227.
7. Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC and Cantilena LR. Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. JAMA 1993;269:1513–1518.
8. Honig PK, Woosley RL, Zamani K, Conner DP and Cantilena LR, Jr. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. Clin Pharmacol Ther 1992;52:231–238.
9. Mathews DR, McNutt B, Okerholm R, Flicker M and McBride G. Torsades de pointes occurring in association with terfenadine use. JAMA 1991;266:2375–2376.
10. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J and Cantilena LR. Torsades de pointes occurring in association with terfenadine use. JAMA 1990;264:2788–2790.
11. Woosley RL, Chen Y, Freiman JP and Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. JAMA 1993;269:1532–1536.
12. Crumb WJ, Wible B, Arnold DJ, Payne JP and Brown AM. Blockade of multiple human cardiac potassium currents by the antihistamine terfenadine: possible mechanism for terfenadine-associated cardiotoxicity. Mol Pharmacol 1995;47:181–190.
13. von Moltke LL and Greenblatt DJ (2010). Clinical drug interactions due to metabolic inhibition: Prediction, assessment, and interpretation. In, Enzyme Inhibition in Drug Discovery and Development. Edited by C. Lu and A. P. Li. Hoboken NJ, John Wiley & Sons. 533–547.
14. Greenblatt DJ and von Moltke LL. Pharmacokinetics and drug interactions. In Comprehensive Textbook of Psychiatry, 8th Edition. Edited by BJ Sadock, VA Sadock. Philadelphia. Lippincott Williams & Williams. 2005:2699–2706.
15. Greenblatt DJ, He P, von Moltke LL and Court MH (2008). The CYP3 family. In, Cytochrome P450: Role in the Metabolism and Toxicology of Drugs and Other Xenobiotics. Edited by C. Ioannides. Cambridge (UK), Royal Society of Chemistry. 354–383.

16. Greenblatt DJ and von Moltke LL (2008). Drug-Drug Interactions: Clinical perspectives. In, Drug-Drug Interactions, 2nd Edition. Edited by A. D. Rodrigues. New York, Informa Healthcare. 643–664.
17. Scavone JM, Greenblatt DJ, Harmatz JS and Shader RI. Kinetic and dynamic interaction of brotizolam and ethanol. Br J Clin Pharmacol 1986;21:197–204.
18. Cysneiros RM, Farkas D, Harmatz JS, von Moltke LL and Greenblatt DJ. Pharmacokinetic and pharmacodynamic interactions between zolpidem and caffeine. Clin Pharmacol Ther 2007;82:54–62.
19. Mattila ME, Mattila MJ and Nuotto E. Caffeine moderately antagonizes the effects of triazolam and zopiclone on the psychomotor performance of healthy subjects. Pharmacol Toxicol 1992;70:286–289.
20. Klotz U, Ziegler G, Ludwig L and Reimann IW. Pharmacodynamic interaction between midazolam and a specific benzodiazepine antagonist in humans. J Clin Pharmacol 1985;25:400–406.
21. Liston HL, DeVane CL, Boulton DW, Risch SC, Markowitz JS and Goldman J. Differential time course of cytochrome P450 2D6 enzyme inhibition by fluoxetine, sertraline, and paroxetine in healthy volunteers. J Clin Psychopharmacol 2002;22:169–173.
22. Zhou S, Yung Chan S, Cher Goh B, Chan E, Duan W, Huang M and McLeod HL. Mechanism-based inhibition of cytochrome P450 3A4 by therapeutic drugs. Clin Pharmacokinet 2005;44:279–304.
23. Zhou SF, Xue CC, Yu XQ, Li C and Wang G. Clinically important drug interactions potentially involving mechanism-based inhibition of cytochrome P450 3A4 and the role of therapeutic drug monitoring. Ther Drug Monit 2007;29:687–710.
24. Fontana E, Dansette PM and Poli SM. Cytochrome P450 enzymes mechanism based inhibitors: common sub-structures and reactivity. Curr Drug Metab 2005;6:413–454.
25. Bertelsen KM, Venkatakrishnan K, von Moltke LL, Obach RS and Greenblatt DJ. Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: comparison with fluoxetine and quinidine. Drug Metab and Dispos 2003;31:289–293.
26. Greenblatt DJ, von Moltke LL, Harmatz JS, Chen G, Weemhoff JL, Jen C, Kelley CJ, LeDuc BW and Zinny MA. Time-course of recovery of cytochrome P450 3A function after single doses of grapefruit juice. Clin Pharmacol Ther 2003;74:121–129.
27. Pelkonen O, Turpeinen M, Hakkola J, Honkakoski P, Hukkanen J and Raunio H. Inhibition and induction of human cytochrome P450 enzymes: current status. Arch Toxicol 2008;82:667–715.
28. Zhou SF. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. Curr Drug Metab 2008;9:310–322.
29. Lin JH. CYP induction-mediated drug interactions: in vitro assessment and clinical implications. Pharm Res 2006;23:1089–1116.
30. Urquhart BL, Tirona RG and Kim RB. Nuclear receptors and the regulation of drug-metabolizing enzymes and drug transporters: implications for interindividual variability in response to drugs. J Clin Pharmacol 2007;47:566–578.
31. Wang H and LeCluyse EL. Role of orphan nuclear receptors in the regulation of drug-metabolising enzymes. Clin Pharmacokinet 2003;42:1331–1357.
32. Waxman DJ. P450 gene induction by structurally diverse xenochemicals: central role of nuclear receptors CAR, PXR, and PPAR. Archives of Biochemistry and Biophysics 1999;369:11–23.
33. Willson TM and Kliewer SA. PXR, CAR and drug metabolism. Nat Rev Drug Discov 2002;1:259–266.
34. Lai AA, Levy RH and Cutler RE. Time-course of interaction between carbamazepine and clonazepam in normal man. Clin Pharmacol Ther 1978;24:316–323.
35. Magnusson MO, Dahl ML, Cederberg J, Karlsson MO and Sandstrom R. Pharmacodynamics of carbamazepine-mediated induction of CYP3A4, CYP1A2, and Pgp as assessed by probe substrates midazolam, caffeine, and digoxin. Clin Pharmacol Ther 2008;84:52–62.
36. von Bahr C, Steiner E, Koike Y and Gabrielsson J. Time course of enzyme induction in humans: effect of pentobarbital on nortriptyline metabolism. Clin Pharmacol Ther 1998; 64:18–26.

37. Ohnhaus EE, Breckenridge AM and Park BK. Urinary excretion of 6 beta-hydroxycortisol and the time course measurement of enzyme induction in man. Eur J Clin Pharmacol 1989;36: 39–46.
38. Venkatakrishnan K, von Moltke LL and Greenblatt DJ. Human drug metabolism and the cytochromes P450: application and relevance of in vitro models. J Clin Pharmacol 2001;41:1149–1179.
39. Venkatakrishnan K, von Moltke LL, Obach RS and Greenblatt DJ. Drug metabolism and drug interactions: application and clinical value of in vitro models. Curr Drug Metab 2003;4:423–459.
40. Volak LP, Greenblatt DJ and von Moltke LL. In vitro approaches to anticipating clinical drug interactions. In, Drug-Drug Interactions in Pharmaceutical Development. Edited by Albert P. Li. Hoboken, NJ, John Wiley & Sons. 2008: p. 75–93.
41. von Moltke LL, Greenblatt DJ, Schmider J, Wright CE, Harmatz JS and Shader RI. In vitro approaches to predicting drug interactions in vivo. Biochem Pharmacol 1998;55:113–122.
42. Nieminen TH, Hagelberg NM, Saari TI, Neuvonen M, Neuvonen PJ, Laine K and Olkkola KT. Grapefruit Juice Enhances the Exposure to Oral Oxycodone. Basic Clin Pharmacol Toxicol 2010;107:782–788.
43. Fennetau F, Poulin P, Nekka F. Physiologically based predictions of the impact of inhibition of intestinal and hepatic metabolism on human pharmacokinetics of CYP3A substrates. J Pharm Sci 2010;99:486–514.
44. Fahmi OA, Hurst S, Plowchalk D, Cook J, Guo F, Youdim K, Dickins M, Phipps A, Darekar A, Hyland R and Obach RS. Comparison of different algorithms for predicting clinical drug-drug interactions, based on the use of CYP3A4 in vitro data: predictions of compounds as precipitants of interaction. Drug Metab Dispos 2009;37:1658–1666.
45. Galetin A, Brown C, Hallifax D, Ito K and Houston JB. Utility of recombinant enzyme kinetics in prediction of human clearance: impact of variability, CYP3A5, and CYP2C19 on CYP3A4 probe substrates. Drug Metab Dispos 2004;32:1411–1420.
46. Youdim KA, Zayed A, Dickins M, Phipps A, Griffiths M, Darekar A, Hyland R, Fahmi O, Hurst S, Plowchalk DR, Cook J, Guo F and Obach RS. Application of CYP3A4 in vitro data to predict clinical drug-drug interactions; predictions of compounds as objects of interaction. Br J Clin Pharmacol 2008;65:680–692.
47. Rostami-Hodjegan A and Tucker GT. Simulation and prediction of in vivo drug metabolism in human populations from in vitro data. Nat Rev Drug Discov 2007;6:140–148.
48. Liu YT, Hao HP, Liu CX, Wang GJ and Xie HG. Drugs as CYP3A probes, inducers, and inhibitors. Drug Metab Rev 2007;39:699–721.
49. Galetin A, Ito K, Hallifax D and Houston JB. CYP3A4 substrate selection and substitution in the prediction of potential drug-drug interactions. J Pharmacol Exp Ther 2005;314:180–190.
50. Galetin A, Hinton LK, Burt H, Obach RS and Houston JB. Maximal inhibition of intestinal first-pass metabolism as a pragmatic indicator of intestinal contribution to the drug-drug interactions for CYP3A4 cleared drugs. Curr Drug Metab 2007;8:685–693.
51. Ito K, Brown HS and Houston JB. Database analyses for the prediction of in vivo drug-drug interactions from in vitro data. Br J Clin Pharmacol 2004;57:473–486.
52. Yao C and Levy RH. Inhibition-based metabolic drug-drug interactions: predictions from in vitro data. J Pharm Sci 2002;91:1923–1935.
53. Ohno Y, Hisaka A and Suzuki H. General framework for the quantitative prediction of CYP3A4-mediated oral drug interactions based on the AUC increase by coadministration of standard drugs. Clin Pharmacokinet 2007;46:681–696.
54. Obach RS, Walsky RL, Venkatakrishnan K, Houston JB and Tremaine LM. In vitro cytochrome P450 inhibition data and the prediction of drug-drug interactions: qualitative relationships, quantitative predictions, and the rank-order approach. Clin Pharmacol Ther 2005;78:582–592.
55. Brown HS, Ito K, Galetin A and Houston JB. Prediction of in vivo drug-drug interactions from in vitro data: impact of incorporating parallel pathways of drug elimination and inhibitor absorption rate constant. Br J Clin Pharmacol 2005;60:508–518.

56. Brown HS, Galetin A, Hallifax D and Houston JB. Prediction of in vivo drug-drug interactions from in vitro data : factors affecting prototypic drug-drug interactions involving CYP2C9, CYP2D6 and CYP3A4. Clin Pharmacokinet 2006;45:1035–1050.
57. Bachmann KA. Inhibition constants, inhibitor concentrations and the prediction of inhibitory drug drug interactions: pitfalls, progress and promise. Curr Drug Metab 2006;7:1–14.
58. Bachmann KA and Lewis JD. Predicting inhibitory drug-drug interactions and evaluating drug interaction reports using inhibition constants. Ann Pharmacother 2005;39:1064–1072.
59. Obach RS, Walsky RL, Venkatakrishnan K, Gaman EA, Houston JB and Tremaine LM. The utility of in vitro cytochrome P450 inhibition data in the prediction of drug-drug interactions. J Pharmacol Exp Ther 2006;316:336–348.
60. Greenblatt DJ. Preparation of scientific reports on pharmacokinetic drug interaction studies. J Clin Psychopharmacol 2008;28:369–373.
61. Greenblatt DJ. Drug-drug noninteractions. Cardiovasc Ther 2009;27:226–229.
62. Venkatakrishnan K, von Moltke LL and Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism in humans: clinical relevance. Clin Pharmacokinet 2000;38: 111–180.
63. Tsunoda SM, Velez RL, von Moltke LL and Greenblatt DJ. Differentiation of intestinal and hepatic cytochrome P450 3A activity with use of midazolam as an in vivo probe: effect of ketoconazole. Clin Pharmacol and Ther 1999;66:461–471.
64. Greenblatt DJ, Peters DE, Oleson LE, Harmatz JS, MacNab MW, Berkowitz N, Zinny MA and Court MH. Inhibition of oral midazolam clearance by boosting doses of ritonavir, and by 4,4-dimethyl-benziso-(2H)-selenazine (ALT-2074), an experimental catalytic mimic of glutathione oxidase. Br J Clin Pharmacol 2009;68:920–927.
65. Knox TA, Oleson L, von Moltke LL, Kaufman RA, Wanke CA and Greenblatt DJ. Ritonavir greatly impairs CYP3A activity in HIV infection with chronic viral hepatitis. JAIDS 2008;49:358–368.

Chapter 2
Mechanisms of Drug Interactions I: Absorption, Metabolism, and Excretion

Kevin C. Brown and Angela D.M. Kashuba

Abstract Understanding the basic mechanisms of drug interactions allows researchers and clinicians to best interpret and apply drug interaction data, and make predictions about patient-specific interactions. Drug interactions can occur at the site of action (pharmacodynamic interactions), and during the absorption, distribution, metabolism and excretion phases of drug distribution (pharmacokinetic interactions). The consequences of unintended interactions can be extremely harmful and potentially fatal, such as those leading to cardiac conduction abnormalities. Knowledge of the mechanisms of drug interactions has also identified useful interactions with therapeutic benefits, such as in the development of feasible dosing regimens for protease inhibitors in the treatment of HIV infection. This chapter describes the mechanisms of drug interactions for each of the aforementioned pharmacokinetic processes. The cytochrome P450 family of enzymes, the P-glycoprotein drug transporter, and their mechanisms for inhibition, induction, and suppression are reviewed. Preclinical methods used to study cytochrome P450 are discussed. The chemical and physiologic changes that affect absorption and elimination, and how they are influenced by drugs, are explained.

2.1 Introduction

It is difficult to assess the overall clinical importance of many drug interactions. Often, drug interaction reports are based on anecdotal or case reports, and their mechanisms are not clearly defined. In addition, determining clinical significance

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requires an assessment of the severity of potential harm. This makes an unequivocal determination of "clinically significant" difficult.

Drug interactions can be pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic interactions result from alterations in a drug's absorption, distribution, metabolism, and/or excretion characteristics. Pharmacodynamic interactions are a result of the influence of combined treatment at a site of biological activity, and yield altered pharmacologic actions at standard plasma concentrations. Although drug interactions occur through a variety of mechanisms, the effects are the same: the potentiation or antagonism of the effects of drugs.

The mechanisms by which changes in absorption, distribution, and excretion occur have been understood for decades. However, only recently has technology allowed for a more thorough understanding of drug-metabolizing isoforms and influences thereon. Much information has been published regarding drug interactions involving the cytochrome P450 enzyme system [1–5]. This will be an important focus of this chapter, since the majority of currently available anti-infectives are metabolized by, or influence the activity of, the cytochrome P450 enzyme system. This chapter provides a detailed review of the mechanisms by which clinically significant pharmacokinetic drug interactions occur.

2.2 Drug Interactions Affecting Absorption

Mechanisms of absorption include passive diffusion, convective transport, active transport, facilitated transport, ion-pair transport, and endocytosis [6]. Certain drug combinations can affect the rate or extent of absorption of anti-infectives by interfering with one or more of these mechanisms [7]. Generally, a change in the extent of a medication's absorption of greater than 20% may be considered clinically significant [8]. The most common mechanisms of drug interactions affecting absorption are discussed in (Table 2.1).

Table 2.1 Potential mechanisms of drug interactions involving absorption and distribution

Absorption
Altered gastric pH
Chelation of compounds
Adsorption of compounds
Altered gastric emptying
Altered intestinal motility
Altered intestinal blood flow
Altered active and passive intestinal transport
Altered intestinal cytochrome P450 isozyme activity
Altered intestinal P-glycoprotein activity
Distribution
Altered protein binding

2.2.1 Changes in pH

The rate of drug absorption by passive diffusion is limited by the solubility, or dissolution, of a compound in gastric fluid. Basic drugs are more soluble in acidic fluids and acidic drugs are more soluble in basic fluids. Therefore, compounds that create an environment with a specific pH may decrease the solubility of compounds needing an opposing pH for absorption. However, drug solubility does not completely ensure absorption, since only un-ionized molecules are absorbed. Although acidic drugs are soluble in basic fluids, basic environments can also decrease the proportion of solubilized acidic molecules that are in an un-ionized state. Therefore, weak acids ($pK_a = 3–8$) may have limited absorption in an alkaline environment and weak bases ($pK_a = 5–11$) have limited absorption in an acidic environment.

These interactions can be clinically significant. For example, since the nucleoside analog didanosine (ddI) is acid-labile and requires a neutral to basic pH to be absorbed, all ddI formulations are buffered. However, medications known to require an acidic environment for dissolution, such as ketoconazole, itraconazole, and dapsone, have demonstrated significantly decreased absorption when given concomitantly [9–12].

Antacids, histamine receptor antagonists, and proton pump inhibitors all raise gastric pH to varying degrees. Antacids transiently (0.5–2 h) raise gastric pH by 1–2 units [13], H_2-antagonists dose-dependently maintain gastric pH > 5 for many hours, and proton pump inhibitors dose-dependently raise gastric pH > 5 for up to 19 h [14]. The concomitant administration of these compounds leads to significant alterations in the extent of absorption of basic compounds such as certain azole antifungals and β-lactam antibiotics [8, 15–20]. However, because of large interindividual variability in the extent of altered gastric pH, significant interactions may not occur in all patients.

2.2.2 Chelation and Adsorption

Drugs may form insoluble complexes by chelation in the gastrointestinal tract. Chelation involves the formation of a ring structure between a metal ion (e.g., aluminum, magnesium, iron, and to a lesser degree calcium) and an organic molecule (e.g., anti-infective medication), which results in an insoluble compound that is unable to permeate the intestinal mucosa due to the lack of drug dissolution.

A number of examples of the influence on anti-infective exposure by this mechanism exist in the literature, involving primarily the quinolone antibiotics in combination with magnesium and aluminum-containing antacids, sucralfate, ferrous sulfate, or certain buffers. These di- and trivalent cations complex with the 4-oxo and 3-carboxyl groups of the quinolones, resulting in clinically significant decreases in the quinolone area under the concentration–time curve (AUC) by 30–50% [21–24]. Cations present in enteral feeding formulations do not appear to interfere significantly with the absorption of these compounds [25, 26]. A second well-documented, clinically significant example of this type of interaction involves the complexation of tetracycline and iron. By this mechanism, tetracycline antibiotic AUCs are decreased by up to 80% [27–29].

Adsorption is the process of ion-binding or hydrogen-binding, and may occur between anti-infectives such as penicillin G, cephalexin, sulphamethoxazole, or tetracycline, and adsorbents such as cholestyramine. Since this process can significantly decrease antibiotic exposure [30, 31], the concomitant administration of adsorbents and antibiotics should be avoided.

2.2.3 Changes in Gastric Emptying and Intestinal Motility

The presence or absence of food can affect the absorption of anti-infectives by a variety of mechanisms [32]. High-fat meals can significantly increase the extent of absorption of fat soluble compounds such as griseofulvin, cefpodoxime, and cefuroxime axetil. Prolonged stomach retention can cause excessive degradation of acid-labile compounds such as penicillin and erythromycin [7].

Since the primary location of drug absorption is the small intestine, changes in gastric emptying and gastrointestinal motility may have significant effects on drug exposure. Rapid gastrointestinal transit effected by prokinetic agents such as cisapride, metoclopramide, and domperidone may decrease the extent of absorption of poorly soluble drugs or drugs that are absorbed in a limited area of the intestine [33]. However, clinically significant effects on anti-infectives have not been documented.

2.2.4 Effects of Intestinal Blood Flow

Intestinal blood flow can be modulated by vasoactive agents and theoretically can affect the absorption of lipophilic compounds. However, there is no evidence to date that this results in clinically significant drug interactions [34].

2.2.5 Changes in Active and Passive Transport

A rapidly expanding field of research is that of intestinal transcellular transport. Recently, multiple intestinal transporters located on the brush-border and basolateral membrane of the enterocyte have been identified [35–37]. The potential for competitive inhibition of these transporters with quinolone antibiotics has recently been documented [38]. This contributes an additional mechanism by which anti-infective drug interactions may occur.

The Caco-2 cell model is a human colonic cell line sharing similarities with enterocytes and is used as a model for oral absorption [39]. Investigations using this cell line have demonstrated that certain compounds can modulate the tight junctions of the intestinal epithelia and alter paracellular drug absorption [40, 41]. There is still

incomplete understanding of the structure and function of tight junctions, which has limited the development of modulating compounds to enhance paracellular absorption [42]. However, this mechanism for pharmacokinetic enhancement will have implications for drug interactions. Research that focuses on understanding the functional characteristics of enterocyte transporters and tight-junction modulators will provide information as to which compounds may participate in these interactions and to what extent.

2.2.6 Changes in Presystemic Clearance

The drug-metabolizing cytochromes P450 (CYP) 3A4 and 5 are expressed at high concentrations in the intestine and contribute to drug inactivation. P-glycoprotein is expressed at the lumenal surface of the intestinal epithelium and serves to extrude unchanged drug from the enterocyte into the lumen. Both CYP3A4/5 and P-glycoprotein share a significant overlap in substrate specificity [43–45], although there is no correlation between affinities [46]. Determining the relative contributions of intestinal P-glycoprotein and CYP3A4/5 activity to drug bioavailability and interactions is an active area of investigation. Potential drug interactions involving these mechanisms are discussed in detail below.

2.2.7 Cytochrome P450 Isozymes

Gastrointestinal cytochrome P450 isozymes, responsible for Phase I oxidative metabolism (for a more detailed discussion of CYP isoforms, see Sect. 2.3.1 Phase I Drug Metabolism), are most highly concentrated in the proximal two-thirds of the small intestine [47]. Two intestinal CYP isoforms, CYP3A4 and CYP3A5 (CYP3A4/5), account for approximately 70% of total intestinal P450 protein and are a major determinant of the systemic bioavailability of orally administered drugs [48–51].

For example, the benzodiazepine midazolam is a specific CYP3A4/5 substrate with no affinity for P-glycoprotein. An investigation of oral and intravenous midazolam plasma clearance in 20 healthy young volunteers [52] revealed an incomplete correlation between the two measures ($r = 0.70$). The large variability in midazolam oral clearance not accounted for by hepatic metabolism most likely represents the contribution of intestinal CYP3A4/5. Therefore, it appears that at least 30–40% of the clearance of many CYP3A compounds may be significantly influenced by CYP3A4/5 located in enterocytes. Since the activity of intestinal CYP3A4/5 can also be influenced by a variety of environmental factors [51, 53, 54], the potential for drug interactions to occur during drug absorption is great.

Some of the most significant effects of drug interactions occurring at the intestinal isozyme level involve the potential suicide inhibition of CYP3A4/5 with grapefruit juice [55, 56]. Generally, this interaction results in a minimum threefold

increase in the extent of absorption and toxicity of the concomitantly administered agent [57], but can also result in decreased efficacy of prodrugs needing CYP3A for conversion to active moieties. The concern of this interaction is strictly limited to orally administered agents, since the active components of grapefruit juice are either inactivated in the gut or are present in such minute quantities in the portal circulation that no effect on hepatic metabolism occurs [58–60].

Clinical data available for anti-infective–grapefruit juice interactions include the protease inhibitor saquinavir [61], the antifungal agent itraconazole [62], and the macrolide clarithromycin [63]. Whereas saquinavir AUC increases twofold with a single 400-mL dose of commercially available grapefruit juice, itraconazole and clarithromycin AUCs do not change significantly. The absence of an effect of grapefruit juice on the oral clearance of these latter two compounds suggests that their first-pass metabolism does not rely significantly on intestinal CYP3A4/5 [43].

Anti-infectives can also inhibit intestinal CYP isozyme activity [53, 54, 64]. For example, the protease inhibitor ritonavir is a potent inhibitor of CYP3A4 activity. This characteristic can be clinically useful, as demonstrated by the increased bioavailability of the protease inhibitors saquinavir [65] and lopinavir [66] when given in combination with ritonavir.

Other CYP isozymes present in enterocytes may also influence drug absorption. Environmental factors may influence their activity as well, and drug–environment interactions may result in significantly altered absorption [67]. However, further research is needed to better characterize these influences before specific interactions can be predicted.

2.2.8 Effects of P-Glycoprotein

P-glycoprotein is a multidrug-resistance gene product found in a variety of human tissues including the gastrointestinal epithelium [68]. This efflux pump is expressed at the lumenal surface of the intestinal epithelium and opposes the absorption of unchanged drug by transporting lipophilic compounds out of enterocytes back into the gastrointestinal lumen. P-glycoprotein has demonstrated up to tenfold variability in activity between subjects [69], and has a significant role in oral drug absorption. Decreased bioavailability occurs because intact drug molecules are pumped back into the gastrointestinal tract lumen and exposed multiple times to enterocyte metabolism.

P-glycoprotein has broad substrate specificity, and inhibiting or inducing the activity of this protein can lead to significant alterations in drug exposure [70]. P-glycoprotein genotype has also been associated with basal expression and induction of CYP3A4 [71]. However, because many drugs have affinities for both P-glycoprotein and CYP3A4/5 [43, 44], it is difficult to determine by what specific mechanism drug interactions occur. For some compounds, inhibition of both P-glycoprotein function and CYP3A4/5 activity may be required to produce clinically significant interactions.

Many antiinfectives have binding affinity for P-glycoprotein. These include erythromycin, clarithromycin [72], ketoconazole, sparfloxacin [73], the nucleoside analog adefovir [74], and the HIV-1 protease inhibitors [75–77]. Since drugs that have affinity for P-glycoprotein are not necessarily removed from the enterocyte by this efflux pump [78], anti-infectives may participate in, but are not necessarily influenced by, drug interactions involving P-glycoprotein. This concept is illustrated by an in vitro investigation of ketoconazole and erythromycin [79]. Both drugs demonstrate significant affinity for P-glycoprotein. However, in combination with verapamil (a classic P-glycoprotein inhibitor), significantly decreased P-glycoprotein-mediated efflux occurred only with erythromycin. Therefore, although ketoconazole exhibits binding affinity for P-glycoprotein, it can be concluded that P-glycoprotein does not contribute significantly to the process of first-pass metabolism of ketoconazole.

Recent in vitro data reveal that grapefruit juice, in addition to inactivating enterocyte CYP3A isozymes, may also increase P-glycoprotein activity [80]. The clinical implications of this have yet to be determined.

2.3 Drug Interactions Affecting Distribution

2.3.1 Protein Binding and Displacement

Drug interactions affecting distribution are those that alter protein binding. Generally, the importance of drug displacement interactions has been overestimated, with the extrapolation of data from in vitro investigations without consideration for subsequent physiologic phenomena. The lack of well-designed studies has prevented precise quantification of the influence of protein binding on anti-infective therapeutic efficacy in vivo. However, redistribution and excretion of drugs generally occurs quickly after displacement, and the effects of any transient rise in unbound concentration of the object drug are rarely clinically important [81].

Albumin constitutes the main protein fraction (~5%) in blood plasma. As albumin contains both basic and acidic groups, it can bind basic and acidic drugs. Acidic drugs (i.e., penicillins, sulfonamides, doxycycline, and clindamycin [82]) are strongly bound to albumin at a small number of binding sites, and basic drugs (i.e., erythromycin) are weakly bound to albumin at a larger number of sites. Basic drugs may also preferentially bind to α-1-acid glycoprotein [83].

Depending on relative plasma concentrations and protein-binding affinities, one drug may displace another with clinically significant results. This interaction is much more likely to occur with drugs that are at least 80–90% bound to plasma proteins, with small changes in protein binding leading to large relative changes in free drug concentration. Drugs that are poorly bound to plasma proteins may also be displaced, but the relative increase in free drug concentration is generally of less consequence. When a protein displacement interaction occurs, the increased free drug in plasma quickly distributes throughout the body and will localize in tissues if the volume of distribution is large. An increase in unbound drug concentrations at

metabolism and elimination sites will also lead to increased rates of elimination. Therefore, many clinically significant drug interactions that have been attributed to protein binding have often involved a second, unrecognized mechanism of interaction [84].

Generally, interactions between basic drugs and albumin are not clinically significant. In subjects with normal concentrations of albumin and antiinfective concentrations of less than 100 μg/mL, the degree of protein binding will be relatively constant. At higher anti-infective concentrations, available binding sites may theoretically become saturated, and the extent of binding subsequently decreased [82]. Clinically significant displacement interactions for α-1-acid glycoprotein have not been described. This is most likely due to the large volume of distribution of these drugs, with plasma containing a very small proportion of the total amount of drug in the body.

In summary, drug interactions involving albumin binding displacement may potentially be clinically significant if the compound is greater than 80% protein bound, has a high hepatic extraction ratio, a narrow therapeutic index, and a small volume of distribution. Although temporary increase in drug concentrations may be clinically significant with such drugs as warfarin and phenytoin, mean steady-state free drug concentrations will remain unaltered [85].

2.4 Drug Interactions Affecting Drug Metabolism

The principal site of drug metabolism is the liver. Metabolism generally converts lipophilic compounds into ionized metabolites for renal elimination. Drug metabolizing activity can be classified according to nonsynthetic (Phase I) and synthetic (Phase II) reactions. Phase I reactions include oxidation, reduction, and hydrolysis and occur in the membrane of hepatocyte endoplasmic reticula. Phase II reactions result in conjugation (i.e., glucuronidation, sulfation) and occur in the cytosol of the hepatocyte.

2.4.1 Phase I Drug Metabolism

The majority of oxidative reactions are catalyzed by a superfamily of mixed-function mono-oxygenases called the cytochrome P450 enzyme system. Although cytochrome P450 (CYP) isozymes are located in numerous tissues throughout the body, the liver is the largest source of CYP protein [48]. Many significant pharmacokinetic drug interactions involve the hepatic CYP isozymes [86–90] (Table 2.2).

Nomenclature for this superfamily is based on amino acid sequence homology and groups enzymes and genes into families and subfamilies [91]. To designate the cytochrome P450 enzymes, the “CYP” prefix is used. All isozymes having at least 40% amino acid sequence homology are members of an enzyme family, as designated by an Arabic number (e.g., CYP3). All isozymes have at least 55% amino acid

Table 2.2 Potential mechanisms of drug interactions involving metabolism

Phase I (nonsynthetic)
Genetic polymorphisms
Inhibition of activity
Suppression of activity
Induction of activity
Phase II (synthetic)
Genetic polymorphisms
Inhibition of activity
Induction of activity

sequence homology are members of an enzyme subfamily, as designated by a capital letter (e.g., CYP3A). An Arabic number is used to represent an individual enzyme (e.g., CYP3A4). Italicized nomenclature represents the gene coding for a specific enzyme (e.g., CYP3A4).

To date, at least 14 human families, 22 human subfamilies, and 36 human CYP enzymes have been identified [92]. However, the CYP1, 2, and 3 families account for 70% of the total hepatic P450 content [93, 94]. Approximately 95% of all therapeutic drug oxidation can be accounted for by the activities of CYP1A2, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Drug interactions involving these isozymes result from enzyme inhibition or induction, although genetic polymorphism can attenuate these interactions [95].

2.4.1.1 Genetic Polymorphisms

Polymorphisms are generated by nonrandom genetic mutations that occur in at least 1% of a population and give rise to distinct subgroups within that population that differ in their ability to metabolize xenobiotics. Clinically significant polymorphisms have been documented for CYP2D6, CYP2C9, and CYP2C19 [96]. Extensive or rapid metabolizers (generally the largest proportion of a population) have heterozygous or homozygous dominant alleles, poor metabolizers possess variant homozygous autosomal recessive alleles, and ultraextensive metabolizers exhibit gene amplification of autosomal dominant alleles.

Poor-metabolizer phenotypes can be at high risk for toxicity from drugs that require CYP inactivation, and at high risk for therapeutic inefficacy from prodrugs that need CYP activation [97]. However, they are at low risk for drug interactions that involve enzyme inhibition or induction, since their activity is preemptively compromised and cannot be induced.

In addition, due to the large variability (e.g., 40-fold or greater) in enzyme activity documented in extensive metabolizers [98], drug interactions may not manifest in all subjects with this phenotype. Inhibition of drug-metabolizing enzymes may result in more significant effects in those with high initial enzyme activity, and induction of drug-metabolizing enzymes may result in more significant effects in those individuals with low initial enzyme activity.

2.4.1.2 Mechanisms of Inhibition

Enzyme inhibition can result in sudden catastrophic drug interactions. Several mechanisms of inhibition exist, and many drugs can interact by multiple mechanisms [99, 100]. Reversible inhibition is most common. Reversible inhibition occurs when compounds quickly form weak bonds with CYP isozymes without permanently disabling them. This can occur both competitively (competition for the same binding site between inhibitor and substrate) and noncompetitively (inhibitor binds at a site on the enzyme distinct from the substrate).

The magnitude of this type of inhibition depends both on the affinity of substrate and inhibitor for the enzyme, and on the concentration of the inhibitor at the enzyme site [46]. Affinity is represented by an inhibitor constant (K_i), which is the concentration of inhibitor required to decrease the maximal rate of the reaction to half of the uninhibited value. For example, potent reversible CYP3A inhibitors generally have K_i values below 1 μM (e.g., ketoconazole, itraconazole, ritonavir, and indinavir), although drugs with K_i values in the low micromolar range can also demonstrate competitive inhibition (e.g., erythromycin and nelfinavir). Compounds with K_i's greater than 100 μM for the CYP3A subfamily tend not to produce clinically significant inhibition [50].

CYP inhibition can also occur as a result of a slowly reversible reaction. When an inhibitor binds to a CYP isozyme and undergoes oxidation to a nitrosoalkane species, it can form a slowly reversible complex with the reduced heme in the CYP isozyme [50]. This interaction has been documented between the macrolide antibiotics and CYP3A [101] and explains why clinically significant interactions (i.e., erythromycin and terfenadine) can occur with compounds that have modest K_i values [87, 102].

It is postulated that irreversible, mechanism-based inhibition (or suicide inhibition) occurs with the CYP-mediated formation of a reactive metabolite. This metabolite can covalently and irreversibly bind to the catalytic site residue and permanently inactivate the enzyme for subsequent reactions. The extent of the clinical importance of this reaction depends on the total amount of CYP isozyme present, the total amount of inhibitor to which the isozyme is exposed, and the rate of new isozyme synthesis [103].

2.4.1.3 Mechanisms of Suppression

As early as the 1960s, inflammation and infection were demonstrated to decrease Phase I metabolism of drugs and toxins in animals, thereby modulating pharmacologic and toxicologic effects [104, 105]. One of the earliest reports of infection altering human drug-metabolizing enzyme activity occurred a decade later, with quinidine concentrations consistently elevated in subjects experimentally infected with Plasmodium falciparum malaria [106]. Since that time, numerous reports have described alterations in drug metabolism with viral and bacterial infections [107–113], in addition to complex events such as surgery and bone marrow transplantation [114, 115].

The effects of inflammation and infection on CYP activity are ascribed to stimulation of the cellular immune response [116]. Although many different mediators may be involved, there has been particular focus on the major proinflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α. Generally, IL-1, IL-6, and TNFα demonstrate a suppressive effect on CYP isozymes by decreasing mRNA up to 80%. However correlations between mRNA, enzyme protein content, and enzyme activity are incomplete both within and between investigations [117–124]. To date, the majority of investigations examining cytokine-induced effects on drug-metabolizing isozyme activities have been performed in the rodent model. Very few of these investigations have been repeated in human hepatocytes. Although rodents are an inexpensive and readily available model, qualitative and quantitative interspecies differences in regulation and activity of drug-metabolizing enzymes [125–127] as well as response to cytokines do not allow the effects of inflammation on isozyme activities, or the underlying mechanisms, to be easily extrapolated to humans [128–131].

A small number of clinical investigations has documented decreased drug metabolizing enzyme activity during the administration of therapeutic interferons and interleukins. These studies demonstrate variable and conflicting results with respect to the magnitude of drug–cytokine interactions [113, 132–138]. With the increasing use of cytokines as therapeutic agents for a variety of disease states, further investigation is required to elucidate the mechanisms of drug–cytokine interactions in order to optimize anti-infective therapeutic regimens.

2.4.1.4 Mechanisms of Induction

An increase in cytochrome P450 activity through induction is less of an immediate concern than inhibition, since induction occurs gradually rather than rapidly, and generally leads to compromised therapeutic goals rather than profound toxicity. Since the time-course of enzyme induction is determined by the half-life of the substrate as well as the rate of isozyme turnover, it is often difficult to predict this time-course specifically. Clinically significant induction results from a >50-fold increase in the number of enzyme molecules. This generally occurs through an increase in P450 synthesis by either receptor-mediated transcriptional activation or mRNA stabilization. However, protein stabilization leading to decreased rates of P450 degradation has also been noted.

Induction of the CYP1 family by cigarette smoke, charcoal-broiled foods, indoles (found in broccoli, cauliflower, cabbage, brussels sprouts, kale, watercress), and omeprazole occurs primarily by substrate binding to the Aryl hydrocarbon receptor (AhR/dioxin receptor). This complex subsequently binds with a receptor nuclear translocator, enters the hepatocyte nucleus, and binds with regulatory DNA sequences to enhance gene transcription and stabilize mRNA [139, 140].

The CYP2 and CYP3 families are induced by a variety of structurally diverse compounds. Activation of CYP2C genes is regulated by constitutive androstane receptor (CAR) and pregnane X receptor (PXR) in addition to multiple co-activators [141].

Both PXR and CAR can regulate CYP2B6 and CYP3A expression, however, induction by efavirenz and nevirapine of these enzymes is mediated by specifically activating CAR [142]. PXR is activated by a range of drugs known to induce CYP3A4/5 expression (i.e., rifampicin, clotrimazole, etc.) [143]. PXR is expressed most abundantly in the liver, but is also present in the small intestine and colon. Transcriptional factors not directly activated by xenobiotics have also been shown to be critical for enzyme induction.

CYP3A can also be induced by posttranscriptional message stabilization and protein stabilization with the following anti-infectives: macrolides, imidazole antifungal agents, and rifampin. A proposed mechanism for posttranscriptional protein stabilization is proteosome inhibition by NF kappaB activation [144], and message stabilization may involve a similar phosphorylation process.

2.4.2 Phase II Drug Metabolism

The term "Phase II" metabolism was developed originally to represent synthetic reactions occurring after "Phase I" processes. It is now known that many xenobiotics do not require Phase I metabolism before undergoing conjugation reactions. The group of Phase II isozymes consists of UDP-glucuronosyltransferases, sulfotransferases, acetyltransferases, glutathione S-transferase, and methyltransferases. Many of these families of enzymes are still growing in complexity, and drug interactions involving these isozymes are under investigation.

2.4.2.1 Genetic Polymorphism

Many of the Phase II enzymes exhibit polymorphism [145–148]. Although these polymorphisms have been implicated in selected anti-infective-associated adverse drug reactions (e.g., dapsone, isoniazid, sulphonamides [148–150]), influences of these polymorphisms on anti-infective drug interactions have not been documented.

2.4.2.2 Inhibition

Phase II drug-metabolizing enzymes do not currently appear to play as prominent a role in clinical drug interactions with anti-infectives as the cytochrome P450 enzyme system. This may be due to the large capacity of the conjugation system, in which only profound disturbances result in clinically significant alterations in drug pharmacokinetics [151].

UDP-glucuronosyltransferase represents the most common conjugation reaction in drug metabolism. Many drugs have been characterized as competitive inhibitors of UDP-glucuronosyltransferases [152], but the roles of these interactions in practical drug metabolism issues are unexplored.

2.4.2.3 Induction

Far less is known about the potential for induction of Phase II enzymes than the cytochrome P450 enzyme system. The UDP-glucuronosyltransferases can be induced, but the clinical significance of this is not fully understood [153]. However, the increased clearance of zidovudine that has been documented with the coadministration of rifampin, suggests that induction of these enzymes may be clinically significant [154]. Glutathione S-transferase is also known to be inducible, although these activities rarely exceed two to threefold times baseline, and are not involved in anti-infective metabolism [155].

2.5 Drug Interactions Affecting Excretion

Renal elimination of drugs involves glomerular filtration, tubular secretion, and tubular reabsorption. Five mechanisms of drug–drug interactions can occur at the site of renal elimination [156]. The most common mechanisms are discussed below (Table 2.3).

2.5.1 Glomerular Filtration

Rates of glomerular filtration can be affected by changes in renal blood flow, cardiac output, and extent of protein binding [157]. With highly protein bound drugs (e.g., >80%), a significant increase in the unbound fraction can lead to an increase in glomerular filtration, and subsequent increased drug elimination [158]. Conversely, with transporter saturation, and renal elimination at maximal, elimination rates may decrease significantly with increased free drug.

2.5.2 Tubular Secretion

The most common renal drug interactions occur at the transport site of tubular secretion. Sharing the same proximal tubular active transport system, many organic anionic and cationic drugs and metabolites compete with each other for secretion.

Table 2.3 Potential mechanisms of drug interactions involving excretion

Glomerular filtration
Tubular secretion
Tubular reabsorption

A classic example of this interaction, used long ago intentionally for therapeutic benefit, is the combination of probenecid and penicillin to increase antibiotic serum concentrations [159]. Examples of other anti-infectives that may exhibit interactions by this mechanism include the sulfonamides, penicillins, and zidovudine [160–162].

P-glycoprotein has been identified in the apical membrane of the proximal tubule and can transport a large variety of drugs into the lumen. A number of experimental drug interaction investigations have implicated the inhibition of renal p-glycoprotein to an increase in plasma drug concentrations. Quinolones [163], macrolides [72], and azole antifungals [164] demonstrate affinity for renal p-glycoprotein, and can potentially contribute to significant drug interactions. Although renal nucleoside transporters have been shown to mediate the secretion and reabsorption of purine and pyrimidine nucleoside analog drugs, their role in clinically significant drug interactions is unknown [165, 166].

2.5.3 Tubular Reabsorption

Reabsorption of drugs from the tubular lumen involves both passive diffusion and active transport processes. Only nonionized compounds are passively reabsorbed from the renal tubule, and thus manipulating urinary pH can alter the reabsorption of weak organic acids and bases. Renal clearance of weak organic bases ($pK_a = 7–10$) is increased with urine acidification (i.e., by salicylates and ascorbic acid) and decreased with urine alkalinization (i.e., by antacids, calcium carbonate, thiazide diuretics, and sodium bicarbonate). Likewise, renal elimination of weak organic acids ($pK_a = 3–7$; nitrofurantoin, sulfonamides, aminoglycosides, and vancomycin) is increased with urine alkalinization and decreased with urine acidification. Generally, these interactions are not clinically significant, since few drugs can have altered urinary excretion to a large enough extent to affect plasma half-life. The role of active transport reabsorption in anti-infective drug interactions is currently unknown [167].

2.6 Pharmacodynamic Drug Interactions

Drug interactions are not limited to mechanisms of absorption, distribution, metabolism, and elimination, but can also result from pharmacodynamic interactions. Pharmacodynamic interactions may occur at the intended site of biological activity, which may result in synergism or antagonism of the therapeutic effect. This is also true for the mechanisms of adverse events. Examples of such interactions include the potential for seizures with quinolones when combined with NSAIDS or other medications that lower seizure thresholds [168], and the increased risk of serotonin syndrome with co-administration of linezolid with other medications with serotonergic activity such as antidepressants and opioids [169]. Generally, the likelihood of pharmacodynamic drug interactions is relatively low. Understanding drug mechanisms and side-effect profiles of the antimicrobial agent and concomitant therapy can prevent these complications.

2.7 Significance of Drug Interactions

Many drug interactions are primarily assessed in vitro (see Sect. 2.7 Preclinical Methods for Predicting Drug Interactions). However, absolute in vitro/in vivo correlations are infrequent. Even with clinical trials, not all statistically significant drug interactions are of clinical significance. In particular, drugs with wide therapeutic indices that demonstrate a less than 20% change in pharmacokinetic parameters when combined with a second agent will most likely be of little, if any, clinical significance.

The greatest risk of documented clinically significant pharmacokinetic drug interactions involving anti-infective-induced altered protein binding, drug-metabolizing enzyme inhibition, and altered renal elimination is the combination of anti-infectives with anticoagulants, antidepressants, and cardiovascular agents [89]. The most clinically significant anti-infective drug interactions involving enzyme induction are subtherapeutic concentrations resulting from the combination of rifampin with warfarin [170], cyclosporine [171], and oral contraceptives [172, 173]. Conversely, the reduction of C_{max} and/or AUC of anti-infectives by other drugs or environmental influences can result in a much greater chance of failure of therapy and possibly an increase in the development of resistance.

Not all pharmacokinetic drug interactions involving anti-infectives are detrimental, however. Ketoconazole has been used for a number of years to inhibit the metabolism of oral cyclosporine by approximately 80%, thereby reducing the cost of therapy as well as the rates of rejection and infection [174, 175]. As mentioned previously, the administration of ritonavir to enhance the oral absorption of saquinavir is a well-known component of potent antiretroviral combination regimens [176].

Beneficial and detrimental pharmacodynamic antimicrobial drug interactions also exist. The use of lower concentrations of two synergistic antibacterials to reduce the toxicity of each while having the same pharmacologic effect has been advocated [177], although the clinical data supporting superior efficacy is weak. Synergistic combinations of antimicrobials may produce better results in the treatment of Pseudomonas aeruginosa and Enterococcus species [178, 179]. Clinical data are also lacking for detrimental effects of potentially antagonistic combinations of antimicrobials (e.g., a bacteriostatic drug combined with a bactericidal agent) [180]. However, these combinations are best avoided unless clinically warranted for the treatment of multiple pathogens.

2.8 Preclinical Methods for Predicting Drug Interactions

Although understanding and anticipating pharmacokinetic drug interactions are important components of rational therapeutics, there is a limit to the number and scope of clinical studies that can reasonably be performed. The development of human in vitro models allows information to be obtained without the expense and potential risks involved in conducting human trials. However, scaling of in vitro data to the clinical situation is not always accurate, and the results of these methods may not be definitive. A primary focus of preclinical screening methods for assessing

drug–drug interactions is the identification of isozymes responsible for the metabolism of these compounds, and the relative contribution of an inhibited pathway to a compound's overall elimination.

Modern technology has allowed in vitro screening techniques to become widely available, and much of these data are currently included in package inserts. However, extrapolating in vitro results to an in vivo situation is often complicated. Preclinical screening of promising compounds frequently uses nonhuman mammalian species, although interspecies differences in expression and regulation of transporters and enzymes are well documented [181, 182]. Supratherapeutic, as opposed to clinically relevant, concentrations of inhibitors and substrates may be utilized. In addition, experimental conditions such as enzyme protein concentration and buffers can critically affect specific results and confound in vitro/in vivo correlations [183]. To account for variability in individual enzyme expression, positive controls for inhibition and induction should always be used (e.g., troleandomycin or ketoconazole for CYP3A inhibition, quinidine for CYP2D6 inhibition, and rifampin for CYP3A induction).

The following briefly summarizes the strengths and weaknesses of currently available in vitro human methodologies for assessing cytochrome P450 drug interactions, and predicting their clinical significance (Table 2.4).

2.8.1 Purified P450 Isozymes

In an attempt to identify specific isozymes responsible for the metabolism of compounds, human cytochrome P450 enzymes have been isolated and purified from hepatic tissue (Table 2.5) [184]. However, only small amounts of protein can be isolated at any one time, and specific isozymes from certain subfamilies often cannot be separated (i.e., CYP2C9 vs. CYP2C19 vs. CYP2C10). To ensure correct interpretation of the results obtained from this method, it is most critical to examine the isozyme purification methods and quality control procedures. This method has been primarily superceded by the use of recombinant human cytochrome P450 isozymes.

2.8.2 Recombinant Human P450 Isozymes

Complementary DNA (cDNA) expression has been used to produce recombinant human cytochrome P450 isozymes in yeast, insects, bacteria, and mammalian cells [185, 186]. An advantage of this system is the ability to identify specific isozymes of a subfamily that are responsible for the metabolism of a compound and to confirm suspected isozyme-selective inhibitors [187]. However, this remains an artificial system, and discrepancies can exist between results obtained by cDNA methods and other in vitro systems. Generally, data obtained from cDNA systems should be confirmed by at least one other in vitro system [188, 189].

Table 2.4 Preclinical methods for predicting drug interactions

	Advantages	Disadvantages
Purified P450 isozymes	Isozyme substrate identification Isozyme inhibitor identification Isozyme specificity	Limited protein yield Certain subfamilies undifferentiated Quality of purification affects result
Recombinant P450 isozymes	Isozyme substrate identification Isozyme inhibitor identification Isozyme specificity	Artificial system Results require confirmation
Human microsomes	Isozyme substrate identification Isozyme inhibitor identification Relative isozyme metabolic contribution Individual variability overcome by pooling Relatively low cost	Genetic/phenotypic variability Lack cellular machinery for induction/suppression
Immortalized cell lines	Ability to identify induction Method/system validation	P450 activity loss Important cellular processes may be lost
Liver slices	Relatively simple preparation Maintains hepatocyte ultrastructure Ability to identify metabolites inhibitors	Short-lived system Genetic/phenotypic variability Tissue-media distribution equilibrium not always achieved
Hepatocyte cultures	Phase I and II activity Physiologic processes maintained Better clinical extrapolation Ability to identify inhibition, induction and suppression	Genetic/phenotypic variability Requires fresh hepatic tissue Culture methods can be complex

2.8.3 Microsomes

Microsomes isolated from human hepatocytes have become the "gold standard" of in vitro experimentation for drug interactions. Microsomes are isolated membranes of hepatocyte endoplasmic reticula and contain the cytochromes P450 in proportion to their in vivo representation. This is an important consideration, since most often multiple isozymes are responsible for drug metabolism. Given the large interindividual variability in CYP expression, using microsomes from a single individual may produce distorted results. To circumvent this, pooling microsomes from multiple sources in order to obtain an average representation of activity is advocated. Human microsomes are widely available at relatively low cost, but they can only be used to determine direct inhibition of metabolism. Investigations of drug–drug interactions involving induction or suppression of CYP isozymes require intact cellular machinery.

Table 2.5 Major cytochrome P450 substrates, inhibitors, and inducers

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4/5
Substrates							
Caffeine	Bupropion	Repaglinide	Tobutamide	Omeprazole	Tamoxifen	Halothane	Midazolam
Clozapine	Efavirenz	Paclitaxel	Ibuprofen	Phenytoin	Metoprolol	Acetaminophen	Cyclosporine
Theophylline	Methadone	Torsemide	Naproxen	Clopidogrel	Amphetamine	Ethanol	Tacrolimus
	Cyclophosphamide		Etravirine	Cyclophosphamide	Chlorpromazine	Theophyline	Protease
			S-warfarin	R-warfarin	Dextromethorphan		Inhibitors
			Losartan	Etravirine	Fluoxetine		Cisapride
					Paroxetine		Terfenadine
					Promethazine		Diltiazem
							Verapamil
							Simvastatin
							Fentanyl
							Sildenafil
							Amiodarone
							Etravirine
Inhibitors							
Ciprofloxacin	Ticlopidine	Gemfibrozil	Fluconazole	Omeprazole	Bupropion	Disulfuram	Ketoconazole
Fluvoxamine	Thiotepa	Trimethoprim	Amiodarone	Lansoprazole	Fluoxetine	Ethanol	Ritonavir
		Montelukast	Probenecid	Chloramphenicol	Paroxetine		Saquinavir
		Sorafanib					
		Quercetin	Isoniazid	Indomethacin	Terbinafine		Nelfinavir
			Sorafanib	Etravirine			Clarithromycin
			Etravirine				Aprepitant
							Grapefruit

Inducers							
Nafcillin	Rifampin	Rifampin	Rifampin	Rifampicin Carbamazepine	Rifampin	Ethanol	Rifampin
Cruciferous	Phenobarbital		Secobarbital	Prednisone	Dexamethasone	Isoniazid	Efavirenz
Vegetables	Phenytoin		Carbamazepine				Nevirapine
Chargrilled							Etravirine
Meat							Carbamazepine
							Phenytoin
Tobacco							St. John's Wort

For a more comprehensive list see http://medicine.iupui.edu/clinpharm/ddis/table.aspx

2.8.4 Immortalized Cell Lines

An ideal in vitro model for studying drug–drug interactions involving induction, inhibition, and suppression would be a validated, immortalized, readily available cell line, the results from which could be extrapolated directly to the clinical environment. However, no such model currently exists. All available immortalized human cell lines do not maintain a full complement of cytochrome P450 enzyme activities, nor do they maintain other potentially important physiologic processes. One commonly used immortalized cell line is derived from a human hepatoma (HepG2 cells). This model has been investigated for CYP1A1 induction, but does not significantly express other cytochrome P450s [190, 191].

2.8.5 Liver Slices

Human liver slices have been used with moderate success in determining the hepatic metabolism of certain compounds. Liver slices are relatively easy to prepare, and they maintain the hepatic ultrastructure. However, up to half of constitutive (baseline) cytochrome P450 activity is lost within the first 24 h after isolation, and all constitutive cytochrome P450 activity is lost by 96 h [192]. This makes investigations of induction and suppression of drug-metabolizing enzyme activity difficult. In addition, a distribution equilibrium is not achieved between all hepatocytes within the slice and the incubation media, resulting in decreased rates of metabolism compared to a hepatocyte monolayer culture system [193].

2.8.6 Human Hepatocyte Cultures

Human hepatocyte monolayer culture systems are ideal for studying drug interactions, as they maintain both Phase I and Phase II activity, and form and maintain physiologic processes such as biliary canaliculi and transporters [194]. Determining drug interactions in this system often allows for the closest prediction of potential drug interactions [195]. Although this system does not mimic the pharmacokinetic alterations in drug concentrations seen clinically, it does allow quantitation of “best” and “worst” scenarios that may be extrapolated to the clinical setting. Induction, suppression, and inhibition interactions can all be performed with this model [196, 197]. Although maintaining constitutive levels of cytochrome P450 activity has been challenging, currently available enriched media and improved culture conditions allow for maintenance of control activity for at least 72–96 h after isolation. Challenges encountered with this system are primarily in obtaining fresh hepatic tissue for digestion, and the specialized technique of perfusion for isolation of the hepatocytes. In addition, with the wide variability in enzyme activity seen clinically, investigations in a limited number of hepatocyte preparations will not be able to definitively reflect the occurrence of drug interactions in an entire population, but only suggest the potential for interactions to occur.

2.9 Overview of Clinical Methods for Predicting Drug Interactions

The primary cause of clinically significant drug interactions is the involvement of drug-metabolizing enzymes. Because great variability exists in drug-metabolizing enzyme activity among subjects, and drug interactions may not achieve clinical significance in all patients, interactions may be better clinically predicted by the knowledge of individual patient isozyme activities. However, there is currently a need for the development of reliable, accurate, and noninvasive methods to monitor drug metabolizing enzyme expression in humans in order to guide drug dosage, reduce toxicity, and predict potential drug interactions.

Genotyping involves identification of mutant genes causing poor- or ultra-extensive metabolizer activity, or phenotype. Genotyping has been demonstrated to predict the clinical outcome of drug interactions involving both Phase I and Phase II metabolism [198, 199]. However, drug-metabolizing enzyme activity can be exquisitely sensitive to environmental and physiologic influences. Therefore genotyping allows for the determination of an individual's genetic predisposition to a specific enzyme activity, but may not reflect true phenotype at any one point in time.

An analytical technique that allows the characterization of specific in vivo drug-metabolizing enzyme activity is the process of phenotyping: using the ratios of parent drug and drug metabolites in blood or urine as a surrogate marker of isozyme activity. Specific methods have been developed to phenotype CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, glutathione S-transferase, glucuronyltransferase, and N-acetyltransferase activities [200]. Phenotyping offers the primary advantage of quantitating time-sensitive enzyme activity and accounts for combined genetic, environmental, and endogenous influences on drug metabolizing enzyme activity. However, a number of currently available phenotyping methods are invasive and impractical, and analytical methods are not readily available. With a simplification of phenotyping methods, and an increase in the availability of analytical procedures, it may be possible to use these methods to determine correlations between enzyme activity and the risk of significant drug interactions in individual patients.

2.10 In Vitro/In Vivo Scaling of Drug Interactions

The process of using in vitro models to predict in vivo drug interactions is still in its infancy, and extensive validation of this approach is needed. In vitro models predictive of in vivo drug interactions will be essential for rapid, cost-effective screening of pharmaceutical compounds and are important for reducing risks to patient safety. Currently these models are constructed from a combination of laboratory and theoretical components. Ideally, in a valid model, the in vivo decrease in clearance caused by coadministration of an inhibitor would be specifically predicted by the decrease in reaction velocity (e.g., formation rate of a metabolite) for the same compound in vitro when the inhibitor is present in the same concentration. However, presently available

models contain a number of weaknesses and assumptions that make scaling of in vitro data to the clinical situation complicated and not always accurate. Poor predictions occur with compounds that have flow-dependent hepatic clearance, with mechanism-based inhibition, and with compounds that concurrently induce and inhibit enzyme activity. In addition, inhibitor and substrate plasma concentrations are not always proportional to the inhibitor and substrate concentrations to which the enzyme is exposed. In vitro and cell culture models demonstrate extensive partitioning of lipophilic compounds into cells, with uptake not restricted by plasma protein binding. As an example, the mean in vivo liver: plasma partition ratios for benzodiazepine derivatives range from 6.4 to 17.4, making predictions of these concentrations at the site of enzyme activity very difficult [201, 202]. Some examples of in vitro scaling with azole antifungal agents can be found in a commentary by von Moltke et al. [202].

In order to establish the feasibility of in vitro to in vivo scaling, most currently reported predictions of inhibitory drug interactions are retrospective. Presently available methods allow a general assessment of what may occur (i.e., an unlikely interaction versus a probable interaction [203, 204]). However, to be most useful, in vitro data should not only indicate the possibility of an interaction but also predict its magnitude and clinical importance. Until such a time, the clinical study remains the ultimate means by which a drug interaction and its importance can be assessed.

2.11 Conclusions and Future Directions

It is difficult to assess the true incidence and clinical significance of drug interactions. Understanding the mechanisms underlying drug interactions is important for the prediction and avoidance of drug toxicity when initiating combination therapy. Although multiple in vitro methods are currently in use to assess drug interactions, not all have allowed the prediction of clinically significant events [205, 206]. As drug interactions most commonly result from influences on drug metabolizing enzymes, future research defining the origins of enzyme activity variability and characterizing individual patient activity will certainly improve our ability to predict these interactions and improve drug therapy.

References

1. Tanaka E. Clinically important pharmacokinetic drug-drug interactions: role of cytochrome P450 enzymes. J Clin Pharm Ther 1998;23:403–416.
2. Lin JH, Lu AY. Inhibition and induction of cytochrome P450 and the clinical implications. Clin Pharmacokinet 1998;35:361–390.
3. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Drug interactions with newer antidepressants: role of human cytochromes P450. J Clin Psych 1998;59(suppl 15):19–27.
4. Shannon M. Drug-drug interactions and the cytochrome P450 system: an update. Ped Emergency Care 1997;13:350–353.

5. Guengerich FP. Role of cytochrome P450 enzymes in drug-drug interactions. Adv Pharmacol 1997;43:7–35.
6. Ritschel WA. (ed.). Handbook of Basic Pharmacokinetics. 4th ed. Hamilton, IL: Drug Intelligence Publications.
7. Welling PG. Interactions affecting drug absorption. Clin Pharmacokinet 1984;9:404–434.
8. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs; an update. Clin Pharmacokinet 1990;18:210–219.
9. Lee BL, Safrin S. Interactions and toxicities of drugs used in patients with AIDS. Clin Infect Dis 1992;14:773–779.
10. Horowitz HW, Jorde UP, Wormser GP. Drug interactions in use of dapsone for Pneumocystis carinii prophylaxis. Lancet 1992;339:747.
11. Moreno F, Hardin TC, Rinaldi MG, et al. Itraconazole-didanosine excipient interaction. JAMA 1993;269:1508.
12. Metroka CE, McMechan MF, Andrada R, et al. Failure of prophylaxis with dapsone in patients taking dideoxyinosine. N Engl J Med 1991;325:737.
13. Fisher RS, Sher DJ, Donahue D, et al. Regional differences in gastric acidity and antacid distribution: is a single pH electrode sufficient? Am J Gastroenterol 1997;92:263–270.
14. Burget DW, Chiverton SG, Hunt RH. Is there an optimal degree of acid suppression for healing duodenal ulcers? Gastroenterology 1990;99:345–351.
15. Kanda Y, Kami M, Matsuyama T, et al. Plasma concentration of itraconazole in patients receiving chemotherapy for hematological malignancies: the effect of famotidine on the absorption of itraconazole. Hematol Oncol 1998;16:33–37.
16. Jaruratanasirikul S, Sriwiriyajan S. Effect of omeprazole on the pharmacokinetics of itraconazole. Eur J Clin Pharmacol 1998;54:159–161.
17. Chin TW, Loeb M, Fong IW. Effects of an acidic beverage (Coca-Cola) on absorption of ketoconazole. Antimicrob Agents Chemother 1995;39:1671–1675.
18. Hansten PD. Drug interactions with antisecretory agents. Aliment Pharmacol Ther 1991;5 (suppl 1):121–128.
19. Somogyi A, Muirhead M. Pharmacokinetic interactions of cimetidine 1987. Clin Pharmacokinet 1987;12:321–366.
20. Sadowski DC. Drug interactions with antacids. Mechanisms and clinical significance. Drug Safety 1994;11:395–407.
21. Knupp CA, Barbhaiya RH. A multiple-dose pharmacokinetic interaction study between didanosine (Videx) and ciprofloxacin (Cipro) in male subjects seropositive for HIV but asymptomatic. Biopharmaceut Drug Disp 1997;18:65–77.
22. Polk RE. Drug-drug interactions with ciprofloxacin and other fluoroquinolones. Am J Med 1989;87:76 S–81 S.
23. Sahai J, Gallicano K, Oliveras L, et al. Cations in the didanosine tablet reduce ciprofloxacin bioavailability. Clin Pharmacol Ther 1993;53:292–297.
24. Lomaestro BM, Bailie GR. Quinolone-cation interactions: a review. DICP 1991;25:1249–1258.
25. Yuk JH, Nightingale CH, Sweeney KR, et al. Relative bioavailability in healthy volunteers of ciprofloxacin administered through nasogastric tube with or without enteral feeding. Antimicrob Agents Chemother 1989;33:1118–1120.
26. Yuk JH, Nightingale CH, Quintiliani R, et al. Absorption of ciprofloxacin administered through a nasogastric or a nasoduodenal tube in volunteers and patients receiving enteral nutrition. Diag Micro Infect Dis 1990;13:99–102.
27. Neuvonen PJ, Gothon G, Hackman R, et al. Interference of iron with the absorption of tetracyclines in man. Br Med J 1970;4:532–534.
28. Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride. Effect of food, milk, and iron. J Am Acad Dermatol 1985;12(2 Pt 1):308–312.
29. Campbell NR, Hasinoff BB. Iron supplements: a common cause of drug interactions. Br J Clin Pharmacol 1991;31:251–255.
30. Questran product monograph, Cholestyramine for oral suspension. BMS. Product Monograph. September 1993.

31. Parsons RL, Paddock GM. Absorption of two antibacterial drugs, cephalexin and cotrimoxazole, in malabsorption syndromes. J Antimicrob Chemother 1975;1(suppl):59–67.
32. Fraga Fuentes MD, Garcia Diaz B, de Juana Velasco P, et al. Influence of foods on the absorption of antimicrobial agents. Nutricion Hospitalaria 1997;12:277–288.
33. Tonini M. Recent advances in the pharmacology of gastrointestinal prokinetics. Pharmacol Res 1996;33(4–5):217–226.
34. Kedderis GL. Pharmacokinetics of drug interactions. Adv Pharmacol 1997;43:189–203.
35. Tsuji A, Tamai I. Carrier-mediated intestinal transport of drugs. Pharm Res 1996;13:963–977.
36. Zhang L, Brett CM, Giacomini KM. Role of organic cation transporters in drug absorption and elimination. Ann Rev Pharmacol Toxicol 1998;38:431–460.
37. Saitoh H, Fujisaki H, Aungst BJ, et al. Restricted intestinal absorption of some beta-lactam antibiotics by an energy-dependent efflux system in rat intestine. Pharm Res 1997;14:645–649.
38. Rabbaa L, Dautrey S, Colas-Linhart N, et al. Absorption of ofloxacin isomers in the rat small intestine. Antimicrob Agents Chemother 1997;41:2274–2277.
39. Yee S. In vitro permeability across Caco-2 cells (colonic) can predict in vivo (small intestinal) absorption in man—fact or myth. Pharm Res 1997;14:763–766.
40. Delie F, Rubas W. A human colonic cell line sharing similarities with enterocytes as a model to examine oral absorption: advantages and limitations of the Caco-2 model. Crit Rev Ther Drug Carrier Syst 1997;14:221–286.
41. Lu AY. Drug-metabolism research challenges in the new millennium: individual variability in drug therapy and drug safety. Drug Met Disp 1998;26:1217–1222.
42. Salama NN, Eddington ND and Fasano A. Tight junction modulation and its relationship to drug delivery. Adv Drug Deliv Rev 2006;58:15–28.
43. Hall SD, Thummel KE, Watkins PB, et al. Molecular and physical mechanisms of first-pass extraction. Drug Met Disp 1999;27:161–166.
44. Wacher VJ, Wu C-Y, Benet LZ. Overlapping substrate specificities and tissue distribution of cytochrome P450 3A and P-glycoprotein: implications for drug delivery and activity in cancer chemotherapy. Mol Carcinog 1995;13:129–134.
45. Schuetz EG, Beck WT, Schuetz JD. Modulation and substrates of P-glycoprotein and cytochrome P4503A coordinately up-regulate these proteins in human colon carcinoma cells. Mol Pharmacol 1996;49:311–318.
46. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmacokinet 1997;32:210–258.
47. Bonkovsky HL, Hauri HP, Marti U, et al. Cytochrome P450 of small intestinal epithelial cells. Gastroenterology 1985;88:458–467.
48. Krishna DR, Klotz U. Extrahepatic metabolism of drugs in humans. Clin Pharmacokinet 1994;26:144–160.
49. Paine MF, Khalighi M, Fisher JM, et al. Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. J Pharmacol Exp Ther 1997;283:1552–1562.
50. Thummel KE, Wilkinson GR. In vitro and in vivo drug interactions involving human CYP3A. Ann Rev Pharmacol Toxicol 1998;38:389–430.
51. Kolars JC, Schmiedlin-Ren P, Schuetz JD, et al. Identification of rifampin-inducible P450IIIA4 (CYP3A4) in human small bowel enterocytes. J Clin Invest 1992;90:1871–1878.
52. Thummel KE, O'Shea D, Paine MF, et al. Oral first-pass elimination of midazolam involves both gastrointestinal and hepatic CYP3A-mediated metabolism. Clin Pharmacol Ther 1996;59:491–502.
53. Gibbs MA, Thummel KE, Shen DD, et al. Inhibition of cytochrome P-450 3A (CYP3A) in human intestinal and liver microsomes: comparison of K_i values and impact of CYP3A5 expression. Drug Met Disp 1999;27:180–187.
54. Gorski JC, Jones DR, Haehner-Daniels BD, et al. The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. Clin Pharmacol Ther 1998;64:133–143.
55. Lown KS, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997;99: 2245–2253.

56. Schmiedlin-Ren P, Edwards DJ, Fitzsimmons ME, et al. Mechanisms of enhanced oral availability of CYP3A4 substrates by grapefruit constituents: decreased enterocyte CYP3A4 concentration and mechanism-based inactivation by furanocoumarins. Drug Metab Disp 1997;25:1228–1233.
57. Ameer B, Weintraub RA. Drug interactions with grapefruit juice. Clin Pharmacokinet 1997;33:103–121.
58. Kupferschmidt HH, Ha HR, Ziegler WH, et al. Interaction between grapefruit juice and midazolam in humans. Clin Pharmacol Ther 1995;58:20–28.
59. Lundahl J, Regardh CG, Edgar B, et al. Effects of grapefruit juice ingestion—pharmacokinetics and haemodynamics of intravenously and orally administered felodipine in healthy men. Eur J Clin Pharmacol 1997;52:139–145.
60. Rashid TJ, Martin U, Clarke H, et al. Factors affecting the absolute bioavailability of nifedipine. Br J Clin Pharmacol 1995;40:51–58.
61. Kupferschmidt HH, Fattinger KE, Ha HR, et al. Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. Br J Clin Pharmacol 1998;45:355–359.
62. Kawakami M, Suzuki K, Ishizuka T, et al. Effect of grapefruit juice on pharmacokinetics of itraconazole in healthy subjects. Int J Clin Pharmacol Ther 1998;36:306–308.
63. Cheng KL, Nafziger AN, Peloquin CA, et al. Effect of grapefruit juice on clarithromycin pharmacokinetics. Antimicrob Agents Chemother 1998;42:927–929.
64. Tsunoda SM, Velez RL, Greenblatt DJ. Ketoconazole inhibition of intestinal and hepatic cytochrome P450 3A4 (CYP3A4) activity using midazolam as an in vivo probe. Clin Pharmacol Ther 1999;65:172.
65. Hsu A, Granneman GR, Cao G, et al. Pharmacokinetic interactions between two human immunodeficiency virus protease inhibitors, ritonavir and saquinavir. Clin Pharmacol Ther 1998;63:453–464.
66. Sham HL, Kempf DJ, Molla A, et al. ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease. Antimicrob Agents Chemother 1998;42:3218–3224.
67. Paine MF, Schmiedlin-Ren P, Watkins PB. Cytochrome P-450 1A1 expression in human small bowel: interindividual variation and inhibition by ketoconazole. Drug Metab Disp 1999;27:360–364.
68. Stein WD. Kinetics of the multidrug transporter (P-glycoprotein) and its reversal. Physiol Rev 1997;77:545–590.
69. Lown KS, Fontana RJ, Schmiedlin-Ren P, et al. Interindividual variation in intestinal mdr1: lack of short term diet effects. Gastroenterology 1995;108:A737.
70. Willie RT, Lown KS, Huszezo UR, et al. Short term effect of medications on CYP3A and P-glycoprotein expression in human intestinal mucosa. Gastroenterology 1997;112 (suppl):A419.
71. Lamba J, Strom S, Venkataramanan R, et al. MDR1 genotype is associated with hepatic cytochrome P450 3A4 basal and induction phenotype. Clin Pharmacol Ther 2006;79:325–38
72. Wakasugi H, Yano I, Ito T, et al. Effect of clarithromycin on renal excretion of digoxin: interaction with P-glycoprotein. Clin Pharmacol Ther 1998;64:123–128.
73. Cormet-Boyaka E, Huneau JF, Mordrelle A, et al. Secretion of sparfloxacin from the human intestinal Caco-2 cell line is altered by P-glycoprotein inhibitors. Antimicrob Agents Chemother 1998;42:2607–2611.
74. Annaert P, Van Gelder J, Naesens L, et al. Carrier mechanisms involved in the transepithelial transport of bis(POM)-PMEA and its metabolites across Caco-2 monolayers. Pharm Res 1998;15:1168–1173.
75. Alsenz J, Steffen H, Alex R. Active apical secretory efflux of the HIV protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers. Pharm Res 1998;15:423–428.
76. Srinivas RV, Middlemas D, Flynn P, et al. Human immunodeficiency virus protease inhibitors serve as substrates for multidrug transporter proteins MDR1 and MRP1 but retain antiviral efficacy in cell lines expressing these transporters. Antimicrob Agents Chemother 1998;42:3157–3162.
77. Kim AE, Dintaman JM, Waddell DS, et al. Saquinavir, an HIV protease inhibitor, is transported by P-glycoprotein. J Pharmacol Exp Ther 1998;286:1439–1445.

78. Salphati L, Benet LZ. Effects of ketoconazole on digoxin absorption and disposition in rat. Pharmacology 1998;56:308–313.
79. Takano M, Hasegawa R, Fukuda T, Yumoto R, Nagai J, Murakami T. Interaction with P-glycoprotein and transport of erythromycin, midazolam and ketoconazole in Caco-2 cells. Eur J Pharmacol 1998;358:289–294.
80. Soldner A, Christians U, Susanto M, et al. Grapefruit juice activates P-glycoprotein-mediated drug transport. Pharm Res 1999;16:478–485.
81. Sansom LN, Evans AM. What is the true clinical significance of plasma protein binding displacement interactions? Drug Safety 1995;12:227–233.
82. Craig WA, Welling PG. Protein binding of antimicrobials: clinical pharmacokinetics and therapeutic implications. Clin Pharmacokinet 1977;2:252.
83. McElnay JC, D'Arcy PF. Protein binding displacement interactions and their clinical importance. Drugs 1983;25:495–513.
84. Rowland M. Plasma protein binding and therapeutic drug monitoring. Ther Drug Monit 1980;2:29–37.
85. Rolan PR. Plasma protein binding displacement interactions—why are they still regarded as clinically important? Br J Clin Pharmacol 1994;37:125–128.
86. Monahan BP, Ferguson CL, Killeavy ES, et al. Torsades des pointes occurring in association with terfenadine use. JAMA 1990;264:2788–2790.
87. Honig PK, Woosley RL, Zamani K, et al. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. Clin Pharmacol Ther 1992;52:231–238.
88. Pohjola-Sintonen S, Viitasalo M, Toivonen L, et al. Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. Eur J Clin Pharmacol 1993;45:191–193.
89. Honig PK, Wortham DC, Zamani K, et al. Terfenadine-ketoconazole interaction, Pharmacokinetic and electrocardiographic consequences. JAMA 1993;269:1513–1518.
90. Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy 1998;18:84–112.
91. Nelson DR, Koymans L, Kamataki T, et al. P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. Pharmacogenetics 1996;6:1–42.
92. Degtyarenko KN, Fábián P. (June 1999) Directory of P450-Containing Systems. http://www.icgeb.trieste.it/p450/P450Nom_Full.html#Animalia.
93. Wrighton SA, Stevens JC. The human hepatic cytochromes P450 involved in drug metabolism. Crit Rev Tox 1992;22:1–21.
94. Smith G, Stubbins MJ, Harries LW, et al. Molecular genetics of the human cytochrome P450 monooxygenase superfamily. Xenobiotica 1998;28:1129–1165.
95. Pelkonen O, Maenpaa J, Taavitsainen P, et al. Inhibition and induction of human cytochrome P450 (CYP) enzymes. Xenobiotica 1998;28:1203–1253.
96. Daly AK, Fairbrother KS, Smart J. Recent advances in understanding the molecular basis of polymorphisms in genes encoding cytochrome P450 enzymes. Toxicol Lett 1998;102,103, 143–147.
97. Kroemer HK, Eichelbaum M. "It's the genes, stupid." Molecular bases and clinical consequences of genetic cytochrome P450 2D6 polymorphism. Life Sci 1995;56:2285–2298.
98. Rendic S, Di Carlo FJ. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. Drug Metab Rev 1997;29:413–580.
99. Vanden Bossche H, Koymans L, Moereels H. P450 inhibitors of use in medical treatment: focus on mechanisms of action. Pharmacol Ther 1995;67:79–100.
100. Murray M. Drug-mediated inactivation of cytochrome P450. Clin Exp Pharmacol Physiol 1997;24:465–470.
101. Babany G, Larrey D, Pessayre D. Macrolide antibiotics as inducers and inhibitors of cytochrome P-450 in experimental animals and man. In: Gibson GG. (ed.). Progress in Drug Metabolism. London: Taylor & Francis, 1988, pp. 61–98.

102. Ludden TM. Pharmacokinetic interactions of the macrolide antibiotics. Clin Pharmacokinet 1985;10:63–79.
103. Gray MR, Tam YK. Pharmacokinetics of drugs that inactivate metabolic enzymes. J Pharmaceut Sci 1991;80:121–127.
104. Wooles WR, Borzelleca JF. Prolongation of barbiturate sleeping time in mice by stimulation of the reticuloendothelial system (RES). J Reticuloendothel Soc 1966;3:41–47.
105. Leeson GA, Biedenbach SA, Chan KY, et al. Decrease in the activity of the drug-metabolizing enzymes of rat liver following the administration of tilorone hydrochloride. Drug Metab Disp 1976;4:232–238.
106. Trenholme GM, Williams RL, Rieckmann KH, et al. Quinine disposition during malaria and during induced fever. Clin Pharmacol Ther 1976;19:459–467.
107. Chang KC, Bell TD, Lauer BA, et al. Altered theophylline pharmacokinetics during acute respiratory viral illness. Lancet 1978;1:1132,1133.
108. Kraemer MJ, Furukawa CT, Koup JR, et al. Altered theophylline clearance during an influenza B outbreak. Pediatrics 1982;69:476–480.
109. Renton KW, Mannering GJ. Depression of the hepatic cytochrome P-450 mono-oxygenase system by administered tilorone (2,7-bis(2-(diethylamino)ethoxy)fluoren-9-one dihydrochloride). Drug Metab Disp 1976;4:223–231.
110. Sonne J, Dossing M, Loft S, et al. Antipyrine clearance in pneumonia. Clin Pharmacol Ther 1985;37:701–704.
111. Shedlofsky SI, Israel BC, McClain CJ, et al. Endotoxin administration to humans inhibits hepatic cytochrome P450-mediated drug metabolism. J Clin Invest 1994;94:2209–2214.
112. Shelly MP, Mendel L, Park GR. Failure of critically ill patients to metabolize midazolam. Anaesthesia 1987;42:619–626.
113. Brockmeyer NH, Barthel B, Mertins L, et al. Changes of antipyrine pharmacokinetics during influenza and after administration of interferon-alpha and -beta. Int J Clin Pharmacol Ther 1998;36:309–311.
114. Gidal BE, Reiss WG, Liao JS, et al. Changes in interleukin-6 concentrations following epilepsy surgery: potential influence on carbamazepine pharmacokinetics. Ann Pharmacother 1996;30:545,546.
115. Chen YL, Le Vraux V, Leneveu A, et al. Acute-phase response, interleukin-6, and alteration of cyclosporine pharmacokinetics. Clin Pharmacol Ther 1994;55:649–660.
116. Morgan ET. Regulation of cytochromes P450 during inflammation and infection. Drug Metab Rev 1997;29:1129–1188.
117. Sewer MB, Morgan ET. Nitric oxide-independent suppression of P450 2C11 expression by interleukin-1beta and endotoxin in primary rat hepatocytes. Biochem Pharmacol 1997;54:729–737.
118. Tinel M, Robin MA, Doostzadeh J, et al. The interleukin-2 receptor down-regulates the expression of cytochrome P450 in cultured rat hepatocytes. Gastroenterology 1995;109:1589–1599.
119. Chen J, Nikolova-Karakashian M, Merrill AH. Jr, et al. Regulation of cytochrome P450 2C11 (CYP2C11) gene expression by interleukin-1, sphingomyelin hydrolysis, and ceramides in rat hepatocytes. J Biol Chem 1995;270:25,233–25,238.
120. Morgan ET, Thomas KB, Swanson R, et al. Selective suppression of cytochrome P-450 gene expression by interleukins 1 and 6 in rat liver. Biochim Biophys Acta 1994;1219:475–483.
121. Wright K, Morgan ET. Regulation of cytochrome P450IIC12 expression by interleukin-1 alpha, interleukin-6, and dexamethasone. Mol Pharmacol 1991;39:468–474.
122. Abdel-Razzak Z, Corcos L, Fautrel A, et al. Interleukin-1 beta antagonizes phenobarbital induction of several major cytochromes P450 in adult rat hepatocytes in primary culture. FEBS Lett 1995;366(2–3):159–164.
123. Fukuda Y, Ishida N, Noguchi T, et al. Interleukin-6 down regulates the expression of transcripts encoding cytochrome P450 IA1, IA2 and IIIA3 in human hepatoma cells. Biochem Biophys Res Comm 1992;184:960–965.
124. Barker CW, Fagan JB, Pasco DS. Interleukin-1 beta suppresses the induction of P4501A1 and P4501A2 mRNAs in isolated hepatocytes. J Biol Chem 1992;267:8050–8055.

125. Berthou F, Ratanasavanh D, Alix D, et al. Caffeine and theophylline metabolism in newborn and adult human hepatocytes; comparison with adult rat hepatocytes. Biochem Pharmacol 1988;37:3691–3700.
126. Veronese ME, McManus ME, Laupattarakasem P, et al. Tolbutamide hydroxylation by human, rabbit and rat liver microsomes and by purified forms of cytochrome P-450. Drug Metab Disp 1990;18:356–361.
127. Parkinson A. An overview of current cytochrome P450 technology for assessing the safety and efficacy of new materials. Toxicol Pathol 1996;24:48–57.
128. Kurokohchi K, Matsuo Y, Yoneyama H, et al. Interleukin 2 induction of cytochrome P450-linked monooxygenase systems of rat liver microsomes. Biochem Pharmacol 1993;45:585–592.
129. Cantoni L, Carelli M, Ghezzi P, et al. Mechanisms of interleukin-2-induced depression of hepatic cytochrome P-450 in mice. Eur J Pharmacol 1995;292(3–4):257–263.
130. Ansher SS, Puri RK, Thompson WC, et al. The effects of interleukin 2 and alpha-interferon administration on hepatic drug metabolism in mice. Cancer Res 1992;52:262–266.
131. Craig PI, Williams SJ, Cantrill E, et al. Rat but not human interferons suppress hepatic oxidative drug metabolism in rats. Gastroenterology 1989;97:999–1004.
132. Pageaux GP, le Bricquir Y, Berthou F, et al. Effects of interferon-alpha on cytochrome P-450 isoforms 1A2 and 3A activities in patients with chronic hepatitis C. Eur J Gastroenterol Hepatol 1998;10:491–495.
133. Okuno H, Kitao Y, Takasu M, et al. Depression of drug metabolizing activity in the human liver by interferon-alpha. Eur J Clin Pharmacol 1990;39:365–367.
134. Okuno H, Takasu M, Kano H, et al. Depression of drug-metabolizing activity in the human liver by interferon-beta. Hepatology 1993;17:65–69.
135. Williams SJ, Farrell GC. Inhibition of antipyrine metabolism by interferon. Br J Clin Pharmacol 1986;22:610–612.
136. Israel BC, Blouin RA, McIntyre W, et al. Effects of interferon-alpha monotherapy on hepatic drug metabolism in cancer patients. Br J Clin Pharmacol 1993;36:229–235.
137. Piscitelli SC, Vogel S, Figg WD, et al. Alteration in indinavir clearance during interleukin-2 infusions in patients infected with the human immunodeficiency virus. Pharmacotherapy 1998;18:1212–1216.
138. Elkahwaji J, Robin MA, Berson A, et al. Decrease in hepatic cytochrome P450 after interleukin-2 immunotherapy. Biochem Pharmacol 1999;57:951–954.
139. Kleman MI, Overvik E, Poellinger L, et al. Induction of cytochrome P4501A isozymes by heterocyclic amines and other food-derived compounds. Princess Takamatsu Symp 1995;23:163–171.
140. Dogra SC, Whitelaw ML, May BK. Transcriptional activation of cytochrome P450 genes by different classes of chemical inducers. Clin Exp Pharmacol Physiol 1998;25:1–9.
141. Rana R, Chen Y, Ferguson SS, Kissling GE, Surapureddi S and Goldstein JA. Hepatocyte nuclear factor 4{alpha} regulates rifampicin-mediated induction of CYP2C genes in primary cultures of human hepatocytes. Drug Metab Dispos 2010;38:591–9.
142. Faucette SR, Zhang TC, Moore R, et al. Relative activation of human pregnane X receptor versus constitutive androstane receptor defines distinct classes of CYP2B6 and CYP3A4 inducers. J Pharmacol Exp Ther 2007;320:72–80.
143. Lehmann JM, McKee DD, Watson MA, et al. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. J Clin Invest 1998;102:1016–1023.
144. Zangar RC, Bollinger N, Verma S, Karin NJ and Lu Y. The nuclear factor-kappa B pathway regulates cytochrome P450 3A4 protein stability. Mol Pharmacol 2008;73:1652–8.
145. Patel M, Tang BK, Kalow W. Variability of acetaminophen metabolism in caucasians and orientals. Pharmacogenetics 1992;2:38–45.
146. Weinshilboum R. Sulfotransferase pharmacogenetics. Pharmacol Ther 1990;45:93–107.
147. Weinshilboum R. Methyltransferase pharmacogenetics. Pharmacol Ther 1989;43:77–90.
148. Evans DA. N-Acetyltransferase. Pharmacol Ther 1989;42:157–234.

149. Lennard MS. Genetically determined adverse drug reactions involving metabolism. Drug Safety 1993;9:60–77.
150. Spielberg SP. N-acetyltransferases: pharmacogenetics and clinical consequences of polymorphic drug metabolism. J Pharmacokinet Biopharm 1996;24:509–519.
151. Park BK, Kitteringham NR. Assessment of enzyme induction and enzyme inhibition in humans: toxicological implications. Xenobiotica 1990;20:1171–1185.
152. Burchell B, McGurk K, Brierly CH, et al. UDP-glucuronosyltransferases. In: Guengerich FP. (ed.). Biotransformation, Vol 3, Comprehensive Toxicology. Oxford: Elsevier Science.
153. Abid A, Sabolovic N, Batt AM, et al. Induction of UDP-glucuronosyltransferases and cytochromes P450 in human hepatocytes. Cell Pharmacol 1994;1:257–262.
154. Burger DM, Meenhorst PL, ten Napel CHH, et al. Pharmacokinetic variability of zidovudine in HIV-infected individuals: subgroup analysis and drug interactions. AIDS 1994;8:1683–1689.
155. Hayes JD, McLeod R, Pulford DJ, et al. Regulation and activity of glutathione S-transferases. ISSX Proc 1996;10:12–18.
156. Bonate PL, Reith K, Weir S. Drug interactions at the renal level: implications for drug development. Clin Pharmacokinet 1998;34:375–404.
157. van Ginneken CA, Russel FG. Saturable pharmacokinetics in the renal excretion of drugs. Clin Pharmacokinet 1989;16:38–54.
158. Kirby WMM, DeMaine JB, Serrill WS. Pharmacokinetics of the cephalosporins in healthy volunteer and uremic patients. Postgrad Med J 1971;47:41–46.
159. Kampmann J, Molholm-Hansen J, Siersbaeck-Nielsen K, et al. Effect of some drugs on penicillin half-life in blood. Clin Pharmacol Ther 1972;13:516–519.
160. Prescott LF. Clinically important drug interactions. Drugs 1973;5:161–186.
161. Chatton JY, Munafo A, Chave JP, et al. Trimethoprim, alone or in combination with sulphamethoxazole, decreases the renal excretion of zidovudine and its glucuronide. Br J Clin Pharmacol 1992;34:551–554.
162. Fletcher CV, Henry WK, Noormohamed SE, et al. The effect of cimetidine and ranitidine administration with zidovudine. Pharmacotherapy 1995;15:701–708.
163. Ito T, Yano I, Tanaka K, et al. Transport of quinolone antibacterial drugs by human P-glycoprotein expressed in a kidney epithelial cell line, LLC-PK1. J Pharmacol Exp Ther 1997;282:955–960.
164. Kaukonen KM, Olkkola KT, Neuvonen PJ. Itraconazole increases plasma concentrations of quinidine. Clin Pharmacol Ther 1997;62:510–517.
165. Bendayan R, Georgis W, Rafi-Tari S. Interaction of 3′-azido-3′-deoxythymidine with the organic base transporter in a cultured renal epithelium. Pharmacotherapy 1995;15:338–344.
166. Sweeney KR, Hsyu PH, Statkevich P, et al. Renal disposition and drug interaction screening of (−)-2′-deoxy-3′-thiacytidine (3TC) in the isolated perfused rat kidney. Pharm Res 1995; 12:1958–1963.
167. Bendayan R. Renal drug transport: a review. Pharmacotherapy 1996;16:971–985.
168. Owens RC, Jr., Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 2005;41 Suppl 2:S144-57.
169. Zyvox (Linezolid) product information. New York, NY: Pfizer, Inc., 2010.170.
170. O'Reilly RA. Interaction of sodium warfarin and rifampin. Studies in man. Ann Intern Med 1974;81:337–340.
171. Modry DL, Stinson EB, Oyer PE, et al. Acute rejection and massive cyclosporine requirements in heart transplant recipients treated with rifampin. Transplantation 1985;39:313–314.
172. Barditch-Crovo P, Trapnell CB, Ette E, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. Clin Pharmacol Ther 1999;65:428–438.
173. LeBel M, Masson E, Guilbert E, et al. Effects of rifabutin and rifampicin on the pharmacokinetics of ethinylestradiol and norethindrone. J Clin Pharmacol 1998;38:1042–1050.
174. Keogh A, Spratt P, McCosker C, et al. Ketoconazole to reduce the need for cyclosporine after cardiac transplantation. N Engl J Med 1995;333:628–633.

175. Jones TE. The use of other drugs to allow a lower dosage of cyclosporine to be used. Therapeutic and pharmacoeconomic considerations. Clin Pharmacokinet 1997;32:357–367.
176. Kempf DJ, Marsh KC, Kumar G, et al. Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. Antimicrob Agents Chemother 1997;41:654–660.
177. Caranasos GJ, Stewart RB, Cluff LE. Clinically desirable drug interactions. Ann Rev Pharmacol Toxicol 1985;25:67–95.
178. Pizzo PA. Management of fever in patients with cancer and treatment-induced. N Engl J Med 1993;328:1323–1332.
179. Eliopoulos GM. The ten most commonly asked questions about resistant enterococcal infections. Infect Dis Clin Pract 1994;13:125–129.
180. Lepper MC, Dowling HF. Treatment of pneumococcal meningitis with penicillin compared with penicillin plus aureomycin. Arch Intern Med 1951;88:489–494.
181. Rice JM, Diwan BA, Ward JM, et al. Phenobarbital and related compounds: approaches to interspecies extrapolation. Prog Clin Biol Res 1992;374:231–249.
182. Strolin Benedetti M, Dostert P. Induction and autoinduction properties of rifamycin derivatives: a review of animal and human studies. Environ Health Perspect 1994;102(suppl 9): 101–105.
183. Maenpaa J, Hall SD, Ring BJ, et al. Human cytochrome P450 3A (CYP3A) mediated midazolam metabolism: the effect of assay conditions and regioselective stimulation by alpha-naphthoflavone, terfenadine and testosterone. Pharmacogenetics 1998;8:137–155.
184. Guengerich FP. Characterization of human microsomal cytochrome P-450 enzymes. Ann Rev Pharmacol Toxicol 1989;29:241–264.
185. Rodrigues AD. Integrated cytochrome P450 reaction phenotyping: attempting to bridge the gap between cDNA-expressed cytochromes P450 and native human liver microsomes. Biochem Pharmacol 1999;57:465–480.
186. Gonzalez FJ, Korzekwa KR. Cytochromes P450 expression systems. Ann Rev Pharmacol Toxicol 1995;35:369–390.
187. Zhang Z, Fasco MJ, Huang Z, et al. Human cytochromes P4501A1 and P4501A2: R-warfarin metabolism as a probe. Drug Metab Disp 1995;23:1339–1346.
188. Fischer V, Vogels B, Maurer G, et al. The antipsychotic clozapine is metabolized by the polymorphic human microsomal and recombinant cytochrome P450 2D6. J Pharmacol Exp Ther 1992;260:1355–1360.
189. Dahl ML, Llerena A, Bondesson U, et al. Disposition of clozapine in man: lack of association with debrisoquine and S-mephenytoin hydroxylation polymorphisms. Br J Clin Pharmacol 1994;37:71–74.
190. Lipp HP, Schrenk D, Wiesmuller T, et al. Assessment of biological activities of mixtures of polychlorinated dibenzo-p-dioxins (PCDDs) and their constituents in human HepG2 cells. Arch Toxicol 1992;66:220–223.
191. Krusekopf S, Kleeberg U, Hildebrandt AG, et al. Effects of benzimidazole derivatives on cytochrome P450 1A1 expression in a human hepatoma cell line. Xenobiotica 1997;27:1–9.
192. VandenBranden M, Wrighton SA, Ekins S, et al. Alterations of the catalytic activities of drug-metabolizing enzymes in cultures of human liver slices. Drug Metab Disp 1998;26:1063–1068.
193. Dogterom P. Development of a simple incubation system for metabolism studies with precision-cut liver slides. Drug Metab Disp 1993;21:699–704.
194. Borchardt RT, Wilson G, Smith P, eds. Model Systems for Biopharmaceutical Assessment of Drug Absorption and Metabolism. New York: Plenum, 1996.
195. LeCluyse EL, Madan A, Forster J, et al. Induction of cytochrome P450 enzymes in primary cultures of human hepatocytes. Drug Metab Dispos 1999, in press.
196. Strom SC, Pisarov LA, Korko K, et al. Use of human hepatocytes to study P450 gene induction. Meth Enzymol 1996;272:388–401.
197. Li AP, Maurel P, Gomez-Lechon MJ, et al. Preclinical evaluation of drug-drug interaction potential: present status of the application of primary human hepatocytes in the evaluation of cytochrome P450 induction. Chemico-Bio Interact 1997;107:5–16.

198. Buchert E, Woosley RL. Clinical implications of variable antiarrhythmic drug metabolism. Pharmacogenetics 1992;2:2–11.
199. Lewis LD, Benin A, Szumlanski CL, et al. Olsalazine and 6-mercaptopurine-related bone marrow suppression: a possible drug-drug interaction. Clin Pharmacol Ther 1997;62:464–475.
200. Brockmoller J, Roots I. Assessment of liver metabolic function. Clinical implications. Clin Pharmacokinet 1994;27:216–248.
201. Scavone JM, Friedman H, Greenblatt DJ. et al. Effect of age, body composition, and lipid solubility on benzodiazepine tissue distribution in rats. Arzeneimittelforschung 1987;37:2–6.
202. von Moltke LL, Greenblatt DJ, Schmider J, et al. In vitro approaches to predicting drug interactions in vivo. Biochem Pharmacol 1998;55:113–122.
203. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Inhibition of triazolam clearance by macrolide antimicrobial agents: in vitro correlates and dynamic consequences. Clin Pharmacol Ther 1998;64:278–285.
204. Thummel KE, Wilkinson GR. In vitro and in vivo drug interactions involving human CYP3A. Annu Rev Pharmacol Toxicol 1998;38:398–430.
205. Posicor. Voluntary market withdrawal. Nutley, NJ: Roche Laboratories; June 8, 1998.
206. Food and Drug Administration. FDA Talk Paper Seldane and Generic Terfenadine Withdrawn from Market. Rockville, MD: US Department of Health and Human Services, Public Health Service, February 27, 1998.

Chapter 3
Mechanisms of Drug Interactions II: Transport Proteins

Catia Marzolini, Manuel Battegay, and David Back

Abstract Most pharmacokinetic studies so far have focused on the role of drug metabolizing enzymes as the key determinants of drug disposition and their contribution to drug-drug interactions. It has now become clear that transporters are responsible for both the uptake and efflux of drugs in various tissues. Their coordinated expression and activities at the basolateral and apical side of transporting epithelia are critical in determining the extent and direction of drug movement in major organs for drug disposition such as the intestine, liver and kidney. Thus, drug transporters represent an important mechanism by which one drug may alter the pharmacokinetic and pharmacological effects (toxicity and efficacy) of another and lead to drug-drug interactions of clinical importance. This chapter focuses on the major drug transporters involved in the disposition of anti-infective agents with special emphasis on their effect on drug disposition, their drug substrate specificities as well as their role in clinically relevant drug-drug interactions.

3.1 Introduction

The movement of drugs across biological membranes was once thought to proceed by simple diffusion depending on their lipophilic properties. However, due to significant advances in molecular biology and biotechnology, a wide variety of drug uptake and efflux transporters have been identified and characterized over the last 15 years. Major membrane transporters have been classified into the solute carrier (SLC) transporter family and the ATP-binding cassette (ABC) transporter family as

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designated by the Human Genome Organization (HUGO) Gene Nomenclature Committee (http://www.genenames.org). With exception of the multidrug and toxin extrusion transporter (MATE), the SLC transporter family is mainly characterized by uptake transporters which transfer substrates, either by facilitated diffusion down the electrochemical gradient or by secondary active transport against a diffusion gradient coupled to the symport or antiport of inorganic or small organic ions to provide the driving force [1]. The SLC transporter family comprises various members of the organic anion transporting polypeptide family (OATP), organic cation transporter (OCT), organic anion transporter (OAT), organic cation/carnitine transporter (OCTN), peptide transporter (PEPT), concentrative nucleoside transporter (CNT), equilibrative nucleoside transporter (ENT), and (MATE) [2]. The ABC transporter family is primarily characterized by efflux transporters that function to export drugs out of a cell against a concentration gradient and are driven by the hydrolysis of adenosine triphosphate (ATP) as an energy source. Members of the ABC transporter family are the multidrug resistance protein (MDR), multidrug resistance-related protein (MRP) family, bile salt export pump (BSEP), and the breast cancer resistance protein (BCRP) [2]. SLC and ABC transporters are involved in the transport of a broad range of drugs in clinical use and share a wide distribution in the body, notably in key organs for drug disposition such as the intestine, liver and kidney. Tables 3.1 and 3.2 list uptake and efflux transporters considered to be relevant for the disposition of anti-infective agents, their tissue distribution as well as selected drug substrates [2, 3].

The role of uptake and efflux transporters in the drug disposition process, including particular emphasis on their documented or potential role in clinically relevant drug-drug interactions involving anti-infective medications will be discussed in the following sections.

3.2 Transporter Effect on Drug Disposition

Most of the SLC and ABC transporters are found at either the apical or basolateral membrane of transporting epithelia (Fig. 3.1). Depending on their function and localization, these transporters will facilitate the entry or the removal of a drug substrate into a given organ. The net pharmacokinetic effect of active transport processes mostly results from the involvement of several transporters that may not always belong to the same family. For example, the transport pathway for the renal elimination of the nucleotide analogue tenofovir involves the uptake from the blood into the renal proximal tubular cells mediated by OAT1/3 and the efflux into urine by MRP4 [4]. Since the coordinated expression and function of transporters are critical in determining the extent and direction of drug movement, modulation of their activity (i.e. inhibition or induction) will directly impact the absorption, distribution, metabolism, and excretion of a drug substrate as described below.

Table 3.1 Uptake transporters and selected drug substrates

Gene	Transporter	Location	Selected drug substrates	Influence on drug disposition
SLCO1A2	**OATP1A2**	Brain, kidney, intestine	Fexofenadine, methotrexate, digoxin, statins, **levofloxacin**, **darunavir**, **lopinavir**, **saquinavir**	• Oral absorption, renal excretion, CNS distribution
SLCO1B1	**OATP1B1**	Liver	Statins, methotrexate, repaglinide, fexofenadine, bosentan, olmesartan, valsartan, torasemide, **rifampin**, **benzylpenicillin**, **capsofungin**, **lopinavir**, **saquinavir**, **darunavir**	• Hepatic uptake • Role in clinically relevant DDI
SLCO1B3	**OATP1B3**	Liver	Statins, methotrexate, paclitaxel, docetaxel, fexofenadine, bosentan, olmesartan, telmisartan, valsartan, digoxin, enalapril, **erythromycin**, **rifampin**	• Hepatic uptake • Role in clinically relevant DDI
SLCO2B1	**OATP2B1**	Liver, intestine, placenta	Statins, fexofenadine, **benzylpenicillin**	• Hepatic uptake, distribution
SLC22A1	**OCT1**	Liver, intestine	Quinidine, cisplatin, imatinib, oxaliplatin, metformin, cimetidine, famotidine, ranitidine, **acyclovir**, **ganciclovir**, **lamivudine**	• Hepatic uptake • Role in clinically relevant DDI
SLC22A2	**OCT2**	Kidney, brain (choroid plexus)	Metformin, ranitidine, amiloride, oxaliplatin, varenicline, **lamivudine**	• CNS distribution, renal excretion • Role in clinically relevant DDI
SLC22A6	**OAT1**	Kidney	Indomethacine, methotrexate, **cidofovir**, **adefovir**, **didanosine**, **zidovudine**, **lamivudine**, **acyclovir**, **tenofovir**,	• Renal excretion • Role in clinically relevant DDI
SLC22A7	**OAT2**	Liver, kidney	5-fluorouracil, methotrexate, paclitaxel, valproic acid, **tetracycline**, **zidovudine**	• Hepatic uptake, renal excretion
SLC22A8	**OAT3**	Kidney, brain	Cimetidine, methotrexate, furosemide, ranitidine, **valacyclovir**, **tetracycline**	• Renal excretion • Role in clinically relevant DDI
SLC22A11	**OAT4**	Kidney, placenta	Methotrexate, **tetracycline**, **zidovudine**	• Renal excretion
SLC15A1	**PEPT1**	Intestine, kidney	Enalapril, captopril, **amoxicillin**, **ampicillin**, **cefaclor**, **valacyclovir**	• Oral absorption, renal excretion • Role in clinically relevant DDI
SLC15A2	**PEPT2**	Kidney	Enalapril, captopril, **amoxicillin**, **valacyclovir**	• Renal excretion
SLC47A1	**MATE1**	Liver, kidney	Cimetidine, metformin, oxaliplatin, **acyclovir**, **ganciclovir**, **tenofovir**, **fluoroquinolones**	• Biliary excretion, renal excretion
SLC47A2	**MATE2-K**	Kidney	Cimetidine, metformin, oxaliplatin, **acyclovir**, **ganciclovir**	• Renal excretion

Anti-infective agents are highlighted in bold
DDI drug drug interaction

Table 3.2 Efflux transporters and selected drug substrates

Gene	Transporter	Location	Selected drug substrates	Influence on drug disposition
ABCB1	**MDR1/P-gp**	Kidney, liver, brain, intestine, placenta, testes, lymphocyte	Anticancer agents, antihypertensive agents, antiarrhythmics, **HIV protease inhibitors**, immunosuppressants, antidepressants, antiepileptics **antifungals**, antihistamines	• Oral absorption, biliary excretion, renal excretion, CNS distribution • Role in clinically relevant DDI
ABCC1	**MRP1**	Many tissues, testes, lymphocyte	Doxorubicin, methotrexate, vincristine etoposide, **HIV protease inhibitors**	• Distribution
ABCC2	**MRP2**	Liver, kidney, intestine	Methotrexate, vinblastine, etoposide, vincristine, valsartan, olmesartan, pravastatin, **HIV protease inhibitors**	• Oral absorption, biliary excretion renal excretion • Role in clinically relevant DDI
ABCC4	**MRP4**	Kidney, liver, brain	Methotrexate, topotecan, furosemide, **adefovir**, **tenofovir**, **abacavir**	• Distribution, renal excretion.
ABCC5	**MRP5**	many tissues	**adefovir**, **lamivudine**	• Distribution
ABCG2	**BCRP**	Intestine, liver, brain, placenta	Mitoxantrone, doxorubicine, topotecan, methotrexate, imatinib, irinotecan, **HIV reverse transcriptase inhibitors**	• Oral absorption, biliary excretion • Role in clinically relevant DDI

Anti-infective agents are highlighted in bold
DDI drug drug interaction

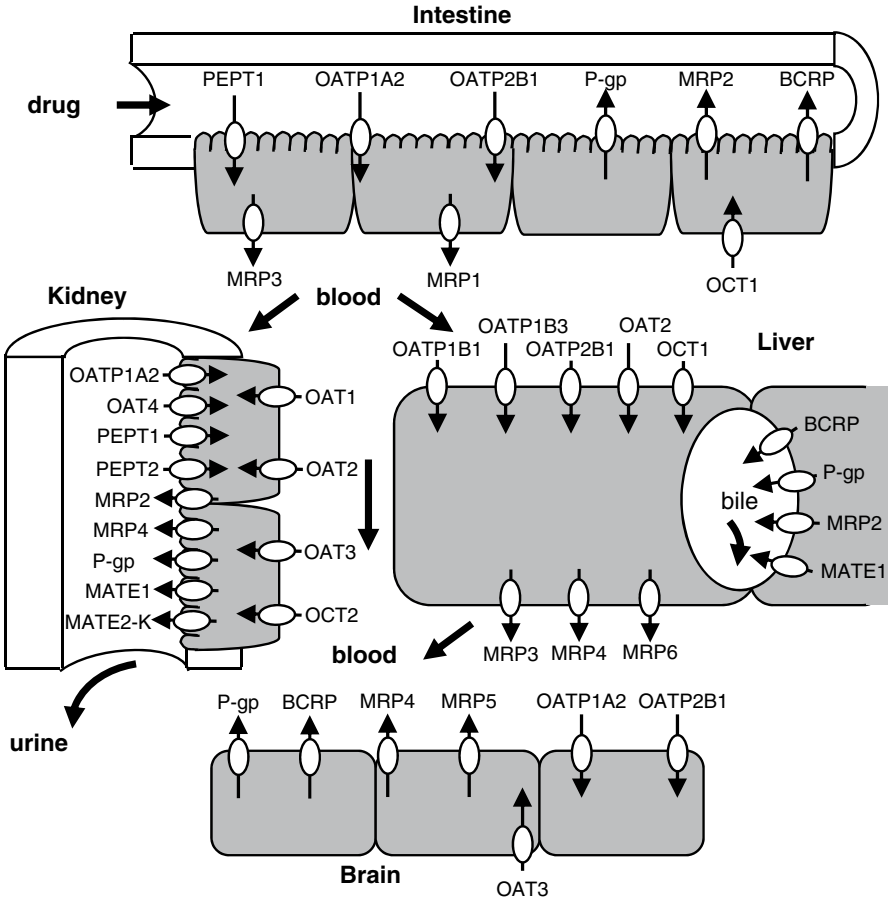

Fig. 3.1 Schematic diagram depicting uptake and efflux transporters relevant for anti-infective drug disposition and their localization in the human intestinal epithelia, hepatocyte, kidney proximal tubule and brain capillary endothelial cell. *BCRP* breast cancer resistance protein, *MATE* multidrug and toxin extrusion protein, *P-gp* P-glycoprotein, *MRP* multidrug resistance associated protein, *OAT* organic anion transporter, *OATP* organic anion transporting polypeptide, *OCT* organic cation transporter, *PEPT* peptide transport protein (From references [3, 59])

3.2.1 Intestinal Absorption

The small intestine not only can limit the absorption of drugs through intestinal metabolism [5], but also through active drug transport back into the lumen by efflux transporters located at the apical brush border membrane of enterocytes such as MDR1 (i.e. P-glycoprotein), MRP2 or BCRP [6]. Conversely, uptake transporters such as PEPT1 or OATP will facilitate the intestinal drug absorption across the brush border membrane [7, 8] (Fig. 3.1). Consequently, modification of the expression or function of uptake or efflux transporters in the gastrointestinal tract will impact the bioavailability of orally administered drug substrates. However, it should be noted that the

transport capacity can be saturated by the high concentration of drugs present in the intestinal lumen. Thus, the relative contribution of intestinal P-glycoprotein to the overall drug absorption is unlikely to be quantitatively important because its transport activity is easily saturated for most drugs at clinically relevant doses [9]. Nevertheless, some drugs administered at high doses are still influenced by the effects of intestinal P-glycoprotein. Typically, such drugs are poorly water soluble, dissolve slowly, and are large in size (>800 Da), e.g. cyclosporine and saquinavir [9]. In general, transporter-mediated drug-drug interactions at the level of intestinal absorption are more likely to be clinically relevant for drugs with a narrow therapeutic index and characterized by an exclusive transporter-mediated disposition profile, e.g. digoxin [10].

3.2.2 Hepatobiliary Elimination

The hepatic elimination of drugs includes several steps: extraction of drugs from the portal blood into the hepatocytes which is often mediated by SLC transporters expressed on the sinusoidal (basolateral) membrane; hepatic metabolism mediated by phase I (cytochrome P450) and phase II (glucuronidation) enzymes; and either secretion of the drug back into the circulation for subsequent renal elimination mediated by ABC transporters expressed on the sinusoidal membrane or secretion into the bile via the efflux transporters expressed on the canalicular (apical) membrane of the hepatocyte [11] (Fig. 3.1). The cooperation of sinusoidal uptake and canalicular efflux transporters allows the directional transport across the hepatocytes. Members of the SLC family are considered to be of particular importance for hepatic drug elimination and drug pharmacokinetics. Specifically, these transporters regulate the amount of drug available for metabolism by liver enzymes and the subsequent biliary excretion of drugs [12]. Inhibition of these hepatic uptake transporters will increase the systemic exposure of a drug substrate and potentially lead to side effects [13]. Clinically relevant drug-drug interactions resulting from the inhibition of OATP1B1/3 have been reported for the statins [14]. For instance, the mean AUC of several statins, not significantly metabolized by drug metabolizing enzymes, increased four to tenfold (i.e. fluvastatin (fourfold), pitavastatin (fivefold), pravastatin (tenfold), rosuvastatin (sevenfold)) in the presence of cyclosporine, an OATP1B1/3 inhibitor [14]. The inhibition of canalicular efflux transporters will impact the biliary clearance of a drug substrate whereas the contribution of sinusoidal efflux transporters to the overall hepatic clearance will depend on the kinetic properties of the drug. Their contribution is expected to be negligible if the uptake is the rate-limiting step in elimination [13].

3.2.3 Renal Excretion

Renal elimination involves both passive and active processes: glomerular filtration and transporter-mediated secretion and reabsorption of drugs. Renal transporters, located mainly in the proximal tubular cells, play a role in several steps: drug uptake

into the proximal tubular cell; drug efflux into the glomerular filtrate; reabsorption of the drug from the filtrate; and drug efflux back into the blood (Fig. 3.1). Overall, renal excretion results from a coordinated function of uptake and efflux transporters located at the basolateral and apical membranes of proximal tubular cells. Members of OAT and OCT families present at the basolateral membrane are characterized by a high clearance capacity and are considered as major renal transporters for the uptake of organic anions and cations, respectively. As a result, highly efficient uptake of certain drugs in the cell can result in accumulation which can cause nephrotoxicity. For instance, preclinical experiments have shown that both cidofovir and adefovir are taken up by OAT1, which contributes to increased cytotoxicity [15, 16]. The large number of efflux transporters expressed at the brush border membrane emphasizes the importance of rapid efflux of potentially toxic compounds into urine. The competitive inhibition of proximal tubular secretion is one of the most common type of drug-drug interaction at the renal level. A decrease in renal secretion can lead to an increase in systemic drug exposure. However, competitive inhibition of renal secretion will result in clinically relevant drug-drug interactions only if the affected drug is actively secreted in the kidney and if the transporter-mediated renal clearance accounts for the majority of the total clearance of the affected drug. In addition, the concentration of the fraction unbound in plasma for the interacting drug must be high enough to produce a pronounced effect. The potential for a significant drug interaction is likely to be small if the concentration of the interacting agent is <Ki (i.e. Michaelis-Menten inhibitory constant), unless the drug has a narrow therapeutic window [17]. For example, interactions with fatal complications have been reported after concomitant administration of tenofovir with didanosine [18] and methotrexate with nonsteroidal anti-inflammatory drugs (NSAID) [19]. These interactions result from interactions on basolateral renal tubular uptake transporters (OAT1 and /or OAT3) as well as on the efflux transporters (MRP2 and/or MRP4) [4, 20].

3.2.4 Tissue Distribution

In organs such as the brain, transporter expression is critical for the brain homeostasis by limiting the entry of potentially harmful endogenous and exogenous substances. The blood–brain barrier consists of endothelial cells connected by complex tight junctions that express various transport proteins [21]. The mechanism of blood–brain barrier transport has been divided into three separate processes: blood uptake of drugs and nutrients into the brain; efflux of compounds to prevent entry into the brain; and uptake of metabolites, neurotransmitters and neurotoxins from the brain into the blood [22, 23]. Successful treatment of certain infections, such as AIDS dementia directly caused by HIV and other HIV related infections, as well as bacterial, fungal or viral meningitis require adequate brain penetration of anti-infective medications. Thus, drug transporters may act as major barrier to current and effective drug treatment. For instance, the critical role of P-glycoprotein in restricting brain uptake of HIV protease inhibitors has been

demonstrated *in vivo*. Mdr1a/b-knockout mice (i.e. mice missing P-glycoprotein) displayed enhanced brain accumulation of nelfinavir (40 fold), indinavir, saquinavir (eight to tenfold) [24] and abacavir (20 fold) [25]. Measurements of antiretroviral concentrations performed in the cerebrospinal fluid of HIV-infected patients indicate indeed that most drugs have very low brain penetration [26, 27].

Expression of several transporters detected in lymphocytes may also have an impact on HIV therapy [28, 29]. Specifically, drug transporters are believed to have a role in limiting drug uptake into lymphocytes. For instance, BCRP has been implicated in conferring cellular resistance to zidovudine and lamivudine by limiting their entry in lymphocytes [30]. Similarly, several studies have shown that P-glycoprotein, MRP, BCRP, OATP limit intracellular levels of various HIV protease inhibitors in lymphocytes. Therefore the effectiveness of antiretroviral therapy may be compromised since HIV virus replicates and is primarily contained within CD4+ cells [31–33].

3.2.5 Impact of Genetic Polymorphisms on Drug Disposition

As highlighted previously, alterations in uptake or efflux transporter function will directly impact the disposition of a drug substrate. Impaired transport function may result from genetic variations in the gene encoding the transporter protein. For example, the variant SLCO1B1*5, which is characterized by a nucleotide change from T to C in position 521 (521 T>C) of the SLCO1B1 gene encoding human OATP1B1, is associated with a reduced *in vitro* transport activity [34]. The clinical importance of this polymorphism has been recently highlighted in antiretroviral therapy as HIV infected patients carrying this genetic variant have higher plasma concentrations of the protease inhibitor lopinavir when compared to non carriers [35, 36]. Conversely, patients homozygous for SLCO1B1*4 (463 C>A) have lower lopinavir plasma levels [36].

The drug disposition of tenofovir has also been shown to be influenced by genetic variants in MRP2 (−24 C>T) and MRP4 (3436A>G and 3463A>G) [37, 38]. Interestingly, the risk for tenofovir induced proximal tubulopathy has been associated with homozygosity for the C allele at position −24 in MRP2 [39]. However, the mechanism by which MRP2 influences the risk of kidney tubular dysfunction is not well understood as *in vitro* studies have shown that tenofovir is not a substrate for human MRP2 [4, 40]. More detailed information regarding genetic variations in drug transporters and their effect on the pharmacokinetic of drugs in clinical use can be found in the following references [41–45]. In addition to genetic variations, modulation of transporter function may result from the inhibiting or inducing properties of a drug substrate, thereby influencing the transport kinetics of a simultaneously administered drug.

3.3 Transporter-Mediated Drug-Drug Interactions

Due to recent identification and characterization of individual transporters, drug-drug interactions observed in the clinic can be linked with the specific transporter protein responsible for the interaction. Specifically, *in vitro* transporter-expressing

systems such as cDNA transfected cell lines or cRNA injected *Xenopus* oocytes are particularly useful in understanding and predicting transporter mediated drug-drug interactions. Table 3.3 compiles the substrate and inhibiting properties of selected anti-infective agents obtained *in vitro* for the major drug transporters with a documented role in drug disposition [4, 15, 25, 30, 31, 35, 40, 46–83]. *In vitro* approaches are now commonly used as a critical first step for the assessment of drug interaction potential and to support subsequent *in vivo* studies which help define the clinical relevance. A guidance document was recently released by the International Transporter Consortium about the conduct and decision making criteria of *in vitro* transporter assay. The main purpose of this guidance is to help determine whether an investigational drug is a substrate or inhibitor of a specific drug transporter and if an *in vivo* drug interaction study is needed [3].

This section will discuss the mechanisms of transporter-mediated interactions and describe examples of clinically relevant drug-drug interactions involving anti-infective agents (Table 3.4) [84–106].

3.3.1 Mechanisms of Inhibition and Induction of Transporters

Transporter-mediated drug interactions in the clinic may be either inhibitory, inductive or both, and may involve influx or efflux transporters. Transporters can be inhibited in a competitive or non-competitive manner in the same way as the drug-metabolizing enzymes can be inhibited. Competitive inhibition occurs when two substrates compete at the same binding site of the transporter protein, where only one substrate can bind. For non-competitive inhibition, two substrates will simultaneously bind at two different sites on the same transporter protein, which might inhibit the subsequent translocation process. Induction of drug transporters and drug metabolizing enzymes occurs indirectly, i.e. through the interaction with nuclear receptors such as the pregnane X receptor (PXR) or constitutive androstane receptor (CAR) [2, 107]. These nuclear receptors share a common signalling pathway, which involve ligand (e.g. rifampin) binding to the receptor, heterodimerization with the 9-cis-retinoic acid receptor (RXR), binding of the heterodimer to response elements of target genes (i.e. drug transporters, drug metabolizing enzymes) and subsequent initiation of the gene transcription [108].

3.3.2 Interplay Between Drug Transporters and Drug Metabolizing Enzymes

Drug transporters and drug metabolizing enzymes often share overlapping tissue expression and substrate specificities. For instance, many P-glycoprotein substrates and inhibitors are also substrates and inhibitors of cytochrome P450 3A4 (CYP3A4) (i.e. erythromycin, itraconazole, HIV protease inhibitors) [109]. This overlap between P-glycoprotein (as well as other transporters) and CYP3A4 has been

Table 3.3 Selected anti-infective agents and their substrate and/or inhibitor properties for key transporters in drug disposition

	OATP				OAT				OCT		PEPT		Pgp	BCRP	MRP			
	1A2	1B1	1B3	2B1	1	2	3	4	1	2	1	2			1	2	4	5
Antibiotics																		
Amoxicillin												x						
Benzylpenicillin							x	x										
Cefaclor							x					x						
Cefazolin					x		x	x										
Clarithromycin		x	x										x					
Erythromycin		x	x			x							x					
Levofloxacin										x								
Rifampin	x	x	x	x														
Tetracycline					x	x		x										
Trimethoprim									x	x								
Antifungals																		
Capsofungin		x																
Itraconazole													x	x				
Ketoconazole		x								x			x	x				
Antivirals																		
Acyclovir					x		x		x									
Adefovir					x											x		
Cidofovir					x											x		
Ganciclovir					x	x	x		x									

Oseltamivir																		
Valacyclovir																		
Antiretrovirals																		
Amprenavir		x	x										x	x	x			
Atazanavir		x	x	x									x	x	x	x		
Darunavir		x	x										x			x		
Indinavir	x	x	x	x					x	x			x		x	x		
Lopinavir		x	x	x									x	x		x		
Nelfinavir	x	x		x					x	x			x	x		x		
Ritonavir	x	x	x	x					x	x			x	x	x	x		
Saquinavir	x	x	x	x					x	x			x	x	x	x		
Tipranavir				x									x					
Efavirenz														x	x	x		
Nevirapine															x	x		
Abacavir									x	x				x				
Didanosine																		
Emtricitabine									x	x					x	x		
Lamivudine									x	x								
Stavudine																		
Tenofovir									x	x								
Zidovudine					x	x	x	x	x	x				x				

This table compiles data obtained from *in vitro* transport/inhibition studies using human isoforms, from references [4, 15, 25, 30, 31, 35, 40, 46–83]. *In vitro* data using rodent isoforms or data resulting from knockout animal model are not included in this table. Substrates are annotated by grey squares and inhibitors by a cross

Table 3.4 Clinical examples of transporter-mediated drug-drug interactions

Drug	Inhibitor/inducer	PK effect/toxicity [a]	Putative mechanism	Reference
Atorvastatin	Rifampin (sd)	AUC ↑ 682%	Inhibition of OATP1B1	[84]
Bosentan	Rifampin	C_{trough} ↑ 5 fold	Inhibition of OATP1B1/3 initial phase	[85]
Bosentan	Rifampin	AUC ↓ 58%, C_{max} ↓ 53%	Induction of CYP3A4 at steady-state	[85]
Bosentan	Lopinavir/r	AUC ↑ 422%, C_{max} ↑ 377%, ↑ AE	Inhibition of OATP1B1/3, CYP3A4	[86]
Rosuvastatin	Lopinavir/r	AUC ↑ 107%, C_{max} ↑ 365%	Inhibition of OATP1B1 and/or BCRP	[87]
Rosuvastatin	Atazanavir/r	AUC ↑ 213%, C_{max} ↑ 600%	Inhibition of OATP1B1 and/or BCRP	[88]
Pravastatin	Clarithromycin	AUC ↑ 110%, C_{max} ↑ 128%	Inhibition of OATP1B1/3	[89]
Lamivudine	Trimethoprim	AUC ↑ 43%, CL ↓ 35%	Inhibition of OCT1/2	[90]
Memantine	Trimethoprim	Myoclonus, delirium	Inhibition of OCT2	[91]
Ciprofloxacin	Probenecid	CL ↓ 65%	Inhibition of OAT3 and/or OCT2	[92]
Cidofovir	Probenecid	CL ↓ 32%	Inhibition of OAT1/3	[93]
Zalcitabine	Probenecid	AUC ↑ 54%, CL ↓ 42%	Inhibition of OAT1	[94]
Flucloxacillin	Piperacillin	CL ↓ 58%	Inhibition of OAT1	[95]
Digoxin	Ritonavir	AUC ↑ 80%, CL ↓ 35%	Inhibition of P-gp	[96]
Tacrolimus	Darunavir/r	Increase in C_{trough}	Inhibition of P-gp, CYP3A4	[97]
Sirolimus	Clarithromycin	Increase in C_{trough}	Inhibition of P-gp, CYP3A4	[98]
Digoxin	Clarithromycin	CL ↓ 50%	Inhibition of P-gp	[99]
Colchicine	Clarithromycin	Colchicine intoxication	Inhibition of P-gp	[100]
Digoxin	Itraconazole	AUC ↑ 50%, CL ↓ 20%	Inhibition of P-gp	[101]
Digoxin	Rifampin	AUC ↓ 30%, C_{max} ↓ 58%	Induction of P-gp	[102]
Atorvastatin	Rifampin	AUC ↓ 80%	Induction of P-gp, CYP3A4	[103]
Indinavir	St John's wort	AUC ↓ 57%, C_{trough} ↓ 81%	Induction of P-gp, CYP3A4	[104]
Mycophenolic acid	Rifampin	AC AUC ↓, metabolites AUC ↑	Induction of UGT, inhibition MRP2	[105]
Tenofovir	Diclofenac	Nephrotoxicity	Inhibition of MRP4	[106]

[a] Percent change refers to the difference between the area under the curve (*AUC*), maximal concentration (C_{max}), concentration just before the next dose (C_{trough}) or renal clearance (*CL*) in the presence and the absence of the interacting drug.

AC active compound, *UGT* uridine diphosphate-glucuronosyltransferase. *AE* adverse effect

hypothesized to result from the fact that drug metabolizing enzymes and drug transporters are regulated through similar mechanisms, which involve transcriptional regulation by nuclear receptors. Drug interactions involving compounds that inhibit both drug metabolizing and transporter pathways may result in profound interactions. For instance, the anti-diabetic drug repaglinide is a substrate for CYP2C8, CYP3A4, and OATP1B1. Gemfibrozil and its metabolite are both inhibitors of CYP2C8 and OATP1B1 [110]. Co-administration of gemfibrozil and repaglinide caused a profound increase in repaglinide area under the curve (AUC) (eightfold), whereas coadministration of repaglinide with itraconazole, a CYP3A4 inhibitor, caused a modest change in repaglinide AUC (1.4 fold) [111]. Interestingly, the simultaneous administration of these three drugs led to a major increase in repaglinide AUC (19 fold). Thus, the interplay between drug metabolizing enzymes and transporter proteins must be considered when evaluating any drug-drug interaction potential.

Emerging evidence suggests that drug transporters such as OATP may indirectly regulate the expression of drug disposition genes through modulation of the intracellular concentrations of PXR or CAR ligands [112]. This concept evolves from previous *in vitro* observations which suggest that OATP1B1 is a major determinant of PXR activation via rifampin [65]. This interplay can result in time-dependent drug-drug interactions. For instance, a single dose of rifampin co-administered with atorvastatin resulted in a sevenfold increase in atorvastatin AUC [84], whereas the treatment with rifampin over 5 days decreased the AUC of atorvastatin by 80% [103] (Table 3.4). The increase in atorvastatin levels after a single dose of rifampin most likely resulted from the immediate OATP1B1/3 inhibition by rifampin [83]. Conversely, the decrease in atorvastatin levels upon continued dosing reflected the time-dependent induction of drug metabolizing enzymes by rifampin. As illustrated by these examples, the interplay between drug transporters and drug metabolizing enzymes presents an emerging challenge for drug interaction prediction [113].

3.3.3 Role of OATP in Drug-Drug Interactions

The organic anion transporting polypeptides (OATP) represent an important family of uptake carriers mediating the transport of relatively large (molecular weight > 400 – 500 Da) and hydrophobic organic anions. Typical endogenous and exogenous substrates include bile salts, thyroid hormones as well as numerous drugs in clinical use such as statins, rifampin, and protease inhibitors [2, 14, 114] (Tables 3.1 and 3.3). The various OATP are expressed in several tissues including the intestine, liver, kidney, brain and placenta [8, 115–119] (Fig. 3.1). As major hepatic uptake transporters, OATP regulate the amount of anionic drugs available for phase I/II metabolism or biliary excretion. Several clinically relevant drug-drug interactions involving OATP have been reported in the literature. A few examples are highlighted below (Table 3.4).

Macrolides are well known to cause drug-drug interactions via the inhibition of drug metabolizing enzymes. For instance, clarithromycin was shown to increase the AUC of several concomitantly administered statins (i.e. simvastatin (tenfold), atorvastatin (fourfold) and pravastatin (twofold)) [89]. For simvastatin and atorvastatin, this increase can be explained by the inhibition of CYP3A4 as both drugs are substrates of this enzyme. In contrast, pravastatin is mainly eliminated as unchanged drug and is not extensively metabolized by the cytochrome P450 enzymes. *In vitro* experiments revealed that not only clarithromycin, but also erythromycin and roxithromycin inhibited OATP1B1 mediated pravastatin uptake whereas azithromycin had no inhibiting activity [52]. Thus, inhibition of OATP1B1 probably explains the observed clinical drug interaction. The co-administration of the HIV protease inhibitor lopinavir boosted with ritonavir (i.e. lopinavir/r) and rosuvastatin surprisingly led to increased plasma concentrations of the statin (i.e. AUC and C_{max} increased 107% and 365%, respectively) [87]. Similarly, rosuvastatin is mainly excreted as unchanged drug and is not extensively metabolized by cytochrome P450 [120]. *In vitro* experiments showed that OATP1B1 contributes predominantly to the hepatic uptake of rosuvastatin [121]. Rosuvastatin is also a substrate of BCRP [122], which is an efflux transporter localized to the apical side of many tissues including the small intestine and the liver. In addition, *in vitro* data have indicated that lopinavir and ritonavir inhibit BCRP and OATP1B1 [51, 55, 66]. Thus, this interaction could possibly result from the inhibition by lopinavir and/or ritonavir of rosuvastatin uptake at either the level of absorption or biliary excretion by BCRP and/or at the level of uptake into the hepatocytes by OATP1B1 [87]. This interaction could possibly negatively impact the pharmacodynamic effect of the statin, by inhibiting its entry into the liver, which is the site of action and elimination. Consequently, the lipid lowering effect of the statin may be attenuated despite the increase in plasma concentration and potential associated risk of myotoxicity. A similar interaction was observed when combining atazanavir/r and rosuvastatin (i.e. AUC and C_{max} increased 213% and 600%, respectively) [88]. Interestingly, the co-administration of fosamprenavir/r did not affect significantly rosuvastatin pharmacokinetics, which could possibly be explained since fosamprenavir is not an inhibitor of BCRP [123]. Bosentan is an endothelin receptor antagonist used for the treatment of pulmonary arterial hypertension. This drug is metabolized by CYP2C9 and CYP3A4 [124] and is a substrate of OATP1B1 and OATP1B3 [125]. The co-administration of bosentan and lopinavir/r, an inhibitor of CYP3A4 and OATP1B1/3 [66], resulted in a marked increase in bosentan exposure (AUC and C_{max} increased 422% and 377%, respectively) as well as an increase in adverse events which were attributed to the high systemic exposure of bosentan [86]. Interestingly, the co-administration of bosentan and rifampin resulted in a time-dependent interaction with an initial fivefold increase in bosentan trough concentrations followed by a decrease in exposure at steady-state. The inhibition of the OATP1B1/3 mediated transport of bosentan by rifampin [83] most likely explains the initial increase in exposure, whereas the CYP inductive properties of rifampin resulted in the decrease in exposure of bosentan observed at steady-state [85].

3.3.4 Role of OAT in Drug-Drug Interactions

The organic anion transporters (OAT) accept relatively small (molecular weight < 400–500 Da), hydrophilic organic anions. Their substrates include products of biotransformation as well as several drugs such as beta-lactams, nonsteroidal anti-inflammatory drugs (NSAID), and antiviral nucleoside analogues [2, 68, 126, 127] (Tables 3.1 and 3.3). OAT1, OAT3 and OAT4 are mainly expressed in the kidney whereas OAT2 is predominantly expressed in the liver [128–131] (Fig. 3.1). OAT are considered as major excretory systems for anionic compounds and have been involved in drug-drug interactions of clinical importance (Table 3.4).

Perhaps the most widely understood drug interaction, first noted six decades ago, is that of penicillin and probenecid, in which co-administration of probenecid resulted in elevated serum penicillin concentrations [132]. *In vitro* experiments have revealed that probenecid strongly inhibits human OAT1 and OAT3 [133]. Interactions between probenecid and beta-lactam antibiotics have been reported extensively [134, 135]. This beneficial interaction has been intentionally utilized to enhance the activity of antibiotics in treating infections. Probenecid has also been used deliberately to alter the renal clearance of a concomitant drug to reduce its toxicity. For instance, cidofovir, a nucleoside analogue used in the treatment of cytomegalovirus retinitis in HIV patients, is predominantly excreted in the urine as unchanged drug [136]. The nephrotoxicity related to this compound is due to its high concentration in the kidney as a result of rapid drug uptake at the basolateral membrane of tubular cells and slower efflux into the urine via transporters of the brush-boarder membrane [15, 16]. Co-administration of probenecid decreased cidofovir clearance which subsequently resulted in reduction of nephrotoxicity [93]. *In vitro* studies have shown that cidofovir is a substrate of OAT1 [16, 68]. Thus, inhibition of OAT1 mediated uptake of cidofovir by probenecid can prevent its nephrotoxicity. Similar findings have been observed when NSAID are co-administered with adefovir, another nucleoside analogue [137]. Although the aforementioned examples have shown some beneficial effects, drug-drug interactions at the level of renal excretion may also have detrimental effects. For instance, the co-administration of methotrexate and NSAID has been associated with severe toxicity of the cytotostatic agent [138] and resulted from competitive inhibition of OAT3 [139].

3.3.5 Role of OCT in Drug-Drug Interactions

The organic cation transporters (OCT) mediate the cellular uptake of small organic cations (molecular weight <400 Da). Typical substrates are endogenously synthesized cationic substances and drugs such as metformin, cytostatic drugs or antiviral nucleoside analogues [2, 140, 141] (Tables 3.1 and 3.3). OCT1 is mostly expressed in the liver whereas OCT2 is most abundant in the kidney [142, 143] (Fig. 3.1). Because OCT1 is localized in the basolateral membrane of hepatocytes and

OCT2 in the basolateral membrane of proximal renal tubular cells, both uptake transporters are important for the hepatic and renal elimination of drugs and have been implicated in drug-drug interactions (Table 3.4).

Trimethoprim is frequently administered in HIV patients with low CD4-cell count for primary and secondary prophylaxis against *Pneumocystis jirovecii* infection. Co-administration of trimethoprim and lamivudine resulted in a 35% reduction in lamivudine renal clearance [90]. *In vitro* experiments have shown that lamivudine is transported by OCT1/2 and that trimethoprim inhibits these same transporters [57]. Thus, the reduced renal elimination of lamivudine likely results from OCT2 inhibition by trimethoprim [57]. The co-administration of trimethoprim with memantine, a drug prescribed for the treatment of Alzheimer's disease and primarily excreted unchanged in the kidney, led to the development of myoclonic activity and delirium [91]. Interestingly, these symptoms rapidly subsided after trimethoprim discontinuation. *In vitro* data have indicated that memantine is transported by OCT2 [144]. Thus, the observed adverse events are most likely attributed to the inhibition of memantine renal excretion by trimethoprim.

3.3.6 Role of PEPT in Drug-Drug Interactions

The peptide transporters (PEPT) are responsible for the cellular uptake of di- and tripeptides and several drugs such as angiotensin-converting enzyme inhibitors, beta-lactam antibiotics, and antiviral drugs [2, 145, 146] (Tables 3.1 and 3.3). Interestingly, PEPT1 has been targeted as a way to improve oral drug absorption. For instance, the bioavailability of acyclovir was considerably enhanced after oral administration of its valine ester (i.e. valacyclovir), which is a PEPT1 substrate [147]. PEPT1 is primarily located in the intestine and kidney whereas PEPT2 is mainly located in the kidney [81, 148] (Fig. 3.1). PEPT1 plays a major role in the intestinal absorption of beta-lactam antibiotics. *In vitro* data showed that the intestinal transport of 23 beta-lactam antibiotics and the bioavailability in humans both correlated with their affinity for PEPT1 [46]. Because of their role in facilitating oral absorption and renal reabsorption of several drugs in clinical use, these transporters may be subject to drug-drug interactions.

3.3.7 Role of P-gp in Drug-Drug Interactions

P-glycoprotein (P-gp), the encoded product of the human MDR1 gene, was first discovered for its role in mediating the multidrug resistance phenotype associated with certain cancers [149]. To date, P-gp is the most studied efflux transporter in terms of its clinical relevance for drug disposition and for drug interactions. P-gp has a large substrate specificity and can recognize hundreds of compounds ranging from small molecules of 350 Da up to polypeptides of 4,000 Da. Therapeutic

compounds transported by P-gp include anticancer drugs, antihypertensive agents, antiarrhythmics, glucocorticoids, HIV protease inhibitors, antibiotics, antimycotics, immunosuppressive agents, antidepressants, neuroleptics, antiepileptics, antacids, opioids, and antiemetics [44] (Tables 3.2 and 3.3). As mentioned previously, many substrates of P-gp are also substrates of drug-metabolizing enzymes, which make it difficult to assess the extent of interactions associated with P-gp. P-gp is expressed in various tissues and serves as a permeation barrier in the gastrointestinal tract, brain, lymphocytes, placenta, testes and ovaries while contributing to the elimination of drugs in the liver and kidney [150–153] (Fig. 3.1). The anatomical localization coupled with the broad variety of drug substrates contributes to the significant role of P-gp in drug disposition. The effect of P-gp on the pharmacokinetics of substrate drugs has been demonstrated in several studies using mdr1a/1b knockout mice. Mice lacking mdr genes usually present increased drug absorption, increased distribution in the brain and decreased drug elimination compared with wild-type mice [24, 154–156]. Interestingly, animal studies revealed that P-gp inhibition had a much greater impact on the tissue distribution of drug substrates than on their systemic exposure. For instance, the co-administration of LY-335979 (a potent and specific P-gp inhibitor) caused a 37-fold increase in the brain concentration of nelfinavir, but only a two-fold increase in plasma concentrations in wild-type mdr1a mice [157]. Thus, the potential risk of P-gp mediated drug interactions might be underestimated if only plasma concentrations are monitored [158].

Several drug-drug interactions mediated by P-gp have been reported in the literature (Table 3.4). Digoxin, a widely prescribed agent for congestive heart failure, has a negligible metabolism and is primarily eliminated in the kidney through glomerular filtration and active secretion. *In vitro* and *in vivo* animal studies have clearly shown that digoxin is a high affinity substrate for P-gp [159, 160]. Concomitant administration of ritonavir, a potent inhibitor of P-gp [161], was shown to substantially increase digoxin exposure and reduce its renal clearance (80% increase in AUC and 35% decrease in clearance) [96]. Decrease in digoxin renal clearance has also been reported with the concomitant use of clarithromycin, itraconazole and erythromycin [99, 101, 162]. All these drugs are potent inhibitors of P-gp mediated digoxin transport [99, 163, 164]. Another clinically relevant interaction with digoxin involves the co-administration of rifampin. The oral bioavailability of digoxin was decreased by 30% during rifampin therapy [102]. Duodenal biopsies obtained before and after the co-administration of rifampin showed a significant increase in the intestinal P-gp expression which correlated inversely with digoxin systemic exposure [102]. Similar interactions with rifampin have been reported for fexofenadine [165], talinolol [166], cyclosporine [167] and tacrolimus [168]. In general, P-gp inhibitors are less likely to affect the pharmacokinetics of a drug that has a high solubility, high permeability and/or is highly metabolized. Conversely, a compound that has poor solubility, limited permeability, and is eliminated primarily as the parent compound, is more likely to demonstrate a pharmacokinetic change in the presence of an inhibitor [3]. Furthermore, P-gp mediated interactions are more likely to be significant for drugs with a narrow therapeutic index, such as digoxin where small changes in exposure can be clinically important. Finally, in barrier

tissues such as tumors, lymphocytes and brain, interactions with P-gp may lead to changes in regional drug distribution that contributes to attenuated efficacy despite no change in systemic exposure [10].

3.3.8 Role of BCRP in Drug-Drug Interactions

The breast cancer resistance protein (BCRP) was originally identified in a breast cancer cell line that exhibit resistance to anthracyclines [169], therefore anticancer drugs are among the first reported substrates [2, 170] (Table 3.2). Some nucleoside analogues have been shown to be transported by BCRP whereas protease inhibitors are BCRP inhibitors [30, 51, 55] (Table 3.3). BCRP is primarily expressed in the small intestine, the liver, the blood–brain barrier and the placenta [171, 172] (Fig. 3.1). The localization of BCRP suggests that this transporter as well as other transporters of the ABC family play a protective role in limiting oral bioavailability and transport across the blood–brain barrier or the placenta [173]. Drug-drug interactions possibly involving BCRP have been described for the combination of protease inhibitors (i.e. atazanavir/r or lopinavir/r) and rosuvastatin (see section: role of OATP in drug interactions) (Table 3.4). However, BCRP interactions are difficult to investigate as BCRP and P-gp have extensive substrate overlap, therefore one transporter may compensate when the other is inhibited.

3.3.9 Role of MRP in Drug-Drug Interactions

The multidrug resistance-related proteins (MRP) also are known to confer multiple drug resistance to cancer cells [174]. Collectively, the MRP often share substrates in common with P-gp and are known to mediate the transport of numerous medications such as anticancer drugs, statins, nucleoside analogues or HIV protease inhibitors [2, 175] (Tables 3.2 and 3.3). These transporters are widely distributed in nearly all human tissues [176–181] (Fig. 3.1). In particular, MRP2 is localized at the canalicular membrane of the hepatocytes and is primarily responsible for hepatobiliary excretion of drugs. In the kidney, MRP2 and MRP4 are expressed at the apical membrane of the tubular cells where they facilitate the renal excretion of anionic compounds. A few examples of drug-drug interactions involving MRP are described below (Table 3.3).

Mycophenolate mofetil (MMF), an immunosuppressant often used for organ transplant recipients, is de-esterified to form mycophenolic acid (MPA), which is the active compound. MPA is subsequently glucuronidated into phenyl (MPAG) and acyl (AcMPAG) glucuronide metabolites whose biliary excretion is mediated by MRP2 [182]. Following excretion into bile, these metabolites can be deconjugated back to MPA and reabsorbed via an enterohepatic cycling process [183]. MPA and AcMPAG are eliminated in the urine via OAT1/3 and possibly MRP2 mediated

tubular secretion [184]. Interestingly, coadministration of rifampin and MMF resulted in a necessary dose increase for a lung graft recipient [185]. The PK analysis of this interaction revealed a significant total MPA AUC decrease of 17.5% after rifampin co-administration whereas, MPAG and AcMPAG AUC increased by 34.4% and 193% respectively [105]. This interaction likely resulted from the induction of MPA glucuronidation through rifampin mediated PXR activation, and possibly through inhibition of MRP2 mediated enterohepatic recirculation or renal excretion [105]. *In vitro* experiments have shown that rifampin is a substrate for MRP2 and thus could compete for this specific transporter [186]. Since MPA has a narrow therapeutic index, this interaction may lead to MPA underexposure and loss of clinical efficacy. In addition, increased plasma levels of toxic glucuronide metabolites may lead to side effects [105].

Adefovir and cidofovir are both inhibitors and substrates of MRP2 [80]. As mentioned previously, these compounds undergo renal tubular secretion and can cause nephrotoxicity resulting from accumulation in proximal renal tubules via OAT mediated cellular uptake. Inhibition of MRP2 in renal cells may also contribute to adefovir and cidofovir nephrotoxicity by reduction in efflux. Similarly, the use of NSAID in HIV patients treated by tenofovir lead to the nucleotide analogue renal accumulation and subsequent nephrotoxicity through MRP4 inhibition [106].

3.4 Challenges in Predicting In Vivo Drug-Drug Interactions

Estimating the contribution of transporters to total tissue uptake and excretion is necessary for predicting their role in drug-drug interactions. Although remarkable advances have been made in the functional characterization of drug transporters over the last decade, the quantitative evaluation of transporter-mediated drug interactions is difficult to predict. Unlike drug metabolizing enzymes which are largely concentrated in the liver and intestine, drug transporters are expressed in various tissues with different function (absorption, distribution and elimination). Therefore the influence of transporters on the disposition of a drug candidate requires investigation of numerous transporters with different functions in both hepatic and extrahepatic tissues. Another difficulty in defining transporter-mediated drug-interactions relates to the overlapping substrate specificities and the considerable functional redundancy in transport proteins. Furthermore, the interplay between transporters and drug-metabolizing enzymes adds complexity in estimating the role of a single transporter in drug disposition. Other limitations include the lack of specific and potent inhibitors for individual transporter which precludes accurate extrapolations from *in vitro* inhibition studies [158]. Differences in tissue localization and in substrates recognition of transporters between humans and animals often complicate translation from preclinical findings to the clinic. In addition, certain transporters may have more than one substrate binding domain. Thus, compounds transported by a particular transporter may not be competitive if they bind to different domains. Finally, drug interactions involving transporters at the level of absorption and

elimination alter the plasma concentrations of drugs. In contrast, interactions occurring at the blood–brain barrier do not affect the drug exposure in the circulating blood but only the pharmacological and/or toxicological effect of the drug. Therefore, drug interactions studies that assess only plasma drug concentrations do not fully characterize the transport-mediated influence of one drug on another; thus changes in the tissue distribution of drugs should also be considered [158].

3.5 Clinical Drug Interaction Studies with Transporters

The understanding of the rate-limiting step in the clearance of a particular drug (i.e. transport *vs* metabolism) and how a potential co-administered drug can alter the clearance is critical for the correct prediction of the drug-drug interaction and subsequent design and data interpretation of clinical drug interaction studies. The International Transporter Consortium has recently published decision trees to help determine when to conduct *in vivo* human interaction studies based on *in vitro* evaluation of transporters [3].

Clinical drug interaction studies are usually designed to assess the effect of a known inhibitor of a transporter on the disposition of a drug candidate or the effect of the drug candidate on the disposition of a known substrate of a transporter. The selection of either a substrate or an inhibitor of a given transporter has to be stringent based on the substrate and inhibitor transporter selectivity properties. Other considerations should include the therapeutic window of the substrate drug and the maximum effect that would be expected if the clearance of the substrate drug was totally inhibited, or the therapeutic use. For instance, a substrate or inhibitor of a drug candidate should be selected based on their likelihood of being co-administered in a therapeutic setting [3, 187]. Guidance for the selection of a substrate or inhibitor of a particular transporter for clinical drug interaction studies has been published in the transporter white paper and is summarized below [3]:

- If the drug candidate is a substrate of OATP, a clinical drug interaction study should be performed with OATP inhibitors such as rifampin or cyclosporine. If the drug candidate is an inhibitor of OATP, possible probe substrates for OATP include atorvastatin, pravastatin, pitavastatin or rosuvastatin.
- If the drug candidate is a substrate of OAT, then inhibition should be studied with probenecid. Multiple probe substrates for OAT can be used in clinical drug interaction studies including zidovudine, lamivudine, acyclovir, ciprofloxacin, tenofovir or methotrexate.
- If the drug candidate is a substrate of OCT2, a clinical drug interaction study should be performed with cimetidine. Possible probe substrates for OCT2 include for metformin or varenicline.
- If the drug candidate is a dual substrate for P-gp and CYP3A4, then inhibition should be studied using an inhibitor that shows strong inhibition for both P-gp and CYP3A4, such as itraconazole, ketoconazole, ritonavir or cyclosporine. Possible probe substrates for P-gp include digoxin or loperamide.

– If the drug candidate is an inhibitor of BCRP, possible probes include sulphasalazine, rosuvastatin, pitavastatin, ciprofloxacin or dipyridamole. However, many of these drugs remain to be tested as selective BCRP probe substrates in clinical studies.

It is important to note that some of these inhibitors or substrates may inhibit or be transported by multiple transporters or may also affect drug metabolizing enzymes, therefore the clinical interaction data should be interpreted cautiously.

3.6 Summary

Whereas drug-drug interactions mediated via known drug metabolizing enzymes have been established over several decades, SLC and ABC transporters are now becoming recognized as significant determinants of drug disposition and drug-drug interactions. The magnitude of transporter-mediated drug interactions is generally smaller when compared to cytochrome-mediated interactions and therefore, to date, few clinically significant drug interactions have been demonstrated to be based on a single mechanism through transporter inhibition. In general, transporter-mediated drug interactions are likely to be most critical when the elimination of the affected drug or the distribution in a target tissue is characterized by an exclusive transporter mediated disposition profile or when the involved drug exhibits a narrow therapeutic window of safety. Since the exposure of a majority of drugs in clinical use is defined by the interplay between enzymes and transporters, both pharmacological pathways need to be considered when evaluating the potential risk for drug-drug interactions.

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References

1. Hagenbuch B. Drug uptake systems in liver and kidney: a historic perspective. Clin Pharm Ther 2010;87:39–47.
2. Klaassen CD, Aleksunes LM. Xenobiotic, bile acid, and cholesterol transporters: function and regulation. Pharmacol Rev 2010;62:1–96.
3. International, Transporter, Consortium. Membranes transporters in drug development. Nat Rev Drug Discov 2010;9:215–36.
4. Ray AS, Cihlar T, Robinson KL, et al. Mechanism of active renal tubular efflux of tenofovir. Antimicrob Agents Chemother 2006;50:3297–304.
5. Bonkovsky HL, Hauri HP, Marti U, Gasser R, Meyer UA. Cytochrome P450 of small intestinal epithelial cells. Immunochemical characterization of the increase in cytochrome P450 caused by phenobarbital. Gastroenterology 1985;88:458–67.
6. Dietrich CG, Geier A, Oude Elferink RP. ABC of oral bioavailability: transporters as gatekeepers in the gut. Gut 2003;52:1788–95.

7. Katsura T, Inui K. Intestinal absorption of drugs mediated by drug transporters: mechanisms and regulation. Drug Metab Pharmacokinet 2003;18:1–15.
8. Glaeser H, Bailey DG, Dresser GK, et al. Intestinal drug transporter expression and the impact of grapefruit juice in humans. Clin Pharmacol Ther 2007;81:362–70.
9. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet 2003;42:59–98.
10. Lee CA, Cook JA, Reyner EL, Smith DA. P-glycoprotein related drug interactions: clinical importance and a consideration of disease states. Expert Opin Drug Metab Toxicol 2010;6:603–19.
11. Nies AT, Schwab M, Keppler D. Interplay of conjugating enzymes with OATP uptake transporters and ABCC/MRP efflux pumps in the elimination of drugs. Expert Opin Drug Metab Toxicol 2008;4:545–68.
12. Smith NF, Figg WD, Sparreboom A. Role of the liver-specific transporters OATP1B1 and OATP1B3 in governing drug elimination. Expert Opin Drug Metab Toxicol 2005;1: 429–45.
13. Kusuhara H, Sugiyama Y. Pharmacokinetic modeling of the hepatobiliary transport mediated by cooperation of uptake and efflux transporters. Drug Metab Rev 2010;42:539–50.
14. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. Br J Pharmacol 2009;158:693–705.
15. Cihlar T, Ho ES, Lin DC, Mulato AS. Human renal organic anion transporter 1 (hOAT1) and its role in the nephrotoxicity of antiviral nucleotide analogs. Nucleosides Nucleotides Nucleic Acids 2001;20:641–8.
16. Ho ES, Lin DC, Mendel DB, Cihlar T. Cytotoxicity of antiviral nucleotides adefovir and cidofovir is induced by the expression of human renal organic anion transporter 1. J Am Soc Nephrol 2000;11:383–93.
17. Li M, Anderson GD, Wang J. Drug-drug interactions involving membrane transporters in the human kidney. Expert Opin Drug Metab Toxicol 2006;2:505–32.
18. Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. Clin Infect Dis 2003;36: 1082–5.
19. Maiche AG. Acute renal failure due to concomitant action of methotrexate and indomethacin. Lancet 1986;1:1390.
20. El-Sheikh AA, van den Heuvel JJ, Koenderink JB, Russel FG. Interaction of nonsteroidal anti-inflammatory drugs with multidrug resistance protein (MRP) 2/ABCC2- and MRP4/ ABCC4-mediated methotrexate transport. J Pharmacol Exp Ther 2007;320:229–35.
21. Urquhart BL, Kim RB. Blood-brain barrier transporters and response to CNS-active drugs. Eur J Clin Pharmacol 2009;65:1063–70.
22. Ohtsuki S, Terasaki T. Contribution of carrier-mediated transport systems to the blood-brain barrier as a supporting and protecting interface for the brain; importance for CNS drug discovery and development. Pharm Res 2007;24:1745–58.
23. Ohtsuki S. New aspects of the blood-brain barrier transporters; its physiological roles in the central nervous system. Biol Pharm Bull 2004;27:1489–96.
24. Kim RB, Fromm MF, Wandel C, et al. The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors. J Clin Invest 1998;101:289–94.
25. Shaik N, Giri N, Pan G, Elmquist WF. P-glycoprotein-mediated active efflux of the anti-HIV1 nucleoside abacavir limits cellular accumulation and brain distribution. Drug Metab Dispos 2007;35:2076–85.
26. Best BM, Letendre SL, Brigid E, et al. Low atazanavir concentrations in cerebrospinal fluid. AIDS 2009;23:83–7.
27. Marra CM, Zhao Y, Clifford DB, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. AIDS 2009;23:1359–66.
28. Turriziani O, Gianotti N, Falasca F, et al. Expression levels of MDR1, MRP1, MRP4, and MRP5 in peripheral blood mononuclear cells from HIV infected patients failing antiretroviral therapy. J Med Virol 2008;80:766–71.

29. Minuesa G, Purcet S, Erkizia I, et al. Expression and functionality of anti-human immunodeficiency virus and anticancer drug uptake transporters in immune cells. J Pharmacol Exp Ther 2008;324:558–67.
30. Wang X, Furukawa T, Nitanda T, et al. Breast cancer resistance protein (BCRP/ABCG2) induces cellular resistance to HIV-1 nucleoside reverse transcriptase inhibitors. Mol Pharmacol 2003;63:65–72.
31. Janneh O, Owen A, Chandler B, et al. Modulation of the intracellular accumulation of saquinavir in peripheral blood mononuclear cells by inhibitors of MRP1, MRP2, P-gp and BCRP. AIDS 2005;19:2097–102.
32. Janneh O, Hartkoorn RC, Jones E, et al. Cultured CD4T cells and primary human lymphocytes express hOATPs: intracellular accumulation of saquinavir and lopinavir. Br J Pharmacol 2008;155:875–83.
33. Janneh O, Anwar T, Jungbauer C, et al. P-glycoprotein, multidrug resistance-associated proteins and human organic anion transporting polypeptide influence the intracellular accumulation of atazanavir. Antivir Ther 2009;14:965–74.
34. Tirona RG, Leake BF, Merino G, Kim RB. Polymorphisms in OATP-C: identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. J Biol Chem 2001;276:35669–75.
35. Hartkoorn RC, Kwan WS, Shallcross V, et al. HIV protease inhibitors are substrates for OATP1A2, OATP1B1 and OATP1B3 and lopinavir plasma concentrations are influenced by SLCO1B1 polymorphisms Pharmacogenet Genomics 2010;20:112–20.
36. Lubomirov R, di Iulio J, Fayet A, et al. ADME pharmacogenetics: investigation of the pharmacokinetics of the antiretroviral agent lopinavir coformulated with ritonavir. Pharmacogenet Genomics 2010;20:217–30.
37. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. Clin Pharmacol Ther 2008;83:265–72.
38. Kiser JJ, Aquilante CL, Anderson PL, King TM, Carten ML, Fletcher CV. Clinical and genetic determinants of intracellular tenofovir diphosphate concentrations in HIV-infected patients. J Acquir Immune Defic Syndr 2008;47:298–303.
39. Rodriguez-Novoa S, Labarga P, Soriano V, et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study. Clin Infect Dis 2009;48:e108–16.
40. Imaoka T, Kusuhara H, Adachi M, Schuetz JD, Takeuchi K, Sugiyama Y. Functional involvement of multidrug resistance-associated protein 4 (MRP4/ABCC4) in the renal elimination of the antiviral drugs adefovir and tenofovir. Mol Pharmacol 2007;71:619–27.
41. Maeda K, Sugiyama Y. Impact of genetic polymorphisms of transporters on the pharmacokinetic, pharmacodynamic and toxicological properties of anionic drugs. Drug Metab Pharmacokinet 2008;23:223–35.
42. Ieiri I, Higuchi S, Sugiyama Y. Genetic polymorphisms of uptake (OATP1B1, 1B3) and efflux (MRP2, BCRP) transporters: implications for inter-individual differences in the pharmacokinetics and pharmacodynamics of statins and other clinically relevant drugs. Expert Opin Drug Metab Toxicol 2009;5:703–29.
43. Choi MK, Song IS. Organic cation transporters and their pharmacokinetic and pharmacodynamic consequences. Drug Metab Pharmacokinet 2008;23:243–53.
44. Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. Clin Pharmacol Ther 2004;75:13–33.
45. Marzolini C, Tirona RG, Kim RB. Pharmacogenomics of the OATP and OAT families. Pharmacogenomics 2004;5:273–82.
46. Bretschneider B, Brandsch M, Neubert R. Intestinal transport of beta-lactam antibiotics: analysis of the affinity at the H+/peptide symporter (PEPT1), the uptake into Caco-2 cell monolayers and the transepithelial flux. Pharm Res 1999;16:55–61.
47. Luckner P, Brandsch M. Interaction of 31 beta-lactam antibiotics with the H+/peptide symporter PEPT2: analysis of affinity constants and comparison with PEPT1. Eur J Pharm Biopharm 2005;59:17–24.

48. Li M, Anderson GD, Phillips BR, Kong W, Shen DD, Wang J. Interactions of amoxicillin and cefaclor with human renal organic anion and peptide transporters. Drug Metab Dispos 2006;34:547–55.
49. Li M, Andrew MA, Wang J, et al. Effects of cranberry juice on pharmacokinetics of beta-lactam antibiotics following oral administration. Antimicrob Agents Chemother 2009;53: 2725–32.
50. Gupta A, Unadkat JD, Mao Q. Interactions of azole antifungal agents with the human breast cancer resistance protein (BCRP). J Pharm Sci 2007;96:3226–35.
51. Gupta A, Zhang Y, Unadkat JD, Mao Q. HIV protease inhibitors are inhibitors but not substrates of the human breast cancer resistance protein (BCRP/ABCG2). J Pharmacol Exp Ther 2004;310:334–41.
52. Seithel A, Eberl S, Singer K, et al. The influence of macrolide antibiotics on the uptake of organic anions and drugs mediated by OATP1B1 and OATP1B3. Drug Metab Dispos 2007;35:779–86.
53. Sakurai Y, Motohashi H, Ueo H, et al. Expression levels of renal organic anion transporters (OATs) and their correlation with anionic drug excretion in patients with renal diseases. Pharm Res 2004;21:61–7.
54. Hill G, Cihlar T, Oo C, et al. The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion-correlation of in vivo and in vitro studies. Drug Metab Dispos 2002;30:13–9.
55. Weiss J, Rose J, Storch CH, et al. Modulation of human BCRP (ABCG2) activity by anti-HIV drugs. J Antimicrob Chemother 2007;59:238–45.
56. Weiss J, Theile D, Ketabi-Kiyanvash N, Lindenmaier H, Haefeli WE. Inhibition of MRP1/ABCC1, MRP2/ABCC2, and MRP3/ABCC3 by nucleoside, nucleotide, and non-nucleoside reverse transcriptase inhibitors. Drug Metab Dispos 2007;35:340–4.
57. Jung N, Lehmann C, Rubbert A, et al. Relevance of the organic cation transporters 1 and 2 for antiretroviral drug therapy in human immunodeficiency virus infection. Drug Metab Dispos 2008;36:1616–23.
58. Polli JW, Jarrett JL, Studenberg SD, et al. Role of P-glycoprotein on the CNS disposition of amprenavir (141 W94), an HIV protease inhibitor. Pharm Res 1999;16:1206–12.
59. Kis O, Robillard K, Chan GN, Bendayan R. The complexities of antiretroviral drug-drug interactions: role of ABC and SLC transporters. Trends Pharmacol Sci 2009;31:22–35.
60. Maeda T, Takahashi K, Ohtsu N, et al. Identification of influx transporter for the quinolone antibacterial agent levofloxacin. Mol Pharm 2007;4:85–94.
61. Minuesa G, Volk C, Molina-Arcas M, et al. Transport of lamivudine [(−)-beta-L-2',3'-dideoxy-3'-thiacytidine] and high-affinity interaction of nucleoside reverse transcriptase inhibitors with human organic cation transporters 1, 2, and 3. J Pharmacol Exp Ther 2009;329: 252–61.
62. Sala-Rabanal M, Loo DD, Hirayama BA, Turk E, Wright EM. Molecular interactions between dipeptides, drugs and the human intestinal H+ −oligopeptide cotransporter hPEPT1. J Physiol 2006;574:149–66.
63. Takeda M, Khamdang S, Narikawa S, et al. Human organic anion transporters and human organic cation transporters mediate renal antiviral transport. J Pharmacol Exp Ther 2002;300:918–24.
64. Babu E, Takeda M, Narikawa S, et al. Human organic anion transporters mediate the transport of tetracycline. Jpn J Pharmacol 2002;88:69–76.
65. Tirona RG, Leake BF, Wolkoff AW, Kim RB. Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampin-mediated pregnane X receptor activation. J Pharmacol Exp Ther 2003;304:223–8.
66. Annaert P, Ye ZW, Stieger B, Augustijns P. Interaction of HIV protease inhibitors with OATP1B1, 1B3, and 2B1. Xenobiotica 2010;40:163–76.
67. Ueo H, Motohashi H, Katsura T, Inui K. Human organic anion transporter hOAT3 is a potent transporter of cephalosporin antibiotics, in comparison with hOAT1. Biochem Pharmacol 2005;70:1104–13.

68. Cihlar T, Lin DC, Pritchard JB, Fuller MD, Mendel DB, Sweet DH. The antiviral nucleotide analogs cidofovir and adefovir are novel substrates for human and rat renal organic anion transporter 1. Mol Pharmacol 1999;56:570–80.
69. Uwai Y, Ida H, Tsuji Y, Katsura T, Inui K. Renal transport of adefovir, cidofovir, and tenofovir by SLC22A family members (hOAT1, hOAT3, and hOCT2). Pharm Res 2007;24:811–5.
70. Yamashita F, Ohtani H, Koyabu N, et al. Inhibitory effects of angiotensin II receptor antagonists and leukotriene receptor antagonists on the transport of human organic anion transporter 4. J Pharm Pharmacol 2006;58:1499–505.
71. Morimoto K, Nakakariya M, Shirasaka Y, et al. Oseltamivir (Tamiflu) efflux transport at the blood-brain barrier via P-glycoprotein. Drug Metab Dispos 2008;36:6–9.
72. Ogihara T, Kano T, Wagatsuma T, et al. Oseltamivir (tamiflu) is a substrate of peptide transporter 1. Drug Metab Dispos 2009;37:1676–81.
73. Sandhu P, Lee W, Xu X, et al. Hepatic uptake of the novel antifungal agent caspofungin. Drug Metab Dispos 2005;33:676–82.
74. Kobayashi Y, Sakai R, Ohshiro N, Ohbayashi M, Kohyama N, Yamamoto T. Possible involvement of organic anion transporter 2 on the interaction of theophylline with erythromycin in the human liver. Drug Metab Dispos 2005;33:619–22.
75. Okuda M, Kimura N, Inui K. Interactions of fluoroquinolone antibacterials, DX-619 and levofloxacin, with creatinine transport by renal organic cation transporter hOCT2. Drug Metab Pharmacokinet 2006;21:432–6.
76. Ye ZW, Camus S, Augustijns P, Annaert P. Interaction of eight HIV protease inhibitors with the canalicular efflux transporter ABCC2 (MRP2) in sandwich-cultured rat and human hepatocytes. Biopharm Drug Dispos 2010;31:178–88.
77. Ci L, Kusuhara H, Adachi M, Schuetz JD, Takeuchi K, Sugiyama Y. Involvement of MRP4 (ABCC4) in the luminal efflux of ceftizoxime and cefazolin in the kidney. Mol Pharmacol 2007;71:1591–7.
78. Susanto M, Benet LZ. Can the enhanced renal clearance of antibiotics in cystic fibrosis patients be explained by P-glycoprotein transport? Pharm Res 2002;19:457–62.
79. VanWert AL, Gionfriddo MR, Sweet DH. Organic anion transporters: discovery, pharmacology, regulation and roles in pathophysiology. Biopharm Drug Dispos 2010;31:1–71.
80. Miller DS. Nucleoside phosphonate interactions with multiple organic anion transporters in renal proximal tubule. J Pharmacol Exp Ther 2001;299:567–74.
81. Ganapathy ME, Brandsch M, Prasad PD, Ganapathy V, Leibach FH. Differential recognition of beta -lactam antibiotics by intestinal and renal peptide transporters, PEPT 1 and PEPT 2. J Biol Chem 1995;270:25672–7.
82. Schuetz JD, Connelly MC, Sun D, et al. MRP4: A previously unidentified factor in resistance to nucleoside-based antiviral drugs. Nat Med 1999;5:1048–51.
83. Vavricka SR, Van Montfoort J, Ha HR, Meier PJ, Fattinger K. Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. Hepatology 2002;36: 164–72.
84. Lau YY, Huang Y, Frassetto L, Benet LZ. effect of OATP1B transporter inhibition on the pharmacokinetics of atorvastatin in healthy volunteers. Clin Pharmacol Ther 2007;81: 194–204.
85. van Giersbergen PL, Treiber A, Schneiter R, Dietrich H, Dingemanse J. Inhibitory and inductive effects of rifampin on the pharmacokinetics of bosentan in healthy subjects. Clin Pharmacol Ther 2007;81:414–9.
86. Dingemanse J, van Giersbergen PL, Patat A, Nilsson PN. Mutual pharmacokinetic interactions between bosentan and lopinavir/ritonavir in healthy participants. Antivir Ther 2010;15:157–63.
87. Kiser JJ, Gerber JG, Predhomme JA, Wolfe P, Flynn DM, Hoody DW. Drug/Drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. J Acquir Immune Defic Syndr 2008;47:570–8.
88. Busti AJ, Bain AM, Hall RG, 2nd, et al. Effects of atazanavir/ritonavir or fosamprenavir/ritonavir on the pharmacokinetics of rosuvastatin. J Cardiovasc Pharmacol 2008;51:605–10.

89. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. Am J Cardiol 2004;94:1140–6.
90. Moore KH, Yuen GJ, Raasch RH, et al. Pharmacokinetics of lamivudine administered alone and with trimethoprim-sulfamethoxazole. Clin Pharmacol Ther 1996;59:550–8.
91. Moellentin D, Picone C, Leadbetter E. Memantine-induced myoclonus and delirium exacerbated by trimethoprim. Ann Pharmacother 2008;42:443–7.
92. Landersdorfer CB, Kirkpatrick CM, Kinzig M, et al. Competitive inhibition of renal tubular secretion of ciprofloxacin and metabolite by probenecid. Br J Clin Pharmacol 2010;69: 167–78.
93. Cundy KC. Clinical pharmacokinetics of the antiviral nucleotide analogues cidofovir and adefovir. Clin Pharmacokinet 1999;36:127–43.
94. Massarella JW, Nazareno LA, Passe S, Min B. The effect of probenecid on the pharmacokinetics of zalcitabine in HIV-positive patients. Pharm Res 1996;13:449–52.
95. Landersdorfer CB, Kirkpatrick CM, Kinzig M, Bulitta JB, Holzgrabe U, Sorgel F. Inhibition of flucloxacillin tubular renal secretion by piperacillin. Br J Clin Pharmacol 2008;66: 648–59.
96. Ding R, Tayrouz Y, Riedel KD, et al. Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers. Clin Pharmacol Ther 2004;76:73–84.
97. Mertz D, Battegay M, Marzolini C, Mayr M. Drug-drug interaction in a kidney transplant recipient receiving HIV salvage therapy and tacrolimus. Am J Kidney Dis 2009;54:e1–4.
98. Capone D, Palmiero G, Gentile A, et al. A pharmacokinetic interaction between clarithromycin and sirolimus in kidney transplant recipient. Curr Drug Metab 2007;8:379–81.
99. Wakasugi H, Yano I, Ito T, et al. Effect of clarithromycin on renal excretion of digoxin: interaction with P-glycoprotein. Clin Pharmacol Ther 1998;64:123–8.
100. Rollot F, Pajot O, Chauvelot-Moachon L, Nazal EM, Kelaidi C, Blanche P. Acute colchicine intoxication during clarithromycin administration. Ann Pharmacother 2004;38:2074–7.
101. Jalava KM, Partanen J, Neuvonen PJ. Itraconazole decreases renal clearance of digoxin. Ther Drug Monit 1997;19:609–13.
102. Greiner B, Eichelbaum M, Fritz P, et al. The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. J Clin Invest 1999;104:147–53.
103. Backman JT, Luurila H, Neuvonen M, Neuvonen PJ. Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. Clin Pharmacol Ther 2005;78:154–67.
104. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. Lancet 2000;355:547–8.
105. Naesens M, Kuypers DR, Streit F, et al. Rifampin induces alterations in mycophenolic acid glucuronidation and elimination: implications for drug exposure in renal allograft recipients. Clin Pharmacol Ther 2006;80:509–21.
106. Morelle J, Labriola L, Lambert M, Cosyns JP, Jouret F, Jadoul M. Tenofovir-related acute kidney injury and proximal tubule dysfunction precipitated by diclofenac: a case of drug-drug interaction. Clin Nephrol 2009;71:567–70.
107. Urquhart BL, Tirona RG, Kim RB. Nuclear receptors and the regulation of drug-metabolizing enzymes and drug transporters: implications for interindividual variability in response to drugs. J Clin Pharmacol 2007;47:566–78.
108. Mangelsdorf DJ, Thummel C, Beato M, et al. The nuclear receptor superfamily: the second decade. Cell 1995;83:835–9.
109. Kim RB, Wandel C, Leake B, et al. Interrelationship between substrates and inhibitors of human CYP3A and P-glycoprotein. Pharm Res 1999;16:408–14.
110. Shitara Y, Hirano M, Sato H, Sugiyama Y. Gemfibrozil and its glucuronide inhibit the organic anion transporting polypeptide 2 (OATP2/OATP1B1:SLC21A6)-mediated hepatic uptake and CYP2C8-mediated metabolism of cerivastatin: analysis of the mechanism of the clinically relevant drug-drug interaction between cerivastatin and gemfibrozil. J Pharmacol Exp Ther 2004;311:228–36.

111. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. Diabetologia 2003;46:347–51.
112. Meyer zu Schwabedissen HE, Kim RB. Hepatic OATP1B transporters and nuclear receptors PXR and CAR: interplay, regulation of drug disposition genes, and single nucleotide polymorphisms. Mol Pharm 2009;6:1644–61.
113. Zhang L, Zhang Y, Huang SM. Scientific and regulatory perspectives on metabolizing enzyme-transporter interplay and its role in drug interactions: challenges in predicting drug interactions. Mol Pharm 2009;6:1766–74.
114. Hagenbuch B, Gui C. Xenobiotic transporters of the human organic anion transporting polypeptides (OATP) family. Xenobiotica 2008;38:778–801.
115. Hsiang B, Zhu Y, Wang Z, et al. A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. J Biol Chem 1999;274:37161–8.
116. Kullak-Ublick GA, Hagenbuch B, Stieger B, et al. Molecular and functional characterization of an organic anion transporting polypeptide cloned from human liver. Gastroenterology 1995;109:1274–82.
117. Konig J, Cui Y, Nies AT, Keppler D. A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane. Am J Physiol Gastrointest Liver Physiol 2000;278:G156–64.
118. Kobayashi D, Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I. Involvement of human organic anion transporting polypeptide OATP-B (SLC21A9) in pH-dependent transport across intestinal apical membrane. J Pharmacol Exp Ther 2003;306:703–8.
119. Tamai I, Nezu J, Uchino H, et al. Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family. Biochem Biophys Res Commun 2000;273:251–60.
120. Martin PD, Warwick MJ, Dane AL, et al. Metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult male volunteers. Clin Ther 2003;25:2822–35.
121. Kitamura S, Maeda K, Wang Y, Sugiyama Y. Involvement of multiple transporters in the hepatobiliary transport of rosuvastatin. Drug Metab Dispos 2008;36:2014–23.
122. Huang L, Wang Y, Grimm S. ATP-dependent transport of rosuvastatin in membrane vesicles expressing breast cancer resistance protein. Drug Metab Dispos 2006;34:738–42.
123. Demby VE, Harmon KA, Naqwe M, Humphreys JE, Wire M, Polli JW. OATP1B1, OATP1B3 and BCRP transporter characterization for fosamprenavir, amprenavir and lopinavir. In Abstracts of the American Association of Pharmaceutical Scientists, Atlanta, GA, September 16–20, Abstract 2355 2008.
124. Dingemanse J, van Giersbergen PL. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. Clin Pharmacokinet 2004;43:1089–115.
125. Treiber A, Schneiter R, Hausler S, Stieger B. Bosentan is a substrate of human OATP1B1 and OATP1B3: inhibition of hepatic uptake as the common mechanism of its interactions with cyclosporin A, rifampicin, and sildenafil. Drug Metab Dispos 2007;35:1400–7.
126. Jariyawat S, Sekine T, Takeda M, et al. The interaction and transport of beta-lactam antibiotics with the cloned rat renal organic anion transporter 1. J Pharmacol Exp Ther 1999;290:672–7.
127. El-Sheikh AA, Masereeuw R, Russel FG. Mechanisms of renal anionic drug transport. Eur J Pharmacol 2008;585:245–55.
128. Sekine T, Cha SH, Tsuda M, et al. Identification of multispecific organic anion transporter 2 expressed predominantly in the liver. FEBS Lett 1998;429:179–82.
129. Sekine T, Watanabe N, Hosoyamada M, Kanai Y, Endou H. Expression cloning and characterization of a novel multispecific organic anion transporter. J Biol Chem 1997;272:18526–9.
130. Race JE, Grassl SM, Williams WJ, Holtzman EJ. Molecular cloning and characterization of two novel human renal organic anion transporters (hOAT1 and hOAT3). Biochem Biophys Res Commun 1999;255:508–14.

131. Cha SH, Sekine T, Fukushima JI, et al. Identification and characterization of human organic anion transporter 3 expressing predominantly in the kidney. Mol Pharmacol 2001;59:1277–86.
132. Burnell JM, Kirby WM. Effectiveness of a new compound, benemid, in elevating serum penicillin concentrations. J Clin Invest 1951;30:697–700.
133. Takeda M, Narikawa S, Hosoyamada M, Cha SH, Sekine T, Endou H. Characterization of organic anion transport inhibitors using cells stably expressing human organic anion transporters. Eur J Pharmacol 2001;419:113–20.
134. Brown GR. Cephalosporin-probenecid drug interactions. Clin Pharmacokinet 1993;24: 289–300.
135. Cunningham RF, Israili ZH, Dayton PG. Clinical pharmacokinetics of probenecid. Clin Pharmacokinet 1981;6:135–51.
136. Cundy KC, Petty BG, Flaherty J, et al. Clinical pharmacokinetics of cidofovir in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 1995;39:1247–52.
137. Mulato AS, Ho ES, Cihlar T. Nonsteroidal anti-inflammatory drugs efficiently reduce the transport and cytotoxicity of adefovir mediated by the human renal organic anion transporter 1. J Pharmacol Exp Ther 2000;295:10–5.
138. Thyss A, Milano G, Kubar J, Namer M, Schneider M. Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. Lancet 1986;1:256–8.
139. Khamdang S, Takeda M, Noshiro R, et al. Interactions of human organic anion transporters and human organic cation transporters with nonsteroidal anti-inflammatory drugs. J Pharmacol Exp Ther 2002;303:534–9.
140. Koepsell H, Lips K, Volk C. Polyspecific organic cation transporters: structure, function, physiological roles, and biopharmaceutical implications. Pharm Res 2007;24:1227–51.
141. Jung N, Taubert D. Organic cation transporters and their roles in antiretroviral drug disposition. Expert Opin Drug Metab Toxicol 2009;5:773–87.
142. Gorboulev V, Ulzheimer JC, Akhoundova A, et al. Cloning and characterization of two human polyspecific organic cation transporters. DNA Cell Biol 1997;16:871–81.
143. Grundemann D, Babin-Ebell J, Martel F, Ording N, Schmidt A, Schomig E. Primary structure and functional expression of the apical organic cation transporter from kidney epithelial LLC-PK1 cells. J Biol Chem 1997;272:10408–13.
144. Busch AE, Karbach U, Miska D, et al. Human neurons express the polyspecific cation transporter hOCT2, which translocates monoamine neurotransmitters, amantadine, and memantine. Mol Pharmacol 1998;54:342–52.
145. Terada T, Inui K. Peptide transporters: structure, function, regulation and application for drug delivery. Curr Drug Metab 2004;5:85–94.
146. Anand BS, Patel J, Mitra AK. Interactions of the dipeptide ester prodrugs of acyclovir with the intestinal oligopeptide transporter: competitive inhibition of glycylsarcosine transport in human intestinal cell line-Caco-2. J Pharmacol Exp Ther 2003;304:781–91.
147. Brandsch M. Transport of drugs by proton-coupled peptide transporters: pearls and pitfalls. Expert Opin Drug Metab Toxicol 2009;5:887–905.
148. Shen H, Smith DE, Yang T, Huang YG, Schnermann JB, Brosius FC, 3 rd. Localization of PEPT1 and PEPT2 proton-coupled oligopeptide transporter mRNA and protein in rat kidney. Am J Physiol 1999;276:F658–65.
149. Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochim Biophys Acta 1976;455:152–62.
150. Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC. Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. Proc Natl Acad Sci USA 1987;84:7735–8.
151. Cordon-Cardo C, O'Brien JP, Casals D, et al. Multidrug-resistance gene (P-glycoprotein) is expressed by endothelial cells at blood-brain barrier sites. Proc Natl Acad Sci USA 1989;86:695–8.
152. Sugawara I, Kataoka I, Morishita Y, et al. Tissue distribution of P-glycoprotein encoded by a multidrug-resistant gene as revealed by a monoclonal antibody, MRK 16. Cancer Res 1988; 48:1926–9.

153. Klimecki WT, Futscher BW, Grogan TM, Dalton WS. P-glycoprotein expression and function in circulating blood cells from normal volunteers. Blood 1994;83:2451–8.
154. Schinkel AH, Smit JJ, van Tellingen O, et al. Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. Cell 1994;77:491–502.
155. Schinkel AH, Wagenaar E, van Deemter L, Mol CA, Borst P. Absence of the mdr1a P-Glycoprotein in mice affects tissue distribution and pharmacokinetics of dexamethasone, digoxin, and cyclosporin A. J Clin Invest 1995;96:1698–705.
156. Sparreboom A, van Asperen J, Mayer U, et al. Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. Proc Natl Acad Sci USA 1997;94:2031–5.
157. Choo EF, Leake B, Wandel C, et al. Pharmacological inhibition of P-glycoprotein transport enhances the distribution of HIV-1 protease inhibitors into brain and testes. Drug Metab Dispos 2000;28:655–60.
158. Lin JH. Transporter-mediated drug interactions: clinical implications and in vitro assessment. Expert Opin Drug Metab Toxicol 2007;3:81–92.
159. de Lannoy IA, Silverman M. The MDR1 gene product, P-glycoprotein, mediates the transport of the cardiac glycoside, digoxin. Biochem Biophys Res Commun 1992;189: 551–7.
160. Kawahara M, Sakata A, Miyashita T, Tamai I, Tsuji A. Physiologically based pharmacokinetics of digoxin in mdr1a knockout mice. J Pharm Sci 1999;88:1281–7.
161. Gutmann H, Fricker G, Drewe J, Toeroek M, Miller DS. Interactions of HIV protease inhibitors with ATP-dependent drug export proteins. Mol Pharmacol 1999;56:383–9.
162. Maxwell DL, Gilmour-White SK, Hall MR. Digoxin toxicity due to interaction of digoxin with erythromycin. BMJ 1989;298:572.
163. Takara K, Tanigawara Y, Komada F, Nishiguchi K, Sakaeda T, Okumura K. Cellular pharmacokinetic aspects of reversal effect of itraconazole on P-glycoprotein-mediated resistance of anticancer drugs. Biol Pharm Bull 1999;22:1355–9.
164. Kiso S, Cai SH, Kitaichi K, et al. Inhibitory effect of erythromycin on P-glycoprotein-mediated biliary excretion of doxorubicin in rats. Anticancer Res 2000;20:2827–34.
165. Hamman MA, Bruce MA, Haehner-Daniels BD, Hall SD. The effect of rifampin administration on the disposition of fexofenadine. Clin Pharmacol Ther 2001;69:114–21.
166. Westphal K, Weinbrenner A, Zschiesche M, et al. Induction of P-glycoprotein by rifampin increases intestinal secretion of talinolol in human beings: a new type of drug/drug interaction. Clin Pharmacol Ther 2000;68:345–55.
167. Hebert MF, Roberts JP, Prueksaritanont T, Benet LZ. Bioavailability of cyclosporine with concomitant rifampin administration is markedly less than predicted by hepatic enzyme induction. Clin Pharmacol Ther 1992;52:453–7.
168. Hebert MF, Fisher RM, Marsh CL, Dressler D, Bekersky I. Effects of rifampin on tacrolimus pharmacokinetics in healthy volunteers. J Clin Pharmacol 1999;39:91–6.
169. Doyle LA, Yang W, Abruzzo LV, et al. A multidrug resistance transporter from human MCF-7 breast cancer cells. Proc Natl Acad Sci USA 1998;95:15665–70.
170. Mao Q, Unadkat JD. Role of the breast cancer resistance protein (ABCG2) in drug transport. AAPS J 2005;7:E118–33.
171. Maliepaard M, Scheffer GL, Faneyte IF, et al. Subcellular localization and distribution of the breast cancer resistance protein transporter in normal human tissues. Cancer Res 2001;61:3458–64.
172. Eisenblatter T, Galla HJ. A new multidrug resistance protein at the blood-brain barrier. Biochem Biophys Res Commun 2002;293:1273–8.
173. van Herwaarden AE, Schinkel AH. The function of breast cancer resistance protein in epithelial barriers, stem cells and milk secretion of drugs and xenotoxins. Trends Pharmacol Sci 2006;27:10–6.
174. Cole SP, Bhardwaj G, Gerlach JH, et al. Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line. Science 1992;258:1650–4.

175. Zhou SF, Wang LL, Di YM, et al. Substrates and inhibitors of human multidrug resistance associated proteins and the implications in drug development. Curr Med Chem 2008;15: 1981–2039.
176. Flens MJ, Zaman GJ, van der Valk P, et al. Tissue distribution of the multidrug resistance protein. Am J Pathol 1996;148:1237–47.
177. Schaub TP, Kartenbeck J, Konig J, et al. Expression of the conjugate export pump encoded by the mrp2 gene in the apical membrane of kidney proximal tubules. J Am Soc Nephrol 1997;8:1213–21.
178. Keppler D, Konig J, Buchler M. The canalicular multidrug resistance protein, cMRP/MRP2, a novel conjugate export pump expressed in the apical membrane of hepatocytes. Adv Enzyme Regul 1997;37:321–33.
179. Zhang Y, Han H, Elmquist WF, Miller DW. Expression of various multidrug resistance-associated protein (MRP) homologues in brain microvessel endothelial cells. Brain Res 2000;876:148–53.
180. van Aubel RA, Smeets PH, Peters JG, Bindels RJ, Russel FG. The MRP4/ABCC4 gene encodes a novel apical organic anion transporter in human kidney proximal tubules: putative efflux pump for urinary cAMP and cGMP. J Am Soc Nephrol 2002;13:595–603.
181. Dazert P, Meissner K, Vogelgesang S, et al. Expression and localization of the multidrug resistance protein 5 (MRP5/ABCC5), a cellular export pump for cyclic nucleotides, in human heart. Am J Pathol 2003;163:1567–77.
182. Westley IS, Brogan LR, Morris RG, Evans AM, Sallustio BC. Role of Mrp2 in the hepatic disposition of mycophenolic acid and its glucuronide metabolites: effect of cyclosporine. Drug Metab Dispos 2006;34:261–6.
183. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. Clin Pharmacokinet 2007;46:13–58.
184. Wolff NA, Burckhardt BC, Burckhardt G, Oellerich M, Armstrong VW. Mycophenolic acid (MPA) and its glucuronide metabolites interact with transport systems responsible for excretion of organic anions in the basolateral membrane of the human kidney. Nephrol Dial Transplant 2007;22:2497–503.
185. Kuypers DR, Verleden G, Naesens M, Vanrenterghem Y. Drug interaction between mycophenolate mofetil and rifampin: possible induction of uridine diphosphate-glucuronosyltransferase. Clin Pharmacol Ther 2005;78:81–8.
186. Cui Y, Konig J, Keppler D. Vectorial transport by double-transfected cells expressing the human uptake transporter SLC21A8 and the apical export pump ABCC2. Mol Pharmacol 2001;60:934–43.
187. Zhang L, Reynolds KS, Zhao P, Huang SM. Drug interactions evaluation: an integrated part of risk assessment of therapeutics. Toxicol Appl Pharmacol 2010; 243:134–45.

Chapter 4
Drug-Food Interactions

Kelly Sprandel-Harris, Liz Yoo, and Keith A. Rodvold

Abstract Drug–food interactions can be a major source of patient inconvenience and nonadherence through disruptions in a patient's daily schedule. Lack of knowledge of potentially significant drug–food interactions can lead to poor clinical outcomes. For example, administering ketoconazole tablets with a meal may decrease absorption. In contrast, each dose of posaconazole oral suspension should be administered with a full meal or liquid nutritional supplement for optimal absorption. Hence, the components of food may interact directly with medications. Different formulation of a drug also affect the magnitude of drug-food interactions. A number of dietary factors, such as dietary protein, cruciferous vegetables, and charcoal-broiled beef are known to have potential for altering metabolism of drugs. This chapter will describe mechanisms of drug–food interactions and U.S. Food and Drug Administration (FDA) guidelines for drug–food interaction studies as well as pharmacokinetic parameters affected by food.

4.1 Introduction

Drug–food interactions can be a major source of patient inconvenience and nonadherence through disruptions in a patient's daily schedule. Unless advised to the contrary, patients often take drugs with meals as a suitable adherence reminder and to lessen gastrointestinal side effects. Lack of knowledge of potentially significant drug–food interactions can lead to poor clinical outcomes. This chapter will describe mechanisms of drug–food interactions and U.S. Food and Drug Administration (FDA) guidelines for drug–food interaction studies. Antimicrobial drug–food

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interactions based on drug classes and pharmacokinetics will be described, as well as the recommended dosing guidelines. In addition, anti-infectives and the disulfiram-like reaction are included.

4.2 Mechanisms of Drug–Food Interactions

4.2.1 Physiologic Effects of Food

The majority of medications are absorbed in the small intestine, with very little absorption occurring directly from the stomach. However, changes in gastrointestinal secretions and gastric pH can have an affect on subsequent absorption [1]. Gastrointestinal secretions increase in response to food ingestion, which increases hydrochloric acid in the stomach thus lowering stomach pH. This acidic environment will accelerate the dissolution and absorption of basic drugs but will cause increased degradation of acid labile drugs [1].

The volume of a meal may also affect the subsequent absorption of the drug. Large fluid volumes tend to increase stomach emptying rates, whereas large solid-food consumption tends to have the opposite effect [1]. Delayed stomach emptying can increase the degradation of drugs that are unstable at low pH as well as increasing absorption time. On the other hand, longer transit time may actually increase absorption for drugs that take more time to dissolve, by increasing the percentage of the drug in solution. Thus, the physiologic effect of food may have variable affects on drug absorption, depending on the characteristics of each individual drug.

4.2.2 Food Composition

The components of food may interact directly with medications in a number of ways. Examples include chelation of the drug by polyvalent metal ions or acting as a mechanical barrier to inhibit the absorption of food across the mucosal surface of the intestines. The formulation of the drug will likely also affect the magnitude of drug–food interactions. Solutions and suspensions are generally less likely to be affected by food, as they pass rapidly through the stomach and become absorbed. Sustained-release formulations such as enteric coated tablets are much more likely to be affected, as the presence of food may delay absorption of the drug by several hours [1].

4.2.3 Effects of Food on Drug Absorption

Drug–food interactions can be divided into three possible outcomes. Drug absorption may be increased, decreased, or not affected. Decreased absorption can be further

subclassified into reduced versus delayed absorption. Reduced absorption is reflected by a decrease in the area under the concentration–time curve (AUC) of the drug. Delayed absorption is reflected by an increase in the time to reach maximum concentration (t_{max}) of the drug. Alterations in the rate of drug absorption caused by the ingestion of food is generally not considered as clinically significant as changes in the extent of drug absorption [2].

4.2.4 Effects of Food on Drug Metabolism

A number of dietary factors are known to have potential for altering the metabolism of drugs [3]. Examples include dietary protein, cruciferous vegetables, and charcoal-broiled beef. In addition, malnutrition has been shown to alter the metabolism of certain drugs [4]. The effects of diet and nutrition have been described in a number of review articles [3, 4]. Grapefruit juice has been demonstrated to increase the bioavailability of drugs that are known to be metabolized by cytochrome P450 (CYP) 3A4 enzymes [5–7]. It appears that grapefruit juice interactions are mediated by inhibition of gut-wall metabolism, which results in reduced presystemic drug metabolism and therefore an increase in drug bioavailability, particularly for drugs with poor bioavailability. Although this field is still in its infancy, studies have shown an effect with grapefruit juice on protease inhibitors and macrolides, among others. The effect of grapefruit juice on P-glycoprotein-mediated drug transport is controversial [8, 9]. A recent study reported that grapefruit juice, Seville orange juice, and apple juice were more potent inhibitors of the organic anion transporting polypeptides (OATPs) than of P-glycoprotein [7]. Although it appears that both drug-metabolizing enzymes and transporters determine drug disposition, further research in this field is necessary. A more complete review of transport proteins is provided in Chap. 3.

4.3 Drug–Food Interaction Studies

The Food-Effect Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the FDA has published guidelines for food-effect bioavailability and bioequivalence studies for oral immediate-release or modified-release dosage forms. The guidance paper provides recommendations for study design, data analysis, and labeling, as well as specifying areas in which food-effect studies may not be important. These guidelines can be accessed at www.fda.gov. Using the FDA search engine on the Internet, limit the search to CDER sites and type in “Food-effect working group” to access the document.

4.3.1 Test Meal

The FDA guidance paper recommends that a food-effect study should be conducted under conditions expected to provide maximal effect with the presence of food in the gastrointestinal (GI) tract. For this effect, they recommend a high-fat (50% of caloric value from the meal), high-calorie (approximately 1,000 cal) breakfast as the test meal. An example of such a meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 oz of hash brown potatoes, with 8 oz of whole milk. This would provide 150 protein calories, 250 carbohydrate calories, and 500–600 fat calories. Details of the meal should be provided in the protocol and final report.

4.3.2 Study Design

A randomized, balanced, single-dose, two-treatment, two-period, two-sequence crossover study is recommended for food-effect studies. These studies are normally performed in healthy volunteers, with the formulation tested under fasted conditions in one treatment arm and immediately following the test meal in the other arm.

4.3.3 Treatment Arms

Following an overnight fast of at least 10 h, subjects should take the drug formulation with a full glass of water (180 mL or 6 fl oz). No food should be allowed for the following 4 h, after which scheduled meals should be permitted. For fed subjects, following an overnight fast of at least 10 h, subjects should be fed the test meal over not more than 30 min. The drug formulation should be given with a full glass of water no later than 5 min after finishing the test meal. As before, no other meals should be allowed for the following 4 h, after which scheduled meals are permitted.

4.3.4 Data and Statistical Analysis

A food effect will be concluded when the 90% confidence interval for the ratio of mean AUC or maximum concentration (C_{max}) of fed versus fasted treatments falls outside 80–125%. Clinical relevance of the observed magnitude should be indicated by the sponsor of the study.

4.4 Anti-Infectives and Drug–Food Interactions Studies

The following sections detail drug–food interaction studies of anti-infective agents by drug class. Within the fluoroquinolones section, the effects of milk, yogurt, caffeine, and enteral feeds are also detailed. It is important to recognize that many

of the earlier studies were completed prior to the FDA guidance paper. In addition, data have frequently been obtained in only one or two clinical studies, and observations made under these particular situations may not be relevant to the current clinical care of patients. However, more recently, well-controlled drug–food interactions studies have used the standardized test meals as recommended by the FDA.

A summary of selected studies reporting the effect of food on the C_{max}, t_{max}, and AUC of oral anti-infective agents is shown in Table 4.1 [10–79].

4.4.1 Penicillins

The absorption of penicillin V and potassium penicillin are both decreased with the coadministration of food [81]. In a study performed in the late 1950s, six groups of ten volunteers were given a standard meal served 60, 30, or 15 min before dosing, with the dose, or 1 or 2 h after the dose of antibiotic. Blood concentrations of penicillin V or potassium penicillin were obtained at 0.5, 1, and 2 h after drug administration. Lower concentrations were observed with both drugs when given with food, although the effect was greater for potassium penicillin. In another study, healthy nurses were given 150-mg doses of penicillin V (K), potassium V (Ca), and potassium V (acid), with or without a standard meal [1]. Reported C_{max} was markedly reduced with all formulations of penicillin V when given with a meal. However, in an earlier study, the absorption of penicillin V (acid) was unaffected by food, possibly due to its greater acid stability and its relatively slow dissolution [1]. Thus, penicillin V should be taken on an empty stomach; however, penicillin V (acid) can probably be safely taken with food, if clinically indicated.

The AUC of ampicillin is decreased by approximately 50% when given with food [1]. This effect was evident when volunteers were given ampicillin with a high-carbohydrate, -protein, or -fat meal, a standard breakfast, or a Sudanese diet [10, 82, 122]. Early research with amoxicillin demonstrated no effect on the absorption of amoxicillin when given with food [83]. In two follow-up studies, one showed decreased absorption when amoxicillin was given with food in six healthy volunteers and another showed no effect in a crossover study of 16 healthy volunteers [10, 122]. In both studies the authors concluded that the effect was not clinically significant, and it was suggested that amoxicillin could be administered without regard to meals. Interestingly, the absorption of amoxicillin was decreased when given with 25 mL of water as compared to 250 mL. Thus, it is recommended that amoxicillin be taken with a full glass (250 mL) of water or other suitable liquid.

Moxatag™ extended-release tablets are intended to provide once-daily dosing of amoxicillin in the treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* [84]. Administration of Moxatag™ with food decreases the rate, but not the extent of amoxicillin absorption. Total amoxicillin exposure (AUC) achieved with Moxatag™ is similar to that observed after oral administration of a comparable dose of immediate-release amoxicillin suspension. The manufacturer recommends that Moxatag™ be taken within 1 h of finishing a meal.

Gastrointestinal side effects appear to be reduced when the combination of amoxicillin and clavulanate potassium (Augmentin®) is administered with food [11].

Table 4.1 The effect of food on the pharmacokinetics of oral anti-infectives

	Ref.	Dosage form	Single or steady state	Status	N and gender	Oral dose (mg)	C_{max} Fasting (μg/ml)	C_{max} Fed (μg/ml)	AUC Fasting μg·h/ml	AUC Fed μg·h/ml	t_{max} Fasting (h)	t_{max} Fed (h)
Penicillins												
Amoxicillin	10	Capsules	Single	Healthy	16 M	500	8.9	8.8	26.9 / 70 kg	22.2 / 70 kg	1.86	2.4
Amoxicillin/ clavulanate	11	Powder	Single	Healthy	9 M,9 F	750	8.48	8.57	21.92	21.03	NR	NR
Ampicillin	10	Capsules	Single	Healthy	16 M	500	5.4	4	17.4 / 70 kg	12.0 / 70 kg	1.49	2.48
Cephalosporins												
Cefadroxil	12	Capsules	Single	Healthy	6NR	1,000	32.1	32.7	NR	NR	NR	NR
Cephalexin	12	Susp	Single	Healthy	6NR	1,000	38.8	23.1	93	70	0.925	1.87
Cefaclor	13	Tablets	Single	Healthy	12 M	250	8.7	4.3	8.6	7.6	0.6	1.3
Cefprozil	14	Susp	Single	Healthy	12 M	250	6.13	5.27	15	14.9	1.2	2
Cefuroxime axetil	15	Susp	Single	Healthy	6 M,6 F	500	8	10.4	19	26.7	1.75	2
Cefixime	16	Tablets	Single	Healthy	40 M	100	NR	NR	NR	NR	2.6	3.2
Cefditoren	17	Tablets	Single	Healthy	8 M	200	2.46	2.72	7.93	10.82	1.46	1.78
Cefpodoxime	18	Susp	Single	Healthy	17 M	200	2.62	3.02	13.5	16.3	2.75	3.22
Ceftibuten	19	Capsules	Single	Healthy	18 M	200	9.85	6.6	42.07	33.7	1.6	3.8
Macrolides and combinations												
Erythromycin ethylsuccinate	20	Susp	Single	Healthy	12 M	400	1.26	0.98	2.8441	2.3677	0.33	0.66
Erythromycin stearate	21	Tablets	Single	Healthy	4 M,2 F	500	3	1.4	13.2	5.2	2.7	2.3
Erythromycin base	22	Tablets	Single	Healthy	9 M,6 F	500	1.2	1	4.6	2.14	4	4.6
Azithromycin	23	Susp	Single	Healthy	28NR	500	0.294	0.474	3.19	3.6	NR	NR
Azithromycin	23	Tablets	Single	Healthy	12NR	500	0.336	0.412	2.49	2.4	NR	NR

Clarithromycin	24	Tablets	Single	Healthy	26 M	500	2.51	1.65	15.67	12.62	2	2.8
Clarithromycin extended-release	25	Tablets	SS	Healthy	36NR	1,000	2.33	3.91	35.9	49.2	5.5	5.6
Ketolides												
Telithromycin	26	Tablets	Single	Healthy	18 M	800	1.44	1.46	7	7.41	2.5	2.25
Tetracyclines												
Tetracycline	27	Capsules	Single	Healthy	4 M,2 F	500	4.5	2.7	55.7	31.7	3.8	4.7
Doxycycline	27	Capsules	Single	Healthy	4 M, 2 F	200	5.1	4	85.3	78.6	3.2	5
Minocycline	28	Capsules	Single	Healthy	8 NR	100	1.75	1.38	22.4	19.8	1.87	3.12
Quinolones												
Ciprofloxacin	29	Tablets	Single	Healthy	12 M	750	2.23	2.74	12.71	13.68	1.42	1.79
Gemifloxacin	30	Tablets	Single	Healthy	13 M, 7 F	320	1.21	1.07	7.57	7.38	1.5	2
Levofloxacin	31	Tablets	Single	Healthy	12 M, 12 F	500	5.9	5.1	50.5	45.6	1	2
Moxifloxacin	32	Tablets	Single	Healthy	16 M	400	2.8	2.5	38.5	37.7	1	2.5
Ofloxacin	33	Tablets	Single	Healthy	12 M	200	2.24	1.56	13.18	11.26	0.83	1.85
Miscellaneous anti-infective												
Trimethoprim	34	Suspension	Single	Healthy	9 M, 3 F	3 mg/kg	2.35	1.84	37.1	28.9	2.68	2.76
Albendazole	35	Capsules	Single	Healthy	6 M	10 mg/kg	0.24	1.55	2.08	19.64	2.5	5.3
Ivermectin	36	Tablets	Single	Healthy	12 NR	30	0.085	0.26	1.72	4.56	4.3	4.6
Praziquantel	37	Tablets	Single	Healthy	9 NR	600	0.32	1.1	0.88	2.47	1.39	1.94
Linezolid	39	Tablets	Single	Healthy	7 M, 5 F	375	7.6	6.2	51.7	50	1.5	2.2
Metronidazole	40	Capsules	Single	Healthy	5 M, 5 F	400	9.12	7.95	5587	5765	1.19	2.31
Antimalarial agents												
Primaquine	41	Tablets	Single	Healthy	10 M, 10 F	30	127	160	1222	1396	2.0	1.5
Chloroquine	42	Base	Single	Healthy	7 M	600	480.06	739.51	4.52	6.41	j	NR
Mefloquine	43	Tablets	Single	Healthy	20 M	750	868	1497	461000	645000	36	1.5
Atovaquone	38	Suspension	SS	HIV Positive	21 M, 1 F	750	12.4	15	238	301	6.5	8.9

(continued)

Table 4.1 (continued)

	Ref.	Dosage form	Single or steady state	Status	N and gender	Oral dose (mg)	C_{max} Fasting (μg/ml)	C_{max} Fed (μg/ml)	AUC Fasting μg·h/ml	AUC Fed μg·h/ml	t_{max} Fasting (h)	t_{max} Fed (h)
Antituberculosis agents												
Ethambutol	44	Tablets	Single	Healthy	8 M, 6 F	25 mg/kg	4.55	3.83	29.8	27.5	2.48	3.21
Isoniazid	45	Tablets	Single	Healthy	8 M, 6 F	300	5.53	2.73	20.16	17.72	1.02	1.93
Pyrazinamide	46	Tablets	Single	Healthy	8 M, 6 F	30 mg.kg	53.4	45.6	673	687	1.43	3.09
Rifabutin	47	Capsules	Single	Healthy	12 M	150	0.1879	0.156	2.516	2.64	3	5.4
Rifampin	48	Capsules	Single	Healthy	8 M, 6 F	600	10.93	7.27	57.15	55.2	2.305	4.43
Antifungals												
Griseofulvin	49	Microsize	Single	Healthy	5 M, 1 F	250	NR	0.6815	NR	14.14	NR	2.515
Itraconazole	50	Solution	Single	Healthy	30 M	200	0.5457	0.3069	4.5199	3.1617	2.2	4.8
Fluconazole	51	Tablets	Single	Healthy	7 M, 5 F	100	2.34	2.22	113	106	3.08	3.08
Ketoconazole	52	Tablets	Single	Healthy	8 M, 4 F	200	4.37	4.42	15.25	20.47	1.21	2.33
Posaconazole	53	Tablets	Single	Healthy	20 M	200	NR	0.413	NR	10.304	NR	5.5
Posaconazole[a]	53	Suspension	Single	Healthy	20 M	200	0.132	0.512	3.553	13.885	5	4.8
Voriconazole	54	Tablets	Single	Healthy	12 M	200	2.038	1.332	19.258	13.065	1.5	2.6
Nonnucleoside reverse transcriptase inhibitors												
Delaviridine	55	Tablets	SS	HIV positive	11 M, 2 F	400	30 uM	23 uM	NR	NR	NR	NR
Efavirenz	56	Capsules	SS	Healthy	5 NR	1,200	NR	NR	50% increase	NR	NR	NR
Etravirine	57	Tablets	Single	Healthy	24 M	100	0.089	0.129	0.921	1.417	2.0	4.0
Emtricitabine	58	Capsules	Single	Healthy	12 M, 12 F	NR	1.910	1.820	11	10.4	NR	NR
Nevirapine	56	Tablets	Single	Healthy	12 M, 12 F	200	2	no change	NR	NR	NR	NR
Nucleoside reverse transcriptase inhibitors												
Abacavir	59	Tablets	Single	HIV Positive	11 M, 7 F	300	2.58	1.91	5.48	5.31	0.63	1.39

Didanosine	60	Tablets	Single	HIV positive	8 M	375	2.789	1.291	3.902	2.083	0.5	0.5
Didanosine enteric coated	61	Tablets	Single	Healthy	20 NR	400	1.204	0.653	3.196	2.599	2	3
Lamivudine (as Combivir)	62	Tablets	Single	Healthy	12 M, 12 F	150	1.6203	1.3676	6.1376	6.0354	0.91	1.86
Stavudine	63	Capsules	Single	HIV positive	13 M, 4 F	70	1.439	0.756	2.527	2.359	0.65	1.73
Zidovudine	64	Capsules	Single	HIV positive	12 M, 6 F	100	0.806	0.341	0.884	0.817	0.681	1.72
Nucleotide reverse transcriptase inhibitors												
Tenofovir	65	Tablets	NR	NR	NR	NR	14% increase	NR	40% increase	NR	NR	NR
Protease inhibitors												
Amprenavir	66	Capsules	Single	Healthy	NR	600		46% decrease		23% decrease		2.5x increase
Darunavir	67	Capsules	Single	HIV negative	12 M, 12 F	200	3609	5326	46750	71929	1.5	3.0
Fosamprenavir	68	Tablets	Single	Healthy	40 M	1,200	4.58	3.93	20.2	17.6	1.25	2.5
Indinavir	69	Capsules	Single	Healthy	11 M	400	4.48 uM	0.62	6.86 uM×h	1.54 uM×h	0.7	2
Indinavir	69	Capsules	Single	Healthy	11 M	800	11.68 uM	9.37	23.15 uM×h	22.71	0.77	1.44
Lopinavir	70	Tablets	Single	NR	NR	NR	NR	26.9% increase[b] 18.9% increase[c]	NR	17.6% increase[b] No change[c]	NR	NR
Lopinavir	70	Solution	Single	NR	NR	NR	NR	80% increase[b] 130% increase[c]	NR	54% increase[b] 56% increase[c]	NR	NR

(continued)

Table 4.1 (continued)

							C_{max}		AUC		t_{max}	
	Ref.	Dosage form	Single or steady state	Status	N and gender	Oral dose (mg)	Fasting (μg/ml)	Fed (μg/ml)	Fasting μg·h/ml	Fed μg·h/ml	Fasting (h)	Fed (h)
Nelfinavir	71	Tablets	Single	Healthy	6 NR	800	NR	NR		27–50% higher	NR	NR
Ritonavir	56	Capsules	Single	Healthy	57 NR	600	NR	NR	105.9	121.7	NR	NR
Ritonavir	56	Solution	Single	NR	18 NR	600	NR	23% decrease	120	129	2	4
Saquinavir	72	Capsules	Single	Healthy	8 NR	600	0.003	0.51	0.024	0.161	2.4	3.8
Entry inhibitor (CCR5 Co-inhibitor Antagonist)												
Maraviroc	73	Tablets	Single	NR	NR	300	NR	33% decrease[a]	NR	33% decrease[a]	NR	NR
Integrase inhibitor												
Raltegravir	74	Tablets	Multiple	Healthy	20	800	2.71	5.32[b]	10	21.2[b]	3	4[b]
								2.85[c]		11.3[c]		4[c]
								1.31[d]		5.38[d]		3[d]
Non-HIV antivirals												
Entecavir	75	Tablets	Single	NR	NR	0.5	NR	44–46% decrease	NR	18–20% decrease	NR	NR
Famciclovir	76	Tablets	Single	Healthy	12 M	500	3.46	1.89	9.53	9.8	0.75	3
Ganciclovir	79	Capsules	SS	HIV Positive	18 M, 2 F	1,000	0.85	0.96	4.7	5.6	1.8	3
Rimantadine	77	Tablets	Single	Healthy	11 M, 1 F	100	0.109	0.115	4.14	4.07	4.03	3.4
Valganciclovir	78	Tablets	SS	HIV Positive	37 M, 2 F	875	5.33	6.07	19	24.8	1.5	1.5

[a]Compared to fasted state
[b]Moderate fat meal (500–682 Kcal)
[c]High fat meal (872 kcal, 56% fat)
[d]Low fat meal (~300 kcal, 7% fat)

In one study, after the administration of two 500 mg Augmentin® tablets, no significant difference was seen in the AUC, peak concentration, or time to reach peak concentration for either amoxicillin or clavulanate when administered in the fed versus fasted state [11]. According to the manufacturer, Augmentin® tablets, powder, and chewable tablets may be administered without regard to meals. There does not appear to be a difference in the pharmacokinetics of amoxicillin when administered in the fed versus fasted state. The absorption of clavulanate potassium is greater when Augmentin is administered at the start of a meal, but reduced when it is given 30 and 150 min after the start of a high fat breakfast [1, 85, 86]. The effect of food on the oral absorption of Augmentin-ES has not been evaluated [87]. The pharmacokinetics of Augmentin XR®, an extended-release formulation, were evaluated in healthy volunteers when administered in the fasted state, at the start of a standardized meal, and 30 min after a high fat meal. The absorption of amoxicillin is decreased in the fasted state. Clavulanate potassium absorption is decreased after the administration of a high-fat meal. As a result, the manufacturer suggests that Augmentin XR® is optimally administered at the start of a meal and should not be taken with a high-fat meal [88]. However, to minimize the potential for gastrointestinal side effects, all amoxicillin-clavulanate potassium formulations should be given at the start of a meal. The manufacturers' dosing recommendations for penicillin antibiotics are shown in Table 4.2.

4.4.2 Cephalosporins

4.4.2.1 First-Generation Oral Cephalosporins

The concomitant administration of cephalexin and food delayed the t_{max} and resulted in a slower rate of clearance of the drug. This delay was minor, however, and not considered clinically significant [89, 90]. The rate and extent of absorption of cefadroxil, another first-generation cephalosporin, was not affected by the administration of a standard breakfast [12]. Cephalexin and cefadroxil can be administered without regard to meals.

4.4.2.2 Second-Generation Oral Cephalosporins

A number of studies have examined the effect of food on the absorption of cefaclor [13, 14, 91]. The maximum achieved concentration of cefaclor pulvules is reduced by approximately 50% and the t_{max} is prolonged when given with food, whereas the AUC of the controlled-release formulation is enhanced with food [14, 92]. The AUC of cefaclor is also decreased by 10–20% when it is given concomitantly with food, but in clinical studies these results did not reach statistical significance [14, 93]. The administration of a standard breakfast did not affect the C_{max} or the AUC for cefprozil, but delayed the t_{max} by approximately 50 min [14, 94]. This delay in absorption was not found to be statistically significant [14].

Table 4.2 Penicillins

Generic	Brand	Company	Manufacturer recommendations
Ampicillin	Principen capsules	Geneva	Administer 1/2 h before or 2 h after meals for maximal absorption.
	Principen powder for oral suspension	Geneva	Administer 1/2 h before or 2 h after meals for maximal absorption.
Amoxicillin	Amoxil capsules, tablets, and chewable tablets	GlaxoSmithKline, various	Can be given without regard to meals.
	Amoxil powder for oral suspension	GlaxoSmithKline, various	Can be given without regard to meals.
	Trimox powder for oral suspension	Sandoz	Can be given without regard to meals.
	Moxatag Extended Release tablets	Middlebrook	Should be taken within 1 h of finishing a meal.
Amoxicillin/ clavulanate	Augmentin chewable tablets	GlaxoSmithKline	May be given without regard to meals. Should be taken at the start of meals to minimize GI upset.
	Augmentin tablets	GlaxoSmithKline	May be given without regard to meals. Should be taken at the start of meals to minimize GI upset.
	Augmentin ES-600 powder for oral suspension	GlaxoSmithKline	Should be taken at the start of meals to minimize GI upset (the effect of food on the oral absorption of AUGMENTIN ES 600 has not been studied).
	Augmentin Extended Release (XR) tablets	GlaxoSmithKline	Should be taken at the start of a meal to enhance absorption of amoxicillin and to minimize GI upset (should not be taken with high fat meals because clavulanate absorption is decreased).
	Amoclan powder for oral suspension	West-Ward	Can be given without regard to meals.
Carbenicillin	Geocillin film-coated tablets	Pfizer	May be given without regard to meals. Should be taken at the start of meals to minimize GI upset.
Dicloxacillin	Generic Only Capsules	Various, e.g., Sandoz	Should be taken on an empty stomach, preferably 1–2 h before meals.
Penicillin V	Penicillin VK tablets, powder for oral solution	Teva	May be given with meals; however, blood levels are slightly higher when given on an empty stomach.
	Veetids	Geneva	May be given with meals; however, blood levels are slightly higher when given on an empty stomach.

The absorption of cefuroxime axetil, an ester cephalosporin, is increased with food or milk [80, 95, 96]. Administration with a standard breakfast caused an almost 100% increase in the C_{max} and the AUC for cefuroxime. However, trough concentrations of cefuroxime were similar in both groups [80]. Likewise, administration of cefuroxime with milk causes a 25–88% increase in the AUC and C_{max} [95]. Thus, it is recommended that cefuroxime axetil be taken ideally with food.

4.4.2.3 Extended-Spectrum Oral Cephalosporins

The food requirements with third-generation cephalosporins can be summarized by dividing this generation into the ester formulations and the nonester formulations. The bioavailability of the ester cephalosporins is enhanced by the presence of food [97]. This effect is not caused by changes in the gastric pH but is probably secondary to increased contact time between the drug and the esterases of the intestinal mucosa secondary to delayed gastric emptying. The nonester cephalosporins, on the other hand, display a decrease in the AUC and C_{max} when given with food.

The absorption of cefpodoxime proxetil, an ester cephalosporin, is higher when given with food [18, 98]. A four-way crossover study assessed a high- or low-fat and high- or low-protein meal versus a lead-in study assessing absorption under fasting conditions. In all cases, giving cefpodoxime with any meal increased the C_{max} and the AUC by approximately 22% and 34%, respectively [18]. Absorption of cefixime, a nonester cephalosporin, is unaffected by food despite a slight delay in the time to reach peak concentration [99, 100].

When cefdinir capsules were administered with a high-fat meal, the C_{max} was reduced by 16% and the AUC was reduced by 10%. However, the magnitude of these changes is not considered to be clinically significant and cefdinir may be administered without regard to meals [101, 102]. The administration of cefdinir with 60 mg of ferrous sulfate or a vitamin with 10 mg of elemental iron reduced the extent of absorption by 80% and 31%, respectively. Another study evaluated the effect of a sustained release ferrous sulfate preparation on the absorption of cefdinir [103]. The authors found that the AUC of cefdinir was significantly lower than when cefdinir was administered alone. The effect of foods fortified with elemental iron on the absorption of cefdinir has not been studied. The manufacturer recommends administering cefdinir at least 2 h before or after iron supplements [101].

Cefditoren is a prodrug ester cephalosporin. The C_{max} and AUC values have been reported to increase when cefditoren is administered after a meal [17]. The estimated bioavailability of cefditoren, under fasting conditions, is approximately 14%. When administered with a low-fat meal (693 cal), the bioavailability is increased to approximately 16%. A moderate (648 cal) or high-fat meal (858 cal) resulted in a 70% increase in mean AUC and a 50% increase in mean C_{max} compared with the fasted state. Thus, the manufacturer recommends taking cefditoren with food to enhance absorption [104].

The administration of a standard meal (530 kcal) had no effect on the pharmacokinetics of ceftibuten, besides a slight increase in the time to reach C_{max} [19, 105].

However, the administration of a high-fat breakfast contrasted these results by an approximate 20% and 33% decrease in the AUC and C_{max}, respectively [19]. However, the official labeling for ceftibuten recommends that the drug be taken 1 h before or 2 h after a meal. The manufacturers' dosing recommendations for cephalosporin antibiotics are shown in Table 4.3.

4.4.3 Macrolides

4.4.3.1 Erythromycin

A variety of dosage forms of erythromycin have been developed to improve stability and absorption of erythromycin when given with food. In general, two formulations were developed to improve the bioavailability of erythromycin [1]. The first was to develop erythromycin as an enteric coated formulation, thus resisting acid degradation in the stomach. The second was to develop relatively acid-fast esters of erythromycin. The majority of these studies were performed in the 1950s and 1960s, making interpretation of results difficult due to the lack of standardization during this time period. However, for the most part, trends can be established for the various dosage forms of erythromycin.

Food decreases the total absorption of erythromycin base capsules and tablets [1, 106]. This was improved by the development of erythromycin-base coated tablets, which tended to improve the overall absorption of the erythromycin and food tended to simply delay the time to peak absorption [1, 20, 106]. A small study did document decreased absorption with the coadministration of enteric coated erythromycin with food [1]. The absorption of enteric coated pellets of erythromycin base was delayed, but not reduced, when taken with a standard breakfast [1].

The absorption of erythromycin stearate was reduced when given after meals in single- and multiple-dose studies [1, 21, 107, 108]. However, the opposite effect was observed when erythromycin stearate was given before meals [22]. Significant increases in erythromycin concentrations occurred in healthy volunteers given erythromycin stearate coated tablets immediately prior to a standard meal. This was hypothesized to be due to a rapid discharge of the dosage form from the stomach or the enteric coating of the formulation.

Erythromycin ethylsuccinate is an ester of the erythromycin base and was developed to improve absorption when coadministered with food. This ester is less water soluble and more resistant to acid degradation [1]. Studies have demonstrated no effect or increased absorption when erythromycin ethylsuccinate is given with food [20, 109–111]. Grapefruit juice has been reported to inhibit first-pass metabolism on CY3A in the small intestine [112] and as a result can cause a significant increase in oral bioavailability of drugs that are CYP3A substrates [113]. Although erythromycin is a potent inhibitor of CYP3A in the liver, less is known about its effect on CYP3A in the small intestine or if the metabolism of erythromycin is affected by inhibition of CYP3A in the small intestine. Therefore, six healthy male subjects were pretreated

Table 4.3 Cephalosporins

Generic	Brand	Company	Manufacturer recommendations
First generation			
Cephradine	Velosef capsule, Gelatin coated, oral suspension	Bristol-Myers Squibb	Can be given without regard to meals.
Cefadroxil	Duricef capsules, powder for oral suspension, tablets	Bristol-Myers Squibb, various	Can be given without regard to meals.
Cephalexin	Keflex oral suspension, capsules	Advantis	Can be given without regard to meals.
	Keftab tablets	Dista, Eli Lilly	Absorption may be delayed by food but the amount absorbed is not affected.
Second generation			
Cefaclor	Raniclor chewable tablets	Ranbaxy	Can be given without regard to meals (total absorption is same) Well absorbed in fasting subjects.
	Ceclor pulvules, powder for oral suspension	Lilly	Can be given without regard to meals.
Cefprozil	Cefzil for oral suspension	Bristol-Myers Squibb	Can be given without regard to meals.
	Cefzil tablets	Bristol-Myers Squibb	Absorption may be delayed by food but the amount absorbed is not affected.
Cefuroxime axetil	Ceftin for oral suspension	GlaxoSmithKline	Must be administered with food.
	Ceftin tablets	GlaxoSmithKline	Can be given without regard to meals.
Extended-spectrum			
Cefixime	Suprax for oral suspension, tablets	Lupin Pharmaceuticals	Can be given without regard to meals.
Cefdinir	Omnicef capsules, oral suspension	Abbott	Can be given without regard to meals.
Cefditoren	Spectracef tablets	Cornerstone Therapeutics Inc.	Should be administered with meals to enhance absorption.
Cefpodoxime	Vantin tablets	Pharmacia and Upjohn	Should be administered with food to enhance absorption.
Ceftibuten	Cedax capsules	Shionogi	Absorption may be delayed by food but the amount absorbed is not affected.
	Cedax oral suspension	Shionogi	Suspension must be administered at least 2 h before or 1 h after a meal.

with 300 mL of water or grapefruit juice 30 min before the single dose administration of 400 mg erythromycin enteric-coated tablets in a crossover fashion to evaluate the effect of grapefruit juice on the pharmacokinetics of erythromycin [113]. The C_{max} and AUC were significantly increased when erythromycin was administered with grapefruit juice compared with water. The t_{max} and half-life values were not significantly different between the two phases. The authors concluded that the bioavailability of erythromycin was increased after the administration of grapefruit juice as a result of inhibition of CYP3A metabolism in the small intestine.

4.4.3.2 Advanced-Generation Macrolides/Azalides

The bioavailability of clarithromycin is unaffected or increased in the presence of food [24]. In a study of healthy volunteers given a single dose of 500 mg of clarithromycin, food increased the absorption of clarithromycin by 25%. The authors speculated that this would offer little clinical benefit and suggested that clarithromycin could be given without regard to food. The effect of grapefruit juice on the pharmacokinetics of clarithromycin and its active metabolite, 14-OH clarithromycin, has been evaluated in 12 healthy subjects [114]. After an overnight fast of at least 8 h, subjects received a single 500 mg dose of clarithromycin with 240 mL of either water or freshly squeezed white grapefruit juice at time 0 and 2 h after administration in a randomized, crossover fashion. Although administration of grapefruit juice significantly delayed the t_{max} of both the parent and active metabolite, it did not affect the extent of absorption of clarithromycin [114].

In contrast to the immediate release formulation, the manufacturer recommends that clarithromycin extended-release tablets be taken with food [115]. Thirty-six healthy subjects were administered two 500 mg clarithromycin extended-release tablets once daily for 5 days in the fasting state and 30 min after starting a high-fat breakfast (1,000 kcal) [25]. Results from this study showed AUC of parent compound clarithromycin was 30% lower under fasting condition compared to nonfasting condition. Confusion has existed as to the absorption of azithromycin with food. Early studies with azithromycin capsules demonstrated a 50% decrease in the overall absorption of azithromycin [116]. However, research with the currently marketed tablet and suspension has shown little effect on the absorption when coadministered with a high-fat meal [23]. An abstract also reported no interaction with food and the oral suspension of azithromycin when given to pediatric patients [117].

The manufacturers' dosing recommendations for macrolide and azalide antibiotics are shown in Table 4.4.

4.4.4 Tetracyclines

In general, the tetracyclines are affected to various degrees by food, milk, and iron products. Tetracycline, the prototype antibiotic for this class, has amassed a substantial

Table 4.4 Macrolides/azalides

Generic	Brand	Company	Manufacturer recommendations
Azithromycin	Zithromax for oral suspension	Pfizer	Can be given without regard to meals.
	Zithromax tablets	Pfizer	Can be given without regard to meals.
	Zmax powder for suspension, extended release	Pfizer	taken on an empty stomach (at least 1 h before or 2 h following a meal).
Clarithromycin	Biaxin Filmtab tablets, granules for oral suspension	Abbott	Can be given without regard to meals.
	Biaxin XL filmtab	Abbott	Should be taken with food.
Erythromycin ethylsuccinate	E.E.S. 400 liquid suspension	Abbott	Can be given without regard to meals.
	E.E.S. 400 filmtab tablets	Abbott	Can be given without regard to meals.
	E.E.S. granules	Abbott	Can be given without regard to meals.
	EryPed 200 and 400 powder for suspension	Abbott	Can be given without regard to meals.
	EryPed drops	Abbott	Can be given without regard to meals.
Erythromycin stearate	Erythrocin stearate filmtab tablets	Abbott	Optimal serum levels of erythromycin are reached when taken in the fasting state or immediately before meals.
Erythromycin base	Ery-Tab delayed release tablets	Abbott	Well absorbed and may be given without regard to meals.
	PCE Dispertab tablets	Abbott	Optimal blood levels are obtained when they are taken on an empty stomach (at least 30 min and preferably 2 h before meals).
	Filmtab tablets	Abbott	Optimum blood levels are obtained when doses are given on an empty stomach.
	Erythromycin delayed-release capsules USP	Abbott	Optimum blood levels are obtained on a fasting stomach (administer at least 1/2 h and preferably 2 h before or after a meal).

body of literature concerning its food and supplement interactions. Studies involving doxycycline and minocycline are plentiful as well, comparing their food, milk, and iron interactions with that of tetracycline. The reduced bioavailability of the tetracyclines is most likely due to chelation of the antibiotic with heavy metals such as iron and calcium and binding to macromolecules found in food [1]. Iron preparations and antacids containing calcium, magnesium, and aluminum cations form poorly

soluble complexes that inhibit, to varying degrees, all of the tetracyclines [118, 119]. It has been hypothesized that the tetracyclines with higher degrees of lipophilicity may display the least interaction with food or milk due to increased absorption and a lesser tendency to form complexes [120]. Of the three main tetracyclines, minocycline is most lipophilic, followed by doxycycline and then tetracycline [118, 121].

The effect of food on the absorption of tetracycline was assessed in a number of healthy-volunteer studies [28, 123–126]. Test meals using high-carbohydrate, -fat, or -protein diets uniformly caused an approximately 50% decrease in the absorption of tetracycline [28, 125, 126]. Likewise, the coadministration of tetracycline with 6 oz of milk caused a 65% decrease in tetracycline absorption, and 300 mg of ferrous sulfate produced a 77% decrease in absorption [28]. Thus, it is always recommended that tetracycline be taken on an empty stomach with a full glass of water (1 h before or 2 h after food). Likewise, any patients who have failed tetracycline therapy should be questioned concerning how they administered the drug and investigate whether the drug was coadministered with milk, multivitamins, or other supplements that might complex with the drug.

Doxycycline is less affected than tetracycline by coadministration with food or milk [127]. The coadministration of doxycycline with meals high in fat, carbohydrates, and protein or 6 oz of homogenized milk produced approximately a 20% decrease in the overall absorption of the drug [27]. Another study reported a 30% decrease in AUC and a 24% decrease in the C_{max} of doxycycline after it was administered with 300 mL of milk compared to water [128]. The authors concluded that, similar to tetracycline, doxycycline should not be administered with milk. Minocycline also is minimally affected when given with food or milk, but coadministration with antacids or other divalent cations caused significantly decreased absorption and is contraindicated [28, 118, 129].

The coadministration of doxycycline with ferrous sulfate not only causes decreased absorption of doxycycline but also reduces the half-life of the drug from 17 to 11 h [130]. Although not as well documented, this interaction probably occurs to the same extent with tetracycline and minocycline as well, as these drugs also undergo enterohepatic recirculation. The inhibitory effects of various iron salts on the absorption of tetracycline were investigated in six healthy volunteers [131]. The iron salt type (each corresponding to 40 mg of elemental iron) all caused varying degrees of decreased absorption of tetracycline. Ferrous sulfate caused the most significant decrease in absorption (80–90%), followed by ferrous fumarate, ferrous succinate, ferrous gluconate (70–80%), ferrous tartrate (50%), and ferrous sodium edetate (30%). Thus, it is recommended that minocycline and doxycline be given with food to decrease incidence of gastrointestinal upset but that the administration of all tetracyclines be spaced by at least 2 h from antacids [28, 118, 121]. Due to the significant gastrointestinal transit time of iron preparations, it is not advisable to prescribe tetracyclines for patients who are taking iron supplementation [28]. The interactions of tetracyclines with food, milk, and antacids are presented in Table 4.5, and the manufacturers' dosing recommendations for tetracycline antibiotics are shown in Table 4.6.

Table 4.5 Decreased absorption of tetracyclines with food and milk

	Percent (%) decreased AUC	
Antibiotic	Food	Milk
Tetracycline	50	65
Minocycline	13	27
Doxycycline	20	20

Table 4.6 Tetracylines

Generic	Brand	Company	Manufacturer recommendations
Demeclocycline	Declomycin tablets	ESP Pharma	Give 1 h before or 2 h after meals or dairy products.
Doxycycline	Adoxa tablet (as monohydrate)	Bioglan	Administration with adequate amounts of fluid is recommended the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.
	Doryx delayed release tablets	Warner Chilcott	Administration with adequate amounts of fluid is recommended. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.
	Monodox capsules	Oclassen	May be given with food if GI upset occurs. Administration with adequate amounts of fluid is recommended.
	Oracea Capsules (sugar spheres)	Galderma	Should be taken at least 1 h prior to or 2 h after meals.
	Periostat tablet (as hyclate)	Galderma	Administration with adequate amounts of fluid is recommended. Should be taken at least 1 h prior to or 2 h after meals.
	Vibramycin calcium oral syrup	Pfizer	May be given with food if GI upset occurs. Administration with adequate amounts of fluid is recommended.
	Vibramycin monohydrate for oral suspension	Pfizer	May be given with food if GI upset occurs. Administration with adequate amounts of fluid is recommended.
	Vibra-tabs film coated tablets (as hyclate)	Pfizer	May be given with food if GI upset occurs. Administration with adequate amounts of fluid is recommended.

(continued)

Table 4.6 (continued)

Generic	Brand	Company	Manufacturer recommendations
Minocycline	Dynacin capsules, film coated tablets	Medicis	Can be given without regards to meals.
	Minocin oral suspension	Lederle labs	Can be given without regards to meals.
	Minocin pellet-filled capsules	Lederle labs	Can be given without regards to meals.
	Solodyn Extended Release tablets	Medicis	Taking SOLODYN® with food may lower your chances of getting irritation or ulcers in your esophagus.
Tetracycline	Sumycin 250 and 500 capsules	Par Pharma	Take on an empty stomach at least1 h before or 2 h after meals.
	Sumycin Syrup oral suspension	Par Pharma	Take on an empty stomach at least1 h before or 2 h after meals.

4.4.5 Fluoroquinolones

In general, food has little clinical effect on the pharmacokinetics of the quinolones. However, the absorption of quinolones are affected by divalent and trivalent cations and thus are affected, to different extents, by calcium-containing foods, iron supplements, and antacids. Enteral feedings can also contain significant amounts of di- and trivalent cations and their influence, on the pharmacokinetics of quinolones has been investigated in a number of published studies. Quinolones, to various extents, also inhibit the liver enzymes responsible for caffeine metabolism, creating another potential interaction.

Food (standard or a high-fat meal) has minimal effects on the absorption of ciprofloxacin suspension, immediate release tablets, or extended-release tablets [29, 133–135].

Levofloxacin is well absorbed after oral administration, with a bioavailability of greater than 90% [132]. Administration with food decreases the C_{max} by approximately 14% and lengthens the t_{max} by approximately 1 h. This is not considered clinically significant, and levofloxacin can be administered without regard to meals. Similar to levofloxacin, moxifloxacin has excellent oral absorption with an absolute bioavailability of approximately 90% [136]. After the administration of a high-fat breakfast, the absorption of moxifloxacin is slightly delayed. The median t_{max} values were 1 h under fasting conditions and 2.5 h in the fed state. The C_{max} and AUC of moxifloxacin were decreased by approximately 12% and 3%, respectively, after the administration of a high-fat meal. However, the magnitude of these effects is not considered clinically significant [32]. The absolute bioavailability of gemifloxacin is approximately 71% and does not appear to be significantly altered by the administration of a high-fat meal [30, 137]. The manufacturers' dosing recommendations for fluoroquinolone antibiotics are shown in Table 4.7.

Table 4.7 Quinolones

Generic	Brand	Company	Manufacturer recommendations
Ciprofloxacin	Cipro tablets, oral suspension	Bayer	Can be given without regards to meals.
	Cipro XR tablets	Bayer	Can be given without regard to meals.
	Proquin XR tablets	Depomed	Should be given with a meal.
Gemifloxacin	Factive tablets	Oscient	Can be given without regard to meals.
Levofloxacin	Levaquin tablets, oral solution	Ortho-McNeil	Can be given without regard to meals.
Moxifloxacin	Avelox tablets	Bayer	Can be given without regard to meals.
Norfloxacin	Noroxin tablets	Merck	Administer 1 h before or 2 h after meals. Patients should be well hydrated.
Ofloxacin	Floxin tablets	Ortho-McNeil	Can be given without regard to meals.

4.4.5.1 Quinolones and Milk or Yogurt

Coadministration with milk and yogurt significantly decreased the C_{max} and AUC of ciprofloxacin in two healthy volunteer studies [138, 139]. The effect of milk and yogurt on the absorption of norfloxacin was investigated in two other healthy volunteer trials [140, 141]. The administration of milk caused a greater-than-50% decrease in the C_{max} and AUC of norfloxacin.

Dairy products did not significantly affect the pharmacokinetics of moxifloxacin or ofloxacin in healthy-volunteer studies [141–143]. Thus, it appears that patients should be counseled to avoid coadministration of milk with ciprofloxacin and norfloxacin and, perhaps, all the fluoroquinolones as a general rule.

4.4.5.2 Quinolones and Vitamin or Mineral-Fortified Foods

Except for norfloxacin and extended-release ciprofloxacin, the flouroquinolones are labeled as being able to administered without regard to meals due to studies conducted with the standard Food and Drug Administration (FDA)-mandated food-drug bioequivalency study meal of a high-fat, high-calorie, low-mineral breakfast [144]. The bioavailability of fluoroquinolones is reduced during the concomitant administration with multi-valent cations (i.e., calcium, magnesium, iron, and aluminum). To minimize this drug interaction, it is recommended to administer the interacting agent at least 2–4 h apart from the dosing of the fluoroquinolone [146]. There are an increasing number of food products available that have been fortified with essential

vitamins and minerals. As a result, new drug-food interactions could exist that were not seen prior to the food products fortification.

Most calcium fortified food products have more calcium per serving than seen in the dietary calcium interaction studies conducted with milk or yogurt [147]. Several recent studies have evaluated the effect of calcium fortification on the bioavailability of fluoroquinolones using calcium-fortified orange juice [145, 147, 148]. In a randomized, three-way crossover study, 15 healthy subjects received a single dose of ciprofloxacin with 12 oz of water, orange juice, and calcium-fortified orange juice. The C_{max} and AUC decreased by 41% and 38%, respectively, when ciprofloxacin was administered with calcium-fortified orange juice compared to water. The authors concluded that administering ciprofloxacin with water was not bioequivalent to administering it with calcium-fortified orange juice [147].

After administering a single 500 mg dose of levofloxacin to 16 healthy subjects, no significant difference in AUC was seen between the intake with either water or calcium-fortified orange juice. The C_{max} was reduced by 18% and the t_{max} increased by 58% when levofloxacin was co-administered with calcium-fortified orange juice compared to water. However, the degree of change in the C_{max} and t_{max} was about the same with both plain and calcium-fortified orange juices. The authors suggest that the interaction with levofloxacin and the orange juices seems less likely to be a chelation interaction similar to the one observed in the ciprofloxacin study [147]. Since levofloxacin is a P-glycoprotein substrate [149] and orange juice is a potential inhibitor of intestinal transport mechanisms [7, 150], one potential explanation includes inhibition of P-glycoprotein or OATP in the gastrointestinal tract by the orange juice in combination with minor chelation. No matter what the actual mechanism of the interaction, the C_{max} of levofloxacin was significantly decreased with the administration of orange juice. The bioavailability of levofloxacin when taken with water alone, subject measured portions of fortified orange juice and cereal, and subject measured portions of fortified orange juice and cereal with milk was also studied [148]. Both phases of food intake were not considered bioequivalent to the water alone phase in terms of the C_{max}.

Although a limited number of studies have evaluated the effect of foods fortified with vitamin or minerals on fluoroquinolone absorption, it may be prudent to instruct patients to avoid the concomitant administration of fluoroquinolones with fortified food products.

4.4.5.3 Quinolones and Caffeine

Inhibition of cytochrome CYP1A2 activity by certain quinolones results in prolonged half-life, increased AUC, and decreased clearance of caffeine [151]. Norfloxacin significantly altered the pharmacokinetics of caffeine, causing similar changes in the clearance and AUC [151, 152]. Ciprofloxacin caused approximately a 50% increase and decrease in the AUC and clearance of caffeine, respectively [153]. In vitro tests with human liver microsomes assessed the inhibitory potency of various quinolones against CYP1A2. Ciprofloxacin and norfloxacin were the strongest inhibitors of

CYP1A2, followed by ofloxacin [151]. Thus, caffeine should be avoided in patients with liver disorders, cardiac arrhythmias, latent epilepsy, or in intensive care units while undergoing treatment with quinolones known to interact with caffeine [154].

4.4.5.4 Quinolones and Enteral Feeds

The effects of enteral feeds on the absorption of fluoroquinolones have produced controversial results. An enteral feeding product (Ensure®) reduced the relative oral bioavailability of ciprofloxacin by 28% in 13 healthy volunteers as well as decreasing the C_{max} and AUC [155]. Another investigator showed no effect on ciprofloxacin absorption with concomitant enteral feeds (Osmolite®) through a nasogastric tube in six healthy volunteers [156]. In another study, a jejunostomy tube, as opposed to a gastrostomy tube, produced a larger reduction in the bioavailability of ciprofloxacin [157].

The effect of enteral feeding on the bioavailability of moxifloxacin administered via nasogastric tube was evaluated in 12 healthy volunteers [158]. Enteral feed (Isosource® Energy) was administered for 30 min prior to the administration of moxifloxacin and immediately resumed after administration for another 2 h. There was no clinically relevant change in the rate or extent of absorption of moxifloxacin.

Enteral feeds contain various cations that may affect the quinolones to different extents [159]. While not contraindicated, it is prudent to avoid the simultaneous administration of enteral feeds and quinolones to assure adequate absorption. It is recommended to hold enteral feeding for 2 h before and after administration of quinolones [160].

4.4.6 Miscellaneous Antibiotics

4.4.6.1 Nitrofurantoin

Food tends to enhance the absorption of nitrofurantoin [161–163]. The increased dissolution time resulting from coadministration of food with nitrofurantoin has been hypothesized as the mechanism behind this increased absorption. Interestingly, food tends to have more of an effect on the urinary levels of nitrofurantoin than on the corresponding serum levels. An explanation for this phenomenon is that food increases the fraction of drug excreted by potentially saturating the metabolic pathway in kidney.

4.4.6.2 Nitroimidazoles

The absorption of metronidazole is delayed but not reduced by the presence of food [40]. In a study of ten healthy volunteers given a single dose of metronidazole with or without food, only slight interindividual variation in absorption was observed.

Tinidazole is a second-generation nitroimidazole approved by the FDA for the treatment of bacterial vaginosis (non-pregnant, adult women), trichomoniasis (adults) and for the treatment of giardiasis, intestinal amebiasis and amebic liver abscess in adults and children more than 3 years of age. Administration of tinidazole tablets with food resulted in a delay in t_{max} of ~2 h and a decrease in C_{max} of ~10%, with no effect on AUC. The manufacturer recommends taking tinidazole with food to minimize gastrointestinal side effects [164].

Metronidazole has been implicated with a disulfiram-like reaction when given with alcohol. Although not specifically studied, the manufacturer of tinidazole recommends avoiding alcohol during treatment and for 3 days afterward similar to metronidazole. Refer to the end of this chapter for a full description of disulfiram-like reactions with anti-infectives.

4.4.6.3 Ketolides

Telithromycin (Ketek®) is the first ketolide, a new class of antibacterial agents structurally related to the macrolides. Unlike erythromycin, telithromycin is acid-stable and can be taken orally while being protected from gastric acid [165]. The effect of a standard high-fat breakfast on the bioavailability of a single 800 mg dose of telithromycin (2×400 mg tablets) was assessed in 18 healthy male volunteers [26]. In this study, the C_{max} and AUC of telithromycin were unaffected by food intake, therefore telithromycin can be administered without regard to meals.

Telithromycin is a substrate of CYP3A4 and P-glycoprotein. The administration of grapefruit juice did not affect the pharmacokinetics of telithromycin in 15 healthy volunteers. This is likely explained by the fact that the majority of telithromycin first-pass metabolism occurs in the liver and grapefruit juice selectively inhibits intestinal CYP3A4 [166, 167].

In January 2006, three case reports of hepatoxicity thought to be secondary to telithromycin were reported in the literature: one case required liver transplantation and one of the cases resulted in death [167]. The FDA issued a public health advisory statement warning health care providers to monitor patients receiving telithromycin for signs and symptoms of liver toxicity on the same day that these case reports were published [168]. In June 2006, changes were made to the product labeling which included a contraindication to therapy in patients with a history of hepatotoxicity associated with telithromycin or a macrolide antibiotic, additional warnings and precautions for hepatotoxicity, reports of hepatotoxicity from post-marketing adverse event reports, and information for patients about the potential for hepatotoxicity [169]. In February 2007, the FDA-approved indications for the use of telithromycin were reduced to community-acquired bacterial pneumonia only. Acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis were removed from the prescribing information because the FDA determined that the balance of benefits and risks no longer supported the approval for these indications. In addition, a black box warning was added to avoid the use of telithromycin

in patients with myasthenia gravis and the inclusion of a medication guide to be provided with each prescription dispensed [170]. Additional case reports of possible telithromycin-associated hepatotoxicity have also been reported in the literature [171, 172] and an *ad hoc* group with expertise in spontaneous adverse event reporting and experience evaluating drug-induced liver damage was formed to adjudicate case reports of liver injury associated with telithromycin [173]. There were 109 cases spontaneously reported to the FDA through the MedWatch system as of April 2006. After excluding cases characterized by minimal elevations of liver enzymes or insufficient clinical or laboratory information to allow assessment of causality there were 42 cases included in the *ad hoc* group review. The group concluded that based on spontaneous reporting, telithromycin is a rare cause of liver-induced injury with a distinctive clinical presentation (short onset time (median 10 days), abrupt onset of fever, abdominal pain, jaundice, and occasionally ascites) and associated with a high mortality rate.

4.4.6.4 Antihelmintics

A fatty meal significantly enhances absorption of albendazole compared to the fasted state [35, 175, 176]. The mean C_{max} was increased 6.5-fold and the AUC increased 9.5-fold in six healthy male subjects after the administration of a fatty meal [35]. Therefore, albendazole tablets are recommended to be administered with meals to enhance absorption.

Administration of ivermectin to healthy volunteers reported the absorption to be 2.5 times higher following a high-fat meal compared to the fasted state [36]. The manufacturer recommends that ivermectin be administered with water [177].

Food has also been reported to increase the bioavailability of praziquantel [37]; therefore, it should be administered with meals [178].

Literature reports suggest that co-administration of mebendazole with a fatty meal increases the peak concentrations and overall absorption [179, 180]. According to the package insert, approximately 98% of administered mebendazole is found in the feces as unchanged drug or a primary metabolite, however the manufacturer does not specifically address the effect of food on mebendazole absorption [181]. The manufacturer of thiabendazole (Mintezol®) recommends that it be administered after meals [182].

Compared to the fasting state, the administration of grapefruit juice enhanced the C_{max} and AUC of albendazole by 3.2-fold and 3.1-fold, respectively [37]. Praziquantel mean C_{max} and AUC were also increased by 1.62-fold and 1.9-fold, respectively, but with a large amount of interindividual variability [183].

4.4.6.5 Antimalarials

Food significantly increased the C_{max} and AUC of primaquine by 26% and 14%, respectively, when a 30 mg dose was administered to healthy volunteers [41]. The administration of half-concentrated grapefruit juice also increased the C_{max} and

AUC of primaquine, however large inter-subject variability was observed. Neither food nor grapefruit juice changed the C_{max} or AUC of the primary metabolite, carboxyprimaquine. The bioavailability of chloroquine was also improved in healthy volunteers by the administration of a meal [42]. Therefore, primaquine and chloroquine should be taken with food to minimize gastrointestinal upset and improve bioavailability.

Bioavailability of mefloquine is improved ~40% when administered with food [43], and the manufacturer recommends that it be taken immediately after a meal [184]. Pyrimethamine (Daraprim®) and sulfadoxine-pyrimethamine (Fansidar® tablets) should be administered after a meal [185, 186].

Food, especially fatty food, enhances the bioavailability of atovaquone by two- to three-fold. Atovaquone has very poor bioavailability, and therapeutic concentrations may not be achieved when it is taken while fasting. Thus, it is recommended that atovaquone always be taken with a meal or nutritional supplement with a moderate amount of fat [38, 174, 187]. Similarly, the combination of atovaquone and proguanil (Malarone® tablets) should also be administered with food [188]. Food enhances the absorption of artemether and lumefantrine (Coartem® tablets) [189]. In healthy volunteers, the relative bioavailability of artemether was increased between two- to three-fold, and that of lumefantrine 16-fold when Coartem® tablets were given after a high-fat meal compared to fasted conditions.

4.4.6.6 Clindamycin

Food does not affect the absorption of clindamycin granules or capsules [190, 191].

4.4.6.7 Linezolid

Linezolid is a novel oxazolidinone antibiotic that has activity against a variety of gram-positive bacteria. The absolute bioavailability of linezolid is approximately 100% [39, 192]. When administered with a high-fat meal (850 cal), linezolid required a slightly longer time to reach peak plasma concentrations than when given under fasting conditions. C_{max} was significantly lower following a high-fat meal compared to fasting. However, no difference was seen in mean AUC values under fasted and fed conditions. The effect of food on the bioavailability is considered minimal [39]. Linezolid is a weak, competitive (reversible) inhibitor of human monoamine oxidase-A [193]. When linezolid is administered at a clinically approved dose (600 mg twice daily) dietary restriction of tyramine containing foods is generally not necessary. However, patients should be advised to avoid consuming large amounts of foods with a high tyramine content (i.e., aged cheeses, fermented meats, sauerkraut, soy sauce, draught beers, and red wines) [194].

The manufacturers' dosing recommendations for miscellaneous antibiotics are shown in Table 4.8.

Table 4.8 Miscellaneous antibiotics

Generic	Brand	Company	Manufacturer recommendations
Sulfonamides and combinations			
Ethylsuccinate and sulfisoxazole	Pediazole suspension	Ross	Can be given without regard to meals.
Trimethoprim and sulfamethoxazole	Bactrim DS tablets	AR Scientific	Not stated.
	Bactrim tablets		Not stated.
	Septra DS tablets	Monarch	Not stated.
	Septra grape suspension	Monarch	Not stated.
	Septra suspension	Monarch	Not stated.
	Septra tablets	Monarch	Not stated.
	Sulfatrim	Actavis Mid Atlantic	Not stated.
Urinary anti-infectives and combinations			
Fosfomycin	Monurol sachet	Forest	Can be given without regard to meals.
Nitrofurantoin	Furadantin oral suspension	Sciele Pharma, Inc.	Should be taken with food to improve absorption and tolerance.
	Macrobid capsules	Proctor and Gamble	Should be taken with food to improve absorption and tolerance.
	Macrodantin capsules	Proctor and Gamble	Should be taken with food to improve absorption and tolerance.
Methenamine Hippurate	generic only	Sanofi-Aventis, Corepharma	Not stated.
Antihelmintics			
Albendazole	Albenza tablets	GlaxoSmithKline	Should be taken with food.
Ivermectin	Stromectol tablets	Merck	Should be taken with water.
Mebendazole	Vermox	Janssen	The tablet may be chewed, swallowed, or crushed and mixed with food.
Thiabendazole	Mintezol	Merck	Give after meals if possible.
Praziquantel	Biltricide tablets	Bayer	Should be taken with water during meals.

(continued)

Table 4.8 (continued)

Generic	Brand	Company	Manufacturer recommendations
Other			
Atovaquone	Mepron suspension	GlaxoSmithKline	Administer with meals.
Clindamycin	Cleocin capsules	Pfizer	To avoid the possibility of esophageal irritation, should be taken with a full glass of water.
	Cleocin pediatric granules oral solution	Pfizer	
Cycloserine	Seromycin puvules capsules	Eli Lilly and Co.	Not stated.
Dapsone	Dapsone tablets USP	Jacobus	Not stated.
Linezolid	Zyvox tablets, oral suspension	Pfizer	Can be given without regard to meals.
Telithromycin	Ketek	Sanofi-Aventis	Can be given without regard to meals.
Tinidazole	Tindamax	Mission Pharma	Should be taken with food to minimize the incidence of epigastric discomfort and other GI adverse reactions.
Vancomycin	Vancocin capsules	ViroPharma	Can be given without regard to meals.
Antimarlarials			
Artemether; lumefantrine	Coartem	Novartis	Should be taken with food.
Primaquine	generic	Sanofi-Aventis	Can be given without regard to meals.
Chloroquine	Aralen tablet	Sanofi-Aventis	Administer with food or milk.
Mefloquine	Generic, tablet	Various	Should not be taken on an empty stomach and should be administered with at least 240 mL of water.
Pyrimethamine	Daraprim	GlaxoSmithKline	Administer with food to minimize vomiting.
Pyrimethamine – sulfadoxine	Fansidar	Roche	Should be taken after a meal.

4.4.7 Antimycobacterials

Peak concentrations and the relative bioavailability of isoniazid decreased by 70% and 40% with the addition of food, respectively, which suggests that isoniazid always be given on an empty stomach [195]. However, the manufacturer claims that isoniazid can be given with food if stomach upset occurs. A more recent study in 14 healthy volunteers investigated the effect of a high-fat breakfast on the absorption of isoniazid [45]. Relative to fasting, the high-fat meal reduced C_{max} by 51%, doubled t_{max}, and reduced AUC by 12% [45]. Because isoniazid is a weak monoamine oxidase inhibitor, several case reports have described adverse reactions in patients taking isoniazid who have ingested foods high in monoamines (e.g., tyramine) [196]. Flushing of the arms, face, and upper body were observed in patients after ingestion of cheese or red wine during isoniazid therapy [197–199]. Other possible symptoms include palpitations, headache, and mild increases in systolic blood pressure. Isoniazid is also an inhibitor of histaminase and at least 30 cases of adverse reactions after ingestion of fish with high histamine contents (e.g., tuna, mackerel, salmon, skipjack) has been reported in patients taking isoniazid [196]. Patients should be cautioned about the potential for adverse reactions with certain cheeses, red wine, and fish with high histamine content while taking isoniazid.

In a normal healthy-volunteer study performed in the 1970s, the coadministration with food caused a 25% reduction in the C_{max} and urinary excretion of rifampicin [200]. In a more recent analysis with 14 normal healthy volunteers, the addition of a high-fat meal reduced the C_{max} of rifampin by 36% and the overall AUC by 6% [48]. An aluminum–magnesium antacid had no effect on the bioavailability of rifampin. Thus, rifampin should be taken on an empty stomach whenever possible, but may be taken with food if stomach upset occurs.

The effect of a high-fat meal on the pharmacokinetics of rifabutin was studied in 12 healthy male volunteers [47]. Although a delay was seen in the t_{max} (5.4 vs. 3.0 h), little effect was seen with the addition of food.

A standardized breakfast produced little to no effect on the mean AUC of ethambutol in 11 normal healthy volunteers [201]. A subsequent study in 14 male and female volunteers showed similar results with the coadministration of a high-fat meal with ethambutol [44]. However, the coadministration with an aluminum–magnesium antacid caused a 29% decrease in the C_{max} and a 10% decrease in AUC. The authors of this paper suggested that antacids should be avoided near the time of ethambutol dosing.

The effect of a high-fat meal on the pharmacokinetics of pyrazinamide was studied in 14 healthy volunteers [46]. A high-fat meal or an aluminum–magnesium antacid had minimal effect on the absorption of pyrazinamide. The manufacturers' dosing recommendations for antimycobacterial antibiotics are shown in Table 4.9.

Table 4.9 Antimycobacterials

Generic	Brand	Company	Manufacturer recommendations
Ethambutol	Myambutol tablets	X-Gen	Can be given without regard to meals.
Rifabutin	Mycobutin capsules	Pharmacia and Upjohn	May be taken with meals if GI upset occurs.
Aminosalicylic acid	Paser granules	Jacobus	Sprinkle on apple sauce or yogurt or by swirling in the glass to suspend the granules in an acidic drink such as tomato or orange juice.
Pyrazinamide	Pyrazinamide tablets	Versa Pharma	Not stated.
Rifampin	Rifadin capsules	Aventis	Take on empty stomach, either 1 h before or 2 h after a meal, with a full glass of water. Absorption reduced by 30% with food.
Rifampin	Rimactane capsules	Novartis	Take 1 h before or 2 h after a meal.
Rifampin-isoniazid	Rifamate capsules	Hoechst Marion Roussell	Administer 1 h before or 1 h after meals.
Cycloserine	Seromycin capsules	Eli Lilly Co.	Not stated.
Ethionamide	Trecator-SC tablets	Wyeth	May be administered without regard to timing of meals. Best to administer at mealtimes to avoid GI upset.
Isoniazid	Generic only		Should not be administered with food.
Rifapentine	Prifitin tablets	Aventis	Administer with food for those patients with propensity to nausea, vomiting or GI upset.

4.4.8 Antifungals

4.4.8.1 Azole Antifungals

A number of healthy-volunteer studies have investigated the influence of food on the pharmacokinetics of ketoconazole, with conflicting results [52, 202–204].

A crossover study of ten volunteers showed a 55–60% decrease in C_{max} and AUC as well as a lengthened t_{max} when 200 mg of ketoconazole were given immediately after a low-fat breakfast [52]. Another study in 18 volunteers investigated the influence of a high-fat breakfast on the pharmacokinetics of ketoconazole over a wider dosing range (200–800 mg) [202]. This study determined that food did not reduce AUC or C_{max} but did tend to lengthen t_{max}. At the 400- and 600-mg dosing regimens, there was a trend toward increased absorption that was not apparent at the 200- or

800-mg dosing regimens. Finally, a third study of 12 volunteers showed that a high-fat meal significantly prolonged t_{max} and a high-carbohydrate meal significantly decreased C_{max} [203]. There was a nonstatistically significant trend toward increased AUC values with the high-fat meal and decreased AUC values with the high-carbohydrate meals. The manufacturer recommends that ketoconazole be given with food, which appears reasonable given the conflicting results from pharmacokinetic studies.

The influence of a low-fat (1,000-kJ) and a high-fat (3,600-kJ) meal on the pharmacokinetics of 100 mg of fluconazole and 100 mg of itraconazole was investigated in 24 healthy volunteers [51]. The C_{max}, AUC, and t_{max} of fluconazole were not significantly affected between test meals when compared to fasting. In contrast, the plasma AUC and C_{max} of itraconazole were significantly increased with the two test meals versus fasting. The AUC of itraconazole when given on an empty stomach was approximately 40% lower than when given with a high-fat meal. Similar results were seen when itraconazole was given to patients with superficial fungal infections [205]. The effect of food on a 200-mg oral solution of itraconazole was studied in 30 healthy male volunteers [50]. Unlike studies with itraconazole capsules, the C_{max} and AUC decreased by 44 and 30%, respectively, when given with a high-fat meal. Thus, itraconazole capsules should be given with food, while the oral solution should be given on an empty stomach.

The effect of cola beverages on the absorption of 100- and 200-mg doses of itraconazole has been assessed in two separate healthy volunteer studies [206, 207]. Results from these studies showed that the addition of a cola product could increase the AUC and C_{max} of itraconazole by approximately 100%. Thus, the addition of an acidic beverage may be an option to increase absorption of itraconazole, especially in patients who are hypochlorhydric or who are taking gastric acid suppressants.

The effect of grapefruit juice on the pharmacokinetics of itraconazole capsules has been evaluated in healthy volunteers. In one study, single-strength grapefruit juice had no effect on the pharmacokinetics of a 100 mg dose itraconazole [208]. In the second study [209], administration of double-strength grapefruit juice (concentrated with half the recommended amount of water) resulted in a decrease in the mean $AUC_{0–48}$ of itraconazole by 43% and a decrease in the mean $AUC_{0–72}$ of the hydroxy-metabolite by 47% after administration of a 200 mg dose. The mechanism by which double concentrated grapefruit juice reduces the absorption of itraconazole capsules is unknown, but the authors suggest a number of possibilities including a reduction in duodenal pH causing an increase in the amount of ionized itraconazole, increased intestinal P-gp mediated efflux of itraconazole, decreased intestinal CYP3A4 expression, a delay in gastric emptying, and interindividual differences in intestinal CYP3A4 and P-gp content between study subjects [209].

Repeated administration of single-strength grapefruit juice with itraconazole oral solution in healthy volunteers increased the $AUC_{0–48}$ and $AUC_{0\text{-inf}}$ of itraconazole by 15.8% and 19.5%, respectively, with no change in the exposure to the hydroxy-metabolite. These findings suggest inhibition of intestinal CYP3A4 [210].

The effect of a high-fat breakfast on the pharmacokinetics of voriconazole was evaluated in 12 healthy male subjects [54]. At steady-state (day 7), the bioavailability of voriconazole was reduced by approximately 22% when taken with food compared

to fasting. The rate of absorption was also significantly delayed by administering voriconazole with food. Therefore, voriconazole tablets should be taken at least 1 h before or 1 h after a meal.

Posaconazole is a lipophilic second-generation antifungal triazole with a similar molecular structure to that of itraconazole. Following the administration of a single 200 mg dose in 20 healthy male volunteers, the AUC and C_{max} of posaconazole were approximately four times higher when administered with a high fat meal (841 cal, 52% fat) and approximately three times higher when administered with a nonfat meal (461 cal, 0% fat) when compared to the fasted state [53] The effect of administration of a nutritional supplement (Boost Plus) on posaconazole pharmacokinetics was evaluated in 24 healthy volunteers [211]. Each subject received a single 400 mg dose of posaconazole in combination with 8 fluid ounces of Boost Plus (360 cal, 16% protein, 34% fat, and 50% carbohydrates) and a single 400 mg dose after an overnight fast. Administration with the nutritional supplement increased the C_{max} and AUC_{0-72} ~3.4- and ~2.6-fold, respectively. Another study evaluated the effect of varying amounts of a nutritional supplement on posaconazole bioavailability in 30 healthy volunteers, to determine if an amount less than 8 oz would also be effective in enhancing absorption [212]. Following administration of a single 400 mg dose, posaconazole bioavailability increased almost linearly with increasing amounts of Boost Plus. The AUC of posaconazole was 35% (fasting), 48% (1 oz), 60% (2 oz), and 77% (4 oz) compared to the AUC achieved with 8 oz of Boost Plus. In this study the AUC and C_{max} of posaconazole increased 2.9- and 3.5-fold, respectively, when given with 8 oz of Boost Plus relative to the fasting state. Alterations in gastric pH are likely to occur in the types of patients who require antifungal therapy for invasive fungal infections. A four-part, randomized, crossover study in healthy volunteers evaluated the effect of gastric pH, dosing frequency and prandial state, food consumption timing, and gastric motility on the absorption of posaconazole [213]. Compared to a fasting state, the administration of posaconazole with an acidic carbonated beverage (to mimic a low pH environment) increased the mean C_{max} and AUC by 92% and 70%, respectively. The administration of posaconazole under increased gastric pH conditions (achieved by coadminstration with esomeprazole) decreased the level of absorption (C_{max} and AUC decreased by 46% and 32%, respectively). The finding that posaconazole absorption is impacted by differences in gastric pH differs from an earlier study which reported that the administration of a 200 mg dose of posaconazole with an antacid (maximum-strength Mylanta) caused a clinically insignificant increase in C_{max} and AUC (7% and 15%, respectively) [214]. The authors suggest that differences in results may be because the earlier study utilized a tablet formulation and not the currently marketed suspension. It may also be explained by differences in acid suppression between an antacid and a proton pump inhibitor. Antacids typically do not raise gastric pH above 4 or 5 and have a duration of ~3 h compared to a proton pump inhibitor like esomeprozole which causes a mean gastric pH of 4.9 and maintains a pH above 4 for ~16.8 h [212]. This study also confirmed previous findings that posaconazole administration during or immediately after a meal or nutritional supplement provide larger increases in AUC than that observed by administration before a meal and that this enhanced absorption

is likely the result of improved solubility rather than a delay in gastric emptying. The authors conclude that strategies for optimizing the absorption of posaconazole in critically ill patients include administration with or immediately after a high-fat meal or nutritional supplement, administration with a carbonated beverage, dividing the total daily dose, and avoiding proton pump inhibitors in patients likely to experience decreased absorption.

In 16 healthy adult volunteers who received a single 400 mg dose of posaconazole suspension 5–10 min after receiving a liquid nutritional supplement, administration via nasogastric tube resulted in C_{max} and AUC values ~20% lower than those observed after oral administration [213]. The reason for lower absorption values after nasogastric tube route is unknown. The authors suggest, that nasogastric route may still provide reasonable exposure in patients unable to take oral therapy but utilization of strategies to improve absorption and obtaining posaconazole concentrations to verify adequate exposure may be warranted.

4.4.8.2 Griseofulvin

The effect of food on the pharmacokinetics of microsized and ultramicrosized griseofulvin was studied in nonfasting volunteers [49]. The results showed similar results between the two products when given with food. A study from the early 1960s showed that serum griseofulvin concentrations were higher when given with a high-fat meal, and thus it is recommended that griseofulvin be given with food (especially a high-fat meal) [215].The manufacturers' dosing recommendations for antifungal agents are shown in Table 4.10.

4.4.9 HIV Medications

4.4.9.1 Nucleoside Reverse Transcriptase Inhibitors

Didanosine is variably absorbed after oral administration due to its poor solubility at low pH, with bioavailability ranging from 25% to 43% [216, 217]. Acid-catalyzed hydrolysis results in significant degradation of the drug, which was slightly overcome by the buffered didanosine formulation [218]. Food alters the absolute bioavailability of didanosine by approximately 50%, most likely due to increased hydrolysis at lower pH and delayed gastric emptying [60]. In healthy volunteers, and in subjects infected with HIV, the AUC is equivalent for didanosine administered as the enteric-coated formulation (Videx® EC) relative to a buffered tablet formulation [219]. The effect of food and timing of meals on the bioavailability of didanosine from encapsulated enteric-coated beads was evaluated in healthy subjects [61]. Concomitant administration with a high-fat (757 cal) or light meal (373 cal) decreased the rate of absorption. Regardless of the caloric content of the meal, the extent of the absorption of didanosine was reduced to a similar degree with a high-fat meal, light meal,

Table 4.10 Antifungals

Generic	Brand	Company	Manufacturer recommendations
Fluconazole	Diflucan tablets	Pfizer	Not stated.
Fluconazole	Diflucan powder, for oral suspension	Pfizer	Not stated.
Itraconazole	Sporanox capsules	Janssen	Should be taken with a full meal to ensure maximal absorption.
Itraconazole	Sporanox oral solution	Janssen	If possible, do not take with food.
Ketoconazole	Nizoral tablets	Mutual Pharmaceuticals	Administration with a meal may decrease absorption.
Ultramicrosize crystals of griseofulvin,	Gris-PEG tablets	Pendinol Pharma	Not stated.
Griseofulvin microsize	Grifulvin V tablet	Ortho	Better blood levels can probably be attained in most patients if the tablets are administered after a meal with a high fat content.
Posaconazole	Noxafil Powder for oral suspension	Schering Corporation	Administer with a full meal or liquid nutritional supplement.
Terbinafine	Lamisil tablets	Novartis	An increase in the AUC of less than 20% is observed when administered with food.
	Lamisil granules	Novartis	Should be taken with food.
Voriconazole	Vfend tablets	Roerig	Should be taken at least 1 h before or 1 h after a meal.
	Vfend powder for oral suspension	Roerig	Should be taken at least 1 h before or 1 h after a meal.

yogurt, and applesauce. Administering the encapsulated enteric-coated beads 1.5, 2, or 3 h before a meal results in similar absorption to those seen under fasting conditions. The overall reduction in AUC is approximately 20–25% when didandosine is administered with food. Although this appears to be a moderate reduction it is recommended to administer this formulation on an empty stomach [220].

Zidovudine is fairly well absorbed after oral administration, with a bioavailability average of between 60% and 70% [221]. However, considerable between-patient variability does exist, and the bioavailability can range from 40% to 100% [224]. Several studies have examined the effect of certain types of food on zidovudine absorption. Overall, food consumption (especially high-fat meals) tends to decrease the rate but not the extent of absorption of zidovudine [223, 224]. Another study investigated the pharmacokinetics of zidovudine in 13 patients with acquired immunodeficiency syndrome (AIDS) who were either fasting or taking a standard breakfast. The mean AUC in the fed state was 24% lower than the fasted AUC and demonstrated more interpatient variability [225]. In a study by Shelton et al [64],

a high-fat breakfast significantly reduced the C_{max} of zidovudine, but did not significantly affect the extent of absorption (AUC). Previous studies sampled blood for zidovudine concentrations for 4–6 h post-dose [223, 225]. The authors concluded that sample collection less than 10 h may not have been adequate to determine the full effect of food on zidovudine pharmacokinetics.

The administration of lamivudine with a standard breakfast (55% fat, 20% carbohydrates, 13% proteins) significantly increased t_{max} and lowered C_{max} but had no significant affect on the extent of absorption (AUC) [226]. Thus, lamivudine can be taken without regard to meals. Administration with meals, however, may decrease the likelihood of gastrointestinal upset. Administration of a high-fat breakfast (1,000 kcal) did not affect the extent of absorption of lamivudine or zidovudine from the combined tablet, Combivir® [62]. Food slowed the rate of absorption, delaying the t_{max} and decreasing the C_{max} of lamivudine and zidovudine, but these changes were not considered clinically significant.

The absorption of stavudine is not affected by food and therefore it can be taken without regard to meals [222, 227]. When single doses of abacavir were taken with food, the C_{max} was reduced by 35% and the AUC by 5% [228]. This was not considered clinically significant, and abacavir can be taken without regard to meals. Ethanol decreases the elimination of abacavir. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC and a 26% increase in abacavir half-life [56]. The extent of absorption of Trizivir® tablets (abacavir, lamivudine, and zidovudine) is not affected by the administration of a meal and this formulation can be given with or without food [229, 230].

Emtricitabine systemic exposure (AUC) was not affected by the administration of a high-fat meal (1,000 kcal) and the C_{max} was reduced by 29% compared to the fasting state [231]. Following a high-fat meal (700–1,000 kcal) the AUC of tenofovir increased by approximately 40% and the C_{max} was increased approximately 14%. Administration with a light meal does not appear to significantly affect the pharmacokinetics of tenofovir [232, 233]. Thus, emtricitabine and tenofovir can both be administered with or without food. Truvada® tablets, the combination of emtricitabine and tenofovir, may also be taken without regard to meals [234].

4.4.9.2 Non-Nucleoside Reverse Transcriptase Inhibitors

A single-dose study of delavirdine showed an approximate 30% reduction in AUC when delavirdine was given with food [55]. During steady-state dosing, delavirdine was not significantly affected by the presence of food, although the t_{max} was delayed. Importantly, trough concentrations of the drug were similar in fasted versus nonfasted individuals [55, 235]. Thus, delavirdine can be taken without regard to meals.

When efavirenz capsules were administered with a high-fat meal (894 kcal) or a reduced fat/normal caloric meal (440 kcal) the AUC was increased by 22% and 17% and the C_{max} was increased by 39% and 51%, respectively, when compared to fasting. Administration of a 600 mg efavirenz tablet with a high-fat meal (1,000 kcal) caused a 28% increase in AUC and a 79% increase in C_{max} relative to fasting conditions.

To avoid an increase in the frequency of adverse events, it is recommended that efavirenz be administered on an empty stomach, preferably at bedtime [236]. The effect of food on the combination product Atripla® (efavirenz, tenofovir, and emtricitabine) has not been studied, however this formulation should also be administered on an empty stomach, preferably at bedtime to minimize adverse effects of efavirenz [237].

Absorption of nevirapine is not affected by food, and thus the drug can be taken without regard to meals [227]. The effect of various food compositions on the pharmacokinetics of etravirine (Intelence®) was evaluated in 12 healthy male volunteers [57] Administration of etravirine in a fasted state reduced the AUC by ~50% when compared to dosing after a standard breakfast. The authors of this study concluded that the exposure observed after a standard breakfast versus other types of food intake (high-fat, enhanced-fiber, or light breakfast) were similar and any differences observed were not clinically relevant. Therefore, etravirine should be administered after a meal to improve absorption [238].

4.4.9.3 Protease Inhibitors

Indinavir is known to be well absorbed after oral administration [239], and the absolute bioavailability is approximately 65% [240]. Eight healthy volunteers received indinavir with or without a high-fat meal consisting of eggs, toast, butter, bacon, whole milk, and hash browns [69]. The high-fat meal caused a reduction in the C_{max} and AUC by 84% and 77%, respectively. A similar study in 12 healthy volunteers investigated the influence of various low-fat meals on the pharmacokinetics of indinavir. In this study, the meal consisted of toast, jelly, apple juice, coffee, skim milk, and sugar; or cornflakes, sugar, and skim milk. These low-fat meals caused no significant reduction in the C_{max} or AUC. When indinavir is administered every 8 h, it should be taken on an empty stomach (1 h before or 2 h after meals). Administration with liquids such as skim milk, juice, coffee, tea, or a low-fat meal should not affect absorption. Indinavir should not be taken with or immediately after a heavy, high-fat meal (>2 g of fat) [227]. Indinavir is metabolized by CYP3A4 enzymes in the liver and gastrointestinal tract [241]. The addition of ritonavir, a known inhibitor of CYP3A4, at doses of 100–200 mg twice daily increases the AUC of indinavir by two- to three-fold, respectively, and is not affected by the administration of food [242]. This pharmacokinetic interaction is advantageous because it eliminates the indinavir food restrictions and allows for twice daily dosing [242]. Grapefruit juice and Seville orange juice have been used to evaluate the influence of intestinal CYP3A4 metabolism of CYP3A4 substrates [243, 244]. Grapefruit juice seems to have the greatest effect on CYP3A4 substrates that undergo significant first-pass metabolism, particularly when bioavailability is less than 20% [6]. The manufacturer reports a decrease in the indinavir AUC by 26% ± 18% after a single 400 mg dose was administered to healthy volunteers with 8 oz of single-strength grapefruit juice [243]. This is in contrast to two other studies where the administration of

grapefruit juice and Seville orange juice had no effect on the bioavailability of indinavir 800 mg doses in HIV infected patients and healthy volunteers [244, 245]. Although double-strength grapefruit juice and Seville orange juice significantly delayed the t_{max}, no other significant differences in pharmacokinetic parameters was observed. These results are consistent with findings that although indinavir undergoes extensive first-pass metabolism, intestinal metabolism accounts for less than 10% [240]. Grapefruit juice and Seville orange juice administration does not result in clinically significant changes in indinavir exposure [244, 245]. To reduce the chance of nephrolithiasis, indinavir should be administered with plenty of liquids, thus increasing the solubility of the drug in urine [69]. Anecdotally, up to four large glasses of water or other liquid per day are recommended.

Saquinavir hard-gel capsule (Invirase®) has historically been poorly absorbed due to high first-pass metabolism and incomplete absorption, with an oral bioavailability of approximately 4% following a high-fat breakfast [246, 247]. The mean AUC of saquinavir after a 600 mg dose (6 × 100 mg hard gel capsules) in healthy volunteers was increased from 24 ng·h/ml in the fasting state to 161 ng·h/ml when administered after a high fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1,006 kcal). Following administration of a higher calorie meal (943 kcal, 54 g fat), the C_{max} and AUC were on average twice of that observed after administration of a lower fat meal (355 kcal, 8 g fat). Therefore, saquinavir bioavailability is improved with concomitant food consumption, in particular if given with high-fat meals. Also, grapefruit juice increased the bioavailability and AUC by approximately twofold in eight healthy volunteers, which the authors attributed to inhibition of intestinal CYP3A4 [248]. A saquinavir soft-gel capsule (Fortovase®) was introduced in 1997. This formulation, which utilized the free base of saquinavir, as opposed to the mesylate salt, improved the bioavailability by more than 300% [227]. As with the hard-gel formulation, the bioavailability of the soft-gel formulation was also improved with the coadministration of food [227]. Unfortunately, this formulation had the disadvantage of a high pill burden (18 capsules per day) and poor gastrointestinal tolerability and it was removed from the US market in February 2006 [249]. In December 2004, a new tablet formulation of saquinavir was approved by the FDA. Similar bioavailability was achieved when Invirase® tablets (2 × 500 mg) and capsules (5 × 200 mg) were administered with ritonavir under fed conditions. When administered with ritonavir, the tablet formulation can be administered twice daily thus reducing the pill burden of saquinavir.

Thus, it is recommended that the hard-gel capsule and tablet formulations of saquinavir (Invirase®) be administered with ritonavir and taken within 2 h after a meal [247]. Since saquinavir is a substrate of CYP3A4 [250], the effect of grapefruit juice on its bioavailability was evaluated. The administration of grapefruit juice to healthy volunteers increased the mean AUC of saquinavir hard-gel capsules by 50%, with large interindividual variability [248].

Nelfinavir appears to be well absorbed after oral administration, with a mean oral bioavailability ranging from 14% to 47% in various animal studies [227, 251]. Bioavailability in humans has not been studied, but increased drug concentrations were noted when the drug was taken concurrently with food. Nelfinavir AUC values

in six fasted volunteers were 27–59% of those achieved in fed volunteers after administration of single doses of 400 and 800 mg [71]. Thus, it is recommended that nelfinavir be administered with food.

Administration of ritonavir with food appears to increase the absorption of the capsule while decreasing the absorption of the liquid formulation [227]. However, neither change is considered significant, and therefore it is recommended that ritonavir be given without regard to meals. However, it is most commonly administered with meals to improve gastrointestinal tolerability.

The soft-gel capsule of amprenavir can be taken without regard to meals; however, it should not be taken with a high-fat meal [252]. In a randomized, crossover study of 12 healthy subjects, the coadministration of grapefruit juice did not significantly affect the pharmacokinetics of a single dose of amprenavir [253].

To reduce the pill burden associated with amprenavir, a phosphate ester prodrug, fosamprenavir (Lexiva®), was approved in 2003. The administration of a high-fat meal had no influence on the AUC of fosamprenavir tablets compared to the fasting state and fosamprenavir tablets can be taken without regard to meals [68]. Administration of fosamprenavir oral suspension with a standard high-fat meal reduced the amprenavir C_{max} by 46% and the AUC by 28% compared to the fasted state. The manufacturer recommends that Lexiva® suspension be administered without food in adults and with food in pediatric patients [254].

The bioavailability of lopinavir/ritonavir capsules or liquid (Kaletra®) is increased with the administration of a moderate-to-high fat meal [255, 256]. A tablet formulation of lopinavir/ritonavir was approved in December 2005. The Kaletra® tablet formulation can be administered without regard to meals, does not have to be refrigerated, and reduces the pill burden from three capsules twice daily to two tablets twice daily [255].

There is a clinically significant increase in the absorption of atazanavir capsules (Reyataz®) when administered with food. After a single 400 mg dose, the AUC of atazanavir was increased by 35% with a light meal and by 70% with a high-fat meal [257, 258]. The manufacturer recommends that atazanavir capsules be administered with food [259]

Tipranavir (Aptivus®) is a P-gp substrate, a weak P-gp inhibitor, and a potent P-gp inducer. As a result, tipranavir must be administered with ritonavir to achieve effective tipranavir plasma concentrations. When tipranavir capsules or solution are co-administered with ritonavir capsules, food has no clinically significant effect on the C_{max} our AUC compared to the fasted state. The effect of food when tipranavir is co-administered with ritonavir tablets has not been studies. Tipranavir capsules or solution taken with ritonavir capsules or solution can be taken without regard to meals, while tipranavir co-administered with ritonavir tablets must be taken with meals [260].

The effect of various meal types on the pharmacokinetics of darunavir (Prezista®) in combination with ritonavir was evaluated in 24 healthy volunteers [67]. Compared to the fasted state, the C_{max} and AUC of darunavir were ~30% higher when administered with food. Darunavir exposure was comparable regardless of the type of meal administered (standard breakfast, high-fat breakfast, nutritional protein drink, or croissant with coffee).

4.4.9.4 Integrase Inhibitors

The effect of a low-, moderate-, and high-fat meal on steady-state raltegravir (Isentress®) pharmacokinetics was assessed in 20 healthy volunteers [74]. When administered with a low-fat meal (~300 kcal, 7% fat), the AUC and C_{max} were both reduced by ~50%. A moderate-fat meal (~600 kcal, 31% fat) had a minimal effect on raltegravir absorption (AUC and C_{max} increased by 13% and 5%, respectively). A high-fat meal (~825 kcal, 57% fat) increased AUC and C_{max} by almost twofold. Because of the considerable inter-subject variability observed with all meal types, the modest magnitude of the varying effects of food on absorption, and the fact that raltegravir was administered without regard to meals in the pivotal safety and efficacy studies in HIV-1-infected patients, the authors conclude that the pharmacokinetic differences observed with various meals are not of clinical importance and support the current recommendation that raltegravir can be administered with or without food [261].

4.4.9.5 Entry Inhibitors

In a phase 1 food effect study, a high-fat meal food reduced the exposure of maraviroc (Selzentry®) by ~33%, primarily by reduction of C_{max}. The effect of food was also assessed in a 10-day Phase 2a study to determine if these effects translated into an effect on antiviral activity. The results of this study showed, that when administered 150 mg twice daily, food reduced the C_{max} and AUC of maraviroc by ~60% and 50%, respectively. However, there was little effect of food on the short-term antiviral activity (change from baseline in viral load log10 copies/mL) of maraviroc and a −0.103 (90% CI −0.390, 0.185) difference between maraviroc 150 mg fasted and fed treatment groups on Day 11. Therefore, there were no food restrictions in the Phase 3 safety and efficacy studies [262].

The manufacturers' dosing recommendations for HIV antiretrovirals antibiotics are shown in Table 4.11.

4.4.10 Non-HIV Antivirals

The effect of a high-fat breakfast on the relative bioavailability of 1,000 mg of oral ganciclovir every 8 h was assessed in 20 HIV-positive patients who were seropositive for cytomegalovirus. C_{max} and AUC were significantly increased, by 15% and 22%, respectively, with the presence of food, and it is recommended that ganciclovir be taken with food [79]. Because of the low bioavailability of ganciclovir, a prodrug has been developed, valganciclovir. The absolute bioavailability of oral valganciclovir is approximately tenfold higher than oral ganciclovir [263, 264]. Compared to the fasted state, the administration of valganciclovir with a standard breakfast increased the AUC by 23–57% depending on the dose administered [78]. Similar to oral ganciclovir, valganciclovir should be taken with food.

Table 4.11 HIV antiretrovirals

Generic	Brand	Company	Manufacturer recommendations
Non-nucleoside reverse transcriptase inhibitors			
Delavirdine	Rescriptor tablets	Agouron	Can be given without regard to meals.
Etravirine	Intelence tablets	Tibotec Therapeutics	Should be taken following a meal.
Efavirenz	Sustiva capsules, tablets	Bristol-Myers Squibb	Should be taken on an empty stomach, preferably at bedtime.
Nevirapine	Viramune tablets and oral suspension	Roxane	Can be given without regard to meals.
Nucleoside reverse transcriptase inhibitors			
Abacavir	Ziagen tablets and oral solution	GlaxoSmithKline	Can be given without regard to meals.
Abacavir/ lamivudine/ zidovudine	Trizivir tablets	GlaxoSmithKline	Can be given without regard to meals.
Didanosine	Videx powder for oral solutions	Bristol-Myers Squibb	Should be taken on an empty stomach, at least 30 min before or 2 h after eating.
	Videx EC capsules	Bristol-Myers Squibb	Should be taken on an empty stomach, at least 30 min before or 2 h after eating.
Emtricitabine	Emtriva capsules and oral solution	Gilead Sciences	Can be given without regard to meals.
Emtricitabine/tenofovir disoproxil fumarate	Truvada tablet	Gilead Sciences	Can be given without regard to meals.
Emtricitabline/tenofir/efavirenz	Atripla tablet	Gilead Sciences	Should be taken on empty stomach, preferably at bedtime.
Lamivudine	Epivir oral solution, tablets	GlaxoSmithKline	Can be given without regard to meals.
Lamivudine/ Zidovudine	Combivir tablets	GlaxoSmithKline	Can be given without regard to meals.
Lamivudine/abacavir	Epzicom tablet	GlaxoSmithKline	Can be given without regard to meals
Stavudine	Zerit capsules, powder for oral solution	Bristol-Myers Squibb	Can be given without regard to meals.
Zidovudine	Retrovir capsules, syrup, tablet	GlaxoSmithKline	May take with meals if GI upset occurs.

Nucleotide reverse transcriptase inhibitors			
Tenofovir	Viread tablets	Gilead Sciences	Can be given without regard to meals.
Protease inhibitors			
Amprenavir	Agenerase capsules and oral solution	GlaxoSmithKline	Can be taken without regard to meals, but should not be taken with a high-fat meal.
Atazanavir	Reyataz capsules	Bristol-Myers Squibb	Should be taken with food.
Darunavir	Prezista tablets	Centocor Ortho	Should be taken with food.
Fosamprenavir	Lexiva tablets	GlaxoSmithKline	Can be taken without regard to meals.
	Lexiva oral suspension	GlaxoSmithKline	Adults should take the suspension without food. Children should take the suspension with food.
Indinavir	Crixivan capsules	Merck	For optimal absorption, should be administered without food but with water 1 h before or 2 h after a meal.
Lopinavir/ritonavir	Kaletra capsules, oral solution	Abbott	Should be taken with food.
Lopinavir/ritonavir	Kaletra tablets	Abbott	Can be taken without regard to food.
Nelfinavir	Viracept tablets, powder	Pfizer	Should be taken with a meal.
Ritonavir	Norvir capsules, oral solution	Abbott	Take with meals if possible.
Saquinavir	Invirase capsules	Roche	Take within 2 h after a full meal.
Tipranavir/ritonavir	Aptivus capsule, oral solution	Boehringer Ingelheim	Can be given without regard to meals.
Entry inhibitor			
Maraviroc	Selzentry tablets	Pfizer	Can be given without regard to meals.
Integrase inhibitor			
Raltegravir	Isentress tablets	Merck Sharp Dohme	Can be given without regard to meals.

Table 4.12 Non-HIV antivirals

Generic	Brand	Company	Manufacturer recommendations
Acyclovir	Zovirax capsules	GlaxoSmithKline, various	Can be given without regard to meals.
	Zovirax suspension	GlaxoSmithKline	Can be given without regard to meals.
	Zovirax tablets	GlaxoSmithKline	Can be given without regard to meals.
Entecavir	Baraclude tablets and oral solution	Bristol Myers Squibb	Should be administered on an empty stomach (at least 2 h after a meal or 2 h before the next meal).
Ganciclovir	Cytovene capsules	Roche	Administer with meals.
Famciclovir	Famvir tablets	Novartis	Can be given without regard to meals.
Valacyclovir	Valtrex caplets	Glaxo Wellcome	Can be given without regard to meals.
Valgancicolovir	Valcyte tablets, oral solution	Roche	Should be administered with food.
Amantadine	Symmetrel capsules	Endo labs	Not stated.
	Symmetrel syrup	Endo labs	Not stated.
Rimantadine	Flumadine syrup	Forest	Not stated.
	Flumadine tablets	Forest	Not stated.

The effect of food was evaluated in two separate studies involving healthy volunteers given 250 or 500 mg of famciclovir [265, 266]. Administration with food decreased the C_{max} by approximately 53% and lengthened the t_{max} by approximately 2 h. However, the AUC was unchanged in the fed-versus-fasting group and the authors hypothesized that famciclovir could be given without regard to meals. Likewise, valacyclovir and the prototype, acyclovir, can be given without regard to meals [267, 268]. Amantadine and rimantadine can also be taken without regard to meals [77, 269].

The manufacturers' dosing recommendations for non-HIV antivirals antibiotics are shown in Table 4.12.

4.5 Anti-Infectives and Disulfiram-Like Reactions

The drug disulfiram (Antabuse®) is a therapeutic option in the treatment of alcoholism that acts to deter further ingestion of alcohol [270]. It works by inhibition of the enzyme aldehyde [271, 272]. Disulfiram is a remarkably effective agent for inhibiting aldehyde dehydrogenase. Accumulation of acetaldehyde in the blood produces a complex of highly unpleasant symptoms referred to as a disulfiram reaction. Anecdotal reports have described local reactions in patients being treated with disulfiram after using a beer-containing shampoo or contact lens solution [273, 274].

Another case report describes a case of a local vaginal reaction while a women was undergoing disulfiram therapy after engaging in sexual intercourse with her husband, who had ingested a large amount of alcohol [275].

By the same mechanism, other compounds have been linked with causing a disulfiram-like reaction, and antibiotics are no exception. Cephalosporins, chloramphenicol, metronidazole, and other antibiotics have been associated with causing a disulfiram-like reaction. In general, these reactions are rare and spontaneously occurring [276]. Although all patients should be counseled and warned of this potential interaction, it appears that patients who chronically consume large amounts of alcohol may be at higher risk of developing these reactions, due to greater accumulation of acetaldehyde [276]. The likelihood of a reaction exists while the drug is still present in the body, and reactions have occurred with minimal amounts of alcohol up to a day after the last dose of an antibiotic [277]. Thus, in general it is recommended that patients abstain from alcohol during and for 2–3 days after therapy with any agents implicated in causing a disulfiram-like reaction.

4.5.1 Signs and Symptoms

Patients experiencing a disulfiram reaction usually develop symptoms 5–10 min after consuming ethanol, and the reaction, assuming that no further alcohol is consumed, usually lasts from 30 min up to several hours. In the majority of cases, symptoms are unpleasant but not life-threatening. However, a death has been reported that was attributed to a disulfiram-like reaction between alcohol and metronidazole [278].

Reactions caused by the co-ingestion of alcohol and the drug disulfiram are manifested clinically by nausea, facial flushing, headache, tachycardia, and hypotension [279, 280]. Disulfiram-like reactions caused by antibiotics present similarly [281]. Symptoms common to case reports describing a disulfiram-like reaction to antibiotics include tachycardia (up to 180 beats per minute), pronounced flushing of face and torso, and hypo- or hypertension. Headache, nausea, dizziness, and a feeling of enhanced intoxication are also common. Hypertension, as opposed to hypotension, which is normally seen with disulfiram reactions, is described in reactions with cephalosporins, especially moxalactam and cefoperazone, but this effect is not universal [282, 283]. It has been hypothesized that this dichotomy is caused by inhibition of norepinephrine production by a metabolite of disulfiram, an effect that is not produced by cephalosporins [284]. However, this hypothesis is challenged by the fact that the hypotensive effect is also seen with other antialcohol drugs such as cyanamide and coprine, which do not have an effect on norepinephrine.

4.5.2 Metronidazole

Disulfiram-like reactions and a decreased desire to consume alcoholic beverages have been described with metronidazole [285–287]. In fact, it was suggested at one time that

metronidazole may have a place in therapy as a preventative agent in the treatment of alcoholism [288, 289]. However, studies using metronidazole in the treatment of alcoholism showed only minor beneficial effects, and metronidazole is not considered a therapeutic option in this area. Studies investigating the mechanism of the alcohol–metronidazole interaction published during the 1960s suggested that metronidazole noncompetitively inhibited liver alcohol dehydrogenase [290]. However, other studies in rats demonstrated that metronidazole did not act as an inhibitor for alcohol dehydrogenase. Authors have speculated that the disulfiram-like reaction with metronidazole might be mediated by the central nervous system [291]. Although rare, patients should still be informed about the possible disulfiram-like reaction when metronidazole is combined with alcohol. The effect of alcohol and disulfuram were not specifically studied with another nitroimidazole, tinidazole (Tindamax®), however since adverse reactions have been reported with metronidazole the manufacturer recommends that patients avoid alcoholic beverages and preparations containing alcohol during therapy and for 3 days afterward. Likewise, tinidazole should not be administered to patients who have taken disulfuram within the last 2 weeks [164].

4.5.3 Cephalosporins

The majority of case reports and research involving disulfiram-like reactions and antimicrobials have focused on the cephalosporins and other beta-lactams. Anecdotal reports have described a disulfiram reaction with cefmenoxime, cefotetan, cefoperazone, cefamandole, and moxalactam after the ingestion of an alcoholic beverage [277, 290, 292–294]. Other reactions have occurred in patients prescribed alcohol-containing medicinals and antibiotics. A case report describes a hospitalized patient who was receiving moxalactam for presumed sepsis who had theophylline additionally prescribed for bronchospasm [295]. He received his dose of theophylline elixir (20% alcohol) and 30 min later became flushed and tremulous, hypotensive, and tachycardic. This reaction abated; however, the reaction reappeared when the patient was rechallenged with the theophylline elixir. His elixir was changed to tablets and he continued to receive moxalactam without further incidents. Another case report describes a similar incident in which the patient was receiving cefmenoxime and an alcohol-containing acetaminophen elixir [277].

A number of studies in animal models and healthy volunteers have attempted to elucidate the mechanism and magnitude of disulfiram-like reactions with the cephalosporins [279, 281, 296, 297]. In general, cephalosporins that have been implicated in causing a disulfiram-like reaction have in common a methyl-tetrazolethiol (MTT) side chain. Rats pretreated with beta-lactams containing the MTT side chain experienced decreased alcohol elimination rates as well as increased acetaldehyde concentrations [279, 296]. Those given beta-lactams without the MTT side chain showed no such effect.

Volunteer trials have studied the potential of moxalactam, cefpirome, cefonicid, ceftizoxime, and cefotetan to cause a disulfiram-like reaction when given with alcohol [280, 297–300]. Patients given cefpirome or ceftizoxime, which do not contain a MTT

side chain, and cefonicid, which contains methylsulphonic acid rather than a methyl group, displayed no signs or symptoms of a disulfiram-like reaction. No change in blood alcohol or aldehyde concentrations were observed in patients receiving cefpirome, ceftizoxime, or cefonicid. On the other hand, 5 of 8 and 2 of 10 volunteers given cefotetan or moxalactam, respectively, experienced a disulfiram-like reaction when combined with alcohol. Both these antibiotics contain the MTT side chain.

A hypothesis for the mechanism of this effect is that the MTT side chain becomes liberated from the rest of the cephalosporin molecule in vivo and is oxidized to a molecule that is structurally similar to disulfiram [281]. A study supporting this hypothesis demonstrated that the MTT side chain had no effect on the metabolizing capabilities of sheep liver cytoplasmic aldehyde dehydrogenase but that a metabolite of the side chain was a potent inactivator [281].

Thus, it appears that cephalosporins that contain the MTT side chain are at higher risk of precipitating a disulfiram-like reaction. Most case reports have involved patients receiving moxalactam, cefoperazone, and cefamondole; however, all cephalosporins with this side chain are likely to provide an increased risk [301]. All patients receiving these medications should be advised of the possibility of a disulfiram-like reaction. Chronic abusers of alcohol appear to be at the most risk of displaying a disulfiram-like reaction to these antibiotics, and an alternative agent may be prudent unless the patient can abstain from alcohol during therapy.

4.5.4 Other Antibiotics

Isolated case reports have described disulfiram-like reactions with trimethoprim-sulfamethoxazole, chloramphenicol, griseofulvin, or furazolidone when combined with alcohol [276, 302–304]. Although most of these reports hypothesized that the reaction was secondary to an accumulation of acetaldehyde, the exact mechanism is unknown.

4.5.5 Ritonavir Oral Solution

Ritonavir oral solution contains alcohol, and thus a potential interaction is possible when the solution is combined with disulfiram or anti-infectives associated with a disulfiram-like reaction [305]. It is advisable to avoid coadministration of disulfiram with ritonavir solution and to be aware of the potential interaction when ritonavir oral solution is co-prescribed with metronidazole or cephalosporins containing the MTT side chain.

References

1. Welling PG. The influence of food on the absorption of antimicrobial agents. J Antimicrob Chemother 1982;9:7–27.
2. Yamreudeewong W, Henann NE, Fazio A, Lower DL, Cassidy TG. Drug-food interactions in clinical practice. J Fam Prac 1995;40:376–384.

3. Singh BN. Effects of food on clinical pharmacokinetics. Clin Pharmacokinet 1999;37:213–255.
4. Krishnaswamy K. Drug metabolism and pharmacokinetics in malnourished children. Clin Pharmacokinet 1988;14:325–346.
5. Lown KS, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997;99:2545–2553.
6. Bailey DG, Malcolm J, Arnold O, et al. Grapefruit-juice-drug interactions. Br J Clin Pharmacol 1998;46:101–110.
7. Dresser GK, Bailey DG, Leake BF, et al. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. Clin Pharmacol Ther 2002;71:11–20.
8. Takanaga H, Ohnishi A, Matsuo H, et al. Inhibition of vinblastine efflux mediated by P-glycoprotein by grapefruit juice components in caco-2 cells. Biol Pharm Bull 1998;21:1062–1066.
9. Soldner A, Christians U, Susanto M, et al. Grapefruit juice activates P-glycoprotein-mediated drug transport. Pharm Res 1999;16:478–485.
10. Eshelman FN, Spyker DA. Pharmacokinetics of amoxicillin and ampicillin: crossover study of the effect of food. Antimicrob Agents Chemother 1978;14:539–543.
11. Staniforth DH, Lillystone RJ, Jackson D. Effect of food on the bioavailability and tolerance of clavulanic acid/amoxicillin combination. J Antimicrob Chemother 1982;10:131–139.
12. Lode H, Stahlmann R, Koepp P. Comparative pharmacokinetics of cephalexin, cefaclor, cefadroxil, and CGP 9000. Antimicrob Agents Chemother 1979;16:1–6.
13. Sourgens H, Derendorf H, Schifferer H. Pharmacokinetic profile of cefaclor. Int J Clin Pharm Ther 1997;35:374–380.
14. Barbhaiya RH, Shukla UA, Gleason CR, Shyu WC, Pittman KA. Comparison of the effects of food on the pharmacokinetics of cefprozil and cefaclor. Antimicrob Agents Chemother 1990;34:1210–1213.
15. Deppermann KM, Garbe C, Hasse K, Borner K, Keippe P, Lode H. Comparative pharmacokinetics of cefotiam hexetil, cefuroxime cefixime, cephalexin, and effect of H_2 blockers, standard breakfast and antacids on the bioavailability of cefuroxime hexetil [abstr 1223]. 29th ICAAC, 1989.
16. Nakashima M, Uematsu T, Takiguchi Y, Kanamaru M. Phase I study of cefixime, a new oral cephalosporin. J Clin Pharmacol 1987;27:425–431.
17. Li JT, Hou F, Lu H, et al. Phase I clinical trial of cefditoren pivoxil (ME 1207): pharmacokinetics in healthy volunteers. Drugs Exp Clin Res 1997;23:145–150.
18. Hughes GS, Heald DL, Barker KB, et al. The effects of gastric pH and food on the pharmacokinetics of a new oral cephalosporin, cefpodoxime proxetil. Clin Pharmacol Ther 1989;46:674–685.
19. Barr WH, Lin CC, Radwanski E, Lim J, Symchowicz S, Afrime M. The pharmacokinetics of ceftibuten in humans. Diagn Microbiol Infect Dis 1991;14:93–100.
20. Bechtol LD, Bessent CT, Perkal MB. The influence of food on the absorption of erythromycin esters and enteric-coated erythromycin in single-dose studies. Curr Ther Res 1979;25:618–625.
21. Welling PG, Huang G, Hewitt PF, Lyons LL. Bioavailability of erythromycin stearate: influence of food and fluid volume. J Pharm Sci 1978;67:764–766.
22. Malmborg AS. Effect of food on absorption of erythromycin. A study of two derivatives, the stearate and the base. J Antimicrob Chemother 1979;5:591–599.
23. Foulds G, Luke DR, Teng R, Willavize SA, Friedman H, Curatolo WJ. The absence of an effect of food on the bioavailability of azithromycin administered as tablets, sachet, and suspension. J Antimicrob Chemother 1996;37(suppl C):37–44.
24. Chu S-Y, Park Y, Locke C, et al. Drug-food interaction potential of clarithromycin, a new macrolide antimicrobial. J Clin Pharmacol 1992;32:32–36.
25. Guay DR, Gustavson LE, Devcich KJ, et al. Pharmacokinetics and tolerability of extended-release clarithromycin. Clin Ther 2001;23:566–577.
26. Ketek® (telithromycin) package insert. Sanofi-Aventis US LLC, Bridgewater NJ, February 2007.

27. Welling PG, Koch PA, Lau CC, Craig WA. Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects. Antimicrob Agents Chemother 1977;11:462–469.
28. Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride: effect of food, milk, and iron. J Am Acad Dermatol 1985;12(2 part 1):308–312.
29. Frost RW, Carlson JD, Dietz AJ Jr, Heyd A, Lettieri JT. Ciprofloxacin pharmacokinetics after a standard or high-fat/high- calcium breakfast. J Clin Pharmacol 1989;29:953–955.
30. Allen A, Bygate E, Clark D, et al. The effect of food on the bioavailability of oral gemifloxacin in healthy volunteers. Int J Antimicrob Agents 2000;16:45–50.
31. Lee LJ, Hafkin B, Lee ID, Hoh J, Dix R. Effects of food and sulcralfate on a single dose of 500 milligrams of levofloxacin in healthy subjects. Antimicrob Agents Chemother 1997;41:2196–2200.
32. Lettieri J, Vargas R, Agarwal V, et al. Effect of food on the pharmacokinetics of a single oral dose of moxifloxacin 400 mg in healthy male volunteers. Clin Pharmacokinet 2001:40 (suppl 1):19–25.
33. Leroy A, Borsa F, Humbert G, et al. The pharmacokinetics of ofloxacin in healthy male volunteers. Eur J Clin Pharmacol 1987;31:629,630.
34. Hoppu K, Tuomisto J, Koskimies O, Simell O. Food and guar decrease absorption of trimethoprim. Eur J Clin Pharmacol 1987;32:427–429.
35. Nagy J, Schipper HG, Koopmans RP, et al. Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability. Am J Trop Med Hyg 2002;66:260–263.
36. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmcol 2002;42:1122–1133.
37. Castro N, Medina R, Sotelo J, et al. Bioavailability of praziquantel increases with concomitant administration of food. Antimicrob Agents Chemother 2000;44:2903,2904.
38. Mepron (atovaquone) package insert. Glaxo Wellcome, Research Triangle Park, NC, 1998.
39. Welshman IR, Sisson TA, Jungbluth GL, et al. Linezolid absolute bioavailability and the effect of food on oral bioavailability. Biopharm Drug Dispos 2001;22:91–97.
40. Melander A, Kahlmeter G, Kamme C, Ursing B. Bioavailability of metronidazole in fasting and non-fasting healthy subjects and in patients with Crohn's disease. Eur J Clin Pharm 1977;12:69–72.
41. Cuong BT, Vinh VQ, Dai B, et al. Does gender, food, or grapefruit juice alter the pharmacokinetics of primaquine in healthy subjects? Br J Clin Pharmacol 2006;61:682–689.
42. Tupule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. Eur J Clin Pharmacol 1982;23:271–273.
43. Crevoisier C, Handschin J, Barré J, et al. Food increases the bioavailability of mefloquine. Eur J Clin Pharmacol 1997;53:135–139.
44. Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, Childs JM, Nix DE. Pharmacokinetics of ethambutol under fasting conditions with food and with antacids. Antimicrob Agents Chemother 1999;43:568–572.
45. Peloquin CA, Namdar R, Dodge AA, Nix DE. Pharmacokinetics of isoniazid under fasting conditions, with food and with antacids. Int J Tuberc Lung Dis 1999;3:703–710.
46. Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, James GT, Nix DE. Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. Pharmacotherapy 1998; 18:1205–1211.
47. Narang PK, Lewis RC, Bianchine JR. Rifabutin absorption in humans: relative bioavailability and food effect. Clin Pharmacol Ther 1992;52:335–341.
48. Peloquin CA, Namdar R, Singleton MD, Nix DE. Pharmacokinetics of rifampin under fasting conditions, with food, and with antacids. Chest 1999;115:12–18.
49. Bijanzadeh M, Mahmoudian M, Salehian P, et al. The bioavailability of griseofulvin from microsized and ultramicrosized tablets in non-fasting volunteers. Indian J Physiol Pharmacol 1990;34:157–161.
50. Barone JA, Moskovitz BL, Guarnieri J, et al. Food interaction and steady-state pharmacokinetics of intraconazole oral solution in healthy volunteers. Pharmacotherapy 1998;18:295–301.

51. Zimmerman T, Yeates RA, Laufen H, et al. Influence of concomitant food intake on the oral absorption of two triazole antifungal agents, itraconazole and fluconazole. Eur J Clin Pharmacol 1994;46:147–150.
52. Lelawongs P, Barone JA, Colaizzi JL, et al. Effect of food and gastric acidity on absorption of orally administered ketoconazole. Clin Pharm 1988;7:228–235.
53. Courtney R, Wexler D, Radwanski E, et. al. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. Br J Clinic Pharmacol 2004;57:218–222.
54. Purkins L, Wood N, Kleinermans D, et al. Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. Br J Clin Pharmacol 2003;56:17–23.
55. Morse GD, Fischl MA, Cox SR, Thompson L, Della-Coletta AA, Freimuth WW. Effect of food on the steady-state pharmacokinetics of delavirdine mesylate in HIV + patients [abstr]. Program Abstracts, 35th Interscience Conference in Antimicrob Agents and Chemotherapeutics (ICAAC), San Francisco, CA, September 17–20, 1995.
56. Hebel SK. Drugs Facts and Comparisons. St. Louis, MO; Facts and Comparisons, 2000.
57. Schöller-Gyüre M, Boffito M, Pozniak AL, et al. Effects of different meal compositions and fasted state on the oral bioavailability of etravirine. Pharmacotherapy 2008;28:1215–1222.
58. German P, Warren D, Wei L. et al. Effect of food on pharmacokinetics of elvitegravir, emtricitabine, tenofovir DF and the Pharmacoenhancer GS-9350 as a Fixed-Dose Combination Tablet. ICAAC Sept 11–15 2009 San Francisco.
59. Chittick GE, Gillotin C, McDowell JA, et al. Abacavir: absolute bioavailability, bioequivalence of three oral formulations, and effect of food. Pharmacotherapy 1999;19:932–942.
60. Shuy WC, Knupp CA, Pittman KA, Dunkle L, Barbhaiya RH. Food-induced reduction in bioavailability of didanosine. Clin Pharmacol Ther 1991;50:503–507.
61. Damle BD, Yan JH, Behr D, et al. Effect of food on the oral bioavailability of didanosine from encapsulated enteric-coated beads. J Clin Pharmacol 2002;42:417–425.
62. Moore KH, Shaw S, Laurent AL, et al. Lamivudine/zidovudine as a combined formulation tablet: bioequivalence compared with lamivudine and zidovudine administered concurrently and the effect of food on absorption. J Clin Pharmacol 1999;39:593–605.
63. Kaul S, Christofalo B, Raymond RH, Stewart MB, Macleod CM. Effect of food on the bioavailability of stavudine in subjects with human immunodeficiency virus infection. Antimicrob Agents Chemother 1998;42:2295–2298.
64. Shelton MJ, Portmore A, Blum MR, et al. Prolonged, but not diminished, zidovudine absorption induced by a high-fat breakfast. Pharmacotherapy 1994;14:671–677.
65. Viread®(tenofovir) package insert. Gilead Sciences, Inc, March 2010.
66. Nishiyama M, Koishi M, Fujioka M, et al. Phase I clinical trial with a novel protease inhibitor for HIV, KVX-478 in healthy male volunteers. Antiviral Res 1996;30:A35.
67. Sekar V, Kestens D, Spinosa-Guzman S, et al. The effect of different meal types on the pharmacokinetics of darunavir (TMC114)/ritonavir in HIV-negative healthy volunteers. J Clin. Pharmacol. 2007 Apr;47(4):479–84.
68. Falcoz C, Jenkins JM, Bye C, et al. Pharmacokinetics of GW433908, a prodrug of amprenavir, in healthy male volunteers. J Clin Pharamcol 2002;42:887–898.
69. Yeh KC, Deutsch PJ, Haddix H, et al. Single-dose pharmacokinetics of indinavir and the effect of food. Antimicrob Agents Chemother 1998;42:332–338.
70. Kaletra®(Lopinavir;Ritonavir) package insert. Abbott Laboratories, North Chicago, IL, April 2010.
71. Perry CM, Benfield P. Nelfinavir. Drugs 1997;54:81–87.
72. McEvoy GK. AHFS Drug Information. Bethesda, MD: American Society of Health System Pharmacists, 1999.
73. Selzentry®(maraviroc) package insert. Pfizer Labs, NY, NY, May 2010.
74. Brainard DM, Friedman EJ, Jin B, et al. Effect of low-, moderate-, and high-fat meals on raltegravir pharmacokinetics. J Clin Pharmacol 2011;51:943–950.
75. Baraclude®(entecavir) package insert. Bristol-Myers Squib Company, Princeton, NJ, Jung 2009.

76. Pue MA, Benet LZ. Pharmacokinetics of famciclovir in man. Antiviral Chemistry Chemother 1993;4(suppl 1):47–55.
77. Wills RJ, Rodriguez LC, Choma N, Oakes M. Influence of a meal on the bioavailability of rimantadine HCL. J Clin Pharmacol 1987;27:821–823.
78. Brown F, Banken L, Saywell K, et al. Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. Clin Pharmacokinet 1999;37:167–176.
79. Lavelle J, Follansbee S, Trapnell CB, et al. Effect of food on the relative bioavailability of oral ganciclovir. J Clin Pharmacol 1996;36:238–241.
80. Sommers DK, Van Wyk M, Moncrieff J, Schoeman HS. Influence of food and reduced gastric acidity on the bioavailability of bacampicillin and cefuroxime axetil. Br J Clin Pharm 1984;18:535–539.
81. Cronk GA, Wheatley WB, Fellers GF, Albright H. The relationship of food intake to the absorption of potassium alpha-phenoxyethyl penicillin and potassium phenoxymethyl penicillin from the gastrointestinal tract. Am J Med Sci 1960;240:219–225.
82. Ali HM, Farouk AM. The effect of Sudanese diet on the bioavailability of ampicillin. Int J Pharm 1980;6:301–306.
83. Neu HC. Antimicrobial activity and human pharmacology of amoxicillin. J Infect Dis 1974;129:S123–S131.
84. Moxatag®(amoxicillin) package insert. MiddleBrook Pharmaceuticals, Inc., Germantown, Maryland, Januarly 2008.
85. Augmentin tablets (amoxicillin/clavulanate potassium) package insert. GlaxoSmithKline, Research Triangle Park, NC, May 2002.
86. Augmentin suspension and chewable tablets (amoxicillin/clavulanate potassium) package insert. GlaxoSmithKline, Research Triangle Park, NC, January 2003.
87. Augmentin ES (amoxicillin/clavulanate potassium) package insert. GlaxoSmithKline, Research Triangle Park, NC, April 2003.
88. Augmentin XR (amoxicillin/clavulanate potassium) package insert. GlaxoSmithKline, Research Triangle Park, NC, November 2003.
89. Gower PE, Dash CH. Cephalexin: human studies of absorption and excretion of a new cephalosporin antibiotic. Br J Pharmacol 1969;37:738–747.
90. Tetzlaff TR, McCracken GH Jr, Thomas ML. Bioavailability of cephalexin in children: relationship to drug formulations and meals. J Pediatr 1978;92:292–294.
91. Glynne A, Goulbourn RA, Ryden R. A human pharmacology study of cefaclor. J Antimicrob Chemother 1978;4:343–348.
92. Cefaclor package insert. Eli Lilly and Company, Indianapolis, IN, 1998.
93. Oguma T, Yamada H, Sawaki M, Narita N. Pharmacokinetic analysis of the effects of different foods on absorption of cefaclor. Antimicrob Agents Chemother 1991;35:1729–1735.
94. Shukla UA, Pittman KA, Barbhaiya RH. Pharmacokinetic interactions of cefprozil with food, propantheline, metoclopramide, and probenecid in healthy volunteers. J Clin Pharmacol 1992;32:725–731.
95. Ginsburg CM, McCracken GH Jr, Petruska M, Olson K. Pharmacokinetics and bactericidal activity of cefuroxime axetil. Antimicrob Agents Chemother 1985;28:504–507.
96. Finn A, Straughn A, Meyer M, et al. Effect of dose and food on the bioavailability of cefuroxime axetil. Biopharm Drug Dispos 1987;8:519–526.
97. Fassbender M, Lode H, Schaberg T, Borner K, Koeppe P. Pharmacokinetics of new oral cephalosporins, including a new carbacephem. Clin Infect Dis 1993;16:646–653.
98. Borin MT, Driver MR, Forbes KK. Effect of timing of food on absorption of cefpodoxime proxetil. J Clin Pharmacol 1995;35:505–509.
99. Nakashima M, Uematsu T, Takiguchi Y, et al. Phase I clinical studies of 7432-S, a new oral cephalosporin: safety and pharmacokinetics. J Clin Pharmacol 1988;28:246–252.
100. Faulkner RD, Bohaychuk W, Haynes JD, et al. The pharmacokinetics of cefixime in the fasted and fed state. Eur J Clin Pharmacol 1988;34:525–528.

101. Omnicef (cefdinir) package insert. Abbott Laboratories, North Chicago, IL. October 2001.
102. Guay DRP. Pharmacodynamics and pharmacokinetics of cefdinir, an oral extended spectrum cephalosporin. Pediatr Infect Dis J 2000;19:S141–S146.
103. Ueno K, Tanaka K, Tsujimura K, et al. Impairment of cefdinir absorption by iron ion. Clin Pharmacol Ther 1993;54:473–475.
104. Spectracef (cefditoren) package insert. TAP Pharmaceutical Products, Inc. Lake Forest, IL, 2001.
105. Kearns GL, Young RA. Ceftibuten pharmacokinetics and pharmacodynamics. Focus on paediatric use. Clin Pharmacokinet 1994;26:169–189.
106. Smith JW, Dyke RW, Griffith RS. Absorption following oral administration of erythromycin. JAMA 1953;151:805–810.
107. Hirsch HA, Finland M. Effect of food on the absorption of erythromycin propionate, erythromycin stearate and triacetyloleandomycin. Am J Med Sci 1959;237:693–708.
108. Clapper WE, Mostyn M, Meade GH. An evaluation of erythromycin stearate and propionyl erythromycin in normal and hospitalized subjects. Antibiotic Med Clin Ther 1960;7:91–96.
109. Hirsch HA, Finland M. Effect of food on absorption of a new form of erythromycin stearate and triacetyloleandomycin. Am J Med Sci 1959;239:198–202.
110. Thompson PJ, Burgess KR, Marlin GE. Influence of food on absorption of erythromycin ethylsuccinate. Antimicrob Agents Chemother 1980;18:829–831.
111. Coyne TC, Shum S, Chun ACH, Jeansonne L, Shirkey HC. Bioavailability of erythromycin ethylsuccinate in pediatric patients. J Clin Pharm 1978;18:192–202.
112. Ameer B, Weintraub RA. Drug Interactions with grapefruit juice. Clin Pharmacokinet 1997;33:103–121.
113. Kanazawa S, Ohkubo T, Sugawara K. The effects of grapefruit juice on the pharmacokinetics of erythromycin. Eur J Clin Pharmacol 2001;56:799–803.
114. Cheng KL, Nafziger AN, Peloquin CA, et al. Effect of grapefruit juice on clarithromycin pharmacokinetics. Antimicrob Agents Chemother 1998;42:927–929.
115. Biaxin XL (clarithromycin extended-release) package insert. Abbott Laboratories, North Chicago, IL, May 2003.
116. Hopkins S. Clinical toleration and safety of azithromycin. Am J Med 1991;91(3A):40S–45S.
117. Thakker KM, Robarge L, Block S, Jefferson T, Broker R, Arrieta A. Pharmacokinetics of azithromycin oral suspension following 12 mg/kg/day (maximum 500 mg/day) for 5 days in fed pediatric patients [abstr A-59]. 38th ICAAC, San Diego, CA, September 24–27, 1998Eur J Clin Pharmacol 1988;34:525–528.
118. Jonas M, Cunha BA. Minocycline. Ther Drug Monit 1982;4:137–145.
119. Mattila MJ, Neuvonen PJ, Gothoni G, Hackman R. Interference of iron preparations and milk with the absorption of tetracyclines. In: Baker SB, Neuhaus GA (eds). Toxicological Problems of Drug Combinations. Amsterdam: Excerpta Medica, 1972, pp. 128–133.
120. Von Wittenau MS. Some pharmacokinetic aspects of doxycycline metabolism in man. Chemother (Basel) (suppl) 1968;13:41–50.
121. Cunha BA, Sibley CM, Ristuccia AM. Doxycycline. Ther Drug Monit 1982;4:125–135.
122. Welling PG, Huang H, Koch PA, Craig WA, Madsen PO. Bioavailability of ampicillin and amoxicillin in fasted and nonfasted subjects. J Pharm Sci 1977;66:549–552.
123. Kirby WMM, Roberts CE, Burdick RE. Comparison of two new tetracyclines with tetracycline and demethylchlortetracycline. Antimicrob Agents Chemother 1962;1961:286–292.
124. Poiger H, Schlatter C. Compensation of dietary induced reduction of tetracycline absorption by simultaneous administration of EDTA. Eur J Clin Pharm 1978;14:129–131.
125. Fabre J, Milek E, Kalfopoulos P, et al. The kinetics of tetracyclines in man. I. Digestive absorption and serum concentrations. Schweiz Med Wchr 1971;101:593–598.
126. Barr WH, Gerbracht LM, Letcher K, Plaut M, Strahl N. Assessment of the biologic availability of tetracycline products in man. Clin Pharmacol Ther 1971;13:97–108.
127. Rosenblatt JE, Barrett JE, Brodie JL, Kirby WMM. Comparison of in vitro activity and clinical pharmacology of doxycycline with other tetracyclines. Antimicrob Agents Chemother 1966;6:134–141.

128. Meyer FP, Specht H, Quednow B, et al. Influence of milk on the bioavailability of doxycycline – new aspects. Infection 1989;17:245–46.
129. Allen JC. Minocycline. Ann Intern Med 1976;85:482–487.
130. Neuvonen PJ, Penttila O. Effect of oral ferrous sulphate on the half-life of doxycycline in man. Eur J Clin Pharmacol 1974;7:361–363.
131. Neuvonen PJ, Turakka H. Inhibitory effect of various iron salts on the absorption of tetracycline in man. Eur J Clin Pharm 1974;7:357–360.
132. Martin SJ, Meyer JM, Chuck SK, Jung R, Messick CR, Pendland SL. Levofloxacin and sparfloxacin: new quinolone antibiotics. Ann Pharmacother 1998;32:320–336.
133. Heyd A, Shah A, Liu MC, Vaughan D, Heller AH. Oral bioavailability and efficacy of ciprofloxacin suspension for treatment of acute urinary tract infection. 38th ICAAC, San Diego, CA, September 24–27, 1998.
134. Shah A, Ming-Chung L, Vaughan D, et al. Oral bioequivalence of three ciprofloxacin formulations following single-dose administration: 500 mg tablet compared with 500 mg/10 mL or 500 mg/5 mL suspension and the effect of food on the absorption of ciprofloxacin oral suspension. J Antimicrob Chemother 1999;43(suppl A):49–54.
135. Cipro XR (ciprofloxacin extended-release) package insert. Bayer Pharmaceuticals Corporation, West Haven, CT, 2003.
136. Ballow C, Lettieri J, Agarwal V, et al. Absolute bioavailability of moxifloxacin. Clin Ther 1999;21:513–522.
137. Factive (gemifloxacin) package insert. Genesoft Pharmaceuticals, 2003.
138. Hoogkamer JFW, Klenbloesem CH. The effect of milk consumption on the pharmacokinetics of fleroxacin and ciprofloxacin in healthy volunteers. Drugs 1995;49(suppl 2):346–348.
139. Neuvonen PJ, Kivisto KT, Lehto P. Interference of dairy products with the absorption of ciprofloxacin. Clin Pharmacol Ther 1991;50(5 pt 1):498–502.
140. Minami R, Inotsume N, Nakano M, Sudo Y, Higashi A, Matsuda I. Effect of milk on absorption of norfloxacin in healthy volunteers. J Clin Pharmacol 1993;33:1238–1240.
141. Kivisto KT, Ojala-Karlsson P, Neuvonen PJ. Inhibition of norfloxacin absorption by dairy products. Antimicrob Agents Chemother 1992;36:489–491.
142. Stass H, Kubitza D. Effects of dairy products on the oral bioavailability of moxifloxacin, a novel 8-methoxyfluoroquinolone, in healthy volunteers. Clin Pharmacokinet 2001;40 Suppl 1:33–38.
143. Dudley MN, Marchbanks CR, Flor SC, Beals B. The effect of food or milk on the absorption kinetics of ofloxacin. Eur J Clin Pharmacol 1991;41:569–571.
144. Food and Drug Administration: Food-effect bioavailability and fed bioequivalence studies: study design, data analysis, and labeling. Draft guidance for industry. Bethesda, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2001.
145. Wallace AW, Victory JM, Amsden GW. Lack of bioequivalence when levofloxacin and calcium-fortified orange juice are coadministered to healthy volunteers. J Clin Pharmcol 2003;43:539–544.
146. Aminimanizani A, Beringer P, Jelliffe R. Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. Clin Pharmacokinet 2001;40:169–187.
147. Neuhofel AL, Wilton JH, Victory JM, et al. Lack of bioequivalence of ciprofloxacin when administered with calcium-fortified orange juice: a new twist on an old interaction. J Clin Pharmacol 2002;42:459–464.
148. Amsden GW, Whitaker AM, Johnson PW. Lack of bioequivalence of levofloxacin when coadministered with a mineral-fortified breakfast of juice and cereal. J Clin Pharmacol 2003;43:990–995.
149. Yamaguchi H, Yano I, Saito H, et al. Pharmacokinetic role of P-glycoprotein in oral bioavailability and intestinal secretion of grepafloxacin in vivo. J Pharmacol Exp Ther 2002;300:1063–1069.
150. Takanaga H, Ohnishi A, Yamada S, et al. Polymethoxylated flavones in orange juice are inhibitors of P-glycoprotein but not cytochrome P450 3A4. J Pharmacol Exp Ther 2000;293:230–236.

151. Fuhr U, Anders EM, Mahr G, Sorgel F, Staib AH. Inhibitory potency of quinolone antibacterial agents against cytochrome P4501A2 activity in vivo and in vitro. Antimicrob Agents Chemother 1992;36:942–948.
152. Carbo M, Segura J, De la Torre R, Badenas JM, Cami J. Effect of quinolones on caffeine disposition. Clin Pharmacol Ther 1989;45:234–240.
153. Healy DP, Polk RE, Kanawati L, Rock DT, Mooney ML. Interaction between oral ciprofloxacin and caffeine in normal volunteers. Antimicrob Agents Chemother 1989;33:474–478.
154. Staib AH, Harder S, Mieke S, Beer C, Stille W, Shah P. Gyrase-inhibitors impair caffeine elimination in man. Meth Find Exp Clin Pharmacol 1987;9:193–198.
155. Mueller BA, Brierton DG, Abel SR, Bowman L. Effect of enteral feeding with ensure on oral bioavailabilities of ofloxacin and ciprofloxacin. Antimicrob Agents Chemother 1994;38:2101–2105.
156. Yuk JH, Nightingale CH, Sweeney K, et al. Relative bioavailability in healthy volunteers of ciprofloxacin administered through a nasogastric tube with and without enteral feeding. Antimicrob Agents Chemother 1989;33:1118–1120.
157. Healy DP, Brodbeck MC, Clendening CE. Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. Antimicrob Agents Chemother 1996;41:6–10.
158. Burkhardt O, Stass H, Thuss U, et al. Effects of enteral feeding on the oral bioavailability of moxifloxacin in healthy volunteers. Clin Pharmacokinet. 2005;44(9):969–76.
159. Wright DH, Pietz SL, Konstantinides FN, Rotschafer JC. Decreased in vitro fluoroquinolone concentrations after admixture with an enteral feeding formulation. J Parent Enteral Nutr 2000;24:42–48.
160. Deppermann KM, Lode H. Fluoroquinolones: interaction profile during enteral absorption. Drugs 1993;45(suppl 3):65–72.
161. D'Arcy PF. Nitrofurantoin. Drug Intell Clin Pharm 1985;19:540–547.
162. Bates TR, Sequeira JA, Tembo AV. Effect of food on nitrofurantoin absorption. Clin Pharm Ther 1974;16:63–68.
163. Rosenberg HA, Bates TR. The influence of food on nitrofurantoin bioavailability. Clin Pharm Ther 1976;20:227–232.
164. Tindamax(tinidazole) package insert. Mission Pharma, San Antonio, Tx, May, 2007.
165. Shi J, Montary G, Bhargava VO. Clinical pharmacokinetics of telithromycin, the first ketolide antibacterial. Clin Pharmacokinet 2005;44:915–934.
166. Shi J, Montay G, Leroy B, Bhargava VO. Effects of itraconazole or grapefruit juice on the pharmacokinetics of telithromycin. Pharmacotherapy 2005;25:42–51.
167. Clay KD, Hanson JS, Pope SD, Rissmiller RW, Purdum PP, Banks PM. Severe hepatotoxicity of telithromycin: three case reports and literature review. Ann Intern Med 2006; 144:415–420.
168. Food and Drug Administration. FDA public health advisory: Ketek (telithromycin) tablets. http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm051301.html. (accessed May 28, 2010).
169. Food and Drug Administration. Safety labeling changes approved by FDA Center for Drug Evaluation and Research (CDER) – June 2006. http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021144s011lbl.pdf. (accessed May 28, 2010).
170. Food and Drug Administration. FDA Announces Label and Indication Changes for the Antibiotic Ketek. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108842.htm. (accessed May 28, 2010).
171. Onur O, Guneysel O, Denizbasi A, et al. Acute hepatitis attack after exposure to telithromycin. Clin Ther 2007;29:1725–1729.
172. Bolesta S, Roslund BP. Elevated hepatic transaminases associated with telithromycin therapy: a case report and literature review. Am J Health Syst Pharm. 2008 Kan 1;65:37–41.
173. Brinker AD, Wassel Rt, Lyndly J, et al. Telithromycin-associated hepatotoxcitiy: Clinical spectrum and causality assessment of 42 cases. Hepatology 2009;49:250–257.

174. Falloon, J, Sargent S, Piscitelli SC, et al. Atovaquone suspension in HIV-infected volunteers: pharmacokinetics, pharmacodynamics, and TMP-SMX interaction study. Pharmacotherapy 1999;19:1050–1056.
175. Albenza (albendazole) package insert. GlaxoSmithKline, Research Triangle Park, NC, September 2001.
176. Lange H, Eggers R, Bircher J. Increased systemic availability of albendazole when taken with a fatty meal. Eur J Clin Pharmacol 1988;34:315–317.
177. Stromectol (Ivermectin) package insert. Merck & Co., Inc., Whitehouse Station, NJ, October 2003.
178. Biltricide (praziquantel) package insert. Bayer Pharmaceuticals Corporation, West Haven, CT, November 2003.
179. Dayan AD. Albendazole, mebendaozle and praziquantel. Review of nonclinical toxicity and pharmacokinetics. Acta Trop 2003;86:141–159.
180. Winstanley PA, Orme M. The effects of food on drug bioavailability. Br J Clin Pharmacol 1989;28:621–628.
181. Mebendazole package insert. Teva Pharmaceuticals, Inc., Sellersville, PA, September 2007.
182. Mintezol package insert. Merck & Co., Inc., Whitehouse Station, NJ, June 2003.
183. Castro N, Jung H, Medina R, et al. Interaction between grapefruit juice and praziquantel in humans. Antimicrob Agents Chemother 2002;46:1614–1616.
184. Lariam®(mefloquine) package insert. Roche Laboratories, Inc., Nutley, NJ, August 2008.
185. Daraprim®(pyrimethamine) package insert. GlaxoSmithKline, Research Triangle Park, NC, March 2003.
186. Fansidar®(pyrimethamine;sulfadoxine) package insert. Roche Laboratories, Inc., Nutley, NJ, Feburary 2004.
187. Freeman et al. Relative bioavailability of atovaquone suspension when administered with an enteral nutrition supplement. Annals of Pharmacotherapy 1998;32:1004–1007.
188. Malarone® (atovaquone and proguanil HCL) package insert. GlaxoSmithKlein, Research Triangle Park, NC, December 2008.
189. Coartem® (artemether/lumefantrine) package insert. Novartis Pharmaceutical Corporation, East Hanover, NJ, February 2010.
190. Cleocin (clindamycin) package insert. Pharmacia and Upjohn, Kalamazoo, MI, 1998.
191. McGehee RF, Smith CB, Wilcox C, Finland M. Comparative studies of antibacterial activity in vitro and absorption and excretion of lincomycin and clindamycin. Am J Med Sci 1968;256:279–292.
192. Zyvox (linezolid) package insert. Pharmacia & Upjohn Company, Kalamazoo, Michigan, January 2002.
193. Martin JP, Herberg, JT, Slatter JG, et al. Although a novel microtiter-plate assay demonstrates that linezolid (PNU-100766) is a weak, competitive (reversible) inhibitor of human monoamine oxidase (MAO A), no clinical evidence of MAO A inhibition in clinical trials has been observed. Paper presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, September 1998.
194. Antal EJ, Hendershot PE, Batts DH, et al. Linezolid, a novel oxazolidinone antibiotic: assessment of monoamine oxidase inhibition using pressor response to oral tyramine. J Clin Pharmacol 2001;41:552–562.
195. Melander A, Danielson K, Hanson A, et al. Reduction of isoniazid bioavailability in normal men by concomitant intake of food. Acta Med Scand 1976;200:93–97.
196. Self TH, Chrisman CR, Baciewicz AM, et al. Isoniazid drug and food interactions. Am J Med Sci 1999;317:304–311.
197. Smith CK, Durack DT. Isoniazid and reaction to cheese. Ann Intern Med 1978;88:502,503.
198. Huser MJ, Baier H. Interactions of isoniazid with foods. Drug Intell Clin Pharm 1982;16:617,618.
199. Baciewicz AM, Self TH. Isoniazid interactions. South Med J 1985;78:714,715.
200. Siegler DI, Bryant M, Burley DM, Citron KM, Standen SM. Effect of meals on rifampicin absorption. Lancet 1974;2(7874):197,198.

201. Ameer B, Polk RE, Kline BJ, Grisafe JP. Effect of food on ethambutol absorption. Clin Pharm 1982;1:156–158.
202. Daneschmend TK, Warnock DW, Ene MD, et al. Influence of food on the pharmacokinetics of ketoconazole. Antimicrob Agent Chemother 1984;25:1–3.
203. Mannisto PT, Mantyla R, Nykanen S. Lamminsivu U, Ottoila P. Impairing effect of food on ketoconazole absorption. Antimicrob Agent Chemother 1982;21:730–733.
204. Brass C, Galgiani JN, Blaschke TF, et al. Disposition of ketoconazole, an oral antifungal in humans. Antimicrob Agents Chemother 1982;21:151–158.
205. Wishart JM. The influence of food on the pharmacokinetics of itraconazole in patients with superficial fungal infections. J Am Acad Dermatol 1987;17:220–223.
206. Lange D, Pavao JH, Klausner M. Effect of a cola beverage on the bioavailability of H_2 blockers. J Clin Pharmacol 1997;37:535–540.
207. Jaruratanasirikul S, Kleepkaew A. Influence of an acidic beverage (Coca-Cola) on the absorption of itraconazole. Eur J Clin Pharmacol 1997;52:235–237.
208. Kawakami M, Suzuki K, Ishizuka T, et al. Effect of grapefruit juice on pharmacokinetics of itraconazole in healthy subjects. Int J Clin Pharmacol Ther. 1998;36:306–8.
209. Penzak SR, Gubbins PO, Gurley BJ, et al. Grapefruit juice decreases the systemic availability of itraconazole capsules in healthy volunteers. Ther Drug Monit. 1999;21:304–9.
210. Gubbins PO, McConnell SA, Gurley BJ, et al. Influence of grapefruit juice on the systemic availability of itraconazole oral solution in healthy adult volunteers. Pharmacotherapy 2004; 24:460–467.
211. Sanone Parsons A, Krishna G, Calzetta A, et al. Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers. Antimicrob Agents Chemother. 2006;50:1881–3.
212. Krishna G, Ma L, Vickery D, Yu x, Wu I, Power E, Beresford E, Komjathy S. Effect of varying amounts of a liquid nutritional supplement on the pharmacokinetics of posaconazole in healthy volunteers. Antimicrob Agents. Chemother 2009;53:4749–52.
213. Krishna G, Moton A, Ma L, et al. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric condition in healthy volunteers. Antimicrob Agents Chemother 2009;53:958–966.
214. Courtney R, Radwanski E, Lim J, et al. Pharmacokinetics of posaconazole coadministered with antacid in fasting or nonfasting healthy men. Antimicrob Agents Chemother. 2004;48: 804–808.
215. Crounse RG. Human pharmacology of griseofulvin: the effect of fat intake on gastrointestinal absorption. J Invest Dermatol 1961;37:529.
216. Hartman NR, Yarchoan R, Pluda JM, et al. Pharmacokinetics of 2′,3′-dideoxy-adenosine and 2′,3′-dideoxyinosine in patients with severe human immunodeficiency virus infection. Clin Pharmacol Ther 1990;47:647–654.
217. Knupp CA, Shyu WC, Dolin R, et al. Pharmacokinetics of didanosine in patients with acquired immunodeficiency syndrome-related complex. Clin Pharmacol Ther 1991;49:523–535.
218. McGowan JJ, Tomaszewski JE, Cradock J, et al. Overview of the preclinical development of an antiretroviral drug, 2′,3′-dideoxyinosine. Rev Infect Dis 1990;12:S513–S520.
219. Damle BD, Kaul S, Behr D, et al. Bioequivalence of two formulations of didanosine, encapsulated enteric-coated beads and buffered tablet, in healthy volunteers and HIV-infected subjects. J Clin Pharmacol 2002;42:791–797.
220. Videx EC (didandosine) package insert. Bristol-Meyers Squibb Company, Princeton, NJ, February 2003.
221. Klecker RW Jr, Collins JM, Yarchoan R, et al. Plasma and cerebrospinal fluid pharmacokinetics of 3′-azido-3′deoxythymidine: a novel pyrimidine analog with potential application for the treatment of patients with AIDS and related diseases. Clin Pharmacol Ther 1987;41:407–412.
222. Dudley MN, Graham KK, Kaul S, et al. Pharmacokinetics of stavudine in patients with AIDS or AIDS-related complex. J Infect Dis 1992;166:480–485.
223. Unadkat JD, Collier AC, Crosby SS, Cummings D, Opheim KE, Corey L. Pharmacokinetics of oral zidovudine (azidothymidine) in patients with AIDS when administered with and without a high-fat meal. AIDS 1990;4:229–232.

224. Sahai J, Gallicano K, Garber G, et al. The effect of a protein meal on zidovudine pharmacokinetics in HIV-infected patients. Br J Clin Pharmacol 1992;33:657–660.
225. Lotterer E, Ruhnke M, Trautmann M, Beyer R, Bauer FE. Decreased and variable systemic availability of zidovudine in patients with AIDS if administered with a meal. Eur J Clin Pharmacol 1991;40:305–308.
226. Angel JB, Hussey EK, Mydlow PK, et al. Pharmacokinetics of (GR 109714X) 3TC administered with and without food to HIV-infected patients [abtr PoB 3008]. Inf Conf AIDS 1992;8(2):B88.
227. Beach JW. Chemotherapeutic agents for human immunodeficiency virus infection: mechanism of action, pharmacokinetics, metabolism, and adverse reactions. Clin Ther 1998:20:2–25.
228. Foster RH, Faulds D. Abacavir. Drugs 1998;55:729–736.
229. Yuen GJ, Lou Y, Thompson NF, et al. Abacavir/lamivudine/zidovudine as a combined formulation tablet: bioequivalence compared with each component administered concurrently and the effect of food on absorption. J Clin Pharmacol 2001;41:277–288.
230. Epzicom®(abacavir sulfate and lamivudine) package insert. GlaxoSmithKlein, Research Triangle Park, NC, March 2009.
231. Emtriva (emtricitabine) package insert. Gilead Sciences, Inc., July 2003.
232. Viread (tenofovir disoproxil fumarate) package insert. Gilead Sciences, Inc., October 2003.
233. Barditch-Crovo P, Deeks SG, Collier A, et al. Phase i/ii trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother 2001;45:2733–2739.
234. Truvada® (emtricitabine/tenofovir disoproxil fumarate) package insert. Gilead Sciences, November 2009.
235. Freimuth WW. Delavirdine mesylate, a potent non-nucleoside HIV-1 reverse transcriptase inhibitor. In: Mills J, Volberding PA, Corey L (eds). Antiviral Chemotherapy. Vol 4. New York: Plenum, 1996, pp. 279–389.
236. Sustiva (efavirenz) package insert. Bristol-Meyers Squibb Company, Princeton, NJ, June 2003.
237. Atripla® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) package insert. Bristol-Myers Squibb & Gilead Sciences, LLC., January 2010.
238. Inteleance® (etravarine) package insert. Tibotec Therapeutics, Raritan, NJ, February 2010.
239. Moyle G, Gazzard B. Current knowledge and future prospects for the use of HIV protease inhibitors. Drugs 1996;51:701–712.
240. Williams GC, Sinko PJ. Oral absorption of the HIV protease inhibitors: a current update. Adv Drug Deliv Rev 1999;39:211–238.
241. Chiba M, Hensleigh M, Nishime JA, et al. Role of cytochrome P450 3A4 in human metabolism of MK-639, a potent human immunodeficiency virus protease inhibitor. Drug Metab Dispos 1996;24:307–314.
242. Saah AJ, Winchell GA, Nessly ML, et al. Pharmacokinetic profile and tolerability of indinavir-ritonavir combinations in healthy volunteers. Antimicrob Agents Chemother 2001;45: 2710–2715.
243. Crixivan (indinavir sulfate) package insert. Merck & Company, Inc., Whitehouse Station, NJ, January 2003.
244. Penzak SR, Acosta EP, Turner M, et al. Effect of Seville orange juice and grapefruit juice on indinavir pharmacokinetics. J Clin Pharmacol 2002;42:1165–1170.
245. Shelton MJ, Wynn HE, Hewitt RG, et al. Effects of grapefruit juice on pharmacokinetic exposure to indinavir in HIV-positive subjects. J Clin Pharmacol 2001;41:435–442.
246. Noble S, Faulds D. Saquinavir: a review of its pharmacology and clinical potential in the management of HIV infection. Drugs 1996;52:93–112.
247. Invirase® (saquanavir) package insert. Roche Laboratories, Inc., Nutley NJ, April 2010.
248. Kupferschmidt HH, Fattinger KE, Ha HR, Follath F, Krahenbuhl S. Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. Br J Clin Pharmacol 1998;45:355–359.

249. Food and Drug Administration. FDA Drug Shortages: Roche Pharmaceutical Dear Health Care Professional Letter regarding Fortovase – May 2005 http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/ucm086073.pdf. (accessed May 28, 2010).
250. Fitzsimmons ME, Collins JM. Selective biotransformation of the human immunodeficiency virus protease inhibitor saquinavir by human small-intestinal cytochrome P4503A4: potential contribution to high first-pass metabolism. Drug Metab Dispos 1997;25:256–266.
251. Shetty BV, Kosa MB, Khalil DA, Webber S. Preclinical pharmacokinetics and distribution to tissue of AG1343, an inhibitor of human immunodeficiency virus type 1 protease. Antimicrob Agents Chemother 1996;40:110–114.
252. Agenerase(amprenavir) package insert. GlaxoSmithKlein, Research Triangle Park, NC, October 2002.
253. Demarles D, Gillotin C, Bonaventure-Paci S, et al. Single-dose pharmacokinetics of amprenavir coadministered with grapefruit juice. Antimicrob Agents Chemother 2002;46:1589–1590.
254. Lexiva®(fosamprenavir) package insert. GlaxoSmithKline, Research Triangle Park, NC, April 2010.
255. Kaletra (lopinavir/ritonavir) package insert. Abbott Laboratories, North Chicago, IL, January 2003.
256. Gustavson L, Lam W, Bertz R, et al. Assessment of the bioequivalence and food effects for liquid and soft elastic capsule co-formulations of ABT-378/ritonavir (ABT-378/r) in healthy subjects [poster]. Presented at: The 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, September 2000.
257. Reyataz (atazanavir sulfate) package insert. Bristol-Meyers Squibb Company, Princeton, NJ, June 2003.
258. O'Mara E, Mummaneni V, Randall D, et al. BMS-232632: A Summary of Multiple Dose Pharmacokinetic, Food Effect and Drug Interaction Studies in Healthy Subjects. Presented at: The 7th Conference on Retroviruses and Opportunistic Infections. www.retroconference.org/2000/abstracts/504.htm.
259. Reyataz® (atanazavir) package insert. Bristol-Meyers Squibb Company, Princeton, NJ, April 2010.
260. Aptivus® (tipranavir) package insert. Boeheringer Ingelheim Pharmaceuticals, Inc., April 2010.
261. Isentress® (raltegravir) package insert. Merck & Co., Inc., Whitehouse Station, NJ, October 2009.
262. Pfizer Inc. Maraviroc tablets NDA 22–28 Drug Approval Package: Clinical Pharmacology Biopharmaceutics Review, Section 2.5.3. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022128s000_ClinPharmR.pdf. (accessed May 30, 2010).
263. Pescovitz MD, Rabkin J, Merion RM, et al. Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. Antimicrob Agents Chemother 2000;44:2811–2815.
264. Jung D, Dorr A. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects. J Clin Pharmacol 1999;39:800–804.
265. Fowles SE, Fairless AJ, Pierce DM, et al. A further study of the effect of food on the bioavailability and pharmacokinetics of penciclovir after oral administration of famciclovir. Br J Clin Pharmacol 1991;32:657P.
266. Fowles SE, Pierce MC, Prince WT, et al. Effect of food on the bioavailability and pharmacokinetics of penciclovir, a novel antiherpes agent, following oral administration of the prodrug, famciclovir. Br J Clin Pharmacol 1990;29:620P,621P.
267. Acosta EP, Fletcher CV. Valacyclovir. Ann Pharmacother 1997;31:185–91.
268. Zovirax package insert. Glaxo Wellcome, Research Triangle Park, NC, 1998.
269. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. Clin Pharmacokinet (DG5) 1988;14:35–51.
270. Fuller RK, Roth HP. Disulfiram for the treatment of alcoholism: an evaluation in 128 men. Ann Intern Med 1979;90:901–904.
271. Kitson TM. The disulfiram-ethanol reaction. J Stud Alcohol 1977;38:96–113.

272. Jungnickel PW, Hunnicutt DM. Alcohol abuse. In: Young LY, Koda-Kimble MA (eds). Applied Therapeutics: The Clinical Use of Drugs. 6th ed. Vancouver, WA: Applied Therapeutics, 1995.
273. Stoll K, King LE. Disulfiram-alcohol skin reaction to beer-containing shampoo. JAMA 1980;244:2045.
274. Refojo MF. Disulfiram-alcohol reaction caused by contact lens wetting solution. Contact Intraocul Lens Med J 1981;7:172.
275. Chick JD. Disulfiram reaction during sexual intercourse. Br J Psychiatry 1988;152:438.
276. Adams WL. Interactions between alcohol and other drugs. Int J Addict 1995;30:1903–1923.
277. Kannangara DW, Gallagher K, Lefrock JL. Disulfiram-like reactions with newer cephalosporins: cefmenoxime. Am J Med Sci 1984;287:45–47.
278. Cina SJ, Russell RA, Conrad SE. Sudden death due to metronidazole/ethanol interaction. Am J Forensic Med Pathol 1996;17:343–346.
279. Freundt KJ, Heiler C, Schreiner E. Ferrous sulfate combined with ascorbic acid does not significantly reduce acetaldehyde accumulation in the blood of alcoholized rats treated with disulfiram or betalactam antibiotics. Alcohol 1990;7:295–298.
280. Elenbaas RM, Ryan JL, Robinson WA, Singsank MJ, Harvey JM, Klaassen CD. On the disulfiram-like activity of moxalactam. Clin Pharmacol Ther 1982; 32:347–355.
281. Kitson TM. The effect of 5,5′-Dithiobis(1-methyltetrazole) on cytoplasmic aldehyde dehydrogenase and its implications for cephalosporin-alcohol reactions. Alcoholism: Clin Exp Res 1986;10:27–32.
282. McMahon FG. Disulfiram-like reaction to a cephalosporin. JAMA 1980;243:2397.
283. Neu HC, Prince AS. Interaction between moxalactam and alcohol. Lancet 1980;1:1422.
284. Kitson TM. The effect of cephalosporin antibiotics on alcohol metabolism: a review. Alcohol 1987;4:143–148.
285. Itil TI. Central effects of metronidazole. Psychiatric Research Report 24, American Psychiatric Association, March 1968.
286. Seixas FA. Alcohol and its drug interactions. Ann Intern Med 1975;83:86–92.
287. Campbell B, Taylor JAT, Haslett Wl. Anti-alcohol properties of metronidazole in rats. Proc Soc Exp Biol Med 1965;124:191–195.
288. Taylor JT. Metronidazole – a new agent for combined somatic and psychic therapy of alcoholism. Los Angeles Neurol Soc Bull 1964;29:158.
289. Penick SB, Carrier RN, Sheldon JB. Metronidazole in the treatment of alcoholism. Am J Psychiatry 1969;125:1063–1066.
290. Edwards JA, Price J. Metronidazole and human alcohol dehydrogenase. Nature 1967;214:190,191.
291. Kalant H, LeBlanc AE, Guttman M. Metabolic and pharmacologic interaction of ethanol and metronidazole in the rat. Can J Physiol Pharmacol 1972;50:476–484.
292. Foster TS, Raehl CL, Wilson HD. Disulfiram-like reaction associated with a parenteral cephalosporin. Am J Hosp Pharm 1980;7:858,859.
293. Umeda S, Arai T. Disulfiram-like reaction to moxalactam after celiac plexus alcohol block. Anesth Analg 1985;64:377.
294. Buening MK, Wold JS, Israel KS, et al. Disulfiram-like reaction to beta-lactams [letter]. JAMA 1981;245:2027.
295. Brown KR, Guglielmo BJ, Pons VG, Jacobs RA. Theophylline elixir, moxalactam, and a disulfiram reaction. Ann Intern Med 1982;97:621,622.
296. Shimada J, Miyahara T, Otsubo S, Yoshimatsu N, Oguma T, Matsubara T. Effects of alcohol-metabolizing enzyme inhibitors and beta-lactam antibiotics on ethanol elimination in rats. Jpn J Pharmacol 1987;45:533–544.
297. Kline SS, Mauro VF, Forney RB Jr, Freimer EH, Somani P. Cefotetan-induced disulfiram-type reactions and hypoprothrombinemia. Antimicrob Agents Chemother 1987;31:1328–1331.
298. Lassman HB, Hubbard JW, Chen BL, Puri SK. Lack of interaction between cefpirome and alcohol. J Antimicrob Chemother 1992;29(suppl 1):47–50.

299. McMahon FG, Ryan JR, Jain AK, LaCorte W, Ginzler F. Absence of disulfiram-type reactions to single and multiple doses of cefonicid: a placebo-controlled study. J Antimicrob Chemother 1987;20:913–918.
300. McMahon FG, Noveck RJ. Lack of disulfiram-like reactions with ceftizoxime. J Antimicrob Chemother 1982;10(suppl C):129–133.
301. Uri JV, Parks DB. Disulfiram-like reaction to certain cephalosporins. Ther Drug Monit 1983;5:219–224.
302. Heelon MW, White M. Disulfiram-cotrimoxazole reaction. Pharmacother 1998;18:869,870.
303. Azarnoff DL, Hurwitz A. Drug interactions. Pharmacol Physicians 1970;4:1–7.
304. Todd RG (ed). Extra Pharmacopoeia – Martindale. 25th ed. London: Pharmaceutical Press, 1967, pp. 844,845.
305. Norvir (ritonavir) Oral Solution package insert. Abbott Laboratories, Abott Park, IL, 1998.

Chapter 5
Interactions Between Herbs and Antiinfective Medications

Scott R. Penzak

Abstract Over 15 million people in the United States report using complementary and alternative medications (CAM). Patients with HIV infection represent an important segment of this population. Because of their ability to modulate a variety of cytochrome P450 (CYP) enzymes and drug transport proteins such as P-glycoprotein (P-gp), a number of herbs have been shown to interact with coadministered medications. Unfortunately, in vitro microsomal studies often fail to predict results obtained in humans. The herb associated with the greatest number of drug interactions in humans is St. John's wort (*Hypericum perforatum*). As a potent inducer of CYP and P-gp, St. John's wort has been shown to reduce the plasma concentrations of certain coadministered medications by >50%. Other herbs have been shown to induce the metabolism of coadministered medications as well. However, the magnitude of these interactions is markedly less than that produced by St. John's wort. Nonetheless, even mild herb-drug interactions may be clinically relevant for coadministered medications with narrow therapeutic indices. To this end, the need for rigorous studies to identify potentially significant herb-drug interactions continues. Clinicians caring for patients taking CAM therapy should maintain a high degree of suspicion for herb-drug interactions in the face of unexplained toxicity or loss of efficacy, and be familiar with resources that can help manage or avoid herb-drug interactions.

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5.1 Introduction

Herbal supplements have been widely used in the East for centuries; more recently their use has expanded to include areas of the Western World such as the United States and Canada. In a national survey of complementary and alternative medicine (CAM) use, over 15 million people in the United States were identified as using herbal supplements or high-dose vitamins [1]. In addition, the total number of visits to CAM providers exceeded those to primary physicians, resulting in out-of-pocket expenses in excess of 34 billion dollars [1]. The increased use in CAM is multifactorial and includes a general desire for good health and wellness, and disease prevention and treatment. Thus, many consumers believe CAM is safer than prescription drugs because they contain "natural" ingredients [2].

The majority of CAM includes herbal supplements, which are generally defined as any form of a plant or plant product, including stems, flowers, leaves, roots and seeds [2]. Herbal products can contain a single herb or combinations of herbs that possess complementary effects. In the United States herbs are regarded as dietary supplements (i.e. food products) and are not subject to intense regulatory oversight by the United States Food and Drug Administration (FDA) [3]. However, herbs and other dietary supplements are subject to regulation as specified in the Dietary Supplement Health and Education Act of 1994 [4]. As a result, herbal supplements may not claim to "treat, prevent, cure, or diagnose a specific disease;" such claims are limited to medications that have been proven to be safe and effective by the FDA.

Recently, the USP Dietary Supplement Verification Program was developed to assess the integrity of dietary supplements. This program performs comprehensive laboratory testing of dietary supplements and their ingredients against standards found in The United States Pharmacopeia and The National Formulary (USP-NF). Products that meet the program's criteria are labeled with a *USP Verified* logo that can be placed on labels, packaging and promotional materials. This logo allows customers and health care practitioners to identify herbal products that are *USP Verified*. Of note, dietary supplement manufacturers who participate in this program do so voluntarily [5].

Despite a relative paucity of scientific data regarding the safety and efficacy of herbal products, a significant number of patient populations report using these supplements on a regular basis. These patients typically include those with chronic medical conditions such as breast cancer (12%), liver disease (7%), asthma (24%), and rheumatological disorders (26%) [6]. An additional group of individuals who commonly report using herbal products are those suffering from -or desiring to prevent, an infectious process. A variety of herbs have been touted for the treatment and/or prevention of the common cold, urinary tract infections, upper respiratory tract infections, prostatitis, hepatitis, and the human immunodeficiency virus (HIV) [7–11]. Patients with HIV infection undoubtedly represent the largest group of CAM users in the infectious disease arena. A telephone survey of 180 HIV infected patients found that 68% of these individuals routinely used herbs, vitamins, or

dietary supplements [12]. In a larger study of 2,466 HIV-infected subjects, 53% reported recent use of CAM therapy [13]. Patients with HIV infection take herbal supplements for purported antiviral activity, "boosting" of the immune system, and for the treatment or prevention of opportunistic infections, and treatment of medication-related side effects such as gastrointestinal disturbances, peripheral neuropathy, weight loss, and fatigue [11].

Due to frequent CAM use in patients taking prescription medications, there is a strong possibility of clinically relevant drug interactions between these classes of compounds. Yet surprisingly, few clinical studies have systematically investigated potential interactions between prescription medications and herbal products [3, 14]. Also of note is the fact that most patients who use CAM do not readily report this information to their health care provider [1]. As a result, potentially dangerous herb-drug interactions are likely to go unnoticed in many patients.

5.2 Potential Mechanisms of Herb-Drug Interactions

A growing number of pre-clinical and clinical studies have shown that a variety of herbal preparations are capable of modulating drug metabolism and transport at various anatomical sites, most notably in the liver and intestines. Greater than 90% of oxidative metabolism in the liver can be attributed to six cytochrome P450 enzymes. These include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [15]. A number of antiinfective medications including antibacterials, antifungals, and antiretrovirals such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolized through one or more of these enzymatic pathways [16]. As will be discussed in detail below, a number of herbal constituents have been shown to inhibit and/or induce CYP enzymes; thereby increasing or decreasing the plasma concentrations of coadministered medications. This may result in untoward toxicity or reduced efficacy (i.e. antimicrobial failure) depending on the nature of the interaction. Similarly, a number of herbs have been shown to modulate the activity of uridine diphosphate (UDP) glucuronosyltransferases (UGT), and drug transport proteins such as P-glycoprotein (P-gp), multidrug resistance proteins (MRPs), organic anion transporting polypeptides (OATP), and organic anion transporters (OATs) [17–19]. Modulation of these metabolic and transport proteins by herbal products are also capable of altering the distribution and/or systemic exposure of concurrently administered medications, potentially resulting in adverse events or poor efficacy [2]. Common herbal preparations that have been shown to modulate CYP and/or P-gp activity in humans are presented in Table 5.1 [20–47]. Known pharmacokinetic interactions between herbal supplements and antiinfective agents are described below; of the studies discussed, those conducted in humans are highlighted in Table 5.2 [25, 29, 34, 39, 48–56].

Table 5.1 Influence of herbal compounds of cytochrome P450 (CYP) and P-glycoprotein (P-gp) activity in humans

	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4/5	P-gp
St. John's wort (*Hypericum perforatum*) [20–25]	↑	↑[a]	↑[b]	↑	↑	↑	↑
Garlic (*Allium sativum*) [20, 26]	ND	ND	ND	↔	↓	↔	ND
Milk Thistle (*Silybum marianum*) [27, 28]	↔	ND	ND	↔	↔	↔	↔
Ginkgo biloba [20, 29–32]	↔	↔	↑[c]	↔	↔	↑, ↔	↔
Echinacea (*Echinacea purpurea*, *Echinacea angustifolia*, *Echinacea pallida*) [21, 27, 34–36]	↓, ↔	↔	ND	↔	↔	↑[d], ↓[d], ↔[d]	↔
Panax ginseng [20, 23, 37]	↔	↔[e]	ND	↔	↔	↑[f], ↔	↔[f]
Black cohosh (*Actaea racemosa*) [21, 28, 38]	↔	ND	ND	↔	↔	↔	↔
Goldenseal (*Hydrastis canadensis*) [38–40]	↔	ND	ND	↓	↔	↔, ↓	↔
Kava Kava (*Piper methysticum*) [38, 40]	↔	ND	ND	↔	↑	↔	↔
Valerian (*Valeriana officinalis*) [38, 41]	↔	ND	ND	↔	↔	↔	ND
Grape seed (*Vitis vinifera*) [42]	↑	ND	ND	ND	ND	ND	ND
Green tea (*Camellia sinensis*) [43]	ND	ND	ND	↔	ND	↔	ND
Ginger (*Zingiber officinale*) [30]	ND	ND	ND	ND	ND	↔	ND
Hawthorn (*Crataegus monogyna*; *Crataegus laevigata*; *Crataegus oxyacantha*) [44]	ND	ND	ND	ND	ND	ND	↔
Saw Palmetto (*Serenoa repens*) [27, 45]	↔	ND	ND	↔	↔	↔	ND
Soy (*Glycine max*) [46, 47]	ND	↔[g]	ND	ND	ND	↔[g]	ND

No human data were found for the following herbs with regard to their ability to modulate specific CYP pathways: Hypoxis hemerocallidea (*African potato*), Sutherlandia (*Sutherlandia frutescens*), Devil's claw (*Harpagophytum procumbens*), and Evening Primrose (*Oenothera biennis*)
Arrows pointing upward: indicates increased enzymatic activity
Arrows pointing downward: indicates decreased enzymatic activity
Arrows pointing side-to-side: indicates no significant change in enzymatic activity
"*ND*" indicates that no human data were located
[a]Increased enzymatic activity was observed regardless of CYP2C9 genotype [24]
[b]Increased enzymatic activity was observed in CYP2C19 wild-type subjects, not in CYP2C19 poor metabolizers [22]
[c]Increased enzymatic activity was observed in CYP2C19 homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers [32]
[d]Decreased activity of intestinal CYP3A and increased activity of hepatic CYP3A4, was observed in one study [35]. A second study observed an increase in CYP3A activity [34] while a third showed no effect [27]
[e]Study examined the effects of Asian ginseng on the CYP2C9 substrate S-warfarin [37]
[f]Unpublished data by Penzak et al.
[g]Study assessed the influence of soy extract on the pharmacokinetics of losartan, which is metabolized by both CYP2C9 and CYP3A4; the study was conducted in an all female population (18 healthy volunteers) [46]. A second study showed no effect of soy on CYP3A4 activity [47].

Table 5.2 Summary of drug interaction studies involving herbal supplements and antiinfective agents conducted in healthy human volunteers

Reference	Herbal preparation (regimen)	N[a]	Standardization	Coadministered drug regimen	Primary outcome; suggested mechanism	Conclusion
[48]	St. Johns wort (300 mg TID ×14 days)	8	0.3% hypericin	Indinavir (800 mg q8h×4 doses)[b]	Indinavir $AUC_{0\text{-}8}$ ↓ 57% ($p=0.0008$); CYP3A4 induction	Avoid St. John's wort with unboosted indinavir and other CYP3A4 substrates
[49]	St. Johns wort (300 mg TID ×15 days)	16	Extract L1 160	Voriconazole (400 mg single doses)[b]	Voriconazole $AUC_{0\text{-}\infty}$ ↓ 59% ($p=0.0004$); intestinal and hepatic CYP2C19, CYP3A4, and P-gp induction	Avoid St. John's wort with voriconazole and other CYP2C19, CYP3A4, and P-gp substrates
[25]	St. Johns wort (300 mg TID ×14 days)	12	Extract L1 160	Midazolam (4 mg PO×1, and 2 mg iv×1)[c] ritonavir (300 mg BID×14 days)	iv and po midazolam ($AUC_{0\text{-}6}$ and $AUC_{0\text{-}8}$, respectively) ↑ 180% and 412%, respectively vs baseline after ritonavir+St. John's wort ($p<0.05$ for each). Two days after stopping St. John's wort and ritonavir, iv and PO midazolam AUCs were reduced below baseline values ($p<0.001$ for each)	The CYP3A inhibitory effects of ritonavir at 300 mg BID superseded CYP3A induction by St. John's wort. CYP3A induction by St. John's wort was unmasked 2 days after stopping its coadministration ×14 days with ritonavir. Note that the ritonavir dose used in this study was 3-fold higher than the typical ritonavir boosting dose
[50]	Garlic caplets; maximum allicin formula (BID ×20 days)	10	Allicin (4.64 mg/caplet) and allin (11.2 mg/caplet)	Saquinavir (soft gel capsule) (1,200 mg TID×10 doses)[b]	Saquinavir $AUC_{0\text{-}8}$ ↓ 51% ($p<0.028$); ↓ saquinavir absorption via unknown mechanism; possible induction of intestinal CYP3A4 and/or P-gp	Avoid garlic supplements with unboosted saquinavir and possibly other CYP3A4 substrates

[51]	Garlic soft gel capsules (10 mg BID×4 days)	10	Allicin content <50 µg/g extract	Ritonavir capsule (400 mg×1 dose)[b]	Ritonavir $AUC_{0-\infty}$ ↓ 17% (p=0.094)	Short term garlic supplementation does not alter ritonavir exposure but may exacerbate GI side effects associated with ritonavir
[52]	Milk thistle (175 mg TID×21 days)	10	153 mg silymarin confirmed	Indinavir (800 mg q8h×4 doses)[b]	Indinavir AUC_{0-8} ↓ 9% (p=0.20)	Milk thistle, in commonly administered doses should not alter the PK of indinavir
[53]	Milk thistle (160 mg TID×14 days)	10	173 mg silymarin confirmed	Indinavir (800 mg q8h×4 doses)[b]	Indinavir AUC_{0-8} ↓ 6% (p=0.64)	Milk thistle, in commonly administered doses should not alter the PK
[54]	Milk thistle (450 mg TID×28 days)	16	456 mg silymarins confirmed	Indinavir (800 mg q8h×4 doses)[b]	Indinavir AUC_{0-8} ↓ 4% (p=0.78)	Milk thistle, in commonly administered doses should not alter the PK of indinavir
[55]	Milk thistle (140 mg/day×9 days)	12	140 mg silymarin	Metronidazole (400 mg Q8h×3 days and 9 days with a 7 day washout period)[b]	Metronidazole AUC_{0-8} ↓ 29% ($p<0.001$); intestinal P-gp and CYP3A4 induction suggested by authors (unlikely based on data from additional studies)	Avoid multiple dose administration of milk thistle with metronidazole
[29]	*Ginkgo biloba* extract (120 mg BID ×14 days in combination with lopinavir-ritonavir)	14	Flavonol glycoside and terpene lactone content consistent with product label	Lopinavir (400 mg) +ritonavir (100 mg) (BID×29.5 days)[b]	lopinavir AUC_{0-12} ↓ 1.6% (p=0.42), ritonavir AUC_{0-12} ↓ 6.5% (p=0.28); concurrent administration of the CYP3A4 inhibitor ritonavir, prevented CYP3A4 induction by *Ginkgo biloba*	*Ginkgo biloba*, in commonly administered doses, should not alter the PK of lopinavir-ritonavir or other ritonavir-boosted PI combinations

(continued)

Table 5.2 (continued)

Reference	Herbal preparation (regimen)	N[a]	Standardization	Coadministered drug regimen	Primary outcome; suggested mechanism	Conclusion
[34]	*Echinacea purpurea* (500 mg TID × 28 days)	13	Standardized amounts of alkylamides, polysaccharides, and cichoris acid	Lopinavir (400 mg) + ritonavir (100 mg) (BID × 29.5 days)[b]	Lopinavir $AUC_{0\text{-}12}$ ↓ 3.7% (p = 0.82), ritonavir $AUC_{0\text{-}12}$ ↓ 8.1% (p = 0.76); concurrent administration of the CYP3A4 inhibitor ritonavir, prevented CYP3A4 induction by *Ginkgo biloba*	*Echinacea purpurea*, in commonly administered doses, should not alter the PK of lopinavir-ritonavir or other ritonavir-boosted PI combinations
[56]	African potato (*Hypoxis hemerocallidea*) (15 mg/kg/day of hypoxoside, prepared by traditional decoction, × 14 days)	10	Samples analyzed *apriori* for hypoxoside content.	Efavirenz 600 mg (2 single doses)[b]	Efavirenz $AUC_{0\text{-}48}$ ↓ 2.1% (90% CIs for $AUC_{0\text{-}48}$ and C_{max} were within 80–125% hence no interaction was observed)	Coadministration of African potato is unlikely to alter efavirenz PK
[39]	Goldenseal root (1,140 mg BID × 14 days)	10	Total alkaloid content consistent with product label	Indinavir 800 mg (2 single doses)[b]	Indinavir CL/F ↓ 4.6% (p = NS)	Coadministration of goldenseal root is unlikely to alter the PK of indinavir; interactions with other CYP3A substrates may depend on the relative degree of hepatic vs. intestinal metabolism of the coadministered drug

AUC area under the concentration vs. time curve, *CL/F* apparent oral clearance, *iv* intravenous administration, *NS* not statistically significant, *PI* protease inhibitor, *PK* pharmacokinetics, *PO* by mouth, *Q8h* every 8 h, *TID* 3 times daily

[a]N: number of healthy volunteers

[b]Pharmacokinetics determined before, and after herbal administration

[c]Midazolam $AUC_{0\text{-}6}$ was determined at baseline, after 14 days for St. John's wort + ritonavir, and 2 days after cessation of both agents

5.3 Interactions Between Herbs and Antiinfective Medications

5.3.1 St. John's Wort (Hypericum perforatum)

St. John's wort is used for a variety of ailments including depression, anxiety, dysthymia, attention deficit hyperactivity disorder (ADHD), chronic fatigue syndrome, insomnia, HIV/AIDS, hepatitis C and numerous others [57]. St. John's wort is a potent inducer of various CYP isoforms as well as P-gp [20–25, 58]. As a result, St. John's wort interacts with numerous medications; in some cases drastically reducing their systemic exposure [59]. Among anti-infectives whose plasma concentrations are significantly reduced by St. John's wort are the CYP3A4 substrate indinavir (57% ↓ in indinavir area under the concentration-time curve from zero to 8 h [$AUC_{0\text{-}8}$]) and the CYP2B6 and CYP3A4 substrate nevirapine (35%↑ in nevirapine apparent oral clearance [Cl/F]) [48, 60]. To this end, St. John's wort should be avoided in combination with all unboosted HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors since all are metabolized to varying degrees by CYP3A4 as well as other CYP isoforms. Of note, a recent study showed that ritonavir 300 mg twice daily, given as a boosting agent for concurrent protease inhibitor therapy, masks CYP3A4 induction by St. John's wort [25]. Whether this occurs with lower boosting doses of ritonavir (i.e. 100 mg twice daily) is unknown.

St. John's wort was also found to interact with the azole antifungal voriconazole in a slightly more complex manner. Fifteen days of St. John's wort administration reduced $AUC_{0\text{-}\infty}$ of voriconazole by 59% ($P=0.0004$) [49]. Voriconazole is metabolized by CYP2C19, CYP3A4, and to a lesser extent, CYP2C9 [61]. Of note, during the first day of St. John's wort administration the voriconazole $AUC_{0\text{-}10}$ actually increased by 22% ($P=0.02$) suggesting that St. John's wort caused a short-term clinically insignificant increase in voriconazole exposure followed by a prolonged excessive reduction in voriconazole concentrations. The mechanism by which St. John's wort (hyperforin) induces a variety of metabolic and transport proteins is directly related to its potent ability to bind to, and subsequently activate the pregnane X receptor (PXR) [62]. PXR is a key regulator of xenobiotic inducible CYP3A gene expression; PXR also regulates the CYP2B and CYP2C subfamilies in addition to UDP-glucuronosyltransferases, OATP2, the multidrug resistant protein (MDR1, which encodes for P-glycoprotein), and MRPs 2 and 3 [59]. To this end, long-term exposure to St. John's wort (>12 days) has the ability to significantly reduce the systemic exposure of coadministered medications that are metabolized by CYP enzymes and transport proteins that are regulated by PXR. St. John's wort should be avoided in individuals taking such medications.

5.3.2 Garlic (Allium sativum)

Garlic is used for the treatment of hypertension, hyperlipidemia (including drug-induced hyperlipidemia in patients with HIV infection) coronary heart disease,

age-related vascular changes, chronic fatigue syndrome and menstrual disorders [57]. In addition, garlic has been used for its antibacterial, anthelmintic, antiviral, immunostimulant, and antithrombotic effects. The major active components of garlic are organosulfur compounds [63]. Alliin (S-allylcysteine sulfoxide) – a major constituent of garlic – is converted by alliinase to allicin. Allicin is then further transformed to additional garlic compounds including diallyl sulfide. These organosulfur compounds have been shown to modulate CYP isoforms *in vitro* and *in vivo* [64]. Indeed, various garlic preparations were shown to inhibit human CYP2C9, 2C19, 3A4, 3A5, and 3A7 activity *in vitro*, whereas CYP2D6 activity was unaltered [65]. CYP2E1 activity, measured using chlorzoxazone as a probe compound, was reduced by 39% ($P = 0.30$) in healthy volunteers receiving garlic oil for 4 weeks [20].

The impact of garlic supplementation on CYP3A4 activity in humans has not yielded consistent results. Piscitelli et al. found that 3 weeks of twice daily garlic administration (containing 4.64 and 11.2 mg of allicin and alliin per caplet, respectively) resulted in a mean 51% decrease in steady state saquinavir (Fortovase®) $AUC_{0\text{-}8}$ and a 54% decrease in maximum concentration (C_{max}) in 10 healthy volunteers [50]. After a 10 day washout period, saquinavir $AUC_{0\text{-}8}$ and C_{max} values only returned to 60–70% of baseline (control) values. Of note, saquinavir is both a CYP3A4 and a P-gp substrate, leading some researchers to speculate that the interaction between garlic and saquinavir occurred primarily due to induction of P-gp rather than CYP3A4. This is consistent with results from other investigations of long-term garlic administration (14–28 days) that did not observe changes in CYP3A4 activity [20, 26].

Markowicz et al. administered garlic extract (1,800 μg allicin, twice daily) to healthy volunteers for 2 weeks to determine the influence of garlic on CYP3A4 activity using alprazolam as a metabolic probe [26]. There were no differences in alprazolam pharmacokinetics following garlic administration. Similarly, administration of garlic oil (500 mg 3 times daily; allicin content not specified) to healthy volunteers for 28 days did not alter CYP3A activity using midazolam as a probe [20].

Inconsistencies in the literature regarding the ability of garlic supplements to modulate CYP activity (CYP3A4 in particular) may be due to several factors. Commercially available garlic supplements have been noted to contain varying amounts of organosulfur compounds (i.e. alliin and allicin), which have been implicated in modulating several CYP isoforms [66, 67]. In addition, garlic also contains numerous flavonoids and isoflavonoids that may alter CYP activity leading to differences among various garlic supplements with regard to their ability to modulate CYP activity [63]. As a result, it is difficult to predict drug interactions with garlic *a priori*. Erring on the side of caution, HIV protease inhibitors and NNRTIs should not be coadministered with garlic supplements. Other anti-infective agents that are metabolized by CYP3A4 such as clarithromycin, erythromycin, and dapsone should be used with caution in patients taking long-term garlic supplementation.

A potential pharmacodynamic interaction between garlic and antiinfectives involves garlic's penchant for causing gastrointestinal toxicities such as mouth and gastrointestinal burning or irritation, heartburn, flatulence, nausea, vomiting, and

diarrhea [57]. When taken in combination with other medications that commonly cause gastrointestinal distress (i.e. numerous antibiotics, certain antifungals and ritonavir), patients may experience additive gastrointestinal toxicity. Indeed, Laroche et al. reported two HIV-infected patients taking garlic supplements for >2 weeks who developed severe gastrointestinal toxicity after commencing therapy with a ritonavir-containing antiretroviral regimen [68]. Separating doses of garlic supplements and prescription medications by several hours may help to alleviate gastrointestinal side effects caused by the coadministration of garlic with anti-infectives known to cause G.I. distress.

5.3.3 Milk Thistle (Silybum marianum)

Orally, milk thistle is used for liver disorders including hepatotoxicity due to highly active antiretroviral therapy (HAART) in patients with HIV infection, jaundice, chronic inflammatory liver disease, hepatic cirrhosis, and chronic hepatitis. Milk Thistle has also been used for other diverse conditions such as loss of appetite, dyspepsia, diabetes, hangover, malaria, and depression [57]. Based on *in vitro* data that showed that milk thistle inhibited CYP3A4 and CYP2C9, several studies examined the influence of milk thistle on the HIV protease inhibitor and CYP3A4 substrate indinavir [69, 70]. Piscitelli et al. observed a non-significant 9% decrease in indinavir $AUC_{0\text{-}8}$ at steady state following 3 weeks of dosing with milk thistle (175 mg [153 mg silymarin] 3 times daily) in 10 healthy volunteers [52]. Similarly, DiCenzo et al. observed a non-significant 6% reduction in steady state indinavir exposure after 2 weeks of silymarin administration (160 mg 3 times daily) to 10 healthy volunteers [53]. In a third study, Mills et al. reported a 4.4% decrease in steady state indinavir $AUC_{0\text{-}8}$ ($P = 0.78$) after 28 days of milk thistle dosing (450 mg capsules 3 times daily) in 16 healthy subjects [54]. In addition, Mills and colleagues conducted a meta-analysis of these 3 drug interaction studies between milk thistle and indinavir; their analysis revealed a non-significant mean difference of 1% in indinavir steady state $AUC_{0\text{-}8}$ ($P = 0.97$). Consistent with these indinavir data, milk thistle did not alter the pharmacokinetics of the CYP3A4 and UGT1A1 substrate irinotecan, or the CYP3A substrate midazolam [27, 71].

In contrast, administration of silymarin (140 mg/day for 9 days) reduced the steady state $AUC_{0\text{-}8}$ of metronidazole (400 mg orally every 8 h) by 29% in 12 healthy volunteers [55]. Metronidazole is a putative substrate for CYP3A4, CYP2C9, and P-gp [55, 72]. Given the lack of an interaction between milk thistle and other CYP3A4 substrates (indinavir, midazolam, and irinotecan) it is unlikely that the interaction between milk thistle and metronidazole occurred via CYP3A4 induction by the former. The authors of this study suggest that induction of intestinal P-gp by milk thistle may have contributed to the interaction. However, Gurley et al., noted an approximate 9% decrease ($P = 0.06$) in the $AUC_{0\text{-}24}$ of the P-gp substrate digoxin (which is not metabolized by CYP enzymes) after milk thistle administration (300 mg 3 times daily) for 14 days [28]. In addition, it is unlikely that milk thistle

induced the metabolism of metronidazole through CYP2C9 since preliminary data suggest that metronidazole would be more apt to reduce – as opposed to enhance – the catalytic activity of this isoform [70, 73].

To this end, with the possible exception of metronidazole, milk thistle appears to have limited clinical impact on antiinfectives metabolized via CYP and/or transported by P-gp (Tables 5.1 and 5.2). Recent preliminary data suggest that milk thistle may decrease the activity of organic anion transporting polypeptide 1B1 (OATP1B1) and increase or decrease the plasma concentrations of medications that undergo glucuronidation [74–76]. Further study is necessary to determine whether these putative interactions are clinically relevant.

5.3.4 Ginkgo Biloba (Ginkgo biloba)

Ginkgo biloba extract (GBE), one of the most popular herbal medicines in the world, is used for dementia, including Alzheimer's disease. Ginkgo is also used for conditions associated with cerebral vascular insufficiency including memory loss, headache, vertigo, difficulty concentrating, mood disturbances, and hearing disorders [57]. Patients with HIV infection take GBE for a variety of conditions including AIDS-related dementia, depressive disorders and CNS side effects associated with antiretroviral use [29]. GBE is characterized by 22–27% flavone glycosides, consisting primarily of quercetin and kaempferol, and 5–7% terpene lactones, which include ginkgolides and bilobalide [57, 77].

Several studies utilizing rat models were conducted to evaluate the effect of standardized ginkgo extracts on CYP3A activity using various probe drugs. In general, results from these animal studies showed induction of 3A activity, though at significantly higher doses of GBE than would normally be administered to humans (as high as 100 times the normal human doses) [78–81]. One investigation in rats noted a decrease in the hypotensive effect of the CYP3A substrate nicardipine after GBE administration, suggesting possible CYP3A4 induction by GBE [79]. In contrast, liver microsomal studies and fluorometric microtitre plate assays have shown inhibition of CYP3A4 using a wide variety of GBE concentrations [67, 82, 83].

Similar to results from the preclinical investigations discussed above, several drug interaction studies conducted with GBE have also shown inconsistent findings. Gurley et al. found that 28 days of GBE (60 mg, 4 times daily) had no apparent effect on CYP3A activity using midazolam as a probe drug in 12 healthy subjects [20]. Another study assessed the influence of an 18 day course of GBE (120 mg/day) on the pharmacokinetics of the CYP3A4 substrate nifedipine [84]. GBE did not significantly alter the mean AUC or C_{max} of nifedipine in eight healthy volunteers; however, two subjects did experience a doubling in C_{max}, which the investigators attributed to GBE. Due to the small sample size and lack of statistically significant findings, results from this study can best be described as inconclusive.

Due to the discordance in results among studies assessing the influence of GBE on CYP3A activity, we conducted a study in 14 healthy volunteers to determine the

influence of GBE on the pharmacokinetics of the protease inhibitor combination lopinavir/ritonavir, and the respective CYP3A and P-gp probes midazolam and fexofenadine [29]. Single dose fexofenadine pharmacokinetics were unaltered by GBE (120 mg twice daily for 28 days), suggesting that the herb does not significantly modulate P-gp activity. Conversely the geometric mean midazolam $AUC_{0-\infty}$ following single doses, was reduced by 34% (P = 0.03) after 28 days of GBE administration; thus suggesting mild induction of CYP3A by GBE. Lastly, volunteers received 2 weeks of lopinavir-ritonavir (400/100 mg twice daily) alone, then in combination with GBE 120 mg twice daily. Geometric mean ratios of lopinavir and ritonavir AUC_{0-12} (post-GBE/pre-GBE) were 1.02 (P = 0.42) and 0.93 (P = 0.28), respectively, indicating that GBE had no effect on either lopinavir or ritonavir exposure despite the fact that both of these agents are metabolized by CYP3A4 [29].

The reason lopinavir exposure was not affected by GBE is likely due to the coadministration of ritonavir, a potent CYP3A inhibitor. Ritonavir is capable of abating CYP3A induction associated with other enzyme inducers, such as efavirenz and rifabutin [85, 86]. Based on these results, it appears unlikely that GBE would reduce the systemic exposure of protease inhibitors that are boosted with low-dose ritonavir. However, it is possible that GBE may reduce the plasma concentrations of lone protease inhibitors (i.e. those not boosted by ritonavir). In addition, GBE may reduce the systemic exposure of other antiinfective agents metabolized by CYP3A including the recently FDA-approved CCR5 co-receptor antagonist, maraviroc, clarithromycin, erythromycin and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine, and efavirenz [16]. In support of this hypothesis, there is a single case report of reduced efavirenz plasma concentrations and virologic failure in an HIV-infected patient taking ginkgo biloba. After developing a K103N mutation and an HIV-1 RNA increase from <50 to 1,780 copies/mL, plasma efavirenz concentrations were determined from stored samples dating back 2 years. Over a 14 month period when the patient was taking ginkgo biloba along with efavirenz, he experienced a 62% decrease in efavirenz concentrations (from 1.26 to 0.48 mg/L; therapeutic range: 1.0–4.0 mg/L). The authors of this report surmised that terpenoids from the ginkgo extract reduced plasma efavirenz concentrations by inducing cytochrome P450 3A4 (CYP3A4) or P-gp [87].

Beyond CYP3A, human data suggest that GBE does not modulate the activity of CYP1A2, CYP2C9, and CYP2D6 (Table 5.1) and is therefore unlikely to interact with antiinfective medications metabolized through these pathways.

5.3.5 Echinacea (Echinacea purpurea, Echinacea angustifolia, Echinacea pallida)

Echinacea is used for treating and preventing upper respiratory infections including the common cold. Echinacea is also used as an immunostimulant to help counter a variety of other infections, including vaginal candidiasis, urinary tract infections, and genital herpes [57]. Of the three common Echinacea species listed above, the

majority of research has been conducted with *Echinacea purpurea*. However, the potential for drug interactions among the three Echinacea species may differ due to varying amounts of alkylamide content within the different species [88].

At least two studies have characterized the effect of *E. purpurea* root on CYP3A activity in healthy volunteers [27, 35]. Using single doses of both oral and intravenous midazolam as a probe compound for intestinal and hepatic CYP3A activity, respectively, Gorski et al. reported an 85% increase in the intestinal availability of midazolam ($P=0.015$) and a 15% decrease in the hepatic availability of midazolam ($P=0.006$) after 12 subjects received a total daily dose of 1,600 mg of *E. purpurea* for 8 days [35]. These data suggest that *E. purpurea* selectively modulates CYP3A activity in the liver and intestine. Conversely, Gurley et al. found that 28 days of *E. purpurea* whole plant extract administration (800 mg twice daily) did not significantly alter CYP3A activity in 12 healthy volunteers as measured by serum ratios of 1-hydroxymidazolam:midazolam collected 1 h post-dose [27]. Due to the conflicting nature of the data presented by Gorski et al. and Gurley et al., we conducted a study to assess the influence of *E. purpurea* on the pharmacokinetics of lopinavir-ritonavir and the CYP3A and P-gp probe drugs oral midazolam and fexofenadine, respectively [34].

Healthy volunteers received lopinavir-ritonavir (400/100 mg) alone for 2 weeks and in combination with *Echinacea purpurea* 500 mg 3 times daily for 2 weeks. Lopinavir and ritonavir pharmacokinetics were determined pre- and post *E. purpurea* administration. Study subjects also received single doses of midazolam (8 mg orally) and fexofenadine (120 mg orally) before- and after 28 days of *Echinacea purpurea* to characterize CYP3A and P-gp activity, respectively. Neither lopinavir nor ritonavir pharmacokinetics were significantly altered by 2 weeks of *Echinacea* administration. The GMRs for lopinavir $AUC_{0\text{-}12}$ and maximum concentration (post-*Echinacea*/pre-*Echinacea*) were 0.96 and 1.00, respectively ($P>0.05$ for both comparisons). Similarly, fexofenadine pharmacokinetics did not significantly differ pre- and post-echinacea administration ($P>0.05$). However, the GMR (post-*Echinacea*/pre-*Echinacea*) for midazolam $AUC_{0\text{-}\infty}$ was 0.73 ($P=0.008$), which is suggestive of a mild induction effect on CYP3A by *E. purpurea* [34]. Despite this mild induction, it is not surprising that lopinavir pharmacokinetics were unaltered by *E. purpurea* given the concurrent administration of the potent CYP3A inhibitor ritonavir [29, 85, 86].

Results from this study suggest that *E. purpurea* may cause mild reductions (≅ 25–30%) in plasma concentrations of CYP3A substrates that are not routinely coadministered with potent CYP3A inhibitors; the clinical relevance of such interactions is apt to be greater in patients receiving medications whose plasma concentrations must be maintained above threshold values for optimal pharmacologic efficacy. Such medications may include unboosted HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and certain azole antifungals and macrolides antibiotics

Due to the selective effects of *E. purpurea* on intestinal versus hepatic CYP3A activity as shown by Gorski et al., the influence of *E. purpurea* on the net exposure of a coadministered CYP3A substrate will likely depend on the extraction ratio of

the concurrent medication [35]. Drugs that are poorly absorbed due to significant intestinal metabolism via CYP3A, may experience an increase in oral bioavailability secondary to intestinal CYP3A inhibition by *E. purpurea*. Conversely, CYP3A substrates with good oral bioavailability and a low clearance may undergo increased oral clearance secondary to induction of hepatic CYP3A by *E. purpurea* [35].

To this end, it is difficult to predict interactions between *E. purpurea* and CYP3A substrates, as the presence or absence of such interactions likely depends on the relative extraction of the coadministered drug by hepatic versus intestinal CYP3A.

In addition to its effect on CYP3A, Echinacea was found to inhibit CYP1A2 as evidenced by a 30% increase in plasma concentrations of the CYP1A2 substrate caffeine, when it was coadministered with Echinacea for 8 days [35]. To date, there are no antiinfective agents that are primarily metabolized by CYP1A2; thus making CYP1A2-mediated drug interactions between Echinacea spp. and antiinfectives unlikely.

Lastly, there are theoretical concerns regarding the use of Echinacea spp. in patients with HIV infection. Patients with HIV may take Echinacea for its immunostimulatory effects or for the short-term treatment/prevention of upper respiratory infections [57, 89]. While solid scientific evidence is lacking, some clinicians believe that the immunostimulatory effects of Echinacea could result in the activation of CD4+ cells, thereby increasing the number of "target cells" for HIV [89]. In addition, an enriched polysaccharide extract of *E purpurea* was recently shown to increase production of tumor necrosis factor (TNF) in mice, and high concentrations of TNF-alpha have been linked to HIV disease progression [90, 91]. Based on these limited data, it is unlikely that short-term (≤14 days) echinacea administration for the treatment of colds and influenza presents any serious risks to patients with HIV infection. However, long-term use of Echinacea in patients with HIV infections should probably be avoided [89].

5.3.6 Panax ginseng

Ginseng root extract, derived from the herb *Panax ginseng*, has been used as a traditional remedy in Eastern Asia for thousands of years. Orally, Panax ginseng is used as an "adaptogen" for promoting resistance to environmental stress and as a tonic for improving well-being. It is also used for stimulating immune function, and improving cognitive function, physical stamina, concentration, memory and work efficiency [57]. Ginseng is administered orally in a variety of forms, including fresh-cut root, alcohol extracts, powder, capsules and teas. Its content is standardized to percent of ginsenosides. Of note, *P. ginseng* should not be confused with Siberian ginseng or American ginseng; each belongs to the same family (*Araliaceae*) but forms a different genus [57, 92].

Several studies have examined the effect of *P. ginseng* on CYP activity in humans. Gurley et al. administered *P. ginseng* (5% ginsenosides, 500 mg, 3 times daily) for 28 days to healthy volunteers, and found no effect on the metabolism of the 3A

substrate midazolam [20]. Anderson et al. investigated the potential of *P. ginseng* to induce 3A4 by measuring the urinary metabolic ratio of cortisol and 6-hydroxycortisol in 20 healthy volunteers given 24 days of ginseng extract (4% ginsenosides, 100 mg twice daily) [47]. Results from this study found that *P. ginseng* did not induce CYP3A4, although the ability of urinary cortisol metabolic ratios to predict CYP3A4 activity is questionable [93]. A third *in vivo* study found a modest increase (29%; P value not reported) in nifedipine C_{max} in healthy volunteers after an 18-day course of ginseng (200 mg/day) [94]. *In vitro* investigations have found varying extents of CYP inhibition, depending on the methodology and concentrations of *P. ginseng* used [35, 82, 83, 95]. A study conducted in rats showed significant increases in the hepatic CYP content of rats fed *Panax* root, suggesting the possibility of enzyme induction [96].

Due to the inconclusive nature of the above studies, we recently determined the influence of *P ginseng* (500 mg twice daily for 28 days) on CYP3A and P-gp activity in 12 healthy volunteers using midazolam, and fexofenadine probes, respectively [97]. Midazolam oral clearance was increased in 11 of the 12 study subjects by an average of 51% (P=0.01). These data suggest that *P ginseng* has the potential to increase CYP3A activity and lower the plasma concentrations of antiinfective medications metabolized by this pathway (Table 5.1). Conversely, *P ginseng* had no effect on fexofenadine pharmacokinetics, suggesting that *P ginseng* is unlikely to alter the pharmacokinetics of coadministered medications via modulation of P-gp. Similarly, *P ginseng* did not alter the activities of CYP2D6, CYP1A2, and CYP2E1 in healthy volunteers [20]. As a result, *P. ginseng* is unlikely to interact with antiinfectives metabolized by routes other than CYP3A.

5.3.7 Hypoxis hemerocallidea (African Potato)

Hypoxis hemerocallidea (African potato) has been used by traditional Zulu healers for hundreds of years for the treatment of bladder and urinary disorders including cystitis; it has also been used for the treatment of benign prostatic hypertrophy, prostate cancer, and lung diseases [57, 98]. The South African community is currently using *hypoxis* as an immunostimulating agent in patients with HIV infection [99].

Mills et al. first provided *in vitro* evidence suggesting that *hypoxis* is capable of modulating CYP3A4 and P-gp activity and binding to PXR [100]. *Hypoxis* inhibited CYP3A4 activity by 86% and P-gp activity to a lesser degree (i.e. *hypoxis* showed 42–51% of the inhibitory strength of verapamil, a potent P-gp inhibitor). In addition, *hypoxis* produced an approximate two-fold dose-dependent activation of PXR. Because the PXR nuclear receptor controls the activation of both CYP3A4 and P-gp, these findings suggest that *Hypoxis* administration may result in initial inhibition of CYP3A4 and P-gp, followed by induction with prolonged administration [100]. Thus, *Hypoxis* may alter the metabolism and transport of antiretroviral agents that are metabolized by CYP3A4 (i.e. the HIV protease inhibitors and NNRTIs) and/or transported by P-gp. Of note, a separate series of *in vitro* investigations

showed that hypoxoside induced P-gp in Caco-2 cells and stigmasterol (another ingredient in the African potato) strongly inhibited CYP3A4, CYP3A5, and CYP2C19 [101].

Based upon the *in vitro* data above, Mogatle et al. examined the influence of the African potato on single-dose efavirenz pharmacokinetics [56]. Ten healthy male volunteers received a single 600 mg dose of efavirenz before, and after 14 days of a freshly prepared African potato decoction (15 mg/kg/day of hypoxoside). In contrast with previous *in vitro* findings, which suggest that *Hypoxis* modulates CYP3A4 and P-gp activity, African potato administration did not alter efavirenz pharmacokinetics in this investigation. The GMRs of C_{max} and $AUC_{0\text{-}48}$ were 0.973 and 1.03. Potential reasons for the differences between *in vivo* and *in vitro* results discussed above are (1) relatively high concentrations of *Hypoxis* used in the *in vitro* investigations, which may not be applicable in human studies (2) the fact that hypoxoside is quickly metabolized to rooperol following oral administration and is not absorbed systemically (3) the fact that efavirenz is largely metabolized by CYP2B6, which the African potato has not yet been shown to modulate [56].

A final *in vitro* study showed that the African potato ingredient *Hypoxis hemerocallidea* significantly decreased the P-gp-mediated efflux of nevirapine across Caco-2 cell monolayers ($P < 0.05$) [102]. The authors concluded that the African potato could increase the oral bioavailability of nevirapine, potentially resulting in higher plasma concentrations and increased toxicity. However, when one considers that the absolute bioavailability of nevirapine exceeds 90%, the potential increase in nevirapine absorption in the presence of the African potato would be expected to be minimal.

5.3.8 Sutherlandia (Sutherlandia frutescens)

Sutherlandia frutescens is an African herb that has been used for numerous maladies including cancer, tuberculosis, chronic fatigue syndrome, diabetes, influenza, osteoarthritis, rheumatoid arthritis, gastritis, clinical depression, anxiety, and HIV infection [98]. The bioactive constituents of *Sutherlandia* include L-canavanine, GABA, and D-pinitol [92].

Similar to their experiments with *Hypoxis*, Mills and coworkers examined the influence of *Sutherlandia* on CYP3A4 and P-gp activity, and PXR activation [100]. *Sutherlandia* produced near complete (96%) inhibition of CYP3A4, while its effects on P-gp activity were less potent (*Sutherlandia* showed 19–31% of the inhibitory strength of verapamil on P-gp activity). Similar to what was observed with *Hypoxis*, *Sutherlandia* produced an approximate twofold dose-dependent activation of PXR. To this end, *Sutherlandia* administration may result in initial inhibition of CYP3A4 and – to a lesser degree – P-gp followed by induction with prolonged administration. However, until drug interaction studies with *Sutherlandia* are conducted in humans, the interaction potential of this herbal preparation remains uncertain.

5.3.9 Black Cohosh (*Actaea racemosa*)

Black cohosh is used to treat symptoms of premenstrual syndrome (PMS), dysmenorrhea, symptoms of menopause, anxiety, dyspepsia, fever, sore throat, and cough [57].

An *in vitro* investigation found that six triterpene glycosides fractionated from black cohosh exhibited potent CYP3A4 inhibition as assessed by nifedipine oxidation [103]. However, in 12 healthy volunteers, 1,090 mg of black cohosh (standardized to 0.2% triterpene glycosides) given twice daily for 28 days did not alter CYP3A activity using a midazolam probe [38]. In this same study, black cohosh had no significant effect on CYP1A2 and CYP2E1 activity using caffeine and chlorzoxazone probes, respectively. Similarly, two studies in healthy volunteers failed to find clinically meaningful changes in debrisoquine 8 h urinary recovery ratios as a measure of CYP2D6 activity after 28 days of black cohosh administration [38, 104]. Lastly, the same researchers assessed the influence of black cohosh (20 mg twice daily for 14 days) on P-gp activity using digoxin as a probe; again, black cohosh did not alter the activity of this protein [28]. Based on these data, black cohosh is unlikely to interact with antiinfective medications via modulation of CYP or P-gp activity.

Due to concern that black cohosh may be linked to cases of liver failure and autoimmune hepatitis, it should not be taken by individuals receiving other hepatotoxic drugs as this may increase the risk of liver damage [57]. Antiinfective agents known to cause liver toxicity include itraconazole, ketoconazole, isoniazid, rifampin, efavirenz, nevirapine, delavirdine, nitrofurantoin, terbinafine, trovafloxacin, and tipranavir-ritonavir.

5.3.10 Goldenseal (*Hydrastis canadensis*)

Goldenseal is used to treat upper respiratory tract infections including the common cold, nasal congestion, allergic rhinitis and a host of other maladies [57]. Goldenseal is often combined with echinacea in products touted for the treatment and prevention of the common cold. The active components of goldenseal are presumed to be the alkaloids berberine and hydrastine [105].

Data are conflicting with regard to goldenseal's ability to modulate CYP3A [38, 39]. Several *in vitro* investigations have identified goldenseal extracts, as well as individual isoquinoline alkaloids, as potent CYP3A4 inhibitors [69, 82, 106]. However, when goldenseal (570 mg capsules; administered as 2 capsules twice daily for 14 days) was given in combination with the CYP3A4 substrate indinavir, it did not alter any of indinavir's pharmacokinetic parameters [39]. Of note, the goldenseal product used in this investigation was analyzed for standard alkaloid content (2% hydrastine and 2.5% berberine) prior to the study and found to meet U.S. Pharmacopeia (USP) standards. Conversely, Gurley and coworkers observed strong CYP3A inhibition with goldenseal (900 mg 3 times daily for 28 days) using serum ratios of 1-hydroxymidazolam/midazolam determined 1 h after midazolam dosing [38]. The reason(s) for the apparent discrepancy in these two studies with

regard to goldenseal's ability to inhibit CYP3A are not immediately clear. One possibility raised by authors from both studies, is that goldenseal may alter the oral bioavailability of drugs that are subject to high first-pass metabolism by CYP3A in the gut wall. Since indinavir is not appreciably metabolized by intestinal CYP3A4, this may explain why goldenseal did not alter indinavir absorption and disposition. Hence, goldenseal's potential to interact with coadministered CYP3A substrates may depend on the comparative degree of intestinal versus hepatic metabolism involved in the biotransformation of the coadministered compound [38].

Separate *in vitro* and *in vivo* studies noted that goldenseal significantly inhibited CYP2D6 activity [38, 104, 106]. As a result, goldenseal should be avoided in individuals taking medications metabolized by CYP2D6. Fortunately, no commonly used antivirals, antifungals, or antibacterial agents use CYP2D6 as their primary metabolic route.

In addition to drug metabolizing enzymes, goldenseal was evaluated for its influence on P-gp-mediated drug transport [40]. Preliminary data in rats showed that the goldenseal constituent berberine produced a dose-dependent increase in the bioavailability of digoxin and cyclosporine A via inhibition of intestinal P-gp [107]. However, an *in vitro* investigation found data to suggest that berberine up-regulates P-gp expression [108]. Contrary to data from these *in vitro* experiments, goldenseal (3,210 mg daily for 14 days) did not significantly alter the systemic exposure of the P-gp substrate digoxin in 20 healthy volunteers [40]. Based on the lack of P-gp modulation *in vivo* by goldenseal, it is unlikely that this herbal preparation will alter the pharmacokinetics of coadministered P-gp substrates.

5.3.11 Kava Kava (Piper methysticum)

Kava is used to treat anxiety, stress, insomnia, and restlessness. It is also used in a variety of other conditions including attention deficit-hyperactivity disorder (ADHD), depression, headache, chronic fatigue syndrome (CFS), respiratory tract infections, tuberculosis, and urinary tract infection (UTI) [57]. The active constituents of kava extracts include a number of kava lactones.

Of the kava lactones assessed, methysticin, dihydromethysticin, and desmethoxyyangonin appear to have the greatest inhibitory effect on CYP enzymes, with all three inhibiting CYP3A4 [109, 110]. Indeed, preliminary evidence from *in vitro* investigations suggest that kava is a significant inhibitor of CYP3A4, CYP2D6, CYP1A2, and P-gp [109, 111, 112]. However, subsequent studies in humans did not find kava to be an inhibitor of any of these enzymes [38, 40, 104]. Kava was found to inhibit CYP2E1 activity by approximately 40% using chlorzoxazone as a probe [38]; however, other than several anesthetics, relatively few medications (and no antiinfectives to our knowledge) are metabolized by this isoform [16]. Several *in vitro* studies have observed inhibition of CYP2C9 and CYP2C19 by kava extracts; however, no data in humans are available [109, 111]. Nonetheless, aside from nelfinavir (HIV protease inhibitor), voriconazole (azole antifungal), and proguanil (prophylactic

antimalarial agent) the CYP2C sub-family is not routinely involved in the metabolism of antiinfective agents [16].

There is concern that kava can cause hepatotoxicity and liver failure in patients taking recommended doses for relatively short time periods [57]. Indeed, the use of kava for as little as 3 months or less has resulted in the need for liver transplantation, and death [113–117]. As a result, kava preparations should not be taken in combination with previously mentioned antiinfective agents known to cause liver toxicity.

Lastly, kava preparations have been associated with drowsiness, dizziness, and disturbances of oculomotor equilibrium and accommodation [57]. As a result, kava should be avoided in individuals taking antiinfective medications with CNS-related side effects such as efavirenz and minocycline.

5.3.12 Valerian (Valeriana officinalis)

Valerian is primarily used to treat insomnia, anxiety, and restlessness [57]. Other uses for valerian include depression, attention deficit-hyperactivity disorder (ADHD), and chronic fatigue syndrome (CFS) [57].

Preliminary data from *in vitro* investigations suggest that valerian may inhibit CYP3A4 and P-gp [82, 118, 119]. However, two separate studies in healthy volunteers reported no statistically significant effect of valerian at 375 mg/day for 28 days, and 1,000 mg/day for 14 days, on CYP3A activity using 1-hydroxymidazolam/midazolam ratios and alprazolam AUC, respectively, as CYP3A probes [38, 41]. In addition, valerian (375 mg/day for 28 days) had no effect on CYP1A2, CYP2D6, and CYP2E1 activity in healthy volunteers [38]. No studies in humans have assessed the influence of valerian on P-gp activity.

Since valerian can cause drowsiness and insomnia, it should probably be avoided or at least used with caution in patients taking efavirenz, which can also cause sleep disturbances and drowsiness in some individuals [120].

5.3.13 Devil's Claw (Harpagophytum procumbens)

Devil's claw is used for non-specific lower back pain, osteoarthritis, gout, myalgia, tendonitis, and rheumatoid arthritis [57]. Devil's claw contains the iridoid glycoside constituents harpagoside, harpagide, and procumbide, which appear to have anti-inflammatory effects [121].

Preliminary data from a single *in vitro* investigation suggest that devil's claw may inhibit CYP3A4, CYP2C9, and CYP2C19; it was not shown to inhibit CYP2D6 [111]. However, the influence of devil's claw on these or other CYP enzymes has not been evaluated in humans. Due to the frequent disparity in data from *in vitro* versus *in vivo* studies assessing the ability of an herbal formulation to modulate CYP activity, it is not possible to predict with any degree of certainty, whether

devil's claw will increase the systemic concentrations of antiinfectives metabolized by CYP3A4, CYP2C9, and CYP2C19; clinical studies are necessary to explore this possibility.

5.3.14 Grape Seed (*Vitis vinifera*)

Grape seed is primarily used for preventing cardiovascular disease, hemorrhoids, varicose veins, hypertension, and peripheral vascular disease [57]. Grape seed has also been used to treat diabetic complications such as retinopathy and neuropathy [57]. Flavonoids found in grape products exhibit a variety of effects that may prevent cardiac disease; these include antioxidant, antiplatelet, and vasodilating properties as well as anti-lipoperoxidant activity [122–124].

Grape seed extract was shown to inhibit the activities of CYP2C9, CYP2D6, and CYP3A4 in human liver microsomes [125]. Conversely, another study conducted in human hepatocytes found that grape seed extract increased CYP3A4 mRNA expression by nearly 300% versus control; thereby suggesting that grape seed extract is capable of inducing CYP3A4 activity [126]. A study in rats failed to find an appreciable effect of grape seed administration on intestinal and hepatic microsomal activity nor midazolam pharmacokinetics [125]. Studies in humans are necessary before any conclusions can be reached regarding the potential for grape seed to interact with antiinfective medications via modulation of CYP2C9, CYP2D6, and CYP3A4. A study in healthy subjects showed that grape juice appeared to induce CYP1A2 activity as evidenced by a 43% reduction in the AUC of the CYP1A2 substrate phenacetin. However, as noted previously, CYP1A2 is not routinely involved in the metabolism of any antiinfective medications.

5.3.15 Green Tea (*Camellia sinensis*)

Green tea is used to improve mental alertness and enhance cognitive performance. It is also used to treat vomiting, diarrhea, and headache. In addition, green tea has been reported to promote weight loss and possess antioxidant, anticancer, and anti-inflammatory properties [57, 92]. Many of the purported therapeutic effects of green tea are thought to be due to the presence of catechins, polyphenols, and phytoestrogens [57]. Green tea also contains 2–4% caffeine [57].

In vitro studies in human liver microsomes, rat hepatic and intestinal microsomes, and a pharmacokinetic study in rats have yielded conflicting results with regard to the influence of green tea on CYP3A activity [125, 127]. In healthy volunteers, green tea extract (844 mg catechins/day for 14 days) had no effect on CYP3A4 or CYP2D6 using alprazolam and dextromethorphan as CYP3A4 and CYP2D6 probes, respectively [43]. One study in human liver microsomes found that green tea extract inhibited CYP2C9 activity; however, the influence of green tea on CYP2C9 has not

been evaluated in humans [125]. Collectively, the data above do not suggest that green tea is likely to alter the metabolism of medications metabolized through CYP. Nonetheless, green tea may still interact with certain antibiotics and antifungals through alternate mechanisms.

As mentioned, green tea contains caffeine (10–80 mg per cup) whose clearance via CYP1A2 is reduced by fluoroquinolone antibiotics [16]. As a result, side effects due to excessive caffeine exposure such as anxiety, insomnia, and headache might be expected when green tea is ingested with quinolone antibiotics such as ciprofloxacin, enoxacin, norfloxacin, sparfloxacin, trovafloxacin, and grepafloxacin [16]. In addition, green tea has been noted to cause liver toxicity. At least 14 cases of hepatotoxicity, mainly linked to green tea extracts in pill form, have been reported [128, 129]. Due to potentially additive hepatotoxic effects, green tea should be avoided in patients receiving those antiinfective medications mentioned earlier, that produce liver toxicity.

5.3.16 Ginger (Zingiber officinale)

Ginger is used for motion sickness, nausea and vomiting, morning sickness during pregnancy, migraine headache, and a host of other ailments [57]. Active components of ginger include gingerdione, shogaol, gingerol, and sesquiterpene and monoterpene volatile oils [130, 131]. These constituents produce a number of pharmacologic properties including analgesic, antitussive antipyretic, sedative, anti-inflammatory, antibiotic, and weak antifungal activities [130, 132].

Relatively few studies have examined ginger for its drug interaction potential and most of these have focused on warfarin, the S isomer of which is metabolized through CYP2C9 [30, 37, 57]. Ginger did not alter warfarin pharmacokinetics or pharmacodynamics in healthy volunteers [30, 37]. As a result, ginger is unlikely to interact with medications metabolized by CYP2C9. Until more data are available, it is not possible to predict the interaction potential between ginger and medications metabolized through other CYP pathways.

5.3.17 Hawthorn (Crataegus monogyna; Crataegus laevigata)

Hawthorn is primarily used for the treatment of congestive heart failure, angina pectoris, hypertension, and dysrhythmias [57]. The constituents of hawthorn preparations that are responsible for its pharmacologic activities include flavonoids and oligomeric proanthocyanidins (OPCs) such as epicatechin and procyanidins [57].

Neither preclinical nor clinical studies have assessed the influence of CYP-mediated drug interactions with hawthorn. However, one study in healthy volunteers showed that 3 weeks of hawthorn and digoxin coadministration did not alter digoxin pharmacokinetics; thereby indicating that hawthorn is unlikely to modulate

the systemic exposure of medications that are P-gp substrates [44]. Until more data are available, it is not possible to predict the interaction potential between hawthorn and drugs metabolized by CYP.

5.3.18 *Saw Palmetto (Serenoa repens)*

Saw palmetto is mainly used to treat symptoms of benign prostatic hyperplasia (BPH) [57]. Additionally, saw palmetto is used as a sedative, anti-inflammatory, mild diuretic, and antiseptic agent [57]. Saw palmetto products are frequently standardized based on their fatty acid content. Most saw palmetto extracts used in clinical studies for the treatment of BPH are berry extracts prepared with lipophilic solvents containing 80–90% free fatty acids [57].

Two studies conducted *in vitro* reported that saw palmetto inhibited CYP2C9, CYP2D6, and CYP3A4 activity [82]. However, a study in healthy volunteers found that 14 days of saw palmetto (197 mg) administration did not alter CYP3A4 or CYP2D6 activity in 12 healthy volunteers [45]. Confirming these results, Gurley et al. observed that saw palmetto supplementation (160 mg twice daily for 28 days) had no significant effect on CYP3A and CYP2D6 activity in 12 healthy volunteers [27]. Based on these results, saw palmetto is unlikely to interact with medications metabolized by CYP3A4 and CYP2D6. Studies in humans are necessary to determine whether saw palmetto modulates other CYP isoforms and/or drug transport proteins such as P-gp.

5.3.19 *Soy (Glycine max)*

Soy is used for the treatment of menopausal symptoms, hyperlipidemia, the prevention of osteoporosis and cardiovascular disease, and numerous other maladies [57]. The active components of soybeans include the phytoestrogens (isoflavones and lignans) phytosterols and stigmasterol [57]. Soy constituents potentially associated with alterations in drug metabolism include genistein and daidzein [47].

In one study, genistein and daidzein were shown to inhibit UDP-glucuronosyltransferase in rat liver extract while genistein was shown to inhibit P-gp activity in another [133, 134]. In human liver microsomes, unhydrolized soy extract produced weak inhibition of CYP1A2 and CYP2D6 [47]. Of note, the majority of soy isoflavones in plasma occur in their unhydrolized form [47, 135]. In a series of *in-vitro* experiments using human liver microsomes, hydrolyzed soy extract inhibited CYP3A4, CYP2C9, CYP1A2, and CYP2D6, with CYP3A4 and CYP2C9 inhibition being the strongest [47]. In contrast to these *in vitro* findings, the same researchers showed that administration of soy extract (50 mg) to 20 healthy females did not alter CYP3A4 activity using 6-β-hydroxycortisol:cortisol ratios as an indicator of CYP3A4 activity [47]. The authors highlighted the lack of agreement between their *in vitro* and *in vivo* findings with regard to soy's ability to induce

CYP3A and they call into question the usefulness of *in vitro* screening studies to detect interactions between herbs and prescription medications. Further supporting this assertion, Wang et al. showed that soy extract had no effect of CYP2C9 activity as evidenced by a lack of an interaction with the CYP2C9 substrate losartan in healthy female volunteers [46]. To this end, soy extracts are unlikely to interact with medications via CYP3A4 or CYP2C9 modulation; whether soy extract inhibits or induces other CYP pathways or transport proteins will need to be determined through studies conducted in humans.

In addition to metabolic interactions, there may be an interaction between isoflavones in soy and antibiotics. Isoflavones are converted by intestinal bacteria to their active forms and this process may be impeded by antibiotics, which interfere with the bacteria's ability to transform isoflavones into their active moiety [136, 137]. While the occurrence of this interaction is probable, it is unlikely to be clinically relevant [57].

5.3.20 Evening Primrose (Oenothera biennis)

Evening primrose is used to treat premenstrual syndrome (PMS), endometriosis, chronic mastalgia, and symptoms of menopause [57]. It is also used orally for atopic eczema, psoriasis, rheumatoid arthritis, and osteoporosis [57]. Evening primrose oil contains 2–16% gamma-linolenic acid (GLA), 65–80% linoleic acid, and vitamin E [138, 139]. GLA is thought to be responsible for the anti-inflammatory effects of evening primrose oil [57].

A purified component of evening primrose oil, *cis*-Linoleic acid, was assessed for its ability to inhibit the catalytic activity of cDNA-expressed CYP isoforms in a series *in vitro* experiments [67]. *cis*-Linoleic acid was found to be a potent inhibitor (IC50 value ≤10 μM) of CYP2C9 and a moderate inhibitor of CYP1A2, CYP2C19, CYP2D6, and CYP3A4 (IC50 values 10–50 10 μM). Unfortunately, no drug interaction studies with evening primrose have been conducted in humans. As a result, it isn't possible to predict the potential of evening primrose to interact with CYP-metabolized medications or medications transported by ATP binding cassette proteins such as P-gp.

5.4 Issues and Concerns Related to the Use of Herbal Supplements

5.4.1 Product Content

Assessing herbal preparations for their potential to interact with prescription medications is wrought with a number of difficulties. First, is a general lack of quality control. There is significant variability in manufacturing techniques and storage of herbal products between manufacturers, which can lead to wide variability in content

within and between products. In one study of ephedra-containing dietary supplements, half of the 20 products tested contained alkaloids that differed by more than 20% of the amount listed on the label [140]. Substantial differences between content and product label claims have also been noted for dehydroepiandrosterone, ginseng, feverfew, and kava [141–145]. Even more concerning is the contamination of herbal products with heavy metals, pharmaceuticals, and prohibited animal and plant ingredients [146, 147]. Indeed, adulteration of herbal preparations with antibiotics, non-steroidal anti-inflammatory drugs, heavy metals, and hormones is not uncommon. To this end, it is difficult, and in many cases impossible, to predict potential drug interactions with herbal products that contain suspect ingredient content and/or adulterant compounds.

Due to the variability in ingredient content between (and in some cases within) brands of herbal products, drug interaction studies should be reviewed carefully. Ideally drug interaction studies should include an independent content analysis of all herbal products used in an investigation to confirm the presence of the putative interacting ingredient(s). In cases where such a content analysis is not performed, the study should use an herbal product that is manufactured by a reputable company; preferably one whose products have been previously analyzed and used in herb-drug interaction studies. In addition, manufacturers of the herbal product(s) under study should offer evidence that U.S. Pharmacopeia-endorsed quality control standards were followed during the manufacturing process of the herbal preparation.

5.4.2 Study Design

Studies assessing herb-drug interactions are typically conducted in human liver microsomes, cDNA expressed CYP isoforms, rat liver microsomes, rats, and humans. The most robust of these scientific approaches are studies conducted in humans. The literature is replete with examples of conflicting data obtained from *in vitro* versus *in vivo* (human) studies. A prime example is seen with St. John's wort. A series of *in vitro* microsomal experiments reported that crude extracts of St. John's wort inhibited CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 [148]. Conversely, studies in humans have clearly shown that St. John's wort is a potent inducer of these enzymes [20–25] (Table 5.1). Reasons for disparity between these *in vitro* and *in vivo* findings is likely multifactorial, including the specific herbal extract under study, methodology used in preparing the extract, concentration of the constituent(s) being tested, presence of concurrent herbal constituents or adulterant pharmaceuticals that may contribute to a positive interaction, and limitations of certain *in vitro* systems that cannot readily assess drug transport, enzymatic induction or phase 2 metabolism. Therefore, clinical studies in humans need to be conducted to identify those herbal preparations that have the potential to significantly interact with prescription medications.

In clinical studies, the duration that an herbal product is administered is an important consideration. Enzymatic induction is dependent on the half-life of the

substrate and the rate of enzymatic turnover; therefore it is a gradual process that requires multi-dose administration [149]. As a result, studies that do not administer an herbal preparation for at least 2 weeks should be interpreted with caution, as results may not be indicative of those that occur with prolonged administration. In addition to treatment duration, sample sizes for herb-drug interaction studies must be sufficiently large to detect relatively small differences in the exposure of coadministered medications, as the magnitude of most herb-drug interaction studies tends to be mild.

In addition to formal studies, a number of herb-drug interactions have been described in case reports [57]. However, case reports of drug interactions involving herbal preparations are often plagued by the following problems: anecdotal data usually in a single patient, confounding medications, missing information, lack of clarity regarding the temporal association between when the herbal product was started in relation to the putative interacting drug, and lack of formal content analysis of the herbal product. As a result, data from case reports should be interpreted as either (1) hypothesis-generating, alerting clinical researchers to potential drug interaction studies that might be profitable to conduct in the future or (2) as confirmatory evidence of a previously conducted herb-drug interaction study.

5.5 Patient Management Issues

Despite frequent use of CAM, many patients fail to disclose this information to their health care provider. In one study, 70% of CAM users didn't inform their primary care provider of their CAM use [150]. Patients may neglect to inform their clinicians about their CAM use since they are unlikely to attribute health problems to an herbal supplement that they assume to be "safe" and "natural" [2]. Or, patients may fear ridicule from their health care provider if they disclose their use of herbal supplements. For these reasons, clinicians should perform a complete medication history at each clinic visit to determine whether a patient has initiated treatment with a new herbal preparation; often patients will not share such information unless specifically prompted [151]. It is important that clinicians remain non-judgmental and supportive when interacting with patients who use CAM. Patients who insist on using CAM should be encouraged to use brands that are USP verified, have been used in clinical trials, or are at least manufactured by a reputable company. Once information regarding CAM use is elicited from patients, it should be recorded in detail in their medical record. Specific information regarding CAM use should include start and stop dates, dosages, and name and manufacturer of the product. This information may be useful in the future when assessing a potential drug interaction between CAM and an antiinfective medication.

CAM therapy should be considered in patients who experience unexplained toxicity or lack of efficacy from a particular antiinfective agent. For example, if a patient with HIV infection had a viral load <50 copies/mL and was tolerating their antiretroviral medications well, then suddenly experienced a large increase in viral

load or a new toxicity, the possibility that the patient initiated herbal therapy should be considered.

Determining whether an herbal product is likely to interact with a particular medication is oftentimes not straightforward and requires a familiarity with several quality resources. A number of web sites are extremely valuable in helping clinicians identify potential herb-drug interactions (Table 5.3). While information may not be available with regard to a specific herb-drug interaction, interactions can often be predicted by knowing which CYP pathways an herb modulates and which

Table 5.3 Selected internet resources for drug interactions involving herbal preparations

Source (web address)	Description	Accessibility
Natural Medicines Comprehensive Database (http://www.naturaldatabase.com)	Includes evidence-based monographs for nearly 1,100 individual natural ingredients and a searchable herb-drug interaction calculator. Primary references with links to PubMed are included for all interactions.	Paid subscription required
Natural Standard: The Authority on Integrative Medicine (www.naturalstandard.com)	Includes monographs with "Interactions" section and PubMed links to primary references.	Paid subscription required
American Botanical Council (www.herbalgram.org)	Includes monographs with "Interactions" section and primary references. Provides access to The Complete German Commission E monographs online as well as *HerbalGram* online.	Level of access is dependent on membership level; some content is free
Office of Dietary Supplements (http://www.ods.od.nih.gov)	Provides link to International Bibliographic Information on Dietary Supplements (IBIDS), which lists bibliographic citations and abstracts from published, international, and scientific literature on dietary supplements; access to additional databases is also provided.	Free
Dietary Supplement Verification Program (http://www.usp.org/USPVerified/)	Includes information on USP-verified dietary supplements and participating manufacturers along with an explanation of the verification process.	Free
Micromedex (http://www.micromedex.com/)	Drug interaction calculator recognizes herbal products in addition to over-the-counter and prescription medications. Monographs for alternative medications include specific information on drug interactions. Includes ratings for risk and documentation, mechanism of drug interactions, pharmacokinetic data, and dosing recommendations. Primary references are included.	Paid subscription required

(continued)

Table 5.3 (continued)

Source (web address)	Description	Accessibility
Medscape (http://www.medscape.com/druginfo/druginterchecker)	Drug interaction calculator recognizes herbal products in addition to over-the-counter and prescription medications. Includes severity rating, pharmacokinetic data, mechanism of drug interactions, and dosing recommendations. Includes primary references.	Free registration required
Lexi-Comp (www.lexi-comp.com)	Allows for interaction reviews of specific medications as well as patient-specific regimens; natural products are included. Assigned risk ratings and patient management information are included.	Paid subscription required
The University of Liverpool (www.hiv-druginteractions.org/)	Includes drug interaction charts for antiretroviral medications in combination with other agents, including 13 herbal supplements/vitamins.	Free
Facts & Comparisons (http://online.factsandcomparisons.com/)	Interactive tool that allows for interaction searches between herbs and prescription and over-the-counter medications. Includes severity, pharmacokinetic data, and mechanism of drug interactions.	Paid subscription required
Stockley's Herbal medicines Interactions; available online through: (http://www.medicinescomplete)	Available as an online subscription, book and CD-ROM package, personal user CD ROM, and book. Includes clinical and experimental interaction data on over 150 common herbs, dietary supplements, and nutraceuticals. Fully referenced and very detailed monographs; updates posted annually.	All formats require purchase

CYP pathways are used by concurrently administered medications. Information contained in Tables 5.1 and 5.2 of this chapter may also be useful in predicting such herb-drug interactions.

In addition to identifying potential herb-drug interactions from a qualitative stand point, it is also important to appreciate the quantitative nature of these putative interactions. For example, St. John's wort is a potent inducer of several CYP enzymes and has the potential to markedly reduce plasma concentrations of coadministered CYP substrates. As a result, St. John's wort should be avoided in patients receiving interacting medications. On the contrary, the majority of drug interactions with herbs other than St. John's wort tend to be of a mild nature, where coadministered drug concentrations are not increased/decreased by more than ≅35%. In these cases, only medications with narrow therapeutic indices are likely to be altered to a clinically significant degree. Fortunately, most antiinfective agents do not fit this description; other medications that do include cyclosporine, tacrolimus, irinotecan, sildenafil and sirolimus.

5.6 Conclusions

CAM use is common in patients with infectious diseases, particularly those with HIV infection. Predicting herb-drug interactions in this population is often difficult, as *in vitro* studies frequently fail to accurately predict the ability/inability of herbal preparations to interact with medications in humans. Therefore, future studies should be conducted in humans, employ a solid study design, and use herbal products that are USP, or otherwise independently verified. Financial support for such studies should be a priority among both private and public funding agencies.

References

1. Eisenberg DM, Davis RB, Ettner SL et al. Trends in alternative medicine use in the United States, 1990–1997. JAMA 1998;280:1569–75.
2. Tachjian A, Maria V, Jahangir A, Use of herbal products and potential interactions in patients with cardiovascular diseases. J Am Coll Cardiol 2010;55:515–25.
3. Jordan SA, Cunningham DG, Marles RJ. Assessment of herbal medicinal products: challenges, and opportunities to increase the knowledge base for safety assessment. Toxicol Appl Pharmacol 2010;243:198–216.
4. Dietary Supplement Health and Education Act 1994, Pub. L. 103–417, Sec,1(a), 108 Stat. 4325 (Oct. 25, 1994).
5. http://www.usp.org/USPVerified/dietarySupplements/ (accessed June 10, 2010).
6. Bent S, Ko R. Commonly used herbal medicines in the United States. Am J Med 2004; 116:478–85.
7. Dreikorn K. Complementary and alternative medicine in urology. BJU Int 2005;96:1177–84.
8. Wu T, Yang X, Zeng X, Poole P. Traditional Chinese medicine in the treatment of acute respiratory tract infections. Respir Med 2008;102:1093–8.
9. Stickel F, Schuppan D. Herbal medicine in the treatment of liver diseases. Dig Liver Dis 2007;39:293–304.
10. Chichon PG. Herbs and the common cold. Adv Nurse Pract 2000;8:31–2.
11. Littlewood RA, Vanable PA. Complementary and alternative medicine use among HIV-positive people: research synthesis and implications for HIV care. AIDS Care 2008;20: 1002–1018.
12. Fairfield KM, Eisenberg DM, Davis RB, Libman H, Phillips RS. Patterns of use, expenditures, and perceived efficacy of complementary and alternative therapies in HIV-infected patients. Arch Intern Med 1998;158:2257–2264.
13. Hsiao AF, Wong MD, Kanouse DE et al. Complementary and alternative medicine use and substitution for conventional therapy by HIV-infected patients. J Acquir Immune Defic Syndr 2003;33:157–65.
14. Cherniak EP, Senzal RS, Pan CX. Correlates of use of alternative medicine by the elderly in an urban population. J Altern Complement Med 2001;7:277–80.
15. Tanaka E, Hisawa S. Clinically significant pharmacokinetic drug interactions with psychoactive drugs: antidepressants and antipsychotics and the cytochrome P450 system. J Clin Pharmacy Ther 1999;24:7–16.
16. Indiana University School of Medicine. Cytochrome P450 Drug Interaction Table. Available at: http://medicine.iupui.edu/clinpharm/ddis/table.asp (accessed June 10, 2010).
17. Marchetti S, Mazzanti R, Beijnen JH, Schellens JH. Concise review: Clinical relevance of drug drug and herb drug interactions mediated by the ABC transporter ABCB1 (MDR1, P-glycoprotein). Oncologist 2007;12:927–41.

18. Garrovo C, Rosati A, Bartoli F, Decorti G. St John's wort modulation and developmental expression of multidrug transporters in the rat. Phytother Res 2006;20:468–73.
19. Harris RZ, Jang GR, Tsunoda S. Dietary effects on drug metabolism and transport. Clin Pharmacokinet 2003;42:1071–88.
20. Gurley BJ, Gardner SF, Hubbard MA et al. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. Clin Pharmacol Ther 2002;72:276–87.
21. Gurley BJ, Swain A, Williams DK, Barone G, Battu SK. Gauging the clinical significance of P-glycoprotein-mediated herb-drug interactions: comparative effects of St. John's wort, Echinacea, clarithromycin, and rifampin on digoxin pharmacokinetics. Mol Nutr Food Res 2008;52:772–79.
22. Wang LS, Zhou G, Zhu B. St John's wort induces both cytochrome P450 3A4-catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole. Clin Pharmacol Ther 2004;75:191–7.
23. Jiang X, Williams KM, Liauw WS et al. Effect of St. John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2004; 57:592–599.
24. Xu H, Liauw KM, Murray M, Day RO, McLachlan AJ. Effects of St. John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. Br J Pharmacol 2008;153:1579–86.
25. Hafner V, Jäger M, Matthée A-K et al. Effect of simultaneous induction and inhibition of CYP3A by St. John's wort and ritonavir an CYP3A activity. Clin Pharmacol Ther 2010;87: 191–196.
26. Markowitz JS, Devane CL, Chavin KD, Taylor RM, Ruan Y, Donovan JL. Effects of garlic (Allium sativum L.) supplementation on cytochrome P450 2D6 and 3A4 activity in healthy volunteers. Clin Pharmacol Ther 2003;74:170–7.
27. Gurley BJ, Gardner SF, Hubbard MA. In vivo assessment of botanical supplementation on human cytochrome P450 phenotypes: Citrus aurantium, Echinacea purpurea, milk thistle, and saw palmetto. Clin Pharmacol Ther 2004;76:428–40.
28. Gurley BJ, Barone GW, Williams DK. Effect of milk thistle (Silybum marianum) and black cohosh (Cimicifuga racemosa) supplementation on digoxin pharmacokinetics in humans. Drug Metab Dispos 2006;34:69–74.
29. Robertson SM, Davey RT, Voell J, Formentini E, Alfaro RM, Penzak SR. Effect of *Ginkgo biloba* extract on lopinavir, midazolam, and fexofenadine pharmacokinetics in healthy subjects. Curr Med Res Opin 2008;24:591–99.
30. Jiang X, Williams KM, Liauw WS et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2005;59: 425–32.
31. Mahutsky MA, Anderson GD, Miller JW, Elmer GW. Ginkgo biloba: evaluation of CYP2C9 drug interactions in vitro and in vivo. Am J Ther 2006;13:24–31.
32. Yin OQP, Tomlinson B, Waye MMY, Chow AHL, Chow MSS. Pharmacogenetics and herb-drug interactions: experience with *Ginkgo biloba* and omeprazole. Pharmacogenetics 2004; 14:841–850.
33. Yasui-Furukori N, Furukori H, Kaneda A, Kaneko S, Tateishi T. The effects of Ginkgo biloba extracts on the pharmacokinetics and pharmacodynamics of donepezil. J Clin Pharmacol 2004;44:538–42.
34. Penzak SR, Robertson SM, Hunt JD et al. *Echinacea Purpurea* significantly induces cytochrome P450 3A (CYP3A) but does not alter lopinavir-ritonavir exposure in healthy subjects. Pharmacotherapy (*in press*).
35. Gorski JC, Huang SM, Pinto A et al. The effect of echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo. Clin Pharmacol Ther 2004;75:89–100.
36. Freeman C, Spelman K. A critical evaluation of drug interactions with Echinacea spp. Mol Nutr Food Res 2008;52:789–98.
37. Jiang X, Blair EY, McLachlan AJ. Investigation of the effects of herbal medicines on warfarin response in healthy subjects: a population pharmacokinetic-pharmacodynamic modeling approach. J Clin Pharmacol 2006;46:1370–8.

38. Gurley BJ, Gardner SF, Hubbard MA et al. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. Clin Pharmacol Ther 2005;77:415–26.
39. Sandhu RS, Prescilla RP, Simonelli TM, Edwards DJ. Influence of goldenseal root on the pharmacokinetics of indinavir. J Clin Pharmacol 2003;43:1283–8.
40. Gurley BJ, Swain A, Barone GW et al. Effect of goldenseal (Hydrastis canadensis) and kava kava (Piper methysticum) supplementation on digoxin pharmacokinetics in humans. Drug Metab Dispos 2007;35:240–5.
41. Donovan JL, DeVane CL, Chavin KD et al. Multiple night-time doses of valerian (Valeriana officinalis) had minimal effects on CYP3A4 activity and no effect on CYP2D6 activity in healthy volunteers. Drug Metab Dispos 2004;32:1333–1336.
42. Dong SX, Ping ZZ, Xiao WZ et al. Possible enhancement of the first-pass metabolism of phenacetin by ingestion of grape juice in Chinese subjects. Br J Clin Pharmacol 1999;48: 638–40.
43. Donovan JL, Chavin KD, Devane CL et al. Green tea (Camellia sinensis) extract does not alter cytochrome p450 3A4 or 2D6 activity in healthy volunteers. Drug Metab Dispos 2004;32:906–8.
44. Tankanow R, Tamer HR, Streetman DS et al. Interaction study between digoxin and a preparation of hawthorn (Crataegus Oxyacantha). J Clin Pharmacol 2003;43:637–42.
45. Markowitz JS, Donovan JL, Devane CL et al. Multiple doses of saw palmetto (Serenoa repens) did not alter cytochrome P450 2D6 and 3A4 activity in normal volunteers. Clin Pharmacol Ther 2003;74:536–42.
46. Wang G, Xiao CQ, Li Z et al. Effect of soy extract administration on losartan pharmacokinetics in healthy female volunteers. Ann Pharmacother 2009;43:1045–9.
47. Anderson GD, Rosito G, Mohustsy MA, Elmer GW. Drug interaction potential of soy extract and Panax ginseng. J Clin Pharmacol. 2003;43:643–8.
48. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St. John's wort. Lancet 2000;355:547–48.
49. Rengelshausen J, Banfield M, Riedel KD et al. Opposite effects of short-term and long-term St. John's wort intake on voriconazole pharmacokinetics. Clin Pharmacol Ther 2005;78:25–33.
50. Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. Clin Infect Dis 2002;34:234–8.
51. Gallicano K, Foster B, Choudhri S. Effect of short-term administration of garlic supplements on single-dose ritonavir pharmacokinetics in healthy volunteers. Br J Clin Pharmacol 2003;55:199–202.
52. Piscitelli SC, Formentini E, Burstein AH, Alfaro R, Jagannatha S, Falloon J. Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers. Pharmacotherapy 2002;22: 551–6.
53. DiCenzo R, Shelton M, Jordan K et al. Coadministration of milk thistle and indinavir in healthy subjects. Pharmacotherapy 2003;23:866–70.
54. Mills E, Wilson K, Clarke M. Milk thistle and indinavir: a randomized controlled pharmacokinetics study and meta-analysis. Eur J Clin Pharmacol 2005;61:1–7.
55. Rajnarayana K, Reddy MS, Vidyasagar J, Krishna DR. Study on the influence of silymarin pretreatment on metabolism and disposition of metronidazole. Arzneimittelforschung. 2004; 54:109–13.
56. Mogatle S, Skinner M, Mills E, Kanfer I. Effect of African potato (Hypoxis hemerocallidea) on the pharmacokinetics of efavirenz. S Afr Med J 2008;98:945–9.
57. Jellin JM. Natural Medicines Comprehensive Database. Therapeutic Research Faculty, Stockton, CA. Available at www.naturaldatabase.com (accessed June 11, 2010).
58. Dürr D, Stieger B, Kullak-Ublick GA et al. St. John's wort induces intestinal P-glycoprotein/ MDR1 and intestinal and hepatic CYP3A4. Clin Pharmacol Ther 2000;68:598–604.
59. Staudinger JL, Ding X, Lichti K. Pregnane X receptor and natural products: beyond drug-drug interactions. Expert Opin Drug Metab Toxicol 2006;2:847–57.
60. de Maat MM, Hoetelmans RM, Math t RA et al. Drug interaction between St John's wort and nevirapine. AIDS 2001;15:420–21.

61. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the *N*-oxidation of voriconazole. Drug Metab Dispos 2003;31:540–47.
62. Moore LB, Goodwin B, Jones SA et al. St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. Proc Natl Acad Sci USA 2009;97:7500–02.
63. Zhou SF, Xue CC, Yu XQ, Wang G. Metabolic activation of herbal and dietary constituents and its clinical and toxicological implications: an update. Curr Drug Metab. 2007;8:526–53.
64. Brady JF, Isizaki H, Fukuto JM et al. Inhibition of cytochrome P-450 2E1 by diallyl sulfide and its metabolites. Chem Res Toxicol 1991;4:642–7.
65. Foster BC, Foster MS, Vandenhoek S. An in vitro evaluation of human cytochrome P450 3A4 and P-glycoprotein inhibition by garlic. J Pharm Pharm Sci 2001;4:176–84.
66. Arnault I, Haffner T, Siess MH, Vollmar A, Kahane R, Auger J. Analytical method for appreciation of garlic therapeutic potential and for validation of a new formulation. J Pharm Biomed Anal 2005;37:963–70.
67. Zou L, Harkey GL, Henderson GL. Effects of herbal components on cDNA-expressed cytochrome P450 enzyme catalytic activity. Life Sci 2002;71:1579–89.
68. Laroche M, Choudhri S, Gallicano K, Foster B. Severe gastrointestinal toxicity with concomitant ingestion of ritonavir and garlic. Can J Infect Dis 1998;9(Suppl A):471P.
69. Budzinski JW, Trudeau VL, Drouin CE, Panahi M, Arnason JT, Foster BC. Modulation of human cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) in Caco-2 cell monolayers by selected commercial-source milk thistle and goldenseal products. Can J Physiol Pharmacol 2007;85:966–78.
70. Sridar C, Goosen TC, Kent UM, Williams JA, Hollenberg PF. Silybin inactivates cytochromes P450 3A4 and 2C9 and inhibits major hepatic glucuronosyltransferases. Drug Metab Dispos 2004;32:587–94.
71. van Erp NP, Baker SD, Zhao M et al. Effect of milk thistle (Silybum marianum) on the pharmacokinetics of irinotecan. Clin Cancer Res 2005;11:7800–6.
72. Sidelmann UG, Cornett C, Tjørnelund J, Hansen SH. A comparative study of precision cut liver slices, hepatocytes, and liver microsomes from the wistar rats using metronidazole as a model substrate. Xenobiotica 1996;26:709–22.
73. Beckmann-Knopp S, Rietbrock S, Weyhenmeyer R, et al. Inhibitory effects of silibinin on cytochrome P-450 enzymes in human liver microsomes. Pharmacol Toxicol 2000;86:250–6.
74. Kim DH, Jin YH, Park JB, Kobashi K. Silymarin and its components are inhibitors of beta-glucuronidase. Biol Pharm Bull 1994;17:443–5.
75. Venkataramanan R, Ramachandran V, Komoroski BJ, et al. Milk thistle, a herbal supplement, decreases the activity of CYP3A4 and uridine diphosphoglucuronosyl transferase in human hepatocyte cultures. Drug Metab Dispos 2000;28:1270–3.
76. Deng JW, Shon JH, Shin HJ, et al. Effect of silymarin supplement on the pharmacokinetics of rosuvastatin. Pharm Res 2008;25:1807–14.
77. Blumenthal M. The Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicines. Austin: American Botanical Council, 1998.
78. Kubota Y, Kobayashi K, Tanaka N et al. Interaction of Ginkgo biloba extract (GBE) with hypotensive agent, nicardipine, in rats. In vivo 2003;17:409–412.
79. Shinozuka K, Umegaki K, Kubota Y et al. Feeding of Ginkgo biloba extract (GBE) enhances gene expression of hepatic cytochrome P-450 and attenuates the hypotensive effect of nicardipine in rats. Life Sci 2002;70:2783–2792.
80. Umegaki K, Saito K, Kubota Y, Sanada H, Yamada K, Shinozuka K. Ginkgo biloba extract markedly induces pentoxyresorufin O-dealkylase activity in rats. Jpn J Pharmacol 2002;90: 345–351.
81. Sugiyama T, Kubota Y, Shinozuka K, Yamada S, Yamada K, Umegaki K. Induction and recovery of hepatic drug metabolizing enzymes in rats treated with Ginkgo biloba extract. Food Chem Toxicol 2004;42:953–957.
82. Budzinski JW, Foster BC, Vandenhoek S, Arnason JT. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 2000;7:273–282.

83. He N, Edeki TI. Effects of ginseng and Ginkgo biloba components on CYP3A4 mediated testosterone 6beta-hydroxylation in human liver microsomes [abstract]. Clin Pharmacol Ther 2003;73:50. Abstract PII-81.
84. Yoshioka M, Ohnishi N, Koishi T, et al. Studies on interactions between functional foods or dietary supplements and medicines. IV. Effects of ginkgo biloba leaf extract on the pharmacokinetics and pharmacodynamics of nifedipine in healthy volunteers. Biol Pharm Bull 2004 Dec;27(12):2006–9.
85. Morse GD, Rosenkranz S, Para MF et al. Amprenavir and Efavirenz Pharmacokinetics before and after the Addition of Nelfinavir, Indinavir, Ritonavir, or Saquinavir in Seronegative Individuals. Antimicrob Agents Chemother 2005;49:3373–81.
86. Gallicano K, Khaliq Y, Carignan G, Tseng A, Walmsley S, Cameron DW. A pharmacokinetic study of intermittent rifabutin dosing with a combination of ritonavir and saquinavir in patients infected with human immunodeficiency virus. Clin Pharmacol Ther 2001;70:149–58.
87. Wiegman DJ, Brinkman K, Franssen EJ. Interaction of Ginkgo biloba with efavirenz. AIDS 2009;23:1184–5.
88. Modarai M, Gertsch J, Suter A, Heinrich M, Kortenkamp A. Cytochrome P450 inhibitory action of Echinacea preparations differs widely and co-varies with alkylamide content. J Pharm Pharmacol 2007;59:567–73.
89. The New Mexico AIDS Education and Training Center at the University of New Mexico Health Sciences Center. Echinacea. Fact Sheet Number 726. Available at: www.aidsinfonet.org (accessed June 11, 2010).
90. Sullivan Al, Laba JG, Moore JA, Lee TDG. *Echinacea*-induced macrophage activation. Immunopharmacol Immunotoxicol 2008;30:553–74.
91. Morlat P, Pereira E, Clayette P et al. Early evolution of plasma soluble TNF-alpha p75 receptor as a marker of progression in treated HIV-infected patients. AIDS Res Hum Retroviruses 2008;24:1383–9.
92. van den Bout-van den Beukel CJ, Koopmans PP, van der Ven AJ, De Smet PA, Burger DM. Possible drug-metabolism interactions of medicinal herbs with antiretroviral agents. Drug Metab Rev 2006;38:477–514.
93. Streetman DS, Bertino JS Jr, Nafziger AN. Phenotyping of drug-metabolizing enzymes in adults: a review of in-vivo cytochrome P450 phenotyping probes. Pharmacogenetics 2000 Apr;10(3):187–216.
94. Smith M, Lin KM, Zheng YP. An open trial of nifedipine-herb interactions: nifedipine with St. John's wort, ginseng, or ginkgo biloba [abstract]. Clin Pharmacol Ther 2001;69:86. Abstract PIII-89.
95. Henderson GL, Harkey MR, Gershwin ME, Hackman RM, Stern JS, Stresser DM. Effects of ginseng components on c-DNA-expressed cytochrome P450 enzyme catalytic activity. Life Sci 1999;65:209–214.
96. Furutsu M, Koyama Y, Kusakabe M, Takahashi S. Preventative effect of the extract of Du-zhong (Tochu) leaf and ginseng root on acute toxicity of chlorpyrifos. Jpn J Toxicol Environ Health 1997;43:92–100.
97. Malati CY, Robertson SM, Hunt JD et al. Influence of Panax ginseng on Cytochrome P450(CYP)3A and P-glycoprotein (P-gp) Activity in Healthy Participants. J Clin Pharmacol. 2011 Jun 6. [Epub ahead of print].
98. Mills E, Cooper C, Seely D, Kanfer. African herbal medicines in the treatment of HIV: Hypoxis and Sutherlandia. An overview of evidence and pharmacology. Nutr J 2005;4:19.
99. Albrecht CF, Kruger PB, Smit BJ et al. The pharmacokinetic behaviour of hypoxoside taken orally by patients with lung cancer in a phase I trial. S Afr Med J 1995;85::861–5.
100. Mills E, Foster BC, van Heeswijk R et al. Impact of African herbal medicines on antiretroviral metabolism. AIDS 2005;19:95–97.
101. Nair VD, Foster BC, Thor Arnason J, Mills EJ, Kanfer I. In vitro evaluation of human cytochrome P450 and P-glycoprotein-mediated metabolism of some phytochemicals in extracts and formulations of African potato. Phytomedicine 2007;14:498–507.
102. Brown L, Heyneke O, Brown D, van Wyk JP, Hamman JH. Impact of traditional medicinal plant extracts on antiretroviral drug absorption. J Ethnopharmacol 2008;119:588–92.

103. Tsukamoto S, Aburatani M, Ohta T. Isolation of CYP3A4 Inhibitors from the Black Cohosh (Cimicifuga racemosa). Evid Based Complement Alternat Med 2005;2:223–226.
104. Gurley BJ, Swain A, Hubbard MA et al. Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: effects of milk thistle, black cohosh, goldenseal, kava kava, St. John's wort, and Echinacea. Mol Nutr Food Res 2008;52:755–63.
105. Abourashed EA, Khan IA. High-performance liquid chromatography determination of hydrastine and berberine in dietary supplements containing goldenseal. J Pharm Sci. J Pharm Sci 2001;90:817–22.
106. Etheridge AS, Black SR, Patel PR, So J, Mathews JM. An in vitro evaluation of cytochrome P450 inhibition and P-glycoprotein interaction with goldenseal, Ginkgo biloba, grape seed, milk thistle, and ginseng extracts and their constituents. Planta Med 2007;73:731–41.
107. Qiu W, Jiang XH, Liu CX, Ju Y, Jin JX. Effect of berberine on the pharmacokinetics of substrates of CYP3A and P-gp. Phytother Res 2009;23:1553–8.
108. Lin HL, Liu TY, Lui WY, Chi CW. Up-regulation of multidrug resistance transporter expression by berberine in human and murine hepatoma cells. Cancer 1999;85(9):1937–42.
109. Mathews JM, Etheridge AS, Black SR. Inhibition of human cytochrome P450 activities by kava extract and kavalactones. Drug Metab Dispos 2002;30:1153–7.
110. Zou L, Henderson GL, Harkey MR, Sakai Y, Li A. Effects of kava (Kava-kava, 'Awa, Yaqona, Piper methysticum) on c-DNA-expressed cytochrome P450 enzymes and human cryopreserved hepatocytes. Phytomedicine 2004;11:285–94.
111. Unger M, Frank A. Simultaneous determination of the inhibitory potency of herbal extracts on the activity of six major cytochrome P450 enzymes using liquid chromatography/mass spectrometry and automated online extraction. Rapid Commun Mass Spectrom 2004;18:2273–81.
112. Weiss J, Sauer A, Frank A, Unger M. Extracts and kavalactones of Piper methysticum G. Forst (kava-kava) inhibit P-glycoprotein in vitro. Drug Metab Dispos 2005;33:1580–3.
113. Escher M, Desmeules J, Giostra E, Mentha G. Drug Points: hepatitis associated with kava, a herbal remedy for anxiety. BMJ 2001;322:139.
114. Russmann S, Lauterberg BH, Hebling A. Kava hepatotoxicity [letter]. Ann Intern Med 2001;135:68.
115. Liver Toxicity with kava. Pharmacist's Letter/Prescriber's Letter 2001;18(1):180115.
116. Consultation letter MLX 286: Proposals to prohibit the herbal ingredient Kava-Kava (Piper methysticum) in unlicensed medicines. Medicines Control Agency, United Kingdom, July 19, 2002.
117. Li XZ, Ramzan I. Role of ethanol in kava hepatotoxicity. Phytother Res 2010;24:475–80.
118. Lefebvre T, Foster BC, Drouin CE, et al. In vitro activity of commercial valerian root extracts against human cytochrome P450 3A4. J Pharm Pharmaceut Sci 2004;7:265–73.
119. Hellum BH, Nilsen OG. In vitro inhibition of CYP3A4 metabolism and P-glycoprotein-mediated transport by trade herbal products. Basic Clin Pharmacol Toxicol 2008;102:466–75.
120. Sustiva Prescribing Information. Bristol Myers Squibb Pharma. Princeton, NJ, USA. March, 2010.
121. Chantre P, Cappelaere A, Leblan D, et al. Efficacy and tolerance or Harpagophytum procumbens versus diacerhein in treatment of osteoarthritis. Phytomedicine 2000;7:177–84.
122. Chisholm A, Mann J, Skeaff M, et al. A diet rich in walnuts favourably influences plasma fatty acid profile in moderately hyperlipidaemic subjects. Eur J Clin Nutr 1998;52:12–6.
123. Freedman JE, Parker C, Li L, et al. Select flavonoids and whole juice from purple grapes inhibit platelet function and enhance nitric oxide release. Circulation 2001;103:2792–8.
124. Nuttall SL, Kendall MJ, Bombardelli E, Morazzoni P. An evaluation of the antioxidant activity of a standardized grape seed extract, Leucoselect. J Clin Pharm Ther 1998;23:385–89.
125. Nishikawa M, Ariyoshi N, Kotani A et al. Effects of continuous ingestion of green tea or grape seed extracts on the pharmacokinetics of midazolam. Drug Metab Pharmacokinet 2004;19:280–9.
126. Raucy JL. Regulation of CYP3A4 expression in human hepatocytes by pharmaceuticals and natural products. Drug Metab Dispos 2003;31:533–9.
127. Sohn OS, Surace A, Fiala ES et al. Effects of green and black tea on hepatic xenobiotic metabolizing systems in the male F344 rat. Xenobiotica 1994;24:119–27.

128. Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (Camellia sinensis). Ann Intern Med 2006;144:68–71.
129. Jimenez-Saenz M, Martinez-Sanchez, MDC. Acute hepatitis associated with the use of green tea infusions. J Hepatol 2006;44:616–9.
130. Suekawa M, Ishige A, Yuasa K, et al. Pharmacological studies on ginger. I. Pharmacological actions of pungent constituents, (6)-gingerol and (6)-shogaol. J Pharmacobiodyn 1984;7: 836–48.
131. Pongrojpaw D, Somprasit C, Chanthasenanont A. A randomized comparison of ginger and dimenhydrinate in the treatment of nausea and vomiting in pregnancy. J Med Assoc Thai 2007;90:1703–9.
132. Langner E, Greifenberg S, Gruenwald J. Ginger: history and use. Adv Ther 1998;15:25–44.
133. Castro AF, Altenberg GA. Inhibition of drug transport by genistein in multidrug-resistant cells expressing P-glycoprotein. Biochem Pharmacol 1997;53:89–93.
134. Jäger W, Zembsch B, Wolschann P et al. Metabolism of the anticancer drug flavopiridol, a new inhibitor of cyclin dependent kinases, in rat liver. Life Sci 1998;62:1861–73.
135. South African Development Committee. Ministerial consultative meeting on nutrition and HIV/AIDS, Johannesburg, South Africa, January 20, 2002.
136. Morito K, Hirose T, Kinjo J, et al. Interaction of phytoestrogens with estrogen receptors alpha and beta. Biol Pharm Bull 2001;24:351–6.
137. Halm BM, Franke AA, Ashburn LA, Hebshi SM, Wilkens LR. Oral antibiotics decrease urinary isoflavonoid excretion in children after soy consumption. Nutr Cancer 2008;60:14–22.
138. Kleijnen J. Evening primrose oil. BMJ 1994;309:824–825.
139. Belch J, Hill A. Evening primrose oil and borage oil in rheumatologic conditions. Am J Clin Nutr 2000;71:352S–6S.
140. Gurley BJ, Gardner SF, Hubbard MA. Content versus label claims in ephedra-containing dietary supplements. Am J Health-Syst Pharm 2000;57:963–69.
141. Parasrampuria J, Schwartz K. Quality control of dehydroepiandrosterone dietary supplement products. JAMA 1998;280:1565. [Letter].
142. Liberti LE, Der Marderosian A. Evaluation of commercial ginseng products. J Pharm Sci 1978;67:1487–89.
143. Cui J, Garle M, Eneroth P, Björkhem I. What do commercial ginseng preparations contain? Lancet. 1994;344:134. [Letter].
144. Heptinstall S, Awang DV, Dawson BA, Kindack D, Knight DW, May J. Parthenolide content and bioactivity of feverfew (*Tanacetum parthenium* (L.) Schulkz-Bip). Estimation of commercial and authenticated feverfew products. J Pharm Pharmacol 1992;44:391–95.
145. Webb G. "fX" chemically adulterated product does not contain kava. Herbalgram 1997;39:9.
146. Saper RB, Phillips RS, Sehgal A et al. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA 2008;300:915–23.
147. Corns CM. Herbal remedies and clinical biochemistry. Ann Clin Biochem 2003;40 (Pt 5):489–507.
148. Obach RS. Inhibition of human cytochrome P450 enzymes by constituents of St. John's Wort, an herbal preparation used in the treatment of depression. J Pharmacol Exp Ther 2000;294:88–95.
149. Kashuba, A.D.M., Bertino Jr., J.S. (2005). Mechanisms of Drug interactions I: Absorption, Metabolism and Excretion. In: S.C. Piscitelli, K.A. Rodvold (Eds.), Drug Interactions in Infectious Diseases (2nd Ed., pp. 13–39). Totowa, NJ: Human Press.
150. Weber K, Schneider M, Sacks H et al. Trends in complementary/alternative medicine (CAM) use in a large cohort of HIV-infected women in the US from 1994–2001. XIV International AIDS Conference, Barcelona Spain. July 7–12, 2002: Abstract WePeB6004.
151. Behm Dillon DM, Penzak SR, Bailey Klepser T. The use of herbals by patients with HIV. Adv Pharm 2004;2:41–60.

Chapter 6
Drug-Cytokine Interactions

Jenna O. McNeil and Kerry B. Goralski

Abstract There are many documented examples of altered drug disposition in human conditions that stimulate host cytokine responses. These include viral, bacterial or parasitic infections, tissue injury, surgery, cancer and autoimmune conditions. Interferons, interleukins-1 and-6 and tumour necrosis factor are the central mediators. These cytokines have been traditionally viewed with respect to their ability to suppress hepatic cytochrome P450 (CYP)-mediated drug detoxification. Such aberrant drug handling has placed patients at risk for adverse drug responses to low therapeutic index, CYP-metabolized drugs like theophylline. It is now evident that drug-cytokine interactions are broader than once appreciated. They involve CYPs and drug transporter proteins like ABCB1 (P-glycoprotein) in the liver, intestine, kidney, blood-brain barrier, placenta and even immune cells. The consequences of drug-cytokine interactions are altered absorption, elimination and/or cellular and tissue distribution of drugs. The outcomes can be negative or positive depending on the drug, the anatomical site of the interaction and the therapeutic objectives. This chapter provides a historical overview of drug-cytokine interactions, discuss recent advances and examines the clinical scenarios in which infections or inflammation might lead to abnormal drug handling and drug responses.

6.1 Introduction

Drug disposition is the general term describing what the body does to a drug and is governed by the processes of drug absorption, distribution, metabolism and elimination. Evidence of altered drug disposition during infection dates back some

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Table 6.1 List of abbreviations

ABC: ATP-binding cassette transporter	**IMID**: immune-mediated inflammatory disease
ABCB1: p-glycoprotein	**LPS**: lipopolysaccharide
ABCC1-4: multidrug resistance proteins (MRP) 1-4	**M3G**: morphine-3-glucuronide
ABCG2: breast cancer resistance protein (BCRP)	**M6G**: morphine-6-glucuronide
AhR: aryl hydrocarbon receptor	**NF-κB**: nuclear factor kappa B
BBB: blood-brain barrier	**NO**: nitric oxide
CD: Crohn's disease	**OAT**: organic anion transporter
CL: clearance	**OATP**: organic anion transporting polypeptide
$\mathbf{CL_R}$: renal clearance	**OCT**: organic cation transporter
CNS: central nervous system	**PolyIC**: polyinosinic-polycytidylic acid
CRP: C reactive protein	**PPI**: proton pump inhibitor
CSF: cerebrospinal fluid	**PRR**: pattern recognition receptor
CYP: cytochrome P450 enzyme	**PXR**: pregnane-x-receptor
ET-1: endothelin-1	**SLC**: solute carrier transporter
HIV: human immunodeficiency virus	**TLR4**: toll-like receptor 4
IBD: inflammatory bowel disease	**TNF**: tumor necrosis factor
IFN: interferon	**UC**: ulcerative colitis
IL: interleukin	

40 years from observations of impaired quinine metabolism in humans with malaria or enhanced cerebrospinal fluid (CSF) accumulation of rifampin and ethambutal in cases of meningitis [1–4]. While the mechanisms were not known at the time, pioneering preclinical work carried out in the mid 1970s solidified the idea of drug-cytokine interactions [5–9]. The traditionally described drug-cytokine interactions referred to reduced hepatic cytochrome P450 (CYP) metabolism that occurred following exposure to mediators of the innate immune response. It is now established that drug transporters and possibly drug receptors are regulated by cytokines [10–12]. Further, the effects of cytokines on drug disposition are not liver specific, but involve the brain, intestine, kidney, placenta and immune and cancer cells [10, 13–20]. To update the definition "drug-cytokine interaction" will herein refer to any interaction between a cytokine and drug-metabolizing enzyme, drug transporter or receptor that leads to altered drug disposition and/or drug response. To assist the reader a complete list of abbreviations used in this chapter is provided in Table 6.1.

Research carried out over the past 30 years has greatly expanded the understanding of drug-cytokine interactions. It is presently well known that inflammatory conditions including several infections, surgical procedures, inflammatory diseases of the central nervous system (CNS), cancer and autoimmune diseases and biological cytokine therapies alter drug disposition processes (Fig. 6.1 and Table 6.2) [13, 55, 56]. These positive primary stimuli elevate, whereas negative primary stimuli (anti-cytokine therapy and resolution of inflammation) decrease the levels of inflammatory cytokines, interleukins 1 and 6 (IL-1 and IL-6), tumor necrosis factor alpha (TNFα) and interferons (IFNs). The inflammatory cytokines (primary mediators)

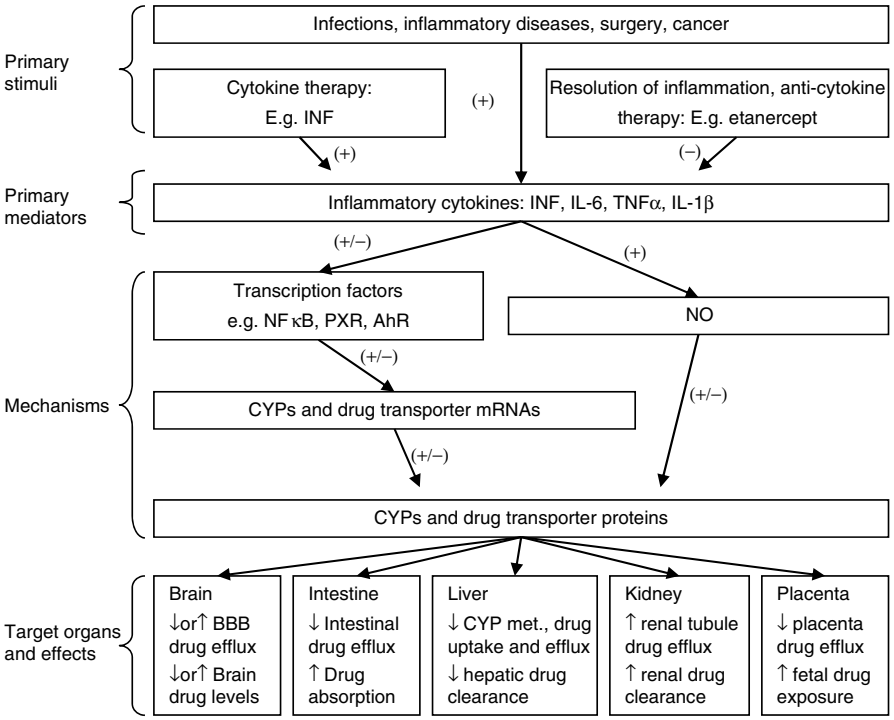

Fig. 6.1 Outline of the proposed pathways and target organs of drug-cytokine interactions in infections and inflammatory diseases. (+) or ↑ symbols and (−) or ↓ symbols denote activation or inhibition, respectively. A complete list of abbreviations is provided in Table 6.1

Table 6.2 Organisms and inflammatory stimuli known to alter CYP metabolism, drug transporter function, drug disposition or drug effectiveness in humans

Viruses	Bacteria	Inflammatory agents	Inflammatory conditions
Hepatitis [21–24]	*Helicobacter pylori* [12, 25–27]	Vaccines [28]	Tissue injury/trauma [29]
Influenza [30, 31]		IFNα, β and γ [32, 33]	Surgical stress [34]
Adenovirus [30]		IL-1α, -1β,-2 and -6 [32, 33]	Cancer [35–39]
Herpes Simplex [40]	**Parasites**	LPS [41, 42]	IBD [43, 44]
Meningitis [2, 3]	*Plasmodium falciparum* [1, 4]	TNFα [32, 33]	CNS diseases [45–48]
HIV [46, 49]	*Schistosoma mansoni* [50]		Heart failure [51]
	Opisthorchiasis viverrini [52]		Sepsis [53, 54]

A complete list of abbreviations is provided in Table 6.1

bind to cell surface receptors in target organs and activate intracellular signaling cascades that increase or decrease transcription factors to regulate CYP and drug transporter gene transcription, protein levels and corresponding metabolic and transport activity [13, 21, 55–58]. A second mechanism involves production of nitric oxide (NO) by nitric oxide synthase (NOS), which affects drug metabolism and transport through transcriptional or post-translational mechanisms [32, 58–62]. The end result is most often a loss in drug metabolism and transport but there are instances where enhanced metabolic or transport activity occurs and these effects appear to be dynamic in time. This ultimately depends on the target organ, the nature and duration of the primary inflammatory stimuli and the CYP or transporter involved. This chapter will provide an overview of organ-specific drug-cytokine interactions and the specific infectious and inflammatory conditions that may lead to drug-cytokine interactions in humans. For the purpose of clarifying nomenclature, italicized abbreviations (e.g. *CYP3A* and *ABCB1*) are used to specifically refer to the CYP or drug transporter gene or mRNA. In all other instances non-italicized abbreviations (e.g. CYP3A and ABCB1) are used.

6.2 Drug Metabolism and Drug Transport

Drug metabolism and transport are integrated processes that dictate drug disposition in the body and provide protection against drugs and chemicals [63, 64]. Both CYP enzymes and transport proteins are sites of drug-cytokine interactions and should be considered with respect to altered drug disposition in conditions where inflammation is present.

The CYPs, a gene superfamily of heme-containing enzymes have a major role in phase 1 drug detoxification [56, 65, 66]. The highest amounts of drug-metabolizing CYPs including CYP1A1/2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 (Table 6.3) are found in the liver and intestine with lower amounts in other major organs. The CYP3A enzymes are particularly important with regard to drug interactions as they comprise 30–50% of CYP content in the liver and metabolize 50–60% of clinically used drugs [65, 67]. Relative to the CYPs, the effects of inflammatory stimuli on the phase II conjugation enzymes, N-acetlytransferases, UDP-glucuronosyltransferases, glutathione-s-transferases, sulfotransferases remain poorly defined.

Drug transporters are a collection of membrane proteins that exist in all major organs where they contribute to organ physiology and drug disposition. [68–70]. Intestinal transporters mediate dietary nutrient and drug absorption into the mesenteric circulation. Hepatic transporters are critical for cholesterol transport, bile secretion and biliary drug elimination. Renal tubule transporters mediate solute reabsorption and urinary drug elimination. Brain capillary endothelial transporters control the uptake of nutrients into the brain while simultaneously preventing harmful compounds from accumulating in the CNS. Transporters are grouped into the solute carrier (SLC) and the ATP-binding Cassette (ABC)

Table 6.3 Drug-metabolizing CYP enzymes and representative substrates

Enzyme	Drug class
CYP1A1/2	**Analgesics**: acetaminophen **Anticancer**: erlotinib, tamoxifen **Methylxanthines**: theophylline, caffeine
CYP2B6	**Antidepressants**: bupropion **Anticancer**: cyclophosphamide, ifosfamide, tamoxifen
CYP2C9	**Antiviral**: ritonavir **Antiinflammatories**: celecoxib, ibuprofen, indomethacin, naproxen **Anticancer**: idarubicin, cyclophosphamide **Anticoagulants**: warfarin **Antidiabetics**: glipizide, glibenclamide
CYP2C19	**Anticancer**: cyclophosphamide **Proton pump inhibitors**: omeprazole, pantoprazole, rabeprazole **Antiplatelet**: clopidogrel
CYP2D6	**Analgesics**: codeine, fentanyl, hydrocodone, oxycodone **Anticancer**: cyclophosphamide, idarubicin, tamoxifen
CYP2E1	**Antibiotics**: dapsone **Analgesics**: acetaminophen **Other**: chlorzoxazone, ethanol
CYP3A4	**Antibiotics**: clarithromycin, erythromycin, metronidazole **Antifungals**: fluconazole, itraconazole, ketoconazole, miconazole **Antivirals**: delavirdine, efavirenz, indinavir, nelfinavir, ritonavir, saquinavir **Antiinflammatories**: cortisol, hydrocortisone, methylprednisolone, prednisolone, prednisone **Analgesics/sedatives**: fentanyl, midazolam, triazolam **Anticancer**: doxorubicin, etoposide, vinblastine, vincristine

superfamilies [69, 70]. Drug uptake into cells is primarily mediated by the SLC22 family (organic cation transporters, OCTs and organic anion transporters, OATs) and the SLC01 family (organic anion transporting polypeptides, OATPs) [71–73]. Additional nutrient transporters including SLC1 (amino acid transporters), SLC15 (oligopeptide transporters) and SLC16 (monocarboxylic acid transporters) mediate the cellular uptake of drugs that structurally resemble the natural transported ligands [74, 75]. The ABC transporters (Table 6.3) including p-glycoprotein (ABCB1), multidrug resistance proteins (ABCC1-4) and breast cancer resistant protein (ABCG2) are the primary mediators of drug transport out of cells (efflux) [76]. ABCB1 is the most well described ABC transporter. It exists in the apical membrane of intestinal enterocytes, the biliary membrane of hepatocytes and the luminal membrane of renal tubules, where it mediates drug efflux into the intestine, bile and urine respectively [77, 78]. Further, ABCB1 is an important blood-brain barrier efflux transporter that limits drug accumulation in CNS (Table 6.4) [79, 80].

Table 6.4 Common ABC drug-efflux transporters and representative substrates

Transporter	Tissues	Substrates
ABCB1 (PGP)	Intestine, kidney, liver, brain, placenta, cancer cells	**Antibiotics**: erythromycin, levofloxacin, rifampin, sparfloxacin **Antifungals**: ketoconazole **Antivirals**: amprenavir, indinavir, nelfinavir, ritonavir, saquinavir **Analgesics**: morphine **Anticancer**: anthracyclines, anthracenes, epipodophyllotoxins, taxanes, vinca alkaloids **Antiinflammatories**: dexamethasone, prednisolone, cortisol
ABCC1 (MRP1)	Ubiquitous, low in the liver	**Antivirals**: indinavir, ritonavir, saquinavir **Anticancer**: anthracenes, anthracyclines, cisplatin, epipodophyllotoxins, flutamide, methotrexate, vinca alkaloids
ABCC2 (MRP2)	Liver, gut, kidney, brain, placenta, gall bladder	**Antibiotics**: ceftriaxone, rifampin **Antivirals**: indinavir, ritonavir, saquinavir **Analgesics**: acetaminophen, diclofenac **Anticancer**: cisplatin, doxorubicin, etoposide, methotrexate, vinblastine, vincristine
ABCC3 (MRP3)	Liver, gut, brain, kidney, lung, prostate, gall bladder, prostate, placenta	**Analgesics**: acetaminophen **Anticancer**: etoposide, leucovorin, methotrexate, teniposide
ABCG2 (BCRP)	Placenta, liver, kidney, intestine, brain	**Antiviral**: azidothymidine, lamivudine **Anticancer**: adriamycin, daunorubicin, doxorubicin, etoposide, flavopiridol, irinotecan, methotrexate, mitoxantrone, topotecan

A complete list of abbreviations is provided in Table 6.1

6.3 Cytokines and the Acute Inflammatory Response

Cytokines are a diverse superfamily of secreted proteins that function in immunity and metabolism [81–83]. These molecules are secreted from monocytes, macrophages, T-cells, mast cells and nonhematopoietic cells such as adipocytes, fibroblasts, hepatocytes, epithelial cells and chondrocytes [84]. Cytokines are not normally produced constitutively, rather their expression and secretion occurs in response to infectious or injurious stimuli.

Drug-cytokine interactions have been commonly associated with acute inflammation, a generalized immune response that provides a potent early defense against primary infection or tissue injury in order to counteract the source of the disturbance

and restore homeostasis [85]. Stressors including infections, trauma and surgery activate the innate immune response leading to local inflammation and systemic responses, which can alter drug disposition in humans (Table 6.2). The primary immune sensors, host tissue macrophages and blood monocytes, contain pattern recognition receptors (PRRs), including the transmembrane toll-like receptors (TLRs) and cytosolic nucleotide-binding oligomerization domain-like receptors (NLRs), which bind conserved pathogen-associated molecular patterns present on infecting microorganisms (e.g. lipopolysaccharide, LPS), virulence factors, particulate irritants and endogenous molecular indicators of cell stress or cell death [86, 87]. This sets in motion a signaling cascade leading to enhanced expression and release of proinflammatory cytokines (e.g. TNFα, IL-1 and IL-6), chemoattractant molecules, prostaglandins, histamine, bradykinin, complement proteins, NO and proteolytic factors [85, 86]. Locally, these mediators enhance vascular permeability and recruit immune cells into the infected or injured tissue for removal of invading pathogens and/or damaged tissue and contribute to wound healing [85, 86]. With increased severity of tissue insult, greater quantities of inflammatory mediators are secreted into the circulation [85]. This allows for activation of their respective receptors in target organs, which produces physiologic changes that define the systemic inflammatory response; fever, appetite suppression, activation of the hypothalamic-pituitary adrenal axis, muscle protein catabolism, production of hepatic acute phase proteins and altered drug disposition [85, 88–91]. The pro-inflammatory cytokines IL-1β, IL-6, IFNα/β/γ and TNFα appear to be particularly important mediators, which link the immune/inflammatory response with altered drug disposition in mammals. When applied individually to cells, cytokines regulate CYPs and transporters with a certain amount of redundancy [32, 33, 92, 93]. Thus, in humans, the overall effects on drug disposition are likely due to the collective and redundant actions of the multiple cytokines that are released upon immune stimulation.

6.4 Drug-Cytokine Interactions and the Liver

The first step in hepatic drug elimination is SLC-mediated passage of the drug from the sinusoids into the hepatocyte where the drug may undergo metabolism by CYPs and conjugating enzymes (Fig. 6.2a). Canalicular ABC transporters then mediate drug or metabolite secretion into bile, whereas sinusoidal ABC transporters deliver drugs or metabolites back into circulation (Fig. 6.2a). Cytokine-mediated losses in hepatic CYP metabolism, drug uptake or efflux transporter function are established and may reduce drug clearance, increase plasma drug levels and enhance pharmacological or toxicological effects.

The pioneering work related to hepatic drug-cytokine interactions were carried out in the 1970s by several research groups. A seminal observation published in 1972 identified that polyinosinic-polycytidylic acid (PolyIC), a molecule that mimics double stranded viral RNA induces an interferon response and suppresses hepatic CYP metabolism *in vitro* and *in vivo* [94]. Morahan and Coworkers correctly

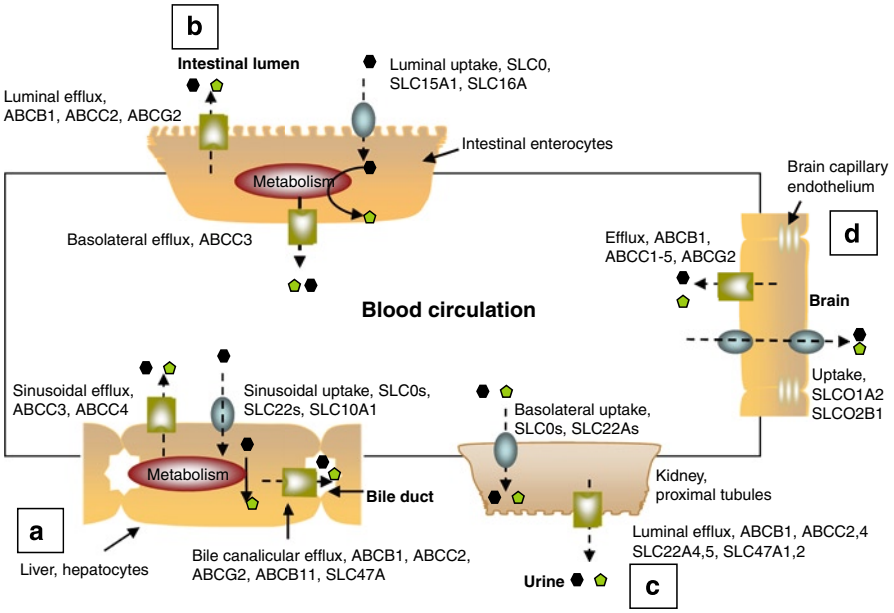

Fig. 6.2 Role of drug transporters in human drug disposition. Drug transporters play an important role in mediating the transfer of drugs (*black octagons*) and metabolites (*green pentagons*) between the extracellular and intracellular environments. The *blue ovals* represent drug uptake transporters and the *green squares* represent drug efflux transporters. Drug transporters mediate drug elimination in the bile (**a**) drug absorption from the intestine (**b**), drug elimination in the urine (**c**) and serve a CNS protective function in the blood-brain barrier (**d**). Representative solute carrier (*SLC*) uptake transporters and ATP-binding cassette (*ABC*) efflux carriers are shown for each anatomical location

speculated that the reduction in hepatic metabolism involved the inhibition of RNA and protein synthesis but the connection between the immune response and reduced hepatic drug metabolism would have to wait for a quite unexpected observation by Drs. Renton and Mannering in 1975. Based on previously reported cell culture studies, these investigators had reason to believe that an interferon-inducing agent, tilorone, would potentiate the induction of hepatic CYP metabolism by barbiturates and polycyclic aromatic hydrocarbons [8, 95]. Instead, the opposite was observed; tilorone administered to rats transiently reduced their total hepatic CYP protein content and microsomal CYP enzyme activity. The loss in hepatic metabolic activity was pharmacologically relevant as it elevated plasma levels of hexobarbital and lengthened barbiturate-induced sleeping time. This pivotal finding led to the hypothesis that interferon or some aspect of the interferon induction mechanism mediates the loss in CYP-mediated drug metabolism [8]. The hypothesis was quickly reinforced by a follow up study in which a diverse array of interferon-inducing agents including an RNA virus (Mengo), fungal mycophage (statolon), PolyIC, *E. coli* LPS and an attenuated bacteria (*B. pertussis*) vaccine similarly inhibited hepatic CYP metabolism [7]. At around the same time, investigations of *Corynebacterium parvum* (*C. parvum*) and *Bacillus Calmette-Guerin* as immunotherapeutic agents for cancer therapy demonstrated similar immune-mediated reductions in hepatic drug

metabolism [5, 9]. These two studies extended the concept that immune stimulation alters drug pharmacokinetics and pharmacodynamics in animals and provided a potential explanation for enhanced toxicity of short-acting barbiturates and hematopoietic toxicity of chemotherapeutic agents in rodents treated with *C. parvum* [96, 97]. Subsequently, it was shown that irradiation or splenectomy could block the *C. parvum*-mediated reduction of hepatic drug-metabolizing activity identifying for the first time that monocytes and macrophages, which release cytokines during the inflammatory response, are cellular mediators of the interaction [98].

In the 30 years hence, the effects of cytokines on hepatic CYP metabolism have been firmly established in animals [21, 55, 56]. The human situation is more complicated, due to inherent variability in drug disposition, combinations of multiple drug treatments and underlying diseases. Nonetheless, the clinical reality of drug-cytokine interactions was recognized early on through observations that asthmatic children previously controlled on theophylline, demonstrated reduced clearance, higher steady-state peak concentrations and toxicity of theophylline during febrile viral illness [30, 31]. In addition to the theophylline interaction, many human studies and/or case reports support the notion that specific hepatic drug-cytokine interactions arise in clinically applicable situations. These include: impaired theophylline elimination and attainment of toxic theophylline levels in recipients of influenza vaccine; increased half-life and decreased clearance of midazolam in critical illness; decreased clearance of cyclosporine, carbamazepine and omeprazole in patients following allogenic bone marrow transplants, temporal lobectomy and spinal cord injuries respectively; decreased metabolism of omeprazole and erythromycin in advanced cancer; decreased dextromethorphan metabolism in patients with active HIV infection and decreased caffeine and mephenytoin metabolism in patients with heart failure [28, 35, 36, 49, 51, 99–101].

The question of whether alterations in drug disposition in humans are explained by hepatic drug-cytokine interactions has been addressed using primary hepatocytes or microsomes prepared from liver biopsies or surgically resected liver from individuals with metastatic cancer, chronic viral hepatitis C or from donor livers that were unsuitable for transplant (Table 6.5) [32, 33, 60, 102–106]. The general effect of IL-6, TNFα, IFNγ, IL-1β and IL-2, is to differentially reduce the basal levels of mRNA, protein and/or activities of hepatic CYP1A, CYP2B, CYP2C, CYP2E and CYP3A [32, 33, 60, 103–106]. One exception is a substantial IL-4-mediated induction of CYP2E1 mRNA and protein in primary human hepatocytes or human hepatoma cells [33, 103]. The cytokine-mediated reductions in CYP mRNA, protein and/or activity typically have ranged between 40 and 90% and occur 1–4 days after cytokine treatment. The degree of reduction depends on the cytokine and CYP in question and the effect may increase in magnitude upon simultaneous exposure to multiple cytokines, as would occur during a systemic inflammatory response [32, 102]. Reduced CYP mRNA levels and subsequent reductions in protein or enzyme activity are usually observed indicating regulation at the level of gene transcription. Donato and Colleagues identified that NO contributes to a portion (50%) of the total loss of hepatic CYP1A1/2 activity after INFγ stimulation [60]. The effect of NO is independent of transcriptional regulation and only affects specific CYP isoforms [102]. Binding of cytokines to their cognate hepatocyte receptors and activation of intracellular signaling mechanisms regulate CYPs, but there are cases of indirect

Table 6.5 Summary of the documented or proposed effects of cytokines or inflammatory diseases on drug metabolism and transport in humans

Inflammatory mediator or disease/model	General effect on CYPs or transporters	Documented or proposed effect on drug disposition *in vivo*	References
Liver			
LPS, IL-6, TNFα, IFNα, γ IL-1β, IL-2 and IL-4	↓ CYP1A1/2, CYP2B6, CYP2C9/19, CYP2E1 and CYP3A4	↓ hepatic drug CL (documented for LPS and IFNα, proposed for other cytokines)	[32, 33, 60, 102–106]
Primary hepatocytes or liver microsomes	↑ CYP2E1 by IL-4	↑ hepatic CL of CYP2E1 substrates (proposed)	
LPS, IL-6, TNFα, IL-1β	↓ sinusoidal uptake transporters SLC10A, SLC22A, SLCO1B1, 1B3 and 2B1,	↓ hepatic drug CL. (proposed)	[92, 93, 107]
Primary hepatocytes or liver slices	↓ canalicular efflux transporters ABCB11, ABCC2 and ABCG2 ↓ sinusoidal efflux transporters ABCC4		
Gastrointestinal tract			
CD and UC/intestinal biopsies	↓ ABCB1 and ABCG2 in inflamed regions of intestine vs. noninflammed regions or vs. healthy controls. ABCB1 and ABCG2 return to control levels in UC remission	↑ oral drug bioavailability (proposed)	[43, 44, 108, 109]
H. pylori + *IL1βT/T and T/C genotypes*	↑ inflammatory response Unknown effect on CYPs or transporters	↑ efficacy of triple therapy in CYP2C19 rapid metabolizers (documented)	[12, 25, 27]
Or H. pylori cagA+/vacA s1	↑ inflammatory response Unknown effect on CYPs or transporters	↑ efficacy of triple therapy (documented)	

Kidney			
Human data not available	Proposed ↓ in proximal tubule uptake and ↑ in proximal tubule ABCB1 efflux transporters based on animal data	↑ renal elimination of ABCB1 substrates and ↓ proximal tubule drug accumulation (proposed based on animal data)	[17, 18, 110–112]
Brain			
IL-1β, IL-6 and TNFα Human brain capillary endothelial cells	↓ ABCG2 with all cytokines, ↓ ABCB1 with IL-6, ↑ABCB1 with TNFα	↑ brain penetration of ABCG2 substrates and ↑↓ ABCB1 substrates (proposed)	[113]
Meningitis	Proposed ↓ in BBB ABCB1	↑ CSF levels of rifampin and ethambutal (documented)	[2, 3]
Postmortem brain from HIV^{-}, $HIVE^{-}$ $HIVE^{+}$ subjects	ABCB1 ↓ in brain capillaries of $HIVE^{-}$ and $HIVE^{+}$ ABCB1 ↑ in astrocytes and microglia of $HIVE^{+}$ compared $HIVE^{-}$ and HIV^{-}	↑ brain penetration of antiretrovirals but ↓ into infected glia (proposed)	[46]
Acute head injury	Proposed ↓ in BBB ABC transporters	↑ CSF levels of M3G and M6G (documented)	[29]
Parkinson's disease	Proposed ↓ in BBB ABCB1	↑ midbrain penetration of ^{11}C-verapamil (documented)	[45]
Placenta			
TNF-α, IL-1β and Il-6 Trophoblasts from term placentas	↓ apical ABCB1, ABCG2 ↑ or ↔ basolateral ABCC1,4	↑ fetal drug exposure (proposed)	[114]

Definition of table symbols: HIV^{-} not infected with HIV, $HIVE^{-}$ HIV infected without encephalitis, $HIVE^{+}$ HIV infected with encephalitis, ↑ increased compared to controls, ↓ decreased compared to controls, and ↔ unchanged compared to controls. A complete list of abbreviations is provided in Table 6.1

effects. IL-2, but not IL-1 or IL-6 reduction in hepatocyte CYP3A4 activity was of greater magnitude and sustained for a longer period of time when hepatocytes were co-cultured with Kupffer cells [105]. This indirect effect could occur following IL-2-mediated release of IL-1 and IL-6 from Kupffer cells, which in turn activate their hepatocyte receptors. Overall the above studies generally support drug-cytokine interactions that involve reduced CYP levels in human hepatocytes.

Equally important is the consideration that inflammatory cytokines impair hepatic drug elimination through suppression of drug transporter function. Activation of the innate immune response in rats by the administration of LPS, inflammatory cytokines or the IL-6 inducer turpentine, reduced the hepatic mRNA, protein expression and function of the canalicular ABCB1 drug efflux transporter [17, 115, 116]. In rodents, the loss of hepatic ABCB1 manifests as reduced biliary clearance and increased hepatic accumulation and/or plasma levels of its substrates, digoxin, doxorubicin, rhodamine123 and ^{99m}-Tc-sestamibi [14, 17, 117–119]. Further, inflammation and competitive inhibitors of ABCB1 reduce biliary drug elimination in an additive fashion in rats indicating the combination of polypharmacy and inflammation is a situation of potential clinical concern [14]. Cytokine effects on hepatic drug transport are potentially broad as reductions in sinusoidal bile salt (SLC10A1), organic anion (SLCO1A1 and SLCO1A5) and organic cation (SLC22A1) uptake transporters, other bile canalicular efflux transporters including bile salt export protein (ABCB11) and multidrug resistant protein 2 (ABCC2) and sinusoidal efflux transporters (ABCC3) occur following treatment of rodents with LPS, turpentine, IL-6 and IL-1 [17, 120–125].

Initial evidence for human cytokine-hepatic drug transporter interactions stems from the finding that LPS decreased the expression of the bile salt uptake transporter (*SLC10A*) and the canalicular efflux transporter *ABCC2* in liver slices [107]. The reduction of *SLC10A* inversely correlated with IL-1β and TNFα production by the liver slices indicating the effect was likely cytokine mediated [107]. The regulatory link has been further evaluated in primary human hepatocytes isolated from hepatic tissue from individuals with primary and secondary tumors [92, 93]. IL-1β, IL-6 and TNFα globally reduced the expression of sinusoidal organic cation (*SLC22A*), organic anion (*SLCO1B1*, *1B3* and *2B1*) and bile acid uptake transporters (*SLC10A*) and differentially reduced drug (*ABCC2*, *ABCC4* and *ABCG2*) or bile salt (*ABCB11*) efflux transporters (Table 6.5). The loss of drug transporter mRNA expression occurred 8–48 h after cytokine treatments. For select transporters, corresponding reductions in protein and transporter activity were shown. The limited data supports that cytokine effects on hepatic drug and bile acid transporters are probable in humans with a potential impact on impaired drug elimination and cholestasis caused by inflammation [126].

6.5 Drug-Cytokine Interactions in the Gastrointestinal System

The intestine is the primary site of absorption for orally administered drugs. Intestinal SLC transporters facilitate drug absorption whereas enterocyte CYP3A metabolism and ABCB1 and ABCC2 efflux transporters provide barriers against drug absorption

(Fig. 6.2b). Reductions in intestinal ABCB1 and ABCC2 mRNA, protein expression and/or function and CYP3A expression and metabolism occur in rodents with bacterial infection, colitis and chronic renal failure [16, 127–131]. Chronic treatment of mice with IL-2 lowered intestinal ABCB1 protein and increased oral bioavailability of digoxin providing evidence of cytokine involvement [132]. Theoretically, such changes to intestinal CYP metabolism or efflux transport could induce variability in oral drug absorption. In humans many inflammatory conditions affect the gastrointestinal system and therefore have the potential to increase local cytokines and modify drug absorption. Two relatively common gastrointestinal conditions in which the evidence supports the possibility of drug-cytokine interactions are inflammatory bowel disease (IBD) and *Helicobacter pylori* (*H. pylori*) infection.

IBD is a term used to encompass a group of autoimmune disorders affecting the GI tract, of which Crohn's disease (CD) and ulcerative colitis (UC) are the most prevalent. In these diseases, the expression of IL-1β, IL-4, IL-5, IL-8, IL-10, IL-12, TNF-α and IFNγ can be elevated [133, 134]. Several studies have documented differential dysregulation of genes involved in intestinal drug detoxification and drug efflux in humans with IBD [43, 44, 108, 109]. Sizable reductions in ABCB1 and ABCG2 mRNA and protein expression have been demonstrated in biopsies from inflamed intestinal regions of subjects newly diagnosed with UC compared to noninflamed sections, treatment refractory patients or healthy mucosa of control patients. A second study demonstrated an induction of IL-6 and IL-1β combined with a 70–80% reduction in ABCB1 and ABCG2 mRNAs and proteins in inflamed colons and rectums of subjects with active UC compared to those in remission or healthy controls [109]. Similarly, *ABCB1* mRNA levels were strongly reduced in inflamed colons of subjects with active UC and CD compared to controls [108]. The depression of *ABCB1* mRNA was recapitulated by treatment of intestinal biopsies with a cytokine cocktail containing TNFα, IL-1β and IFNγ [108]. In comparison, Langmann reported that *ABCB1* mRNA was reduced in the colons but not ileums of those with UC but not CD suggesting there could be disease and tissue-specific regulation of *ABCB1* [44]. These studies generally support that a reduction of intestinal ABCB1 and ABCG2 drug efflux transporters occurs during active IBD and that this effect is related to the inflammatory process (Table 6.5). A second observation was that ABCB1 and ABCG2 mRNA and protein levels in the colonic mucosa of UC subjects in remission were similar or higher than in healthy controls indicating that the intestinal barrier function afforded by these transporters returns to normal with resolution of the inflammatory process [43, 109]. While more pharmacokinetic studies are needed, some have hypothesized that reduced intestinal drug efflux may have implications for oral drug absorption, aggravate intestinal inflammation or contribute to increased rates of colorectal cancer in UC patients due to an accumulation of carcinogens [43, 108, 109].

H. pylori infection is a second relevant condition in which drug-cytokine interactions occur in the gastrointestinal tract. *H. pylori* colonizes the gastric mucosa of humans with relatively high prevalence, 25% in developed countries and up to 80–95% in the developing world [12]. Infection with *H. pylori* causes chronic gastritis, which leads to gastric atrophy and metaplasia, a known risk factor for gastric cancer [25]. The current gold standard for *H. pylori* eradication is triple therapy with two

antibiotics (generally amoxicillin and clarithromycin) and a proton pump inhibitor (PPI). This combination therapy reaches eradication rates of 80–90% but individual success depends on many factors including host genetics, bacteria virulence factors, and level of gastric acid inhibition [12, 25, 26]. Gastric acid suppression is crucial as it decreases degradation of the acid sensitive antibiotics and increases antibiotic susceptibility of the bacteria [12, 25]. In this regard, a positive correlation between the level of gastric inflammation caused by *H. pylori* and the success of bacterial eradication using triple therapy has been shown. A possible explanation for this is that inflammatory mediators IL-1β and TNFα that are produced in the gastric mucosa are also potent inhibitors of gastric acid secretion [12, 25]. Further insight into this relationship stems from studies of *H. pylori* virulence factors and naturally occurring genetic polymorphisms in human IL-1β, IL-1 receptor antagonist and TNFα. Of these, an IL-1β polymorphism (IL-1β -511) is associated with differences in acid inhibition in response to *H. pylori* infection [25]. *H pylori* infected individuals with the IL1β -511T/T and T/C genotypes have significantly higher IL-1β production and elevated median intragastric pH levels compared to those with the IL-1β -511C/C allele [135]. Correspondingly, the IL-1β-511C/C allele is associated with reduced clinical effectiveness of PPI/amoxicillin/clarithromycin triple therapy in CYP2C19 extensive metabolizers [25, 27]. A second group of polymorphisms concerns the *cagA* and *vacA H. pylori* virulence factors. The *cagA*-positive *H. pylori* strains are associated with severe gastric inflammation and produce significantly higher levels of IL-1β [12]. Although there have been conflicting results, the most recent publication by Sugimoto et al. concluded that the cure rates of patients with the *cagA*-positive/*vacA* s1 *H. pylori* strains were significantly higher than those with *cagA*-negative/*vacA s2* strains [12, 26]. This elevated cure rate is considered to be the result of higher cytokine levels in the gastric mucosa. These interesting relationships suggest a previously unrecognized and beneficial drug-cytokine interaction in which the degree of inflammation produced by infection enhances antibiotic effectiveness. This could occur by reducing antibiotic degradation and increasing bacterial susceptibility to antibiotic action as compared to what would occur in a more acidic environment. The notion that the pharmacodynamic response involves inflammation-mediated reductions in CYP metabolism and/or drug efflux transport of drugs (PPIs, macrolides and amoxicillin) used in the triple therapy regimen is unknown but is an intriguing possibility.

6.6 Drug-Cytokine Interactions and the Kidney

The kidney proximal tubules are home to a variety of drug transporters that facilitate the secretion of potentially harmful drugs, endogenous compounds and metabolic wastes into the urinary ultrafiltrate [76]. The first step in drug secretion is SLC22A- and SLCO-mediated drug transfer from the peritubular capillaries into the proximal tubule cells (Fig. 6.2c). The second step is ABC- and SLC-mediated drug transfer from the proximal tubule cells into the nephron lumen. As commonly seen in acute

renal failure, inflammatory cytokines alter the renal tubule expression of glucose, sodium and urea transporters [136–138], decrease glucose reabsorption, urine osmolarity and the urine-to plasma urea quotient [136–138]. In a similar fashion, alteration of renal tubule drug transporters by inflammatory cytokines would be expected to impact urinary drug elimination.

In rats, *E. coli* LPS treatment reduced the mRNA, protein and function of the proximal tubule basolateral membrane organic cation uptake transporters SLC22A1 and SLC22A2 [110]. Contrasting that result and the response to inflammation seen in the liver and intestine, the expression and function of the proximal tubule apical efflux ABCB1 transporter is enhanced in rodent models of *E. coli* endotoxemia and ischemia reperfusion injury [17, 111, 112]. In one study, enhanced ABCB1 levels were associated with increased renal clearance of doxorubicin [17]. In another, *Klebsiella pneumoniae* endotoxin transiently reduced the renal tubule secretion of rhodamine123 [117]. This discrepancy could be attributed to the fact that the rate-limiting step in rhodamine123 renal elimination is tubule uptake by the SLC22A1 and SLC22A2 transporters. Therefore, the suppression of the basolateral membrane organic cation transporters and not a loss in ABCB1 is the most likely explanation for the reduction in rhodamine123 renal clearance [110, 139]. The reduction of proximal tubule drug uptake combined with enhanced efflux are particularly interesting observations, which could indicate that changes in kidney drug transport occur to diminish the renal proximal tubule accumulation of harmful metabolites or cytokines thereby counteracting the extent of proximal tubule damage created by endotoxemia or ischemic injury [110–112].

The effect of endotoxemia or ischemia/reperfusion on renal tubule ABCB1 expression and function could be recapitulated by treatment of spontaneously immortalized rat kidney proximal tubule cells with TNFα indicating direct cytokine involvement [18]. The study by Heemskerk et al. also evaluated the process by which this upregulation occurs, suspecting NO produced by renal inducible NO-synthase (iNOS) plays a central role [18, 111]. Interestingly the induction of renal ABCB1 by LPS occurred via a NO-dependent mechanism whereas TNFα increased ABCB1 de novo synthesis via TLR4 activation and NF-κB signaling without NO involvement.

Despite the known importance of renal elimination of many commonly used drugs and of the role of cytokines in drug disposition, only recently have studies begun to look at local drug-cytokine interactions in the kidney. Overall, the preliminary results in animal models are intriguing, some showing opposing effects of inflammatory stimuli on Abcb1 compared to other tissues. This is an area that requires further investigation including clinical studies in human participants (Table 6.5).

6.7 Drug-Cytokine Interactions at the Blood-Brain Barrier

The blood-brain barrier formed by brain capillary endothelial cells limits paracellular and transcellular diffusion of macromolecules and hydrophilic drugs into the brain [140, 141]. Uptake transporters that facilitate passage of nutrients, hormones and

some drugs into the brain are integral components of the blood-brain barrier (Fig. 6.2d). Energy-dependent efflux transporter systems simultaneously limit the passage of potentially harmful and therapeutic substances into the CNS [141, 142]. Neuroinflammatory conditions, including meningitis, acute traumatic brain injury, multiple sclerosis, Parkinson's and Alzheimer's diseases and HIV-related encephalopathy are associated with altered blood-brain permeability [143–146]. Investigation into whether these inflammatory conditions affect drug transporter function at the blood-brain barrier interface and impact brain accumulation and pharmacological effects of CNS drugs has garnered particular interest of late [13, 29, 45–48, 58, 147].

The primary focus has been on ABCB1, a CNS-protecting blood-brain barrier efflux transporter [148–150]. The CNS-protective function of ABCB1 is exemplified by animal studies in which its absence, mutation or blockade is associated with increased CNS accumulation and/or toxicity of anticonvulsants, antidepressants, antineoplastics, antiretrovirals, antipsychotics, calcineurin inhibitors, calcium channel blockers, glucocorticoids and opioids, among others medications [79, 80, 151–162]. Similarly, humans with polymorphisms in *ABCB1*, or those receiving ABCB1 inhibitors, may exhibit significantly altered CNS pharmacological responses. [155, 163–165].

Expression and/or function of blood-brain barrier ABCB1 is decreased in animals with CNS bacterial and/or fungal infections and following stroke or neuronal injury [14, 55, 166–168]. Decreased activity of this transporter promotes enhanced accumulation of ABCB1 substrates in the CNS, which may alter pharmacological or toxicological responses [14, 166–168]. Similarly, some have reported that blood-brain barrier ABCB1 function is reduced by inflammatory and infectious stimuli that originate in compartments peripheral to the CNS such as in the circulation or the highly vascular peritoneal cavity [119, 169, 170]. In contrast, others found increased ABCB1 expression and function in cerebral capillaries isolated from rats exposed to a painful peripheral inflammatory stimulus or to particulate irritants [171, 172]. These contrasting results most likely indicate that the direction and degree of change in ABCB1 activity depends upon the particular inflammatory stimulus studied, the anatomical site in which the inflammatory response was generated and the particular drug substrate [13]. Differential effects could also relate to short versus long-term exposure to an inflammatory stimuli such as would be observed during an acute versus chronic inflammatory response. In support of this idea, ABCB1 activity in isolated rat brain capillaries was decreased after short-term exposure to LPS, TNFα, and endothelin-1 (ET-1) whereas prolonged exposure to TNFα and ET-1 produced a biphasic response with an initial decrease in ABCB1 function, and then an increase in both ABCB1 expression and activity [61, 62, 173, 174]. The effects of inflammatory stimuli on blood-brain barrier transport are not restricted to ABCB1. There are reports of differential regulation of ABCB1, ABCC2, ABCC4 and ABCG2 by multiple inflammatory mediators including TNFα, IL-6 and IL-β in human or rodent capillary endothelial and glial cells [59, 62, 113, 171, 175–178]. These collective findings indicate modified CNS drug accumulation through an alteration in blood-brain barrier efflux transport processes during episodes of infection and inflammation is probable.

Altered ABCB1 expression and/or activity or enhanced CNS drug levels during meningitis, HIV infection, Parkinson's disease, epilepsy and after acute traumatic brain injury suggests that a regulatory link exists between inflammation and blood-brain barrier transport in humans (Table 6.5) [2, 3, 29, 45, 46, 179, 180]. Further investigations are needed, however, to delineate if drug-cytokine interactions involving blood-brain barrier transporters impact CNS drug efficacy and toxicity in humans. In this regard, it should be recognized that alterations in blood-brain barrier ABCB1 activity during inflammatory or infectious conditions may have either positive or negative consequences depending on the drug in question and the therapeutic goals for the patient. For example, a transient reduction in blood-brain barrier ABCB1 activity could improve the CNS delivery of neuroprotectant agents in diseases such as ischemic or hemorrhagic stroke or antibiotics in meningitis with the potential for enhanced therapeutic efficacy. This is a plausible explanation for the historical observations that patients with meningitis had higher cerebrospinal fluid concentrations of the anti-tuberculosis agents, ethambutal and rifampin [2, 3, 181]. In contrast, chronic diseases such as epilepsy appear to increase levels of blood-brain barrier ABCB1 that may reduce CNS drug levels resulting in drug resistance and even pharmacotherapeutic failure.

A second finding of note is competitive drug interactions at the blood-brain barrier may amplify the pharmacological effects of ABCB1 substrate drugs during episodes of CNS inflammation. [168, 178, 182]. In animals with CNS infection or ischemia, the administration of competitive inhibitors of ABCB1 enhances the CNS concentration and efficacy of itraconazole, rifampin, and FK506 above that of the disease process alone, suggesting a beneficial drug-immune system interaction [168, 182]. Conversely, near-maximal inhibition of ABCB1 activity during CNS inflammation could contribute to neurotoxicity. A novel clinical example of such a situation is implied from data derived from critically ill patients with acute inflammatory brain injury. These patients receive upwards of 30 drugs concomitantly, including ABCB1 substrates (e.g., dexamethasone, morphine, and ranitidine) and inhibitors (e.g., amiodarone and diltiazem) as part of their routine care. Such polypharmacy during an acute neuroinflammatory reaction could place these patients at risk for drug interactions involving blood-brain barrier ABCB1 [29].

6.8 Drug-Cytokine Interactions During Pregnancy

In pregnancy, the placenta is an additional location of many drug transporters [183]. Placental transporters are expressed on the apical (facing maternal blood) and basolateral (facing fetal capillaries) surfaces of syncytiotrophoblasts and facilitate the exchange of drugs and endogenous compounds between the maternal and fetal circulations (Fig. 6.3) [184–187]. On the apical surface of the syncytiotrophoblasts, ABCB1 and ABCG2 are the most abundant of the ABC transporters and are prominent contributors to the efflux of drugs and metabolites from the fetoplacental space [114]. This is exemplified by several-fold increases in the fetal exposure to digoxin,

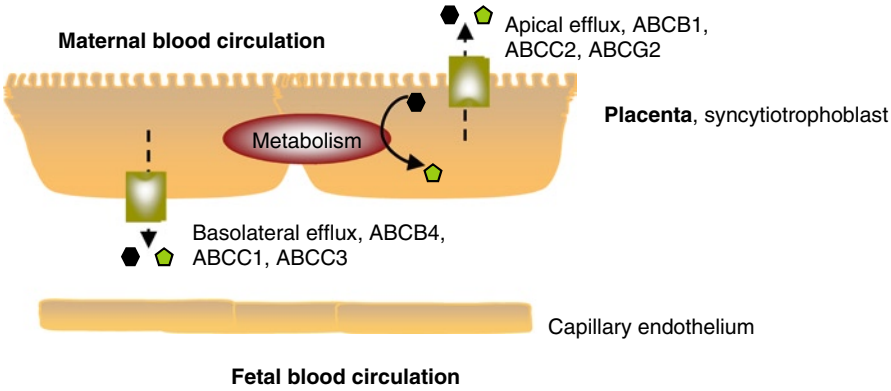

Fig. 6.3 Select drug efflux transporters in the human placenta at term. ATP-binding cassette transporters (*ABC*) exist in the apical and basolateral membranes of the syncytiotrophoblast where they mediate drug (*black octagons*) or metabolite (*green pentagons*) efflux into the maternal blood circulation or in the direction of the fetal circulation. The *green squares* represent drug efflux transporters. For simplicity only those transporters that are discussed in this chapter are shown on the diagram

saquinavir and taxol in mice with complete deficiency in *ABCB1,* and nitrofurantoin and glyburide in *ABCG2*-deficient mice [188–190]. There are similar relevant examples of human placental drug transport of clinically used medications. In term human placentas *ex vivo,* inhibition of ABCB1 led to enhanced maternal-placental transfer of indinavir, vinblastine and saquinavir, whereas inhibition of ABCG2 enhanced the maternal-placental transfer of glyburide [191–194]. Opposing the actions of the apical transporters are the transporters located on the basolateral side of the syncytiotrophoblasts including MDR3 (ABCB4) ABCC1 and ABCC3 [114]. While the human data remains limited, the above studies identify that placental drug transporters are likely to be important determinants of fetal drug exposure and fetal development and safety (Table 6.5).

The role of cytokines in the regulation of placental drug transport has gained considerable attention as the placenta is a source of TNFα, IL-1β and Il-6 production and there are reports that the circulating levels of these cytokines are aberrantly increased in common complications of pregnancy such as placental insufficiency/fetal growth restriction, preeclampsia and gestational diabetes as well as a number of unrelated comorbid conditions [195–197]. Evseenko et al. evaluated the effect of TNFα, IL-1β, IL-6 on the prominent ABC transporters in primary trophoblasts from term human placentas [114]. TNFα and IL-1β but not Il-6 significantly decreased *ABCB1* and *ABCG2* mRNA by >40% after 12 h and corresponding ABCB1 and ABCG2 protein levels by 50% after 48 h. With respect to the basolateral transporters, ABCB4 mRNA and protein was specifically and significantly increased following IL-6 but not TNFα and IL-1β. Comparatively, TNFα, IL-6 and IL-1β significantly increased the expression of *ABCC1* mRNA but not ABCC1 protein. The combined depression of the maternal facing ABCB1 and ABCG2 apical transporters and increased or static expression of the fetal circulation facing ABCC1 and ABCB4 basolateral transporters indicate that placental exposure to inflammatory

cytokines may decrease fetal protection from drugs and enhance active transport of drugs to the fetus in conditions in which those cytokines are aberrantly elevated. Both of these alterations could be potentially detrimental to the fetus. While there is presently no human data to substantiate this claim, animal studies do provide some evidence that it occurs [10, 119, 198]. For instance, treatment of near term rats with LPS, dose-dependently increased plasma TNFα and IL-6 levels while reducing the placental mRNA and protein expression of ABCB1 and ABCG2 among other uptake and efflux transporters [20]. The functional outcome was an increase in the fetal to maternal concentration of glyburide, an agent that is used for treating gestational diabetes in humans and is primarily restricted from accessing the fetal circulation by ABCG2 [20, 199].

6.9 Drug-Cytokine Interactions and Cancer

The role of inflammation in the pathophysiology of cancer is becoming increasingly accepted. It is now thought that inflammatory components are present in the microenvironment of most, if not all, tumors and the level of inflammation appears to correlate with the severity of the cancer [200]. An interesting connection is that IL-6, a potent regulator of drug disposition is produced by tumor cells and its circulation concentration increases with many cancers [19, 37, 38, 55, 201, 202]. Increasing evidence indicates that the elevated IL-6 levels that occur in malignancy affect pharmacological responses to chemotherapy drugs by activating multi-drug resistance mechanisms in tumor cells and/or through alteration of host drug disposition.

Multidrug resistance occurs when tumors develop cross-resistance to a number of structurally and mechanistically unrelated drugs. This has become an increasing problem in the field of oncology [203]. It can arise through tumor cell modifications including the inhibition of apoptosis, activation of DNA repair mechanisms and decreased intracellular chemotherapeutic drug accumulation due to suppression of SLC drug uptake transporters or increased levels of the ABC drug efflux transporters [203–207]. Autocrine production of IL-6 by breast, osteosarcoma and ovarian cancer cells caused the cells to develop resistance to the cytotoxic effects of doxorubicin, paclitaxel or cisplatin [37, 39, 201]. Depending on the cell, different mechanisms were implicated. These included IL-6 induction of ABCB1 efflux (breast and ovarian cancer), inhibition of apoptosis (osteosarcoma and ovarian cancer) and increased glutathione-s-transferase (ovarian cancer)[37, 39, 201]. In mice inoculated with Englebreth-Holm-Swarm (EHS) sarcoma, *ABCB1a,* but not *ABCG2*, *ABCC2*, *ABCC3* and *ABCB4* mRNA increased significantly in the developing tumor in association with increasing levels plasma IL-6 and intratumoral IL-6 [19]. Contrary to the effects observed in tumor cells, mice bearing extra-hepatic tumors displayed widespread repression hepatic uptake (*SLC10A1*, *SLCO1B1*), sinusoidal efflux (*ABCC3*) and biliary efflux (*ABCB4*, *ABCC2*, *ABCG2* and *ABCB11*) transporters [19]. This indicates the possibility of drug-cytokine interactions involving IL-6-mediated induction of multidrug resistant efflux transport in tumors *in vivo* and/or reduction in hepatic drug transport capacity. However, the effects of these

drug transporter gene expression changes on chemotherapy resistance or biliary drug elimination were not investigated. Although IL-6 is a predominantly elevated inflammatory cytokine in cancer, this does not imply other cytokines are not involved in regulation of specific transporters. For example, Mosaffa et al. demonstrated that IL-1β and TNFα increased ABCG2 efflux transport of mitoxantrone to a greater degree in mitoxantrone-sensitive versus mitoxantrone-resistant MCF7 breast cancer cells [208]. Consistent with the study by Sharma et al., IL-6 did not regulate ABCG2 mRNA or function in human breast cancer cells [19, 208].

In humans, the main enzyme responsible for inter-patient variability in anticancer drug metabolism is CYP3A4 as it metabolizes many important classes of chemotherapeutic drugs including the taxanes, vinca alkaloids, camptothecins, cyclophosphamide, etoposide, tamoxifen, imatinib and gefitinib [55, 209]. The reported inverse associations between CYP3A4 metabolic activity and the inflammatory mediators IL-6 and CRP in patients with advanced cancer suggest that cytokine-CYP interactions may contribute to the clinically observed variations [19, 36, 209]. Supporting this, when breast, melanoma and EHS sarcoma tumors were introduced into in mice, circulating levels of IL-6 increased, but IL-1β and TNFα levels were unchanged. With the three tumors, the increased plasma IL-6 concentration corresponded with activation of the hepatic acute phase response, a precipitous drop in hepatic CYP3A11 (mouse equivalent of human CYP3A4) mRNA and protein levels and extended sedation by midazolam, a CYP3A11-specific substrate [19, 209]. Direct evidence that cytokines mechanistically link malignancy and human CYP3A4 metabolism stems from the demonstration of reduced expression of a human CYP3A4 transgene in the livers of mice with extrahepatic tumors [209]. Further, the similar reduction in *CYP3A11* mRNA using several cancer models would argue that the tumor-derived inflammation and suppressed hepatic drug metabolism is a common occurrence among malignancies [19, 38]. Less is known regarding the effect of malignancy on other hepatic CYPs. Two studies have reported that a proportion of patients with advanced cancer displayed a CYP2C19 poor metabolizer phenotype despite having a rapid metabolizer genotype [35, 210]. However, an association between the reduced CYP2C19 metabolism and circulating levels of IL-1α/β, IL-6, TNFα/β or CRP was not demonstrated [210]. While some individuals with advanced cancer may have decreased ability to metabolize CYP2C19 substrates like cyclophosphamide, the involvement of cytokines in this interaction remains inconclusive.

It is worth reflecting upon the apparent differential activation of multidrug resistance in cancer cells versus a loss of drug metabolism and transport capacity in the liver caused by inflammatory cytokines. This presents a potential situation of double jeopardy, whereby reduced hepatic elimination of chemotherapeutic agents could pose problems for host toxicity at the same time that the drugs are becoming less effective against the tumors because of activation of cellular multidrug resistance. As chemotherapeutic drugs have a very narrow therapeutic window and individual variability in response is so vast, a comprehensive understanding of how inflammatory cytokines alter the disposition of these agents at the level of the cancer cell and in the host is an essential area for continued study.

6.10 Drug-Cytokine Interactions and Interferon Therapy

A clinical situation in which cytokine-drug interactions may occur is during use of recombinant IFN preparations for treatment of chronic hepatitis B and C and metastatic diseases. Two studies of human subjects with chronic active hepatitis B indicated variable (5–63%) reductions in hepatic CYP-mediated drug metabolism after a single high dose (4.5–18 × 10^6 units) of IFNα and after chronic IFNα (6 × 10^6 units for 4 weeks) treatment [211, 212]. The effects of IFN appeared dose-dependent as treatment of subjects with chronic active hepatitis C for 1-month with a lower IFNα dose (3 × 10^6 units/3 times/week) did not reduce metabolism of CYP1A2 or CYP3A substrates [213]. A fourth study showed a trend towards higher CYP2D6 and CYP3A4 enzyme activities in individuals with chronic active hepatitis C who responded to 1 month of IFNα (3 × 10^6 units/3 times/week)/ribavarin (600 mg/BID) combination therapy compared to nonresponders [22]. While the effect of IFN on CYP2D6 and CYP3A4 appears to be opposite of what would be expected, a possible explanation is that the active hepatitis C infection reduces the activity of certain CYPs followed by an improvement of liver metabolic function with successful antiviral therapy.

A particularly informative study has examined the effect of high-dose IFN2α-2b therapy on the ability of individuals with high-risk melanoma to metabolize a drug cocktail containing substrates for CYP1A2 (caffeine), CYP2C19 (mephenytoin), CYP2D6 (debrisoquine), CYP2E1 (chlorzoxazone) and CYP2C8/9, CYP3A4/5, CYP2E1 and N-acetyltransferase (dapsone) [214]. One-day after a single IFN2α-2b dose, the metabolism of the CYP1A2 and CYP2D6 probe substrates was lowered by 20% and 10%, respectively. After 4 weeks of chronic IFN2α-2b treatment, the magnitudes of the reductions in CYP1A2 (53%) and CYP2D6 (25%) metabolism increased. Further, metabolism of the CYP2C19 substrate mephenytoin was now reduced by 25%. The metabolism of the CYP2E1 substrate, chlorzoxazone and the CYP2C8/9, CYP3A4/5, CYP2E1 and N-acetyltransferase substrate dapsone was not altered indicating that IFN differently effects CYP metabolism in humans. Since IFN's effects on drug metabolism range from no effect to moderate reductions in CYP metabolism, reduced metabolism should not be of consequence in all individuals treated with this cytokine. If impairment of metabolism does occur it would be most likely following administration of higher IFN doses used for treatment of metastatic cancer opposed to lower IFN doses used for hepatitis treatment. A further consideration is that IFN treatment may not produce a large reduction in drug metabolic activity in all individuals with metastasis or chronic viral hepatitis because inflammation associated with those conditions may have already reduced baseline metabolic capacity [22, 38, 215].

The clinical demonstration of harmful drug interactions that could be related to metabolic changes caused by IFN therapies is limited. Two case reports of acute severe gastrointestinal symptoms and hepatitis have been reported when individuals were started on gemfibrozil to treat hypertriglyceridemia that developed during IFNα treatment [216, 217]. In one case, where INFα was continued but the gemfibrozil dose was reduced, the symptoms of toxicity subsided [217]. It was inferred

that inhibition of hepatic CYP1A2 and CYP2C19 metabolism was a plausible mechanism for this drug-cytokine interaction.

6.11 Drug-Cytokine Interactions and Immunosuppression Therapy

An untoward effect of immunosuppression therapy is increased susceptibility to opportunistic viral (e.g. cytomegalovirus, polyoma virus and influenza) and bacterial (e.g. pneumonia, urinary tract infection, sepsis etc.) infections [218–222]. A number of human studies and case reports support a potential interaction between opportunistic infections and the disposition of the low therapeutic index calcineurin inhibitors, cyclosporine and tacrolimus. For instance, higher blood cyclosporine levels have been reported in lung transplant recipients with cytomegalovirus infection compared to uninfected patients [223]. Tacrolimus blood levels over time (AUC, area under the curve) were higher in adult renal transplant patients presenting with infections compared to those without [224]. In a third example, adult renal transplant patients with hepatitis C infection required 25% lower daily doses of cyclosporine or tacrolimus to maintain target blood levels of these drugs compared to uninfected patients [225]. In addition to a potential pharmacokinetic interaction, clinical findings of renal impairment after low-dose cyclosporine therapy in patients with human immunodeficiency virus and autoimmune diseases [226, 227] suggests a potential interaction between immune responses and calcineurin inhibitors that may augment nephrotoxicity produced by lower doses of those drugs. Presumably, these pharmacokinetic changes could be due to altered intestinal, hepatic and/or renal CYP metabolism and transport; however, this remains to be determined.

6.12 Drug-Cytokine Interactions and Rheumatic Diseases and Anticytokine Therapy

Immune mediated inflammatory diseases (IMID) are a broad array of conditions with diverse clinical presentations that share common inflammatory pathways and therapeutic goals: gain control of the inflammation, prevent tissue damage, improve quality of life and if possible, achieve long term remission [228]. Common examples of these diverse diseases are rheumatoid arthritis, IBD and psoriasis. The etiology of these diseases remains unknown but substantial advances have been made in identification of many cytokines involved in the underlying pathophysiology [228]. This has lead to the development of anti-cytokine therapy, the latest evolution in treatment options for patients with IMID.

The initial and most common class of biologic agents for inflammatory diseases are the TNFα inhibitors; infliximab, etanercept, adalimumab, golimumab and

certolizumab pegol. With the emergence of this new class of anti-cytokine drugs comes the potential of new drug interactions. As proinflammatory cytokines reduce the extent of drug metabolism and elimination through suppression of hepatic CYPs and drug transporters it is reasonable to hypothesize that when anti-cytokine agents are administered to patients experiencing chronic inflammation a relative induction in these same enzymes should initially occur [229]. This induction would increase the clearance of medications and may be clinically relevant for pre-existing low therapeutic index drugs. Arguing against this hypothesis, two clinical studies found no effect of etanercept on the pharmacokinetics or pharmacodynamics of digoxin, an ABCB1 substrate nor warfarin, a CYP2C9-metabolized drug [230, 231]. However, these studies were completed in healthy volunteers whom would not have had preexisting inflammation. Thus, whether or not anti-cytokine therapy alters metabolism and drug transport in a clinical setting in those individuals with rheumatic diseases is unknown at present.

Although the current understanding of interactions between anti-cytokine therapy and drug disposition is limited, a novel interaction being investigated is between TNFα and insulin resistance. Compared to the typical drug-cytokine interactions discussed in this chapter this one is unique because it involves a receptor mechanism. TNFα is increased during times of chronic hyperglycemia, has detrimental effects on insulin sensitivity and induces insulin resistance when administered to healthy volunteers [232, 233]. TNFα is thought to exert these insulin-resistance effects by decreasing tyrosine kinase activity at the insulin receptor, which in turn impairs insulin-mediated glucose uptake in skeletal muscle [11]. In patients with chronic inflammatory rheumatic diseases the degree of insulin resistance has been correlated with the level of inflammation and severity of the disease [11]. A limited number of studies have examined the effect of TNFα inhibitors and reversal of insulin resistance in patients with co-morbid rheumatic diseases [232, 233]. The results are not conclusive, but there is suggestion of substantial improvement in insulin sensitivity in those patients with the most severe insulin resistance. This provides an example of where anti-cytokine therapy may reverse the negative effects of a preexisting receptor-mediated drug-cytokine interaction involving insulin action and TNFα.

6.13 Drug-Cytokine Interactions and Vaccines

There is some evidence to support that the known interactions between drugs and cytokines may be utilized to enhance the effectiveness of vaccine adjuvants. The particular situation applies to the CYP-mediated production of calcitriol, a known immune adjuvant. Calcitriol produced and secreted by myeloid dendritic cells causes those cells to migrate from cutaneous vaccination sites into multiple secondary lymphoid organs where they stimulate B and T lymphocyte cell responses [234]. Enioutina et al. recently showed that monphosphoryl lipid A, an LPS derivative

elicited a similar immune response. Interestingly, it was found that the mucosal adjuvant properties monophosphory A directly correlated with its capacity to induce in dendritic cells, the expression of CYP27B1 the enzyme that converts vitamin D to its active form (calcitiol) [234]. Further, monophosphoryl A was unable to upregulate CYP27B1 in interferon receptor deficient ($IFNR^{-/-}$) dendritic cells, nor stimulate the migration of $IFNR^{-/-}$ dendritic cells to secondary lymphoid organs confirming that it was an interferon-CYP interaction.

6.14 Concluding Remarks

The ability of infectious and inflammatory stimuli to alter the disposition of commonly used drugs through cytokine-mediated reductions in hepatic CYP metabolism has been recognized for some time. Based on recent discoveries it is likely that some of the historical reports of altered drug disposition during infectious diseases also involved cytokine-mediated reductions in hepatic drug transporters.

There is an immediate need for human studies to determine the broader clinical importance of drug-cytokine interactions involving extrahepatic tissues. For example, do reduced intestinal ABCB1 and ABCG2 in IBD increase oral drug absorption or serve as risk factors for colorectal cancer? Is human kidney ABCB1 upregulated in inflammatory diseases and does this compensate for an inflammation-mediated loss in intestinal and hepatic drug elimination? When infectious or inflammatory complications arise in pregnancy, does altered placental drug transport increase fetal exposure to medications? Do HIV-encephalitis, Alzheimer's and Parkinson's diseases or acute brain injuries impart cytokine-mediated changes to blood-brain barrier ABCB1 such that drug efficacy or disease progression is affected? Answering these questions will help address the primary challenges, which are to identify: the situations in which drug-cytokine interactions are most likely to occur, the pharmacological outcomes of the interactions and who is most at risk. With this information, it will then be possible to appropriately inform and caution physicians and pharmacists about the potential positive and negative impact of infectious and inflammatory diseases on safe and effective use of medications. Until this information becomes available it would be correct to assume that hepatic drug elimination will be impaired in any disease state that has an inflammatory component or one that activates host defense. This especially applies to the elderly and critically ill, who may be more susceptible because they have a reduced capacity to eliminate drugs and tend to receive multiple medications concurrently. In order to circumvent aberrant drug-cytokine interactions in these situations, empirical dose reductions and/or more rigorous patient monitoring may be warranted until the infectious or inflammatory condition is resolved.

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References

1. Brooks MH, Malloy JP, Bartelloni PJ, Sheehy TW, Barry KG. Quinine, pyrimethamine, and sulphorthodimethoxine: clinical response, plasma levels, and urinary excretion during the initial attack of naturally acquired falciparum malaria. Clin Pharmacol Ther 1969;10:85–91.
2. Place VA, Pyle MM, De la Huerga J. Ethambutol in tuberculous meningitis. Am Rev Respir Dis 1969;99:783–5.
3. Sippel JE, Mikhail IA, Girgis NI, Youssef HH. Rifampin concentrations in cerebrospinal fluid of patients with tuberculous meningitis. Am Rev Respir Dis 1974;109:579–80.
4. Trenholme GM, Williams RL, Rieckmann KH, Frischer H, Carson PE. Quinine disposition during malaria and during induced fever. Clin Pharmacol Ther 1976;19:459–67.
5. Farquhar D, Loo TL, Gutterman JU, Hersh EM, Luna MA. Inhibition of drug-metabolizing enzymes in the rat after Bacillus Calmette-Guerin treatment. Biochem Pharmacol 1976;25:1529–35.
6. Leeson GA, Biedenbach SA, Chan KY, Gibson JP, Wright GJ. Decrease in the activity of the drug-metabolizing enzymes of rat liver following the administration of tilorone hydrochloride. Drug metabolism and disposition: the biological fate of chemicals 1976;4:232–8.
7. Renton KW, Mannering GJ. Depression of hepatic cytochrome P-450-dependent monooxygenase systems with administered interferon inducing agents. Biochem Biophys Res Commun 1976;73:343–8.
8. Renton KW, Mannering GJ. Depression of the hepatic cytochrome P-450 mono-oxygenase system by administered tilorone (2,7-bis(2-(diethylamino)ethoxy)fluoren-9-one dihydrochloride). Drug metabolism and disposition: the biological fate of chemicals 1976;4:223–31.
9. Soyka LF, Hunt WG, Knight SE, Foster RS, Jr. Decreased liver and lung drug-metabolizing activity in mice treated with Corynebacterium parvum. Cancer Res 1976;36:4425–8.
10. Petrovic V, Teng S, Piquette-Miller M. Regulation of drug transporters during infection and inflammation. Molecular interventions 2007;7:99–111.
11. Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Llorca J. Insulin resistance in rheumatoid arthritis: the impact of the anti-TNF-alpha therapy. Ann N Y Acad Sci 2010;1193:153–9.
12. Sugimoto M, Furuta T, Yamaoka Y. Influence of inflammatory cytokine polymorphisms on eradication rates of Helicobacter pylori. J Gastroenterol Hepatol 2009;24:1725–32.
13. Roberts DJ, Goralski KB. A critical overview of the influence of inflammation and infection on P-glycoprotein expression and activity in the brain. Expert Opin Drug Metab Toxicol 2008;4:1245–64.
14. Goralski KB, Hartmann G, Piquette-Miller M, Renton KW. Downregulation of mdr1a expression in the brain and liver during CNS inflammation alters the in vivo disposition of digoxin. Br J Pharmacol 2003;139:35–48.
15. Xu DX, Wang JP, Sun MF, Chen YH, Wei W. Lipopolysaccharide downregulates the expressions of intestinal pregnane X receptor and cytochrome P450 3a11. Eur J Pharmacol 2006;536:162–70.
16. Kalitsky-Szirtes J, Shayeganpour A, Brocks DR, Piquette-Miller M. Suppression of drug-metabolizing enzymes and efflux transporters in the intestine of endotoxin-treated rats. Drug metabolism and disposition: the biological fate of chemicals 2004;32:20–7.
17. Hartmann G, Vassileva V, Piquette-Miller M. Impact of endotoxin-induced changes in P-glycoprotein expression on disposition of doxorubicin in mice. Drug metabolism and disposition: the biological fate of chemicals 2005;33:820–8.
18. Heemskerk S, Peters JG, Louisse J, Sagar S, Russel FG, Masereeuw R. Regulation of P-glycoprotein in renal proximal tubule epithelial cells by LPS and TNF-alpha. J Biomed Biotechnol 2010;2010:525180.

19. Sharma R, Kacevska M, London R, Clarke SJ, Liddle C, Robertson G. Downregulation of drug transport and metabolism in mice bearing extra-hepatic malignancies. Br J Cancer 2008; 98:91–7.
20. Petrovic V, Wang JH, Piquette-Miller M. Effect of endotoxin on the expression of placental drug transporters and glyburide disposition in pregnant rats. Drug metabolism and disposition: the biological fate of chemicals 2008;36:1944–50.
21. Aitken AE, Richardson TA, Morgan ET. Regulation of drug-metabolizing enzymes and transporters in inflammation. Ann Rev Pharmacol Toxicol 2006;46:123–49.
22. Becquemont L, Chazouilleres O, Serfaty L, et al. Effect of interferon alpha-ribavirin bitherapy on cytochrome P450 1A2 and 2D6 and N-acetyltransferase-2 activities in patients with chronic active hepatitis C. Clin Pharmacol Ther 2002;71:488–95.
23. Kirby GM, Batist G, Alpert L, Lamoureux E, Cameron RG, Alaoui-Jamali MA. Overexpression of cytochrome P-450 isoforms involved in aflatoxin B1 bioactivation in human liver with cirrhosis and hepatitis. Toxicol Pathol 1996;24:458–67.
24. Pasanen M, Rannala Z, Tooming A, Sotaniemi EA, Pelkonen O, Rautio A. Hepatitis A impairs the function of human hepatic CYP2A6 in vivo. Toxicology 1997;123:177–84.
25. Sugimoto M, Furuta T, Shirai N, Ikuma M, Hishida A, Ishizaki T. Influences of proinflammatory and anti-inflammatory cytokine polymorphisms on eradication rates of clarithromycin-sensitive strains of Helicobacter pylori by triple therapy. Clin Pharmacol Ther 2006;80:41–50.
26. Zambon CF, Fasolo M, Basso D, et al. Clarithromycin resistance, tumor necrosis factor alpha gene polymorphism and mucosal inflammation affect H. pylori eradication success. J Gastrointest Surg 2007;11:1506–14; discussion 14.
27. Furuta T, Shirai N, Xiao F, et al. Polymorphism of interleukin-1beta affects the eradication rates of Helicobacter pylori by triple therapy. Clin Gastroenterol Hepatol 2004;2:22–30.
28. Renton KW, Gray JD, Hall RI. Decreased elimination of theophylline after influenza vaccination. Can Med Assoc J 1980;123:288–90.
29. Roberts DJ, Goralski KB, Renton KW, et al. Effect of acute inflammatory brain injury on accumulation of morphine and morphine 3- and 6-glucuronide in the human brain. Crit Care Med 2009;37:2767–74.
30. Chang KC, Bell TD, Lauer BA, Chai H. Altered theophylline pharmacokinetics during acute respiratory viral illness. Lancet 1978;1:1132–3.
31. Kraemer MJ, Furukawa CT, Koup JR, Shapiro GG, Pierson WE, Bierman CW. Altered theophylline clearance during an influenza B outbreak. Pediatrics 1982;69:476–80.
32. Aitken AE, Morgan ET. Gene-specific effects of inflammatory cytokines on cytochrome P450 2 C, 2B6 and 3A4 mRNA levels in human hepatocytes. Drug metabolism and disposition: the biological fate of chemicals 2007;35:1687–93.
33. Abdel-Razzak Z, Loyer P, Fautrel A, et al. Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human hepatocytes in primary culture. Mol Pharmacol 1993;44:707–15.
34. Haas CE, Kaufman DC, Jones CE, Burstein AH, Reiss W. Cytochrome P450 3A4 activity after surgical stress. Crit Care Med 2003;31:1338–46.
35. Williams ML, Bhargava P, Cherrouk I, Marshall JL, Flockhart DA, Wainer IW. A discordance of the cytochrome P450 2 C19 genotype and phenotype in patients with advanced cancer. Br J Clin Pharmacol 2000;49:485–8.
36. Rivory LP, Slaviero KA, Clarke SJ. Hepatic cytochrome P450 3A drug metabolism is reduced in cancer patients who have an acute-phase response. Br J Cancer 2002;87:277–80.
37. Conze D, Weiss L, Regen PS, et al. Autocrine production of interleukin 6 causes multidrug resistance in breast cancer cells. Cancer Res 2001;61:8851–8.
38. Kacevska M, Robertson GR, Clarke SJ, Liddle C. Inflammation and CYP3A4-mediated drug metabolism in advanced cancer: impact and implications for chemotherapeutic drug dosing. Expert Opin Drug Metab Toxicol 2008;4:137–49.

39. Duan Z, Lamendola DE, Penson RT, Kronish KM, Seiden MV. Overexpression of IL-6 but not IL-8 increases paclitaxel resistance of U-2OS human osteosarcoma cells. Cytokine 2002;17:234–42.
40. Anolik R, Kolski GB, Schaible DH, Ratner J. Transient alteration of theophylline half-life: possible association with Herpes simplex infection. Ann Allergy 1982;49:109–11.
41. Shedlofsky SI, Israel BC, McClain CJ, Hill DB, Blouin RA. Endotoxin administration to humans inhibits hepatic cytochrome P450-mediated drug metabolism. J Clin Invest 1994;94:2209–14.
42. Shedlofsky SI, Israel BC, Tosheva R, Blouin RA. Endotoxin depresses hepatic cytochrome P450-mediated drug metabolism in women. Br J Clin Pharmacol 1997;43:627–32.
43. Gutmann H, Hruz P, Zimmermann C, et al. Breast cancer resistance protein and P-glycoprotein expression in patients with newly diagnosed and therapy-refractory ulcerative colitis compared with healthy controls. Digestion 2008;78:154–62.
44. Langmann T, Moehle C, Mauerer R, et al. Loss of detoxification in inflammatory bowel disease: dysregulation of pregnane X receptor target genes. Gastroenterology 2004;127:26–40.
45. Kortekaas R, Leenders KL, van Oostrom JC, et al. Blood-brain barrier dysfunction in parkinsonian midbrain in vivo. Annals of Neurology 2005;57:176–9.
46. Langford D, Grigorian A, Hurford R, et al. Altered P-glycoprotein expression in AIDS patients with HIV encephalitis. Journal of neuropathology and experimental neurology 2004;63:1038–47.
47. Loscher W, Potschka H. Drug resistance in brain diseases and the role of drug efflux transporters. Nature Reviews 2005;6:591–602.
48. Vogelgesang S, Warzok RW, Cascorbi I, et al. The role of P-glycoprotein in cerebral amyloid angiopathy; implications for the early pathogenesis of Alzheimer's disease. Current Alzheimer research 2004;1:121–5.
49. O'Neil WM, Gilfix BM, Markoglou N, Di Girolamo A, Tsoukas CM, Wainer IW. Genotype and phenotype of cytochrome P450 2D6 in human immunodeficiency virus-positive patients and patients with acquired immunodeficiency syndrome. Eur J Clin Pharmacol 2000;56:231–40.
50. Masimirembwa CM, Beke M, Hasler JA, Tang BK, Kalow W. Low CYP1A2 activity in rural Shona children of Zimbabwe. Clin Pharmacol Ther 1995;57:25–31.
51. Frye RF, Schneider VM, Frye CS, Feldman AM. Plasma levels of TNF-alpha and IL-6 are inversely related to cytochrome P450-dependent drug metabolism in patients with congestive heart failure. J Card Fail 2002;8:315–9.
52. Satarug S, Lang MA, Yongvanit P, et al. Induction of cytochrome P450 2A6 expression in humans by the carcinogenic parasite infection, opisthorchiasis viverrini. Cancer Epidemiol Biomarkers Prev 1996;5:795–800.
53. Carcillo JA, Doughty L, Kofos D, et al. Cytochrome P450 mediated-drug metabolism is reduced in children with sepsis-induced multiple organ failure. Intensive Care Med 2003;29:980–4.
54. Novotny AR, Emmanuel K, Maier S, et al. Cytochrome P450 activity mirrors nitric oxide levels in postoperative sepsis: predictive indicators of lethal outcome. Surgery 2007;141:376–84.
55. Morgan ET, Goralski KB, Piquette-Miller M, et al. Regulation of drug-metabolizing enzymes and transporters in infection, inflammation, and cancer. Drug metabolism and disposition: the biological fate of chemicals 2008;36:205–16.
56. Renton KW. Regulation of drug metabolism and disposition during inflammation and infection. Expert Opin Drug Metab Toxicol 2005;1:629–40.
57. Renton KW. Alteration of drug biotransformation and elimination during infection and inflammation. Pharmacology & therapeutics 2001;92:147–63.
58. Miller DS. Regulation of P-glycoprotein and other ABC drug transporters at the blood-brain barrier. Trends Pharmacol Sci 2010;31:246–54.
59. Bauer B, Hartz AM, Miller DS. Tumor necrosis factor alpha and endothelin-1 increase P-glycoprotein expression and transport activity at the blood-brain barrier. Mol Pharmacol 2007;71:667–75.
60. Donato MT, Guillen MI, Jover R, Castell JV, Gomez-Lechon MJ. Nitric oxide-mediated inhibition of cytochrome P450 by interferon-gamma in human hepatocytes. J Pharmacol Exp Ther 1997;281:484–90.

61. Hartz AM, Bauer B, Fricker G, Miller DS. Rapid regulation of P-glycoprotein at the blood-brain barrier by endothelin-1. Mol Pharmacol 2004;66:387–94.
62. Hartz AM, Bauer B, Fricker G, Miller DS. Rapid modulation of P-glycoprotein-mediated transport at the blood-brain barrier by tumor necrosis factor-alpha and lipopolysaccharide. Mol Pharmacol 2006;69:462–70.
63. Kim RB. Transporters and drug discovery: why, when, and how. Molecular pharmaceutics 2006;3:26–32.
64. Petzinger E, Geyer J. Drug transporters in pharmacokinetics. Naunyn-Schmiedeberg's Arch Pharmacol 2006;372:465–75.
65. Anzenbacher P, Anzenbacherova E. Cytochromes P450 and metabolism of xenobiotics. Cell Mol Life Sci 2001;58:737–47.
66. Chang GW, Kam PC. The physiological and pharmacological roles of cytochrome P450 isoenzymes. Anaesthesia 1999;54:42–50.
67. Gonzalez FJ, Tukey RH. Chapter 3. Drug Metabolism (Chapter). In: Brunton L, Lazo J, Parker K, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 11 ed, 2006.
68. Giacomini KM, Sugiyama Y. Chapter 2. Membrane transporters and drug response (Chapter). In: Brunton L, Lazo J, Parker K, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 11 ed, 2006.
69. Dean M, Rzhetsky A, Allikmets R. The human ATP-binding cassette (ABC) transporter superfamily. Genome research 2001;11:1156–66.
70. Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA. The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteinsIntroduction. Pflugers Arch 2004;447:465–8.
71. Hagenbuch B, Meier PJ. The superfamily of organic anion transporting polypeptides. Biochimica et biophysica acta 2003;1609:1–18.
72. Koepsell H, Schmitt BM, Gorboulev V. Organic cation transporters. Reviews of physiology, biochemistry and pharmacology 2003;150:36–90.
73. Rizwan AN, Burckhardt G. Organic anion transporters of the SLC22 family: biopharmaceutical, physiological, and pathological roles. Pharm Res 2007;24:450–70.
74. Tsuji A, Tamai I. Carrier-mediated intestinal transport of drugs. Pharm Res 1996;13:963–77.
75. Yang CY, Dantzig AH, Pidgeon C. Intestinal peptide transport systems and oral drug availability. Pharm Res 1999;16:1331–43.
76. Giacomini KM, Huang SM, Tweedie DJ, et al. Membrane transporters in drug development. Nature reviews;9:215–36.
77. Tsuruoka S, Sugimoto KI, Fujimura A, Imai M, Asano Y, Muto S. P-glycoprotein-mediated drug secretion in mouse proximal tubule perfused in vitro. J Am Soc Nephrol 2001;12:177–81.
78. van Asperen J, van Tellingen O, Beijnen JH. The role of mdr1a P-glycoprotein in the biliary and intestinal secretion of doxorubicin and vinblastine in mice. Drug metabolism and disposition: the biological fate of chemicals 2000;28:264–7.
79. Schinkel AH, Smit JJ, van Tellingen O, et al. Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. Cell 1994;77:491–502.
80. Schinkel AH, Wagenaar E, van Deemter L, Mol CA, Borst P. Absence of the mdr1a P-Glycoprotein in mice affects tissue distribution and pharmacokinetics of dexamethasone, digoxin, and cyclosporin A. J Clin Invest 1995;96:1698–705.
81. Borish LC, Steinke JW. 2. Cytokines and chemokines. The Journal of allergy and clinical immunology 2003;111:S460–75.
82. Steinke JW, Borish L. 3. Cytokines and chemokines. The Journal of allergy and clinical immunology 2006;117:S441–5.
83. Commins SP, Borish L, Steinke JW. Immunologic messenger molecules: cytokines, interferons, and chemokines. The Journal of allergy and clinical immunology;125:S53–72.
84. SK D, T H, J V, NA N. Cytokine reference. In: JJ O, M F, eds: Academic Press, 2010.
85. Medzhitov R. Inflammation 2010: new adventures of an old flame. Cell;140:771–6.

86. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008;454:428–35.
87. Barton GM. A calculated response: control of inflammation by the innate immune system. J Clin Invest 2008;118:413–20.
88. Baumann H, Gauldie J. The acute phase response. Immunol Today 1994;15:74–80.
89. Gruys E, Toussaint MJ, Niewold TA, Koopmans SJ. Acute phase reaction and acute phase proteins. J Zhejiang Univ Sci B 2005;6:1045–56.
90. Moshage H. Cytokines and the hepatic acute phase response. The Journal of pathology 1997;181:257–66.
91. Ramadori G, Christ B. Cytokines and the hepatic acute-phase response. Semin Liver Dis 1999;19:141–55.
92. Le Vee M, Gripon P, Stieger B, Fardel O. Down-regulation of organic anion transporter expression in human hepatocytes exposed to the proinflammatory cytokine interleukin 1beta. Drug metabolism and disposition: the biological fate of chemicals 2008;36:217–22.
93. Vee ML, Lecureur V, Stieger B, Fardel O. Regulation of drug transporter expression in human hepatocytes exposed to the proinflammatory cytokines tumor necrosis factor-alpha or interleukin-6. Drug metabolism and disposition: the biological fate of chemicals 2009;37:685–93.
94. Morahan PS, Munson AE, Regelson W, Commerford SL, Hamilton LD. Antiviral activity and side effects of polyriboinosinic-cytidylic acid complexes as affected by molecular size. Proceedings of the National Academy of Sciences of the United States of America 1972;69:842–6.
95. Nebert DW, Friedman RM. Stimulation of aryl hydrocarbon hydroxylase induction in cell cultures by interferon. J Virol 1973;11:193–7.
96. Castro JE. The effect of Corynebacterium parvum on the structure and function of the lymphoid system in mice. Eur J Cancer 1974;10:115–20.
97. Foster RS, Jr. The immunostimulant Corynebacterium parvum and hematopoietic toxicity of chemotherapy. Surg Forum 1976;27:140–2.
98. Soyka LF, Stephens CC, MacPherson BR, Foster RS, Jr. Role of mononuclear phagocytes in decreased hepatic drug metabolism following administration of Corynebacterium parvum. Int J Immunopharmacol 1979;1:101–12.
99. Chen YL, Le Vraux V, Leneveu A, et al. Acute-phase response, interleukin-6, and alteration of cyclosporine pharmacokinetics. Clin Pharmacol Ther 1994;55:649–60.
100. Gidal BE, Reiss WG, Liao JS, Pitterle ME. Changes in interleukin-6 concentrations following epilepsy surgery: potential influence on carbamazepine pharmacokinetics. Ann Pharmacother 1996;30:545–6.
101. Shelly MP, Mendel L, Park GR. Failure of critically ill patients to metabolise midazolam. Anaesthesia 1987;42:619–26.
102. Aitken AE, Lee CM, Morgan ET. Roles of nitric oxide in inflammatory downregulation of human cytochromes P450. Free Radic Biol Med 2008;44:1161–8.
103. Lagadic-Gossmann D, Lerche C, Rissel M, et al. The induction of the human hepatic CYP2E1 gene by interleukin 4 is transcriptional and regulated by protein kinase C. Cell Biol Toxicol 2000;16:221–33.
104. Muntane-Relat J, Ourlin JC, Domergue J, Maurel P. Differential effects of cytokines on the inducible expression of CYP1A1, CYP1A2, and CYP3A4 in human hepatocytes in primary culture. Hepatology 1995;22:1143–53.
105. Sunman JA, Hawke RL, LeCluyse EL, Kashuba AD. Kupffer cell-mediated IL-2 suppression of CYP3A activity in human hepatocytes. Drug metabolism and disposition: the biological fate of chemicals 2004;32:359–63.
106. Yang J, Hao C, Yang D, et al. Pregnane X receptor is required for interleukin-6 mediated downregulation of cytochrome P450 3A4 in human hepatocytes. Toxicol Lett 2010;197:219–26.
107. Elferink MG, Olinga P, Draaisma AL, et al. LPS-induced downregulation of MRP2 and BSEP in human liver is due to a posttranscriptional process. Am J Physiol Gastrointest Liver Physiol 2004;287:G1008–16.
108. Blokzijl H, Vander Borght S, Bok LI, et al. Decreased P-glycoprotein (P-gp/MDR1) expression in inflamed human intestinal epithelium is independent of PXR protein levels. Inflamm Bowel Dis 2007;13:710–20.

109. Englund G, Jacobson A, Rorsman F, Artursson P, Kindmark A, Ronnblom A. Efflux transporters in ulcerative colitis: decreased expression of BCRP (ABCG2) and Pgp (ABCB1). Inflamm Bowel Dis 2007;13:291–7.
110. Heemskerk S, Wouterse AC, Russel FG, Masereeuw R. Nitric oxide down-regulates the expression of organic cation transporters (OCT) 1 and 2 in rat kidney during endotoxemia. Eur J Pharmacol 2008;584:390–7.
111. Heemskerk S, van Koppen A, van den Broek L, et al. Nitric oxide differentially regulates renal ATP-binding cassette transporters during endotoxemia. Pflugers Arch 2007;454:321–34.
112. Huls M, van den Heuvel JJ, Dijkman HB, Russel FG, Masereeuw R. ABC transporter expression profiling after ischemic reperfusion injury in mouse kidney. Kidney Int 2006;69:2186–93.
113. Poller B, Drewe J, Krahenbuhl S, Huwyler J, Gutmann H. Regulation of BCRP (ABCG2) and P-glycoprotein (ABCB1) by cytokines in a model of the human blood-brain barrier. Cellular and molecular neurobiology 2010;30:63–70.
114. Evseenko DA, Paxton JW, Keelan JA. Independent regulation of apical and basolateral drug transporter expression and function in placental trophoblasts by cytokines, steroids, and growth factors. Drug metabolism and disposition: the biological fate of chemicals 2007;35:595–601.
115. Piquette-Miller M, Pak A, Kim H, Anari R, Shahzamani A. Decreased expression and activity of P-glycoprotein in rat liver during acute inflammation. Pharm Res 1998;15:706–11.
116. Sukhai M, Yong A, Kalitsky J, Piquette-Miller M. Inflammation and interleukin-6 mediate reductions in the hepatic expression and transcription of the mdr1a and mdr1b Genes. Mol Cell Biol Res Commun 2000;4:248–56.
117. Ando H, Nishio Y, Ito K, et al. Effect of endotoxin on P-glycoprotein-mediated biliary and renal excretion of rhodamine-123 in rats. Antimicrob Agents Chemother 2001;45:3462–7.
118. Hidemura K, Zhao YL, Ito K, et al. Shiga-like toxin II impairs hepatobiliary transport of doxorubicin in rats by down-regulation of hepatic P glycoprotein and multidrug resistance-associated protein Mrp2. Antimicrob Agents Chemother 2003;47:1636–42.
119. Wang JH, Scollard DA, Teng S, Reilly RM, Piquette-Miller M. Detection of P-glycoprotein activity in endotoxemic rats by 99mTc-sestamibi imaging. J Nucl Med 2005;46:1537–45.
120. Cherrington NJ, Slitt AL, Li N, Klaassen CD. Lipopolysaccharide-mediated regulation of hepatic transporter mRNA levels in rats. Drug metabolism and disposition: the biological fate of chemicals 2004;32:734–41.
121. Geier A, Dietrich CG, Voigt S, et al. Effects of proinflammatory cytokines on rat organic anion transporters during toxic liver injury and cholestasis. Hepatology 2003;38:345–54.
122. Hartmann G, Cheung AK, Piquette-Miller M. Inflammatory cytokines, but not bile acids, regulate expression of murine hepatic anion transporters in endotoxemia. J Pharmacol Exp Ther 2002;303:273–81.
123. Sukhai M, Yong A, Pak A, Piquette-Miller M. Decreased expression of P-glycoprotein in interleukin-1beta and interleukin-6 treated rat hepatocytes. Inflamm Res 2001;50:362–70.
124. Teng S, Piquette-Miller M. The involvement of the pregnane X receptor in hepatic gene regulation during inflammation in mice. J Pharmacol Exp Ther 2005;312:841–8.
125. Siewert E, Dietrich CG, Lammert F, et al. Interleukin-6 regulates hepatic transporters during acute-phase response. Biochem Biophys Res Commun 2004;322:232–8.
126. Fardel O, Le Vee M. Regulation of human hepatic drug transporter expression by pro-inflammatory cytokines. Expert Opin Drug Metab Toxicol 2009;5:1469–81.
127. Buyse M, Radeva G, Bado A, Farinotti R. Intestinal inflammation induces adaptation of P-glycoprotein expression and activity. Biochem Pharmacol 2005;69:1745–54.
128. Iizasa H, Genda N, Kitano T, et al. Altered expression and function of P-glycoprotein in dextran sodium sulfate-induced colitis in mice. J Pharm Sci 2003;92:569–76.
129. Masubuchi Y, Enoki K, Horie T. Down-regulation of hepatic cytochrome P450 enzymes in rats with trinitrobenzene sulfonic acid-induced colitis. Drug metabolism and disposition: the biological fate of chemicals 2008;36:597–603.
130. Naud J, Michaud J, Boisvert C, et al. Down-regulation of intestinal drug transporters in chronic renal failure in rats. J Pharmacol Exp Ther 2007;320:978–85.

131. Veau C, Leroy C, Banide H, et al. Effect of chronic renal failure on the expression and function of rat intestinal P-glycoprotein in drug excretion. Nephrol Dial Transplant 2001;16:1607–14.
132. Veau C, Faivre L, Tardivel S, et al. Effect of interleukin-2 on intestinal P-glycoprotein expression and functionality in mice. J Pharmacol Exp Ther 2002;302:742–50.
133. Niessner M, Volk BA. Altered Th1/Th2 cytokine profiles in the intestinal mucosa of patients with inflammatory bowel disease as assessed by quantitative reversed transcribed polymerase chain reaction (RT-PCR). Clin Exp Immunol 1995;101:428–35.
134. Sawa Y, Oshitani N, Adachi K, Higuchi K, Matsumoto T, Arakawa T. Comprehensive analysis of intestinal cytokine messenger RNA profile by real-time quantitative polymerase chain reaction in patients with inflammatory bowel disease. Int J Mol Med 2003;11:175–9.
135. Furuta T, Shirai N, Takashima M, Xiao F, Sugimura H. Effect of genotypic differences in interleukin-1 beta on gastric acid secretion in Japanese patients infected with Helicobacter pylori. Am J Med 2002;112:141–3.
136. Schmidt C, Hocherl K, Bucher M. Cytokine-mediated regulation of urea transporters during experimental endotoxemia. Am J Physiol Renal Physiol 2007;292:F1479–89.
137. Schmidt C, Hocherl K, Bucher M. Regulation of renal glucose transporters during severe inflammation. Am J Physiol Renal Physiol 2007;292:F804–11.
138. Schmidt C, Hocherl K, Schweda F, Kurtz A, Bucher M. Regulation of renal sodium transporters during severe inflammation. J Am Soc Nephrol 2007;18:1072–83.
139. Masereeuw R, Moons MM, Russel FG. Rhodamine 123 accumulates extensively in the isolated perfused rat kidney and is secreted by the organic cation system. Eur J Pharmacol 1997;321:315–23.
140. Oldendorf WH. Blood-brain barrier permeability to drugs. Annual review of pharmacology 1974;14:239–48.
141. Graff CL, Pollack GM. Drug transport at the blood-brain barrier and the choroid plexus. Curr Drug Metab 2004;5:95–108.
142. Kusuhara H, Sugiyama Y. Active efflux across the blood-brain barrier: role of the solute carrier family. NeuroRx 2005;2:73–85.
143. de Vries HE, Kuiper J, de Boer AG, Van Berkel TJ, Breimer DD. The blood-brain barrier in neuroinflammatory diseases. Pharmacol Rev 1997;49:143–55.
144. Eikelenboom P, Bate C, Van Gool WA, et al. Neuroinflammation in Alzheimer's disease and prion disease. Glia 2002;40:232–9.
145. Ghafouri M, Amini S, Khalili K, Sawaya BE. HIV-1 associated dementia: symptoms and causes. Retrovirology 2006;3:28.
146. Whitton PS. Inflammation as a causative factor in the aetiology of Parkinson's disease. British journal of pharmacology 2007;150:963–76.
147. Bauer B, Hartz AM, Pekcec A, Toellner K, Miller DS, Potschka H. Seizure-induced up-regulation of P-glycoprotein at the blood-brain barrier through glutamate and cyclooxygenase-2 signaling. Mol Pharmacol 2008;73:1444–53.
148. Beaulieu E, Demeule M, Ghitescu L, Beliveau R. P-glycoprotein is strongly expressed in the luminal membranes of the endothelium of blood vessels in the brain. Biochem J 1997;326 (Pt 2):539–44.
149. Virgintino D, Robertson D, Errede M, et al. Expression of P-glycoprotein in human cerebral cortex microvessels. J Histochem Cytochem 2002;50:1671–6.
150. Volk H, Potschka H, Loscher W. Immunohistochemical localization of P-glycoprotein in rat brain and detection of its increased expression by seizures are sensitive to fixation and staining variables. J Histochem Cytochem 2005;53:517–31.
151. Thuerauf N, Fromm MF. The role of the transporter P-glycoprotein for disposition and effects of centrally acting drugs and for the pathogenesis of CNS diseases. European archives of psychiatry and clinical neuroscience 2006;256:281–6.
152. Lankas GR, Cartwright ME, Umbenhauer D. P-glycoprotein deficiency in a subpopulation of CF-1 mice enhances avermectin-induced neurotoxicity. Toxicology and applied pharmacology 1997;143:357–65.

153. Umbenhauer DR, Lankas GR, Pippert TR, et al. Identification of a P-glycoprotein-deficient subpopulation in the CF-1 mouse strain using a restriction fragment length polymorphism. Toxicology and applied pharmacology 1997;146:88–94.
154. Choo EF, Leake B, Wandel C, et al. Pharmacological inhibition of P-glycoprotein transport enhances the distribution of HIV-1 protease inhibitors into brain and testes. Drug metabolism and disposition: the biological fate of chemicals 2000;28:655–60.
155. Uhr M, Tontsch A, Namendorf C, et al. Polymorphisms in the drug transporter gene ABCB1 predict antidepressant treatment response in depression. Neuron 2008;57:203–9.
156. Luurtsema G, Molthoff CF, Windhorst AD, et al. (R)- and (S)-[11 C]verapamil as PET-tracers for measuring P-glycoprotein function: in vitro and in vivo evaluation. Nuclear medicine and biology 2003;30:747–51.
157. Schinkel AH, Wagenaar E, Mol CA, van Deemter L. P-glycoprotein in the blood-brain barrier of mice influences the brain penetration and pharmacological activity of many drugs. J Clin Invest 1996;97:2517–24.
158. van Asperen J, Schinkel AH, Beijnen JH, Nooijen WJ, Borst P, van Tellingen O. Altered pharmacokinetics of vinblastine in Mdr1a P-glycoprotein-deficient Mice. Journal of the National Cancer Institute 1996;88:994–9.
159. King M, Su W, Chang A, Zuckerman A, Pasternak GW. Transport of opioids from the brain to the periphery by P-glycoprotein: peripheral actions of central drugs. Nature neuroscience 2001;4:268–74.
160. Mealey KL, Greene S, Bagley R, et al. P-glycoprotein contributes to the blood-brain, but not blood-cerebrospinal fluid, barrier in a spontaneous canine p-glycoprotein knockout model. Drug metabolism and disposition: the biological fate of chemicals 2008;36:1073–9.
161. Mealey KL, Bentjen SA, Gay JM, Cantor GH. Ivermectin sensitivity in collies is associated with a deletion mutation of the mdr1 gene. Pharmacogenetics 2001;11:727–33.
162. Sartor LL, Bentjen SA, Trepanier L, Mealey KL. Loperamide toxicity in a collie with the MDR1 mutation associated with ivermectin sensitivity. Journal of veterinary internal medicine/American College of Veterinary Internal Medicine 2004;18:117–8.
163. Loscher W. Drug transporters in the epileptic brain. Epilepsia 2007;48 Suppl 1:8–13.
164. Greenberg ML, Fisher PG, Freeman C, et al. Etoposide, vincristine, and cyclosporin A with standard-dose radiation therapy in newly diagnosed diffuse intrinsic brainstem gliomas: a pediatric oncology group phase I study. Pediatric blood & cancer 2005;45:644–8.
165. Sadeque AJ, Wandel C, He H, Shah S, Wood AJ. Increased drug delivery to the brain by P-glycoprotein inhibition. Clin Pharmacol Ther 2000;68:231–7.
166. Chen X, Zhou ZW, Xue CC, Li XX, Zhou SF. Role of P-glycoprotein in restricting the brain penetration of tanshinone IIA, a major active constituent from the root of Salvia miltiorrhiza Bunge, across the blood-brain barrier. Xenobiotica; the fate of foreign compounds in biological systems 2007;37:635–78.
167. Yu XY, Lin SG, Chen X, et al. Transport of cryptotanshinone, a major active triterpenoid in Salvia miltiorrhiza Bunge widely used in the treatment of stroke and Alzheimer's disease, across the blood-brain barrier. Curr Drug Metab 2007;8:365–78.
168. Imbert F, Jardin M, Fernandez C, et al. Effect of efflux inhibition on brain uptake of itraconazole in mice infected with Cryptococcus neoformans. Drug metabolism and disposition: the biological fate of chemicals 2003;31:319–25.
169. Zhao YL, Du J, Kanazawa H, et al. Shiga-like toxin II modifies brain distribution of a P-glycoprotein substrate, doxorubicin, and P-glycoprotein expression in mice. Brain Res 2002;956:246–53.
170. Zhao YL, Du J, Kanazawa H, et al. Effect of endotoxin on doxorubicin transport across blood-brain barrier and P-glycoprotein function in mice. Eur J Pharmacol 2002; 445:115–23.
171. Hartz AM, Bauer B, Block ML, Hong JS, Miller DS. Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier. Faseb J 2008;22:2723–33.

172. Seelbach MJ, Brooks TA, Egleton RD, Davis TP. Peripheral inflammatory hyperalgesia modulates morphine delivery to the brain: a role for P-glycoprotein. Journal of neurochemistry 2007;102:1677–90.
173. Bauer B, Hartz AM, Fricker G, Miller DS. Modulation of p-glycoprotein transport function at the blood-brain barrier. Experimental biology and medicine (Maywood, NJ 2005;230: 118–27.
174. Miller DS, Bauer B, Hartz AM. Modulation of P-Glycoprotein at the Blood-Brain Barrier: Opportunities to Improve Central Nervous System Pharmacotherapy. Pharmacol Rev 2008;60:196–209.
175. Ronaldson PT, Ashraf T, Bendayan R. Regulation of multidrug resistance protein 1 by tumor necrosis factor alpha in cultured glial cells: involvement of nuclear factor-kappaB and c-Jun N-terminal kinase signaling pathways. Mol Pharmacol 2010;77:644–59.
176. Ronaldson PT, Bendayan R. HIV-1 viral envelope glycoprotein gp120 triggers an inflammatory response in cultured rat astrocytes and regulates the functional expression of P-glycoprotein. Mol Pharmacol 2006;70:1087–98.
177. Theron D, Barraud de Lagerie S, Tardivel S, et al. Influence of tumor necrosis factor-alpha on the expression and function of P-glycoprotein in an immortalised rat brain capillary endothelial cell line, GPNT. Biochem Pharmacol 2003;66:579–87.
178. Yu C, Kastin AJ, Tu H, Waters S, Pan W. TNF activates P-glycoprotein in cerebral microvascular endothelial cells. Cell Physiol Biochem 2007;20:853–8.
179. Lazarowski A, Czornyj L, Lubienieki F, Girardi E, Vazquez S, D'Giano C. ABC transporters during epilepsy and mechanisms underlying multidrug resistance in refractory epilepsy. Epilepsia 2007;48 Suppl 5:140–9.
180. Potschka H. Targeting regulation of ABC efflux transporters in brain diseases: a novel therapeutic approach. Pharmacology & therapeutics 2010;125:118–27.
181. Hartkoorn RC, Chandler B, Owen A, et al. Differential drug susceptibility of intracellular and extracellular tuberculosis, and the impact of P-glycoprotein. Tuberculosis (Edinburgh, Scotland) 2007;87:248–55.
182. Spudich A, Kilic E, Xing H, et al. Inhibition of multidrug resistance transporter-1 facilitates neuroprotective therapies after focal cerebral ischemia. Nature neuroscience 2006;9: 487–8.
183. Vahakangas K, Myllynen P. Drug transporters in the human blood-placental barrier. Br J Pharmacol 2009;158:665–78.
184. Evseenko DA, Paxton JW, Keelan JA. ABC drug transporter expression and functional activity in trophoblast-like cell lines and differentiating primary trophoblast. Am J Physiol Regul Integr Comp Physiol 2006;290:R1357–65.
185. Jonker JW, Smit JW, Brinkhuis RF, et al. Role of breast cancer resistance protein in the bioavailability and fetal penetration of topotecan. J Natl Cancer Inst 2000;92:1651–6.
186. Lankas GR, Wise LD, Cartwright ME, Pippert T, Umbenhauer DR. Placental P-glycoprotein deficiency enhances susceptibility to chemically induced birth defects in mice. Reprod Toxicol 1998;12:457–63.
187. Nagashige M, Ushigome F, Koyabu N, et al. Basal membrane localization of MRP1 in human placental trophoblast. Placenta 2003;24:951–8.
188. Smit JW, Huisman MT, van Tellingen O, Wiltshire HR, Schinkel AH. Absence or pharmacological blocking of placental P-glycoprotein profoundly increases fetal drug exposure. The J Clin Invest 1999;104:1441–7.
189. Zhang Y, Wang H, Unadkat JD, Mao Q. Breast cancer resistance protein 1 limits fetal distribution of nitrofurantoin in the pregnant mouse. Drug metabolism and disposition: the biological fate of chemicals 2007;35:2154–8.
190. Zhou L, Naraharisetti SB, Wang H, Unadkat JD, Hebert MF, Mao Q. The breast cancer resistance protein (Bcrp1/Abcg2) limits fetal distribution of glyburide in the pregnant mouse: an Obstetric-Fetal Pharmacology Research Unit Network and University of Washington Specialized Center of Research Study. Mol Pharmacol 2008;73:949–59.

191. Molsa M, Heikkinen T, Hakkola J, et al. Functional role of P-glycoprotein in the human blood-placental barrier. Clin Pharmacol Ther 2005;78:123–31.
192. Sudhakaran S, Rayner CR, Li J, Kong DC, Gude NM, Nation RL. Inhibition of placental P-glycoprotein: impact on indinavir transfer to the foetus. Br J Clin Pharmacol 2008;65:667–73.
193. Hemauer SJ, Patrikeeva SL, Nanovskaya TN, Hankins GD, Ahmed MS. Role of human placental apical membrane transporters in the efflux of glyburide, rosiglitazone, and metformin. Am J Obstet Gynecol 2010;202:383 e1–7.
194. Pollex E, Lubetsky A, Koren G. The role of placental breast cancer resistance protein in the efflux of glyburide across the human placenta. Placenta 2008;29:743–7.
195. Hamai Y, Fujii T, Yamashita T, et al. Evidence for an elevation in serum interleukin-2 and tumor necrosis factor-alpha levels before the clinical manifestations of preeclampsia. Am J Reprod Immunol 1997;38:89–93.
196. Saji F, Samejima Y, Kamiura S, Sawai K, Shimoya K, Kimura T. Cytokine production in chorioamnionitis. J Reprod Immunol 2000;47:185–96.
197. Steinborn A, Niederhut A, Solbach C, Hildenbrand R, Sohn C, Kaufmann M. Cytokine release from placental endothelial cells, a process associated with preterm labour in the absence of intrauterine infection. Cytokine 1999;11:66–73.
198. Chen YH, Wang JP, Wang H, et al. Lipopolysaccharide treatment downregulates the expression of the pregnane X receptor, cyp3a11 and mdr1a genes in mouse placenta. Toxicology 2005;211:242–52.
199. Gedeon C, Behravan J, Koren G, Piquette-Miller M. Transport of glyburide by placental ABC transporters: implications in fetal drug exposure. Placenta 2006;27:1096–102.
200. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454: 436–44.
201. Wang Y, Niu XL, Qu Y, et al. Autocrine production of interleukin-6 confers cisplatin and paclitaxel resistance in ovarian cancer cells. Cancer Lett 2010;295:110–23.
202. Brozek W, Bises G, Girsch T, Cross HS, Kaiser HE, Peterlik M. Differentiation-dependent expression and mitogenic action of interleukin-6 in human colon carcinoma cells: relevance for tumour progression. Eur J Cancer 2005;41:2347–54.
203. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer 2002;2:48–58.
204. Clarke R, Leonessa F, Trock B. Multidrug resistance/P-glycoprotein and breast cancer: review and meta-analysis. Semin Oncol 2005;32:S9–15.
205. Ho EA, Piquette-Miller M. Regulation of multidrug resistance by pro-inflammatory cytokines. Curr Cancer Drug Tar 2006;6:295–311.
206. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. J Pathol 2005;205:275–92.
207. Szakacs G, Paterson JK, Ludwig JA, Booth-Genthe C, Gottesman MM. Targeting multidrug resistance in cancer. Nature reviews 2006;5:219–34.
208. Mosaffa F, Lage H, Afshari JT, Behravan J. Interleukin-1 beta and tumor necrosis factor-alpha increase ABCG2 expression in MCF-7 breast carcinoma cell line and its mitoxantrone-resistant derivative, MCF-7/MX. Inflamm Res 2009;58:669–76.
209. Charles KA, Rivory LP, Brown SL, Liddle C, Clarke SJ, Robertson GR. Transcriptional repression of hepatic cytochrome P450 3A4 gene in the presence of cancer. Clin Cancer Res 2006;12:7492–7.
210. Helsby NA, Lo WY, Sharples K, et al. CYP2C19 pharmacogenetics in advanced cancer: compromised function independent of genotype. Br J Cancer 2008;99:1251–5.
211. Okuno H, Kitao Y, Takasu M, et al. Depression of drug metabolizing activity in the human liver by interferon-alpha. Eur J Clin Pharmacol 1990;39:365–7.
212. Williams SJ, Farrell GC. Inhibition of antipyrine metabolism by interferon. Br J Clin Pharmacol 1986;22:610–2.
213. Pageaux GP, le Bricquir Y, Berthou F, et al. Effects of interferon-alpha on cytochrome P-450 isoforms 1A2 and 3A activities in patients with chronic hepatitis C. Eur J Gastroenterol Hepatol 1998;10:491–5.

214. Islam M, Frye RF, Richards TJ, et al. Differential effect of IFNalpha-2b on the cytochrome P450 enzyme system: a potential basis of IFN toxicity and its modulation by other drugs. Clin Cancer Res 2002;8:2480–7.
215. Nakai K, Tanaka H, Hanada K, et al. Decreased expression of cytochromes P450 1A2, 2E1, and 3A4 and drug transporters Na+-taurocholate-cotransporting polypeptide, organic cation transporter 1, and organic anion-transporting peptide-C correlates with the progression of liver fibrosis in chronic hepatitis C patients. Drug metabolism and disposition: the biological fate of chemicals 2008;36:1786–93.
216. Grubisic-Cabo F, Vrdoljak E. Drug-induced hepatitis in a patient with malignant melanoma treated with interferon alfa 2b adjuvantly who had been administered gemfibrozil in therapy. Medical oncology (Northwood, London, England) 2006;23:121–4.
217. Wong SF, Jakowatz JG, Taheri R. Potential drug-drug interaction between interferon alfa-2b and gemfibrozil in a patient with malignant melanoma. Clin Ther 2005;27: 1942–8.
218. Kumar D. Emerging viruses in transplantation. Curr Opin Infect Dis 2010;23:374–8.
219. Sayegh MH, Carpenter CB. Transplantation 50 years later--progress, challenges, and promises. N Engl J Med 2004;351:2761–6.
220. Nampoory MR, Johny KV, Costandy JN, et al. Infection related renal impairment: a major cause of acute allograft dysfunction. Exp Clin Transplant 2003;1:60–4.
221. Dharnidharka VR, Stablein DM, Harmon WE. Post-transplant infections now exceed acute rejection as cause for hospitalization: a report of the NAPRTCS. Am J Transplant 2004;4:384–9.
222. Acott PD, Lee SH, Bitter-Suermann H, Lawen JG, Crocker JF. Infection concomitant with pediatric renal allograft rejection. Transplantation 1996;62:689–91.
223. Monforte V, Bullich S, Pou L, et al. Blood cyclosporine C0 and C2 concentrations and cytomegalovirus infections following lung transplantation. Transplant Proc 2003;35:1992–3.
224. Kuypers DR, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. Clinical efficacy and toxicity profile of tacrolimus and mycophenolic acid in relation to combined long-term pharmacokinetics in de novo renal allograft recipients. Clin Pharmacol Ther 2004;75:434–47.
225. Latorre A, Morales E, Gonzalez E, et al. Clinical management of renal transplant patients with hepatitis C virus infection treated with cyclosporine or tacrolimus. Transplant Proc 2002;34:63–4.
226. Mignogna MD, Fedele S, Lo Russo L, Bonadies G, Nappa S, Lo Muzio L. Acute cyclosporine nephrotoxicity in a patient with oral pemphigus vulgaris and HIV infection on antiretroviral therapy. J Am Acad Dermatol 2005;53:1089–90.
227. Vercauteren SB, Bosmans JL, Elseviers MM, Verpooten GA, De Broe ME. A meta-analysis and morphological review of cyclosporine-induced nephrotoxicity in auto-immune diseases. Kidney Int 1998;54:536–45.
228. Kuek A, Hazleman BL, Ostor AJ. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J 2007;83:251–60.
229. Morgan ET. Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics. Clin Pharmacol Ther 2009;85:434–8.
230. Zhou H, Parks V, Patat A, Le Coz F, Simcoe D, Korth-Bradley J. Absence of a clinically relevant interaction between etanercept and digoxin. J Clin Pharmacol 2004;44:1244–51.
231. Zhou H, Patat A, Parks V, Buckwalter M, Metzger D, Korth-Bradley J. Absence of a pharmacokinetic interaction between etanercept and warfarin. J Clin Pharmacol 2004; 44:543–50.
232. Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis 2005;64:765–6.
233. Rosenvinge A, Krogh-Madsen R, Baslund B, Pedersen BK. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNFalpha therapy. Scand J Rheumatol 2007;36:91–6.
234. Enioutina EY, Bareyan D, Daynes RA. TLR-induced local metabolism of vitamin D3 plays an important role in the diversification of adaptive immune responses. J Immunol 2009;182: 4296–305.

Chapter 7
Beta-Lactam Antibiotics

Larry H. Danziger and Melinda Neuhauser

Abstract This chapter describes the drug–drug interactions of the beta-lactam antibiotics: penicillins, cephalosporins, carbapenems, and monobactams. The beta-lactam antibiotics are a large class of diverse compounds used clinically in oral, parenteral, and inhaled dosage formulations. The beta-lactam antibiotic agents have become the most widely used therapeutic class of antimicrobials because of their broad antibacterial spectrum and excellent safety profile. Reports of drug–drug interactions with the beta-lactam antimicrobials are a relatively rare phenomenon, and when they do occur they are generally of minor significance.

In this chapter each beta-lactam drug interaction has been categorized as major, moderate or minor and is presented in Table 7.1. Interactions classified as major are considered well documented and have the potential to be life threatening or dangerous. Moderate interactions are those for which more documentation is needed and/or potential harm to the patient is less. Minor interactions are either poorly documented, present minimal potential harm to the patient, or occur with a low incidence.

The drug interactions of most concern with the beta-lactam antibiotics are those with oral contraceptive products, methotrexate and valproic acid. In the case oral contraceptives, even though a small percentage of women may potentially experience decreased effectiveness of these birth control products while taking beta-lactam antibiotic, alternative birth control methods should be considered while taking these antibiotics. Weak organic acids such as penicillins and cephalosporins can compete with methotrexate for renal tubular secretion which may increase the risk of adverse effects of methotrexate. Lastly, decreased plasma concentrations to subtherapeutic ranges have been reported in patients taking the carbapenems and valproic acid concomitantly.

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7.1 Beta-Lactam Antibiotics

The beta-lactam antibiotics are a large class of diverse compounds used clinically in oral, parenteral, and inhaled dosage formulations. The beta-lactam antibiotic agents have become the most widely used therapeutic class of antimicrobials because of their broad antibacterial spectrum and excellent safety profile. Reports of drug–drug interactions with the beta-lactam antimicrobials are a relatively rare phenomenon, and when they do occur they are generally of minor significance. This chapter describes the drug–drug interactions of the beta-lactam antibiotics: penicillins, cephalosporins, carbapenems, and monobactams.

As an overview, each beta-lactam drug interaction has been categorized as major, moderate or minor and is presented in Table 7.1. Interactions classified as major are considered well documented and have the potential to be life threatening or dangerous. Moderate interactions are those for which more documentation is needed and/or potential harm to the patient is less. Minor interactions are either poorly documented, present minimal potential harm to the patient, or occur with a low incidence.

After reading this chapter the reader will recognize the clinical significance of drug–drug interactions associated with the beta-lactam antibiotics and understand the management of these drug–drug interactions.

7.2 Penicillin Drug Interactions

7.2.1 Acid-Suppressive Agents

The combination of various penicillins (ampicillin, amoxicillin, bacampicillin, and amoxicillin/clavulanate) and H_2-receptor antagonists (cimetidine and ranitidine) or omeprazole have been evaluated for effects on the bioavailability of the specific penicillin investigated [1–5]. With the exception of bacampicillin, the bioavailability of the penicillins was unaffected. The area under of the curve (AUC) of bacampicillin was reduced in the presence of food, ranitidine, and sodium bicarbonate [5]; however, another study did not demonstrate a difference in AUC with coadministration of omeprazole and bacampicillin [2].The concurrent administration of most penicillins and acid-suppressive agents poses no problems except possibly with bacampicillin.

7.2.2 Allopurinol

An increased incidence of skin rash has been reported in patients receiving either ampicillin or amoxicillin concomitantly with allopurinol. In an analysis of data collected in 4,686 patients receiving ampicillin, 252 of which were also receiving

Table 7.1 Significance of beta-lactam drug interactions

	Penicillins	Cephalosporins	Carbapenems	Monobactam
Major	– In vitro amino-glycoside inactivation – Contraceptives, oral estrogen – Methotrexate	– Contraceptives, oral estrogen – Methotrexate	Valproic acid	
Moderate	– In vivo amino-glycoside inactivation – Aminoglycoside inactivation in sampling serum concentrations – Neomycin (oral) – Probenecid – Warfarin	– Acid suppressive agents – Antacids – Iron – Ethanol – Probenecid – Ranitidine – Warfarin	– Probenecid – Ganciclovir	– Probenecid
Minor	– Acid suppressive agents – Allopurinol – Aspirin – Beta-adrenergic blockers – Calcium channel blockers – Chloramphenicol – Chloroquine – Ciprofloxacin – Cyclosporine – Heparin – Interferon-gamma – Guar gum – Khat – Metformin – Phenytoin – Proguanil – Tetracyclines – Vecuronium	– Aminoglycoside nephrotoxicity – Calcium channel blocker – Colistin – Furosemide – Metoclopramide – Nonsteroidal anti-inflammatory drugs – Phenytoin – Propantheline – Theophylline	– Cyclosporine – Theophylline	

allopurinol, rash was reported in 5.7% of the patients receiving ampicillin compared to 13.9% of patient's receiving both ampicillin and allopurinol ($p = 0.0000001$) [6]. There were no differences of age, sex, diagnosis, or admission laboratory value of blood urea nitrogen (BUN) that could be identified between the two groups. Similar results of an increased incidence of a rash have also been reported in patients receiving both amoxicillin and allopurinol (22%) versus amoxicillin alone (5.9%) [6].

Fessel and colleagues attempted to determine the possible reasons for the higher incidence of rash in patients receiving allopurinol and ampicillin [7]. They compared

the history of allergies to penicillin, allergies to other antibiotics, presence of hay fever, use of antihistamine medications, and the prevalence of asthma in 124 asymptomatic hyperuricemic individuals compared to 224 matched normouricemic controls. The following results were considered significant in asymptomatic hyperuricemic subjects versus the control subjects: history of penicillin allergy (14.1% versus 4.9%), hay fever (18.8% versus 8.0%), and use of antihistamine medications (9.9% versus 2.7%). The incidence of allergies to antibiotics excluding penicillin and prevalence of asthma were not significant between groups. The authors hypothesized that hyperuricemic individuals tend to have a higher frequency of allergic reactions; therefore, this altered immunologic state may explain the increased incidence of ampicillin rashes rather than an ampicillin–allopurinol interaction.

The significance of this pharmacodynamic interaction tends to be minor. Clinicians may continue to prescribe these agents concomitantly. Patients should be monitored and counseled regarding this potential increased incidence of skin rashes when these two agents are prescribed concurrently.

7.2.3 Aminoglycosides

Penicillins and aminoglycosides are commonly used in combination together to treat a variety of infections. However, concomitant use of the extended-spectrum penicillin antimicrobials may result in inactivation of the aminoglycosides. Although the majority of interactions are reported in vitro, the potential for in vivo interactions are of concern, especially in those patients with end-stage renal failure [8–15].

7.2.3.1 In Vivo Aminoglycoside Inactivation

McLaughlin and Reeves reported a case report of a patient undergoing hemodialysis and receiving gentamicin for 8 days for the treatment of a soft tissue infection [9]. Carbenicillin therapy was added on day 8. The authors reported that therapeutic serum concentrations for gentamicin could not be achieved despite administration of high doses following the addition of carbenicillin. Of note, the patient received more frequent dialysis sessions during this period, which may have also contributed to subtherapeutic gentamicin concentrations. Uber et al. noted similar pharmacokinetic findings when tobramycin and piperacillin where administered concomitantly in a chronic hemodialysis patient [10]. McLauglin and Reeves also studied this interaction in an animal model [9]. Rabbits that received only gentamicin were reported to have normal gentamicin concentrations (n = 2), while rabbits receiving carbenicillin and gentamicin had undetectable levels at 30 h (n = 3).

Other investigators have described a reduction in aminoglycoside concentration when co-administered with extended-spectrum penicillins particularly in patients with end-stage renal failure [11–16]. Davies et al. evaluated gentamicin half-lives in the presence of therapeutic doses of ticarcillin or carbenicillin in eight patients

with end-stage renal failure [12]. In patients receiving gentamicin concomitantly with ticarcillin, the gentamicin half-life was reduced from 31 to 22 h whereas gentamicin half-life was reduced from 50 to 8 h in patients receiving carbenicillin and gentamicin.

Halstenson et al. assessed the effect of piperacillin administration on the disposition of netilmicin and tobramycin in 12 chronic hemodialysis patients [11]. The half-life of netilmicin was not significantly altered when netilmicin was given concurrently with piperacillin. In comparison, the half-life of tobramycin was considerably reduced in the presence of piperacillin (59.62 ± 25.18 versus 24.71 ± 5.41 h). Lau et al. were unable to document any such drug–drug interaction between piperacillin and tobramycin in subjects with normal renal function (defined as creatinine clearances of greater than or equal to 60 mL/min) [17]. Hitt and colleagues reported no differences in pharmacokinetic parameters of once-daily gentamicin with the co-administration of several piperacillin-tazobactam regimens in subjects with normal renal function [18]. Similarly, Dowell et al. were unable to demonstrate differences in the pharmacokinetic parameters of tobramycin when administered alone or with piperacillin/tazobactam in subjects with moderate renal impairment (creatinine clearance between 40 and 59 mL/min), mild renal impairment (creatinine clearance between 20 and 39 mL/min) or normal renal function (creatinine clearance greater than 90 mL/min) [19].

It has been suggested that the extended spectrum penicillins interact chemically with the aminoglycosides to form biologically inactive amides. The degree of inactivation is dependent on the specific aminoglycoside and beta-lactam used [12, 20]. In vivo inactivation of aminoglycosides occurs at such a slow rate that it appears to be clinically insignificant in patients with normal renal function [17, 20]. Some investigators have stated that this interaction could possibly be relevant for patients with renal failure who have high serum concentrations of penicillins [11, 12, 21]; therefore, close therapeutic monitoring of aminoglycosides is warranted in this specific clinical situation.

7.2.3.2 Neomycin

Concomitant administration of oral neomycin and penicillin V has been reported to reduce serum concentrations of penicillin [22]. In healthy volunteers, penicillin V concentrations decreased by over 50% following the administration of oral neomycin concomitantly with penicillin V [22]. Due to the significant decrease in penicillin exposure, oral neomycin should not be coadministered with penicillin V.

In Vitro Aminoglycoside Inactivation

McLaughlin and Reeves described undetectable gentamicin concentrations and clinical failure in a patient who received an infusion of carbenicillin and gentamicin for *Pseudomonas* bacteremia [9]. In vitro inactivation of aminoglycosides can be

significant when these agents are prepared in the same intravenous mixture for administration [20]. Within 2 h of admixing at room temperature, an intravenous fluid mixture containing ampicillin (concentration equivalent to 12 g/day) and gentamicin resulted in a 50% decline in the gentamicin activity. After 24 h, no measurable gentamicin activity was noted [20]. An intravenous fluid mixture containing gentamicin and carbenicillin demonstrated a 50% reduction in activity between 8 and 12 h after admixing at room temperature. Aminoglycosides and penicillins should not be mixed together prior to infusion

7.2.3.3 In Vitro Inactivation Aminoglycoside in Sampling Serum Concentrations

If high concentrations of penicillins are present in serum samples that are to be assayed for aminoglycoside concentrations, inactivation of the aminoglycosides by the penicillins can result in falsely decreased aminoglycoside concentrations [8]. Penicillin concentration, period of time prior to sampling, and storage temperature of the sample are factors that affect the extent of inactivation [8]. When measuring aminoglycoside serum concentrations through intravenous tubing, one should flush 5–10 mL of either normal saline or 5% dextrose in water (based on drug compatibilities) through the tubing before withdrawing blood to minimize the amount of beta-lactam present in the intravenous tubing prior to sampling.

7.2.3.4 Aminoglycosides—Synergy

The concomitant use of beta-lactam and aminoglycoside antimicrobials has been described as synergistic for several Gram-positive and Gram-negative organisms [23–26]. By inhibiting the cell-wall synthesis, beta-lactams increase the porosity of the bacterial cell wall resulting in greater aminoglycoside penetration and access to target ribosomes [27].

The use of penicillin or ampicillin in combination with an aminoglycoside has been documented to be advantageous in the treatment of enterococcal infections [28]. Moellering also noted that whereas penicillin exhibits only bacteriostatic activity against enterococci; the combination of penicillin and streptomycin possesses bactericidal activity [23]. As a result, most severe enterococcal infections are routinely treated with penicillin or ampicillin plus an aminoglycoside.

Despite the well-documented in vitro synergy between beta-lactams and aminoglycosides, limited clinical data are available supporting superior efficacy of synergistic versus nonsynergistic combinations for the treatment of Gram-negative infections. Anderson et al. retrospectively evaluated Gram-negative bacteremias to determine if the treatment with one or two antimicrobials effected outcome and whether in vitro synergy correlated with superior efficacy [29]. Of the 173 patients treated with two drugs, the clinical response rate was 83% in patients who received synergistic versus 64% with nonsynergistic antimicrobial regimens ($p < 0.05$). The use of synergistic antimicrobial combinations (aminoglycoside plus ampicillin or carbenicillin)

were associated with better clinical response in patients with neutropenia ($p < 0.001$), shock ($p < 0.001$), *Pseudomonas aeruginosa* bacteremias ($p < 0.05$), and "rapidly or ultimately fatal" conditions ($p < 0.005$). In critically ill patients with Gram-negative bacteremia, the combination of an extended spectrum penicillin and aminoglycoside is a reasonable therapeutic approach.

7.2.4 Anticoagulants

7.2.4.1 Heparin

A number of case reports have suggested that parenteral penicillins in combination with heparin have caused coagulopathies [30–36], and may predispose patients to clinically significant bleeding [33–35, 37]. The exact mechanism of this interaction is unknown but may be a result of a direct effect on platelet function by penicillins, which may have an additive anticoagulant effect when combined with heparin [31, 32, 37].

Wisloff et al. evaluated the bleeding time of patients receiving heparin and penicillins compared to heparin alone [36]. Fifty patients were placed on heparin (5,000 IU subcutaneously for 7 days) following an elective vascular surgery procedure and were also randomized to receive a combination of ampicillin and cloxacillin or no antibiotics. The patients that were receiving heparin along with the penicillins had a slightly longer bleeding time; however, this was still within an acceptable range in most cases.

Since patients receiving heparin are routinely monitored closely for coagulopathies and clinically significant bleeding, the potential interaction between these two drugs does not warrant further precautions.

7.2.4.2 Warfarin

A decreased anticoagulant effect for warfarin has been documented when given concomitantly with nafcillin [38–42] or dicloxacillin [38, 42–44]. It has been postulated that these antibiotics induce the cytochrome P450 system and may increase the metabolism of warfarin [40, 45–47]. Another possible explanation may involve the ability of these highly protein-bound agents to displace warfarin. However, Qureshi et al. performed an in vitro study and demonstrated that nafcillin did not effect the protein binding of warfarin [40]. Cropp and Busey reported that the usual onset of this interaction between nafcillin and warfarin was seen within 1 week after initiation of nafcillin therapy and with warfarin requirements returning to baseline usually within 4 weeks after the discontinuation of the nafcillin [48].

Krstenansky et al. studied the effect of dicloxacillin in seven patients stabilized on warfarin therapy [43]. Prothrombin times (PTs) were obtained prior to treatment and on days 1, 3, 6, and 7 of dicloxacillin administration. A decrease in the PT was observed in all patients on day 6 or 7 compared to baseline PT values. The decrease in PT ranged from 0.3 to 5.6 s (mean ± SD of −1.9 ± 1.8 s) and was statistically significant ($p < 0.05$).

Brown et al. presented a case report of a patient on warfarin 2.5 mg daily who developed an increased hypoprothrombinemic response after receiving high-dose intravenous penicillin (24 million units/day). Upon withdrawal of the penicillin, the patient's prothrombin time subsequently returned to his baseline [49]. More recently, Davydov et al. reported a case of a 58 year old woman, in which warfarin interacted with amoxicillin/clavulanate resulting in an elevated international normalized ratio (INR) and hematuria. [50] Although the exact mechanism of this interaction remains unknown, it has been proposed that broad spectrum antibiotic use may lead to a decrease in vitamin K producing bacteria within the gastrointestinal tract. This may then result in a vitamin K deficient state (especially in patients with low dietary intake of vitamin K) potentially leading to an increased effect of warfarin. Clinicians should be aware of the potential interaction between penicillins and oral anticoagulants and monitor the PT and INR in patients receiving these agents concurrently.

7.2.4.3 Aspirin

Large doses of aspirin may increase the serum concentrations and half-lives of penicillin, oxacillin, nafcillin, cloxacillin, and dicloxacillin when administered concurrently [51, 52]. Eleven patients with arteriosclerotic disorders received penicillin G before and after high doses of aspirin (3 g/day) [51]. During aspirin administration, penicillin half-life increased from 44.5 ± 15.8 m to 72.4 ± 35.9 m ($p < 0.05$) [51]. The mechanism of this interaction remains unknown. Some have speculated that this interaction may occur as a result of aspirin displacing penicillin from protein-binding sites or of aspirin competing with penicillins for the renal tubular secretory proteins [51–55]. Avoidance of this combination is unnecessary.

7.2.5 Beta-Adrenergic Blockers

Coadministration of ampicillin and atenolol may lead to a decrease in the serum concentration of atenolol. In a crossover study, six healthy subjects were orally administered 100 mg atenolol alone and with 1 g ampicillin. Atenolol pharmacokinetics was assessed after a single dose, and after reaching steady state. These subjects previously received intravenous atenolol in another study, which was utilized to determine oral bioavailability in the present study. The bioavailability of atenolol was reduced from 60% (atenolol alone) to 36% (single dose atenolol and ampicillin, $p < 0.01$) to 24% (steady-state concentrations of atenolol and ampicillin, $p < 0.01$) [56]. Other atenolol pharmacokinetic parameter values for AUC, C_{max}, and mean steady-state concentrations were also significantly reduced ($p < 0.01$). Despite the differences in atenolol serum concentration, blood pressure measurements did not differ between the groups over a 4-week treatment period.

McLean and colleagues also performed a crossover study administering oral atenolol and ampicillin to six volunteers [57]. Unlike the previous study, these investigators dosed ampicillin at clinically applicable doses of 250 mg 4 times a

day, as well as higher doses of 1 g. The mean reduction of AUC was lower in the former dosing regimen compared to the latter one (18.2% versus 51.5%).

Although the clinical significance of this interaction is questionable, it would seem reasonable that patients should be monitored for this interaction when higher doses of ampicillin are used, especially in the presence of renal dysfunction; however, no empiric dosage alterations are recommended at this time.

7.2.6 Calcium Channel Blockers

Nifedipine appears to increase the bioavailability of amoxicillin by facilitating its active transport mechanism within the gastrointestinal tract [58]. In a randomized cross-over study conducted in eight healthy volunteers, each subject received 1 g oral amoxicillin with 20 mg nifedipine or placebo. The absolute bioavailability of amoxicillin was noted to increase from 65.25% to 79.2% with the addition of nifedipine ($p < 0.01$) [58]. The AUC also increased from 29.7 ± 5.3 mg · h/L (amoxicillin alone) compared to 36.26 ± 6.9 mg · h/L (amoxicillin and nifedipine) ($p < 0.01$). Since no adverse events were associated with the alterations of these pharmacokinetic parameters, no dosage adjustments are recommended.

Nafcillin has been postulated to enhance the elimination of agents metabolized through the cytochrome P450 system [45, 46]. A cross-over study was conducted to evaluate the induction potential of nafcillin on nifedipine, a substrate of the cytochrome P450 3A4 enzyme [59]. Healthy volunteers were randomized to receive 5 days of oral nafcillin (500 mg 4 times daily) or placebo, which was followed by a single dose of nifedipine. The subjects who received nafcillin along with nifedipine were found to have a significant reduction in the nifedipine $AUC_{0-\infty}$ (80.9 ± 32.9 μg · h/L versus 216.4 ± 93.2 μg·h/L; $p < 0.001$) and enhanced plasma clearance (138.5 ± 42.0 L/h versus 56.5 ± 32.0 L/h; $p < 0.002$) compared to the nifedipine-placebo group. Due to the limited available data, the clinical significance of this interaction is unknown.

7.2.7 Chloramphenicol

The administration of a bacteriostatic agent such as chloramphenicol may antagonize the bactericidal activity of beta-lactam antimicrobials [60, 61]. Beta-lactam antimicrobials exhibit their bactericidal effect by binding to penicillin-binding proteins and inhibiting bacterial cell wall synthesis. For beta-lactams to exert optimal bactericidal effects, bacteria should be actively growing and dividing. However, bacteriostatic agents such as chloramphenicol, which may inhibit protein synthesis, may interfere with the bactericidal activity of penicillins.

In vitro studies have demonstrated the concomitant of penicillin and chloramphenicol to be antagonistic [60, 62]. However, human data do not support these findings [63, 64]. Patients with gonococcal infections who were treated with a combination of penicillin and chloramphenicol had better clinical outcomes than patients

treated with penicillin alone [63]. Superior outcomes were also reported among patients infected with typhoid fever who were treated with chloramphenicol plus ampicillin compared to chloramphenicol alone [64].

Relevant clinical information is limited for this drug–drug interaction. Since the in vivo and in vitro data concerning this interaction are contradictory, it is unnecessary to avoid the concurrent use of these antimicrobials.

7.2.8 Chloroquine

Investigators conducted a study in healthy volunteers to evaluate the coadministration of chloroquine and ampicillin on the pharmacokinetics of ampicillin [65]. Ampicillin pharmacokinetics alone or in the presence of chloroquine was determined by characterizing the drug's renal elimination. The mean percent of dose excreted was 29% for ampicillin alone versus 19% for the ampicillin/chloroquine combination ($p < 0.005$). The coadministration of ampicillin and chloroquine resulted in a significant reduction in ampicillin bioavailability, but not in time of maximal excretion [65]. Based on limited data, coadministration of these agents may lead to a reduction in ampicillin concentrations. Although the clinical significance of this interaction remains unknown, concomitant administration of chloroquine and ampicillin should be avoided.

7.2.9 Ciprofloxacin

Interactions between the penicillins and fluoroquinolones have been rarely documented [66, 67]. Barriere et al. assessed the effect of the concurrent administration of ciprofloxacin and azlocillin in a crossover trial [66]. Six subjects were administered single doses of ciprofloxacin and azlocillin alone and in combination. Similar pharmacokinetic profiles were noted with azlocillin; however, when coadministered with azlocillin, a statistically significant reduction in total clearance and renal clearance of ciprofloxacin was noted. Based on limited data, coadministration of these agents need not be avoided.

7.2.10 Contraceptives, Oral Estrogen

Several case reports of breakthrough bleeding and pregnancies have been reported in patients receiving oral contraceptives and antibiotics concomitantly [68–72]. It has been postulated that antibiotics interfere with the enterohepatic circulation of oral estrogens, resulting in subtherapeutic estrogen concentrations [70–72]. After oral estrogens are absorbed, they undergo hepatic metabolism to glucuronide and sulfate

conjugates and are excreted into the bile. Bacteria residing in the gut hydrolyze the conjugates to active drug, which is then reabsorbed by the body [70]. The proposed mechanism of this interaction involves the ability of antibiotics to destroy the gut bacteria that are required to hydrolyze the conjugated estrogen to their active form.

Studies in animal models assessing this interaction have shown mixed results [73, 74]. One investigation demonstrated no alterations in the pharmacokinetics of ethinylestradiol when administered with ampicillin [73]. Another study found differences in both AUC and plasma clearance in the group that received antibiotics compared to ethinylestradiol alone [74].

Several studies have been performed in humans to determine if the case reports and animal data represent significant findings [75–77]. Freidman and colleagues prospectively evaluated the serum concentrations of gonadotropins and other hormones in 11 volunteers receiving Demulen® (50 μg of ethinylestradiol and 1 mg of ethynodiol diacetate) plus ampicillin or placebo during two consecutive menstrual cycles [76]. Progesterone concentrations were similar between the Demulen-ampicillin and Demulen–placebo groups. Follicle-stimulating hormone and luteinizing hormone appeared to be similar between the two groups. None of the 11 patients underwent ovulation. Freidman and colleagues concluded that ampicillin should not reduce the effectiveness of Demulen. Other researchers have criticized the results of this study because of its study design which included a small number of subjects, a short duration of antimicrobial therapy, and a relatively high dose of estrogens (present in Demulen) [71].

Back and colleagues evaluated seven women receiving oral contraceptives for at least 3 months (all containing ≥ 30 μg of ethinyloestradiol) who presented to their clinic with an infection that required the administration of ampicillin of 8 days duration [75]. Blood samples were taken during concomitant oral estrogen and ampicillin therapy and during the next menstrual cycle without ampicillin. Six female volunteers receiving only oral contraceptives for at least 3 months were similarly evaluated for the potential drug interaction. Plasma concentrations of ethinyloestradiol, levonorgestrel, follicle-stimulating hormone, and progesterone were not significantly different between the two groups (oral contraceptive-ampicillin versus oral contraceptive alone). Despite the fact that a lower concentration of ethinyloestradiol was seen with two women on ampicillin, the authors concluded that alternative methods of protection are not necessary in most women [75].

Another study in volunteers analyzed the effect of administering ampicillin or metronidazole with an oral contraceptive preparation [77]. This summary will be limited to the group using ampicillin (n = 6). Subjects initially received a low-dose oral contraceptive (1 mg norethisterone acetate and 30 μg ethinyl estradiol). On days 6 and 7, plasma concentrations of ethinylestradiol and norethisterone were obtained. Subsequently, subjects were administered ampicillin (500 mg twice daily orally for 5–7 days) and the contraceptive steroid. Following antibiotic treatment, serum hormones, ampicillin, and progesterone concentrations were measured in the subjects. The concentrations of norethisterone and ethinylestradiol were not altered in the presence of ampicillin, and progesterone concentrations were in the appropriate range to suppress ovulation [77].

It is difficult to determine the clinical significance of this interaction because of the small number of clinical trials, small numbers of patients, minimal number of case reports, and the limited number of oral contraceptives studied. A review article by Weisberg suggests that the possibility of a clinically significant interaction between antibiotics and oral contraceptives is likely less than 1% [78]. The author states that women with a greater extent of enterohepatic circulation, previous breakthrough bleeding, or contraceptive failure may have a higher risk for this interaction [78]. More recently, Dickinson et al. reviewed this literature from 1969 through 1999. They concluded that although a rare occurrence certain penicillins may affect plasma ethinyl estradiol concentration in some women. Given the serious nature of an unexpected pregnancy they advised that women should consider other protective measures while taking these antibiotics [79].

Although clinical trials have not been able to demonstrate any consistent interaction between oral contraceptives and antibiotics due to the potential risk of contraceptive failure, clinicians should still counsel patients on this potential interaction and suggest alternative method(s) of contraception if antimicrobial therapy is necessary.

7.2.11 Cyclosporine

Although nafcillin is not well-established as an inducer of the cytochrome P450 system, the following case report suggests that nafcillin may reduce the serum concentrations of cyclosporine via induction of the cytochrome P450 system [80]. On two separate occasions, a 34-year-old woman, status post-renal transplant, experienced a reduction in cyclosporine serum concentration following nafcillin administration [80]. The patient received 2 g nafcillin intravenously every 6 h for a positive culture of methicillin-susceptible *Staphylococcus aureus* from a perinephric abscess. Upon admission, the patient was receiving 400 mg cyclosporine daily with a corresponding trough serum concentration of 229 ng/mL. After initiation of nafcillin, her cyclosporine concentrations decreased to 119 and 68 ng/mL on days 3 and 7 of nafcillin, respectively, despite stable daily doses of 400 mg of cyclosporine. Upon discontinuation of nafcillin, trough serum concentrations of cyclosporine increased to 141 and 205 ng/mL on days 2 and 4 without nafcillin therapy, respectively. No change in renal or hepatic function was noted throughout this entire treatment period. The second cyclosporine–nafcillin interaction occurred when the patient was later readmitted for drainage of retroperitoneal fluid collection. The patient experienced a similar decline in cyclosporine concentrations during concomitant therapy, and subsequent increases in cyclosporine concentrations following discontinuation of nafcillin. Based on the findings of this case report, cyclosporine concentrations should be closely monitored during concomitant nafcillin administration.

7.2.12 Erythromycin

The concurrent administration of erythromycin and penicillin may result in antagonism, synergy or no effect (indifference) on the antibacterial activity of penicillin. Beta-lactams exert their cidal effects on bacteria by binding to penicillin-binding proteins and inhibiting cell-wall synthesis. For beta-lactams to exercise their optimal bactericidal activity, bacteria should be actively growing and dividing; therefore, erythromycin can interfere with the bactericidal activity of penicillin by inhibiting protein synthesis.

In vitro studies have demonstrated the concomitant administration of penicillin and erythromycin to be synergistic, antagonistic, additive, or indifferent [81–89]. These differences may be due to such factors as the specific microorganism involved, susceptibility patterns to both agents, antibiotic concentrations, the inoculum effect, and time of incubation [81, 83, 85, 87, 88, 90]. Similar to the disparate results demonstrated in vitro, case reports have shown penicillin and erythromycin antagonism in the treatment of scarlatina [91] and *Streptococcus bovis* septicemia [92], whereas clinical improvement has been reported with the concurrent use of ampicillin and erythromycin in the treatment of pulmonary nocardiosis [93].

Although there has been concern about the use of the combination of beta-lactams and macrolides because of the possibility of antagonism, they have recently gained favor for the treatment of community-acquired pneumonia in the hospitalized patient. Several recently published studies found that patients with bacteremic pneumococcal pneumonia treated with a beta-lactam plus a macrolide had a lower mortality rate compared to those treated with a single agent [94–96]. As such, treatment guidelines for community-acquired pneumonia recommend a beta-lactam and macrolide as a preferred treatment option for hospitalized patients [97]. As evident from these clinical reports and in vitro testing, the antagonism risk between beta-lactams and macrolides appears to be minimal.

7.2.13 Guar Gum

Guar gum, which may be utilized as a food additive, has been reported to reduce serum concentrations of phenoxymethyl penicillin [98]. In a double-blind study, ten healthy volunteers received guar gum or placebo granules along with 3 MU of phenoxymethyl penicillin. The peak penicillin concentration decreased significantly from $7{,}560 \pm 1{,}720$ to $5{,}680 \pm 1{,}390$ ng/mL ($p < 0.01$) when administered with placebo compared to guar gum. The $AUC_{0-6\,h}$ of penicillin decreased significantly from $14{,}500 \pm 1{,}860$ to $10{,}380 \pm 2{,}720$ ng · h/mL ($p < 0.001$) when administered with guar gum. The time to peak concentration was not altered significantly. As a result of the significant decrease in the peak serum concentrations and $AUC_{0-6\,h}$, phenoxymethyl penicillin should not be administered concomitantly with guar gum.

7.2.14 Interferon-Gamma

Recent data suggest that penicillin may interact with a variety of cytokines by conjugating these biological proteins [99–100]. Benzylpenicillin has been shown to conjugate IFN-gamma, IL-1beta, IL-2, IL-5, IL-13, and TNF-alpha; however, based on a series of in vitro experiments, benzylpenicillin only appears to alter the biologic activity of IFN-gamma [99]. Using an in vitro bioassay, Brooks et al. noted that benzylpenicillin inhibited the ability of IFN-gamma to induce CD54 expression on epithelial cells. Additional preclinical studies suggest that other regulatory functions of IFN-gamma may also be modulated by benzylpenicillin [100]. Because IFN-gamma promotes Th1 responses and inhibits Th2 and IgE-mediated responses, disruption of IFN-gamma activity by benzylpenicillin may result in clinically significant immunomodulatory effects, which promote allergy. The reader is referred to Chap. 6 for additional information on drug-cytokine interactions.

7.2.15 Khat

The chewing of khat (a natural substance that obtained from shrubs grown in East Africa and Yemen) may reduce the bioavailability of ampicillin and amoxicillin [101]. In a crossover design, eight healthy adult male Yemeni subjects received ampicillin or amoxicillin under various conditions of khat chewing [101]. The urinary excretion method was utilized to determine the bioavailabilities of ampicillin and amoxicillin under the following conditions: antibiotic alone, 2 h before khat chewing, immediately prior to khat chewing, immediately prior to khat chewing with a meal, midway through khat chewing, and 2 h after khat chewing. The bioavailability of ampicillin (measured by percentage of ampicillin excreted unchanged in the urine, peak excretion, and time to peak excretion) was significantly decreased during all conditions except when administered 2 h after khat chewing. In contrast, amoxicillin's bioavailability was only affected when amoxicillin was taken midway through khat chewing. Considering the limited use of khat in the developed countries, this should not be considered a clinically relevant drug–drug interaction. However, if ampicillin and amoxicillin are administered to an individual using khat, these agents should be taken at least 2 h following khat chewing.

7.2.16 Metformin

In a crossover study, healthy volunteers were randomized to receive metformin alone or metformin along with cephalexin [102]. The coadministration of metformin and cephalexin led to an increase in C_{max} and AUC of metformin by approximately 30%. It appears that cephalexin interferes with renal clearance of metformin, which may be due to competition for renal transport proteins such as organic anion or

cation transporter (OAT or OCT, respectively) [102, 103]. Limited data are available on the clinical significance of this interaction. Clinicians should exercise caution when using these two agents together.

7.2.17 Methotrexate

Weak organic acids such as penicillins can compete with methotrexate for renal tubular secretion [104, 105] and reduce the renal elimination of methotrexate. Various studies in rabbits have demonstrated a reduction in the renal clearance of methotrexate and 7-hydroxymethotrexate [104–107]. One of the studies demonstrated nearly 50% reduction in methotrexate (MTX) clearance when piperacillin was administered 10 min before and 4 h after a single dose of MTX ($p \leq 0.05$) [106]. The AUC of MTX and its 7-hydroxy-methotrexate metabolite also differed significantly from the control ($p \leq 0.05$).

Despite the rather significant results reported from animal studies, few case reports have documented this potential interaction [108–113]. Bloom and colleagues reported four cases in which the administration of various penicillins concomitantly with MTX resulted in the decreased clearance of methotrexate [109]. Methotrexate clearance before and after the addition of the following antimicrobials agents are as follows: penicillin, 2.8 L/h versus 1.8 L/h; piperacillin, 11 L/h versus 3.6 L/h; ticarcillin, 5.8 L/h versus 2.3 L/h; and dicloxacillin/indomethacin, 6.4 L/h versus 0.45 L/h, respectively. Due to reduction in clearance, these patients required an extended leucovorin rescue. Titier et al., published a case report describing severe methotrexate toxicity following the concomitant administration of high-dose methotrexate and oxacillin, which lead to a series of complications and ultimately the death of the patient [113]. More recently, Zarychanski and colleagues reported the interaction of piperacillin/tazobactam with methotrexate resulting in prolonged toxic concentrations of methotrexate [114]. In contrast, Herrick and colleagues reported no differences in renal clearance of methotrexate administered alone or with flucloxacillin in ten patients [115].

Avoiding the concomitant use of penicillins and methotrexate is justified to avoid potential toxicity. If the concomitant administration of penicillins and methotrexate is necessary, close monitoring of methotrexate concentrations and signs of toxicity are warranted.

7.2.18 Oseltamivir

A pharmacokinetic study conducted in healthy volunteers evaluated the concurrent administration of oseltamivir (a prodrug) and amoxicillin [116]. No differences in the pharmacokinetic parameters of oseltamivir's active metabolite, Ro 64-0802, were noted when administered alone compared to coadministration with amoxicillin.

Also, no pharmacokinetic differences were noted for amoxicillin with or without the administration of oseltamivir [116]. Based upon these finding, oseltamivir may be prescribed with amoxicillin.

7.2.19 Phenytoin

Highly protein-bound antibiotics such as nafcillin and oxacillin (both approximately 90% bound to plasma proteins) [117] have the potential to interact with other highly protein-bound agents such as phenytoin [118, 119]. Due to drug displacement from protein binding sites, high doses of nafcillin or oxacillin may increase unbound concentrations of phenytoin in certain patient populations [118, 119].

Dasgupta et al. conducted an in vitro study to determine the potential drug interaction between oxacillin and phenytoin [118]. Serum was collected from three separate patient populations (A, B, and C). Serum for group A was collected from healthy patients receiving phenytoin. Serums for group B and C were obtained from hypoalbuminemic and hyperuremic individuals, respectively. Subjects in these latter two groups were not receiving phenytoin; therefore, the serum was supplemented with phenytoin. Each group was tested for total and unbound phenytoin concentrations with and without 15 μg/mL or 50 μg/mL of oxacillin, which represented estimated peak oxacillin concentrations following a 500 mg oral dose and a 1 g intravenous dose, respectively. Serum from group A showed no statistical difference in unbound phenytoin concentrations with 15 μg/mL oxacillin; however, a significantly higher unbound phenytoin concentration with 50 μg/mL of oxacillin was observed when compared to serum not containing oxacillin (1.67 μg/mL versus 1.47 μg/mL) ($p < 0.05$). Serum from subjects in groups B and C also demonstrated a statistically significant increase in unbound phenytoin concentrations for both oxacillin concentrations compared to the group without oxacillin.

Dasgupta and colleagues performed another study to determine the potential effect of nafcillin on unbound phenytoin concentrations [119]. The study consisted of both in vitro and in vivo components. The authors observed both in vitro and in vivo displacement of phenytoin with the addition of nafcillin to serum. Although increases in unbound phenytoin appeared to be minor for the in vitro portion of the experiment, a significant increase in unbound phenytoin concentrations was noted in all groups compared to the control group ($p < 0.05$). Unbound phenytoin concentrations were also measured in four patients receiving phenytoin and nafcillin concurrently [119]. The investigators obtained unbound phenytoin concentrations during and after nafcillin therapy. Unbound phenytoin concentrations decreased following the discontinuation of nafcillin, although baseline phenytoin concentrations were not obtained.

Patients receiving antimicrobials with a high percentage of protein binding (90% or greater) and concomitant phenytoin should be monitored closely for signs of phenytoin toxicity. Furthermore, patients receiving high doses of any penicillin should have their unbound and total phenytoin concentrations monitored closely. Phenytoin dosage adjustments should be made according to extent of the interaction.

7.2.20 Probenecid

The interaction of probenecid and penicillins (weak organic acids) occurs primarily as a result of the inhibition of the tubular secretion of penicillin, although other mechanisms may be possible as well [120, 121]. The decrease in renal elimination results in increased penicillin serum concentrations. Studies have shown that the AUCs of amoxicillin, ampicillin, ticarcillin and nafcillin may increase by approximately 50–100% when coadministered with probenecid [51, 121–124]. Other beta-lactams such penicillin and dicloxacillin have also demonstrated increased serum concentrations in the presence of probenecid [51, 124–128]. Although probenecid significantly effects renal clearance of piperacillin/tazobactam, it does not significantly effect area under the curve or half-life of piperacillin/tazobactam [129].

This drug–drug interaction may be clinically beneficial in certain situations in which higher penicillin serum concentrations are necessary especially when using oral agents. However, careful monitoring or avoidance of this combination should be considered in certain patient populations in whom drug accumulation may occur (e.g., elderly patients or patients with impaired renal function).

7.2.21 Proguanil

Babalola et al. conducted a study in healthy volunteers to evaluate the coadministration of proguanil and cloxacillin on the pharmacokinetics of cloxacillin [130]. Differences in pharmacokinetic parameter values for cloxacillin alone or in the presence of proguanil were determined by assaying urinary samples. Both the maximum excretion rate and total amount of excreted unchanged cloxacillin were reduced by approximately 50% when taken with proguanil compared to proguanil alone ($p < 0.0001$). No differences were noted in cloxacillin half-life or T_{max}. The authors suggest that separating these two agents by 1–2 h may avoid this potential interaction.

7.2.22 Sulfonamides

The concurrent administration of penicillins and sulfonamides was evaluated in a pharmacokinetic study [52]. The unbound concentrations of penicillin G, penicillin V, nafcillin, and dicloxacillin were increased with the concurrent administration of several sulfonamides. The researcher postulated that this interaction occurred as a result of the displacement of penicillins from protein-binding sites [52]. In a separate study, Kunin reported that the coadministration of oral oxacillin and sulfonamides caused a decrease in oxacillin serum concentrations. The author postulated that perhaps the sulfonamides may cause reduced absorption of oral oxacillin; however, additional mechanisms cannot be ruled out [52]. Based on this limited clinical data, avoidance of penicillins and sulfonamides is not warranted.

7.2.23 Tetracyclines

As previously stated, the administration of a bacteriostatic agent, such as tetracycline or related compounds, may antagonize the bactericidal activity of beta-lactams. Nonetheless, both antagonism and synergy between penicillins and tetracyclines has been documented in vitro and in vivo studies [131–136].

Lepper and Dowling reported the outcome of 57 patients diagnosed with pneumococcal meningitis who were treated with high-dose penicillin (n = 43) or high-dose penicillin along with the tetracycline antibiotic, aureomycin (n = 14) [136]. Although the severity of illness appeared similar between the treatment groups, mortality rates were significantly higher in the patients who received combination therapy compared to penicillin alone (79% versus 30%). Olsson and colleagues also noted a trend toward increased mortality in patients with pneumococcal meningitis treated with penicillin in combination with a tetracycline derivative (85%; n = 7) versus penicillin alone (52%; n = 23) or erythromycin alone (50%; n = 6) [137]. Strom noted that treatment of hemolytic streptococci with penicillin in combination with chlortetracycline compared to penicillin alone had similar initial clinical response but the penicillin/chlortetracycline group experienced a higher incidence of reinfection [138].

Unlike the case studies involving meningitis, Ahern and Kirby reported similar clinical outcomes in patients treated with penicillin alone versus penicillin in combination with aureomycin for pneumococci pneumonia [139]. The authors suggested that the role of rapid, bactericidal activity of penicillin is of more clinical significance in treating meningitis compared to less severe infections such as pneumonia. Adhern and Kirby stressed the importance of penicillin's role in treating meningitis due to the relatively limited phagocytic activity in the subarachnoid space compared to nonmeningeal infections such as pneumonia [139].

Avoiding the combination of penicillin and tetracycline derivatives appears appropriate in severe infections requiring rapid bactericidal activity such as meningitis. In less severe infections, the use of these drugs in combination has not been documented to adversely affect outcomes.

7.2.24 Vecuronium

The concurrent administration of vecuronium and acylaminopenicillins has been reported to prolong muscle paralysis in both humans and animals [140–143]. Condon et al. conducted a double-blind clinical trial to determine the ability of piperacillin or cefoxitin (control agent) to prolong the muscular blockade of vecuronium [144]. Patients were eligible for study enrollment if they were undergoing an elective operation with general anesthesia that required antibiotic prophylaxis. Patients were subsequently randomized to receive piperacillin or cefoxitin as the prophylactic antibiotic prior to the operation. All patients received vecuronium for muscle relaxation. Prolongation of neuromuscular blockade was determined before and after the administration of the antibiotic by the electromyographic twitch response. Of the 27

evaluable patients enrolled in the study, 5 patients (2 piperacillin and 3 cefoxitin) exhibited a non-clinically significant prolongation of neuromuscular blockade. Otherwise, the rate and extent of neuromuscular blockade was similar between groups. It appears that this interaction is clinically insignificant, although knowledge of this potential prolongation may be useful in certain surgical settings.

7.2.25 Miscellaneous Agents

The concomitant administration of penicillins and acidic drugs such as phenylbutazone, sulfinpyrazone, indomethacin, and sulfaphenazole may prolong the half-life of penicillin. This is postulated to occur as a result of competition between the acidic drugs and penicillin for renal tubular secretory proteins [51]. In this investigation, the half-life of penicillin was not noted to change significantly with concomitant administration of chlorothiazide, sulfamethizole, and sulfamethoxy-pyridazine [51].

Potential drug–drug interactions between the penicillins and theophylline have also been investigated. The coadministration of amoxicillin, ampicillin, ticarcillin/clavulanic acid, or ampicillin/sulbactam with theophylline was noted not to alter theophylline's properties [145–149].

Deppermann et al. assessed the effect of the coadministration of pirenzepine, an antimuscarinic, with various antibiotics including amoxicillin in a double-blind, randomized crossover study [4]. Coadministration of pirenzepine with amoxicillin did not significantly alter the pharmacokinetics of amoxicillin.

7.3 Cephalosporin Drug Interactions

7.3.1 Acid-Suppressive Agents

7.3.1.1 Ranitidine, Famotidine, and Omeprazole

Concomitant administration of the prodrugs, cefpodoxime proxetil, cefuroxime axetil and cefditoren pivoxil, with agents that increase gastric pH, such as ranitidine, results in a reduction of the antibiotic serum concentrations [5, 150]. The bioavailability of the cefpodoxime proxetil has been reported to decrease by approximately 30–40% with concurrent administration of an H_2-receptor antagonist [150, 151]. However, no impact on the bioavailability of cefpodoxime was noted when famotidine administration was separated from cefpodoxime by 2 h. Similarly, the AUC of cefuroxime axetil was reduced by approximately 40% with pretreatment of ranitidine and sodium bicarbonate [5]. The C_{max} and AUC of cefditoren pivoxil were reduced by approximately 25% with the concurrent administration of famotidine [152]. Other studies have found no significant effect on the bioavailability of cephalexin and cefaclor AF when administered concomitantly with H_2-receptor antagonists or omeprazole [4, 153–155]. Madras-Kelly and colleagues reported that

the administration of omeprazole or ranitidine with cephalexin had only a minimal effect on the pharmacokinetics of cephalexin, with the exception of a significant delay in T_{max} which increased almost 2-fold [154]. Based on the results from these studies, concurrent administration of H_2-receptor antagonists and cefuroxime axetil, cefpodoxime proxetil and cefditoren pivoxil should be avoided. If these agents need to be administered concurrently, the cephalosporins should be given at least 2 h after the H_2-receptor antagonist.

7.3.1.2 Antacids

The coadministration of antacids and certain cephalosporins including Cefaclor CD®, cefdinir, cefpodoxime and cefditoren may lead to decreased concentrations of the antibiotics [150–153, 155]. A variety of studies have reported decreases in cephalosporin AUC and C_{max} to be in the range of 20–40% for cefaclor, cefdinir, and cefpodoxime when administered with an antacid [150, 153, 155]. A minimal reduction in C_{max} (14%) and AUC (11%) was noted with the concurrent administration of cefditoren with an antacid [152]. Other investigators have found no effect with cephalexin [4] or cefixime [156] when administered concomitantly with antacids. Certain cephalosporins including Cefaclor CD, cefdinir, cefpodoxime and cefditoren should not be coadministered with antacids. If antacids are required during therapy, the cephalosporins should be separated from the antacid administration by at least 2 h.

7.3.2 Calcium

Recently, several regulatory agencies have issued warnings regarding the use of ceftriaxone concomitantly with intravenous products containing calcium [157, 158] Reports indicate that ceftriaxone may be incompatible with calcium-containing solutions, depending on the concentrations used [159, 160]. These warnings were based originally on the reports of seven cases of neonatal or infant death and/or sudden cardiorespiratory arrest [159]. These authors reported that these patients received higher than normal ceftriaxone doses (150–200 mg/kg/day) and the use of higher concentration of calcium supplements administered via intravenous bolus [159]. In some cases these deaths were believed to have occurred as a result of the formation of these precipitates in the lungs or kidneys. Ceftriaxone being an anion, when present in high concentrations can bind with calcium ions to form insoluble complexes that can precipitate out in various tissues [161, 162].

This warning of the concomitant use of ceftriaxone and calcium products has recently been reassessed by the FDA, resulting in the issuance of a less restrictive advisory. The most recent FDA advisory states that [163]:

- "Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in neonates (≤28 days of age). Ceftriaxone should not be used in neonates (≤28 days of age) if they are receiving (or are expected to receive) calcium-containing intravenous products."

- "In patients >28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid."
- "Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions via a Y-site in any age group."
- "FDA now recommends that ceftriaxone and calcium-containing products may be used concomitantly in patients >28 days of age, using the precautionary steps above because the risk of precipitation is low in this population."

Steadman and colleagues recently reviewed the FDA Adverse Event Reporting Systems to determine the risk of serious ceftriaxone- calcium interactions in adults [164]. In these authors' opinion, their analysis of this FDA data base supported the FDA's recently revised recommendations suggesting that patients greater than 28 days of age may receive calcium and ceftriaxone sequentially. However, these authors do caution that in certain populations (such as those with intravascular depletion) the sequential administration of these two agents still warrants caution.

7.3.3 Calcium Channel Blockers

Variable data exist regarding the effects of nifedipine on cephalosporin pharmacokinetics [165, 166]. In a randomized crossover study, each healthy volunteer received cefixime with nifedipine or placebo [166]. The absolute bioavailability of cefixime was increased from 31% (cefixime alone) to 53% (cefixime and nifedipine) ($p<0.01$). The $AUC_{0-\infty}$ also increased from 16.1 mg · h/L (cefixime alone) compared to 25.4 mg · h/L (cefixime and nifedipine) ($p<0.01$) [166]. These investigators have also shown increased cephalexin concentrations with co-administration of nifedipine or diltiazem in an animal model [167]. The authors concluded that nifedipine can increase the absorption of these cephalosporins by enhancing the active transport mechanism in the intestine. In contrast, another study demonstrated that the pharmacokinetics of cefpodoxime did not change when coadministered with nifedipine [165]. Due to differences in specific antimicrobials and lack of adverse events seen with calcium channel blocker and cephalosporin combinations, no dosage changes are recommended when these agents are coadministered.

7.3.4 Cholestyramine

The coadministration of cholestyramine with cefadroxil or cephalexin has been shown to cause a delay in absorption, which is associated with a prolonged T_{max} and reduction in C_{max} [168, 169]. Despite these pharmacokinetic alterations, other important parameters such as AUC or amount of drug excreted in the urine were minimally affected. Although data for this interaction are limited, the clinical significance is doubtful, particularly when one considers that cholestyramine does not appear to alter cephalosporin exposure.

7.3.5 Cyclosporine

The data regarding drug interactions between cephalosporins and cyclosporine is contradictory. Soto and colleagues reported that two patients that had undergone renal transplants presented with significantly increased cyclopsorin serum concentrations 2–3 days after the initiation of ceftriaxone 1 g twice a day [170]. These authors reported a 2–4 fold increase in cyclosporin concentration in these two patients. Cockburn reported that the concomitant use of ceftazidime or latamoxef (moxalactam) had been associated with an increase in cyclosporine concentrations [171]. Other investigators have shown no problems with the concomitant use of cyclosporine and ceftazidime. Verhagen and colleagues reported no significant impact upon renal function in 28 patients who underwent allogeneic bone marrow transplantation receiving both ceftazidime and cyclosporine for febrile neutropenia as measured by serum creatinine concentrations or creatinine clearance [172]. Since the data concerning the use of cyclosporine and cephalosporins is limited and contradictory no firm recommendation can be made regarding their use together.

7.3.6 Contraceptives, Oral Estrogen

Refer to this topic in the discussion of penicillin.

7.3.7 Ethanol: Disulfiram-Like Reactions

Semisynthetic cephalosporins containing a methyltetrazolethiol (MTT) side chain such as cefamandole, cefoperazone, cefmenoxime, cefotetan, and moxalactam, have been documented to cause disulfiram-like reactions in patients who consume ethanol during antibiotic treatment [173–175]. Cephalosporins with an MTT side chain inhibit acetaldehyde dehydrogenase, which results in the accumulation of acetaldehyde, a toxic metabolite of ethanol. Patients should be instructed not to consume alcohol during and for several days following antibiotic therapy. Refer to Chap. 4 regarding antimicrobials and food interactions for a more detailed review of this topic.

7.3.8 Iron

Coadministration of ferrous sulfate appears to cause a chelation complex and reduce the absorption of cefdinir [176]. In a randomized three-way crossover study, six healthy male subjects received the following regimens: 200 mg cefdinir alone, 200 mg cefdinir plus 1,050 mg ferrous sulfate sustained release, or 200 mg cefdinir

followed by 1,050 mg ferrous sulfate sustained release 3 h later [176]. The $AUC_{0-12} \pm SD$ (μg · h/mL) was significantly lower in the groups that received cefdinir concomitantly with ferrous sulfate (0.78 ± 0.25 μg · h/mL) or at 3 h following the dose of cefdinir (6.55 ± 1.61 μg · h/mL) compared to cefdinir alone (10.3 ± 1.35 μg · h/mL) ($p < 0.05$). To avoid the potential for therapeutic failure of cefdinir, it should not be taken together with ferrous sulfate.

Three cases of red stools associated with cefdinir and iron containing products have been reported in the literature [177, 178]. In all cases the discoloration of the stool was not associated with GI symptoms and in all three instances stool guaiac tests were negative. The reddish discoloration of the stools is thought to be due to formation of a nonabsorbable complex between iron and cefdinir or some of its breakdown products in the GI tract [178].

7.3.9 Metoclopramide

A healthy volunteer, cross-over study evaluated the effect of food, metoclopramide, propantheline and probenecid on the pharmacokinetics of cefprozil [179]. In the metoclopramide arm of the study, volunteers received cefprozil alone or cefprozil given 0.5 h after a dose of metoclopramide. Both isomers of cefprozil, cis and trans, were assayed in blood and urine. Cefprozil's isomers demonstrated a statistically significant reduction in mean residence time when administered after metoclopramide; however, there was no difference in $AUC_{0-\infty}$ or half-life of cefprozil among the treatment groups. Administration of metoclopramide prior to cefprozil did not affect its extent of absorption. Concurrent administration of these agents need not be avoided.

7.3.10 Methotrexate

Rabbits receiving concomitant infusions of methotrexate and a cephalosporin (ceftriaxone, ceftazidime, ceftizoxime, or cefoperazone) have been demonstrated to have an increased renal elimination of methotrexate and 7-hydroxymethotrexate [104, 105].

In a case report, an eight-year-old boy receiving methotrexate for non-Hodgkins lymphoma experienced a decrease in methotrexate clearance when methotrexate was coadministered with piperacillin [108]. The patient subsequently received methotrexate along with ceftazidime without any impact on methotrexate clearance. The differences seen in methotrexate renal elimination between cephalosporins and piperacillin may be due to the extent of tubular secretion (penicillins > cephalosporins) [104, 180].

Based upon the limited data available, there have been no documented interactions resulting in decreased renal elimination of methotrexate with the concurrent administration of cephalosporins. However, because of the documented interaction

between some penicillins and methotrexate, close monitoring of methotrexate concentrations and signs of toxicity (e.g., bone marrow suppression, nephrotoxicity, mucositis) are suggested during concurrent use of cephalosporins and methotrexate.

7.3.11 Nonsteroidal Anti-inflammatory Drugs

Diclofenac has been reported to cause an increase in the biliary excretion of ceftriaxone [181]. A study was conducted in patients in whom a cholecystectomy was performed and a drain was placed in the common bile duct [181]. The subjects who received ceftriaxone along with diclofenac demonstrated a 320% ($p<0.05$) increase in the amount of ceftriaxone excreted in the bile and a 56% ($p<0.05$) reduction in the amount excreted in the urine. Due to the limited data, no therapeutic recommendations can be made.

7.3.12 Phenytoin

Highly protein bound antibiotics such as ceftriaxone (approximately 90% bound to plasma proteins) [117] have the potential to interact with other highly protein-bound agents such as phenytoin [119]. Due to protein displacement, high doses of ceftriaxone may increase unbound concentrations of phenytoin in certain patient populations [119]. Dasgupta and colleagues performed an in vitro study to determine the effect of ceftriaxone in displacing phenytoin from protein binding sites [119]. Estimated peak ceftriaxone concentrations (270 and 361 μmol/L) were added to pooled sera from patients receiving phenytoin. Three groups with varying albumin concentrations were evaluated. The greatest ceftriaxone-induced displacement effect was seen the group with the lowest albumin concentration (25 g/L). In this group, the unbound phenytoin concentrations (μmol/L) (SD) were 8.12 (0.28) for the control, 9.39 (0.12) for ceftriaxone 270 μmol/L, and 9.93 (0.36) for ceftriaxone 361 μmol/L, respectively. Although the increases appear minor, significant increases in unbound phenytoin concentrations were noted in all groups compared to the control group ($p<0.05$). In patients receiving ceftriaxone concomitantly with phenytoin, monitoring of unbound and total serum concentrations of phenytoin in addition to watching for signs of phenytoin toxicity is warranted.

7.3.13 Oral Anticoagulants

Semisynthetic cephalosporins containing an MTT substituent at the 3-position, such as cefamandole, cefoperazone, cefmenoxime, cefotetan and moxalactam, have been associated with the development of a hypoprothrombinemia [182].

Several case reports have implicated these agents in prolonged prothrombin time and/or bleeding episodes in patients [183–189]. Anagaran and colleagues retrospectively assessed the effect of prophylactic administration of cefamandole or vancomycin on the warfarin anticoagulation response in 60 postsurgical patients [190]. Patients who received cefamandole had a higher proportion of elevated prothrombin times compared those who received vancomycin (14 versus 1, $p < 0.05$). In another study, these same investigators characterized the effect of cefazolin, cefamandole and vancomycin on warfarin anticoagulation in post cardiac valve replacement patients [191]. They noted that the greatest number of patients ($n = 6$) with elevated prothrombin times received cefamandole compared to cefazolin ($n = 1$) and vancomycin ($n = 1$). In addition, cefamandole therapy was associated with a 15–20% greater change in prothrombin times compared to the cefazolin and vancomycin ($p < 0.01$). Patients who are malnourished or who have renal insufficiency may be at higher risk for this interaction [183]. The exact mechanism of the hypoprothrombinemic phenomenon is unknown, although several mechanisms have been proposed [192–195]. Clinicians are cautioned to monitor for signs and symptoms of bleeding, prothrombin time, and activated partial thromboplastin time in patients receiving cephalosporins with an MTT side chain and concomitant therapy with oral anticoagulants.

7.3.14 Probenecid

Probenecid can increase the serum concentrations of most renally eliminated cephalosporins [153, 179, 196–210]. Although other mechanisms may contribute, probenecid appears to inhibit tubular secretion of cephalosporins resulting in their decreased renal elimination [120, 121]. The AUCs of ceftizoxime, cefoxitin, cefaclor and cefdinir have been reported to increase by approximately 50–100% with the coadministration of probenecid [120, 198, 199]. Probenecid has been documented to prolong the half-life and increase the serum concentration of many other cephalosporins as well [153, 154, 196–211]. Certain cephalosporins such as ceforanide, ceftazidime, ceftriaxone, and moxalactam are eliminated through a different pathway and their pharmacokinetics are not significantly altered by probenecid [196, 197, 212–217]. Caution or avoidance of this combination should be considered in certain patient populations in which drug accumulation may occur (e.g., elderly patients or patients with impaired renal function).

7.3.15 Propantheline

A healthy volunteer, cross-over study evaluated the effect of food, metoclopramide, propantheline and probenecid on the pharmacokinetics of cefprozil [179]. In the propantheline arm of the study, volunteers received cefprozil alone or cefprozil

given 0.5 h after a dose of propantheline. Both isomers of cefprozil, cis and trans, were assayed in blood and urine samples. There was no difference in cefprozil $AUC_{0-\infty}$ or half-life in either treatment group. The administration of propantheline prior to cefprozil does not affect the extent of cefprozil absorption. No special precautions seem necessary for this combination.

7.3.16 Theophylline

The coadministration of cephalexin or cefaclor with theophylline has been documented to not significantly alter any pharmacokinetic parameters of theophylline [218–220]. However, Hammond and Abate reported a case of a possible interaction between theophylline and cefaclor, which resulted in theophylline toxicity [221]. It was unclear whether this was an actual drug–drug interaction or the effect of an acute viral illness on theophylline disposition. Based on these limited data, no dosage recommendations are necessary.

7.3.17 Miscellaneous Agents

Older cephalosporins such as cephalothin and cephaloridine have been reported to cause nephrotoxicity [222, 223]. The coadministration of these older cephalosporins with other potential nephrotoxic agents including colistin [223, 224], various aminoglycosides [222, 225–231] and furosemide [232–235] has been associated with an increased incidence of nephrotoxicity. The clinical impact of this interaction is limited because these cephalosporins are rarely used in current clinical practice; however, careful monitoring of renal function is warranted if such combinations are prescribed. These drug–drug interactions have not been documented as a clinically significant problem for any of the newer cephalosporins [236–238].

7.4 Carbapenems

7.4.1 Probenecid

Concomitant probenecid can increase the concentration of the carbapenems. It is proposed that probenecid inhibits tubular secretion of the carbapenems, resulting in their decreased renal elimination.

Of the four commercially available carbapenems in the United States, probenecid has the most impact on the renal elimination of doripenem followed by meropenem, ertapenem, and imipenem. The combination of doripenem and probenecid produced a 53% increase in half-life and 75% increase in the AUC of doripenem compared to

doripenem alone [239]. Meropenem's half-life and AUC were increased by 33% and 55%, respectively, when co-administered with probenecid [240]. Ertapenem's half-life and AUC increased by 20% and 25% with the combination of ertapenem and probenecid compared to ertapenem alone [241]. In contrast, imipenem's half-life and AUC only increased 6% and 13%, respectively, when coadministered with probenecid [242]. Caution and/or avoidance of this combination should be considered in patient populations in which drug accumulation may occur (such as elderly patients or patients with impaired renal function). The increased serum concentration noted as a result of this drug–drug interaction may increase the risk of central nervous system toxicity of these agents.

7.4.2 Valproic Acid

The co-administration of carbapenems and valproic acid may lead to decreased concentrations of valproic acid [239]. The proposed mechanism is that carbapenems may interfere with the hydrolysis of valproic acid's glucuronide metabolite to valproic acid [239, 243]. A healthy volunteer study evaluated the pharmacokinetics of valproic acid and glucuronide metabolite in subjects receiving doripenem [239]. Valproic acid's C_{max}, C_{min} and AUC were decreased by 44.5%, 77.7%, and 63% respectively, when co-administered with doripenem. In contrast, an increase in the C_{max} and AUC of valproic acid's glucuronide metabolite was seen when co-administered with doripenem [239]. Two retrospective studies showed decreased valproic acid concentrations of 82% and 66% in patients receiving concomitant meropenem and valproic acid compared to valproic acid alone [244, 245]. In both studies, the authors noted that the decrease in valproic concentrations could be seen within 24h of concomitant administration of these two agents. Animal models have also found decreased valproic acid concentrations with the concurrent administration of imipenem [246], meropenem [247] or panipenem [248] and valproic acid. Recently, there have been many case reports published describing the potential pharmacokinetic interaction of carbapenems and valproic acid including patients experiencing breakthrough seizures secondary to decreased concentrations of valproic acid [248–257]. Providers should avoid prescribing carbapenems in patients receiving valproic acid to prevent subtherapeutic valproic acid serum concentrations [239]. If no alterative therapy is available, close monitoring of valproic acid concentrations and dosage modifications of valproic acid is recommended [239].

7.4.3 Cyclosporine

Based on case reports, cyclosporine and imipenem/cilastatin may demonstrate additive central nervous system toxicity when administered concomitantly. Bösmuller and colleagues reported five transplant patients experiencing central nervous system

toxicity during administration of cyclosporine and imipenem/cilastatin [258]. None of these patients reported a history of seizures. Four of the five patients experienced a seizure despite cyclosporine concentrations within normal therapeutic range. The fifth patient experienced a myclonia; this was associated with an elevated cyclosporine concentration of 900 ng/mL. Symptoms of central nervous toxicity occurred within 1 day in four patients, and symptoms resolved in all patients with discontinuation of imipenem/cilastatin or discontinuation, or dose reduction of cyclosporine. Zazgornik and colleagues published a case report of a 62-year-old female receiving imipenem/cilastatin and cyclosporine who developed central nervous system toxicity [259]. The patient had recently received a renal transplant secondary to interstitial nephritis and was receiving imipenem/cilastatin for a urinary tract infection. Following the second dose of imipenem/cilastatin, the patient experienced confusion, agitation, and tremors, which resulted in the discontinuation of imipenem/cilastatin. The serum cyclosporine concentration, which was obtained four days after imipenem/cilastatin therapy, was elevated at 1,000 ng/mL compared to a previous level of 400 ng/mL. In contrast, an investigation in a rat model has demonstrated decreased cyclosporine serum concentrations when it was coadministered with imipenem/cilastatin [260].

Since both imipenem and cyclosporine administered alone may have the potential to cause central nervous system side effects, it is difficult to determine what role the combination of these agents may have played in these reports. Based on this limited clinical data, avoidance of imipenem and cyclosporine is not warranted.

7.4.4 Theophylline

Semel and Allen reported three cases of seizures occurring in patients receiving imipenem/cilastatin and theophylline [261]. None of the patients had a previous history of neurologic or seizure disorder. The authors concluded that the seizures could be due to both of the drugs' ability to inhibit gamma aminobutyric acid binding to receptors, thus resulting in increased excitation of the central nervous system. It is difficult to differentiate the potential for seizures between the administration of imipenem/cilastatin alone or the combination of imipenem/cilastatin and theophylline. Avoiding coadministration of theophylline and imipenem/cilastatin is not warranted.

7.4.5 Ganciclovir

Patients have experienced generalized seizures during concomitant imipenem/cilastatin and ganciclovir therapy [262]. No additional information is available on these patients. Due to this limited data, it is difficult to differentiate the potential for seizures of imipenem/cilastatin alone or the combination of imipenem/cilastatin and ganciclovir. The manufacturer does not recommend coadministration of imipenem/cilastatin and ganciclovir unless the benefits outweigh the risks.

7.4.6 Valganciclovir

After oral administration of valganciclovir, it is rapidly converted to ganciclovir by intestinal and hepatic esterases. Although no in vivo drug-drug interaction studies have be conducted with valganciclovir, because of its rapid conversion to ganciclovir in the body [263] any drug-drug interaction seen with ganciclovir would be expected to occur with valganciclovir [264]. Due to the possibility of an interaction between valganciclovir and imipenem/cilastatin, the use of these drugs concomitantly should be avoided unless the benefit outweighs the risk [265].

7.5 Monobactams

7.5.1 Probenecid

Concomitant probenecid can increase aztreonam concentrations [266]. It is proposed that probenecid inhibits tubular secretion resulting in decreased aztreonam renal elimination. In a randomized crossover trial, six healthy men received aztreonam alone or aztreonam along with probenecid [266]. Coadministration of probenecid with aztreonam increased aztreonam concentrations from 81.7 ± 3.4 to 86.0 ± 2.2 μg/mL. This interaction seems to carry minimal clinical risk. No recommendation to avoid the concurrent administration of probenecid and aztreonam seems warranted.

7.5.2 Miscellaneous Agents

A number of other anitimicrobial agents have been evaluated for the potential of drug interactions with aztreonam. Studies in healthy subjects administered aztreonam concomitantly with linezolid [267], daptomycin [268], nafcillin [269], gentamicin plus metronidazole [266] or amikacin [270] identified no clinically significant drug interactions.

References

1. Rogers HJ, James CA, Morrison PJ. Effect of cimetidine on oral absorption of ampicillin and cotrimoxazole. J Antimicrob Chemother 1980;6:297–300.
2. Paulsen O, Hoglund P, Walder M. No effect of omeprazole-induced hypoacidity on the bioavailability of ampicillin and bacampicillin. Scand J Infec Dis 1989;21:219–223.
3. Stainforth DH, Clarke HL, Horton R, et al. Augmentin bioavailability following cimetidine, aluminum hydroxide and milk. Int J Clin Pharmacol Ther Toxicol 1985;23:154–157.

4. Deppermann KM, Lode H, Hoffken G, et al. Influence of ranitidine, pirenzepine, and aluminum magnesium hydroxide on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline, and amoxicillin-clavulanic acid. Antimicrob Agents Chemother 1989;33:1901–1907.
5. Sommers DK, Van Wyk M, Moncrieff J. Influence of food and reduced gastric acidity on the bioavailability of bacampicillin and cefuroxime axetil. Br J Clin Pharm 1984:18:535–539.
6. Jick H, Porter JB. Potentiation of ampicillin skin reactions by allopurinol or hyperuricemia. J Clin Pharmacol 1981;21:456–458.
7. Fessel WJ. Immunologic reactivity in hyperuricemia. N Engl J Med 1972;286:1218.
8. Townsend RS. In vitro inactivation of gentamicin by ampicillin. Am J Hosp Pharm 1989;46: 2250–2251.
9. McLaughlin JE, Reeves DS. Clinical and laboratory evidence for inactivation of gentamicin by carbenicillin. Lancet 1971;1:261–264.
10. Uber WE, Brundage RC, White RL, et al. In vivo inactivation of tobramycin by piperacillin. DICP Ann Pharmacother 1991;25:357–359.
11. Halstenson CE, Hirata CA, Heim-Duthoy KL, et al. Effect of concomitant administration of piperacillin on the disposition of netilmicin and tobramycin in patients with end-stage renal disease. Antimicrob Agents Chemother 1990;34:128–133.
12. Davies M, Morgan JR, Anand C. Interactions of carbenicillin and ticarcillin with gentamicin. Antimicrob Agents Chemother 1975;7:431–434.
13. Weibert R, Keane W, Shapiro F. Carbenicillin inactivation of aminoglycosides in patients with severe renal failure. Trans Am Soc Artif Organs 1976;22:439–445.
14. Eykyn S, Philips I, Ridley M. Gentamicin plus carbenicillin. Lancet 1 1971;13: 545–546.
15. Kradjian WA, Burger R. In vivo inactivation of gentamicin by carbenicillin and ticarcillin. Arch Intern Med 1980;140:1668–1670.
16. Davies M, Morgan JR, Anand C. Interactions of carbenicillin and ticarcillin with gentamicin. Antimicrob Agents Chemother 1975:7:431–434.
17. Lau A, Lee M, Flascha S, et al. Effect of piperacillin on tobramycin pharmacokinetics in patients with normal renal function. Antimicrob Agents Chemother 1983;24:533–537.
18. Hitt CM, Patel KB, Nicolau DP, Zhu Z, Nightingale CH. Influence of piperacillin-tazobactam on pharmacokinetics of gentamicin given once daily. Am J Health Syst Pharm 1997;1:2704–2708.
19. Dowell JA, Korth-Bradley J, Milisci M, et al. Evaluating possible pharmacokinetic interactions between tobramycin, piperacillin, and a combination of piperacillin and tazobactam in patients with various degrees of renal impairment. J Clin Pharmacol 2001;41:979–986.
20. Noone P, Pattison JR. Therapeutic implications of interaction of gentamicin and penicillins. Lancet 1971;2:575–578.
21. Ervin FR, Bullock WE, Nuttall CE. Inactivation of gentamicin by penicillins in patients with renal failure. Antimicrob Agents Chemother 1976;9:1009–1011.
22. Cheng SH, White A. Effect of orally administered neomycin on the absorption of penicillin V. N Engl J Med 1962;267:1296–1297.
23. Moellering RC, Wennersten C, Weinberg AN. Synergy of penicillin and gentamicin against Enterococci. J Infect Dis 1971;124(suppl):S207–S209.
24. Guenthner SH, Chao HP, Wenzel RP. Synergy between amikacin and ticarcillin or mezlocillin against nosocomial bloodstream isolates. J Antimicrob Chemother 1986;18:550–552.
25. Laverdiere M, Gallimore B, Restieri C, et al. In vitro synergism of ceftriaxone combined with aminoglycosides against Pseudomonas aeruginosa. Diagn Microbiol Infect Dis 1994;19:39–46.
26. Marks MI, Hammerberg S, Greenstone G, et al. Activity of newer aminoglycosides and carbenicillin, alone, and in combination against gentamicin-resistant Pseudomonas aeruginosa. Antimicrob Agents Chemother 1976;10:399–401.
27. Moellering RC, Wennersten, Weinberg AJ. Studies on antibiotic synergism against Enterococci. I. Bacteriologic studies. J Lab Clin Med 1971;77:821–828.
28. Weinstein AJ, Moellering RC. Penicillin and gentamicin therapy for enterococcal infections. JAMA 1973;223:1030–1032.
29. Anderson ET, Young LS, Hewitt WL. Antimicrobial synergism in the therapy of Gram-negative rod bacteremia. Chemotherapy 1978;24:45–54.

30. Brown CH, Natelson EA, Bradshaw MW, et al. The hemostatic defect produced by carbenicillin. N Engl J Med 1974;291:265–270.
31. Brown CH, Natelson EA, Bradshaw MW, et al. Study of the effects of ticarcillin on blood coagulation and platelet function. Antimicrob Agents Chemother 1975;7:652–657.
32. Brown CH, Bradshaw MW, Natelson EA, et al. Defective platelet function following the administration of penicillin compounds. Blood 1976;6:949–956.
33. Andrassy K, Ritz E, Hasper B, et al. Penicillin-induced coagulation disorder. Lancet 1976;2:1039–1041.
34. Andrassy K, Weischedel E, Ritz E, et al. Bleeding in uremic patients after carbenicillin. Thrombos Haemost 1976;36:115–126.
35. Tabernero Romo JM, Corbacho L, Sanchez S, et al. Effects of carbenicillin on blood coagulation; a study in patients with chronic renal failure. Clin Nephrol 1979;11:31–34.
36. Wisloff F, Larsen JP, Dahle A, et al. Effect of prophylactic high-dose treatment with ampicillin and cloxacillin on bleeding time and bleeding in patients undergoing elective vascular surgery. Scand J Haematol 1983;31:97–101.
37. Lurie A, Ogilvie M, Gold CH, et al. Carbenicillin-induced coagulopathy. S Afr Med J 1974;48:457–461.
38. Taylor AT, Pritchard DC, Goldstein AO, et al. Continuation of warfarin-nafcillin interaction during dicloxacillin therapy. J Fam Pract 1994;39:182–185.
39. Heilker GM, Fowler JW, Self TH, et al. Possible nafcillin-warfarin interaction. Arch Intern Med 1994;154:822–824.
40. Qureshi GD, Reinders TP, Somori GJ, et al. Warfarin resistance with nafcillin therapy. Ann Intern Med 1984;100:527–529.
41. Shovick VA, Rihn TL. Decreased hypoprothrombinemic response to warfarin secondary to the warfarin-nafcillin interaction. Drug Intell Clin Pharm 1991;25:598–600.
42. Kim KY, Frey RJ, Epplen K, Foruhari F. Interaction between warfarin and nafcillin: Case report and review of the literature. Pharmacotherapy 2007;27:1467–1470.
43. Krstenansky PM, Jones WN, Garewal HS. Effect of dicloxacillin sodium on the hypoprothrombinemic response to warfarin sodium. Clin Pharm 1987;6:804–806.
44. Mailloux AT, Gidal BE, Sorkness CA. Potential interaction between warfarin and dicloxacillin. Ann Pharmacother 1996:30:1402–1407.
45. Davis RL, Berman W, Wernly JA, et al. Warfarin-nafcillin interaction. J Pediatr 1991;118: 300–303.
46. Rolinson GN, Sutherland R. The binding of antibiotics to serum proteins. Br J Pharmacol 1965;25:638–650.
47. Lang CC, Jamal SK, Mohmaed Z, Mustafa MR, Mustafa AM, Lee TC. Evidence of an interaction between nifedipine and nafcillin in humans. Br J Clin Pharmacol. 2003;55:588–590.
48. Cropp JS, BusseyHI. A review of enzyme induction of warfarin metabolism with recommendations for patient management. Pharmacotherapy. 1997; 17: 917–928.
49. Brown MA, Korchinski ED, Miller DR. Interaction of penicillin-G and warfarin? Can J Hosp Pharm 1979;32:18,19.
50. Davydov L, Yermolnik M, Cuni LJ. Warfarin and amoxicillin/clavulanate drug interaction. Ann Pharmacother 2003;37:367–370.
51. Kampmann J, Molholm Hansen J, Siersbaek-Nielsen K, Laursen H. Effect of some drugs on penicillin half-life in blood. Clin Pharmacol Ther 1972;13:516–519.
52. Kunin CM. Clinical pharmacology of the new penicillins. II. Effect of drugs which interfere with binding to serum proteins. Clin Pharmacol Ther 1966;7:180–188.
53. Suffness M, Rose BS. Potential drug interactions and adverse effects related to aspirin. Drug Intell Clin Pharm 1974;8:694–699.
54. Moskowitz B, Somani SM, McDonald RH. Salicylate interaction with penicillin and secobarbital binding sites on human serum albumin. Clin Toxicol 1973;6:247–256.
55. Hayes AH. Therapeutic implications of drug interactions with acetaminophen and aspirin. Arch Intern Med 1981:141:301–304.
56. Schafer-Korting M, Kirch W, Axthelm T, et al. Atenolol interaction with aspirin, allopurinol, and ampicillin. Clin Pharmacol Ther 1983;33:283–288.

57. McLean AJ, Tonkin A, McCarthy P, et al. Dose-dependence of atenolol-ampicillin interaction. Br J Clin Pharmacol 1984;18:969–971.
58. Westphal JF, Trouvin JH, Deslandes A, et al. Nifedipine enhances amoxicillin absorption kinetics and bioavailability in humans. J Pharmacol Exp Ther 1990;255:312–317.
59. Lang CC, Jamal SK, Mohamed Z, et al. Evidence of an interaction between nifedipine and nafcillin in humans. Br J Clin Pharmacol 2003;55:588–590.
60. Jawetz E. Gunnison JB, Coleman VR. The combined action of penicillin with streptomycin or chloromycetin on Enterococci in vitro. Science 1950;3:254–256.
61. Wallace JF, Smith H, Garcia M, et al. Studies on the pathogenesis of meningitis. VI Antagonism between penicillin and chloramphenicol in experimental pneumococcal meningitis. J Lab Clin Med 1967;70:408–418.
62. Yourassowsky E, Monsieur R. Antagonism limit of penicillin G and chloramphenicol against Neisseria meningitidis. Arzneimittel Forsch 1971;21:1385–1387.
63. Gjessing HC, Odegaard K. Oral chloramphenicol alone and with intramuscular procaine penicillin in the treatment of gonorrhoea. Br J Vener Dis 1967;43:133–136.
64. DeRitis F, Giammanco G, Manzillo G. Chloramphenicol combined with ampicillin in treatment of typhoid. Br Med J 1972;4:17,18.
65. Ali HM. Reduced ampicillin bioavailability following oral coadministration with chloroquine. J Antimicrob Chemother 1985;15:781–784.
66. Barriere SL, Catlin DH, Orlando PL, et al. Alteration in the pharmacokinetic disposition of ciprofloxacin by simultaneous administration of azlocillin. Antimicrob Agents Chemother 1990;34:823–826.
67. Peterson LR, Moody JA, Fasching CE, et al. In vivo and in vitro activity of ciprofloxacin plus azlocillin against 12 streptococcal isolates in a neutropenic site model. Diagn Microbiol Infect Dis 1987;7:127–136.
68. Dossetor J. Drug interaction with oral contraceptive steroids [editorial]. Br Med J 1980; 280:467,468.
69. DeSano EA, Hurley SC. Possible interaction of antihistamines and antibiotics with oral contraceptive effectiveness. Fertil Steril 1982;1:853,854.
70. Bainton R. Interaction between antibiotic therapy and contraceptive medication. Oral Surg Oral Med Oral Pathol 1986;61:453–455.
71. Silber TJ. Apparent oral contraceptive failure associated with antibiotic administration. J Adolesc Health Care 1983;4:287–289.
72. Miller DM, Helms SE, Brodell RT. A practical approach to antibiotic treatment in women taking oral contraceptives. J Am Acad Dermatol 1994;30:1008–1011.
73. Fernandez N, Sierra M, Diez MJ, et al. Study of the pharmacokinetic interaction between ethinylestradiol and amoxicillin in rabbits. Contraception 1997:55:47–52.
74. Back DJ, Brenckenridge AM, Cross KJ, et al. An antibiotic interaction with ethinyloestradiol in the rat and rabbit. J Steroid Biochem 1982;16:407–413.
75. Back DJ, Breckenridge AM, MacIver M, et al. The effects of ampicillin on oral contraceptive steroids in women. Br J Clin Pharmacol 1982;14:43–48.
76. Friedman CI, Huneke AL, Kim MH, et al. The effect of ampicillin on oral contraceptive effectiveness. Obstet Gynecol 1980;55:33–37.
77. Joshi JV, Joshi UM, Sankholi GM, et al. A study of interaction of low-dose combination oral contraceptive with ampicillin and metronidazole. Contraception 1980;22:643–652.
78. Weisberg E. Interactions between oral contraceptives and antifungals/antibacterials. Is contraceptive failure the result? Clin Pharmacokinet 1999;36:309–13.
79. Dickinson BD, Altman RD, Nielsen NH, Sterling ML. Drug Interactions between oral contraceptives and antibiotics. Obstet Gynecol 2001;98:853–860.
80. Veremis SA, Maddux MS, Pollak R, et al. Subtherapeutic cyclosporine concentrations during nafcillin therapy. Transplantation 1987;43:913–915.
81. Finland M, Bach MC, Garner C, et al. Synergistic action of ampicillin and erythromycin against Nocardia asteroides: effect of time of incubation. Antimicrob Agents Chemother 1974;5:344–353.

82. Roberts CE, Rosenfeld LS, Kirby WM. Synergism of erythromycin and penicillin against resistant staphylococci: mechanism and relation to synthetic penicillins. Antimicrob Agents Chemother 1962:831–842.
83. Waterworth PM. Apparent synergy between penicillin and erythromycin or fusidic acid. Clin Med 1963:70:941–953.
84. Oswald EJ, Reedy RJ, Wright WW. Antibiotic combinations: an in vitro study of antistaphylococcal effects of erythromycin plus penicillin, streptomycin, or tetracycline. Antimicrob Agents Chemother 1961:904–910.
85. Herrell WE, Balows A, Becker J. Erythrocillin: a new approach to the problem of antibiotic-resistant Staphylococci. Antibiot Med Clin Ther 1960;7:637–642.
86. Manten A. Synergism and antagonism between antibiotic mixtures containing erythromycin. Antibiot Chemother 1954;4:1228–1233.
87. Allen NE, Epp JK. Mechanism of penicillin-erythromycin synergy on antibiotic resistant Staphylococcus aureus. Antimicrob Agents Chemother 1978;13:849–853.
88. Manten A, Terra JI. The antagonism between penicillin and other antibiotics in relation to drug concentration. Chemotherapia 1964;8:21–29.
89. Chang TW, Weinstein L. Inhibitory effects of other antibiotics on bacterial morphologic changes induced by penicillin G. Nature 1966:211:763–765.
90. Garrod LP, Waterworth PM. Methods of testing combined antibiotic bactericidal action and the significance of the results. J Clin Pathol 1962;15:328–338.
91. Strom J. Penicillin and erythromycin singly and in combination in scarlatina therapy and the interference between them. Antibiot Chemother 1961;11:694–697.
92. Robinson L, Fonseca K. Value of the minimum bactericidal concentration of antibiotics in the management of a case of recurrent Streptococcus bovis septicaemia. J Clin Pathol 1982;35:879,880.
93. Bach MC, Monaco AP, Finland M. Pulmonary nocardiosis therapy with minocycline and with erythromycin plus ampicillin. JAMA 1973;224:1378–1381.
94. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003;36:389–95.
95. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001;161:1837–1842.
96. Mutson MA, Stanek. Bacteremic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978–1997. Am J Med 1999;107:S34–43.
97. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72.
98. Huupponen R, Seppala P, Iisalo E. Effect of guar gum, a fibre preparation on digoxin and penicillin absorption in man. Eur J Clin Pharmacol 1984;26:279–281.
99. Brooks BM, Thomas AL, Coleman JW. Benzylpenicillin differentially conjugates to IFN-gamma, TNF-alpha, IL-1beta, IL-4 and IL-13 but selectively reduces IFN-gamma activity. Clin Exp Immunol 2003;131:268–74.
100. Brooks BM, Hart CA, Coleman JW. Differential effects of beta-lactams on human IFN-gamma activity. J Antimicrob Chemother 2005;56:1122–1125.
101. Attef OA, Ali AA. Effect of khat chewing on the bioavailability of ampicillin and amoxycillin. J Antimicrob Chemother 1997;39:523–525.
102. Jayasagar G, Krishna Kumar M, Chandrasekhar K, et al. Effect of cephalexin on the pharmacokinetics of metformin in healthy human volunteers. Drug Metabol Drug Interact 2002;19:41–48.
103. Wang DS, Kusuhara H, Kato Y, et al. Involvement of organic cation transporter 1 in the lactic acidosis caused by metformin. Mol Pharmacol 2003;63:844–848.
104. Iven H, Brasch H. The effects of antibiotics and uricosuric drugs on the renal elimination of methotrexate and 7-hydroxymethotrexate in rabbits. Cancer Chemother Pharmacol 1988;21:337–342.

105. Iven H, Brasch H. Influence of the antibiotics piperacillin, doxycycline, and tobramycin on the pharmacokinetics of methotrexate in rabbits. Cancer Chemother Pharmacol 1986;17: 218–222.
106. Najjar TA, Abou-Auda HS, Ghilzai NM. Influence of piperacillin on the pharmacokinetics of methotrexate and 7-hydroxymethotrexate. Cancer Chemother Pharmacol 1998:42:423–428.
107. Iven H, Brasch H. Cephalosporins increase the renal clearance of methotrexate and 7-hydroxymethotrexate in rabbits. Cancer Chemother Pharmacol 1990;26:139–143.
108. Yamamoto K, Sawada Y, Mutsashita Y, et al. Delayed elimination of methotrexate associated with piperacillin administration. Ann Pharmacother 1997;31:1261–1262.
109. Bloom NJ, Ignoffo RJ, Reis CA, et al. Delayed clearance (Cl) of methotrexate (MTX) associated with antibiotics and antiinflammatory agents [abstr]. Clin Res 1986;34:560A.
110. Nierenberg DW, Mamelok RD. Toxic reaction to methotrexate in a patient receiving penicillin and furosemide: a possible interaction [letter]. Arch Dermatol 1983;119:449,450.
111. Dean R, Nachman J, Lorenzana AN. Possible methotrexate-mezlocillin interaction. Am J Pediatr Hematol Oncol 1992;14:88–92.
112. Ronchera CL, Hernández T, Peris JE. Pharmacokinetic interaction between high-dose methotrexate and amoxycillin. Ther Drug Monit 1993;15:375–379.
113. Titier K, Lagrange F, Péhourcq, Moore N, et al. Pharmacokinetic interaction between high-dose methotrexate and oxacillin. Ther Drug Monit 2002;24:570–572.
114. Zarychanski R, Wlodarczyk K, Ariano R, Bow E. Pharmacokinetic interaction between methotrexate and piperacillin/tazobactam resulting in prolonged toxic concentrations of methotrexate. 2006;58:228–230.
115. Herrick AL, Grennan DM, Aarons L. Lack of interaction between methotrexate and penicillins. Rheumatology 1999;38:284,285.
116. Hill G, Cihlar T, Oo C, et al. The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion-correlation of in vivo and in vitro studies. Drug Metab Dispos 2002;30:13–19.
117. Brunton LL, Lazo JS, Parker KL (ed.). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition, New York: McGraw-Hill, 2005.
118. Dasgupta A, Sperelakis A, Mason A, et al. Phenytoin-oxacillin interactions in normal and uremic sera. Pharmacotherapy 1997;17:375–378.
119. Dasgupta A, Dennen DA, Dean R, et al. Displacement of phenytoin from serum protein carriers by antibiotics: studies with ceftriaxone, nafcillin, and sulfamethoxazole. Clin Chem 1991;37:98–100.
120. Welling PG, Selen SD, Kendall MJ, et al. Probenecid: an unexplained effect on cephalosporin pharmacology. Br J Clin Pharma 1979;8:491–495.
121. Gibaldi M, Schwartz MA. Apparent effect of probenecid on the distribution of penicillins in man. Clin Pharmacol Ther 1968;9:345–349.
122. Barbhaiya R, Thin RN, Turner P, et al. Clinical pharmacological studies of amoxycillin: effect of probenecid. Br J Vener Dis 1979;55:211–213.
123. Waller ES, Sharanevych MA, Yakatan GJ. The effect of probenecid on nafcillin disposition. J Clin Pharmacol 1982;22:482–489.
124. Corvaia L, Li SC, Ioannides-Demos LL, et al. A prospective study of the effects of oral probenecid on the pharmacokinetics of intravenous ticarcillin in patients with cystic fibrosis. J Antimicrob Chemother 1992;30:875–878.
125. Ziv G, Sulman FG. Effects of probenecid on the distribution, elimination, and passage into milk of benzylpenicillin, ampicillin, and cloxacillin. Arch Int Pharmacodyn Ther 1974;207: 373–382.
126. Shanson DC, McNabb R, Hajipieris P. The effect of probenecid on serum amoxycillin concentrations up to 18 hours after a single 3 g oral dose of amoxycillin: possible implications for preventing endocarditis. J Antimicrob Chemother 1984;13:629–632.
127. Krogsgaard MR, Hansen BA, Slotsbjerg T, et al. Should probenecid be used to reduce the dicloxacillin dosage in orthopaedic infections? A study of the dicloxacillin-saving effect of probenecid. Pharmacol Toxicol 1994;74:181–184.

128. Hoffstedt B, Haidl S, Walder M. Influence of probenecid on serum and subcutaneous tissue fluid concentrations of benzylpenicillin and ceftazidime in human volunteers. Eur J Clin Microbiol 1983;2:604–6.
129. Ganes D, Batra A, Faulkner D, et al. Effect of probenecid on the pharmacokinetics of piperacillin and tazobactam in healthy volunteers. Pharm Res 1991;8:S299.
130. Babalola CP, Iwheye GB, Olaniyi AA. Effect of proguanil interaction on bioavailability of cloxacillin. J Clin Pharm Ther 2002;27:461–464.
131. Speck RS, Jawetz E, Gunnison JB. Studies on antibiotic synergism and antagonism. The interference of aureomycin or terramycin with the action of penicillin in infections in mice. Arch Intern Med 1951;88:168–174.
132. Gunnison JB, Coleman VR, Jawetz E. Interference of aureomycin and of terramycin with the action of penicillin in vitro. Proc Soc Exp Biol Med 1950;75:549–452.
133. Chuang YC, Liu JW, Ko WC, et al. In vitro synergism between cefotaxime and minocycline against Vibrio vulnificus. Antimicrob Agents Chemother 1997;41:2214–2217.
134. Chuang YC, Ko WC, Wang ST, et al. Minocycline and cefotaxime in the treatment of experimental murine Vibrio vulnificus infection. Antimicrob Agents Chemother 1998;42: 1319–1322.
135. Ko WC, Lee HC, Chuang YC, et al. In vitro and in vivo combinations of cefotaxime and minocycline against Aeromonas hydrophilia. Antimicrob Agents Chemother 2001;45: 1281–1283.
136. Lepper MH, Dowling HP. Treatment of pneumococcic meningitis with penicillin compared with penicillin plus aureomycin: studies including observations on an apparent antagonism between penicillin and aureomycin. Arch Intern Med 1951:88:489–494.
137. Olsson RA, Kirby JC, Romansky MJ. Pneumococcal meningitis in the adult. Clinical, therapeutic and prognostic aspects in forty-three patients. Ann Intern Med 1961;55: 545–549.
138. Strom J. The question of antagonism between penicillin and chlortetracycline, illustrated by therapeutical experiments in scarlatina. Antibiot Med 1955;1:6–12.
139. Ahern JJ, Kirby WMM. Lack of interference of aureomycin in treatment of pneumococcic pneumonia. Arch Intern Med 1953;91:197–203
140. Tryba M. Potentiation of non-depolarizing muscle relaxants of acetylaminopenicillin. Studies on the example of vecuronium [English abstr]. Anaethesist 1985;34:651–655.
141. Singh YN, Harvey AL, Marshall IG. Antibiotic-induced paralysis of the mouse phrenic nerve-hemidiaphragm preparation, and reversibility by calcium and by neostigmine. Anesthesiology 1978;48:418–424.
142. Harwood TN, Moorthy SS. Prolonged vecuronium-induced neuromuscular blockade in children. Anesth Analg 1989;68:534–536.
143. Mackie K, Pavlin EG. Recurrent paralysis following pipercillin administration. Anesthesiology 1990;72:561–563.
144. Condon RE, Munshi CA, Arfman RC. Interaction of vecuronium with pipercillin or cefoxitin evaluated in a prospective, randomized, double-blind clinical trial. Am Surg 1995;61: 403–406.
145. Kadlec GJ, Ha LH, Jarboe CH, et al. Effect on ampicillin on theophylline half-life in infants and young children. South Med J 1978;71:1584.
146. Jonkman JH, Van der Boon WJ, Schoenmaker R, et al. Lack of effect of amoxicillin on theophylline pharmacokinetics. Br J Clin Pharmacol 1985;19:99–101.
147. Matera MG, Cazzola M, Lampa E, et al. Clinical pharmacokinetics of theophylline during co-treatment with ticarcillin plus clavulanic acid in patients suffering from acute exacerbation of chronic bronchitis. J Chemother 1993;5:233–236.
148. Cazzola M, Santangelo G, Guidetti E, et al. Influence of sulbactam plus ampicillin on theophylline clearance. Int J Clin Pharmacol Res 1991;11:11–15.
149. Jonkman JH, Van der Boon WJ, Schoenmaker R, et al. Clinical pharmacokinetics of amoxycillin and theophylline during cotreatment with both medicaments. Chemotherapy 1985;31: 329–335.

150. Hughes GS, Heald DL, Barker KB, et al. The effects of gastric pH and food on the pharmacokinetics of a new oral cephalosporin, cefpodoxime proxetil. Clin Pharmacol Ther 1989;46: 674–685.
151. Saathoff N, Lode H, Neider K, et al. Pharmacokinetics of cefpodoxime proxetil and interactions with an antacid and an H_2 receptor antagonist. Antimicrob Agents Chemother 1992;36:796–800.
152. Spectracef® (cefditoren) package insert, Purdue Pharmaceutical Products L. P., 2003.
153. Omnicef® (cefdinir) package insert, Abbott Laboratories, 2001.
154. Madara-Kelly K, Michas P, George M, May MP, Adejare A. A randomized crossover study investigating the influence of ranitidine or omeprazole on the pharmacokinetics of cephalexin monohydrate. J Clin Pharmacol 2004;44:1391–1397.
155. Satterwhite JH, Cerimele BJ, Coleman DL. Pharmacokinetics of cefaclor AF: effects of age, antacids, and H_2-receptor antagonists. Postgrad Med J 1992;68:S3–S9.
156. Healy DP, Sahia J, Sterling LP, et al. Influence of antacid containing aluminum and magnesium on the pharmacokinetics of cefixime. Antimicrob Agents Chemother 1989;33:1994–1997.
157. Food and Drug Adminstration. Rocefin (ceftriaxone sodium) for injection. Available at. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152863.htm. Date accessed: August 3, 2010.
158. Health Canada. Fatal interactions ceftriaxone-calcium-Notice to Hospitals. Available at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/ceftriaxone_nth-aah-eng.php. Date accessed: August 3, 2010.
159. Grasberger H, Otto B, Loeschke K. Ceftriaxone-associate nephrolithiasis. Ann Pharmacother 2000;34:1076,1077.
160. Bradley JS, Wassel RT, Lee L, Nambiar S. Intravenous ceftriaxone and calcium in the neonate: Assessing the risk for cardiopulmonary adverse events. Pediatrics 2009;123: e609–e613.
161. Avci Z, Koktener A, Uras N, Catal F, Karadag A, Tekin O, et al. Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children. Arch Dis Child 2004;89: 1069–1072.
162. Park HZ, Lee SP, Schy AL. Ceftriaxone-associated gallbladder sludge. Identification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. Gastroenterology 1991; 100:1665–1667.
163. Food and Drug Administration. Information for healthcare professionals, Ceftriaxone (marketed as Rocephin). Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm084263.htm. Date accessed: August 3, 2010.
164. Steadman E, Raisch DW, Bennett CL, Esterly JS, Tischa B, Postelnick M, et al. Evaluation of a potential clinical interaction between ceftriaxone and calcium. Antimicrob Agents Chemother 2010;54:1534–1540.
165. Deslandes A, Camus F, Lacroix C, et al. Effects of nifedipine and diltiazem on pharmacokinetics of cefpodoxime following its oral administration. Antimicrob Agents Chemother 1996;40:2879–2881.
166. Duverne C, Bouten A, Deslandes A, et al. Modification of cefixime bioavailability by nifedipine in humans: involvement of the dipeptide carrier system. Antimicrob Agents Chemother 1992;36:2462–2467.
167. Berlioz F, Julien S, Tsocas A, et al. Neural modulation of cephalexin intestinal absorption through the di- and tripeptide brush border transporter of rat jejunum in vivo. J Pharmacol Exp Ther 1999;288:1037–1044.
168. Marino EL, Vicente MT, Dominguez-Gil A. Influence of cholestyramine on the pharmacokinetic parameters of cefadroxil after simultaneous administration. Int J Pharmaceut 1983;16: 23–30.
169. Parsons RL, Paddock GM, Hossack GM. Cholestryamine induced antibiotic malabsorption. Chemotherapy 4. In: Williams JD, Geddes AM (eds.). Pharmacology of Antibiotics. New York–London: Plenum, 1975; pp. 191–198.

170. Soto Alvarez J, Sacristan Del Castillo JA, Alsar Oritz MJ. Interaction between ciclosporin and ceftriaxone. Nephron 1991;59:681,682.
171. Cockburn I. Cyclosporin A: a clinical evaluation of drug interactions. Transplant Proc 1986;18 (Suppl 5):50–55.
172. Verhagen C, De Pauw BE, de Witte T, Holdrinset RSG, Janssen JTP, Williams KJ. Ceftazidime does not enhance cyclosporine-A nephrotoxicity in febrile bone marrow transplantation patients. Blut 1986;53:333–339.
173. Kannangara DW, Gallagher K, Lefrock JL. Disulfiram-like reactions with newer cephalosporins: cefmenoxime. Am J Med Sci 1984;287:45–47.
174. Foster TS, Raehl CL, Wilson HD. Disulfiram-like reaction associated with a parenteral cephalosporin. Am J Hosp Pharm 1980;37:858,859.
175. Uri JV, Parks DB. Disulfiram-like reaction to certain cephalosporins. Ther Drug Monit 1983;5:219–224.
176. Ueno K, Tanaka K, Tsujimura K, et al. Impairment of cefdinir absorption by iron ion. Clin Pharmacol Ther 1993;54:473–475.
177. Nelson J. Red stools and Omnicef. J Pediatr 2000;136:853,854.
178. Lancaster J, Sylvia LM, Schainker E. Nonbloody, red stools from coadministration of cefdinir and iron-supplemented infant formulas. Pharmacotherapy 2008;28:678–681.
179. Shukla UA, Pittman KA, Barbhiaya RH. Pharmacokinetic interactions of cefprozil with food, propantheline, metoclopramide, and probenecid in healthy volunteers. J Clin Pharmacol 1992;32:725–731.
180. Neu HC. The in vitro activity, human pharmacology, and clinical effectiveness of new beta-lactam antibiotics. Annu Rev Pharmacol Toxicol 1982;22:599–642.
181. Merle-Melet M, Bresler L, Lokiec F, et al. Effects of diclofenac on ceftriaxone pharmacokinetics in humans. Antimicrob Agents Chemother 1992;36:2331–2333.
182. Andrassy K, Bechtold H, Ritz E. Hypoprothrombinemia caused by cephalosporins. J Antimicrob Chemother 1985;15:133–136.
183. Freedy HR, Cetnarowski AB, Lumish RM, et al. Cefoperazone-induced coagulopathy. Drug Intell Clin Pharm 1986;20:281–283.
184. Rymer W, Greenlaw CW. Hypoprothrombinemia associated with cefamandole. Drug Intell Clin Pharm 1980;40;780–783.
185. Osborne JC. Hypoprothrombinemia and bleeding due to cefoperazone [letter]. Ann Intern Med 1985;102:721,722.
186. Cristiano P. Hypoprothrombinemia associated with cefoperazone treatment. Drug Intell Clin Pharm 1984;18:314–316.
187. Hooper CA, Haney BB, Stone HH. Gastrointestinal bleeding due to vitamin K deficiency in patients on parenteral cefamandole [letter]. Lancet 1980;1:39,40.
188. Pakter RL, Russell TR, Mielke CH, et al. Coagulopathy associated with the use of moxalactam. JAMA 1982;248:1100.
189. Marier RL, Faro S, Sanders CV, et al. Moxalactam in the therapy of serious infections. Antimicrob Agents Chemother 1982;21:650–654.
190. Angaran DM, Dias VC, Arom KV, et al. The influence of prophylactic antibiotics on the warfarin anticoagulation response in the postoperative prosthetic cardiac valve patient. Cefamandole versus vancomycin. Ann Surg 1984;199:107–111.
191. Angaran DM, Virgil MS, Dias VC. The comparative influence of prophylactic antibiotics on the prothrombin response to warfarin in the postoperative prosthetic cardiac valve patient. Cafamandole, cefazolin, vancomycin. Ann Surg 1987;206:155–161.
192. Bechtold H, Andrassy K, Jahnchen E, et al. Evidence for impaired hepatic vitamin K_1 metabolism in patients treated with N-methyl-thiotetrazole cefalosporins. Thrombosis and Haemost 1984;51:358–361.
193. Frick P, Riedler G, Brogli H. Dose response and minimal daily requirement for vitamin K in man. Applied Physiol 1967;23:387–389.
194. Lipsky J. N-methyl-thio-tetrazole inhibition of the gamma carboxylation of glutamic acid: possible mechanism for antibiotic associated hypothrombinemia. Lancet 1983;2:192,193.

195. Lipsky J, Lewis J, Novick W. Production of hypoprothrombinemia by moxalactam and 1-methyl-5-thiotetrazole in rats. Antimicrob Agents Chemother 1984;25:380,381.
196. Verhagen CA, Mattie H, Van Strijen E. The renal clearance of cefuroxime and ceftazidime and the effect of probenecid on their tubular excretion. Br J Clin Pharmacol 1994;37:193–197.
197. Luthy R, Blaser J, Bonetti A, et al. Comparative multiple-dose pharmacokinetics of cefotaxime, moxalactam, and ceftazidime. Antimicrob Agents Chemother 1981;20:567–575.
198. LeBel M, Paone RP, Lewis GP. Effect of probenecid on the pharmacokinetics of ceftizoxime. J Antimicrob Chemother 1983;12:147–155.
199. Reeves DS, Bullock DW, Bywater MJ, et al. The effect of probenecid on the pharmacokinetics and distribution of cefoxitin in healthy volunteers. Br J Clin Pharm 1981;11:353–359.
200. Marino EL, Dominquez-Gil A. The pharmacokinetics of cefadroxil associated with probenecid. Int J Clin Pharmacol Ther Toxicol 1981;19:506–508.
201. Stoeckel K. Pharmacokinetics of Rocephin®, a highly active new cephalosporin with an exceptionally long biological half-life. Chemotherapy 1981;27:42–46.
202. Kaplan KS, Reisberg BE, Weinstein L. Cephaloridine: antimicrobial activity and pharmacologic behavior. Am J Med Sci 1967;253:667–674.
203. Duncan WC. Treatment of gonorrhoea with cefazolin plus probenecid. J Infect Dis 1974;130:398–401.
204. Mischler TW, Sugerman AA, Willard SA, Barmick L, Neiss ES. Influence of probenecid and food on the bioavailability of cephradine in normal male subjects. J Clin Pharmacol 1974;14:604–611.
205. Tuano SB, Brodie JL. Kirby WM. Cephaloridine versus cephalothin: relation of the kidney to blood level differences after parenteral administration. Antimicrob Agents Chemother 1966;6:101–106.
206. Griffith RS, Black HR, Brier GL, et al. Effect of probenecid on the blood levels and urinary excretion of cefamandole. Antimicrob Agents Chemother 1977;11:809–812.
207. Bint AJ, Reeves DS, Holt HA. Effect of probenecid on serum cefoxitin concentrations. J Antimicrob Chemother 1977;3:627,628.
208. Taylor WA, Holloway WJ. Cephalexin in the treatment of gonorrhea. Int J Clin Pharmacol 1972;6:7–9.
209. Ko H, Cathcart KS, Griffith DL, et al. Pharmacokinetics of intravenously administered cefmetazole and cefoxitin and effects of probenecid on cefmetazole elimination. Antimicrob Agents Chemother 1989; 33:356–361.
210. Vlasses PH, Holbrook AM, Schrogie J, et al. Effect of orally administered probenecid on the pharmacokinetics of cefoxitin. Antimicrob Agents Chemother 1980;17:847–855.
211. Spina SP, Dillon EC Jr. Effect of chronic probenecid therapy on cefazolin serum concentrations. Ann Pharmother 2003;37:621–4.
212. Stoeckel K, Trueb V, Dubach UC, et al. Effect of probenecid on the elimination and protein binding of ceftriaxone. Eur J Clin Pharmacol 1988;34:151–156.
213. O'Callaghan CH, Acred P, Harper PB, et al. GR 20263, a new broad-spectrum cephalosporin with antipseudomonal activity. Antimicrob Agents Chemother 1980;17:876–883.
214. DeSante KA, Israel KS, Brier GL, et al. Effect of probenecid on the pharmacokinetics of moxalactam. Antimicrob Agents Chemother 1982;21:58–61.
215. Patel IH, Soni PP, Carbone JJ, et al. Lack of probenecid effect on nonrenal excretion of ceftriaxone in anephric patients. J Clin Pharmacol 1990;30:449–453.
216. Kercsmar CM, Stern RC, Reed MD, et al. Ceftazidime in cystic fibrosis: pharmacokinetics and therapeutic response. J Antimicrob Chemother 1983;12:289–295.
217. Jovanovich JF, Saravolatz LD, Burch K, et al. Failure of probenecid to alter the pharmacokinetics of ceforanide. Antimicrob Agents Chemother 1981;20:530–532.
218. Pfeifer HJ, Greenblatt DJ, Friedman P. Effects of three antibiotics on theophylline kinetics. Clin Pharmacol Ther 1979;26:36–40.
219. Bachmann K, Schwartz J, Forney RB, et al. Impact of cefaclor on the pharmacokinetics of theophylline. Ther Drug Monitor 1986;8:151–154.
220. Jonkman JH, Van der Boon WJ, Schoenmaker R, et al. Clinical pharmacokinetics of theophylline during co-treatment with cefaclor. Int J Clin Pharmacol Ther Toxicol 1986;24:88–92.

221. Hammond D, Abate MA. Theophylline toxicity, acute illness, and cefaclor. Drug Intell Clin Pharm 1989;23:339,340.
222. Foord RD. Cephaloridine, cephalothin, and the kidney. J Antimicrob Chemother 1975;1(suppl): 119–133.
223. Koch-Weser J, Sidel VW, Federman EB, et al. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. Ann Intern Med 1970;72:857–868.
224. Adler S, Segel DP. Nonoliguric renal failure secondary to sodium colistimethate: a report of four cases. Am J Med Sci 1971;262:109–114.
225. Plager JE. Association of renal injury with combined cephalothin-gentamicin therapy among patients severely ill with malignant disease. Cancer 1976;37:1937–1943.
226. Wade JC, Smith CR, Petty BG, et al. Cephalothin plus an aminoglycoside is more nephrotoxic than methicillin plus an aminoglycoside. Lancet 1978;2:604–606.
227. Gurwich EL, Sula J, Hoy RH. Gentamicin-cephalothin drug reaction. Am J Hosp Pharm 1978;35:1402,1403.
228. Hansen MM, Kaaber K. Nephrotoxicity in combined cephalothin-gentamicin therapy among patients severely ill with malignant disease. Cancer 1976;37:1937–1943.
229. Cabanillas F, Burgos RC, Rodriquez RC, et al. Nephrotoxicity of combined cephalothin-gentamicin regimen. Arch Intern Med 1975;135:850–852.
230. Fillastre JP, Laumonier R, Humbert G, et al. Acute renal failure associated with combined gentamicin and cephalothin therapy. Br Med J 1973;2:396,397.
231. Bobrow SL, Jaffe E, Young RC, et al. Anuria and acute tubular necrosis associated with gentamicin and cephalothin. JAMA 1972;222:1546,1547.
232. Kleinknecht D, Jungers P, Fillastre JP. Nephrotoxicity of cephaloridine. Ann Intern Med 1974;80:421,422.
233. Dodds MG, Foord RD. Enhancement by potent diuretics of renal tubular necrosis induced by cephaloridine. Br J Pharmacol 1970;40:227–236.
234. Norrby R, Stenqvist K, Elgefors B, et al. Interaction between cephaloridine and furosemide in man. Scand J Infect Dis 1976;8:209–212.
235. Simpson IJ. Nephrotoxicity and acute renal failure associated with cephalothin and cephaloridine. N Z Med J 1971;74:312–315.
236. Trollfors B, Norrby R, Kristianson K. Effects on renal function of treatment with cefoxitin sodium alone or in combination with furosemide. J Antimicrob Chemother 1978;4: S85–S89.
237. Korn A, Eichler HG, Gasic S. A drug interaction study of ceftriaxone and frusemide in healthy volunteers. Int J Clin Pharmacol Ther Toxicol 1986;24:262–264.
238. Walstad RA, Dahl K, Hellum KB, et al. The pharmacokinetics of ceftazidime in patients with impaired renal function and concurrent frusemide therapy. Eur J Clin Pharmacol 1988;35:273–279.
239. Doribax® (doripenem) package insert. Ortho McNeil Janssen, 2008.
240. Bax RP, Bastain W, Featherstone A, et al. The pharmacokinetics of meropenem in volunteers. J Antimicrob Chemother 1989:24:311–320.
241. Invanz® (ertapenem) package insert. Merck & Co, 2010.
242. Norrby SR, Alestig K, Ferber F, et al. Pharmacokinetics and tolerance of N-formimidoyl thienamycin (MK0787) in humans. Antimicrob Agents Chemother 1983;23:293–9.
243. Suzuki E, Yamamura N, Ogura Y et al. Identification of valproic acid glucuronide hydrolase as a key enzyme for the interaction of valproic acid with carbapenem antibiotics. Drug Metab Dispos 2010; Dispos 2010;38:1538–1544.
244. Haroutiunian S, Ratz Y, Rabinovich B, et al. Valproic acid plasma concentration decreases in a dose-dependent manner following administration of meropenem: A retrospective study. J Clin Pharmacol 2009;49:1363–1369.
245. Spriet I, Goyens J, Meersseman W, et al. Interaction between valproate and meropenem: a retrospective study. Ann Pharmacother 2007;41:1130–1136.
246. Torii M, Takiguchi Y, Saito F, et al. Inhibition by carbapenem antibiotic imipenem of intestinal absorption of valproic acid in rats. Pharm Pharmacol 2001;53:823–829.

247. Yokogawa K, Iwashita S, Kubota A, et al. Effect of meropenem on disposition kinetics of valproate and its metabolites in rabbits. Pharm Res 2001;18:1320–1326.
248. Yamamura N, Imura K, Naganuma H, et al. Panipenem, a carbapenem antibiotic, enhances the glucuronidation of intravenously administered valproic acid in rats. Drug Metab Dispos 1999;27:724–730.
249. DeTurck BJ, Diltoer MW, Cornelis PJ, et al. Lowering of plasma valproic acid concentrations during concomitant therapy with meropenem and amikacin [letter]. J Antimicrob Chemother 1998;42:563,564.
250. Nagai K, Shimizu T, Togo A, et al. Decrease in serum levels of valproic acid during treatment with a new carbapenem, panipenem/betamipron. J Antimicrob Chemother 1997;39:295,296.
251. Coves-Orts FJ, Borrás-Blasco J, Navarro-Ruiz A, et al. Acute seizures due to a probable interaction between valproic acid and meropenem. Ann Pharmacother 2005;39:533–537.
252. Santucci M, Parmeggiani A, Riva R. Seizure worsening caused by decreased serum valproate during meropenem therapy. J Child Neurol 2005;20:456,457.
253. Fudio S, Carcas A, Piñana E, Ortega R. Epileptic seizures caused by low valproic acid levels from an interaction with meropenem. J Clin Pharm Ther 2006;31:393–396.
254. Lunde JL, Nelson RE, Storandt HF. Acute seizures in a patient receiving divalproex sodium after starting ertapenem therapy. Pharmacotherapy 2007;27:1202–1205.
255. Tobin JK, Golightly LK, Kick SD, Jones MA. Valproic acid-carbapenem interaction: report of six cases and a review of the literature. Drug Metabol Drug Interact 2009;24:153–182.
256. Gu J, Huang Y. Effect of concomitant administration of meropenem and valproic acid in an elderly Chinese patient. Am J Geriatr Pharmacother 2009;7:26–33.
257. Lioa F, HuangY, Chen C. Decrease in serum valproic acid levels during treatment with ertapenem. Am J Health-Syst Pharm 2010;67:1260–1264.
258. Bösmuller C, Steurer W, Königsrainer A, et al. Increased risk of central nervous system toxicity in patients treated with cyclosporine and imipenem/cilastatin. Nephron 1991;58:362–364.
259. Zazgornik J, Schein W, Heimberger K, et al. Potentiation of neurotoxic side effects by coadministration of imipenem to cyclosporine therapy in a kidney transplant recipient—synergism of side effects or drug interaction. Clin Nephrol 1986;26:265,266.
260. Mraz W, Sido B, Knedel M, et al. Concomitant immunosuppressive and antibiotic therapy—reduction of cyclosporine A blood levels due to treatment with imipenem/cilastatin. Transplant Proc 1992;24:1704–1708.
261. Semel JD, Allen N. Seizures in patients simultaneously receiving theophylline and imipenem or ciprofloxacin or metronidazole. South Med J 1991;84:465–468.
262. Primaxin® (imipenem and cilastatin) package insert. Merck & Co, 2010.
263. Jung D, Dorr A. Single dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects. J Clin Pharmacol 1999;39:800–804.
264. Valcyte® (valganciclovir) package insert. Roche, 2010.
265. Valcyte® (valganciclovir powder for Oral Solution) Roche Products Ltd. UK Summary of Product Characteristics, June 2010.
266. Swabb EA, Sugerman AA, Frantz M, et al. Renal handling of the monobactam aztreonam in healthy subjects. Clin Pharmacol Ther 1983;33:609–614.
267. Sisson TL, Jungbluth GL, Hopkins NK. A pharmacokinetic evaluation of concomitant administration of linezold and astreonam. J Clin Pharmacol 1999;39:1277–1282.
268. Cubicin® (daptomycin) package insert. Cubist Pharmaceuticals, Inc. August 2010.
269. Creasy WA, Adamvics J, Dhruv R, Platt TB, Sugerman AA. Pharmacokinetic interaction of aztreonam with other antibiotics. J Clin Pharmacol 1984;24:174–180.
270. Adamis G, Papaioannou MG, Giamarellos-Bourboulis EJ, Gargalianos P, Kosmidis J, Giamarellou H. Pharmacokinetic interactions of ceftazidime, imipenem and aztreonam with amikacin in healthy volunteers. Int J Antimicrob Agents 2004;23:144–149.

Chapter 8
Macrolides, Azalides, and Ketolides

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Abstract The macrolides, azalides, and ketolides represent an important class of drugs that are used for their antimicrobial and non-antimicrobial properties. Erythromycin inhibits the cytochrome P450 (CYP) 3A4 isoenzyme system via mechanism based inhibition. Erythromycin has also been shown to inhibit P-glycoprotein (P-gp) and organic anion transporting polypeptide drug transport proteins. These metabolic and transport systems affect the disposition of numerous drug classes and so the drug interaction potential of erythromycin is high. Recent epidemiologic evidence for a higher risk of sudden death with the use of oral erythromycin, especially when combined with CYP3A4 inhibitors provides an illustrative example of the risks associated with this class of agents. Clarithromycin and telithromycin are stronger inhibitors of CYP3A4 and P-gp compared to erythromycin. Azithromycin is a weak inhibitor of CYP3A4 compared to erythromycin, and bears the lowest potential for drug interactions when considering use of this class of agents. This chapter summarizes the key drug interaction potential of this antimicrobial class that can lead to serious adverse events such as cardiac dysrhythmias, hypoglycemia, nephrotoxicity, neurotoxicity, neutropenia, and rhabdomyolysis.

8.1 Introduction

Erythromycin was marketed in 1952 as the first antimicrobial macrolide under the trade names Ilosone® and Ilotycin® after the Philippine province of Iloilo, the site where soil samples of *Streptomyces erythreus* were collected [1]. This agent provided a viable alternative to treat infections in patients with hypersensitivity reactions to penicillin [1]. Several macrolide derivatives have been generated over

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the past 60 years in order to identify safer, better tolerated agents with a lower drug interaction potential [2]. These newer compounds have demonstrated a variable degree of success toward reducing the drug interaction potential of the macrolides [3]. Erythromycin is associated with drug interactions that can lead to serious adverse events including death when coadministered with drugs that have a narrow therapeutic index [4]. Macrolides interact with drugs through several mechanisms, the most common of which includes inhibition of the cytochrome P450 (CYP) 3A4 isoenzyme system [5]. Macrolides also inhibit the drug transport proteins, P-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP), which can alter the distribution, metabolism and elimination of substrates of these transporters [6–8]. Macrolides are also associated with prolongation of the QTc interval, which can progress to cardiac dysrhythmias and sudden death especially when used with agents known to prolong the QTc interval [9]. Consequently, a clear understanding of the pharmacokinetic and pharmacodynamic drug interaction potential of this class of antimicrobials is essential.

Macrolides are classified by the number and type of members (macrocyclic) in their lactone ring, which include a 14-membered ring (erythromycin, clarithromycin, dirithromycin, roxithromycin), 15-membered ring (azithromycin), or 16-membered ring (spiramycin) [10, 11]. Azithromycin contains a nitrogen atom in the macrocyclic lactone structure and so is classified as an azalide [12]. The ketolides are derivates of erythromycin that include replacement of cladinose with a 3-keto group and inclusion of a cyclic carbamate group within the lactone ring [11]. To date, only one ketolide agent known as telithromycin has received regulatory approval, however the United States Food and Drug Administration (US FDA) narrowed the clinical indications of telithromycin to only mild-to-moderate pneumonia in 2007. This regulatory modification has reduced the clinical use of telithromycin due to a perceived unfavorable risk of hepatotoxicity [13]. A second ketolide agent, cethromycin was reviewed by the US FDA in 2008 and was deemed to have a favorable safety profile but to not have sufficient evidence to support efficacy against community-acquired pneumonia [13]. Although the fate of the ketolides as a class remains uncertain from a regulatory perspective, continued development of this class is likely to occur due to macrolide resistance. The ketolides extend the microbiologic spectrum of macrolides through chemical modifications that have rendered them less prone to efflux (*mef* or *msr*) and methylase (*erm*) mediated mechanisms of macrolide resistance [11]. However, the similarity in structure of clarithromycin and ketolides to erythromycin confer a similar drug interaction potential [2, 14]. In contrast, the structural difference between azithromycin and these agents has been associated with a lower drug interaction potential [14]. Dirithromycin, roxithromycin and spiramycin have a limited drug interaction potential and are used in a limited number of countries worldwide [3, 14, 15]. Therefore, the current chapter focuses on the drug interaction potential of key macrolide, azalide and ketolide (MAK) agents namely erythromycin, clarithromycin, azithromycin and telithromycin. Given that azithromycin (azalide) has a lower propensity for drug interactions, the key interaction potential of macrolide and ketolide (MK) agents is discussed with a greater emphasis. The degree of pharmacokinetic interaction of MAK agents is

often based on the changes in exposure of the substrate drug. Consequently, the degree of interaction is reported in this chapter as a percentage change in the area under the plasma/serum concentration time curve (AUC).

8.2 Basic Pharmacology

MAK antibiotics exert a bacteriostatic effect by binding reversibly to the 50S ribosomal subunit of sensitive microorganisms. Erythromycin (MW = 733.93 g/mol) specifically inhibits the translocation step by blocking the transfer of the peptide chain from the transferase site to the donor site. Inhibition of transpeptidation and release of incomplete peptide chains has also been proposed [16]. Resistance to macrolides and azalides occurs through four known mechanisms which include drug efflux, ribosomal protection by constitutive or inducible production of methylase enzyme, hydrolysis by esterases, and chromosomal mutations that modify the 50S ribosome [17, 18]. Ketolides are less likely to induce production of methylase and to undergo drug efflux [19]. However, the use of the only approved ketolide (telithromycin) is technically limited to the treatment of community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumonia* (including multi-drug resistant isolates), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*, for patients 18 years and older due to its hepatotoxic potential [20, 21]. However, off-label use of telithromycin is likely to still be occurring in the United States [21]. As a result, the MAK agents continue to be prescribed for respiratory and non-respiratory infections secondary to these pathogens. In addition clarithromycin and azithromycin are used as prophylaxis and treatment of *Mycobacterium avium-intracellularae* in AIDS and other immunocompromised patient populations [22, 23]. These agents are utilized to treat common opportunistic infections noted in patients infected with HIV [24]. Clarithromycin (MW = 747.95 g/mol) is a key agent in the treatment of peptic ulcer disease secondary to *Helicobacter pylori* [22]. Finally, macrolides and azalides are used clinically for their non-antimicrobial properties [25]. Erythromycin demonstrates prokinetic effects through stimulation of the motilin receptor and is used in critically ill patients with gastroparesis [26–28]. Azithromycin (MW = 748.98 g/mol) has recently been demonstrated to have comparable antroduodenal effects as erythromycin [29]. Macrolides exert anti-inflammatory effects that have been exploited for chronic respiratory diseases such as diffuse panbronchiolitis and cystic fibrosis [30]. Although, the exact mechanisms have not been elucidated, use of chronic azithromycin has been shown to reduce the rate of pulmonary decline in cystic fibrosis patients colonized with *Pseudomonas aeruginosa* but not *Staphylococcus aureus* [31, 32]. MAK antimicrobials can directly affect neuromuscular transmission. Telithromycin (MW = 812.00 g/mol) has been shown to inhibit postsynaptic nicotinic acetylcholine receptors and its use is contraindicated in patients with myasthenia gravis [20, 33]. Finally, the MAK antibiotics are associated with drug-induced QT prolongation and sudden death especially when combined with other agents implicated with QT prolongation that are metabolized by CYP3A4 [4].

Table 8.1 Available systemic formulations of macrolides, azalides, and ketolides in the United States [20, 22, 23, 34–37]

Drug	Formulations
Erythromycin (base)	Injectable (100 mg/mL), Injectable (200 mg/mL), Capsule (250 mg), Coated Tablet (250 mg), Timed-Release Tablet (250 mg), Enteric coated Tablet (500 mg), Delayed-Release (250 mg)
Erythromycin estolate	Capsule (125 mg), Suspension (125 mg/mL)
Erythromycin ethylsuccinate	Suspension (200 mg/5 mL), Suspension (400 mg/5 mL), Coated tablet (400 mg), Tablet (400 mg)
Erythromycin lactobionate	Injectable (500 mg vial), Injectable (1,000 mg vial)
Erythromycin stearate	Coated Tablet (250 mg), Coated Tablet (500 mg), Tablet (500 mg)
Clarithromycin	Suspension (125 mg/5 mL), Suspension (250 mg/5 mL), Tablet (250 mg), Tablet (500 mg), Extended-Release Tablet (500 mg)
Azithromycin	Extended-Release Suspension (2 g), Injectable (500 mg), Solution (2.5 g), Solution (500 mg), Suspension (500 mg), Suspension (100 mg/5 mL), Suspension (200 mg/5 mL), Suspension (1 g/packet), Tablet (250 mg), Tablet (500 mg), Tablet (600 mg)
Telithromycin	Tablet (300 mg), Tablet (400 mg)

8.2.1 Absorption

Erythromycin is degraded by gastric acid, and food significantly decreases the rate and extent of its absorption [34]. Overall, significant intersubject variability in the absorption of erythromycin exists [34–37]. Modification of erythromycin through esterification and enteric-coating helps to reduce gastric degradation and improve bioavailability. Available formulations of erythromycin as the base, estolate, ethylsuccinate, and stearate derivatives are included in Table 8.1. Erythromycin estolate is least susceptible to acid hydrolysis, however enteric coating leads to the most predictable absorption profile [34–37]. Erythromycin is also available as an intravenous formulation that is delivered as a lactobionate derivative. Clarithromycin is available as both an intravenous and oral formulations in several countries (Klaricid IV) but is currently only available as an immediate and extended release oral formulation (Table 8.1) in the United States [22, 38]. Clarithromycin undergoes significant first pass metabolism and has a bioavailability of approximately 50% that is not affected by the co-administration of food [22]. However, the bioavailability of the extended release formulation is significantly improved when taken with food and is the recommended approach to administration [22].

Azithromycin is available (Table 8.1) as intravenous, immediate release, and extended release oral formulations [23, 39, 40]. The oral bioavailability of azithromycin capsule (not commercially available) is 38% [23]. The extended release formulation is not bioequivalent to the immediate release oral suspension and so the dosages of these agents are not interchangeable [40]. Food reduces the bioavailability of extended release oral suspension but has marginal effects on the immediate

release formulations [23, 40]. Telithromycin is available as an oral formulation only and has a bioavailability of 57% that is not adversely affected by the co-administration of food [20].

8.2.2 Distribution

Erythromycin is approximately 70–95% protein bound, with variability noted based on the specific derivative [41]. The volume of distribution (Vd) of erythromycin is approximately 40 L in adults [42]. Clarithromycin is less protein bound (42–50%) and has a correspondingly larger apparent Vd of 243–266 L [22]. The principal 14-hydroxy metabolite of clarithromycin has an apparent Vd of 304–309 L [22]. Azithromycin demonstrates concentration dependent protein binding with a range of 7–50% and has an apparent Vd that exceeds 1,000 L [23]. Telithromycin in comparison, has similar protein binding to clarithromycin (60–70%) and an apparent Vd of 200–250 L [20]. The large Vd of the later three agents compared to erythromycin are consistent with high measured tissue intracellular concentrations of these agents. In addition, pulmonary tissue concentrations of these agents exceed serum unbound drug concentrations by several fold [43]. Exposures in epithelial lining fluid have been documented to be 3.15–24.10 fold higher than serum total concentrations [43]. Alveolar macrophage concentrations have been documented to be 84.2–3,234 fold higher than serum total concentrations [43]. The underlying mechanisms that explain the enhanced accumulation of macrolides in the lung is not well known and may partially be explained by technical limitations of current methods to estimate pulmonary concentrations [2, 43]. However, recent data with telithromycin indicate that the distribution into epithelial lining fluid may occur through active transport mechanisms regulated by P-gp [44]. Hence the enhanced distribution of MAK into pulmonary tissue are likely to be mediated by active transport mechanisms.

8.2.3 Metabolism

MAK antibiotics have a tertiary amine function, -N-$(CH_3)_2$ that is known to undergo N-demethylation by hepatic microsomes [45]. In addition, these agents undergo dealkylation and are oxidized to metabolites that form stable complexes with Fe^{2+} of reduced CYP to inactivate enzymatic activity [46, 47]. Erythromycin has been demonstrated to first induce CYP, which is followed by rapid complexation and inactivation by its metabolite [46]. In contrast, azithromycin induces N-demethylase but does not induce CYP and no inactive CYP complexes are detectable in the rat despite high azithromycin accumulation in this tissue [48]. Clarithromycin is primarily metabolized in the liver to 14-hydroxy clarithromycin and n-demethyl clarithromycin [49]. The 14-(R)-hydroxy clarithromycin is an active metabolite with more potent activity against *Haemophilus influenzae* compared to the parent

compound [50]. Clarithromycin and its metabolites have been shown to induce CYP3A and form inactive complexes with CYP in vivo [51, 52]. Telithromycin undergoes similar biotransformation as clarithromycin and has a N-bis-demethyl derivative that is 4–16 fold less active than the parent compound [53]. However, telithromycin has been shown to decrease the activity of both CYP1A2 and CYP3A, while clarithromycin principally decreases the activity of CYP3A [54, 55]. The mechanism-based inhibition of CYP3A by erythromycin, clarithromycin and telithromycin suggest that several days of drug free period may be necessary to permit generation of CYP3A isoenzymes to normalize the intrinsic activity of this metabolic pathway.

8.2.4 Elimination

The mode of drug administration (intravenous or oral) and dose administered affects the elimination pathway of macrolides [22, 56]. Concentration dependent protein binding may account for these alterations in elimination [34–37, 57]. A small fraction (2.5%) of erythromycin is eliminated as unchanged drug in urine, with fecal elimination serving as the principal pathway [56]. Elimination of clarithromycin through the kidney accounts for 20–40% of its excretion [22]. In addition, 10–15% of 14-hydroxy clarithromycin is excreted in urine [22]. In contrast to other agents in this class, elimination of clarithromycin through the bile and feces is limited [22]. Biliary excretion accounts for 50% of the elimination of azithromycin, while approximately 12% is eliminated in urine [22]. Three quarters of telithromycin and its metabolites are eliminated in feces, with 12–14% of dose eliminated as unchanged drug in urine [20].

8.3 Drug Interactions

MAK agents interact with drugs and biologics through multiple mechanisms, the most common involving the CYP3A system in the small intestine and liver [58]. However, the inhibitory effects of MAK on drug transport systems such as P-gp and OATP has increasingly been recognized to contribute to significant drug interactions that cannot be solely explained by CYP inhibition [6–8]. Given the specific expression of human transporters within select tissues, inhibition of these systems can affect absorption, distribution, metabolism and elimination of several compounds [59]. Inhibition of P-gp in the intestine can lead to increased bioavailability of the substrate, while inhibition of P-gp in the kidney can reduce elimination. Inhibition of P-gp in the brain will lead to accumulation of the substrate within this tissue. Hence, prediction of the degree of MAK drug-drug interactions on a specific substrate is complex, when the distribution, metabolism and elimination pathways are regulated by multiple systems.

MAK can increase or decrease the bioavailability of drugs through an alteration in normal intestinal flora. Digoxin and digitoxin can be metabolized by *Eubacterium lentum* found in the gastrointestinal tract of certain individuals [60, 61]. Inhibition of *E. lentum* by erythromycin has been proposed as a mechanism leading to enhanced bioavailability of digoxin [61]. Conversely, macrolides can theoretically attenuate the activity of conjugated estrogens by reducing enterohepatic recirculation of these oral contraceptive agents [62]. However, this mechanism has not been substantiated, and systematic reviews have failed to confirm these historic findings [63]. Clarithromycin is active against Bacillus Calmette Guerin (BCG) and so can reduce the viability of this microorganism during intravesical instillation to treat bladder cancer [64]. Finally MAK have been shown to induce QTc prolongation and have the potential for a synergistic pharmacodynamic interaction with agents known to also prolong the QTc interval [65]. Multiple substrates that have the potential to increase the QTc interval are metabolized by CYP3A4 and transported by P-gp [66]. Use of verapamil with erythromycin serves as a prime example where this interaction has been associated with a five-fold higher risk for sudden death [4]. The following sections highlight the key known pharmacokinetic and pharmacodynamic interactions of MAK antimicrobials.

8.3.1 Pharmacokinetic Drug-Drug Interactions

8.3.1.1 Absorption Related Drug Interactions

The bioavailability of erythromycin, clarithromycin, and telithromycin are not known to be affected by the concomitant use of antacids [20, 22, 67]. In contrast, the mean C_{max} of azithromycin was reduced by 24%, while the AUC was not affected when coadministered with aluminum/magnesium containing antacids [68]. The bioequivalence of the extended-release microsphere 2 g suspension formulation of azithromycin was not affected by its coadministration with a single dose of antacid [69]. Despite the low likelihood of a clinically significant interaction, the coadministration of antacids and azithromycin is discouraged [23]. Spacing the administration of these agents by 2 h is likely to overcome this potential interaction.

Drug absorption through the intestinal barrier is regulated by transporters belonging to the two major families, namely Adenosine triphosphate (ATP)-binding cassette (ABC) drug transporters and the solute carrier (SLC) transporters [70]. Multiple aliases exist for these transporters, P-gp (MDR1), a primarily apical localized ABC transporter and OATP, a basolaterally expressed SLC transporter are both inhibited by macrolides. In addition, human MDR1 gene polymorphisms can influence the bioavailability and interaction potential of macrolides [71]. The bioavailability of digoxin (P-gp substrate) has been documented to increase with the concomitant use of clarithromycin [72]. Furthermore, a 15-year population-based nested case control study identified clarithromycin to have a four-fold higher associated risk for digoxin toxicity compared to either erythromycin or azithromycin [73]. The relative clinical

risk of telithromycin on this interaction pathway is comparable to clarithromycin and a clinically significant interaction has been documented [20, 74]. Telithromycin is a substrate for P-gp and multidrug resistance-associated protein 2 (MRP2) and so is likely to affect and be affected by compounds that alter the activity of these intestinal transporters [75].

In addition, certain OATP type transporters are specifically expressed in the liver (OATP1B1, OATP1B3). Inhibition of hepatic OATP can reduce first-pass uptake of xenobiotics and increase oral bioavailability. The IC_{50} for inhibition of OATP1B3-mediated uptake of pravastatin was determined to be 11, 32, and 34 μM for telithromycin, clarithromycin, and erythromycin, respectively [8]. Clarithromycin inhibits OATP1B1 and so has the ability to inhibit the hepatic uptake of HMG-CoA reductase inhibitors such as pitavastatin, pravastatin, and rosuvastatin, leading to an increase in the bioavailability of these agents [76]. Identification of these transport properties help explain the 200% increase in exposure of pravastatin with the macrolides even through pravastatin is not a substrate of CYP3A4 [77].

The prokinetic effects of intravenous erythromycin has not been shown to affect the absorption of sustained-release acetaminophen [78]. However, the potential adverse influence of prokinetic effects of MAK agents on the absorption of gastroretentive formulations used to deliver drugs to the upper gastric absorption window has not been investigated to date.

8.3.1.2 Distribution Related Drug Interactions

Other than the intestine and liver, P-gp is also expressed in various organs such as the brain, kidney, placenta, adrenal, testes, and retina [79–81]. Inhibition of P-gp in these target organs should reduce drug efflux leading to higher concentrations in these organs relative to normal. Erythromycin and clarithromycin have been shown to increase nimodipine brain concentrations in the rat to an extent similar to the potent P-gp inhibitor, cyclosporine [81, 82]. Similarly, the brain-to-plasma concentrations of quinine were demonstrated to be approximately 2-fold higher when used concomitantly with erythromycin in mice [83]. *In vitro* data suggest that all MAK inhibit P-gp-mediated digoxin transport in Caco-2 cells with an IC_{50} value of 1.8, 4.1, 21.8, and 22.7 μg/mL for telithromycin, clarithromycin, azithromycin, and erythromycin, respectively [84]. Although data are presently lacking, the potential for increased exposure of drugs that are substrates of P-gp are likely to increase in typically restricted distribution compartments (brain, eyes, testes) when MAK agents are co-administered.

Data on altered distribution due to plasma-protein binding displacement with the use of MAK agents is limited. Recent data suggest that this mechanism of interaction is possible with erythromycin when used concomitantly with quinine, which is 90% bound in plasma, primarily to α_1-acid glycoprotein. Orlando and colleagues studied the effects of erythromycin on the disposition of quinine in 10 healthy volunteers, and 20 patients with mild or severe liver dysfunction [85]. The unbound fraction of quinine was significantly higher in patients with severe liver dysfunction

compared to healthy and mild liver dysfunction subjects. In addition, the mean [95% CI] ratio of the unbound fraction of quinine in patients with severe liver dysfunction who received erythromycin was 1.76 [1.42, 2.11]. In comparison the mean [95% CI] ratio of the unbound fraction of quinine in healthy volunteers who received erythromycin was 1.41 [1.28, 1.55] [85]. Taken together, data on the effects of MAK agents on distribution mediated interactions are limited and requires further study. However, the contribution of altered distribution may explain tissue specific toxicities when drugs with narrow therapeutic indices are used with MAK agents.

8.3.1.3 Metabolism Related Drug Interactions

Erythromycin is a moderate inhibitor of CYP3A, while clarithromycin and telithromycin are strong inhibitors of this isoenzyme [14, 86, 87]. Strong inhibitors are generally classified as agents that have the ability to raise substrate AUC values at least 5 fold, while moderate inhibitors have the potential of raising AUC values by 2 to less than 5 fold [86]. Azithromycin in contrast is a very weak inhibitor of CYP3A. Hisaka and colleagues have put forth a pharmacokinetic interaction significance classification system in order to attach clinical significance for data generated through *in vitro* and *in vivo* experiments [87]. The CYP3A4 Inhibition ratio (IR_{CYP3A4}) of mechanism based inhibitors were calculated as a function of degeneration constant, inactivation rate constants, and inactivator potency. This analysis also included estimation of the impact of metabolites known to inhibit CYP3A4. Using this function a value that approaches 0 represents a very weak to non-inhibitor of CYP3A4, while values approaching 1.0 represent a very strong-inhibitor of CYP3A4.

The IR_{CYP3A4} values estimated for azithromycin, erythromycin, clarithromycin, and telithromycin were 0.11, 0.82, 0.88, and 0.91 respectively. For reference, the azole antifungal agents; ketoconazole, voriconazole, itraconazole, and fluconazole have IR_{CYP3A4} values of 1.0, 0.98, 0.95, and 0.79, respectively [87]. Evaluation of the CYP3A4 drug interaction potential in healthy volunteers often includes use of ketoconazole or itraconazole [86]. Hence, comparison of the relative inhibition potential of CYP3A4 by these agents is very important for potential dose modification of substrates are that used concomitantly with MAK. In addition, the interaction potential of clarithromycin and telithromycin are expected to be equivalent and/or higher than that of erythromycin. Azithromycin is expected to not lead to any clinically significant CYP3A4-mediated interactions [87]. In addition, to inhibition of CYP3A4, macrolides have also demonstrated significant drug interactions with substrates of CYP2C9 and CYP2C19. As a result, the interaction of key drug classes with MAK agents where documented serious adverse events have occurred are listed in Table 8.2 and detailed as follows. Please note that a detailed summary of the interaction potential of all approved drugs that are metabolized by the CYP system and have the potential to interact with MAK agents is not feasible in this review. The following sections serve as relevant examples of the spectrum and extent of metabolism related drug interactions secondary to MAK agents.

Table 8.2 Pharmacokinetic alterations of key drugs when combined with the macrolides and ketolides

Drugs	Erythromycin	Clarithromycin	Telithromycin	References
Antidiabetic				
Glyburide	↑ 18% C_{max}	↑ 18% C_{max}[a]	↑ 18% C_{max}[a]	[88–91]
Glibencamide	↑ 25% C_{max}[a]	↑ 25% C_{max}	↑ 25% C_{max}[a]	[88–91]
Repaglinide	↑ 40% AUC[a]	↑ 40% AUC	↑ 40% AUC[a]	[92, 93]
Saxagliptin	↑ 100%[a] AUC	↑ 250%[a] AUC	↑ 250%[a] AUC	[94]
Antimigraine				
Dihydroergocryptine	↑ 1,650% AUC	↑ 1,650% AUC[a]	↑ 1,650% AUC[a]	[95–102]
Eletriptan	↑ 400% AUC	↑ 600% AUC[a]	↑ 600% AUC[a]	[103]
Benzodiazepines				
Alprazolam	↑ 60% AUC	↑ 100% AUC	↑ 100% AUC	[87, 104]
Midazolam	↑ 400% AUC	↑ 200–800% AUC	↑ 200–800% AUC	[105–110]
Triazolam	↑ 52% AUC	↑ 100% AUC[a]	↑ 100% AUC[a]	[87, 111]
Immunosuppressants				
Cyclosporine	↑ 100% AUC	↑ 200% AUC[a]	↑ 200% AUC[a]	[112–116]
Everolimus	↑440% AUC	↑1,500% AUC[a]	↑1,500% AUC[a]	[117, 118]
HMG-CoA inhibitors				
Atorvastatin	↑ 32.5% AUC	↑ 82% AUC	↑ 82% AUC[a]	[119, 120]
Lovastatin	↑ 390% AUC[a]	↑ 1,000% AUC[a]	↑ 890% AUC[a]	[20, 77, 87, 121]
Simvastatin	↑ 390% AUC	↑ 1,000% AUC	↑ 890% AUC	[20, 77, 121]
Pitavastatin	↑ 280% AUC	↑ 280–460% AUC[a]	↑ 280–460% AUC[a]	[122]
Pravastatin	↑ 100% AUC[a]	↑ 200% AUC	↑ 200% AUC[a]	[77]
PDE5 inhibitors				
Sildenafil	↑ 182% AUC	↑ 230% AUC	↑ 230% AUC[a]	[123, 124]
Tadalafil	↑ 107% AUC	↑ 107–312% AUC[a]	↑ 107–312% AUC[a]	[125]
Vardenafil	↑ 400% AUC	↑ 1,000% AUC[a]	↑ 1,000% AUC[a]	[126]

[a]Change in area under the curve (AUC) estimated based on data available for an alternate CYP inhibitor with a comparable degree of inhibition [86, 87]

Antidiabetic Medications

There are currently six classes of oral agents that are approved for the treatment of patients with type 2 diabetes. These include the α-glucosidase inhibitors, biguanides, dipeptidyl peptidase 4 (DPP4) inhibitors, meglitinides, sulfonylureas, and thiazolidinediones [127]. The primary metabolic pathway for metabolism of the sulfonylureas and thiazolidinediones is via the CYP2C system. The pharmacokinetics of glyburide (sulfonylurea) was evaluated to be marginally altered in combination with erythromycin. The C_{max} of glyburide was demonstrated to increase by 18%, with an associated reduction in the T_{max} from 4.9 to 3.0 h. These results are thought to be a result of enhanced gastric motility by erythromycin, which increased the rate but not extent of glyburide absorption [88]. The AUC of glyburide, a substrate of CYP2C9 was increased by a mean [90% CI] of 25% [12%, 50%] when combined with clarithromycin [88].

Despite this mild pharmacokinetic interaction, reports of severe and potentially life threatening hypoglycemia have been documented with use of clarithromycin and sulfonylureas [89, 90]. Schelleman and colleagues recently performed two case-crossover studies using US Medicaid data to evaluate if the use of oral antimicrobials increases the risk of severe hypoglycemia [91]. An association between sulfonylurea induced hypoglycemia and the use of fluconazole, ciprofloxacin, levofloxacin, azithromycin, clarithromycin, erythromycin, trimethoprim/sulfamethoxazole, or cephalexin was measured. Interestingly the odds ratio [95% CI] for glyburide-induced hypoglycemia and concomitant use of an antimicrobial was 2.66 [2.02, 3.49]-cephalexin, 2.65 [1.87, 3.76]-azithromycin, 3.60 [2.35, 5.50]-erythromycin, and 13.28 [10.26, 17.18]-clarithromycin [91]. Similarly the odds ratio for glipizide-induced hypoglycemia was at least 2.5-fold higher with the use of clarithromycin versus azithromycin [91]. These data suggest that although MAK agents are theoretically not likely to interact with sulfonylureas, an interaction does exist and this interaction is likely to be exacerbated in patients with acute infections. A mechanistic explanation for this finding does not presently exist, however, the higher propensity for interaction with clarithromycin suggests that a metabolism mediated mechanism of interaction plays a role [91].

A double-blind crossover study demonstrated a 40% increase in the exposure of repaglinide when coadministered with clarithromycin [92]. Clarithromycin was also demonstrated to increase the plasma exposure of insulin without a corresponding decline in blood glucose concentrations [92]. However, severe hypoglycemia has been reported with the concomitant use of repaglinide in a patient with type 2 diabetes who was initiated on clarithromycin to treat *Helicobacter pylori* infection [93]. *In vitro* studies suggest that the potential interaction of nateglinide and clarithromycin to be unlikely, given that CYP3A4 is not a primary metabolic pathway for this meglitinide [128].

Pioglitazone and rosiglitazone are currently the two thiazolidinediones that are used in patients with type 2 diabetes and have a low propensity to cause hypoglycemia unless used in combination with other antidiabetic agents [129]. Rosiglitazone is metabolized by CYP2C8 and CYP2C9, while pioglitazone is metabolized by CYP2C8 and CYP3A4 [130, 131]. Use of pioglitazone with ketoconazole has been associated with a 34% increase in the AUC of pioglitazone, hence the interaction potential of pioglitazone with MK agents is likely to be low [131]. In contrast, the exposure of saxagliptin (DPP4 inhibitor) a CYP3A4 substrate, increased by 250% when coadministered with ketoconazole [94]. Sitagliptin is not metabolized significantly by CYP3A4 [132]. Although no cases of hypoglycemia have been reported with use of saxagliptin and CYP3A4 inhibitors, the product label recommends that the daily dosage of saxagliptin be limited to 2.5 mg once daily when used with agents like clarithromycin and telithromycin [94]. Overall, patients with diabetes receiving treatment with an oral antidiabetic agent should be counseled on the signs and symptoms of hypoglycemia, such as headache, dizziness, drowsiness, nervousness, tremor, weakness, perspiration and palpitations when initiated on agents like clarithromycin or telithromycin. This is especially important given recent epidemiologic evidence that suggests a risk of interaction between clarithromycin and oral sulfonylureas despite a low predicted potential for a CYP mediated interaction [91].

Antimigraine Medications

The ergopeptide alkaloids and the triptans represent the two major drug classes that are used to treat migraine attacks [133]. Although ergotamine has been used to treat migraines for nearly a century, the pharmacokinetic profile and potency of this agent has not been well characterized [134]. Dihydroergotamine, a synthetic derivative is better characterized and like ergotamine is metabolized by CYP3A4 [135]. The oral bioavailability of both ergotamine and dihydroergotamine is <1% [134]. Despite this low intrinsic oral bioavailability, severe adverse events have been reported with the use of ergopeptides in combination with erythromycin and clarithromycin. Acute limb ischemia, necrosis and gangrene have been reported with the combined use of ergotamine and macrolides [95–101]. Evaluation of the interaction potential of alpha-dihydroergocryptine and erythromycin suggests that there is a mean [95% CI] of 1,650% [870%, 3,150%] increase in the AUC of this ergoline [102]. As a result, the use of erythromycin and clarithromycin is contraindicated with ergoline derivatives such as bromocriptine and cabergoline. The product labels for telithromycin and azithromycin do not specifically contraindicate their use with ergopeptide alkaloids [20, 23]. However, the clinical evidence coupled with knowledge of the potent inhibition of CYP3A4 by telithromycin suggest that the same risk exists with this agent [86, 87].

In contrast to the ergopeptide alkaloids, not all of the triptans are solely metabolized by CYP3A4. The currently available triptans include; sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, and avitriptan [133, 136]. Most of the triptans are metabolized by monoamine oxidase A or alternatively by CYP1A2 [133, 136]. Almotriptan is metabolized by CYP3A4 and CYP1A2 and its exposure has demonstrated to increase by 57% when used with the potent CYP3A4 inhibitor, ketoconazole [137]. The exception to the group when considering drug interaction potential with MAK agents is eletriptan, which is principally transported by P-gp and metabolized by CYP3A4 [138]. The exposure of eletriptan was demonstrated to increase by 400% when coadministered with erythromycin and 600% when coadministered with ketoconazole [103]. Hence, the interaction between clarithromycin or telithromycin with eletriptan is expected to be significant. The current eletriptan product recommends avoiding its concomitant use within 72 h of use of CYP3A4 inhibitors such as clarithromycin [103]. This is especially important in patients with known ischemic heart disease, cerebrovascular disease, and peripheral vascular disease, which are common comorbidities where the use of eletriptan is contraindicated [103, 139].

Benzodiazepines

The interaction potential of alprazolam, triazolam, and midazalam have been studied with the concomitant use of erythromycin. Erythromycin was demonstrated to increase the AUC of single-dose oral alprazolam by approximately 60% but was not demonstrated to alter psychomotor function as assessed by the Digit Symbol Substitution Test [104]. In contrast, the clearance of triazolam was demonstrated to

be reduced by 52% with the concomitant use of erythromycin and was associated with psychomotor dysfunction and amnesia [111]. Loss of consciousness in an 8 year old child has been reported with the concomitant use of midazolam and erythromycin [105]. Olkkola et al., evaluated the interaction of erythromycin and midazolam, a well recognized selective CYP3A4 substrate in two double-blind studies using oral and intravenous midazolam [106]. The exposure of oral midazolam increased by 400%, while that of intravenous midazolam increased by 54% [106]. The dual inhibition of both intestinal and hepatic CYP3A4 is assumed to contribute to the enhanced oral bioavailability of midazolam with this interaction [106].

Azithromycin has not demonstrated a significant interaction with midazolam [140]. In contrast, the potent inhibitors, clarithromycin and telithromycin, are expected to increase the exposure of midazolam by 200–800% with expected psychomotor adverse events [107–110]. This potential interaction is especially important in elderly patients and those sensitive to the effects of benzodiazepines. Although a reduction in the dose of the benzodiazepine is recommended, coadministration of midazolam with clarithromycin, telithromycin, or erythromycin is not advisable. Use of an alternate comparable antibiotic or azithromycin may be advisable in cases where concomitant use of these benzodiazepines are necessary. Alternatively, use of sedative hypnotics such as zolpidem, zopiclone and zaleplon have a lower potential for interaction with agents like clarithromycin [141, 142].

Calcineurin Inhibitors and Proliferation Signal Inhibitors

Calcineurin inhibitors (cyclosporine and tacrolimus) and proliferation signal inhibitors (sirolimus and everolimus) are commonly used immunosuppressive agents with a high potential for drug interactions [143]. This is especially true given patients on these immunosuppressive agents are often at an increased risk for pulmonary infection that can be treated with the use of a MAK agent [144]. Increased exposure of agents such as cyclosporine and tacrolimus can induce nephrotoxicity, which is of major concern in renal transplant recipients on this agent [145]. The increased exposure of cyclosporine when combined with erythromycin is likely to be a function of both increased oral bioavailability and reduced CYP3A metabolism [146, 147]. The exposure of cyclosporine can increase by 100–500% when combined with erythromycin [112, 113]. This combination has also been demonstrated to exacerbate the nephrotoxic potential of cyclosporine, which mandates cyclosporine dosage reduction and therapeutic drug monitoring when used with MAK agents [114]. Initial dosage reductions of at least 33% may be necessary when combined with clarithromycin and by inference, telithromycin [115, 116]. A possible interaction between azithromycin and cyclosporine has been documented in the literature [148]. However, the degree of interaction is likely to be minimal (7% increase in AUC) when azithromycin is combined with cyclosporine [149, 150]. Similarly, a major interaction has been documented with the combination of tacrolimus and erythromycin or clarithromycin [151, 152]. Again, an interaction has been documented with azithromycin and tacrolimus, but the impact of this interaction is expected to also be low [153].

When considering the proliferation signal inhibitors, a comparable degree of interaction has been noted with the MAK agents. The pharmacokinetics of everolimus was evaluated in a two-period, single-sequence crossover study among 16 healthy volunteers. The mean [90% CI] AUC of everolimus increased by 440% [350%, 540%] with a non-significant alteration of erythromycin concentrations [117]. Population pharmacokinetics of everolimus in renal transplant patients has also demonstrated that erythromycin reduces the clearance of everolimus by 19% [154]. This analysis suggested an unlikely interaction of everolimus with azithromycin, which may be a misclassification of azithromycin as part of the "erythromycins" [154]. Use of itraconazole was associated with a 74% decrease in everolimus clearance, which may be reflective of the potential impact of coadministration of either clarithromycin or telithromycin with everolimus [154]. Use of reduced doses of everolimus is recommended when used with erythromycin, and its concomitant use with either clarithromycin or telithromycin is not recommended [118]. Similarly, sirolimus should not be used concomitantly with strong CYP3A4 inhibitors. The combined use of sirolimus and clarithromycin has been associated with an eight fold increase in the blood trough concentration of sirolimus and acute nephrotoxicity [155].

Hydroxymethylglutaryl Coenzyme A (HMG-CoA) Reductase Inhibitors

The currently marketed HMG-CoA reductase inhibitors include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin [156, 157]. The HMG-CoA reductase inhibitors are commonly prescribed agents. Simvastatin and atorvastatin accounted for over 100 million prescriptions in the US in the year 2008 [158]. When considering these agents, atorvastatin, lovastatin, and simvastatin are primarily metabolized by CYP3A4 [157]. Fluvastatin is primarily metabolized by CYP2C9 and rosuvastatin is primarily metabolized by CYP2C9 and CYP2C19 [157]. Pravastatin is not a substrate of CYP and instead is primarily metabolized by sulfation pathways and undergoes elimination via the kidney [157]. Pitavastatin is metabolized by CYP2C8 and CYP2C9 and forms a lactone metabolite via uridine5′-diphosphate (UDP) glucuronosyltransferase (UGT; UGT1A3 and UGT2B7) [122]. Despite the lack of CYP3A4 metabolism for select HMG-CoA, all marketed statins are likely substrates of OATP and are expected to interact with MAK agents to varying degrees with a corresponding risk for myopathy, rhabdomyolysis, and death [157]. In addition, multidrug resistance-associated protein (MRP) is now known to be highly expressed in skeletal muscle and contributes to reduced intracellular accumulation of agents like atorvastatin and rosuvastatin [122]. To date, the MAK agents have not been shown to inhibit MRP1 but a potential synergistic adverse interaction exists if HMG-CoA inhibitors are used with MAK agents and an MRP1 inhibitor, such as probenecid or ritonavir [159].

The incidence of myopathy and rhabdomyolysis is estimated to be 5 and 1.6/100,000 person-years from randomized clinical trials and cohort studies and up to 13.5/million statin prescriptions [160, 161]. An estimated 60% of cases of

statin-related rhabdomyolysis are thought to be a result of drug interactions [162]. Simvastatin doses of 80 mg/day have been associated with a higher risk of rhabdomyolysis compared to standard doses of fluvastatin and pravastatin [162]. Fluvastatin appears to have the lowest risk of muscular adverse events but is also the weakest inhibitor of HMG-CoA [162].

The pharmacokinetic drug interaction potential of atorvastatin has been studied against erythromycin, clarithromycin and azithromycin [119, 120]. The AUC of atorvastatin increased by 0.72%, 32.5%, and 82% when coadministered with azithromycin, erythromycin, and clarithromycin, respectively [119, 120]. A substantial pharmacokinetic interaction exists between clarithromycin and erythromycin when combined with simvastatin. A 390% and 1,000% increase in the $AUC_{0\text{-}24}$ of simvastatin is expected with the concomitant use of erythromycin or clarithromycin, respectively [77, 121]. A comparable degree of interaction between simvastatin and telithromycin has been documented [20]. The interaction potential between azithromycin and simvastatin is expected be low [87]. However, data from the World Health Organization Adverse Drug Reaction database suggest an association (albeit rare) with azithromycin-HMG-CoA reductase inhibitor use and rhabdomyolysis [163].

The plasma exposure of rosuvastatin has been demonstrated to be unaltered when combined with erythromycin [164]. Similarly, fluvastatin is unlikely to have a pharmacokinetic interaction when used with MAK agents. In contrast, the most recently marketed HMG Co-A reductase inhibitor, pitavastatin, is regarded to not be a substrate of CYP and so has a low potential for drug interactions [122, 156]. However, the combined use of erythromycin and pitavastatin was associated with a 280% increase in the AUC of pitavastatin [122]. Use of the UGT inhibitor, atazanavir, was associated with only a 31% increase in pitavastatin concentrations [122]. Use of itraconazole, was associated with a 23% decrease in pitavastatin concentrations, while cyclosporine increased pitavastatin exposure by 460% [122]. Erythromycin is not known to be an inhibitor of UGT1A3 and UGT2B7 [165]. Recent data suggest that erythromycin, clarithromycin and telithromycin inhibit OATP1B1 and OAT1B3 in the liver and contribute to the uptake of pravastatin [8]. Cyclosporine is a known inhibitor of this pathway [86] and so this transporter mediated interaction is expected to be the mechanistic pathway that explains the enhanced plasma exposure of pitavastatin when combined with erythromycin.

These data suggest that macrolides interact with HMG-CoA reductase inhibitors via both metabolic and transporter mediated interactions. The marked elevation of simvastatin exposures is a testament to this point [77]. These agents are commonly used chronically in populations over the age of 50 years, and so the potential for polypharmaceutical combination is great. Hence, MK should be avoided in patients receiving simvastatin. A 50–80% reduction in the dose of other HMG-CoA inhibitors may be necessary when used with MK agents. Most importantly, patients who must receive these agents concurrently should be warned to contact their healthcare provider immediately if they experience muscle pain, tenderness or weakness [160–162].

Phosphodiesterase 5 (PDE5) Inhibitors

Sildenafil, tadalafil and vardenafil are approved clinically to treat erectile dysfunction and are increasingly used for non-urological conditions [123, 125, 126, 166]. The PDE5 inhibitors are also increasingly being used to treat idiopathic pulmonary arterial hypertension [166]. Sildenafil is recognized to be a very selective substrate of CYP3A4 like buspirone, simvastatin, and midazolam [167]. Hence, the combined use of sildenafil with erythromycin would be expected to result in elevated concentrations of sildenafil. The AUC of sildenafil was documented to increase by 182–280% when administered with erythromycin [123, 168]. The AUC of sildenafil has also been documented to increase by 230% when combined with clarithromycin and so this level of interaction is also expected with the use of telithromycin [124]. [22, 36, 169, 170] Azithromycin does not affect the pharmacokinetics of sildenafil [168]. Use of a lower starting dose of sildenafil (25 mg) should be considered if its concomitant use with MK agents cannot be avoided [123, 168]. Similarly tadalafil exposures are expected to increase with the concomitant use of CYP3A4 inhibitors. However, single doses of up to 500 mg and multiple doses of 100 mg of tadalafil have been evaluated in subjects and is well above the recommended starting dose of 2.5 mg [125]. Despite this potential lower risk, the product label does not recommend that doses exceed 2.5 mg when combined with potent CYP3A4 inhibitors like the MK agents [125]. A similar dosing recommendation is provided for vardenafil in patients receiving treatment for erectile dysfunction [126].

Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors

The protease inhibitors are a pivotal group of antiretrovirals that provide the necessary decreases in the viral load in patients infected with HIV [171]. Like MK agents, this class of agents are significant inhibitors of both CYP3A4 and P-gp. Within this class, ritonavir is specifically recognized to be the most potent inhibitor of CYP3A4 and P-gp, which supports its use to 'boost' the exposure of coadministered protease inhibitors [171]. Seven boosted protease inhibitors (with ritonavir) are currently licensed in the US and Europe and include; indinavir, saquinavir, lopinavir, fosamprenavir, atazanavir, tripanavir, and darunavir [171]. Clarithromycin is often used in patients with HIV for prophylaxis and treatment of opportunistic infections [24]. As a result, the combinations of two or more classes of agents with major drug interaction potential are likely in patients with HIV. Development of drug-induced rhabdomyolysis in a 34 year old HIV-infected patient receiving atorvastatin, clarithromycin, and lopinavir/ritonavir is an illustration of the potential complications that can occur due to a combined drug-interaction [172].

The pharmacokinetics of clarithromycin have been evaluated in combination with indinavir, ritonavir, saquinavir, lopinavir/ritonavir, amprenavir, atazanavir, darunavir, and tripanavir [173–181]. The exposure of clarithromycin has been demonstrated to increase by 45%, 53%, and 77% when combined with saquinavir, indinavir and ritonavir, respectively [173–176]. A lower degree of interaction

has been reported or is expected with agents boosted with ritonavir [182]. As an example, the use of tripanavir/ritonavir in combination with clarithromycin as an example was associated with a mean [90% CI] of 19% [4%, 37%] increase in the AUC of clarithromycin [182]. The AUC of the 14-hydroxy metabolite of clarithromycin was reduced by 97% when used with tripanavir/ritonavir [182]. In addition, the use of clarithromycin increased the AUC of tripanavir by 66% [182]. The AUC of saquinavir has been demonstrated to increase by 177% when used in combination with clarithromycin [176]. Given the low intrinsic bioavailability of most protease inhibitors, a dose reduction of protease inhibitors is not necessary when used with clarithromycin [173–182]. Clarithromycin exposures increase in patients' with reduced kidney function, hence, dose alteration of clarithromycin for this interaction has been stratified by the patients estimated creatinine clearance. A 50% and 75% reduction in the dose of clarithromycin is recommended in patients with a creatinine clearance of 30–60 mL/min and <30 mL/min, respectively, when used in combination with a protease inhibitor [173–181]. The current product labels do not specifically provide recommendations on dose alterations of erythromycin or telithromycin. However, the use of agents like ritonavir are expected to also yield elevated concentrations of erythromycin and telithromycin to a degree that is comparable to that noted with clarithromycin, which may cause QTc prolongation.

In contrast to the protease inhibitors, the non-nucleoside reverse transcriptase inhibitors (NNRTI) can induce CYP3A4 and reduce the exposure of clarithromycin. Efavirenz and nevirapine decrease the AUC of clarithromycin by 39% and 31%, respectively [183, 184]. A comparable decrease in the AUC of 14-hydroxy clarithromycin occurs with this combination. In addition, 46% of healthy volunteers exposed to the combination of efavirenz and clarithromycin developed a rash [183]. An explanation of this increased risk for an adverse event has not been elucidated. Regardless, the use of an alternate agent such as azithromycin is recommended in patients receiving treatment with a NNRTI [183, 184].

Proton Pump Inhibitors

The proton pump inhibitors (PPIs) are potent inhibitors of gastric acid secretion. This class is used extensively to treat gastrointestinal reflux disease, peptic and duodenal ulcer disease and in combination with macrolides to treat *H. pylori* as a causative factor of gastrointestinal ulcers. The current US FDA approved PPIs include omeprazole, lansoprazole, rabeprazole, pantoprazole. In addition, the *S*-enantiomer of omeprazole (esomeprazole) and *R*-enantiomer of lansoprazole (dexlansoprazole) are approved for use by the US FDA. All PPIs undergo metabolism by CYP2C19 and to a lesser extent by CYP3A4 [185]. An exception to this rule has been demonstrated with esomeprazole, which is primarily metabolized by CYP3A4 [185].

The coadministration of clarithromycin and esomeprazole was associated with a 70–129% increase in the plasma AUC of esomeprazole without an alteration in clarithromycin exposure [186]. An 89% increase in the plasma AUC of omeprazole

and 55–80% increase in the plasma AUC of lansoprazole has been documented with the coadministration of clarithromycin [187]. In contrast, clarithromycin does not interact with rabeprazole or pantoprazole to a significant degree [188, 189]. The interaction profile of PPIs as documented with clarithromycin is likely to be comparable to that with erythromycin and telithromycin. Regardless, the documented degree of interaction has not been demonstrated to yield an increased risk of adverse events. On the contrary, the concurrent use of these PPIs and MAK agents without dose alteration may be more beneficial when used to eradicate *H. pylori* [185].

Rifamycins

The drug interaction potential of the rifamycin class of antimicrobials are reviewed extensively in previous chapter on Drugs for Tuberculosis. The rifamycins, rifampin and rifabutin are known inducers of multiple CYP isoenzymes and have been documented to have bidirectional interactions with clarithromycin. A phase 1 study was designed to evaluate the safety and pharmacokinetics of rifabutin alone and in combination with either azithromycin or clarithromycin over 14 days. This study was terminated on day 10 due to development of neutropenia in 14 of 30 subjects, which included 2 subjects on rifabutin alone and all 12 subjects who received the combination of rifabutin with either clarithromycin or azithromycin [190]. In patients with HIV, the coadministration of rifabutin and clarithromycin was associated with a 44% decrease in the AUC of clarithromycin and 99% increase in the AUC of rifabutin. However, 14-hydroxy-clarithromycin and 25-*O*-desacetyl-rifabutin was documented to have increased by 57% and 375%, respectively [191]. A key adverse event observed with the coadministration of clarithromycin and rifabutin is uveitis, or inflammation of the inner eye. The risk of developing uveitis is dose-dependent, such that the risk of uveitis was reduced from 43% to 13% with the use of 300 mg/day instead of 600 mg/day of rifabutin [192]. The induction of CYP is known to occur to a greater extent with the use of rifampin compared to rifabutin. An 80–90% reduction in the AUC of clarithromycin and telithromycin have been documented with the use of rifampin [20, 191]. Hence the concurrent use of rifampin with clarithromycin or telithromycin should be avoided. In addition, the nonconcomitant use of rifabutin with MAK agents should include frequent evaluation of white cell counts. Finally, patients with symptoms consistent with uveitis such as blurred vision, photophobia, dark floating spots, redness of the eye and pain should be referred for further evaluation by an ophthalmologist.

Miscellaneous Agents

Buspirone is a generically available anxiolytic agent that is known to be a selective substrate of CYP3A4 [167]. The plasma AUC of buspirone increased by 600% with the coadministration of this agent with erythromycin [193]. This marked pharmacokinetic interaction was also associated with drowsiness and altered

psychomotor performance as documented by a digital symbol substitution test [193]. A greater than 50% reduction in the dose of buspirone is likely to be necessary if used concomitant with erythromycin, clarithromycin or telithromycin. In contrast to buspirone, the anticonvulsant/mood stabilizing agent carbamazepine has been documented to have numerous adverse events when coadministered with erythromycin or clarithromycin despite a limited (20–50% increase in the AUC) pharmacokinetic interaction in phase 1 studies [3, 194, 195]. The dose of carbamazepine should be reduced by at least 50% when coadministered with erythromycin or clarithromycin [3]. Similarly, data in healthy volunteers documents no pharmacokinetic interaction of the antipsychotic agent clozapine (CYP1A2 substrate) with erythromycin [196]. However, seizures, drowsiness and neutropenia have been documented in case-reports of the combination of erythromycin and clozapine [196–199]. Finally numerous isolated case-reports exist that link a potential interaction between the CYP1A2 substrate, theophylline and macrolides, however, pharmacokinetic studies in healthy volunteers have failed to document a significant interaction [3, 200]. Given that acute respiratory infections may be associated with cytokine-mediated alterations in drug transport and metabolism, the effects observed with CYP1A2 substrates and MK agents may not be simply a consequence of CYP inhibition by MK [201]. Hence, it is theoretically possible that additional metabolism related interactions exist with MAK agents that may be potentiated by cytokine-mediated interactions on drug metabolism and transport.

8.3.1.4 Elimination Related Interactions

MAK agents have the ability to reduce the elimination of drugs primarily through inhibition of P-gp in the biliary tract and renal tubular system. Given that substrates of P-gp and are also likely to be substrates of CYP3A4 [6], the interaction potential of such substrates can be serious. Key examples of serious drug interactions with substrates of P-gp and MAK agents include; colchicine, digoxin, and the vinca alkaloids [86]. Colchicine has been in clinical use for over two centuries and has seen a resurgence in its use since receiving US FDA approval in August 2009 to treat acute flares of gout and familial Mediterranean fever [202]. Clarithromycin increases the mean [min, max] AUC of colchicine by 281.5% [88.7%, 851.6%] and its use is contraindicated with colchicines [202]. Although not explicitly stated in the product label, use of erythromycin or telithromycin should be avoided with colchicine given the risk for life threatening and fatal toxic reactions [203]. Rhabdomyolysis, neuromyopathy, acute kidney injury, agranulocytosis, fever, diarrhea, convulsions, alopecia, and death are potential complications that can occur with the coadministration of colchicine with MAK agents [204–208]. The degree of interaction is further exacerbated in patients with chronic kidney disease [209, 210].

Digoxin is a key substrate of P-gp that undergoes minimal metabolism and interacts to a greater degree with clarithromycin than other MAK agents [86]. The inhibition of *E. lentum* by MAK agents [60, 61] is also expected to enhance the systemic

exposure of digoxin but the primary driver of this interaction is most likely P-gp mediated. In a large population based study conducted in Taiwan, the risk for hospitalization secondary to digoxin intoxication increased by 5.07 (95% CI 2.36, 10.89) fold if clarithromycin was used within 14 days of the index day [211]. Gomes and colleagues completed a 15 year population-based, case-control study and demonstrated an increased risk for hospitalization secondary to digoxin toxication with erythromycin, clarithromycin, and azithromycin [73]. The odds ratio [95% CI] for digoxin toxicity related hospitalization was 3.7 [1.7, 7.9], 3.7 [1.1, 12.5], and 14.8 [7.9, 27.9] with the recent exposure to erythromycin, azithromycin, and clarithromycin, respectively. The relative degree of interaction of MAK agents with P-gp has been well described *in vitro* and is predictive of these documented clinical events [84]. Hence, telithromycin is expected to have a P-gp mediated interaction potential that is greater than or equal to that of clarithromycin, while azithromycin is expected to have a P-gp mediated interaction potential that is equal or greater than that of erythromycin [20, 73, 84]. Enhanced exposure of melagatran, the active form of the prodrug thrombin inhibitor ximelagatran by azithromycin serves as further evidence that although azithromycin does not inhibit CYP3A4, it is an inhibitor of P-gp [212].

The vinca alkaloids such as vinblastine, vincristine, vinorelbine, and vindesine are substrates of both P-gp and CYP3A [213–215]. Severe adverse events have been observed with the combination of vinblastine and erythromycin when used in combination with cyclosporine [216]. The incidence of vinorelbine-associated grade 4 neutropenia was reported in 31.6% of patients treated with clarithromycin versus 2.5% of patients not treated with this agent [213]. Numerous reports of neurotoxicity are available in the literature documenting the risk of using a vinca alkaloid with the combined P-gp/CYP3A4 inhibitor itraconazole [217]. These data suggest that the use of clarithromycin or telithromycin should be avoided in patients receiving treatment with vinca alkaloids.

8.3.2 Pharmacodynamic

8.3.2.1 Torsades De Pointes

The primary pharmacodynamic interaction of concern is the synergistic potentiation of the QTc interval and development of cardiac dysrhythmias such as torsades de pointes (TdP). Intravenous erythromycin infusion was demonstrated to increase the QTc interval in seven critically ill patients, with the extent of QTc prolongation dependent on the rapidity of infusion. Three patients developed ventricular fibrillation and one patient died [218]. Oberg and Bauman retrospectively evaluated the effect of erythromycin lactobionate infusion on changes in the QTc interval. Data from 49 patients in this study revealed a change in the QTc interval from 432 ± 39 to 483 ± 62 ms at baseline compared to during erythromycin therapy respectively [219]. Only one patient developed TdP in this evaluation but brought the potential risk of intravenous erythromycin and QTc prolongation to the forefront.

Ray and colleagues extended our knowledge of the risk of oral erythromycin and sudden death from cardiac causes through a population-based study of 1,249,943 person years of data through a Tennessee Medicaid cohort [4]. The incidence-rate ratio [95% CI] for sudden death with the current use of erythromycin was 2.01 [1.08–3.75] and increased to 5.35 [1.72–16.64] with the use of a CYP3A inhibitor such as the calcium channel blocker, verapamil [4]. Although this study was not designed to evaluate the mechanistic basis for this interaction, the data suggest the necessity for caution when using macrolides with CYP3A inhibitors, especially when both agents carry the risk for dysrhythmias.

The primary mechanism for drug induced QTc prolongation includes inhibition of the rapid component of the delayed rectifier potassium current through a potassium channel that is regulated by the human ether-a-go-go-related gene (HERG). Volberg and colleagues have demonstrated that macrolides inhibit HERG, and that in the case of clarithromycin, the level of inhibition was voltage and time-dependent [220]. The ratio of IC_{50} to the serum C_{max} value (IC_{50}/C_{max}) has been used as a surrogate marker for the potential clinical risk for an agent known to inhibit HERG. The inhibition of HERG by agents withdrawn from the market such as terfenadine, astemizole, and cisapride occurs at the nanomolar concentration range with IC_{50}/C_{max} values of 0.075–5.2. Lin and colleagues evaluated 20 drugs known to induce QTc prolongation in order to identify cutoff values that could predict a higher risk of torsades de pointes [221]. Although IC_{50}/C_{max} cutoff values predictive of TdP have not been identified, values of 9.1, 12.8, and 17.5 were documented for clarithromycin, telithromycin, and erythromycin, respectively [221]. Higher IC_{50}/C_{max} values are expected with azithromycin but despite this lower risk for QTc prolongation, reports of TdP have been recorded in the literature with this agent [222, 223]. Increasing age, female sex, concomitant illness, and use of concomitant agents that prolong the QTc interval have been associated with an increased risk of TdP when using macrolides [224]. Table 8.3 includes a current list of agents that are contraindicated with the use of MAK agents based on a review of regulatory approved product labels.

As tabulated, azithromycin has no contraindications [23], while telithromycin is contraindicated with cisapride and pimozide due to the potential risk of TdP [20]. Clarithromycin has the longest list of contraindications and is comparable to erythromycin [22]. It is also critically important to recognize that the identification of the true risk potential of clarithromycin, azithromycin, and telithromycin and sudden death will require a population-based surveillance program comparable to that conducted with erythromycin. Until such a study is completed, it is reasonable to assume that telithromycin and clarithromycin carry a very similar risk for QTc prolongation and CYP3A4 inhibition. Hence, extension of the outlined list of agents contraindicated with clarithromycin to telithromycin would be rational. Finally, the impact of the potential combination of multiple agents known to induce QTc prolongation on the risk for TdP is not known. Table 8.4 outlines a list of drugs, where the risk for combined QTc prolongation is known, probable or theoretically possible. The drugs outlined in this table demonstrate that several commercially available antiarrhythmic, antibiotic, antifungal, antihypertensive, antimalarial, antipsychotic, and anesthetic drugs have the potential to induce QTc prolongation [9, 219, 225–232]. The combined

Table 8.3 Pharmacological agents contraindicated with the use of erythromycin, clarithromycin, azithromycin and telithromycin

Erythromycin	Clarithromycin	Azithromycin	Telithromycin
1. Astemizole	1. Astemizole	None	1. Cisapride
2. Bepridil	2. Bepridil		2. Pimozide
3. Cisapride	3. Cisapride		
4. Dihydroergotamine	4. Colchicine		
5. Dronedarone	5. Conivaptan		
6. Ergoloid mesylates	6. Dihydroergotamine		
7. Ergonovine	7. Dronedarone		
8. Ergotamine	8. Eplerenone		
9. Grepafloxacin	9. Ergoloid Mesylates		
10. Levomethadyl	10. Ergonovine		
11. Mesoridazine	11. Ergotamine		
12. Methylergonovine	12. Levomethadyl		
13. Methysergide	13. Mesoridazine		
14. Pimozide	14. Methylergonovine		
15. Sparfloxacin	15. Methysergide		
16. Terfenadine	16. Pimozide		
17. Thioridazine	17. Ranolazine		
18. Ziprasidone	18. Silodosin		
	19. Terfenadine		
	20. Thioridazine		
	21. Tolvaptan		
	22. Ziprasidone		

Table 8.4 Drugs with a known, probable and theoretical potential for QTc prolongation when combined with clarithromycin [4, 9, 208–211, 215]

Known	Probable	Theoretical		
Astemizole	Ajmaline	Artemether	Fluoxetine	Procainamide
Atazanavir	Dofetilide	Bretylium	Foscarnet	Prochlorperazine
Cisapride	Dolasetron	Telavancin	Gemifloxacin	Propafenone
Desipramine	Doxepin	Acecainide	Halofantrine	Protriptyline
Diltiazem	Dronedarone	Amiodarone	Haloperidol	Sematilide
Disopyramide	Droperidol	Amisulpride	Halothane	Sertindole
Itraconazole	Hydroquinidine	Amitriptyline	Ibutilide	Sotalol
Pimozide	Ketoconazole	Amoxapine	Imipramine	Sulfamethoxazole
Quetiapine	Mesoridazine	Aprindine	Isoflurane	Sultopride
Quinidine	Pazopanib	Arsenic Trioxide	Isradipine	Tedisamil
Risperidone	Ranolazine	Azimilide	Lidoflazine	Thioridazine
Terfenadine	Salmeterol	Bepridil	Lorcainide	Trifluoperazine
Verapamil	Voriconazole	Chloral hydrate	Mefloquine	Trimethoprim
		Chloroquine	Moxifloxacin	Trimetrexate
		Chlorpromazine	Nortriptyline	Trimipramine
		Dibenzepin	Octreotide	Vasopressin
		Encainide	Pentamidine	Ziprasidone
		Enflurane	Pirmenol	Zolmitriptan
		Flecainide	Prajmaline	Zotepine
		Fluconazole	Probucol	

risk of CYP3A4 inhibition coupled with QTc prolongation can lead to synergistic PK/PD drug interactions that can be fatal as documented with agents such as verapamil, pimozide, and cisapride in recent years [4, 9, 225–228, 232].

8.4 Summary

The pharmacology of erythromycin has been well characterized over the past 60 years and has revealed numerous antimicrobial and non-antimicrobial properties. Clarithromycin and telithromycin represent important derivatives of erythromycin that have expanded the spectrum of activity of this agent and improved its tolerability. However, the drug interaction potential of these agents have now been revealed to be greater than that of the parent agent. Azithromycin represents a substantially different agent that shares pharmacologic similarities to clarithromycin and telithromycin without their major drug interaction potential. However, increasing antimicrobial resistance coupled with continued development of ketolides suggests that the benefits of this class of agents will constantly needed to be weighed against the risk of drug interactions. The data thus far suggest that CYP3A4 is the primary phase 1 drug metabolic pathway and P-gp the primary drug transport protein that are inhibited by this antimicrobial class (to varying degrees). Given that these drug disposition pathways account for the clearance of a vast majority of pharmacological agents, the drug interaction potential of this class is expected to remain high. Hence, a careful review of an individual patient's medication regimen should be performed prior to the prescription of macrolides and ketolides.

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References

1. Haight TH, Finland M. Laboratory and clinical studies on erythromycin. N Engl J Med 1952;247:227–32.
2. Zeitlinger M, Wagner CC, Heinisch B. Ketolides--the modern relatives of macrolides: the pharmacokinetic perspective. Clin Pharmacokinet 2009;48:23–38.
3. Pai MP, Graci DM, Amsden GW. Macrolide drug interactions: an update. Ann Pharmacother 2000;34:495–513.
4. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. N Engl J Med 2004;351:1089–96
5. Zhou SF. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. Curr Drug Metab 2008;9:310–22.
6. Pal D, Mitra AK. MDR- and CYP3A4-mediated drug-drug interactions. J Neuroimmune Pharmacol 2006;1:323–39.
7. Lan T, Rao A, Haywood J, et al. Interaction of macrolide antibiotics with intestinally expressed human and rat organicanion-transporting polypeptides. Drug Metab Dispos 2009;37: 2375–82.

8. Seithel A, Eberl S, Singer K, et al. The influence of macrolide antibiotics on the uptake of organic anions and drugs mediated by OATP1B1 and OATP1B3. Drug Metab Dispos 2007;35:779–86.
9. Iannini PB. Cardiotoxicity of macrolides, ketolides and fluoroquinolones that prolong the QTc interval. Expert Opin Drug Saf 2002;1:121–8.
10. Mazzei T, Mini E, Novelli A, Periti P. Chemistry and mode of action of macrolides. J Antimicrob Chemother 1993;31 Suppl C:1–9.
11. Zhanel GG, Dueck M, Hoban DJ, et al. Review of macrolides and ketolides: focus on respiratory tract infections. Drugs 2001;61:443–98.
12. Mutak S. Azalides from azithromycin to new azalide derivatives. J Antibiot (Tokyo) 2007;60: 85–122.
13. Rafie S, MacDougall C, James CL. Cethromycin: a promising new ketolide antibiotic for respiratory infections. Pharmacotherapy 2010;30:290–303.
14. Ohno Y, Hisaka A, Suzuki H. General framework for the quantitative prediction of CYP3A4-mediated oral drug interactions based on the AUC increase by coadministration of standard drugs. Clin Pharmacokinet 2007;46:681–96.
15. Descotes J, Vial T, Delattre D, Evreux JC. Spiramycin: safety in man. J Antimicrob Chemother 1988;22 Suppl B:207–10.
16. Di Giambattista M, Chinali G, Cocito C. The molecular basis of the inhibitory activities of type A and type B synergimycins and related antibiotics on ribosomes. J Antimicrob Chemother 1989;24:485–507.
17. Tenover FC. Mechanisms of antimicrobial resistance in bacteria. Am J Infect Control 2006;34 Suppl 1:S3–10.
18. Maravić G. Macrolide resistance based on the Erm-mediated rRNA methylation. Curr Drug Targets Infect Disord 2004;4:193–202.
19. Zhanel GG, Hisanaga T, Nichol K, Wierzbowski A, Hoban DJ. Ketolides: an emerging treatment for macrolide-resistant respiratory infections, focusing on S. pneumoniae. Expert Opin Emerg Drugs 2003;8:297–321
20. Ketek® (telithromycin) product information. Bridgewater, NJ: Sanofi-Aventis U.S. LLC, 2010.
21. Gleason PP, Walters C, Heaton AH, Schafer JA. Telithromycin: the perils of hasty adoption and persistence of off-label prescribing. J Manag Care Pharm. 2007 Jun;13(5):420–5.
22. Biaxin® Filmtab® (clarithromycin tablets, USP), Biaxin® XL Filmtab® (clarithromycin extended-release tablets), Biaxin® Granules (clarithromycin for oral suspension, USP) product information. North Chicago, IL: Abbott Laboratories, 2009.
23. Zithromax® (azithromycin tablets) and (azithromycin for oral suspension). New York, NY: Pfizer Inc., 2009.
24. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58(RR-4):1–207.
25. Williams JD. Non-antimicrobial activities of macrolides. Int J Antimicrob Agents 2001;18 Suppl 1:S89–91.
26. Janssens J, Peeters TL, Vantrappen G, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. N Engl J Med 1990;322:1028–31.
27. Peeters T, Matthijs G, Depoortere I, Cachet T, Hoogmartens J, Vantrappen G. Erythromycin is a motilin receptor agonist. Am J Physiol 1989;257(3 Pt 1):G470–4.
28. Itoh Z, Nakaya M, Suzuki T, Arai H, Wakabayashi K. Erythromycin mimics exogenous motilin in gastrointestinal contractile activity in the dog. Am J Physiol 1984;247(6 Pt 1):G688–94.
29. Moshiree B, McDonald R, Hou W, Toskes PP. Comparison of the effect of azithromycin versus erythromycin on antroduodenal pressure profiles of patients with chronic functional gastrointestinal pain and gastroparesis. Dig Dis Sci 2010;55:675–83.
30. Amsden GW. Anti-inflammatory effects of macrolides--an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? J Antimicrob Chemother 2005;55:10–21.

31. Saiman L, Anstead M, Mayer-Hamblett N, et al.; AZ0004 Azithromycin Study Group. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA 2010;303:1707–15.
32. Florescu DF, Murphy PJ, Kalil AC. Effects of prolonged use of azithromycin in patients with cystic fibrosis: a meta-analysis. Pulm Pharmacol Ther 2009;22:467–72.
33. Liu CN, Somps CJ. Telithromycin blocks neuromuscular transmission and inhibits nAChR currents in vitro. Toxicol Lett 2010;194:66–9.
34. DiSanto AR, Chodos DJ. Influence of study design in assessing food effects on absorption of erythromycin base and erythromycin stearate. Antimicrob Agents Chemother 1981;20:190–6.
35. Croteau D, Bergeron MG, LeBel M. Pharmacokinetic advantages of erythromycin estolate over ethylsuccinate as determined by high-pressure liquid chromatography. Antimicrob Agents Chemother 1988;32:561–5.
36. Henry J, Turner P, Garland M, Esmieu F. Plasma and salivary concentrations of erythromycin after administration of three different formulations. Postgrad Med J 1980;56:707–10.
37. Fraser DG. Selection of an oral erythromycin product. Am J Hosp Pharm 1980;37(9):1199–205.
38. Ruenis AP, Moreno RA, Abib-Júnior E, et al. Comparative bioavailability of clarithromycin formulations in healthy brazilian volunteers. Int J Clin Pharmacol Ther 2005;43:399–404.
39. Zithromax® (azithromycin for injection) product information. New York, NY: Pfizer Inc., 2009.
40. Zmax® (azithromycin extended release for oral suspension) product information. New York, NY: Pfizer Inc., 2009.
41. Gordon RC, Regamey C, Kirby WM. Serum protein binding of erythromycin, lincomycin, and clindamycin. J Pharm Sci 1973;62:1074–7.
42. Welling PG, Craig WA. Pharmacokinetics of intravenous erythromycin. J Pharm Sci 1978;67: 1057–9.
43. Kiem S, Schentag JJ. Interpretation of antibiotic concentration ratios measured in epithelial lining fluid. Antimicrob Agents Chemother 2008;52:24–36.
44. Togami K, Chono S, Seki T, Morimoto K. Distribution characteristics of telithromycin, a novel ketolide antimicrobial agent applied for treatment of respiratory infection, in lung epithelial lining fluid and alveolar macrophages. Drug Metab Pharmacokinet 2009;24:411–7.
45. Mao JC, Tardrew PL. Demethylation of erythromycins by rabbit tissues in vitro. Biochem Pharmacol 1965;14:1049–58.
46. Danan G, Descatoire V, Pessayre D. Self-induction by erythromycin of its own transformation into a metabolite forming an inactive complex with reduced cytochrome P-450. J Pharmacol Exp Ther 1981;218:509–14.
47. Pessayre D, Larrey D, Vitaux J, Breil P, Belghiti J, Benhamou JP. Formation of an inactive cytochrome P-450 Fe(II)-metabolite complex after administration of troleandomycin in humans. Biochem Pharmacol 1982;31:1699–704.
48. Amacher DE, Schomaker SJ, Retsema JA. Comparison of the effects of the new azalide antibiotic, azithromycin, and erythromycin estolate on rat liver cytochrome P-450. Antimicrob Agents Chemother 1991;35:1186–90.
49. Rodrigues AD, Roberts EM, Mulford DJ, Yao Y, Ouellet D. Oxidative metabolism of clarithromycin in the presence of human liver microsomes. Major role for the cytochrome P4503A (CYP3A) subfamily. Drug Metab Dispos 1997;25:623–30.
50. Hoover WW, Barrett MS, Jones RN. Clarithromycin in vitro activity enhanced by its major metabolite, 14-hydroxyclarithromycin. Diagn Microbiol Infect Dis 1992;15:259–66.
51. Jones DR, Ekins S, Li L, Hall SD. Computational approaches that predict metabolic intermediate complex formation with CYP3A4 (+b5). Drug Metab Dispos 2007;35:1466–75.
52. Ohmori S, Ishii I, Kuriya S, et al. Effects of clarithromycin and its metabolites on the mixed function oxidase system in hepatic microsomes of rats. Drug Metab Dispos 1993;21:358–63.
53. Evrard-Todeschi N, Gharbi-Benarous J, Gaillet C, et al. Conformations in solution and bound to bacterial ribosomes of ketolides, HMR 3647 (telithromycin) and RU 72366: a new class of highly potent antibacterials. Bioorg Med Chem 2000;8:1579–97.
54. Nosaka H, Nadai M, Kato M, Yasui K, et al. Effect of a newly developed ketolide antibiotic, telithromycin, on metabolism of theophylline and expression of cytochrome P450 in rats. Life Sci 2006;79:50–6.

55. Bruce MA, Hall SD, Haehner-Daniels BD, Gorski JC. In vivo effect of clarithromycin on multiple cytochrome P450s. Drug Metab Dispos 2001;29:1023–8.
56. Griffith RS. Pharmacology of erythromycin in adults. Pediatr Infect Dis 1986;5:130–40.
57. Periti P, Mazzei T, Mini E, Novelli A. Clinical pharmacokinetic properties of the macrolide antibiotics. Effects of age and various pathophysiological states (Part I). Clin Pharmacokinet 1989;16:193–214.
58. Thelen K, Dressman JB. Cytochrome P450-mediated metabolism in the human gut wall. J Pharm Pharmacol 2009;61:541–58.
59. Franke RM, Gardner ER, Sparreboom A. Pharmacogenetics of drug transporters. Curr Pharm Des 2010;16:220–30.
60. Morton MR, Cooper JW. Erythromycin-induced digoxin toxicity. DICP 1989;23:668–70.
61. Saha JR, Butler VP Jr, Neu HC, Lindenbaum J. Digoxin-inactivating bacteria: identification in human gut flora. Science 1983;220:325–7.
62. Donley TG, Smith RF, Roy B. Reduced oral contraceptive effectiveness with concurrent antibiotic use: a protocol for prescribing antibiotics to women of childbearing age. Compendium 1990;11:392–6.
63. Weaver K, Glasier A. Interaction between broad-spectrum antibiotics and the combined oral contraceptive pill. A literature review. Contraception 1999;59:71–8.
64. Durek C, Rüsch-Gerdes S, Jocham D, Böhle A. Sensitivity of BCG to modern antibiotics. Eur Urol 2000;37 Suppl 1:21–5.
65. Tschida SJ, Guay DR, Straka RJ, Hoey LL, Johanning R, Vance-Bryan K. QTc-interval prolongation associated with slow intravenous erythromycin lactobionate infusions in critically ill patients: a prospective evaluation and review of the literature. Pharmacotherapy 1996;16:663–74.
66. Owens RC Jr. QT prolongation with antimicrobial agents: understanding the significance. Drugs 2004;64:1091–124.
67. Yamreudeewong W, Scavone JM, Paone RP, Lewis GP. Effect of antacid coadministration on the bioavailability of erythromycin stearate. Clin Pharm 1989;8:352–4.
68. Foulds G, Hilligoss DM, Henry EB, Gerber N. The effects of an antacid or cimetidine on the serum concentrations of azithromycin. J Clin Pharmacol 1991;31:164–7.
69. Chandra R, Liu P, Breen JD, et al. Clinical pharmacokinetics and gastrointestinal tolerability of a novel extended-release microsphere formulation of azithromycin. Clin Pharmacokinet 2007;46:247–59.
70. Oostendorp RL, Beijnen JH, Schellens JH. The biological and clinical role of drug transporters at the intestinal barrier. Cancer Treat Rev 2009;35:137–47.
71. Kurata Y, Ieiri I, Kimura M, et al. Role of human MDR1 gene polymorphism in bioavailability and interaction of digoxin, a substrate of P-glycoprotein. Clin Pharmacol Ther 2002;72: 209–19.
72. Rengelshausen J, Göggelmann C, Burhenne J, et al. Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin-clarithromycin interaction. Br J Clin Pharmacol 2003;56:32–8.
73. Gomes T, Mamdani MM, Juurlink DN. Macrolide-induced digoxin toxicity: a population-based study. Clin Pharmacol Ther 2009;86:383–6.
74. Nenciu LM, Laberge P, Thirion DJ. Telithromycin-induced digoxin toxicity and electrocardiographic changes. Pharmacotherapy 2006;26:872–6.
75. Yamaguchi S, Zhao YL, Nadai M, et al. Involvement of the drug transporters p glycoprotein and multidrug resistance-associated protein Mrp2 in telithromycin transport. Antimicrob Agents Chemother 2006;50:80–7.
76. Hirano M, Maeda K, Shitara Y, Sugiyama Y. Drug-drug interaction between pitavastatin and various drugs via OATP1B1. Drug Metab Dispos 2006;34:1229–36.
77. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. Am J Cardiol 2004;94:1140–6.
78. Amato CS, Wang RY, Wright RO, Linakis JG. Evaluation of promotility agents to limit the gut bioavailability of extended-release acetaminophen. J Toxicol Clin Toxicol 2004;42: 73–7.

79. Mannermaa E, Vellonen KS, Ryhänen T, Kokkonen K, Ranta VP, Kaarniranta K, Urtti A. Efflux protein expression in human retinal pigment epithelium cell lines. Pharm Res 2009;26:1785–9.
80. Hemauer SJ, Nanovskaya TN, Abdel-Rahman SZ, Patrikeeva SL, Hankins GD, Ahmed MS. Modulation of human placental P-glycoprotein expression and activity by MDR1 gene polymorphisms. Biochem Pharmacol 2010;79:921–5.
81. Liu XD, Zhang L, Xie L. Effect of P-glycoprotein inhibitors erythromycin and cyclosporin A on brain pharmacokinetics of nimodipine in rats. Eur J Drug Metab Pharmacokinet 2003; 28:309–13.
82. Zhang L, Liu XD, Xie L, Wang GJ. P-glycoprotein restricted transport of nimodipine across blood-brain barrier. Acta Pharmacol Sin 2003;24:903–6.
83. Pussard E, Merzouk M, Barennes H. Increased uptake of quinine into the brain by inhibition of P-glycoprotein. Eur J Pharm Sci 2007;32:123–7.
84. Eberl S, Renner B, Neubert A, et al. Role of p-glycoprotein inhibition for drug interactions: evidence from in vitro and pharmacoepidemiological studies. Clin Pharmacokinet 2007;46: 1039–49.
85. Orlando R, De Martin S, Pegoraro P, Quintieri L, Palatini P. Irreversible CYP3A inhibition accompanied by plasma protein-binding displacement: a comparative analysis in subjects with normal and impaired liver function. Clin Pharmacol Ther 2009;85:319–26.
86. Guidance for Industry. Drug interaction studies – study design, data analysis, and implications for dosing and labeling. US Department of Health and Human Services, Food and Drug Administration, Rockville, MD, September 2006.
87. Hisaka A, Kusama M, Ohno Y, Sugiyama Y, Suzuki H. A proposal for a pharmacokinetic interaction significance classification system (PISCS) based on predicted drug exposure changes and its potential application to alert classifications in product labeling. Clin Pharmacokinet 2009;48:653–66.
88. Fleishaker JC, Phillips JP. Evaluation of a potential interaction between erythromycin and glyburide in diabetic volunteers. J Clin Pharmacol 1991;31:259–62.
89. Leiba A, Leibowitz A, Grossman E. An unusual case of hypoglycemia in a diabetic patient. Ann Emerg Med 2004;44:427–8.
90. Bussing R, Gende A. Severe hypoglycemia from clarithromycin-sulfonylurea drug interaction. Diabetes Care 2002;25:1659–61.
91. Schelleman H, Bilker WB, Brensinger CM, Wan F, Hennessy S. Anti-Infectives and the Risk of Severe Hypoglycemia in Users of Glipizide or Glyburide. Clin Pharmacol Ther 2010 Jun 30. [Epub ahead of print].
92. Niemi M, Neuvonen PJ, Kivistö KT. The cytochrome P4503A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. Clin Pharmacol Ther 2001;70:58–65.
93. Khamaisi M, Leitersdorf E. Severe hypoglycemia from clarithromycin-repaglinide drug interaction. Pharmacotherapy 2008;28:682–4.
94. Onglyza® (saxagliptin tablets) product information. Princeton, NJ: Bristol-Myers Squibb, 2009.
95. Demir S, Akin S, Tercan F, Ariboğan A, Oğuzkurt L. Ergotamine-induced lower extremity arterial vasospasm presenting as acute limb ischemia. Diagn Interv Radiol 2010;16:165–7.
96. Ausband SC, Goodman PE. An unusual case of clarithromycin associated ergotism. J Emerg Med 2001;21:411–3.
97. Bird PA, Sturgess AD. Clinical ergotism with severe bilateral upper limb ischaemia precipitated by an erythromycin--ergotamine drug interaction. Aust N Z J Med 2000;30:635–6.
98. Karam B, Farah E, Ashoush R, Jebara V, Ghayad E. Ergotism precipitated by erythromycin: a rare case of vasospasm. Eur J Vasc Endovasc Surg 2000;19:96–8.
99. Horowitz RS, Dart RC, Gomez HF. Clinical ergotism with lingual ischemia induced by clarithromycin-ergotamine interaction. Arch Intern Med 1996;156:456–8.
100. Ghali R, De Léan J, Douville Y, Noël HP, Labbé R. Erythromycin-associated ergotamine intoxication: arteriographic and electrophysiologic analysis of a rare cause of severe ischemia of the lower extremities and associated ischemic neuropathy. Ann Vasc Surg 1993;7:291–6.

101. Francis H, Tyndall A, Webb J. Severe vascular spasm due to erythromycin-ergotamine interaction. Clin Rheumatol 1984;3:243–6.
102. de Mey C, Althaus M, Ezan E, Retzow A. Erythromycin increases plasma concentrations of alpha-dihydroergocryptine in humans. Clin Pharmacol Ther 2001;70:142–8.
103. Relpax® (eletriptan hydrobromide tablets) product information. New York, NY: Pfizer Inc., 2008.
104. Yasui N, Otani K, Kaneko S, et al. A kinetic and dynamic study of oral alprazolam with and without erythromycin in humans: in vivo evidence for the involvement of CYP3A4 in alprazolam metabolism. Clin Pharmacol Ther 1996;59:514–9.
105. Hiller A, Olkkola KT, Isohanni P, Saarnivaara L. Unconsciousness associated with midazolam and erythromycin. Br J Anaesth 1990;65:826–8.
106. Olkkola KT, Aranko K, Luurila H, et al. A potentially hazardous interaction between erythromycin and midazolam. Clin Pharmacol Ther 1993;53:298–305.
107. Quinney SK, Zhang X, Lucksiri A, Gorski JC, Li L, Hall SD. Physiologically based pharmacokinetic model of mechanism-based inhibition of CYP3A by clarithromycin. Drug Metab Dispos 2010;38:241–8.
108. Quinney SK, Haehner BD, Rhoades MB, Lin Z, Gorski JC, Hall SD. Interaction between midazolam and clarithromycin in the elderly. Br J Clin Pharmacol 2008;65:98–109.
109. Gorski JC, Jones DR, Haehner-Daniels BD, Hamman MA, O'Mara EM Jr, Hall SD. The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. Clin Pharmacol Ther 1998;64:133–43.
110. Yeates RA, Laufen H, Zimmermann T. Interaction between midazolam and clarithromycin: comparison with azithromycin. Int J Clin Pharmacol Ther 1996;34:400–5.
111. Phillips JP, Antal EJ, Smith RB. A pharmacokinetic drug interaction between erythromycin and triazolam. J Clin Psychopharmacol 1986;6:297–9.
112. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin (Part I). Clin Pharmacokinet 1990;19:319–32.
113. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin (Part II). Clin Pharmacokinet 1990;19:400–15.
114. Jensen CW, Flechner SM, Van Buren CT, et al. Exacerbation of cyclosporine toxicity by concomitant administration of erythromycin. Transplantation 1987;43:263–70.
115. Sádaba B, López de Ocáriz A, Azanza JR, Quiroga J, Cienfuegos JA. Concurrent clarithromycin and cyclosporin A treatment. J Antimicrob Chemother 1998;42:393–5.
116. Ferrari SL, Goffin E, Mourad M, Wallemacq P, Squifflet JP, Pirson Y. The interaction between clarithromycin and cyclosporine in kidney transplant recipients. Transplantation 1994;58: 725–7.
117. Kovarik JM, Beyer D, Bizot MN, et al. Effect of multiple-dose erythromycin on everolimus pharmacokinetics. Eur J Clin Pharmacol 2005;61:35–8.
118. Affinitor® (everolimus tablets) product label. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2010.
119. Amsden GW, Kuye O, Wei GC. A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. J Clin Pharmacol 2000;42:444–9.
120. Siedlik PH, Olson SC, Yang BB, Stern RH. Erythromycin coadministration increases plasma atorvastatin concentrations. J Clin Pharmacol 1999;39:501–4.
121. Kantola T, Kivistö KT, Neuvonen PJ. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. Clin Pharmacol Ther 1998;64:177–82.
122. Livalo® (pitavastatin tablets) product information. Montgomery, AL: Kowa Pharmaceuticals America, Inc, 2010.
123. Viagra® (sildenafil citrate tablets) product information. New York, NY: Pfizer Inc., 2010.
124. Hedaya MA, El-Afify DR, El-Maghraby GM. The effect of ciprofloxacin and clarithromycin on sildenafil oral bioavailability in human volunteers. Biopharm Drug Dispos 2006; 27:103–10.
125. Cialis® (tadalafil tablets, film coated) product information. Indianapolis, IN: Eli Lily and Company, 2010.

126. Levitra® (vardenafil hydrochloride tablets) product information. Wayne, NJ: Bayer HealthCare Pharmaceuticals, 2010.
127. Gavin JR 3 rd, Bohannon NJ. A review of the response to oral antidiabetes agents in patients with type 2 diabetes. Postgrad Med 2010;122:43–51.
128. Takanohashi T, Koizumi T, Mihara R, Okudaira K. Prediction of the metabolic interaction of nateglinide with other drugs based on in vitro studies. Drug Metab Pharmacokinet 2007; 22:409–18.
129. Rizos CV, Elisaf MS, Mikhailidis DP, Liberopoulos EN. How safe is the use of thiazolidinediones in clinical practice? Expert Opin Drug Saf 2009;8:15–32.
130. Avandia® (rosiglitazone maleate tablets) product information. Research Triangle Park, NC: GlaxoSmithKline, 2008.
131. Actos® (pioglitazone hydrochloride tablets) product information. Deerfeild, IL: Takeda Pharmaceuticals, Inc., 2009.
132. Januvia® (sitagliptin tablets) product information. Whitehouse Station, NJ: MERCK & CO., Inc., 2010.
133. Mehrotra S, Gupta S, Chan KY, et al. Current and prospective pharmacological targets in relation to antimigraine action. Naunyn Schmiedebergs Arch Pharmacol 2008;378:371–94.
134. Silberstein SD. The pharmacology of ergotamine and dihydroergotamine. Headache 1997;37 Suppl 1:S15–25.
135. Delaforge M, Rivière R, Sartori E, Doignon JL, Grognet JM. Metabolism of dihydroergotamine by a cytochrome P-450 similar to that involved in the metabolism of macrolide antibiotics. Xenobiotica 1989;19:1285–95.
136. Loder E. Triptan therapy in migraine. N Engl J Med 2010;363:63–70.
137. Fleishaker JC, Herman BD, Carel BJ, Azie NE. Interaction between ketoconazole and almotriptan in healthy volunteers. J Clin Pharmacol 2003;43:423–7.
138. Evans DC, O'Connor D, Lake BG, Evers R, Allen C, Hargreaves R. Eletriptan metabolism by human hepatic CYP450 enzymes and transport by human P-glycoprotein. Drug Metab Dispos 2003;31:861–9.
139. Mathew NT, Hettiarachchi J, Alderman J. Tolerability and safety of eletriptan in the treatment of migraine: a comprehensive review. Headache 2003;43:962–74.
140. Yeates RA, Laufen H, Zimmermann T, Schumacher T. Pharmacokinetic and pharmacodynamic interaction study between midazolam and the macrolide antibiotics, erythromycin, clarithromycin, and the azalide azithromycin. Int J Clin Pharmacol Ther 1997;35:577–9.
141. Farkas D, Volak LP, Harmatz JS, von Moltke LL, Court MH, Greenblatt DJ. Short-term clarithromycin administration impairs clearance and enhances pharmacodynamic effects of trazodone but not of zolpidem. Clin Pharmacol Ther 2009;85:644–50.
142. Hesse LM, von Moltke LL, Greenblatt DJ. Clinically important drug interactions with zopiclone, zolpidem and zaleplon. CNS Drugs 2003;17:513–32.
143. Kuypers DR. Influence of interactions between immunosuppressive drugs on therapeutic drug monitoring. Ann Transplant 2008;13:11–8.
144. White DA. Drug-induced pulmonary infection. Clin Chest Med 2004;25:179–87.
145. Hesselink DA, Bouamar R, van Gelder T. The pharmacogenetics of calcineurin inhibitor-related nephrotoxicity. Ther Drug Monit 2010 Jun 19. [Epub ahead of print].
146. Gupta SK, Bakran A, Johnson RW, Rowland M. Cyclosporin-erythromycin interaction in renal transplant patients. Br J Clin Pharmacol 1989;27:475–81.
147. Freeman DJ, Martell R, Carruthers SG, Heinrichs D, Keown PA, Stiller CR. Cyclosporin-erythromycin interaction in normal subjects. Br J Clin Pharmacol 1987;23:776–8.
148. Page RL 2nd, Ruscin JM, Fish D, Lapointe M. Possible interaction between intravenous azithromycin and oral cyclosporine. Pharmacotherapy 2001;21:1436–43.
149. Bachmann K, Jauregui L, Chandra R, Thakker K. Influence of a 3-day regimen of azithromycin on the disposition kinetics of cyclosporine A in stable renal transplant patients. Pharmacol Res 2003;47:549–54.
150. Gómez E, Sánchez JE, Aguado S, Alvarez Grande J. Interaction between azithromycin and cyclosporin? Nephron 1996;73:724.

151. Kunicki PK, Sobieszczańska-Małek M. Pharmacokinetic interaction between tacrolimus and clarithromycin in a heart transplant patient. Ther Drug Monit 2005;27:107–8.
152. Padhi ID, Long P, Basha M, Anandan JV. Interaction between tacrolimus and erythromycin. Ther Drug Monit 1997;19:120–2.
153. Mori T, Aisa Y, Nakazato T, Yamazaki R, Ikeda Y, Okamoto S. Tacrolimus-azithromycin interaction in a recipient of allogeneic bone marrow transplantation. Transpl Int 2005; 18:757–8.
154. Kovarik JM, Hsu CH, McMahon L, Berthier S, Rordorf C. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedications. Clin Pharmacol Ther 2001;70:247–54.
155. Capone D, Palmiero G, Gentile A, et al. A pharmacokinetic interaction between clarithromycin and sirolimus in kidney transplant recipient. Curr Drug Metab 2007;8:379–81.
156. Wensel TM, Waldrop BA, Wensel B. Pitavastatin: a new HMG-CoA reductase inhibitor. Ann Pharmacother 2010;44:507–14.
157. Chatzizisis YS, Koskinas KC, Misirli G, Vaklavas C, Hatzitolios A, Giannoglou GD. Risk factors and drug interactions predisposing to statin-induced myopathy: implications for risk assessment, prevention and treatment. Drug Saf 2010;33:171–87.
158. Pharmacy Times Website. Available at: www.pharmacytimes.com. Date accessed: July 13, 2010.
159. Knauer MJ, Urquhart BL, Meyer zu Schwabedissen HE, et al. Human skeletal muscle drug transporters determine local exposure and toxicity of statins. Circ Res 2010;106:297–306.
160. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006;97(8A): 52C–60C.
161. Davidson MH, Clark JA, Glass LM, Kanumalla A. Statin safety: an appraisal from the adverse event reporting system. Am J Cardiol 2006;97(8A):32C–43C.
162. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation 2006;114:2788–97.
163. Strandell J, Bate A, Hägg S, Edwards IR. Rhabdomyolysis a result of azithromycin and statins: an unrecognized interaction. Br J Clin Pharmacol 2009;68:427–34.
164. Cooper KJ, Martin PD, Dane AL, Warwick MJ, Raza A, Schneck DW. The effect of erythromycin on the pharmacokinetics of rosuvastatin. Eur J Clin Pharmacol 2003;59:51–6.
165. Kiang TK, Ensom MH, Chang TK. UDP-glucuronosyltransferases and clinical drug-drug interactions. Pharmacol Ther 2005;106:97–132.
166. Vlachopoulos C, Terentes-Printzios D, Ioakeimidis N, Rokkas K, Stefanadis C. PDE5 inhibitors in non-urological conditions. Curr Pharm Des 2009;15:3521–39.
167. Foti RS, Rock DA, Wienkers LC, Wahlstrom JL. Selection of alternative CYP3A4 probe substrates for clinical drug interaction studies using in vitro data and in vivo simulation. Drug Metab Dispos 2010;38:981–7.
168. Muirhead GJ, Faulkner S, Harness JA, Taubel J. The effects of steady-state erythromycin and azithromycin on the pharmacokinetics of sildenafil in healthy volunteers. Br J Clin Pharmacol 2002;53 Suppl 1:37S–43S.
169. Vannuffel P, Cocito C. Mechanism of action of streptogramins and macrolides. Drugs 1996;51 Suppl 1:20–30.
170. Zhou SF. Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. Xenobiotica 2008;38:802–32.
171. Youle M. Overview of boosted protease inhibitors in treatment-experienced HIV-infected patients. J Antimicrob Chemother 2007;60:1195–205.
172. Mah Ming JB, Gill MJ. Drug-induced rhabdomyolysis after concomitant use of clarithromycin, atorvastatin, and lopinavir/ritonavir in a patient with HIV. AIDS Patient Care STDS 2003;17:207–10.
173. Crixivan® (indinavir sulfate capsules) product information. Whitehouse Station, NJ: MERCK & CO., Inc., 2010.
174. Norvir® (ritonavir capsules-soft gelatin and oral solution) product information. North Chicago, IL: Abbott Laboratories, 2010.
175. Norvir® (ritonavir tablets and oral solution) product information. North Chicago, IL: Abbott Laboratories, 2010.

176. Fortovase® (saquinavir-soft gelatin capsules) product information. Nutley, NJ: Roche Laboratories Inc., 2003.
177. Kaletra® (lopinavir and ritonavir tablets and oral solution) product information. North Chicago, IL: Abbott Laboratories, 2010.
178. Lexiva® (fosamprenavir calcium tablets) product information. Research Triangle Park, NC: GlaxoSmithKline, 2010.
179. Reyataz® (atazanavir sulfate capsules) product information. Princeton, NJ: Bristol-Myers Squibb, 2010.
180. Prezista® (darunavir tablets-film coated) product information. Raritan, NJ: Tibotec, Inc., 2010.
181. Aptivus® (tripanavir capsules and oral solution) product information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc., 2010.
182. la Porte CJ, Sabo JP, Elgadi M, Cameron DW. Interaction studies of tipranavir-ritonavir with clarithromycin, fluconazole, and rifabutin in healthy volunteers. Antimicrob Agents Chemother 2009;53:162–73.
183. Sustiva® (efavirenz capsules and tablets) product information. Princeton, NJ: Bristol-Myers Squibb, 2010.
184. Viramune® (nevirapine tablets and oral suspension) product information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc., 2010.
185. Klotz U. Clinical impact of CYP2C19 polymorphism on the action of proton pump inhibitors: a review of a special problem. Int J Clin Pharmacol Ther 2006;44:297–302.
186. Hassan-Alin M, Andersson T, Niazi M, Liljeblad M, Persson BA, Röhss K. Studies on drug interactions between esomeprazole, amoxicillin and clarithromycin in healthy subjects. Int J Clin Pharmacol Ther 2006;44:119–27.
187. Saito M, Yasui-Furukori N, Uno T, et al. Effects of clarithromycin on lansoprazole pharmacokinetics between CYP2C19 genotypes. Br J Clin Pharmacol 2005;59:302–9.
188. Calabresi L, Pazzucconi F, Ferrara S, di Paolo A, Del Tacca M, Sirtori C. Pharmacokinetic interactions between omeprazole/pantoprazole and clarithromycin in healthy volunteers. Pharmacol Res 2004; 49:493–9.
189. Shimizu M, Uno T, Yasui-Furukori N, Sugawara K, Tateishi T. Effects of clarithromycin and verapamil on rabeprazole pharmacokinetics between CYP2C19 genotypes. Eur J Clin Pharmacol 2006;62:597–603.
190. Apseloff G, Foulds G, LaBoy-Goral L, Willavize S, Vincent J. Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. J Clin Pharmacol 1998;38:830–5.
191. Wallace RJ, Brown BA, Griffith DE, Girard W, Tanaka K. Reduced serum levels of clarithromycin in patients treated with multidrug regimens including rifampin or rifabutin for *Mycobacterium avium-M. intracellulare* infection. J Infect Dis 1995;171:747–50.
192. Shafran SD, Singer J, Zarowny DP, et al. Determinants of rifabutin-associated uveitis in patients treated with rifabutin, clarithromycin, and ethambutol for *Mycobacterium avium* complex bacteremia: a multivariate analysis. J Infect Dis 1998;177:252–5.
193. Kivistö KT, Lamberg TS, Kantola T, Neuvonen PJ. Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. Clin Pharmacol Ther 1997;62:348–54.
194. Yasui N, Otani K, Kaneko S, Shimoyama R, Ohkubo T, Sugawara K. Carbamazepine toxicity induced by clarithromycin coadministration in psychiatric patients. Int Clin Psychopharmacol 1997;12:225–9.
195. Richens A, Chu S-Y, Sennello LT, Sonders RC. Effect of multiple doses of clarithromycin (C) on the pharmacokinetics of carbamazepine. Intersci Conf Antimicrob Agents Chemother 1990;30:213.
196. Hägg S, Spigset O, Mjörndal T, Granberg K, Persbo-Lundqvist G, Dahlqvist R. Absence of interaction between erythromycin and a single dose of clozapine. Eur J Clin Pharmacol 1999;55:221–6.
197. Funderburg LG, Vertrees JE, True JE, Miller AL. Seizure following addition of erythromycin to clozapine treatment. Am J Psychiatry 1994;151:1840–1.
198. Cohen LG, Chesley S, Eugenio L, Flood JG, Fisch J, Goff DC. Erythromycin-induced clozapine toxic reaction. Arch Intern Med 1996;156:675–7.

199. Usiskin SI, Nicolson R, Lenane M, Rapoport JL. Retreatment with clozapine after erythromycininduced neutropenia. Am J Psychiatry 2000;157:1021.
200. Gillum JG, Israel DS, Scott RB, Climo MW, Polk RE. Effect of combination therapy with ciprofloxacin and clarithromycin on theophylline pharmacokinetics in healthy volunteers. Antimicrob Agents Chemother 1996;40:1715–16.
201. de Leon J. Respiratory infections rather than antibiotics may increase clozapine levels: a critical review of the literature. J Clin Psychiatry 2004;65:1144–5.
202. Colcrys® (colchicine, USP tablets) product information. Philadelphia, PA: URL Pharma Inc., 2009.
203. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila) 2010;48:407–14.
204. McKinnell J, Tayek JA. Short term treatment with clarithromycin resulting in colchicine-induced rhabdomyolysis. J Clin Rheumatol 2009;15:303–5.
205. van der Velden W, Huussen J, Ter Laak H, de Sévaux R. Colchicine-induced neuromyopathy in a patient with chronic renal failure: the role of clarithromycin. Neth J Med 2008;66:204–6.
206. Akdag I, Ersoy A, Kahvecioglu S, Gullulu M, Dilek K. Acute colchicines intoxication during clarithromycin administration in patients with chronic renal failure. J Nephrol 2006;19:515–7.
207. Cheng VC, Ho PL, Yuen KY. Two probable cases of serious drug interaction between clarithromycin and colchicine. South Med J 2005;98:811–3.
208. Caraco Y, Putterman C, Rahamimov R, Ben-Chetrit E. Acute colchicines intoxication--possible role of erythromycin administration. J Rheumatol 1992;19:494–6.
209. Hung IF, Wu AK, Cheng VC, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. Clin Infect Dis 2005;41:291–300.
210. Rollot F, Pajot O, Chauvelot-Moachon L, Nazal EM, Kélaïdi C, Blanche P. Acute colchicine intoxication during clarithromycin administration. Ann Pharmacother 2004;38:2074–7.
211. Chan AL, Wang MT, Su CY, Tsai FH. Risk of digoxin intoxication caused by clarithromycin-digoxin interactions in heart failure patients: a population-based study. Eur J Clin Pharmacol 2009 Aug 5. [Epub ahead of print].
212. Dorani H, Schützer KM, Sarich TC, et al. Pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor ximelagatran co-administered with different classes of antibiotics in healthy volunteers. Eur J Clin Pharmacol. 2007;63(6):571–81.
213. Yano R, Tani D, Watanabe K, et al. Evaluation of potential interaction between vinorelbine and clarithromycin. Ann Pharmacother 2009;43:453–8.
214. Torresin A, Cassola G, Penco G, Crisalli MP, Piersantelli N. Vinca alkaloids and macrolides in human immunodeficiency virus-related malignancies: a safe association. Cancer Chemother Pharmacol 1996;39:176–7.
215. Zhou-Pan XR, Sérée E, Zhou XJ, et al. Involvement of human liver cytochrome P450 3A in vinblastine metabolism: drug interactions. Cancer Res 1993;53:5121–6.
216. Tobe SW, Siu LL, Jamal SA, Skorecki KL, Murphy GF, Warner E. Vinblastine and erythromycin: an unrecognized serious drug interaction. Cancer Chemother Pharmacol 1995;35:188–90.
217. Bermúdez M, Fuster JL, Llinares E, Galera A, Gonzalez C. Itraconazole-related increased vincristine neurotoxicity: case report and review of literature. J Pediatr Hematol Oncol 2005;27:389–92.
218. Haefeli WE, Schoenenberger RA, Weiss P, Ritz R. Possible risk for cardiac arrhythmia related to intravenous erythromycin. Intensive Care Med 1992;18:469–73.
219. Oberg KC, Bauman JL. QT interval prolongation and torsades de pointes due to erythromycin lactobionate. Pharmacotherapy 1995;15:687–92
220. Volberg WA, Koci BJ, Su W, Lin J, Zhou J. Blockade of human cardiac potassium channel human ether-a-go-go-related gene (HERG) by macrolide antibiotics. J Pharmacol Exp Ther 2002;302:320–7.
221. Lin YL, Hsiao CL, Wu YC, Kung MF. Electrophysiologic, pharmacokinetic, and pharmacodynamic values indicating a higher risk of torsades de pointes. J Clin Pharmacol 2010 Jun 14. [Epub ahead of print].

222. Del Rosario ME, Weachter R, Flaker GC. Drug-induced QT prolongation and sudden death. Mo Med 2010;107:53–8.
223. Huang BH, Wu CH, Hsia CP, Yin Chen C. Azithromycin-induced torsade de pointes. Pacing Clin Electrophysiol 2007;30:1579–82.
224. Shaffer D, Singer S, Korvick J, Honig P. Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. Clin Infect Dis 2002;35:197–200.
225. Yamreudeewong W, DeBisschop M, Martin LG, Lower DL. Potentially significant drug interactions of class III antiarrhythmic drugs. Drug Saf 2003;26:421–38.
226. Highleyman L. FDA issues Hismanal warning. Food and Drug Administration. BETA 1998 Apr:3.
227. Jenkins IR, Gibson J. Cisapride, erythromycin and arrhythmia. Anaesth Intensive Care. 1996 Dec;24(6):728. Disopyramide: interactions with marcolide antibiotics. Prescrire Int 2001; 10:151.
228. Flockhart DA, Drici MD, et al. Studies on the mechanism of a fatal clarithromycin-pimozide interaction in a patient with Tourette syndrome. J Clin Psychopharmacol 2000;20:317–24.
229. Desta Z, Kerbusch T, Flockhart DA. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). Clin Pharmacol Ther 1999;65:10–20.
230. Schulz-Du Bois C, Schulz-Du Bois AC, Bewig B, et al. Major increase of quetiapine steady-state plasma concentration following co-administration of clarithromycin: confirmation of the pharmacokinetic interaction potential of quetiapine. Pharmacopsychiatry 2008;41:258–9.
231. Fisman S, Reniers D, Diaz P. Erythromycin interaction with risperidone or clomipramine in an adolescent. J Child Adolesc Psychopharmacol 1996;6:133–8.
232. Goldschmidt N, Azaz-Livshits T, Gotsman, Nir-Paz R, Ben-Yehuda A, Muszkat M. Compound cardiac toxicity of oral erythromycin and verapamil. Ann Pharmacother 2001;35:1396–9.

Chapter 9
Quinolones

David R.P. Guay

Abstract Fluoroquinolone (FQ) antimicrobials are among the most commonly used agents in the outpatient and institutional patient care environments. Due to this high frequency of utilization, the potential for deleterious drug-drug interactions with non-antimicrobials is also high. The majority of interactions with the FQs involve deleterious effects on the FQ component. These are also the most clinically-important interactions with these agents. Multivalent cations such as Mg^{2+}, Ca^{2+}, Fe^{2+}, Zn^{2+}, Al^{3+}, and other minerals as well as drugs such as sucralfate, lanthanum, sevelamer, and didanosine (the cation-supplemented version of the latter) can substantially reduce FQ bioavailability, leading the subtherapeutic drug concentrations at the infection site and clinical failure. Separation of dose administrations may or may not reduce the magnitude of these interactions. Ciprofloxacin, norfloxacin, and two experimental FQs in clinical trials (pazufloxacin and prulifloxacin) act as moderate cytochrome P450 enzyme inhibitors and may increase serum concentrations of theophylline and caffeine. Warfarin pharmacodynamics are variably affected by the FQs. The pharmacodynamic interactions between NSAIDs and FQs are only relevant if fenbufen is used concurrently with enoxacin or, possibly, prulifloxacin. Caution is warranted if sparfloxacin or moxifloxacin is used concurrently with other medications prolonging the QTc interval or if patients have other risk factors for prolongation of the QTc interval (e.g. abnormal QTc interval pre-treatment, electrolyte abnormalities, use of starvation-liquid diets, or history of heart disease). Fluoroquinolone antimicrobials can be used effectively and safely in the vast majority of patients if the clinician remembers those few drug-drug interactions that are clinically-important.

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9.1 Introduction

Drug-drug interactions can be categorized into those originating from pharmacokinetic mechanisms and those originating from pharmacodynamic mechanisms. Pharmacokinetic interactions are those that result in alterations of drug absorption, distribution, metabolism and elimination; pharmacodynamic interactions occur when one drug affects the actions of another drug. This chapter deals only with the pharmacokinetic and pharmacodynamic interactions of fluoroquinolones (hereafter referred to as quinolones) with non-antimicrobial agents. Additive, synergistic or antagonistic antimicrobial activity interactions between quinolones and other antimicrobials are not discussed.

Some drug interactions can be predicted from the chemical structure of the agent, its pharmacologic activity, its toxicologic profile, and other characteristics determined in its premarketing evaluation. Other interactions cannot be prospectively predicted and can only be detected through intense, large-scale clinical studies or postmarketing surveillance. The quinolones exhibit drug-drug interactions of both types.

There are a number of problems in the prospective clinical evaluation of drug-drug interactions in humans. First, there may be ethical concerns when administering interacting drug combinations to patients or volunteers, depending on the potential consequences of the interaction. Second, because there are an endless number of drug combinations, doses, and timings of administration that could be investigated, it is economically impossible to fund the study of all possibilities. Third, the prospective evaluation of an interaction in a manageable number of patients is unlikely to uncover a rare interaction. Finally, studies that are carried out in normal volunteers and demonstrate a pharmacokinetic interaction, such as slightly decreased absorption of a drug, may be of uncertain clinical relevance.

Despite these obstacles, delineating the frequencies and types of pharmacokinetic interactions of the quinolones with other drugs is important for several reasons. Since quinolones are often administered orally, absorptive interactions may compromise the efficacy of antimicrobial therapy. Due to their breadth of activity, agents of this class find substantial use in the critically ill and elderly, many of whom receive potentially interacting medications [1–4]. Because the elderly have an increased sensitivity to drug-induced toxicity and experience more adverse drug reactions, they may also exhibit an increased incidence and severity of drug-drug interactions. Finally, the quinolones are such a structurally diverse group that the extrapolation of drug-drug interactions from one to another of these agents may not be appropriate.

9.2 Pharmacokinetic Interactions

9.2.1 Absorption Interactions

The deleterious effect of multivalent cations on the oral bioavailability of quinolones was first reported in 1985 [5]. Since this pivotal report, numerous investigations have duplicated and extended this observation; these are detailed in Table 9.1 [5–70].

Table 9.1 Effects of multivalent cations on quinolone absorption

Quinolone	Cation/preparation/schedule	Mean % change in C_{max}	Mean % change in AUC	Reference
Flerox	Al OH/0.5,12,24,36 h post-quinolone	−24[a]	−17	[6]
Levoflox	Al OH/simultaneous with quinolone	−65[a]	−44[a]	[7]
Norflox	Al OH/simultaneous with quinolone	–	−86[a,b]	[8]
Norflox	Al OH/simultaneous with quinolone	−28[c]	−29[c]	[9]
Oflox	Al OH/simultaneous with quinolone	−29[a]	−19	[10]
Pruli	Al OH/1 h prequinolone	−93[a,d]	−85[a,d]	[11]
Pruli	Al OH/3 h prequinolone	−40[a,d]	−35[a,d]	[11]
	Al OH/2 h prequinolone	−36[d]	−46[d]	
	Al OH/1 h postquinolone	+6[d]	−13[d]	
	Al OH/2 h postquinolone	−10[d]	−18[d]	
Tosu	Al OH/simultaneous with quinolone	−41[a]	−37[a]	[12]
Tosu	Al OH/simultaneous with quinolone	−41[a]	−32[a]	[13]
Oflox	Al phos/simultaneous with quinolone	−10	−3	[14]
Oflox	Al phos/simultaneous with quinolone	–	−7	[8]
Norflox	Bi subsalicylate/simultaneous with quinolone	–	−10[b]	[7]
Cipro	Bi subsalicylate/simultaneous with quinolone	−13	−13	[15]
Cipro	Ca carb/simultaneous with quinolone	−38[a]	−41[a]	[16]
Cipro	Ca carb antacid/simultaneous with quinolone	−47[a]	−42[a]	[17]
Cipro	Ca carb antacid/with meals (PO4 binder)	+13	–	[18]
Cipro	Ca carb/2 h pre-quinolone	+22[a]	0	[19]
Cipro	Ca carb/simultaneous with quinolone	–	−29[a,b]	[20]
Cipro	Ca carb/(TID × 11 doses) 2 h after dose 10	−24[a]	−14	[21]
Gati	Ca carb/simultaneous with quinolone	−7	−8	[22]
	2 h pre-quinolone	−13	−8	
	2 h post-quinolone	+2	0	
Levoflox	Ca carb/simultaneous with quinolone	−23	−3	[7]
Levoflox	Ca carb/spaced 2 h prequinolone	−9	+16	[18]
	and 2 h postquinolone	−19[a,e]	−3[e]	
Lomeflox	Ca carb/simultaneous with quinolone	−14[a]	−2	[23]
Moxi	Ca carb/simultaneous with quinolone +12 and 24 h post-quinolone	−15[a]	−2	[24]
Gemi	Ca carb/simultaneous with quinolone	−21[a]	−17[a]	[25]
	2 h pre-quinolone	−11	−10	
	2 h post-quinolone	0	−7	

(continued)

Table 9.1 (continued)

Quinolone	Cation/preparation/schedule	Mean % change in C_{max}	Mean % change in AUC	Reference
Norflox	Ca carb/simultaneous with quinolone	−28[c]	−47[a,c]	[9]
Norflox	Ca carb antacid/simultaneous with quinolone	−66[a]	−63[a]	[26]
Norflox	Ca carb antacid/simultaneous with quinolone	−66	−62	[25]
Oflox	Ca carb/simultaneous with quinolone	–	0[b]	[20]
Oflox	Ca carb/simultaneous with quinolone	−18	+10	[10]
Oflox	Ca carb antacid/			[27]
	2 h pre-quinolone	+3	−4	
	24 h pre-quinolone	+9	−4	
	2 h post-quinolone	+3	−3	
Pruli	Ca carb/1 h prequinolone	−60[a,d]	−55[a,d]	[11]
Tosu	Ca carb/simultaneous with quinolone	−47[a]	−42[a]	[12]
Cipro	Ca acetate/simultaneous with quinolone	−50[a]	−51[a]	[28]
Cipro	Ca polycarbophil 1,200 mg (5.0 mmol Ca)/			[29]
	simultaneous with quinolone	−64[a]	−52[a]	
Cipro	Ca-fortified orange juice/			[30]
	simultaneous with quinolone	−41[a]	−38[a]	
Gati	Ca-fortified orange juice/			[31]
	simultaneous with quinolone	−14	−12[a]	
Levo	Ca-fortified orange juice/	−23[a]	−14[a]	[32]
	Ca-fortified orange juice + milk/	−24[a]	−16[a]	
	(both simultaneous with ready-to-eat cereal and quinolone)			
Moxi	Ca lact – gluc + carb/			[24]
	immed. before and 12 + 24 h after quinolone	−15[a]	−2	
Cipro	Didanosine (+ cations)/3 doses			[33]
	(dose 3 simultaneous with quinolone)	−93[a]	−98[a]	
Cipro	Didanosine (+ cations)/6 doses			[34]
	(quinolone 2 h pre-didanosine)	−16	−26[a]	
Cipro	Didanosine (−cations)/			[35]
	simultaneous with quinolone	−8	−9	
Tosu	Fe cit/simultaneous with quinolone	−31[a]	−16[a]	[12]
Cipro	Fe gluc/600 mg simultaneous with quinolone	−57[a]	−64[a]	[28]
Cipro	$FeSO_4$/300 mg simultaneous with quinolone	−33[a]	−42[a]	[36]
Cipro	$FeSO_4$/325 mg tid × 7 days	−75[a]	−63[a]	[37]
Cipro	$FeSO_4$/simultaneous with quinolone	−54[a]	−57[a]	[38]
Gati	$FeSO_4$/simultaneous with quinolone	−52	−28	[39]

(continued)

Table 9.1 (continued)

Quinolone	Cation/preparation/schedule	Mean % change in C_{max}	Mean % change in AUC	Reference
Gati	$FeSO_4$/simultaneous with quinolone	−54[a]	−35[a]	[22]
	2 h pre-quinolone	−12	−10	
	2 h post-quinolone	−3	−5	
Levoflox	$FeSO_4$/simultaneous with quinolone	−45[a]	−19[a]	[7]
Lomeflox	$FeSO_4$/simultaneous with quinolone	−28[a]	−14	[23]
Moxi	$FeSO_4$/simultaneous with quinolone	−59[a]	−39[a]	[40]
Norflox	$FeSO_4$/simultaneous with quinolone	−75[a]	−73[a]	[38]
Norflox	$FeSO_4$/simultaneous with quinolone	−97[a,c]	−97[a,c]	[9]
Norflox	$FeSO_4$/simultaneous with quinolone	–	−55[a,b]	[8]
Oflox	$FeSO_4$/simultaneous with quinolone	–	−10[a,b]	[41]
Oflox	$FeSO_4$/simultaneous with quinolone	−36[a]	−25[a]	
Oflox	$FeSO_4$/simultaneous with quinolone	+9	+35	[10]
Gemi	$FeSO_4$/			[42]
	3 h before quinolone	−20[a]	−11	
	2 h after quinolone	−4	−10	
Pruli	Fe SO_4/1 h prequinolone	−85[a,d]	−75[a,d]	[11]
Cipro	Lanthanum carbonate/quinolone taken immediately post-dose 1 on day 2 of 3-day regimen of 1 g tid with meals	−56[a]	−54[a]	[43]
Norflox	Mg OH/simultaneous with quinolone	–	−90[a,b]	[8]
Levoflox	Mg O/simultaneous with quinolone	−38[a]	−22[a]	[7]
Pruli	Mg O/1 h prequinolone	−61[a,d]	−57[a,d]	[11]
Tosu	Mg O/simultaneous with quinolone	−63[a]	−54[a]	[12]
Norflox	Mg trisilicate/simultaneous with quinolone	−72[a,c]	−81[a,c]	[9]
Oflox	Mg trisilicate/simultaneous with quinolone	−2	+19	[10]
Cipro	Mg/Al antacid/simultaneous with quinolone	−81[a]	−84[a]	
Cipro	Mg/Al antacid/			[44]
	5–10 min pre-quinolone	−80[a]	−85[a]	
	2 h pre-quinolone	−74[a]	−77[a]	
	4 h pre-quinolone	−13	−30[a]	
	6 h pre-quinolone	0	+9	
	2 h post-quinolone	+32[a]	+7	
Cipro	Mg/Al antacid/			[45]
	10 doses over 24 h pre-quinolone	−93[a]	−91[a]	
Cipro	Mg/Al antacid/with meals (PO4 binder)	−65	–	
Cipro	Mg/Al antacid/24 h pre-quinolone	−94[a]	–	[5]
Enox	Mg/Al antacid/			[46]
	0.5 h pre-quinolone	−70[a]	−73[a]	
	2 h pre-quinolone	−38	−48[a]	
	8 h pre-quinolone	−9	−17	
Garen	Mg/Al antacid/4 h pre-quinolone	−9	−16[a]	[47]

(continued)

Table 9.1 (continued)

Quinolone	Cation/preparation/schedule	Mean % change in C_{max}	Mean % change in AUC	Reference
	2 h pre-quinolone	−22[a]	−22[a]	
	simultaneous with quinolone	−61[a]	−58[a]	
	2 h post-quinolone	−3	−12[a]	
	4 h post-quinolone	+1	+7	
Gati	Mg/Al antacid/			[48]
	2 h pre-quinolone	−45	−42	
	simultaneous with quinolone	−68[a]	−64[a]	
	2 h post-quinolone	−3	−18[a]	
	4 h post-quinolone	+3	+1	
Lomeflox	Mg/Al antacid/simultaneous with quinolone	−46[a]	−41[a]	[49]
Moxi	Mg/Al antacid/simultaneous with quinolone	−61[a]	−59[a]	[50]
	2 h post-quinolone	−7	−26[a]	
	4 h pre-quinolone	−1	−23[a]	
Norflox	Mg/Al antacid/			[26]
	simultaneous with quinolone	−95[a]	–	
	2 h post-quinolone	−24[a]	−20	
Norflox	Mg/Al antacid/			[51]
	simultaneous with quinolone	−95	−98	
	2 h post-quinolone	−24	−22	
Oflox	Mg/Al antacid/			[45]
	10 doses over 24 h pre-quinolone	−73[a]	−69[a]	
Oflox	Mg/Al antacid/			[27]
	2 h pre-quinolone	−30[a]	−21[a]	
	24 h pre-quinolone	−5	−5	
	2 h post-quinolone	+3	+5	
Oflox	Mg/Al antacid/simultaneous with quinolone	−24	–	[52]
Peflox	Mg/Al antacid/13 doses			[53]
	quinolone 1 h after dose 10	−61[a]	−54[a]	
Ruflox	Mg/Al antacid/			[54]
	simultaneous with quinolone	−43[a]	−38[a]	
	4 h post-quinolone	+6	−15[a]	
Tema	Mg/Al antacid/			[55]
	8 doses day prior to study and 5 doses on study day	−59[a]	−61[a]	
Trovaflox	Mg/Al antacid/			[56]
	2,200 h the night before and 1 and 3 h after meals and at bedtime on the study day and 0.5 h before quinolone	−60	−66	
	2,200 h the night before and 1 and 3 h			

(continued)

Table 9.1 (continued)

Quinolone	Cation/preparation/schedule	Mean % change in C_{max}	Mean % change in AUC	Reference
	after meals and at bedtime on the study day			
	and 2 h after the quinolone	−11	−28	
Gemi	Mg/Al antacid/			[57]
	3 h before quinolone	−17[a]	−15	
	10 min after quinolone	−87[a]	−85[a]	
	2 h after quinolone	+10	+3	
Cipro	Multivit with Zn/once daily × 7 days	−32[a]	−22[a]	[37]
Cipro	Multivit with Fe/Zn/			[36]
	once simultaneous with quinolone	−53[a]	−52[a]	
Norflox	Na CHO_3/simultaneous with quinolone	+5[c]	+5[c]	[9]
Cipro	Sevelamer hydrochloride/seven 403 mg caps			[28]
	simultaneous with quinolone	−34[a]	−48[a]	
Cipro	Sucralfate/1 g 6 and 2 h pre-quinolone	−30[a]	−30[a]	[58]
Cipro	Sucralfate/1 g QID × 1 day then			[59]
	simultaneous with quinolone	−90[a]	−88[a]	
Cipro	Sucralfate/2 g BID × 5 doses			[60]
	quinolone simultaneous with dose 5	−95[a]	−96[a]	
	quinolone 2 h before dose 5	+5	−20	
	quinolone 6 h before dose 5	0	−7	
Enox	Sucralfate/			[61]
	1 g simultaneous with quinolone	−91[a]	−88[a]	
	1 g 2 h pre-quinolone	−51[a]	−54[a]	
	1 g 2 h post-quinolone	0	−8	
Flerox	Sucralfate/1 g QID × 12 doses			[62]
	quinolone simultaneous with dose 5	−26[a]	−24[a]	[63]
Levoflox	Sucralfate/1 g 2 h post-quinolone	+14	−5	[64]
Lomeflox	Sucralfate/1 g 2 h pre-quinolone	−30[a]	−25[a]	[23]
Lomeflox	Sucralfate/1 g simultaneous with quinolone	−65[a]	−51[a]	[65]
Moxi	Sucralfate/1 g simultaneous with quinolone + 5, 10, 15, 24 h post-quinolone	−71[a]	−c60[a]	
Norflox	Sucralfate/			[51]
	simultaneous with quinolone	−90	−98	
	2 h pre-quinolone	−28	−42	
Norflox	Sucralfate/			[66]
	1 g simultaneous with quinolone	−92[a]	−91[a]	
	1 g 2 h post-quinolone	+9	−5	
Norflox	Sucralfate/			[67]
	1 g simultaneous with quinolone	−90[a]	−98[a]	

(continued)

Table 9.1 (continued)

Quinolone	Cation/preparation/schedule	Mean % change in C_{max}	Mean % change in AUC	Reference
	1 g 2 h pre-quinolone	−28	−43	
Oflox	Sucralfate/			[66]
	1 g simultaneous with quinolone	−70[a]	−61[a]	
	1 g 2 h post-quinolone	+7	−5	
Oflox	Sucralfate/			[68]
	Fasting + 1 g simultaneous with quinolone	−70[a]	−61[a]	
	Nonfasting + 1 g simultaneous with quinolone	−39[a]	−31[a]	
Spar	Sucralfate/			[69]
	1 g QID × 8 doses			
	quinolone 0.5 h post dose 8	−39[a]	−47[a]	
Spar	Sucralfate/1.5 g bid × 5 doses/			[70]
	quinolone simultaneous with dose 5	−52[a]	−50[a]	
	quinolone 2 h before dose 5	−30[a]	−36[a]	
	quinolone 4 h before dose 5	+3	−8	
Gemi	Sucralfate/			[42]
	2 g 3 h before quinolone	−69[a]	−53[a]	
	2 g 2 h after quinolone	−2	−8	
Norflox	Tripotassium citrate/			[9]
	simultaneous with quinolone	−48[a,b]	−40[a,c]	
Norflox	Zn SO_4/simultaneous with quinolone	–	−56[a,b]	[8]

% change change from baseline or placebo control, C_{max} peak serum or plasma concentration, *AUC* area under the plasma or serum concentration–time curve, *enox* enoxacin, *oflox* ofloxacin, *cipro* ciprofloxacin, *norflox* norfloxacin, *carb* carbonate, *PO4* phosphate, *lomeflox* lomefloxacin, *levoflox* levofloxacin, *tid* 3 times daily, *qid* 4 times daily, *bid* twice daily, *gluc* gluconate, *trovaflox* trovafloxacin, *spar* sparfloxacin, *gati* gatifloxacin, *moxi* moxifloxacin, *gemi* gemifloxacin, *lact* lactate, *multivit* multivitamin, *tosu* tosufloxacin, *pazu* pazufloxacin, *pruli* prulifloxacin, *garen* garenoxacin

[a] Statistically significant change from baseline or placebo control

[b] Based on urinary excretion data

[c] Based on salivary AUC data

[d] Based on ulifloxacin (active metabolite) data

[e] Adults with cystic fibrosis

The concomitant oral administration of magnesium- or aluminum-containing antacids has been found to result in six to tenfold decreases in the absorption of oral quinolones. Even when dose administrations of the agents were separated by two or more hours, substantial reductions in quinolone absorption persisted [3, 10–13, 16–18, 21, 26, 27, 36, 37, 44, 46–48, 51, 52, 54–56, 71, 72]. Studies of the oral coadministration of calcium-containing antacids with oral quinolones have produced conflicting results, with some reporting no significant effect [7, 10, 18–20, 22,

24, 27], and others reporting significant reductions in absorption [9, 11, 12, 16, 17, 20, 21, 23, 25, 26, 51]. Studies have also documented significant reductions in quinolone bioavailability during coadministration with calcium-fortified orange juice and calcium polycarbophil, calcium acetate, lanthanum carbonate, and sevelamer hydrochloride [28–32, 43].

Studies have documented substantial reductions in quinolone bioavailability when coadministered with sucralfate. Again, this interaction persisted even when dose administrations of the agents were spaced two or more hours apart [42, 51, 58, 59, 61, 64, 67, 70]. Further studies have documented substantial reductions in quinolone bioavailability when coadministered with iron preparations or multiple vitamins with minerals such as zinc, magnesium, copper, and manganese [36, 37], although one study did not find a significant interaction with iron [10]. A pharmacokinetic-pharmacodynamic model has been created, incorporating the pharmacokinetic data for gatifloxacin, ciprofloxacin, and norfloxacin after metal cation administration at various time intervals before and after quinolone administration and the pharmacodynamic data of complex formulation. This model predicted, in the cases of usual doses of ciprofloxacin with magnesium and aluminum hydroxides (Maalox®), gatifloxacin with magnesium and aluminum hydroxides (Maalox® 70), and norfloxacin with sucralfate, that the quinolone should be administered at least 4.5, 4.5, and 3.5 h after, at least, or at least 1, 1, and 0.5 h before the administration of metal cations, respectively, to ensure a relative bioavailability of at least 90% versus control [73].

It is hypothesized that the reduction in quinolone absorption is caused by the formation of insoluble and hence unabsorbable drug-cation complexes or chelates in the gastrointestinal tract [74–78]. This has been confirmed in binding experiments utilizing nuclear magnetic resonance spectroscopy [36, 49, 79]. It appears that the complexation or chelation involves the 4-keto and 3-carboxyl groups of the quinolones. *In vitro* studies have presented the results of the physical chemistry of the gatifloxacin-aluminum hydroxide interaction in detail. This interaction was characterized by complete monolayer adsorption by the mechanism of chemisorption. It was an irreversible reaction that was ionic in nature (i.e. aluminum hydroxide being positively charged in aqueous solution and gatifloxacin being weakly negatively charged). In the everted goat intestinal model, this was a concentration-dependent reaction in that gatifloxacin availability for absorption decreased as the aluminum hydroxide concentration increased [80]. *In vitro* work with the ciprofloxacin-magnesium complex validated the marked stability of these complexed products [81]. The stoichiometry (i.e. the ratio of divalent/trivalent metal cation to quinolone in the stable complexes) varied as a function of the quinolone involved. For example, norfloxacin, nalidixic acid, and ciprofloxacin/gatifloxacin exhibited ratios of 1:1 or 2:1, 1:1–3:1, and 3:1, respectively [73]. In addition, it appears that the presence of these ions results in impaired dissolution of the quinolones, at least *in vitro* [82–87]. It is thus recommended to not use magnesium-, aluminum-, or calcium-containing antacids, sucralfate, or iron/vitamin-mineral preparations concomitantly with quinolones. Histamine H_2-receptor antagonists such as ranitidine, cimetidine, and famotidine

have not been shown, in general, to alter quinolone absorption. However, these agents do result in significantly decreased absorption of enoxacin and prulifloxacin [7, 11, 13, 45, 50, 63, 64, 88–100]. Of interest, *in vitro* studies have demonstrated that enoxacin, cimetidine, ranitidine, and famotidine dissolution and availability for absorption in simulated gastric juice and simulated intestinal fluid are mutually reduced for all three enoxacin-histamine H_2-receptor antagonist pairings [88]. Omeprazole has also not been shown to alter the pharmacokinetics of quinolones to a clinically-significant degree [56, 101–103]. Thus, these agents can be recommended as alternative noninteracting antiulcer and antiesophagitis therapy. In addition, intensive antacid therapy does not alter the kinetics of intravenous enoxacin to a clinically significant degree [104].

Agents that alter gastric motility may affect quinolone absorption. Pirenzepine, a gastrointestinal tract-specific anticholinergic not available in the United States, delayed gastric emptying and absorption of ciprofloxacin, thus delaying the time to achievement of maximal serum concentration (T_{max}). However, the extent of absorption was not altered [45, 89]. N-butylscopolamine, another anticholinergic, interacted with oral ciprofloxacin in an identical manner [91]. In contrast, absorption of ciprofloxacin was accelerated by the gastrointestinal motility stimulant metoclopramide; again, the extent of absorption was unaltered [91]. Similarly, cisapride (no longer available in the U.S.) accelerated the absorption of sparfloxacin, resulting in a significant increase in peak plasma concentration (C_{max}) but no significant effect on the extent of absorption [69]. These quinolone-drug interactions are thought to be of no clinical importance during usual multiple-dose regimens.

The absorption of temafloxacin and ciprofloxacin is not significantly altered in the presence of Osmolite® enteral feedings [105, 106]. However, other studies have found significant interaction potential between the quinolones and enteral feedings. Concurrent administration of Osmolite® and Pulmocare® enteral feedings significantly reduced single-dose ciprofloxacin bioavailability as assessed using C_{max} (mean −26 and −31%, respectively) and area under the serum concentration-vs-time curve (AUC; mean −33 and −42%, respectively) data [107]. Concurrent administration of Sustacal® enteral feeding orally significantly reduced single-dose ciprofloxacin bioavailability as assessed using C_{max} (mean −43%) and AUC (mean −27%) data. In the same study, continuous administration of Jevity® enteral feeding via gastrostomy and jejunostomy tubes significantly reduced single-dose ciprofloxacin bioavailability as assessed using C_{max} (mean −37 and −59%, respectively) and AUC (mean −53 and −67%, respectively) data [108]. Concurrent administration of Ensure® enteral feeding significantly reduced single-dose ciprofloxacin and ofloxacin bioavailability as assessed using C_{max} (mean −47 and −36%, respectively) and AUC (mean −27 and −10%, respectively) data. However, the extent of the interaction was significantly greater for ciprofloxacin than for ofloxacin [109].

The interaction potential between quinolones and dairy products appears to be quinolone specific. Studies have demonstrated no significant interaction between lomefloxacin, fleroxacin, gatifloxacin, moxifloxacin, and ofloxacin and milk (200, 240, or 300 mL) or yogurt (250–300 mL) [23, 39, 110–113]. In contrast, ciprofloxacin, prulifloxacin, and norfloxacin bioavailability is substantially reduced (by 28–58%)

by concurrent administration with milk or yogurt [112, 114–116]. Recent *in vitro* dissolution studies have demonstrated that the major mechanism whereby concurrent milk administration reduces the bioavailability of some quinolones is adsorption on the surface of milk proteins, especially casein. Complexation with calcium is much less important in this regard [117].

9.2.1.1 Therapeutic Implications of Absorption Interactions

Five cases of therapeutic failure due to the interaction of oral quinolones with metal cations have been published [118, 119]. The combination therapies included gatifloxacin with multiple vitamins with minerals and iron; ciprofloxacin with calcium carbonate, magnesium oxide, and multiple vitamins with minerals and iron; levofloxacin with calcium carbonate and aluminum hydroxide; levofloxacin with calcium carbonate and magnesium oxide; and levofloxacin with calcium carbonate and sucralfate. In all cases, spacing of the administration times of the quinolones and the metal cations, temporary discontinuation of metal cations until the end of quinolone therapy, and/or substitution with non-interacting agents (e.g. histamine H_2-receptor antagonist for sucralfate) allowed subsequent successful oral quinolone therapy.

The potential extent of quinolone-metal cation interactions was explored in a case-control study conducted in a 625-bed tertiary-care medical center in the U.S. Data from all patients receiving oral levofloxacin from July 1, 1999 through June 30, 2001 were included. Coadministration was defined as any divalent or trivalent cation-containing agent being administered within 2 h of levofloxacin administration. Complete coadministration was defined as coadministration complicating every dose of an entire course of levofloxacin. Overall, 1,904 (77%) of 2,470 doses (427 courses of therapy) were complicated by coadministration. Also, 386/427 courses (90%) had at least one dose complicated by coadministration. In 238 courses (56%), complete coadministration occurred. Only three factors were significantly associated with complete coadministration upon multivariate analysis. A higher number of prescribed medications on the first day of levofloxacin therapy was a risk factor (per increase of one drug, odds ratio [OR], 1.05; 95% CI, 1.01–1.10; p=0.036). Two factors were protective (i.e. decreased the risk): location in an intensive care unit (OR, 0.51; 95% CI, 0.30–0.87; p=0.013) and longer duration of levofloxacin therapy (OR, 0.92; 95% CI, 0.88–0.97; p=0.001). Extrapolating these results to all oral levofloxacin recipients at the institution, one in every three doses would be complicated by deleterious coadministration with at least one multivalent cation-containing agent [4].

Therapeutic failure due to quinolone-metal cation interactions may occur not only through the production of subtherapeutic drug concentrations due to malabsorption. These subtherapeutic drug concentrations may also lead to the emergence of bacterial resistance to the quinolone class. A case-control study of 46 inpatients receiving oral levofloxacin and divalent/trivalent cations was conducted. Of the 46 individuals, 32 (70%) had levofloxacin-resistant pathogens while 14 (30%) had levofloxacin-susceptible pathogens. Patients with levofloxacin-resistant isolates had previously been exposed to nearly twice as many days of coadministration

(as defined previously) compared with those having susceptible isolates (median 5 vs. 3 days, respectively; p=0.04). Upon multivariate analysis, the relationship between the number of days of coadministration and the presence of resistant isolates was no longer statistically significant but nevertheless did show a statistical trend (OR, 1.26; 95% CI, 0.98–1.63; p=0.07). Last, the percentage of subjects with quinolone-resistant isolates varied directly with the number of days of coadministration. Zero to 2, 3–4, 5–7, and 8–31 days of coadministration were linked to 42%, 78%, 68%, and 90% frequencies of quinolone resistance, respectively [120].

A second case-control trial was conducted using data from all inpatients at a tertiary care hospital and an urban hospital who received oral levofloxacin between January 1, 2001 and December 31, 2005. Coadministration was defined as receipt of levofloxacin and multivalent cation-containing agents during the same day (regardless of the times of administration). A total of 3,134 patients had courses of oral levofloxacin at least 3 days in duration. Of the 3,134 patients, 895 (29%) had 100% coadministration (i.e. on all days of the course of therapy) while 606 (19%) had partial coadministration (i.e. on ≥1 but not all days of the course of therapy). The remainder (52%) had no coadministration at all. Levofloxacin-resistant isolates were found in 198 patients (6%). Coadministration was significantly associated with subsequent identification of a quinolone-resistant isolate (≥48 h after initiation of levofloxacin). On univariate analysis, the ORs for resistant pathogens with 100%, ≥75%, ≥50%, and ≥25% coadministration were 1.49 (p=0.005), 1.48 (p=0.005), 1.61 (p<0.001), and 1.44 (p=0.007), respectively. On multivariate analysis, the ORs for resistant pathogens with 100% (vs. <100%), ≥50% (vs. <50%), and 100% (vs. 0) coadministration were significant (OR, 1.43; p=0.03; OR, 1.52; p=0.006; and OR, 1.36; p=0.05; respectively). For ≥75% (vs. <75%) and ≥25% (vs. <25%) coadministration, statistical significance was not achieved [121].

Another important issue is the antimicrobial activity of quinolone-metal cation complexes. Even though these complexes are not bioavailable to the systemic circulation, they theoretically could still be active against bacterial pathogens in the gastrointestinal (GI) tract. Several evaluations of the *in vitro* activity of drug-cation complexes compared with drug alone have been published [81, 85, 88]. Minimum inhibitory concentrations (MICs) were determined, with a rise in MIC demonstrating reduced susceptibility and a fall in MIC demonstrating increased susceptibility. With ciprofloxacin and magnesium, the MICs for *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were significantly higher for the drug-cation complex compared with the drug alone (all p<0.05) [81]. With lomefloxacin and 11 cations, the MICs did not change with *Salmonella typhi*, *Streptococcus pneumoniae* (except for increases with exposure to nickel and cadmium), and *P. aeruginosa* (except for increases with exposure to copper and zinc). For *Bacteroides fragilis*, MICs increased in the presence of all cations except nickel (for latter, MIC was the same as control). For *S. aureus*, MICs were unaltered in the presence of magnesium, manganese, cobalt, zinc, and cadmium. They were increased upon exposure to calcium, chromium, iron, nickel, and copper [85]. In another study, enoxacin MICs to a variety of 10 organisms fell (in 9/10) or remained the same (in 1/10) in the presence of cimetidine. With exposure to ranitidine, MICs rose up to tenfold (in 6/10) or stayed the same (in 4/10). Last, with exposure to famotidine, MICs rose up to tenfold (in 7/10) or fell (in 3/10) [88]. Overall, because of the drug-, cation-, and organism-specific effects on

quinolone-cation complex bioactivity, it would be prudent to not consider quinolone-cation complexes to be potentially useful in the therapy of bacterial infections of the GI tract.

9.2.2 Distribution Interactions

The quinolones are plasma protein bound to the extent of only 20–30%. Ciprofloxacin does not displace bilirubin from albumin, which suggests that interactions involving displacement of other drugs from their carrier proteins are unlikely to occur during co-administration of quinolones [122]. The absence of such an interaction with the quinolones may be of particular importance to elderly debilitated patients with hypoalbuminemia who receive multiple drugs.

9.2.3 Metabolism Interactions

The effect of quinolones on the metabolism of antipyrine, a probe drug for hepatic drug metabolism, has been evaluated. Ofloxacin given as 200 mg twice daily for 7 days did not influence antipyrine metabolism significantly [123]. Similarly, 125 mg ciprofloxacin twice daily for 7 or 8 days did not influence antipyrine metabolism significantly [124]. In contrast, a regimen of 500 mg ciprofloxacin twice daily for 8–10 days (a clinically-relevant dosing regimen) was associated with a significant mean 39% reduction in antipyrine clearance and mean 58% increase in terminal disposition half-life (t½) [125].

A number of case reports have documented a clinically significant drug-drug interaction between ciprofloxacin and theophylline, in some cases leading to death [126–132]. A number of the quinolones have been found to reduce the hepatic metabolism of coadministered drugs such as the xanthines theophylline [133–170] and caffeine [171–180] (Table 9.2). In contrast to the absorption interactions with multivalent cations, which appear to be generalizable to the entire quinolone drug class, differences do exist between individual quinolones in their propensity to inhibit hepatic xanthine metabolism. A meta-analysis of quinolone-theophylline interaction studies revealed that enoxacin, grepafloxacin (based on Ref. [163]), ciprofloxacin, pazufloxacin (IV) (based on Ref. [168]), tosufloxacin (based on Ref. [12]), prulifloxacin (based on Ref. [170]), and norfloxacin (in descending order) are clinically significant inhibitors of theophylline metabolism; ofloxacin, lomefloxacin, and (based on Refs. [141, 146, 147, 158–160, 165–167, 169, 181, 182]) levofloxacin, temafloxacin, trovafloxacin, sparfloxacin, gatifloxacin, moxifloxacin, gemifloxacin, pazufloxacin (PO), and rufloxacin are clinically insignificant inhibitors [183]. Using a simple pharmacokinetic model that allowed cross-comparison between quinolone-caffeine interaction studies, Barnett and colleagues developed a relative potency index of quinolone interaction as follows: enoxacin [100], ciprofloxacin [11], norfloxacin [9], and ofloxacin (0) [184]. The inhibition of xanthine

Table 9.2 Effect of quinolones on methylxanthine pharmacokinetics

Quinolone		Mean % change in Steady state conc.	CL	t½	Reference
Theophylline					
• Enox	400 bid	+109[a]	+55[a]	–	[133]
• Norflox	400 bid	–	−8[a]	+9[a]	[134]
• Norflox	400 bid	–	+10	+26	[135]
• Cipro	750 bid	–	−31[a]	–	[136]
• Oflox	400 bid	+9[a]	−15[a]	–	[137]
• Norflox	400 bid	–	−15[a]	+13[a]	[138]
• Lomeflox	400 qd	–	−7	+4[a]	[139]
• Enox	25 bid	–	−53[a]	+35[a]	[140]
	100 bid	–	−66[a]	+74[a]	
	400 bid	–	−73[a]	+83[a]	
• Enox	400 bid	+91[a]	−65[a]	+187	[141]
• Enox	400–600 bid	+155[a]	−42[a]	–	[141]
• Tema	400 bid	−55	−10	+9	[142]
• Enox	200 tid	+118[a]	−65[a]	–	[143]
• Enox	400 bid	+163[a]	−64[a]	+159[a]	[144]
• Cipro	500 bid	+66[a]	−30[a]	+42[a]	[144]
• Oflox	400 bid	+2	−5	+2	[144]
• Oflox	200 tid	–	0	+6	[145]
• Ruflox	200 mg qd	–	+2	−1	[146]
• Spar	200 qd	–	−9	–	[147]
• Norflox	200 tid	–	−7	+15	[145]
• Enox	200 tid	–	−50[a]	+53[a]	[148]
• Oflox	200 tid	–	0	+6	[148]
• Norflox	200 tid	–	−7	+15	[148]
• Cipro	500 bid	–	−27[a]	–	[148]
• Lomeflox	400 bid	–	−2	–	[149]
• Lomeflox	400×1 dose	+1	−2	+1	[150]
	400 bid	+8	−7	+7	
• Flerox	400 bid	–	−6[a]	+9	[151]
• Flerox	200 bid	–	0	–	[152]
• Enox	400 bid	+243[a]	−74[a]	–	[153]
• Lomeflox	400 bid	–	+7	+3	[154]
• Norflox	200 tid	–	−4	–	[155]
• Enox	200 tid	–	−84[a]	–	[155]
• Oflox	200 tid	–	−11	–	[155]
• Cipro	200 tid	–	−22[a]	–	[155]
• Enox	600 bid	+248[a]	–	–	[156]
• Cipro	750 bid	+87[a]	–	–	[157]
• Levoflox	500 bid	–	+3	−1	[158]
• Trovaflox	300 qd	–	−8[a]	+13[a]	[159]
• Trovaflox	200 qd	–	−7	–	[160]
• Oflox	200 bid	–	−5	+5	[161]
• Cipro	500 bid	–	−20[a]	+25[a]	[162]

(continued)

Table 9.2 (continued)

Quinolone		Mean % change in			Reference
		Steady state conc.	CL	t½	
• Grepa	600 qd	–	−52[a]	–	[163]
• Gati	400 bid	–	0	–	[164]
• Moxi	200 bid	–	−4	+4	[165]
• Moxi	200 bid	–	+5	+3	[166]
• Gemi	320 qd	–	−1	–	[167]
• Tosu	150 tid	–	−24[a]	–	[12]
• Pazu	500 bid IV	+27[a,b]	−25[a]	–	[168]
	200 tid	−3[b]	−4	–	[169]
• Pruli	600 qd	–	−15[a,c]	+14[a,c]	[170]
Caffeine					
• Peflox	400 bid	–	−47[a]	+96[a]	[171]
• Enox	400 bid	–	−83[a]	+492[a]	[171]
• Norflox	800 bid	–	−35[a]	+23	[172]
• Cipro	750 bid	–	−45[a]	+58[a]	[173]
• Cipro	750 bid	+877[a]	−145[a]	+116[a]	[174]
• Oflox	200 bid	–	+2	−3	[174]
• Norflox	400 bid	–	−16	+16[a]	[175]
• Cipro	100 bid	–	−17	+6	[175]
	250 bid	–	−57[a]	+15[a]	
	500 bid	–	−58[a]	+26	
• Enox	100 bid	–	−138[a]	+103[a]	[175]
	200 bid	–	−176[a]	+126[a]	
	400 bid	–	−346[a]	+258[a]	
• Enox	400 bid	–	−79[a]	+475[a]	[176]
• Oflox	200 bid	–	+4	−3	[177]
• Cipro	250 bid	–	−33[a]	+15[a]	[177]
• Enox	400 bid	–	−78[a]	+258[a]	[177]
• Pip	400 bid	–	−65[a]	−121[a]	[178]
• Lomeflox	400 qd	−6	−3	0	[179]
• Trovaflox	200 mg qd	–	−17	–	[180]

% change change from baseline or placebo control, *CL* total body clearance, *t½* elimination half-life, *enox* enoxacin, *norflox* norfloxacin, *cipro* ciprofloxacin, *lomeflox* lomefloxacin, *levoflox* levofloxacin, *tema* temafloxacin, *oflox* ofloxacin, *pip* pipemidic acid, *trovaflox* trovafloxacin, *ruflox* rufloxacin, *spar* sparfloxacin, *peflox* pefloxacin, *grepa* grepafloxacin, *gati* gatifloxacin, *moxi* moxifloxacin, *gemi* gemifloxacin, *qd* once daily, *bid* twice daily, *tid* three times a day, *tosu* tosufloxacin, *pazu* pazufloxacin, *pruli* prulifloxacin

[a] Statistically significant change from baseline or placebo control

[b] Peak concentration

[c] Ulifloxacin (active metabolite)

metabolism is dose-dependent, at least for enoxacin, ciprofloxacin, and pazufloxacin for which adequate data are available [140, 141, 168, 169, 175, 185].

Few other substrates have been examined. Enoxacin decreased the metabolism of the less-active enantiomer of warfarin, R-warfarin, without potentiation of anticoagulant effect [186]. In addition, levofloxacin, norfloxacin, temafloxacin, trovafloxacin,

grepafloxacin, moxifloxacin, gemifloxacin, sparfloxacin, and ciprofloxacin have been shown not to potentiate the anticoagulant effect of warfarin in healthy subjects and patients requiring long-term anticoagulation [163, 187–197]. Based on rat studies, ciprofloxacin and pefloxacin significantly increased prothrombin time (PT)/international normalized ratio (INR) results after acenocoumarin administration [198]. These results need to be validated in humans. In these same studies, acenocoumarin coadministration significantly enhanced the serum concentrations of both quinolones and their penetration into mandibular bone but not femur. The mechanism of this effect is unknown [198]. However, case reports have documented quinolone-associated increases in PT/INR in patients receiving warfarin concurrently with ciprofloxacin, ofloxacin, norfloxacin, gatifloxacin, levofloxacin, and moxifloxacin [199–214].

Several epidemiological studies have examined the association of antimicrobial use with laboratory and clinical outcomes in warfarin recipients. A nested case-control and case-crossover study using the Medicaid database assessed the risk of hospitalization for gastrointestinal (GI) bleeding in warfarin users who also received oral sulfonamides, azole antifungals, and three quinolones (ciprofloxacin, levofloxacin, gatifloxacin). When adjusted for all confounders, and using cephalexin as a control, none of the quinolones were statistically associated with the target outcome [215]. A retrospective case-cohort study was designed to measure INR changes occurring in warfarin recipients after initiation of oral azithromycin, levofloxacin, trimethoprim-sulfamethoxazole (TMP-SMX), and terazosin (control) between January 1998 and December 2002. Subjects were outpatients in a University-affiliated VA Medical Center. The mean changes in INR were +0.51, +0.85, +1.76, and −0.15, respectively (all antimicrobial-terazosin pairs, $p < 0.05$). The frequencies of supratherapeutic INRs (i.e. above the upper limit of the desired range) were 31%, 33%, 69%, and 5%, respectively (all antimicrobial-terazosin pairs, $p < 0.05$). The frequencies of INRs exceeding 4.0 were 16%, 19%, 44%, and 0, respectively (only TMP-SMX vs. terazosin, $p < 0.05$) [216]. A retrospective case-cohort study was conducted in an outpatient oral anticoagulation clinic for patients on long-term warfarin therapy (between January 1, 1998 and March 31, 2003). Forty-three patients received warfarin: 21 were prescribed felodipine (as control) while 22 were prescribed oral levofloxacin (16 on 500 mg/day, 6 on 250 mg/day). The differences in pre- versus post-drug INR values and the proportions of patients requiring a change in dose due to the post-drug INR values were not significantly different between groups. Eight levofloxacin and eight felodipine recipients had INR differences of >0.5 while four levofloxacin and one felodipine recipients had INR differences of >1.0. For the levofloxacin and felodipine groups, 7/9 (78%) and 3/7 (43%) of dose changes were reductions due to supratherapeutic INR values [217]. A retrospective review was conducted of all hospitalized patients in a University hospital in Spain (from 2000 to 2005) who had received levofloxacin and warfarin concurrently. A total of 21 patients were identified and evaluable (mean age 75 years old [range, 49–92], 57.1% were women). Concurrent therapy lasted for 7 ± 4.4 days (mean ± SD). The routes of administration of

levofloxacin were intravenous (N = 4), oral (N = 8), and intravenous-to-oral (N = 9). Three subjects had bleeding due to INR elevations (to 3.43, 4.8, and 6.32). The mean INR values before, during, and following concurrent therapy were 1.85 (range 1.01–4.08), 2.64 (1–6.32), and 2.32 (1.11–4.15) (before vs. during, p = 0.001; before vs. following, p = not significant) [218].

A nested case-control analysis of multiple linked healthcare databases in Ontario, Canada was conducted between April 1, 1998 through March 31, 2002. Subjects were a minimum of 65 years old. Cases were those on continuous warfarin therapy admitted to hospital with any type of bleeding. The cohort was a population of elders on continuous warfarin therapy, wherein observation began with the first warfarin prescription following the 66th birthday and ended with the occurrence of one of the following events: first recurrence of hospital admission for bleeding, death, warfarin discontinuation, or the end of the study period. Study medications included oral levofloxacin, ocular antimicrobials, and cefuroxime (as control). A total of 158,510 elders met the inclusion criteria (mean age at start was 79 years old, 48% were women). Cases (N = 4,269) were matched to 17,048 controls. For 14 days of exposure, the odds ratio of only cefuroxime was significant (1.62; 95% CI, 1.28–2.20). For 28 days of exposure, only the odds ratio of cefuroxime was again significant (1.63; 95% CI, 1.23–1.89). Both times, cefuroxime was associated with an enhanced risk of bleeding. Ocular antimicrobials were weakly associated with a decreased risk of bleeding with 28 days of exposure (OR, 0.94; 95% CI, 0.76–0.98). Levofloxacin was not associated with bleeding in these elderly warfarin recipients [219].

The effects of various antimicrobials, being used to treat UTIs in warfarin recipients, on upper gastrointestinal (UGI) tract hemorrhage rates were evaluated. This trial utilized a population-based, nested case-control trial design using healthcare databases in Ontario, Canada over the period of April 1, 1997 through March 31, 2007. Cases were Ontario residents 66 years old and older with UGI tract hemorrhage who were being continuously treated with warfarin. Up to ten age- and sex-matched controls were selected for each case. Adjusted odds ratios for antimicrobial exposure within 14 days before UGI tract hemorrhage were calculated for six commonly-used antimicrobials for UTI, including ciprofloxacin and norfloxacin. Only trimethoprim-sulfamethoxazole and ciprofloxacin use were significantly associated with UGI tract hemorrhage (aORs of 3.84 and 1.94, respectively). All other agents, including norfloxacin (aOR of 0.38), were not associated with this outcome [220].

Last, the efficacy of preemptively reducing warfarin doses by 10–20% when starting oral TMP-SMX or levofloxacin therapy in warfarin recipients was compared with no preemptive dose reduction. Of 40 patients, 18 were dose-reduced (in eight TMP-SMX patients, the mean dose reduction was 16.3% while in ten levofloxacin patients, the mean dose reduction was 16.2%) and in 22, there was no dose alteration. In the dose-reduced TMP-SMX group, the mean difference in pre- versus on-therapy INR values was not significant but 25% still developed INR values >4.0 and none had subtherapeutic INR values. In the control TMP-SMX group, there was

a significant rise in INR values on-therapy versus pre ($p<0.02$) and 89% had INR values >4.0 (25% vs. 89%, $p<0.02$). In the dose-reduced levofloxacin group, the mean difference in pre- versus on-therapy INR values was not significant, 40% developed subtherapeutic INR values, and none had INR values >4.0. In the control levofloxacin group, there was a significant rise in INR values on-therapy versus pre ($p<0.02$), 38.5% developed INR values >4.0, and none had subtherapeutic INR values (differences between levofloxacin groups in proportions with subtherapeutic or supratherapeutic INR values were significant: $p<0.03$ and $p<0.02$, respectively). Thus, more pronounced effects were seen with TMP-SMX compared with levofloxacin. For the pooled dose-reduction group, 11% of subjects needed temporary interruption of warfarin therapy due to supratherapeutic INR values. In the pooled control group, 55% of subjects required such interruption ($p=0.007$) [221].

Pending additional information, patients who are receiving long-term warfarin therapy in whom a quinolone is to be used should be monitored for changes in PT/INR.

Temafloxacin does not interact with low-dose heparin as measured by changes in activated factor levels, activated partial thromboplastin time (aPTT), PT, and thrombin time (TT) tests [222].

Case reports have suggested that the quinolones may reduce the metabolism of cyclosporine and hence potentiate the nephrotoxicity of this agent [223–226]. In addition, results of one study conducted in pediatric renal transplant recipients suggested that norfloxacin may interfere with cyclosporine disposition, as evidenced by the difference in mean daily dose of cyclosporine required to maintain trough blood cyclosporine concentrations of 150–400 ng/mL (4.5 mg/kg/day in norfloxacin recipients versus 7.4 mg/kg/day in non-recipients) [227]. A study was conducted in renal transplant recipients requiring therapy for urinary tract infections wherein the effect of high-dose oral levofloxacin (1 g daily) on cyclosporine pharmacokinetics was evaluated. Levofloxacin therapy resulted in significant increases in cyclosporine C_{max} (mean 23%, $p=0.0049$), AUC (mean 26%, $p=0.005$), C_{min} (mean 36%, $p=0.0013$) and C_{avg} (mean 26%, $p=0.0005$). A slight fall in polyclonal assay C_{max} (mean 5%, $p=0.014$), which measures parent compound plus metabolites, was also seen [228]. However, numerous formal *in vitro* and other pharmacokinetic studies have not found a significant interaction between cyclosporine and ciprofloxacin, pefloxacin, and levofloxacin [229–237]. This suggests that these agents with the possible exception of high-dose levofloxacin, may be used together with routine monitoring. In addition, high-dose levofloxacin (1 g/day) significantly increased tacrolimus systemic exposure (means 24–28%) and combination therapy would appear to warrant enhanced monitoring [228, 238].

Studies have documented nonsignificant interactions of moxifloxacin, sparfloxacin, gemifloxacin, levofloxacin, and gatifloxacin with digoxin [239–243]. Coadministration of oral trovafloxacin and intravenous morphine results in 36% and 46% reductions in trovafloxacin bioavailability (based on AUC and C_{max} data, respectively). Morphine pharmacokinetics and pharmacodynamics are not altered by concurrent oral trovafloxacin administration [244]. Similar findings of reduced quinolone bioavailability have been noted with coadministration of oral

ciprofloxacin and intramuscular papaveretum [245]. In contrast, oral oxycodone had no significant effect on oral levofloxacin pharmacokinetics [246]. Ciprofloxacin significantly reduced the total body clearance, renal clearance, and nonrenal clearance and increased t ½ and urinary excretion of R(−) and S(+) mexiletine in both smokers and nonsmokers. However, these changes were modest in degree (≤20%) and suggested the absence of a clinically-relevant drug interaction between the two agents [247].

Ciprofloxacin may impair the elimination of diazepam [248], although this is controversial [249]. Gatifloxacin does not significantly alter the pharmacokinetics of intravenous midazolam [250]. Waite and coworkers demonstrated that elderly subjects are not more sensitive than younger subjects to the inhibitory effect of ciprofloxacin on hepatic metabolism of antipyrine [251]. Similarly, Loi and coworkers demonstrated that elderly subjects are not more sensitive to the inhibitory effect of ciprofloxacin on hepatic metabolism of theophylline [252].

Chandler and colleagues showed that rifampin does not induce the metabolism of ciprofloxacin, suggesting that the two agents may be used concomitantly in standard clinical dosing regimens [253]. A study conducted in rats suggested that levofloxacin pharmacokinetics were also not altered by concurrent rifampin administration [254]. The results of this study must be validated in humans.

In contrast, Bernard and colleagues demonstrated that rifampin does induce the metabolism of grepafloxacin, resulting in a statistically significant 25% decrease in t½ and a 48% increase in apparent oral clearance [255]. In addition, rifampin coadministration significantly enhanced fleroxacin apparent oral clearance (mean 15%) and reduced t½ (mean 19%) by significantly enhancing metabolic clearance by N-demethylation (no effect on N-oxidation) [256]. Examining the rifampin component of the combination, single-dose ciprofloxacin coadministration significantly increased t½ and reduced the C_{max} but had no effect on the AUC, volume of distribution, or urinary excretion of single-dose rifampin [257, 258]. Single-dose pefloxacin coadministration significantly increased t½, C_{max}, AUC (from 0 to 24 h and 0–∞), volume of distribution, absorption t ½, and urinary excretion of single-dose rifampin [259, 260].

In a multiple-dose healthy volunteer trial evaluating the steady-state interaction of rifampin with moxifloxacin, moxifloxacin C_{max} and AUC were reduced by means of 6% and 27%, respectively ($p \leq 0.047$ and $p < 0.0001$, respectively). Rifampin coadministration also increased C_{max} and AUC of the M-1 metabolite by means of 255% and 116%, respectively, and decreased t½ of this metabolite by a mean of 68% (no statistical results were presented) [261]. In a study conducted in patients with tuberculosis receiving thrice weekly therapy with rifampin and isoniazid, steady-state moxifloxacin serum concentrations fell in 18/19 patients (95%). Significant ($p < 0.05$) reductions were also found for steady-state moxifloxacin AUC (mean 31%), C_{max} (mean 32%), C_{min} (mean 62%), and t½ (mean 28%). In addition, significant ($p < 0.05$) increases were found for steady-state T_{max} (median rose from 1.00 to 2.51 h) and total body clearance (mean 45%). The correlations of moxifloxacin AUC (in the absence of rifampin) and rifampin AUC with the change in moxifloxacin AUC in the presence of rifampin were both non-significant [262]. It would

be of benefit to repeat this study using daily dosing of the same antitubercular agents.

A single-dose study was conducted in healthy volunteers, evaluating the effects of a fixed dose combination of rifampin 600 mg/isoniazid 300 mg/pyrazinamide 1,600 mg on the pharmacokinetics of gatifloxacin and vice versa. Coadministration of the antitubercular combination produced a delay in gatifloxacin absorption, manifested by a prolongation of median T_{max} from 1.5 to 2.25 h ($p=0.037$). Both t½ and AUC of gatifloxacin were increased as well (by mean 6% [$p=0.023$] and mean 10% [$p<0.05$], respectively). Gatifloxacin coadministration produced a number of significant kinetic changes in the three antitubercular drugs. Rifampin T_{max} was increased (by median 25%, $p=0.01$), C_{max} was decreased (by median 27%, $p<0.05$) and AUC was decreased (by median 14%, $p<0.05$). Isoniazid t½ was slightly decreased (by median 3%, $p=0.047$) [263]. In contrast, two other studies have found that ciprofloxacin does not interact pharmacokinetically with isoniazid [264, 265]. Pyrazinamide t½ was increased (by median 19%, $p=0.027$) [263].

In a single-dose pharmacokinetic trial conducted in rats, azithromycin 45 mg/kg IV significantly reduced pazufloxacin total body clearance and increased pazufloxacin mean residence time by 28% and 24%, respectively, when pazufloxacin was dosed at 45 mg/kg administered IV 10 min after azithromycin [266]. The effects of acute (single-dose) and chronic (7-day) exposure to ketoconazole and itraconazole on the pharmacokinetics of ciprofloxacin were assessed in mice (all drugs were administered intraperitoneally). Acute/chronic ketoconazole dosing was associated with increased C_{max} (by means 50/19%), t½ (by means 136/256%), and AUC (by means 98/73%) and decreased total body clearance (by means 52/41%). Acute/chronic itraconazole dosing was associated with increased C_{max} (by means 37/31%), t½ (by means 103/269%), and AUC (by means 99/66%) and decreased total body clearance (by means 51/35%). Ciprofloxacin volume of distribution at steady-state was increased by chronic ketoconazole and itraconazole dosing by means of 106% and 117%, respectively, but not by acute dosing. Chronic ketoconazole dosing produced mean 46% and 76% reductions in 2 and 4-h postdose ciprofloxacin urine concentrations. Corresponding reductions with chronic itraconazole dosing were 65% and 76%. All of these changes were statistically-significant. Presumably, this interaction was mediated by CYP inhibition and inhibition of renal tubular secretion by the azole antifungals [267].

Single-dose ciprofloxacin coadministration reduced single-dose acetaminophen C_{max} by mean 30% and increased T_{max} and t½ by means of 86% and 29%, respectively (all $p<0.05$) [268]. The effects of single-dose acetaminophen coadministration on single-dose ciprofloxacin pharmacokinetics were non-significant [269]. Single-dose chloroquine coadministration produced mean reductions in single-dose ciprofloxacin C_{max} and AUC of 18% and 43%, respectively, and a mean increase in cumulative urinary excretion as a percentage of the dose of 1,000% (all $p<0.05$) [270, 271].

The effect of phenazopyridine, a urinary tract analgesic, on the pharmacokinetics of ciprofloxacin were evaluated using a commercially-available combination tablet (containing ciprofloxacin 500 mg + phenazopyridine 200 mg). The only significant alterations noted were mean 29% and 30% increases in ciprofloxacin AUC and

mean residence time, respectively (both parameters did not fulfill at least one of the lower [80%] or upper [125%] limits of bioequivalence). The mechanism of this effect is not known [272]. Multiple-dose enoxacin coadministration exerted modest effects on the pharmacokinetics of fluvoxamine. The only significant alterations in the presence of enoxacin were an increase in C_{max} (mean 14%, $p<0.05$) and a reduction in T_{max} (mean 24%, $p<0.05$) of the parent compound. No significant effect was noted on the pharmacokinetics of the fluvoxamino acid metabolite. There were no significant differences in enoxacin effect based on CYP2D6 genotype status. These minor alterations in fluvoxamine pharmacokinetics were mirrored by the pharmacodynamic results (Stanford Sleepiness Scale scores). Scores from 0.5 to 4 h postdose were significantly higher (i.e. patients were more sleepy) during enoxacin coadministration compared with placebo coadministration ($p<0.05$) [273]. A single-dose trial evaluating the effect of ciprofloxacin on sildenafil pharmacokinetics found that ciprofloxacin coadministration resulted in significant increases in t½ (mean 38%), AUC (mean 112%) and C_{max} (mean 117%) (all $p<0.05$). The 90% CIs for AUC (119–159%) and for C_{max} (127–152%) document a potential drug-drug interaction of considerable magnitude [274].

Two cases have been described of an interaction between ciprofloxacin and levothyroxine (T_4), wherein coadministration produced a substantial loss of T_4 pharmacological effect manifested by increases in thyroid-stimulating hormone concentrations to 19 and 44 IU/mL and reductions in free T_4 concentrations to 13 and 4 pmol/L, respectively. In one case, spacing the administration times of the two agents by 6 h led to rapid normalization of thyroid function test results. Despite this finding, the mechanism of this interaction remains unknown at present [275].

One case of an interaction between ciprofloxacin and tizanidine has been described. Upon initiation of ciprofloxacin therapy for a urinary tract infection, signs of tizanidine toxicity (bradycardia, hypotension, hypothermia) began almost immediately in this 45 year old with multiple sclerosis. Drowsiness and continuing hypotension led to discontinuation of ciprofloxacin with subsequent improvement and then disappearance of the signs of tizanidine intoxication [276]. The authors then surveyed the medical records of 1,165 patients, looking for the combined use of tizanidine with ciprofloxacin. Eight cases were found. Examining these eight cases and comparing them to 11 cases of combined use of tizanidine and fluvoxamine found in the literature (fluvoxamine being another CYP1A2 inhibitor), both combinations were characterized by similar patterns of systolic and/or diastolic hypotension and hypothermia. This suggested that inhibition of CYP1A2-mediated metabolism of tizanidine was the mechanism involved [276]. This mechanism was confirmed by a drug interaction study conducted in ten healthy volunteers. Steady-state ciprofloxacin coadministration led to significant increases in single-dose tizanidine C_{max} (mean 564%), t½ (mean 23%), and AUC (mean 876%) (all $p\leq0.007$). Significant decreases were also seen in systolic and diastolic blood pressures (post-tizanidine vs. baseline differences during ciprofloxacin vs. no coadministration of −17 and −11 mmHg, respectively; both $p<0.001$). Visual analog scales for drowsiness and drug effect and the Digit Symbol Substitution Test results demonstrated significant negative effects of the combination compared with tizanidine

alone (p = 0.009–0.02). Correlation analyses with caffeine/paraxanthine concentration ratios (a marker for CYP1A2 activity) supported CYP1A2 inhibition as the mechanism of the interaction [277].

Recently, ciprofloxacin has been used to augment pentoxifylline plasma concentrations in cancer patients undergoing interleukin therapy [278]. Pentoxifylline inhibits interleukin-induced capillary leak syndrome in these patients. In addition, the plasma concentrations of (R)-metabolite-1, an even more potent inhibitor of this syndrome than the parent pentoxifylline, were evaluated during concurrent therapy with ciprofloxacin [278, 279]. *In vitro* and *in vivo* (murine) studies revealed that pentoxifylline and metabolite-1 C_{max} and AUC were doubled by coadministration of ciprofloxacin. These two moieties were interconvertable *in vivo*. The underlying mechanism was inhibition of CYP1A2 (thus increasing pentoxifylline) and induction of CYP2E1 (thus increasing generation of the R-enantiomer of metabolite-1) [280, 281].

Seven case reports have suggested inhibition of clozapine (N = 5), olanzapine (N = 1) and methadone (N = 1) metabolism by ciprofloxacin [282–287]. In a study conducted in seven patients with schizophrenia, ciprofloxacin 250 mg twice daily caused significant elevations in serum clozapine and N-desmethylclozapine concentrations (mean 29% and 31%, respectively) after 1 week of concurrent therapy [288].

Two cases of severe methotrexate toxicity due to concomitant use of ciprofloxacin have been reported. In both cases, elimination of methotrexate after high-dose therapy for cancer was substantially delayed with resultant dermatologic, bone marrow, hepatic, and renal toxicity. The mechanism is unclear but may involve alterations of methotrexate plasma protein binding, reduction in renal function (thus enhancing drug retention), inhibition of hepatic aldolase (thus reducing drug metabolism), or inhibition of renal tubular secretion (again, enhancing retention). Another issue with combination quinolone-high-dose methotrexate therapy is the effect of urinary alkalinization (required for safe high-dose methotrexate use) on the crystalluria risk of the quinolones [289].

A case report of lithium toxicity caused by concurrent levofloxacin use has also been reported. It appears that an acute deterioration in renal function occurred, causing retention of lithium. Whether the deterioration in renal function was due to the quinolone or the combination of the two drugs is not known [290].

Ciprofloxacin and moxifloxacin do not interact pharmacokinetically and pharmacodynamically with low-dose oral contraceptives containing 30 μg of ethinyl estradiol and 150 μg desogestrel per tablet [240, 291]. Levofloxacin does not alter the pharmacokinetics of zidovudine, efavirenz, or nelfinavir, and ciprofloxacin does not alter the pharmacokinetics of didanosine [33, 292, 293]. Note that there is an absorption interaction between ciprofloxacin and didanosine with cations as discussed previously [33, 34]. Ciprofloxacin does not interact pharmacokinetically with metronidazole [95].

The effect of quinolones on the pharmacokinetics and pharmacodynamics of ethanol are uncertain. One study using healthy volunteers found no pharmacokinetic or pharmacodynamic interaction with ciprofloxacin [294]. However, another study, again using healthy volunteers, found that ciprofloxacin 750 mg twice

daily significantly reduced the ethanol elimination rate (by mean 9%, range 5–18%) and increased the AUC (mean 12%) and time to zero blood ethanol concentration (mean 10%). This pharmacokinetic interaction was felt to be caused by the effect of ciprofloxacin on the ethanol-metabolizing intestinal flora and not its hepatic effects (on enzymes and blood flow) [295]. Perhaps the discrepancies between results of these two studies are caused by differences in subject numbers (statistical power), drug doses, or study design (randomized, parallel group vs. crossover).

The effects of multiple-dose oral ciprofloxacin of the single-dose pharmacokinetics of intravenous ropivacaine have been evaluated in nine healthy volunteers. The clearance of ropivacaine was significantly reduced (mean 31%) during concomitant therapy, with considerable intersubject variability (range 52% reduction to 39% enhancement). The CYP 1A2-mediated formation of 3-OH-ropivacaine was significantly retarded; the AUC and 24-h urinary excretion of this metabolite fell 38% and 27%, respectively. In contrast, the CYP3A4-mediated formation of (S)-2′,6′-pipecoloxylidide (PPX) was significantly enhanced, as manifested by mean increases in AUC and 24-h urinary excretion of 71% and 97%, respectively [296].

Pharmacokinetics of single-dose lidocaine and its monoethylglycinexylidide (MEGX) and 3-hydroxylidocaine metabolites were evaluated after multiple-dose oral ciprofloxacin administration. Ciprofloxacin at steady-state produced significant increases in lidocaine C_{max} (mean 12%, $p<0.05$), AUC (mean 26%, $p<0.01$), and t½ (mean 7%, $p<0.01$) and a decrease in total body clearance (mean 22%, $p<0.01$). Alterations seen with the MEGX metabolite included significant reductions in C_{max} (mean 40%, $p<0.01$), AUC (mean 21%, $p<0.01$), and the ratio of MEGX/lidocaine AUCs (mean 40%, $p<0.001$) while an increase was noted in t½ (mean 34%, $p<0.05$). Alterations with the 3-hydroxy metabolite included significant reductions in C_{max} (mean 23%, $p<0.05$), AUC (mean 14%, $p<0.01$) and the ratio of 3-hydroxy metabolite to lidocaine AUCs (mean 35%, $p<0.001$) [297].

A number of case reports have documented substantial reductions in serum phenytoin concentrations when ciprofloxacin therapy was initiated, an unexpected finding for a drug usually associated with enzyme inhibition and reduced drug clearance [298–303]. Indeed, results of a small study revealed that ciprofloxacin cotherapy was associated with nonsignificant reductions in mean steady-state phenytoin C_{max} (4%) and AUC (6%) [304]. The mechanism underlying this interaction may involve CYP2E1 induction by ciprofloxacin [281]. Caution is warranted when coadministering phenytoin and quinolones on the basis of this kinetic interaction as well as the epileptogenic potential of the quinolones (when quinolones and nonsteroidal anti-inflammatory drugs are coadministered).

The effect of combinations of enzyme inhibitors such as ciprofloxacin plus clarithromycin and ciprofloxacin plus cimetidine has been evaluated [252, 305–307]. Interestingly, clarithromycin (1,000 mg twice daily) did not significantly augment the effect of ciprofloxacin (500 mg twice daily) on steady-state theophylline pharmacokinetics [306]. In contrast, coadministration of cimetidine (400 mg twice daily or 600 mg four times a daily) plus ciprofloxacin (500 mg twice daily) exerted

a greater inhibitory effect on theophylline elimination than each agent alone, although the combined effect was less than the additive sum produced by the individual drugs [252, 305, 307].

Virtually no data are available regarding the interaction potential of quinolones with herbal products. Turmeric (*Curcuma longa*) is a medicinal plant extensively used in Ayurveda, Unani, and Siddha medicine as a home remedy for various disorders. Curcumin is the active moiety of this plant. It is known to inhibit CYP3A4 in the liver and induce P-glycoprotein. After oral curcumin pretreatment for 3 days in rabbits, single oral dose norfloxacin pharmacokinetics were significantly modified compared with those in the non-pretreated group. Mean absorption half-life was decreased (by 23%) while increases were seen in the absorption rate constant (by 41%), t½ (by 19%), AUC (by 52%), AUC (first moment) (by 69%), mean residence time (by 12%), and Vd (area) (by 31%) (all $p < 0.05$) [308].

The mechanism of these metabolic interactions is largely unexplored. It has been suggested that inhibition of metabolism may be related to the 4-oxo-metabolites of the quinolones but more recent data suggests that the sequence N* – C = N – C – N – C (where N* = nitrogen on the piperazine ring) is the entity responsible for metabolic inhibition [175, 309].

The structure-activity relationships for *in vitro* inhibition of human CYP1A2 have been investigated by Fuhr and coworkers. 3^1-oxo derivatives had similar or reduced activity and M1 metabolites (cleavage of piperazinyl substituent) had greater inhibitory activity compared with the parent molecule. Alkylation of the 7-piperazinyl substituent resulted in reduced inhibitory potency. Naphthyridines with an unsubstituted piperazinyl group in position 7 displayed greater inhibitory potency than did corresponding quinolone derivatives. Molecular modeling studies revealed that the keto group, carboxylate group, and core nitrogen at position 1 are likely to be the most important groups for binding to the active site of CYP1A2. These investigators also developed an equation to estimate *a priori* using quantitative structure-activity relationship analysis the potency of a given quinolone to inhibit CYP1A2 [310]. These investigators as well as Sarkar and coworkers have also developed *in vitro* human liver microsome models that may be useful in qualitatively predicting relevant drug interactions between quinolones and methylxanthines [311, 312].

Antofloxacin and caderofloxacin, new quinolones being developed in China, are derivatives of levofloxacin and ciprofloxacin, respectively. Neither agent appears to inhibit the activities of CYP1A2 or CYP2C9 in human microsomes [313]. However, no data have been published addressing their effects on other CYP isoenzymes in humans.

Clinically, caution is advised when using any quinolone in combination with a xanthine compound such as theophylline. Close monitoring of serum theophylline concentrations is recommended in any patient receiving these drugs. The clinical significance of inhibited metabolism of other drugs remains largely unclear at present. Until further data become available, clinicians should be aware of the possibility of reduced drug metabolism resulting in adverse effects whenever the quinolones are coadministered with drugs that depend on hepatic metabolism for their elimination.

9.2.4 Excretion Interactions

The quinolone antimicrobials are generally excreted into the urine at a rate higher than creatinine clearance, implying that tubular secretion is a prominent excretory pathway. Indeed, the administration of probenecid, a blocker of the anionic renal tubular secretory pathway, substantially reduces the renal elimination of norfloxacin, levofloxacin, gatifloxacin, ulifloxacin (active metabolite of prulifloxacin), and ciprofloxacin, reflecting competitive blockade of quinolone tubular secretion [314–319]. In contrast, probenecid coadministration does not affect the pharmacokinetics of moxifloxacin [320]. In addition, furosemide and ranitidine reduce the renal tubular secretion of lomefloxacin, again reflecting competitive blockade [321, 322]. There is thus a possibility that other drugs or endogenous compounds may interact with the quinolones at this site to competitively impair their mutual renal elimination, thus elevating blood concentrations and perhaps enhancing therapeutic and/or toxic effects.

For example, *in vitro*, the quinolones DX-619 and levofloxacin significantly and dose-dependently inhibited the uptake of creatinine in HEK cells expressing the renal organic cation transporter (hOCT2). At the highest quinolone concentrations tested, creatinine transport fell by 88% with both drugs. Whether these agents can interfere with creatinine clearance estimation *in vivo* to a clinically relevant degree is unknown [323].

In a related phenomenon, cyclosporine, a substrate of P-glycoprotein (P-gp), competed with pazufloxacin and sparfloxacin for renal tubular secretion via P-gp and related renal transporters in rats. This resulted in a significant increase in steady-state drug concentrations and significant reductions in total body clearance, renal clearance, unbound renal clearance, and tubular secretion clearance for both quinolones. This effect was not due to effects on multidrug resistance-associated protein-2 (MRP-2). These results must be validated in humans [324].

No data are available regarding the effects of antofloxacin and caderofloxacin on transporters such as P-gp, MRP-2, or organic anion and cation transporters in humans. However, in rats, inhibitors of multiple transporters (P-gp, MRP-2, organic anion and cation transporters, and breast cancer resistance protein) significantly reduced the biliary clearance of antofloxacin (all $p < 0.05$). The effects of antofloxacin on these transporters were not assessed [325].

Another example has been noted in a recent study of the interaction between ofloxacin and procainamide in healthy volunteers. Ofloxacin coadministration was associated with 22% and 30% falls in procainamide oral total body and renal clearances, respectively. However, neither the pharmacokinetics of N-acetylprocainamide nor the pharmacodynamics of the antiarrhythmic, as assessed by standard 12-lead and signal-averaged electrocardiograms, were affected by ofloxacin coadministration [326]. A more recent trial has compared oral levofloxacin to oral ciprofloxacin with regard to the interaction potential with procainamide and NAPA in ten healthy volunteers. The only significant effects of ciprofloxacin (500 mg twice daily for 5 days) were a mean 15% reduction in procainamide renal clearance and a mean 10% reduction in the ratio of NAPA renal clearance to creatinine clearance (both

$p < 0.05$). In levofloxacin (500 mg once daily for 5 days) recipients, the following significant ($p < 0.05$) effects were noted: mean reductions in procainamide total body and renal clearances, fraction excreted in urine in unchanged form, and ratio of procainamide renal clearance to creatinine clearance of 17%, 26%, 11%, and 29%, respectively; mean increase in procainamide t½ of 19%; and mean reductions in NAPA renal clearance, fraction eliminated in urine in unchanged form, and the ratio of NAPA renal clearance to creatinine clearance of 21%, 20%, and 28%, respectively. This interaction was thus potentially more clinically-problematic with levofloxacin than with ciprofloxacin. In fact, of the ten volunteers, only one had a reduction in procainamide total body clearance exceeding 25% with ciprofloxacin while four had reductions in total body clearance of 30% or greater and three of the four had reductions in NAPA renal clearance of 30% or greater with levofloxacin [327].

The 14.4% decrease in garenoxacin clearance in recipients of pseudoephedrine, identified in a population pharmacokinetic analysis of phase II respiratory tract infection clinical trial data (N = 721 patients, N = 1,908 plasma concentrations), was felt to be due to competition for active tubular secretion [328].

9.3 Pharmacodynamic Interactions

9.3.1 Quinolones and NSAIDs

Central nervous system (CNS) toxicity, including tremulousness and seizures, is rare with quinolones [329–338]. In some cases, concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) have been noted [332, 333, 336, 339]. It was the report of multiple cases of seizures associated with the concurrent use of enoxacin and fenbufen (the latter being an NSAID not available in the US) to Japanese regulatory authorities that led to a plethora of investigations into the possible interaction between quinolones and NSAIDs [336, 339].

Some rat studies have suggested that NSAIDs such as fenbufen may enhance CNS uptake of quinolones such as ciprofloxacin, norfloxacin, and ofloxacin [340, 341]. However, other studies conducted in the same species have documented an absence of a pharmacokinetic interaction between fenbufen and sparfloxacin, ciprofloxacin, enoxacin, and ofloxacin [342–345]. In addition, human studies have the documented absence of a pharmacokinetic interaction between ciprofloxacin and fenbufen and between pefloxacin or ofloxacin and ketoprofen [346–348]. However, with single-dose diclofenac coadministration, ciprofloxacin pharmacokinetics were modestly affected. Mean ciprofloxacin C_{max}, AUC, and apparent oral clearance increased 58% and 46% and decreased 28%, respectively [349]. Overall, any interaction that occurs between quinolones and NSAIDs is thus probably purely pharmacodynamic in nature.

Numerous *in vitro* models have been utilized to elucidate the mechanism(s) underlying the epileptogenic effects of quinolones with/without concurrent NSAID

administration: voltage-clamped rat hippocampal or dorsal root ganglion or frog dorsal root ganglion neurons in cell culture, (^{3}H)-muscimol or GABA (γ-aminobutyric acid) binding to rat GABA synaptic receptors, and (^{3}H)-muscimol binding to human GABA synaptic receptors [350–355]. Quinolones function as weak, dose-dependent $GABA_A$ receptor antagonists [350, 351, 354, 356]. Quinolones vary in their potencies as receptor antagonists [350–355, 357–361], probably at least partly because of differences in the degree to which their 7-piperazine substituents look like GABA [352]. In one study, the rank order of quinolones in terms of potency as inhibitors of (^{3}H)-muscimol binding to murine GABA synaptic receptors was prulifloxacin = norfloxacin > ciprofloxacin ≥ enoxacin > gatifloxacin ≥ ofloxacin = tosufloxacin = lomefloxacin > levofloxacin ≥ sparfloxacin ≥ pazufloxacin = fleroxacin [362]. This receptor antagonism is greatly enhanced by concurrent exposure to fenbufen or its active metabolite, biphenyl acetic acid [351, 352, 354–356, 358, 360, 363–365]. Flurbiprofen, indomethacin, ketoprofen, naproxen, and ibuprofen are much weaker potentiators [354, 361]; diclofenac and piroxicam do not potentiate quinolone $GABA_A$ receptor binding at all [353, 361]. In one study, the rank order of NSAIDs in potentiating receptor antagonism was biphenyl acetic acid (potent, concentration-dependent inhibition) followed by zaltoprofen, loxoprofen, lornoxicam, and diclofenac, all of which were virtually inactive [362]. This receptor antagonism appears to occur principally in the hippocampus and frontal cortex [355, 366]. *In vivo* studies in rats evaluating the epileptogenic potential of quinolones and potentiation by biphenyl acetic acid corroborate these *in vitro* data [367, 368]. The mechanism underlying this interaction is not established but does not appear to be mediated via benzodiazepine receptor effects [361]. Studies have suggested that the mechanism may involve enhanced cerebral glutamate (an excitatory amino acid neurotransmitter) or nitric acid concentrations [369–371]. Using a pharmacodynamic model created using *in vitro* receptor occupancy data and *in vivo* human pharmacokinetic data, the combination of fenbufen with prulifloxacin or enoxacin were considered the most hazardous in terms of seizure risk [362].

Although of theoretical interest, the pharmacodynamic interaction between quinolones and NSAIDs is probably of little clinical relevance so long as fenbufen is not concurrently used with enoxacin or, possibly, prulifloxacin.

9.3.2 Quinolones and Electrophysiology

Sparfloxacin, grepafloxacin, levofloxacin, ciprofloxacin, gatifloxacin, and moxifloxacin have been associated with prolongation of the QTc interval on the electrocardiogram, which in a few cases has been associated with the development of polymorphous ventricular tachycardia (torsades des pointes), which in turn can degenerate into ventricular fibrillation [372–390]. One case of levofloxacin-associated torsades des pointes in the absence of QTc interval prolongation has also been reported [391]. Grepafloxacin was removed from the market by its manufacturer in October 1999 because of its electrophysiologic adverse event profile.

Few data are available regarding the epidemiology of electropathophysiology in quinolone recipients. One group utilized the Varese province of Italy as the study database, performing a case-control study of subjects with ventricular arrhythmias or cardiac arrest between July 1998 and December 2003. A total of 1,275 cases and, 9,189 controls formed the study population. The adjusted odds ratio for recent (within 4 weeks) exposure to quinolones was 3.58 (95% CI, 2.51–5.12) [392]. Another group evaluated drug-induced torsades des pointes in patients at least 80 years old. In 24 reports on 25 patients 80–95 years old, the most prevalent risk factors were non-modifiable (88% were female, 76% had structural heart disease, and 64% were female with structural heart disease). Among potentially-modifiable risk factors, 44% received QT interval-prolonging drugs despite pre-existing prolonged QT intervals and 36% received two or more concurrent QT interval-prolonging drugs. The most prevalent QT interval-prolonging drugs were quinolone (N = 3) and macrolide (N = 7) antimicrobials in 36%. All but three individuals had at least one modifiable risk factor [393].

Almost no data are available regarding the relative risk of cardiac arrhythmias with various quinolones. In a retrospective analysis utilizing the FDA adverse event reporting database from January 1, 1996 through May 2, 2001, the rates of torsades des pointes with ciprofloxacin, levofloxacin, and gatifloxacin were 0.3, 5.4, and 27 per 10 million prescriptions, respectively ($p < 0.05$ for all pairwise comparisons) [378]. However, the numerous potential problems with study design preclude generalizability of these results [378, 379].

Numerous *in vitro* models have been utilized to elucidate the mechanism underlying the arrhythmogenic effects of these agents: HERG (human ether-a-go-go-related gene) potassium channels, mouse atrial tumor cells, guinea pig myocardium, and canine Purkinje fibers [394–396]. The potency of quinolones in inhibiting HERG-mediated outward potassium currents was sparfloxacin > grepafloxacin > moxifloxacin = gatifloxacin > levofloxacin = ciprofloxacin > ofloxacin in one study; for the other, it was sparfloxacin > moxifloxacin = grepafloxacin >>> ciprofloxacin [394, 397]. Similar findings were noted for mouse atrial tumor cell potassium channels (sparfloxacin > moxifloxacin >> gatifloxacin = grepafloxacin) [395]. In guinea pig ventricular myocardium, prolongation of action potential duration was 41%, 25%, 24%, and 13% for sparfloxacin, moxifloxacin, grepafloxacin, and gatifloxacin, respectively, and the prolongation with levofloxacin, sitafloxacin, trovafloxacin, ciprofloxacin, gemifloxacin, and tosufloxacin was essentially zero [396]. Similar findings were noted with canine cardiac Purkinje fibers (sparfloxacin > grepafloxacin = moxifloxacin > ciprofloxacin) [398]. The maximum degree of blockade of HERG current in transfected HEK293 cells was only $12.3 \pm 3.3\%$ at the highest tested concentration (335 μM) of ulifloxacin, the active metabolite of prulifloxacin [399].

In vivo, quinolones again differed in their propensity to alter cardiac electrophysiology and cause ventricular arrhythmias. In rabbits, the potency of quinolones in prolonging the maximum QT interval was sparfloxacin > moxifloxacin = gatifloxacin = grepafloxacin, and ventricular tachycardia and torsades des pointes were only induced in sparfloxacin-treated animals [395]. In rabbits, the rank order potency of quinolones in prolonging the maximum QT interval was sparfloxacin = gatifloxacin

>> levofloxacin = ulifloxacin and conduction blocks, premature ventricular contractions, and torsades des pointes were only induced in sparfloxacin- and gatifloxacin-treated animals [400]. In dogs receiving 3 and 30 mg/kg iv doses of sparfloxacin, cardiac output and ventricular repolarization and refractory periods rose, and heart rate fell. Blood pressure fell only after the high-dose administration. The increase in repolarization exceeded that of refractoriness, enhancing arrhythmia vulnerability and the prolongation in repolarization was of a reverse use-dependent type (i.e., prolongation was especially enhanced at lower heart rates) [401]. In dogs with complete atrioventricular block and dogs under halothane anesthesia, oral and intravenous levofloxacin produced essentially no adverse electrophysiologic and hemodynamic effects, and sparfloxacin had dose-dependent arrhythmogenic, electrophysiologic, and negative chronotropic effects [402]. In conscious dogs dosed with oral prulifloxacin 150 mg/kg/day for 5 days and followed by telemetry, no significant effect was noted on the QTc interval at any time [399].

In summary, the *in vitro* and *in vivo* (animal) studies revealed that quinolones cause a drug-specific, dose-dependent prolongation in QTc interval by inhibiting outward potassium currents in myocytes. In turn, this prolongation in action potential duration leads to a drug-specific risk of ventricular tachycardia and torsades des pointes. However, the lack of full agreement of the results of evaluations of potassium channel inhibition and QT interval prolongation, in terms of relative drug potencies, suggests that more than potassium channel inhibition may be involved [395].

In healthy volunteers, multiple doses of oral sparfloxacin (200, 400, 800 mg daily for 3 days) produced a dose-dependent prolongation in QTc interval (mean increases from baseline on day 1 were 9, 16, and 28 ms, respectively; and on day 3 were 7, 12, and 26 ms respectively) [403]. The pharmacodynamic interaction of sparfloxacin and terfenadine administered in usual therapeutic doses to healthy volunteers, in terms of QTc interval prolongation, was additive in nature (no pharmacokinetic interaction was found) [404]. In a retrospective review of 23 patients receiving 500 mg levofloxacin once daily in whom pre- and intratherapy electrocardiograms were available, the QTc prolongation exceeded 30 ms in four patients (17%) and 60 ms in two patients (9%), with an absolute QT prolongation to more than 500 ms in four patients (17%) [405]. Single oral doses of moxifloxacin 400 and 800 mg caused 4.0 ± 5.1 (mean ± SD) and 4.5 ± 3.8% prolongation of the QTc interval at rest, respectively (both $p < 0.05$) in healthy volunteers. Significant QTc interval prolongation occurred at all heart rates and across the entire RR interval range (400–1,000 ms). The effect was similar in males and females and did not show dose dependence. No significant reverse rate dependence was seen. Statistically significant but weak correlations existed between moxifloxacin plasma concentrations versus QT interval ($r = 0.35$) and change in QT interval with placebo ($r = 0.72$) [406].

In another healthy volunteer study, periodic and continuous ECGs were recorded before and after administration of single doses of intravenous levofloxacin 500, 1,000, and 1,500 mg. Using periodic ECG data, the only significant differences noted were the mean QTc intervals at 1.5 h after administration of 1,500 mg (Bazett formula: 415.33 vs 399.48 ms with placebo; Fredericia correction: 409.67 vs 400.46 ms with placebo) and 2.0 h after administration of 1,500 mg (corresponding values of 414.10 vs 398.92 and 409.58 vs 400.10 ms) (all $p < 0.05$). Using continuous

Table 9.3 Drugs prolonging the QTc interval that may potentially interact pharmacodynamically with selected quinolone antimicrobials

• Cisapride	• Macrolides (erythromycin, clarithromycin, spiramycin)
• Trimethoprim/sulfamethoxazole	• Chloroquine
• Pentamidine	• Phenothiazines
• Halofantrine	• Tricyclic and tetracyclic antidepressants
• Quinidine	• Disopyramide
• Procainamide	• Lidocaine, mexiletine (rare)
• Ibutilide	• Amiodarone (rare)
• β-Blockers (rare)	• Lidoflazine
• Bepridil	• Dofetilide
• Sotalol	• Encainide
• Flecainide	

Source: From Doig [409]

ECG data, significant QTc interval prolongation occurred after administration of 1,000 mg (Bazett correction: in 3/4 baseline correction methods, mean change ranged from 2.8 to 3.9 ms [$p \leq 0.05$]; Fredericia correction: in 1/4 baseline correction methods, the mean change was 2.8 ms [$p \leq 0.05$]) and 1,500 mg (Bazett correction: in 4/4 baseline correction methods, mean change ranged from 6.4 to 7.7 ms [$p \leq 0.001$]; Fredericia correction: in 4/4 baseline correction methods, mean change ranged from 4.9 to 6.9 ms [$p \leq 0.001$]) [407].

Only one comparative study of the effect of quinolones on QTc interval in humans has been published. Single oral doses of 1,000 mg levofloxacin, 1,500 mg ciprofloxacin, and 800 mg moxifloxacin were compared in healthy volunteers. Mean QT and QTc interval prolongation was significantly greater for moxifloxacin compared to placebo for all end points, but it was generally not so for levofloxacin and ciprofloxacin (the exception was that the postdose QTc and QTc at 1.5, 2, and 2.5 h postdose, using the Bazett method, were significantly increased for levofloxacin vs. placebo). The proportion of subjects with prolongation in QTc interval of 30 ms or greater was higher with moxifloxacin (72–81%) compared to levofloxacin (33–38%) and ciprofloxacin (34–40%) [408].

Caution is warranted with the use of these agents in patients receiving other drugs with similar electrophysiologic effects (Table 9.3) [409–411]. In addition, caution is warranted in using these agents in patients with an abnormal pretreatment QT interval, pretreatment electrolyte abnormalities (e.g. hypokalemia, hypomagnesemia, rarely hypocalcemia), starvation/liquid-protein fast diets, and a prior or current history of coronary heart disease, bradyarrhythmias, or atrial fibrillation [409–411].

9.3.3 Quinolones and Immunosuppressants

Based upon the ability of the quinolones to significantly enhance interleukin 2 production significantly, *ex vivo* studies have been conducted evaluating the effect of

quinolones on lymphocyte proliferation and the ability of tacrolimus and sirolimus to inhibit it. Quinolones had no significant effect on either human lymphocyte proliferation or the ability of tacrolimus or sirolimus to inhibit it. Enoxacin, lomefloxacin, norfloxacin, and ciprofloxacin were the quinolones tested. Thus, no significant pharmacodynamic interaction between the quinolones and tacrolimus/sirolimus appears to exist [412, 413].

9.3.4 Quinolones and Glucose Homeostasis

Case reports have documented pharmacodynamic interactions between quinolones and oral hypoglycemics in patients with type 2 diabetes mellitus, leading to symptomatic, prolonged hypoglycemia. Implicated agents have included oral levofloxacin with 20 mg glyburide daily [414]; oral ciprofloxacin with 2.5 and 5 mg glyburide daily [415, 416]; and oral gatifloxacin with 1.5 mg repaglinide daily, 5 mg glyburide daily plus 30 mg pioglitazone daily, 3 mg glimepiride daily [417], 5 mg glyburide daily [418], 2.5 mg glyburide daily [419], and insulin plus repaglinide 6 mg daily plus voglibose 0.6 mg daily [420]. In the cases involving gatifloxacin, the profound hypoglycemia occurred after the first dose of gatifloxacin and persisted until the drug was discontinued. After recovery of the blood glucose, oral hypoglycemic therapy was restarted and blood glucose values returned to pre-gatifloxacin baseline levels. Case reports have also documented gatifloxacin-associated hyperglycemia, including hyperosmolar nonketotic hyperglycemia, in patients with no history of diabetes [420, 421].

During the postmarketing period, reports have been made to the US Food and Drug Administration's MedWatch® program regarding serious disturbances in glucose homeostasis in gatifloxacin recipients. Hypoglycemic episodes, some severe, have been reported in patients with diabetes mellitus treated with either sulfonylurea or nonsulfonylurea oral hypoglycemics. These events frequently occurred on day 1 of therapy and usually within 3 days of initiating gatifloxacin therapy. Hyperglycemic episodes, in some cases severe and associated with hyperosmolar nonketotic hyperglycemic coma, have also been reported in patients with diabetes mellitus, mainly between days 4 and 10 of gatifloxacin therapy. Some of these hypo- and hyperglycemic events were life-threatening, and many required hospitalization. Episodes of hyperglycemia, including hyperosmolar nonketotic hyperglycemic coma, have also occurred in patients without prior documented diabetes mellitus. Elderly subjects with age-related reductions in renal function and underlying medical problems or concomitant medications associated with hyperglycemia may be at particular risk [422].

Glucose homeostasis abnormalities (GHAs) reported to the FDA in the MedWatch® program from November 1997 to September 2003, inclusive, have been reviewed for concurrent use of ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin. These events were identified under 14 unique coding items. Rates were calculated using US retail pharmacy prescriptions as the denominator. These four

quinolones accounted for 16,868 adverse event reports (10,025 unique US reports). Of these US reports, 568 were GHA reports and 25 fatal GHA reports. Gatifloxacin was associated with 80% of all GHA reports and 68% of fatal GHA reports. Spontaneous reporting rates were higher for gatifloxacin than the three comparators combined for both total GHA reports (477/10 million prescriptions vs. 8, $p<0.0001$) and fatal GHA reports (18/10 million prescriptions vs 0.6, $p<0.0001$). GHA reports constituted 24% of gatifloxacin and 1.4% of the combined comparator quinolone adverse event reports. For gatifloxacin, subjects involved in GHA reports were older (median 74 vs 61 years old, $p<0.0001$) and were more likely to be taking antidiabetic medications (69 vs 14%, $p<0.0001$) than subjects with other types of adverse events. Whether or not the true population rate of GHAs is 56-fold higher for gatifloxacin compared with the other quinolones can be questioned, based on the multiple biases and limitations of the database. These data need to be assessed in the context of other data in order to establish causality [423].

In another population-based analysis, two nested case-control studies were conducted, using data from 1.4 million elderly (≥66 years old) residents of Ontario, Canada. In study 1, case patients were treated in the hospital setting for hypoglycemia after outpatient treatment with macrolide, second-generation cephalosporin, or respiratory quinolone (gatifloxacin, levofloxacin, moxifloxacin, or ciprofloxacin) agents. In study 2, case patients were those who received hospital care for hyperglycemia. For each case patient, up to five controls were identified, matched by age, sex, presence/absence of diabetes, and timing of antimicrobial therapy [424].

For study 1, 788 patients treated for hypoglycemia within 30 days of completion of antimicrobial therapy were identified (April 2002-March 2004). As compared with macrolides (e.g. erythromycin, azithromycin, and clarithromycin), gatifloxacin and levofloxacin recipients were at significantly greater risk for the development of hypoglycemia (adjusted odds ratio [aOR] of 4.3 [95% CI, 2.9–6.3] and 1.5 [95% CI, 1.2–2.0], respectively) in the overall population. In contrast, there was no relationship of the development of hypoglycemia with the use of moxifloxacin, ciprofloxacin, or second-generation cephalosporins (e.g. cefaclor and cefuroxime axetil). Similar findings held true when the analysis was repeated in patients with/without diabetes with one exception. The relationship of hypoglycemia to levofloxacin use in patients without diabetes was not significant (aOR, 2.1; 95% CI, 0.7–6.0) [424].

For study 2, 470 patients treated for hyperglycemia within 30 days of completion of antimicrobial therapy were identified. Compared with macrolides, only gatifloxacin use was significantly associated with the development of hyperglycemia (aOR, 4.3; 95% CI, 2.9–6.3). Similar findings were noted in patients with or without diabetes, with the additional finding of a borderline increase in risk in levofloxacin recipients in the population of patients with diabetes (aOR, 1.5; 95% CI, 1.2–2.0) [424].

Last, all patients ≥66 years old treated with antimicrobials during the study period were identified. Those hospitalized within 90 days before receiving an antimicrobial prescription as well as those who received another antimicrobial prescription within

30 days were excluded. Hospital visits for dysglycemia during the 30-day period after the start of antimicrobial therapy were identified for each patient. In the context of multiple antimicrobial prescriptions, each treatment course was considered separately. A total of 16,697 gatifloxacin treatment courses were associated with 178 hospitalizations (1.1%) for dysglycemia within 30 days. This rate substantially exceeded those for ciprofloxacin (0.3%), levofloxacin (0.3%), moxifloxacin (0.2%), second-generation cephalosporins (0.2%), and macrolides (0.1%) [424].

A retrospective case-control study of the risk of severe hypo- or hyperglycemia in recipients of gatifloxacin, levofloxacin, ciprofloxacin, and azithromycin (control) was conducted using the Veteran's Affairs outpatient database (from October 1, 2000 to September 30, 2005). In the final study cohort, 874,682 and 402,566 patients received the three quinolones and azithromycin, respectively. The event rates for hypoglycemia and hyperglycemia/1,000 patients (gatifloxacin/levofloxacin/ciprofloxacin/azithromycin) were 0.35/0.19/0.10/0.07 and 0.45/0.18/0.12/0.10, respectively (both $p < 0.001$). In patients without diabetes, no quinolone was statistically associated with either hypo- or hyperglycemia but the statistical power of this analysis was low due to the small number of events (total $N = 51$). In patients with diabetes, significant odds ratios (ORs) for severe hypoglycemia (versus azithromycin) were 4.5 (95% CI, 2.7–6.6) and 2.1 (95% CI, 1.4–3.3) for gatifloxacin and levofloxacin, respectively. Corresponding significant ORs for severe hyperglycemia were 4.5 (95% CI, 3.0–6.9) and 1.8 (95% CI, 1.2–2.7). Ciprofloxacin was not statistically associated with either glucose perturbation. The effects of gatifloxacin significantly exceeded those of levofloxacin and ciprofloxacin for both hypo- and hyperglycemia (all $p < 0.001$) [425].

The hypo- and hyperglycemic effects of gatifloxacin and ceftriaxone (control) were compared in hospitalized patients with community-acquired pneumonia/acute exacerbation of chronic bronchitis. This was done in a retrospective cohort study conducted using data collected in a tertiary care U.S. hospital from July 1, 2001 through December 31, 2004. Of the 1,504 patients enrolled, 825 and 679 received gatifloxacin and ceftriaxone, respectively. The overall OR for hypoglycemia (i.e. blood sugar <46 mg%) for gatifloxacin (versus ceftriaxone) was 2.34 (95% CI, 1.4–4.0), and was similar for those with (OR, 2.5) and those without (OR, 2.4) a diagnosis of diabetes. The overall OR for hyperglycemia (i.e. >200 mg%) for gatifloxacin (versus ceftriaxone) was non-significant (1.06, [95% CI, 0.8–1.4]). In those with diabetes, the OR was 0.4 (95% CI, 0.2–0.6) while for those without diabetes, the OR was 1.64 (95% CI, 1.1–2.4) [426].

Studies have been conducted to evaluate the mechanism of this interaction. Altered pharmacokinetics of oral hypoglycemics do not appear to be the explanation as gatifloxacin, ciprofloxacin, and moxifloxacin do not significantly alter glyburide pharmacokinetics [240, 427, 428].

Most studies have concentrated on a pharmacodynamic etiology for this interaction. In healthy volunteers treated for 14 days with various doses of once-daily intravenous gatifloxacin (200, 400, 600, 800 mg), a transient, dose-dependent reduction in fasting serum glucose concentration at the end of the infusion without corresponding changes in serum insulin/C-peptide concentrations occurred.

No drug-associated effect was noted on predose fasting serum glucose concentrations throughout therapy or on the dynamics of the oral glucose tolerance test (OGTT) at the end of therapy [429].

In patients with type 2 diabetes mellitus stabilized on diet and exercise therapy, multiple oral dose gatifloxacin (400 mg once daily for 10 days) produced no significant effects on the dynamics of the OGTT, fasting serum insulin and glucose profiles over 6 h after dosing on study days 1 and 10 and predose fasting insulin, glucose, and C-peptide concentrations on study days 2, 4, 6, 8, and 11 compared with placebo. The only significant drug-associated effect was a significant increase in the 0- to 6-h postdose fasting serum insulin concentrations on study day 1. In the same study, 500 mg ciprofloxacin twice daily produced virtually identical results except that the significant drug-associated increase in the 0- to 6-h postdose fasting serum insulin concentrations occurred on study day 10 [430].

In patients with type 2 diabetes mellitus stabilized on metformin or metformin-glyburide combination therapy, 400 mg oral gatifloxacin once daily for 14 days produced an initial hypoglycemia (study days 1 and 2) caused by elevations in serum insulin concentrations, followed by hyperglycemia (study day 4 onwards). In some cases, the hyperglycemia was symptomatic, requiring single doses of insulin for correction. Serum glucose concentrations did not always return to baseline, even by 1 month after stopping the drug [422]. In a similar patient population being treated with glyburide, 10 days of 400 mg gatifloxacin once daily caused serum insulin concentrations to fall by 30–40% during OGTT. No significant effect on serum glucose concentrations was noted [427]. Last, moxifloxacin has been reported not to alter serum insulin dynamics in patients with type 2 diabetes mellitus stabilized on glyburide therapy. The increases reported in serum glucose 0- to 6-h postdose AUC (mean 7%) and C_{max} (mean 6%), although statistically significant, were felt to be clinically-insignificant [240].

At present, gatifloxacin appears to be the quinolone most associated with perturbations in glucose homeostasis, especially in patients diagnosed with diabetes mellitus and receiving insulin or oral hypoglycemic therapy. This effect is seen only with systemic use of the drug and not with topical (ophthalmic) use. Due to the prevalence of GHAs with systemic gatifloxacin therapy and its contraindication in patients with diabetes [431], the manufacturer made the decision to withdraw systemic formulations from the marketplace worldwide [432].

9.4 Physiochemical Interactions

Physicochemical interactions involve physical incompatibilities between injectable quinolones and intravenous fluids and admixed medications. Studies of these types of interactions involve combinations of visual inspection (for precipitation), assessment of pH changes, and quantitation of drug and breakdown products. Table 9.4 illustrates the known incompatibilities of the injectable quinolones [433]. A case report of an interaction between indomethacin and ciprofloxacin, both administered as eyedrops following phototherapeutic keratectomy, has been published.

Table 9.4 Intravenous fluid and admixed drug incompatibilities with injectable quinolones

	Incompatibilities	
Quinolone	LVP IV fluid	Admixed drugs
Ciprofloxacin	Sodium bicarbonate[a], sodium phosphate[a]	Amoxicillin, amphotericin B, amoxicillin/clavulanate, clindamycin, floxacillin, furosemide[b], cefepime[b], ceftazidime, cefuroxime, heparin[c], metronidazole, propofol[b], hydrocortisone[b], potassium phosphates[b], mezlocillin[c], ampicillin/sulbactam[c], piperacillin, ticarcillin, aminophylline[c], teicoplanin, magnesium[b], dexamethasone[b], phenytoin[b], warfarin[b], methylprednisolone[b], TPN[b], pantoprazole[d], azithromycin[b], drotrecogin alfa (activated)[b], lansoprazole[b], pemetrexed[b]
Gatifloxacin	None reported	Amphotericin B[b], cefoperazone[b], cefoxitin[b], diazepam[b], furosemide[b], heparin[b], phenytoin[b], piperacillin[b], piperacillin/tazobactam[b], potassium phosphates[b], vancomycin[b], amphotericin B cholesteryl sulfate complex[b], lansoprazole[b]
Levofloxacin	Mannitol, sodium bicarbonate	Acyclovir[b], alprostadil[b], furosemide[b], heparin[b], indomethacin[b], insulin[b], nitroglycerin[b], nitroprusside[b], propofol[b], azithromycin[b], drotrecogin alfa (activated) [b], lansoprazole[b]
Moxifloxacin	None reported	Not assessed
Ofloxacin	None reported[e]	Floxacillin, cefepime[b], amphotericin B cholesteryl sulfate complex[b], doxorubicin[b], heparin[b], lansoprazole[b]
Trovafloxacin (alatrofloxacin)	Lactated Ringer's, normal saline (with/without other diluents)	Aztreonam[b], ceftazidime[b], ceftriaxone[b], famotidine[b], furosemide[b], heparin[b], insulin[b], magnesium sulfate[b], midazolam[b], morphine[b], piperacillin/tazobactam[b], ticarcillin/clavulanate[b]

Source: From Trissel [433]
LVP large volume parenteral
[a]Incompatible on simulated Y-site administration as well as when used as an LVP intravenous fluid
[b]Incompatible (evaluated only on simulated Y-site administration)
[c]Incompatible on simulated Y-site administration as well as when admixed into an LVP intravenous fluid
[d]Incompatible (evaluated only in syringe)
[e]Use caution in light of the issues with mannitol and sodium bicarbonate LVP solutions and levofloxacin

The interaction appeared to be physicochemical in nature, as a precipitate containing both drugs was deposited in the cornea [434].

9.5 Summary

The quinolone antimicrobials have proven to be important additions to our therapeutic armamentarium based on their broad spectra of activity, favorable pharmacologic properties, and ease and cost-efficiency of administration. However, with their

Table 9.5 Clinically-significant pharmacokinetic quinolone-drug interactions

Interacting drug	Results	Comments
Ca, Mg, Al-containing antacids; Ca supplements; iron or mineral preparations; sucralfate; didanosine	Reduced quinolone absorption	Avoid quinolone therapy if possible; otherwise space administrations as far apart as possible
Theophylline	Reduced theophylline metabolism	Follow levels if on enoxacin, grepafloxacin, tosufloxacin, prulifloxacin, pazufloxacin (IV), ciprofloxacin or norfloxacin; watch clinical status if on other quinolones
Caffeine	Reduced caffeine metabolism	Reduce consumption of caffeinated foods/beverages, follow clinical status
Warfarin	(?) Reduced warfarin metabolism	Follow INR intra- and post-quinolone therapy and adjust warfarin dose accordingly

widespread use comes the realization that drug-drug interactions will occur with these agents. It is important that the clinician be aware of clinically-significant interactions with these agents and pay attention to other potential interactions with drugs exhibiting narrow therapeutic/toxic dose ratios (Table 9.5).

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References

1. Yuk JH, Williams TW Jr. Drug interaction with quinolone antibiotics in intensive care unit patients [letter]. Arch Intern Med 1991;151:619.
2. Lomaestro BM, Lesar TS. Concurrent administration of ciprofloxacin and potentially interacting drugs [letter]. Am J Hosp Pharm 1989;46:1770.
3. Bowes J, Graffunder EM, Lomaestro B, Venezia RA. Concomitant administration of drugs known to decrease the systemic availability of gatifloxacin. Pharmacotherapy 2002; 22:800,801.
4. Barton TD, Fishman NO, Weiner MG, et al. High rate of coadministration of di- or tri-valent cation-containing compounds with oral fluoroquinolones: risk factors and potential implications. Infect Control Hosp Epidemiol 2005;26:93–99.
5. Hoffken G, Borner K, Glatzel PD, et al. Reduced enteral absorption of ciprofloxacin in the presence of antacids [letter]. Eur J Clin Microbiol 1985;4:345.
6. Shiba K, Saito A, Shimada J, et al. Interactions of fleroxacin with dried aluminum hydroxide gel and probenecid. Rev Infect Dis 1989;11(suppl 5):S1097,S1908.
7. Shiba K, Sakai O, Shimada J, Okazaki O, Aoki H, Hakusui H. Effects of antacids, ferrous sulfate, and ranitidine on absorption of DR-3355 in humans. Antimicrob Agents Chemother 1992;36:2270–2274.
8. Campbell NRC, Kara M, Hasinoff B, Haddara WM, McKay DW. Norfloxacin interaction with antacids and minerals. Br J Clin Pharmacol 1992;33:115,116.

9. Okhamafe AO, Akerele JO, Chukuka CS. Pharmacokinetic interactions of norfloxacin with some metallic medicinal agents. Int J Pharm 1991;68:11–18.
10. Akerele JO, Akhamafe AO. Influence of co-administered metallic drugs on ofloxacin pharmacokinetics. J Antimicrob Chemother 1991;28:87–94.
11. Shiba K, Yoshida M, Sakai O, et al. Pharmacokinetics and clinical studies on NM441. Jap J Chemother 1996;44(suppl 1):263–278.
12. Niki Y. Pharmacokinetics and safety assessment of tosufloxacin tosilate. J Infect Chemother 2002;8:1–18.
13. Minami R, Nakamura C, Inotsume N, et al. Effects of aluminum hydroxide and famotidine on bioavailability of tosufloxacin in healthy volunteers. Antimicrob Agents Chemother 1998;42:453–455.
14. Sanchez Navarro A, Martinez Cabarga M, Dominguez-Gil Hurle A. Oral absorption of ofloxacin administered together with aluminum. Antimicrob Agents Chemother 1994;38: 2510–2512.
15. Rambout L, Sahai J, Gallicano K, Oliveras L, Garber G. Effect of bismuth subsalicylate on ciprofloxacin bioavailability. Antimicrob Agents Chemother 1994;38:2187–2190.
16. Sahai J, Healy D, Stotka J, Polk R. The influence of chronic administration of calcium carbonate on the bioavailability of oral ciprofloxacin. Br J Clin Pharmacol 1993;35:302–304.
17. Frost DW, Lasseter KC, Noe AJ, Shamblen EC, Lettieri J. Effect of aluminum hydroxide and calcium carbonate antacids on the bioavailability of ciprofloxacin. Antimicrob Agents Chemother 1992;36:830–832.
18. Fleming LW, Moreland TA, Stewart WK, Scott AC. Ciprofloxacin and antacids [letter]. Lancet 1986;2:294.
19. Lomaestro BM, Baillie GR. Effect of staggered dose of calcium on the bioavailability of ciprofloxacin. Antimicrob Agents Chemother 1991;35:1004–1007.
20. Sanchez Navarro A, Martinez Cabarga M, Dominguez-Gil Hurle A. Comparative study of the influence of Ca^{2+} on absorption parameters of ciprofloxacin and ofloxacin. J Antimicrob Chemother 1994;34:119–125.
21. Lomaestro BM, Baillie GR. Effect of multiple staggered doses of calcium on the bioavailability of ciprofloxacin. Ann Pharmacother 1993;27:1325–1328.
22. Lacreta FP, Kaul S, Kollia GD, Duncan G, Randall DM, Grasela DM. Pharmacokinetics (PK) and safety of gatifloxacin in combination with ferrous sulfate or calcium carbonate in healthy volunteers. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1999. Abstract 198.
23. Lehto P, Kivisto KT. Different effects of products containing metal ions on the absorption of lomefloxacin. Clin Pharmacol Ther 1994;56:477–482.
24. Stass H, Wandel C, Delesen H, Moller JG. Effect of calcium supplements on the oral bioavailability of moxifloxacin in healthy male volunteers. Clin Pharmacokinet 2001;40(suppl 1):27–32.
25. Pletz MW, Petzold P, Allen A, Burkhardt O, Lode H. Effect of calcium carbonate on bioavailability of orally administered gemifloxacin. Antimicrob Agents Chemother 2003; 47:2158–2160.
26. Nix DE, Wilton JH, Ronald B, et al. Inhibition of norfloxacin absorption by antacids. Antimicrob Agents Chemother 1990;34:432–435.
27. Flor S, Guay DRP, Opsahl JA, et al. Effects of magnesium-aluminum hydroxide and calcium carbonate antacids on bioavailability of ofloxacin. Antimicrob Agents Chemother 1990; 34:2436–2438.
28. Kays MB, Overholser BR, Mueller BA, Moe SM, Sowinski KM. Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. Am J Kid Dis 2003;42:1253–1259.
29. Kato R, Ueno K, Imano H, et al. Impairment of ciprofloxacin absorption by calcium polycarbophil. J Clin Pharmacol 2002;42:806–811.
30. Neuhofel AL, Wilton JH, Victory JM, Hejmanowsky LG, Amsden GW. Lack of bioequivalence of ciprofloxacin when administered with calcium-fortified orange juice: a new twist on an old interaction. J Clin Pharmacol 2002;42:461–466.

31. Wallace AW, Victory JM, Amsden GW. Lack of bioequivalence of gatifloxacin when coadministered with calcium-fortified orange juice in healthy volunteers. J Clin Pharmacol 2003;43:92–96.
32. Amsden GW, Whitaker A-M, Johnson PW. Lack of bioequivalence of levofloxacin when coadministered with a mineral-fortified breakfast of juice and cereal. J Clin Pharmacol 2003; 43:990–995.
33. Sahai J, Gallicano K, Oliveros L, Khaliq S, Hawley-Foss N, Garber G. Cations in the didanosine tablet reduce ciprofloxacin bioavailability. Clin Pharmacol Ther 1993;53:292–297.
34. Knupp CA, Barbhaiya RH. A multiple-dose pharmacokinetic interaction study between didanosine (Videx®) and ciprofloxacin (Cipro®) in male subjects seropositive for HIV but asymptomatic. Biopharm Drug Dispos 1997;18:65–77.
35. Damle BD, Mummaneni V, Kaul S, Knupp C. Lack of effect of simultaneously administered didanosine encapsulated enteric bead formulation (Videx EC) on oral absorption of indinavir, ketoconazole, or ciprofloxacin. Antimicrob Agents Chemother 2002;46:385–391.
36. Kara M, Hasinoff BB, McKay D, Campbell NRC. Clinical and chemical interactions between iron preparations and ciprofloxacin. Br J Clin Pharmacol 1991;31:257–261.
37. Polk RE, Healy DP, Sahai J, et al. Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother 1989;33: 1841–1844.
38. Lehto P, Kivisto KT, Neuvonen PJ. The effect of ferrous sulphate on the absorption of norfloxacin, ciprofloxacin and ofloxacin. Br J Clin Pharmacol 1994;37:82–85.
39. Shiba K, Sakamoto M, Saito A, et al. Effect of ferrous sulfate, tea, and milk on absorption of AM-1155, a 6-fluoro-8-methyoxy quinolone, in humans. Proceedings of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1995. Abstract A43.
40. Stass H, Kubitza D. Effect of iron supplements on the oral bioavailability of moxifloxacin, a novel 8-methoxyfluoroquinolone, in humans. Clin Pharmacokinet 2001;40(suppl 1):57–62.
41. Martinez Cabarga M, Sanchez Navarro A, Colino Gandarillas CI, Dominguez-Gil A. Effects of two cations on gastrointestinal absorption of ofloxacin. Antimicrob Agents Chemother 1991;35:2102–2105.
42. Allen A, Bygate E, Faessel H, Isaac L, Lewis A. The effect of ferrous sulphate and sucralfate on the bioavailability of oral gemifloxacin in healthy volunteers. Int J Antimicrob Agents 2000;15:283–289.
43. How PP, Fischer JH, Arruda JA, et al. Effects of lanthanum carbonate on the absorption and oral bioavailability of ciprofloxacin. Clin J Am Soc Nephrol 2007;2:1235–1240.
44. Nix DE, Watson WA, Lener ME, et al. Effects of aluminum and magnesium antacids and ranitidine on the absorption of ciprofloxacin. Clin Pharmacol Ther 1989;46:700–705.
45. Hoffken G, Lode H, Wiley R, et al. Pharmacokinetics and bioavailability of ciprofloxacin and ofloxacin: effect of food and antacid intake. Rev Infect Dis 1988;10(suppl 1):S138,S139.
46. Grasela TH Jr, Schentag JJ, Sedman AT, et al. Inhibition of enoxacin absorption by antacids or ranitidine. Antimicrob Agents Chemother 1989;33:615–617.
47. Krishna G, Kisicki JC, Olsen S, et al. Effect of an aluminum- and magnesium-containing antacid on the bioavailability of garenoxacin in healthy volunteers. Pharmacotherapy 2007; 27:963–969.
48. Lober S, Ziege S, Rau M, et al. Pharmacokinetics of gatifloxacin and interaction with an antacid containing aluminum and magnesium. Antimicrob Agents Chemother 1999;43: 1067–1071.
49. Shimada J, Shiba K, Oguma T, et al. Effect of antacid on absorption of the quinolone lomefloxacin. Antimicrob Agents Chemother 1992;36:1219–1224.
50. Stass H, Bottcher MF, Ochmann K. Evaluation of the influence of antacids and H2 antagonists on the absorption of moxifloxacin after oral administration of a 400 mg dose to healthy volunteers. Clin Pharmacokinet 2001;40(suppl 1):39–48.
51. Nix DE, Wilton JH, Ronald B, et al. Inhibition of norfloxacin absorption by antacids and sucralfate. Rev Infect Dis 1989;11(suppl 5):S1096.

52. Maesen FPV, Davies BI, Geraedts WH, Sumajow CA. Ofloxacin and antacids [letter]. J Antimicrob Chemother 1987;19:848,849.
53. Jaehde U, Sorgel F, Stephan U, Schunack W. Effect of an antacid containing magnesium and aluminum on absorption, metabolism, and mechanism of renal elimination of pefloxacin in humans. Antimicrob Agents Chemother 1994;38:1129–1133.
54. Lazzaroni M, Imbimbo BP, Bargiggia S, et al. Effects of magnesium-aluminum hydroxide antacid on absorption of rufloxacin. Antimicrob Agents Chemother 1993;37: 2212–2216.
55. Granneman GR, Stephan U, Birner B, et al. Effect of antacid medication on the pharmacokinetics of temafloxacin. Clin Pharmacokinet 1992;22(suppl 1):83–89.
56. Teng R, Dogolo LC, Willavize SA, Friedman HL, Vincent J. Effect of Maalox and omeprazole on the bioavailability of trovafloxacin. J Antimicrob Chemother 1997;39 (suppl B):93–97.
57. Allen A, Vousden M, Porter A, Lewis A. Effect of Maalox® on the bioavailability of oral gemifloxacin in healthy volunteers. Chemotherapy 1999;45:504–511.
58. Nix DE, Watson WA, Handy L, et al. The effect of sucralfate pretreatment on the pharmacokinetics of ciprofloxacin. Pharmacotherapy 1989;9:377–380.
59. Garrelts JC, Godley PJ, Peterie JD, et al. Sucralfate significantly reduces ciprofloxacin concentrations in serum. Antimicrob Agents Chemother 1990;34:931–933.
60. Van Slooten AD, Nix DE, Wilton JH, Love JH, Spivey JM, Goldstein HR. Combined use of ciprofloxacin and sucralfate. DICP Ann Pharmacother 1991;25:578–582.
61. Ryerson B, Toothaker R, Schleyer I, Sedman A, Colburn W. Effect of sucralfate on enoxacin pharmacokinetics. Proceedings of the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, Houston, TX, September, 1989. Abstract 214.
62. Lubowski TJ, Nightingale CH, Sweeney K, Quintiliani R. Effect of sucralfate on pharmacokinetics of fleroxacin in healthy volunteers. Antimicrob Agents Chemother 1992;36: 2758–2760.
63. Lee L-J, Hafkin B, Lee I-D, Hoh J, Dix R. Effects of food and sucralfate on a single oral dose of 500 mg of levofloxacin in healthy subjects. Antimicrob Agents Chemother 1997;41: 2196–2200.
64. Nix D, Schentag J. Lomefloxacin (L) absorption kinetics when administered with ranitidine (R) and sucralfate (S). Proceedings of the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, Houston, TX, September, 1989. Abstract 1276.
65. Stass H, Schuhly U, Moller JG, Delesen H. Effects of sucralfate on the oral bioavailability of moxifloxacin, a novel 8-methoxyfluoroquinolone. Clin Pharmacokinet 2001;40(suppl 1): 49–55.
66. Lehto P, Kivisto KT. Effect of sucralfate on absorption of norfloxacin and ofloxacin. Antimicrob Agents Chemother 1994;38:248–251.
67. Parpia SH, Nix DE, Hejmanowski LG, et al. Sucralfate reduces the gastrointestinal absorption of norfloxacin. Antimicrob Agents Chemother 1989;33:99–102.
68. Kawakami J, Matsuse T, Kotaki H, et al. The effect of food on the interaction of ofloxacin with sucralfate in healthy volunteers. Eur J Clin Pharmacol 1994;47:67–69.
69. Zix JA, Geerdes-Fenge HF, Rau M, et al. Pharmacokinetics of sparfloxacin and interaction with cisapride and sucralfate. Antimicrob Agents Chemother 1997;41:1668–1672.
70. Kamberi M, Nakashima H, Ogawa K, Oda N, Nakano S. The effect of staggered dosing of sucralfate on oral bioavailability of sparfloxacin. Br J Clin Pharmacol 2000;49:98–103.
71. Golper T, Hartstein AI, Morthland VH, Christensen JM. Effects of antacids and dialysate dwell times on multiple dose pharmacokinetics of oral ciprofloxacin in patients on continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1987;31:1787–1790.
72. Preheim LC, Cuevas TA, Roccaforte JS, Mellencamp MA, Bittner MJ. Ciprofloxacin and antacids [letter]. Lancet 1986;2:48.
73. Miyata K, Ohtani H, Tsujimoto M, et al. Antacid interaction with new quinolones: dose regimen recommendations based on pharmacokinetic modeling of clinical data for ciprofloxacin, gatifloxacin and norfloxacin and metal cations. Int J Clin Pharmacol Ther 2007;45: 63–70.

74. Tuncel T, Bergisadi N. In vitro adsorption of ciprofloxacin hydrochloride on various antacids. Pharmazie 1992;47:304,305.
75. Wallis SC, Charles BG, Gahan LR, Filippich LJ, Bredhauer MG, Duckworth PA. Interaction of norfloxacin with divalent and trivalent pharmaceutical cations. In vitro complexation and in vivo pharmacokinetic studies in the dog. J Pharm Sci 1996;85:803–809.
76. Ross DL, Elkington SK, Knaub SR, Riley CM. Physicochemical properties of the fluoroquinolone antimicrobials VI. Effect of metal-ion complexation on octan-1-ol-water partitioning. Int J Pharmaceutics 1993;93:131–138.
77. Ross DL, Riley CM. Physicochemical properties of the fluoroquinolone antimicrobials V. Effect of fluoroquinolone structure and pH on the complexation of various fluoroquinolones with magnesium and calcium. Int J Pharmaceutics 1993;93:121–129.
78. Ross DL, Riley CM. Physicochemical properties of the fluoroquinolone antimicrobials III. complexation of lomefloxacin with various metal ions and the effect of metal ion complexation on aqueous solubility. Int J Pharmaceutics 1992;87:203–213.
79. Helena M, Teixeira SF, Vilas-Boas LS, Gil VMS, Teixeira F. Complexes of ciprofloxacin with metal ions contained in antacid drugs. J Chemother 1995;7:126–132.
80. Mallick S, Pattnaik S, Swain K, et al. Interaction characteristics and thermodynamic behavior of gatifloxacin by aluminum hydroxide. Drug Devel Indust Pharm 2007;33:535–541.
81. Adepoju-Bello AA, Coker HA, Eboka CJ, et al. The physiochemical and antibacterial properties of ciprofloxacin-Mg2+ complex. Nigerian Quart J Hosp Med 2008;18:133–136.
82. Sonia Rodriguez Cruz M, Gonzalez Alonso I, Sanchez-Navarro A, Luisa Sayalero Marinero M. In vitro study of the interaction between quinolones and polyvalent cations. Pharm Acta Helv 1999;73:237–245.
83. Sultana N, Arayne MS, Yasmeen N. In vitro availability of ofloxacin in presence of metals essential to human body. Pak J Pharm Sci 2007;20:42–47.
84. Hussain F, Arayne MS, Sultana N. Interactions between sparfloxacin and antacids--dissolution and adsorption studies. Pak J Pharm Sci 2006;19:16–21.
85. Sultana N, Arayne MS, Furqan H. In vitro availability of lomefloxacin hydrochloride in presence of essential and trace elements. Pak J Pharm Sci 2005;18:59–65.
86. Sultana N, Arayne MS, Yasmeen N. In vitro availability of ofloxacin in presence of metals essential to human body. Pak J Pharm Sci 2007;20:36–42.
87. Arayne MS, Sultana N, Hussain F. Interactions between ciprofloxacin and antacids—dissolution and adsorption studies. Drug Metab Drug Interact 2005;21:117–129.
88. Arayne MS, Sultana N, Haroon U, et al. In vitro availability studies of enoxacin in presence of H2 receptor antagonists. Pak J Pharm Sci 2007;20:235–243.
89. Hoffken G, Lode H, Wiley P D, et al. Pharmacokinetics and interaction in the bioavailability of new quinolones. Proceedings of the International Symposium of the New Quinolones, Geneva, Switzerland, July, 1986. Abstract 141.
90. Sorgel F, Seelmann R, Granneman G R, Locke C. Effect of cimetidine on the pharmacokinetics of temafloxacin. Clin Pharmacokinet 1992;22(suppl 1):75–82.
91. Wingender W, Foerster D, Beermann D, et al. Effect of gastric emptying time on rate and extent of the systemic availability of ciprofloxacin. Proceedings of the 14th International Congress of Chemotherapy, Kyoto, Japan, June, 1985. Abstract P-37–91.
92. Sorgel F, Mahr G, Uwe Koch H, Stephan U, Wiesemann HG, Malter U. Effects of cimetidine on the pharmacokinetics of pefloxacin in healthy volunteers. Rev Infect Dis 1988;10 (suppl 1):S137.
93. Misiak PM, Eldon MA, Toothaker RD, Sedman AJ. Effects of oral cimetidine or ranitidine on the pharmacokinetics of intravenous enoxacin. J Clin Pharmacol 1993;33:53–56.
94. Levofloxacin. Data on file (protocol HR 355/1/GB/101). Raritan, NJ: RW Johnson Pharmaceutical Research Institute.
95. Ludwig E, Graber H, Szekely E, Csiba A. Metabolic interactions of ciprofloxacin. Diagn Microbiol Infect Dis 1990;13:135–141.
96. Lebsack ME, Nix D, Ryerson B, et al. Effect of gastric acidity on enoxacin absorption. Clin Pharmacol Ther 1992;52:252–256.

97. Efthymiopoulos C, Bramer SL, Maroli A. Effect of food and gastric pH on the bioavailability of grepafloxacin. Clin Pharmcokinet 1997;33(suppl 1):18–24.
98. Gries JM, Honorato J, Taburet AM, et al. Cimetidine does not alter sparfloxacin pharmacokinetics. Int J Clin Pharmacol Ther Toxicol 1995;33:585–587.
99. Perry CM, Barman Balfour JA, Lamb HM. Gatifloxacin. Drugs 1999;58:683–696.
100. Stass HH, Ochmann K. Study to evaluate the interaction between BAY 12–8039 and ranitidine. Proceedings of the 20th International Congress of Chemotherapy, Sydney, Australia, June–July, 1997. Abstract 3357.
101. Stuht H, Lode H, Koeppe P, Rost KL, Schaberg T. Interaction study of lomefloxacin and ciprofloxacin with omeprazole and comparative pharmacokinetics. Antimicrob Agents Chemother 1995;39:1045–1049.
102. Allen A, Vousden M, Lewis A. Effect of omeprazole on the pharmacokinetics of oral gemifloxacin in healthy volunteers. Chemotherapy 1999;45:496–503.
103. Washington C, Hou E, Hughes N, et al. Effect of omeprazole on bioavailability of an oral extended-release formulation of ciprofloxacin. Am J Health-Sys Pharm 2006;63:653–656.
104. Nix DE, Lebsack ME, Chapelsky M, Sedman AJ, Busch J, Norman A. Effect of oral antacids on disposition of intravenous enoxacin. Antimicrob Agents Chemother 1993;37:775–777.
105. Yuk JH, Nightingale CH, Sweeney KR, et al. Relative bioavailability in healthy volunteers of ciprofloxacin administered through a nasogastric tube with and without enteral feeding. Antimicrob Agents Chemother 1989;33:1118–1120.
106. Lubowski TJ, Nightingale CH, Sweeney K, Quintiliani R. The relative bioavailability of temafloxacin administered through a nasogastric tube with and without enteral feeding. Clin Pharmacokinet 1992;22(suppl 1):43–47.
107. Noer BL, Angaran DM. The effect of enteral feedings on ciprofloxacin pharmacokinetics. Pharmacotherapy 1990;10:254. Abstract 154.
108. Healy DP, Brodbeck MC, Clendenning CE. Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. Antimicrob Agents Chemother 1996;40:6–10.
109. Mueller BA, Brierton DG, Abel SR, Bowman L. Effect of enteral feeding with Ensure on oral bioavailabilities of ofloxacin and ciprofloxacin. Antimicrob Agents Chemother 1994;38: 2101–2105.
110. Dudley MN, Marchbanks CR, Flor SC, Beals S. The effect of food or milk on the absorption kinetics of ofloxacin. Eur J Clin Pharmacol 1991;41:569–571.
111. Neuvonen PJ, Kivisto KT. Milk and yoghurt do not impair the absorption of ofloxacin. Br J Clin Pharmacol 1992;33:346–348.
112. Hoogkamer JFW, Kleinbloesem CH. The effect of milk consumption on the pharmacokinetics of fleroxacin and ciprofloxacin in healthy volunteers. Drugs 1995;49(suppl 2):346–348.
113. Stass H, Kubitza D. Effects of dairy products on the oral bioavailability of moxifloxacin, a novel 8-methoxyfluoroquinolone, in healthy volunteers. Clin Pharmacokinet 2001; 40(suppl 1):33–38.
114. Neuvonen PJ, Kivisto KT, Lehto P. Interference of dairy products with the absorption of ciprofloxacin. Clin Pharmacol Ther 1991;50:498–502.
115. Kivisto KT, Ojala-Karlsson P, Neuvonen PJ. Inhibition of norfloxacin absorption by dairy products. Antimicrob Agents Chemother 1992;36:489–491.
116. Saito A, Tarao F. Influence of milk on absorption of NM441, a prodrug type of quinolone antibiotic. Jap J Chemother 1996; 44(suppl 1):221–228.
117. Papai K, Budai M, Ludanyi K, et al. In vitro food-drug interaction study: which milk component has a decreasing effect on the bioavailability of ciprofloxacin? J Pharm Biomed Anal 2010;52:37–42.
118. Mallet L, Huang A. Coadministration of gatifloxacin and multivitamin preparation containing minerals: potential treatment failure in an elderly patient. Ann Pharmacother 2005; 39:150–152.
119. Suda KJ, Garey KW, Danziger LH. Treatment failures secondary to drug interactions with divalent cations and fluoroquinolone. Pharm World Sci 2005;27:81,82.

120. Quain RD, Barton TD, Fishman NO, et al. Coadministration of oral levofloxacin with agents that impair its absorption: potential impact on emergence of resistance. Int J Antimicrob Agents 2005;26:327–330.
121. Cohen KA, Lautenbach E, Weiner MG, et al. Coadministration of oral levofloxacin with agents that impair absorption: impact on antibiotic resistance. Infect Control Hosp Epidemiol 2008;29:975–977.
122. Stutman HR, Parker KM, Marks MI. Potential of moxalactam and other new antimicrobial agents of bilirubin-albumin displacement in neonates. Pediatrics 1985;75:294–298.
123. Graber H, Ludwig E, Magyar T, Csiba A, Szekely E. Ofloxacin does not influence antipyrine metabolism. Rev Infect Dis 1989;11(suppl 5):S1093,S1094.
124. Ludwig E, Graber H, Szekely E, Csiba A. Effect of ciprofloxacin on antipyrine metabolism. Rev Infect Dis 1989;(suppl 5):S1100,S1101.
125. Ludwig E, Szekely E, Csiba A, Graber H. The effect of ciprofloxacin on antipyrine metabolism. J Antimicrob Chemother 1988;22:61–67.
126. Rybak MJ, Bowles SK, Chandrasekar PH, Edwards DJ. Increased theophylline concentrations secondary to ciprofloxacin. Drug Intell Clin Pharm 1987;21:879–881.
127. Duraski RM. Ciprofloxacin-induced theophylline toxicity [letter]. South Med J 1988; 81:1206.
128. Paidipaty B, Erickson S. Ciprofloxacin-theophylline drug interaction [letter]. Crit Care Med 1990;18:685,686.
129. Holden R. Probable fatal interaction between ciprofloxacin and theophylline [letter]. Br Med J 1988;297:1339.
130. Bem JL, Mann RD. Danger of interaction between ciprofloxacin and theophylline [letter]. Br Med J 1988;296:1131.
131. Spivey JM, Laughlin PH, Goss TF, Nix DE. Theophylline toxicity secondary to ciprofloxacin administration. Ann Emerg Med 1991;20:1131–1134.
132. Thomson AH, Thomson GD, Hepburn M, Whiting B. A clinically significant interaction between ciprofloxacin and theophylline. Eur J Clin Pharmacol 1987;33:435,436.
133. Rogge MC, Solomon WR, Sedman AJ, et al. The theophylline-enoxacin interaction: II. changes in disposition of theophylline and its metabolites during intermittent administration of enoxacin. Clin Pharmacol Ther 1989;46:420–428.
134. Davis RL, Kelly HW, Quenzer RW, et al. Effect of norfloxacin on theophylline metabolism. Antimicrob Agents Chemother 1989;33:212–214.
135. Bowles SK, Popovski Z, Rybak MJ, et al. Effect of norfloxacin on theophylline pharmacokinetics at steady state. Antimicrob Agents Chemother 1988;32:510–512.
136. Schwartz J, Jauregui L, Lettieri J, Bachmann K. Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. Antimicrob Agents Chemother 1988;32:75–77.
137. Gregoire SL, Grasela TH Jr, Freer JP, et al. Inhibition of theophylline clearance by coadministered ofloxacin without alteration of theophylline effects. Antimicrob Agents Chemother 1987;31:375–378.
138. Ho G, Tierney MG, Dales RE. Evaluation of the effect of norfloxacin on the pharmacokinetics of theophylline. Clin Pharmacol Ther 1988;44:35–38.
139. Nix DE, Norman A, Schentag JJ. Effect of lomefloxacin on theophylline pharmacokinetics. Antimicrob Agents Chemother 1989;33:1006–1008.
140. Rogge MC, Solomon WR, Sedman AJ, et al. The theophylline–enoxacin interaction: I. effect of enoxacin dose size on theophylline disposition. Clin Pharmacol Ther 1988;44:579–587.
141. Sorgel F, Mahr G, Granneman R, Stephan U. Effects of two quinolone antibacterials, temafloxacin and enoxacin, on theophylline pharmacokinetics. Clin Pharmacokinet 1992; 22(suppl 1):65–74.
142. Wijnands WJA, Vree TB, van Herwaarden CLA. Enoxacin decreases the clearance of theophylline in man. Br J Clin Pharmacol 1985;20:583–588.
143. Takagi K, Hasegawa T, Ogura Y, et al. Comparative studies on interaction between theophylline and quinolones. J Asthma 1988;25:63–71.

144. Wijnands WJA, Vree TB, van Herwaarden CLA. The influence of quinolone derivatives on theophylline clearance. Br J Clin Pharmacol 1986;22:677–683.
145. Sano M, Yamamoto I, Ueda J, et al. Comparative pharmacokinetics of theophylline following two fluoroquinolones co-administration. Eur J Clin Pharmacol 1987;32:431,432.
146. Kinzig-Schippers M, Fuhr U, Cesana M, et al. Absence of effect of rufloxacin on theophylline pharmacokinetics in steady-state. Antimicrob Agents Chemother 1998;42: 2359–2364.
147. Takagi K, Yamaki K, Nadai M, Kuzuya T, Hasegawa T. Effect of a new quinolone, sparfloxacin, on the pharmacokinetics of theophylline in asthmatic patients. Antimicrob Agents Chemother 1991;35:1137–1141.
148. Sano M, Kawakatsu K, Ohkita C, et al. Effects of enoxacin, ofloxacin and norfloxacin on theophylline disposition in humans. Eur J Clin Pharmacol 1988;35:161–165.
149. Robson RA, Begg EJ, Atkinson HC, Saunders CA, Frampton CM. Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline. Br J Clin Pharmacol 1990;29:491–493.
150. LeBel M, Vallee F, St. Laurent M. Influence of lomefloxacin on the pharmcokinetics of theophylline. Antimicrob Agents Chemother 1990;34:1254–1256.
151. Seelmann R, Mahr G, Gottschalk B, Stephan U, Sorgel F. Influence of fleroxacin on the pharmacokinetics of theophylline. Rev Infect Dis 1989;11(suppl 5):S1100.
152. Soejima R, Niki Y, Sumi M. Effect of fleroxacin on serum concentrations of theophylline. Rev Infect Dis 1989;11(suppl 5):S1099.
153. Beckman J, Elsasser W, Gundert-Remy U, Hertrampf R. Enoxacin—a potent inhibitor of theophylline metabolism. Eur J Clin Pharmacol 1987;33:227–230.
154. Wijnands WJA, Cornel JH, Martea M, Vree TB. The effect of multiple dose oral lomefloxacin on theophylline metabolism in man. Chest 1990;98:1440–1444.
155. Niki Y, Soejima R, Kawane H, et al. New synthetic quinolone antibacterial agents and serum concentration of theophylline. Chest 1987;92:663–669.
156. Wijnands WJA, van Herwaarden CLA, Vree TB. Enoxacin raises plasma theophylline concentrations [letter]. Lancet 1984;2:108,109.
157. Raoof S, Wollschlager C, Khan FA. Ciprofloxacin increases serum levels of theophylline. Am J Med 1987;82(suppl 4A):115–118.
158. Gisclon LG, Curtin CR, Fowler CL, Nayak RK. Absence of pharmacokinetic interaction between intravenous theophylline and orally administered levofloxacin. Proceedings of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1995. Abstract A39.
159. Dickens GR, Wermeling D, Vincent J. Phase I pilot study of the effects of trovafloxacin (CP-99,219) on the pharmacokinetics of theophylline in healthy men. J Clin Pharmacol 1997;37:248–252.
160. Vincent J, Teng R, Dogolo LC, Willavize S A, Friedman HL. Effect of trovafloxacin, a new fluoroquinolone antibiotic, on the steady-state pharmacokinetics of theophylline in healthy volunteers. J Antimicrob Chemother 1997;39(suppl B):81–86.
161. Fourtillan J B, Granier J, Saint-Salvi B, et al. Pharmacokinetics of ofloxacin and theophylline alone and in combination. Infection 1986;14(suppl 1):S67–S69.
162. Batty KT, Davis TME, Ilett KF, Dusci LJ, Langton SR. The effect of ciprofloxacin on theophylline pharmacokinetics in healthy subjects. Br J Clin Pharmacol 1995;39:305–311.
163. Efthymiopoulos C, Bramer SL, Maroli A, Blum B. Theophylline and warfarin interaction studies with grepafloxacin. Clin Pharmacokinet 1997;33(suppl 1):39–46.
164. Niki Y, Hashiguchi K, Miyashita N, Nakajima M, Matsushima T, Soejima R. Effects of AM-1155 on serum concentration of theophylline. Proceedings of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, September, 1996. Abstract F73.
165. Stass HH, Kubitza D, Schweitert H, Wemer R. BAY 12–8039 does not interact with theophylline. Proceedings of the 20th International Congress of Chemotherapy, Sydney, Australia, June–July, 1997. Abstract 3356.

166. Stass H, Kubitza D. Lack of pharmacokinetic interaction between moxifloxacin, a novel 8-methoxyfluoroquinolone, and theophylline. Clin Pharmacokinet 2001;40(suppl 1):63–70.
167. Davy M, Allen A, Bird N, Rost KL, Fuder H. Lack of effect of gemifloxacin on the steady-state pharmacokinetics of theophylline in healthy volunteers. Chemotherapy 1999;45:478–484.
168. Niki Y, Watanabe S, Yoshida K, et al. Effect of pazufloxacin mesilate on the serum concentration of theophylline. J Infect Chemother 2002;8:33–36.
169. Hashiguchi K, Miyashita N, Kubota Y, et al. Effect of pazufloxacin on serum concentration of theophylline. Chemotherapy (Tokyo) 1995;43:270–275.
170. Fattore C, Cipolla G, Gatti G, et al. Pharmacokinetic interactions between theophylline and prulifloxacin in healthy volunteers. Clin Drug Invest 1998;16:387–392.
171. Kinzig-Schippers M, Fuhr U, Zaigler M, et al. Interaction of pefloxacin and enoxacin with the human cytochrome P450 enzyme CYP 1A2. Clin Pharmacol Ther 1999;65:262–274.
172. Carbo M, Segura J, de la Torre R, et al. Effect of quinolones on caffeine disposition. Clin Pharmacol Ther 1989;45:234–240.
173. Healy DP, Polk RE, Kanawati L, et al. Interaction between oral ciprofloxacin and caffeine in normal volunteers. Antimicrob Agents Chemother 1989;33:474–478.
174. Mahr G, Sorgel F, Granneman R, et al. Effects of temafloxacin and ciprofloxacin on the pharmacokinetics of caffeine. Clin Pharmacokinet 1992;22(suppl 1):90–97.
175. Harder S, Staib AH, Beer C, et al. 4-quinolones inhibit biotransformation of caffeine. Eur J Clin Pharmacol 1988;35:651–656.
176. Peloquin CA, Nix DE, Sedman AJ, et al. Pharmacokinetics and clinical effects of caffeine alone and in combination with oral enoxacin. Rev Infect Dis 1989;11(suppl 5):S1095.
177. Stille W, Harder S, Mieke S, et al. Decrease of caffeine elimination in man during coadministration of 4-quinolones. J Antimicrob Chemother 1987;20:729–734.
178. Janknegt R. Drug interactions with quinolones. J Antimicrob Chemother 1990;26(suppl D): 7–29.
179. Healy DP, Schoenle JR, Stotka J, Polk RE. Lack of interaction between lomefloxacin and caffeine in normal volunteers. Antimicrob Agents Chemother 1991;35:660–664.
180. LeBel M, Teng R, Dogolo LC, Willavize S, Friedman HL, Vincent J. The effect of steadystate trovafloxacin on the steady-state pharmacokinetics of caffeine in healthy subjects. Proceedings of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, September, 1996. Abstract A1.
181. Stahlberg HJ, Gohler K, Guillaume M, Mignot A. Effects of gatifloxacin (GTX) on the pharmacokinetics of theophylline in healthy young volunteers. J Antimicrob Chemother 1999;44(suppl A):136. Abstract P435.
182. Manita S, Toriumi C, Kusajima H, Momo K. The influence of gatifloxacin (AM-1155) on pharmacokinetics and metabolism of theophylline in rats and humans. Proceedings of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, September, 1998. Abstract A-16a.
183. Parent M, LeBel M. Meta-analysis of quinolone-theophylline interactions. DICP Ann Pharmacother 1991;25:191–194.
184. Barnett G, Segura J, de la Torre R, Carbo M. Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition. Eur J Clin Pharmcol 1990;39: 63–69.
185. Hasegawa T, Nadai M, Haghgoo S, et al. Influence of a newly-developed quinolone, T-3761, on pharmacokinetics of theophylline in rats. Antimicrob Agents Chemother 1995;39: 2138–2140.
186. Toon S, Hopkins KJ, Garstang FM, et al. Enoxacin-warfarin interaction: pharmacokinetic and stereochemical aspects. Clin Pharmacol Ther 1987;42:33–41.
187. Millar E, Coles S, Wyld P, Nimmo W. Temafloxacin does not potentiate the anticoagulant effect of warfarin in healthy subjects. Clin Pharmacokinet 1992;22(suppl 1):102–106.
188. Rindone JP, Keuey CL, Jones WN, Garewal HS. Hypoprothrombinemic effect of warfarin is not influenced by ciprofloxacin. Clin Pharm 1991;10:136–138.

189. Rocci ML Jr, Vlasses PH, Dislerath LM, et al. Norfloxacin does not alter warfarin's disposition or anticoagulant effect. J Clin Pharmacol 1990;30:728–732.
190. Bianco TM, Bussey HI, Farnett LE, Linn WD, Roush MK, Wong YWJ. Potential warfarin–ciprofloxacin interaction in patients receiving long-term anticoagulation. Pharmacotherapy 1992;12:435–439.
191. Israel DS, Stotka JL, Rock W, et al. Effect of ciprofloxacin on the pharmacokinetics and pharmacodynamics of warfarin. Clin Infect Dis 1996;22:251–256.
192. Levofloxacin. Data on file (protocol LOFBO-PH10-098). Raritan, NJ: RW Johnson Pharmaceutical Research Institute.
193. Teng R, Apseloff G, Vincent J, Pelletier SM, Willavize AS, Friedman HL. Effect of trovafloxacin (CP-99,129) on the pharmacokinetics and pharmacodynamics of warfarin in healthy male subjects. Proceedings of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, September, 1996. Abstract A2.
194. Muller FO, Hundt HKL, Muir AR, et al. Study to investigate the influence of 400 mg BAY 12–8039 (M) given once daily to healthy volunteers on PK and PD of warfarin (W). Proceedings of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, September, 1998. Abstract A-13.
195. Sparfloxacin (Zagam®) [package insert]. Research Triangle Park, NC: Bertek Pharmaceuticals, February 2003.
196. Davy M, Bird N, Rost KL, Fuder H. Lack of effect of gemifloxacin on the steady-state pharmacodynamics of warfarin in healthy volunteers. Chemotherapy 1999;45:491–495.
197. Washington C, Hou SY, Hughes NC, et al. Ciprofloxacin prolonged-release tablets do not affect warfarin pharmacokinetics and pharmacodynamics. J Clin Pharmacol 2007;47:1320–1326.
198. Kotsiou A, Diamanti E, Potamianou A, et al. Anticoagulant-induced changes on antibiotic concentrations in the serum and bones. Eur J Drug Metab Pharmacokinet 2008;33:173–179.
199. Jolson HM, Tanner LA, Green L, Grasela TH Jr. Adverse reaction reporting of interaction between warfarin and fluoroquinolones. Arch Intern Med 1991;151:1003,1004.
200. Kamada A. Possible interaction between ciprofloxacin and warfarin. DICP Ann Pharmacother 1990;24:27,28.
201. Leor J, Matetzki S. Ofloxacin and warfarin [letter]. Ann Intern Med 1988;109:761.
202. Linville D, Emory C, Graves L. Ciprofloxacin and warfarin interaction [letter]. Am J Med 1991;90:765.
203. Linnville T, Matanin D. Norfloxacin and warfarin [letter]. Ann Intern Med 1989;110:751,752.
204. Mott FE, Murphy S, Hunt V. Ciprofloxacin and warfarin [letter]. Ann Intern Med 1989; 1989;111:542,543.
205. Dugoni-Kramer BM. Ciprofloxacin–warfarin interaction [letter]. DICP Ann Pharmacother 1991;25:1397.
206. Renzi R, Finkbeiner S. Ciprofloxacin interaction with sodium warfarin. Am J Emerg Med 1991;9:551,552.
207. Ravnan SL, Locke C. Levofloxacin and warfarin interaction. Pharmacotherapy 2001; 21:884,885.
208. Ellis RJ, Mayo MS, Bodensteiner DM. Ciprofloxacin–warfarin coagulopathy: a case series. Am J Hematol 2000;63:28–31.
209. Jones CB, Fugate SE. Levofloxacin and warfarin interaction. Ann Pharmacother 2002;36:1554–1557.
210. Artymowicz RJ, Cino BJ, Rossi JG, Walker JL, Moore S. Possible interaction between gatifloxacin and warfarin [letter]. Am J Health-Sys Pharm 2002;59;1205,1206.
211. Byrd DC, Gaskins SE, Parrish AM, Freeman LB. Warfarin and ciprofloxacin interaction: case report and controversy. J Am Board Fam Pract 1999;12:486–488.
212. Anonymous. Fluoroquinolones and warfarin: suspected interactions. Can Fam Physician 2004;50:1417.
213. Vadlamudi RS, Smalligan RD, Ismail HM. Interaction between warfarin and levofloxacin: case series. South Med J 2007;100:720–724.

214. Chock AW, Stading JA. Indeterminable international normalized ratio with concurrent use of warfarin and gatifloxacin. Am J Health-Sys Pharm 2006;63:1539–1542.
215. Schelleman H, Bilker WB, Brensinger CM, et al. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. Clin Pharmacol Ther 2008;84:581–588.
216. Glasheen JJ, Fugit RV, Prochazka AV. The risk of overanticoagulation with antibiotic use in outpatients on stable warfarin regimens. J Gen Intern Med 2005;20:653–656.
217. McCall KL, Scott JC, Anderson HG. Retrospective evaluation of a possible interaction between warfarin and levofloxacin. Pharmacotherapy 2005;25:67–73.
218. Mercadal Orfila G, Gracia Garcia B, Leiva Badosa E, et al. Retrospective assessment of potential interaction between levofloxacin and warfarin. Pharm World Sci 2009;31:224–229.
219. Stroud LF, Mamdami MM, Kopp A, et al. The safety of levofloxacin in elderly patients on warfarin. Am J Med 2005;118:1417.
220. Fischer HD, Juurlink DN, Mamdani MM, et al. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents. a population-based study. Arch Intern Med 2010;170:617–621.
221. Ahmed A, Stephens JC, Kauc CA, et al. Impact of preemptive warfarin dose reduction on anticoagulation after initiation of trimethoprim-sulfamethoxazole or levofloxacin. J Thromb Thrombol 2008;26:44–48.
222. Mant T, Morrison P, Millar E. Absence of drug interaction between temafloxacin and low dose heparin. Clin Pharmacokinet 1992;22(suppl 1):98–101.
223. Avent CK, Krinsky D, Kirklin JK, et al. Synergistic nephrotoxicity due to ciprofloxacin and cyclosporine. Am J Med 1988;85:452,453.
224. Elston RA, Taylor J. Possible interaction of ciprofloxacin with cyclosporin A [letter]. J Antimicrob Chemother 1988;21:679,680.
225. Thomson DJ, Menkis AH, McKenzie FN. Norfloxacin–cyclosporine interaction. Transplantation 1998;46:312,313.
226. Nasir M, Rotellar C, Hand M, Kulczycki L, Alijani MR, Winchester JF. Interaction between ciclosporin and ciprofloxacin [letter]. Nephron 1991;57:245,246.
227. McLellan R, Drobitch RK, McLellan H, Acott PD, Crocker JFS, Renton KW. Norfloxacin interferes with cyclosporin disposition in pediatric patients undergoing renal transplantation. Clin Pharmacol Ther 1995;58:322–327.
228. Federico S, Carrano R, Capone D, et al. Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. Clin Pharmacokinet 2006;45:169–175.
229. Kruger HU, Schuler U, Proksch B, et al. Investigations of potential interaction between ciprofloxacin and cyclosporin A in patients with renal transplants. Antimicrob Agents Chemother 1990;34:1048–1052.
230. Lang J, de Villaine FJ, Guemi A, et al. Absence of pharmacokinetic interaction between pefloxacin and cyclosporin A in patients with renal transplants. Rev Infect Dis 1989; 11(suppl 5):S1094.
231. Lang J, de Villaine FJ, Garraffo R, Touraine J-L. Cyclosporine (cyclosporin A) pharmacokinetics in renal transplant patients receiving ciprofloxacin. Am J Med 1989;87(suppl 5A): 82S–85S.
232. Pichard L, Fabre I, Fabre G, et al. Screening for inducers and inhibitors of cytochrome P-450 (cyclosporin A oxidase) in primary cultures of human hepatocytes and in liver microsomes. Drug Metab Dispos 1990;18:595–606.
233. Robinson JA, Venezio FR, Costanzo-Nordin MR, et al. Patients receiving quinolones and cyclosporin after heart transplantation. J Heart Transplant 1990;9:30,31.
234. Tan KKC, Trull AK, Shawket S. Co-administration of ciprofloxacin and cyclosporin: lack of evidence for a pharmacokinetic interaction. Br J Clin Pharmacol 1989;28:185–187.
235. Hooper TL, Gould FK, Swinburn CR, et al. Ciprofloxacin: a preferred treatment for legionella infections in patients receiving cyclosporin A [letter]. J Antimicrob Chemother 1988;22: 952,953.

236. Van Buren DH, Koestner J, Adedoyin A, et al. Effect of ciprofloxacin on cyclosporine pharmacokinetics. Transplantation 1990;50:888,889.
237. Levofloxacin. Data on file (protocol N93-059). Raritan, NJ: RW Johnson Pharmaceutical Research Institute.
238. Capone D, Carrano R, Gentile A, et al. Pharmacokinetic interaction between tacrolimus and levofloxacin in kidney transplant recipients [abstract]. Nephrol Dial Transpl 2001; 16:A207.
239. Olsen SJ, Uderman HD, Kaul S, Kollia GD, Birkhofer MJ, Grasela DM. Pharmacokinetics (PK) of concomitantly administered gatifloxacin and digoxin. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1999. Abstract 199.
240. Stass H, Kubitza D. Profile of moxifloxacin drug interactions. Clin Infect Dis 2001; 32(suppl 1):S47–S50.
241. Vouden M, Allen A, Lewis A, Ehren N. Lack of pharmacokinetic interaction between gemifloxacin and digoxin in healthy elderly volunteers. Chemotherapy 1999;45:485–490.
242. Chien S-C, Rogge MC, Williams RR, Natarajan J, Wong F, Chow AT. Absence of a pharmacokinetic interaction between digoxin and levofloxacin. J Clin Pharm Ther 2002;27:7–12.
243. Johnson RD, Dorr MB, Hunt TL, Conway S, Talbot GH. Pharmacokinetic interaction of sparfloxacin and digoxin. Clin Ther 1999;21:368–379.
244. Vincent J, Hunt T, Teng R, Robarge L, Willavize SA, Friedman HL. The pharmacokinetic effects of coadministration of morphine and trovafloxacin in healthy subjects. Am J Surg 1998;176(suppl 6A):32S–38S.
245. Morran C, McArdle C, Pettitt L, et al. Pharmacokinetics of orally administered ciprofloxacin in abdominal surgery. Am J Med 1989;87(suppl 5A):86S–88S.
246. Grant EM, Zhong MK, Fitzgerald JF, Nicolau DP, Nightingale C, Quintiliani R. Lack of interaction between levofloxacin and oxycodone: pharmacokinetics and drug disposition. J Clin Pharmacol 2001;41:206–209.
247. Labbe L, Robitaille NM, Lefez C et al. Effects of ciprofloxacin on the stereoselective disposition of mexiletine in man. Ther Drug Monit 2004;26:492–498.
248. Kamali F, Thomas SHL, Edwards C. The influence of steady-state ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of diazepam in healthy volunteers. Eur J Clin Pharmacol 1993;44:365–367.
249. Wijnands WJA, Trooster JFG, Teunissen PC, et al. Ciprofloxacin does not impair the elimination of diazepam in humans. Drug Metab Dispos 1990;18:954–957.
250. Grasela DM, LaCreta FP, Kollia GD, Randall DM, Uderman HD. Open-label, nonrandomized study of the effects of gatifloxacin on the pharmacokinetics of midazolam in healthy male volunteers. Pharmacotherapy 2000;20:330–335.
251. Waite NM, Rybak MJ, Krakovsky DJ, et al. Influence of subject age on the inhibition of oxidative metabolism by ciprofloxacin. Antimicrob Agents Chemother 1991;35:130–134.
252. Loi C-M, Parker BM, Cusack BJ, Vestal RE. Aging and drug interactions. III. individual and combined effects of cimetidine and ciprofloxacin on theophylline metabolism in healthy male and female nonsmokers. J Pharmacol Exp Ther 1997;280:627–637.
253. Chandler MHH, Toler SM, Rapp RP, et al. Multiple-dose pharmacokinetics of concurrent oral ciprofloxacin and rifampin therapy in elderly patients. Antimicrob Agents Chemother 1990;34:442–447.
254. Murillo O, Pachón ME, Euba G, et al. Antagonistic effect of rifampin on the efficacy of high-dose levofloxacin in staphylococcal experimental foreign-body infection. Antimicrob Agents Chemother 2008;52:3681–3686.
255. Bernard E, Garraffo R, Leclercq-Boscherel B, Garret C, Bidault R, Dellamonica P. Drug interaction between grepafloxacin (GFX) and rifampin (RIF) in healthy volunteers. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1999. Abstract 6.
256. Schrenzel J, Dayer P, Leemann T, Weidekamm E, Portmann R, Lew DP. Influence of rifampin on fleroxacin pharmacokinetics. Antimicrob Agents Chemother 1993;37:2132–2138.

257. Orisakwe OE, Agbasi PU, Afonne OJ, Ofeofule SI, Obi E, Orish CN. Rifampicin pharmacokinetics with and without ciprofloxacin. Am J Ther 2001;8:151–153.
258. Orisakwe OE, Afonne OJ, Agbasi PU, Ofoefule SI. Urinary excretion of rifampicin in the presence of ciprofloxacin. Am J Ther 2004;11:171–174.
259. Orisakwe OE, Akunyili DN, Agbasi PU, Ezejiofor NA. Some plasma and saliva pharmacokinetics parameters of rifampicin in the presence of pefloxacin. Am J Ther 2004;11:283–287.
260. Orisakwe OE, Agbasi PU, Ofoefule SI, et al. Effect of pefloxacin on the urinary excretion of rifampicin. Am J Ther 2004;11:13–16.
261. Weiner M, Burman W, Luo C-C, et al. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. Antimicrob Agents Chemother 2007;51: 2861–2866.
262. Nijland HMJ, Ruslami R, Juwon Suroto A, et al. Rifampin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. Clin Infect Dis 2007;45:1001–1007.
263. McIlleron H, Norman J, Kanyok TP, et al. Elevated gatifloxacin and reduced rifampicin concentrations in a single-dose interaction study amongst healthy volunteers. J Antimicrob Chemother 2007;60:1398–1401.
264. Ofoefule SI, Obodo CE, Orisakwe OE, et al. Some plasma pharmacokinetic parameters of isoniazid in the presence of a fluoroquinolone antibacterial agent. Am J Ther 2001;8: 243–246.
265. Ofoefule SI, Obodo CE, Orisakwe OE, et al. Salivary and urinary excretion and plasma saliva concentration ratios of isoniazid in the presence of co-administered ciprofloxacin. Am J Ther 2002;9:15–18.
266. Lou S, Li W, Hu Q. Influence of cefoperazone and azithromycin on the pharmacokinetics of pazufloxacin in rats. Eur J Drug Metab Pharmacokinet 2007;32:219–223.
267. Abou-Auda HS, Mustafa AA, Al-Humayyd MS. Pharmacokinetic interaction of ketoconazole and itraconazole with ciprofloxacin. Biopharm Drug Dispos 2008;29:29–35.
268. Issa MM, Nejem RN, El-Abadia NS. Oral ciprofloxacin affects the pharmacokinetics of paracetamol in saliva. Clin Drug Invest 2006;26:223–226.
269. Issa MM, Nejem RM, El-Abadia NS, et al. Effects of paracetamol on the pharmacokinetics of ciprofloxacin in plasma using a microbiological assay. Clin Drug Invest 2007;27: 463–467.
270. Ilo CE, Ezejiofor NA, Agbakoba N, et al. Effect of chloroquine on the urinary excretion of ciprofloxacin. Am J Ther 2008;15:419–422.
271. Ilo CE, Ilondu NA, Okwoli N, et al. Effect of chloroquine on the bioavailability of ciprofloxacin in humans. Am J Ther 2006;13:432–435.
272. Marcelin-Jimenez G, Angeles AP, Martinez-Rossier L, et al. Ciprofloxacin bioavailability is enhanced by oral co-administration with phenazopyridine: a pharmacokinetic study in a Mexican population. Clin Drug Invest 2006;26:323–328.
273. Kunii T, Fukasawa T, Yasui-Furukori N, et al. Interaction study between enoxacin and fluvoxamine. Ther Drug Monitor 2005;27:349–353.
274. Hedaya MA, El-Afify DR, El-Maghraby GM. The effect of ciprofloxacin and clarithromycin on sildenafil oral bioavailability in human volunteers. Biopharm Drug Dispos 2006;27: 103–110.
275. Cooper JG, Harboe K, Frost SK, et al. Ciprofloxacin interacts with thyroid replacement therapy. BMJ 2005;330:1002.
276. Momo K, Homma M, Kohda Y, et al. Drug interaction of tizanidine and ciprofloxacin: case report [letter]. Clin Pharmacol Ther 2006;80:717–719.
277. Granfors MT, Backman JT, Neuvonen M, et al. Ciprofloxacin greatly increases concentrations and hypotensive effects of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. Clin Pharmacol Ther 2004;76:598–606.
278. Thompson JA, Bianco JA, Benyunes MC, et al. Phase Ib trial of pentoxifylline and ciprofloxacin in patients treated with interleukin-2 and lymphokine-activated killer cell therapy for metastatic renal cell carcinoma. Cancer Res 1994;54:3436–3441.

279. Cleary JD. Ciprofloxacin (CIPRO) and pentoxifylline (PTF): a clinically significant drug interaction. Pharmacotherapy 1992;12:259 (abstract 106).
280. Raoul JM, Peterson MR, Peterson TC. A novel drug interaction between the quinolone antibiotic ciprofloxacin and a chiral metabolite of pentoxifylline. Biochem Pharmacol 2007; 74:639–646.
281. Peterson TC, Peterson MR, Wornell PA, et al. Role of CYP1A2 and CYP2E1 in the pentoxifylline ciprofloxacin drug interaction. Biochem Pharmacol 2004;68:395–402.
282. Markowitz JS, Gill HS, Devane CL, Mintzer JE. Fluoroquinolone inhibition of clozapine metabolism [letter]. Am J Psychiatry 1997;153:881.
283. Markowitz JS, DeVane CL. Suspected ciprofloxacin inhibition of olanzapine resulting in increased plasma concentration [letter]. J Clin Psychopharmacol 1999;19:289–291.
284. Herrlin K, Segerdahl M, Gustafsson LL, Kalso E. Methadone, ciprofloxacin, and adverse drug reactions [letter]. Lancet 2000;356:2069,2070.
285. Brownlowe K, Sola C. Clozapine toxicity in smoking cessation and with ciprofloxacin. Psychosomatics 2007;48:170–175 (letter).
286. Sambhi RS, Puri R, Jones G. Interaction of clozapine and ciprofloxacin: a case report [letter]. Eur J Clin Pharmacol 2007;63:895,896.
287. Brouwers EE, Sohne M, Kuipers S, et al. Ciprofloxacin strongly inhibits clozapine metabolism: two case reports: Clin Drug Invest 2009;29:59–63.
288. Raaska K, Neuvonen PJ. Ciprofloxacin increases serum clozapine and N-desmethylclozapine: a study in patients with schizophrenia. Eur J Clin Pharmacol 2000;56:585–589.
289. Dalle J-H, Auvrignon A, Vassal G, Leverger G. Interaction between methotrexate and ciprofloxacin. J Pediatr Hematol Oncol 2002;24:321,322.
290. Takahashi H, Higuchi H, Shimizu T. Severe lithium toxicity induced by combined levofloxacin administration [letter]. J Clin Psychiatry 2000;61:321,322.
291. Scholten PC, Droppert RM, Zwinkels MGJ, Moesker HL, Nauta JJP, Hoepelman IM. No interaction between ciprofloxacin and an oral contraceptive. Antimicrob Agents Chemother 1998;42:3266–3268.
292. Chien SC, Chow AT, Rogge MC, Williams RR, Hendrix CW. Pharmacokinetics and safety of oral levofloxacin in human immunodeficiency virus-infected individuals receiving concomitant zidovudine. Antimicrob Agents Chemother 1997;41:1765–1769.
293. Villani P, Viale P, Signorini L, et al. Pharmacokinetic evaluation of oral levofloxacin in human immunodeficiency virus-infected subjects receiving concomitant antiretroviral therapy. Antimicrob Agents Chemother 2001;45:2160–2162.
294. Kamali F. No influence of ciprofloxacin on ethanol disposition. Eur J Clin Pharmacol 1994;47:71–74.
295. Tillonen J, Homann N, Rautio M, Jousimies-Somer H, Salaspuro M. Ciprofloxacin decreases the rate of ethanol elimination in humans. Gut 1999;44:347–352.
296. Jokinen MJ, Olkkola KT, Ahonen J, Neuvonen PJ. Effect of ciprofloxacin on the pharmacokinetics of ropivacaine. Eur J Clin Pharmacol 2003;58:653–657.
297. Isohanni MH, Ahonen J, Neuvonen PJ, et al. Effect of ciprofloxin on the pharmacokinetics of intravenous lidocaine. Eur J Anaesthesiol 2005;22:795–799.
298. Springuel P. Risk of seizures from concomitant use of ciprofloxacin and phenytoin in patients with epilepsy. CMAJ 1998;158:104,105.
299. Hull RL. Possible phenytoin–ciprofloxacin interaction [letter]. Ann Pharmacother 1993;27:1283.
300. Pollak PT, Slayter KL. Hazards of doubling phenytoin dose in the face of an unrecognized interaction with ciprofloxacin. Ann Pharmacother 1997;31:61–64.
301. Dillard ML, Fink RM, Parkerson R. Ciprofloxacin–phenytoin interaction [letter]. Ann Pharmacother 1992;26:263.
302. Brouwers PJ, DeBoer LE, Guchelaar H-J. Ciprofloxacin–phenytoin interaction [letter]. Ann Pharmacother 1997;31:498.
303. Otero M-J, Moran D, Valverde M-P, Dominguez-Gil A. Interaction between phenytoin and ciprofloxacin [letter]. Ann Pharmacother 1999;33:251,252.

304. Job ML, Arn SK, Strom JG, Jacobs NF, D'Souza MJ. Effect of ciprofloxacin on the pharmacokinetics of multiple-dose phenytoin serum concentrations. Ther Drug Monitor 1994;16:427–431.
305. Davis RL, Quenzer RW, Kelly HW, Powell JR. Effect of the addition of ciprofloxacin on theophylline pharmacokinetics in subjects inhibited by cimetidine. Ann Pharmcother 1992;26:11–13.
306. Gillum JG, Israel DS, Scott RB, Climo MW, Polk RE. Effect of combination therapy with ciprofloxacin and clarithromycin on theophylline pharmacokinetics in healthy volunteers. Antimicrob Agents Chemother 1996;40:1715,1716.
307. Loi C-M, Parker BM, Cusack BJ, Vestal RE. Individual and combined effects of cimetidine and ciprofloxacin on theophylline metabolism in male nonsmokers. Br J Clin Pharmacol 1993;36:195–200.
308. Pavithra BH, Prakash N, Jayakumar K. Modification of pharmacokinetics of norfloxacin following oral administration of curcumin in rabbits. J Vet Sci 2009;10:293–297.
309. Hasegawa T, Nadai M, Kuzuya T, et al. The possible mechanism of interaction between xanthines and quinolone. J Pharm Pharmacol 1990;42:767–772.
310. Fuhr U, Strobl G, Manaut F, et al. Quinolone antibacterial agents: relationship between structure and in vitro inhibition of the human cytochrome P-450 isoform CYP1A2. Mol Pharmacol 1993;43:191–199.
311. Fuhr U, Anders E-M, Mahr G, Sorgel F, Staib AH. Inhibitory potency of quinolone antibacterial agents against cytochrome P-450 1A2 activity in vivo and in vitro. Antimicrob Agents Chemother 1992;36:942–948.
312. Sarkar M, Polk RE, Guzelian PS, Hunt C, Karnes HT. In vitro effect of fluoroquinolones on theophylline metabolism in human liver microsomes. Antimicrob Agents Chemother 1990;34:594–599.
313. Zhang h, Wei M-j, Zhao C-y, et al. Determination of the inhibiting potential of 6 fluoroquinolones on CYP1AZ and CYP1C9 in human liver microsomes. Acta Pharmacol Sin 2008; 29: 1507–1514.
314. Wingender W, Beerman D, Foerster D, et al. Mechanism of renal excretion of ciprofloxacin, a new quinolone carboxylic acid derivative in humans. Chemioterapia 1985;4(suppl2):403,404.
315. Levofloxacin. Data on file (protocol HR355/1/GB/101). Raritan, NJ: RW Johnson Pharmaceutical Research Institute.
316. Shimada J, Yamaji T, Ueda Y, Uchida H, Kusajima H, Irikura T. Mechanism of renal excretion of AM-715, a new quinolone carboxylic acid derivative, in rabbits, dogs, and humans. Antimicrob Agents Chemother 1983;23:1–7.
317. Jaehde U, Sorgel F, Reiter A, Sigl G, Naber KG, Schunack W. Effect of probenecid on the distribution and elimination of ciprofloxacin in humans. Clin Pharmacol Ther 1995; 58:532–541.
318. Nakashima M, Uematsu T, Kosuge K, et al. Single- and multiple-dose pharmacokinetics of AM-1155, a new 6-fluoro-8-methoxy quinolone, in humans. Antimicrob Agents Chemother 1995;39:2635–2640.
319. Totsuka K, Kikuchi K, Shimizu K. Pharmacokinetics in concomitant administration with probenecid and clinical study of NM441. Jap J Chemother 1996; 44(suppl 1):279–288.
320. Stass H, Sachse R. Effect of probenecid on the kinetics of a single oral 400 mg dose of moxifloxacin in healthy volunteers. Clin Pharmacokinet 2001;40(suppl 1):71–76.
321. Sudoh T, Fujimura A, Shiga T, et al. Renal clearance of lomefloxacin is decreased by furosemide. Eur J Clin Pharmacol 1994;46:267–269.
322. Sudoh T, Fujimura A, Harada K, Sunaga K, Ohmori M, Sakamoto K. Effect of ranitidine on renal clearance of lomefloxacin. Eur J Clin Pharmacol 1996;51:95–98.
323. Okuda M, Kimura N, Inui K. Interactions of fluoroquinolone antibacterials, DX-619 and levofloxacin, with creatinine transport by renal organic cation transporter hOCT2. Drug Metab Pharmacokinet 2006;21:432–436.
324. Shimizu A, Miyoshi M, Sugie M, et al. Possible involvement of P-glycoprotein in renal excretion of pazufloxacin in rats. Eur J Pharmacol 2004;501:151–159.

325. Hu JH, Liu XD, Xie L, et al. Possible multiple transporters were involved in hepatobiliary excretion of antofloxacin in rats. Xenobiotica 2007;37:579–591.
326. Martin DE, Shen J, Griener J, Raasch R, Patterson JH, Cascio W. Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. J Clin Pharmacol 1996;36: 85–91.
327. Bauer LA, Black DJ, Lill JS, et al. Levofloxacin and ciprofloxacin decrease procainamide and N-acetylprocainamide renal clearances. Antimicrob Agents Chemother 2005;49: 1649–1651.
328. Van Wart S, Phillips L, Ludwig EA, et al. Population pharmacokinetics and pharmacodynamics of garenoxacin in patients with community-acquired respiratory tract infections. Antimicrob Agents Chemother 2004;48:4766–4777.
329. Christ W. Central nervous system toxicity of quinolones: human and animal findings. J Antimicrob Chemother 1990;26(suppl B):219–225.
330. Anastasio GD, Menscer D, Little JM Jr. Norfloxacin and seizures [letter]. Ann Intern Med 1988;109:169,170.
331. Lucet J-C, Tilly H, Lerebours G, Gres J-J, Piguet H. Neurological toxicity related to pefloxacin [letter]. J Antimicrob Chemother 1988;21:811,812.
332. Rollof J, Vinge E. Neurologic adverse effects during concomitant treatment with ciprofloxacin, NSAIDs, and chloroquine: possible drug interaction. Ann Pharmacother 1993;27:1058,1059.
333. Slavich IL, Gleffe RF, Haas EJ. Grand mal epileptic seizures during ciprofloxacin therapy [letter]. JAMA 1989;261:558,559.
334. Simpson KJ, Brodie MJ. Convulsions related to enoxacin [letter]. Lancet 1985;2:161.
335. Rumsey S, Wilkinson TJ, Scott SD. Ciprofloxacin-induced seizures—the need for increased vigilance. Aust J Hosp Pharm 1995;25:145–147.
336. Yamamoto K, Naitoh Y, Inoue Y, et al. Seizure discharges induced by the combination of new quinolone carboxylic acid drugs and non-steroidal anti-inflammatory drugs. Chemotherapy 1988;36(suppl 2):300–324.
337. Bellon A, Perez-Garcia G, Coverdale JH, et al. Seizures associated with levofloxacin: case presentation and literature review. Eur J Clin Pharmacol 2009;65:959–962.
338. Agbaht K, Bitik B, Piskinpasa S, et al. Ciprofloxacin-associated seizures in a patient with underlying thyrotoxicosis: case report and literature review. Int J Clin Pharmacol Ther 2009; 47:303–310.
339. Matsuno K, Kunihiro E, Yamatoya O, et al. Surveillance of adverse reactions due to ciprofloxacin in Japan. Drugs 1995;49:(suppl 2):495,496.
340. Naora K, Katagiri Y, Ichikawa N, Hayashibara M, Iwamoto K. Enhanced entry of ciprofloxacin into the rat central nervous system induced by fenbufen. J Pharmacol Exp Ther 1991;258:1033–1037.
341. Ichikawa N, Naora K, Hayashibara M, Katagiri Y, Iwamoto K. Effect of fenbufen on the entry of new quinolones, norfloxacin and ofloxacin, into the central nervous system in rats. J Pharm Pharmacol 1992;44:915–920.
342. Naora K, Katagiri Y, Iwamoto K, Tanaka K, Yamaguchi T, Sekine Y. Effect of fenbufen on the pharmacokinetics of sparfloxacin in rats. J Antimicrob Chemother 1992;30:673–683.
343. Naora K, Katagiri Y, Ichikawa N, Hayashibara M, Iwamoto K. A possible reduction in the renal clearance of ciprofloxacin by fenbufen in rats. J Pharm Pharmacol 1990;42: 704–707.
344. Katagiri Y, Naora K, Ichikawa N, Hayashibara M, Iwamoto K. Absence of pharmacokinetic interaction between ofloxacin and fenbufen in rats. J Pharm Pharmacol 1989;41:717–719.
345. Naora K, Katagiri Y, Ichikawa N, Hayashibara M, Iwamoto K. A minor possibility of pharmacokinetic interaction between enoxacin and fenbufen in rats. J Pharmacobiodyn 1990;13:90–96.
346. Kamali F. Lack of a pharmacokinetic interaction between ciprofloxacin and fenbufen. J Clin Pharm Ther 1994;19:257–259.

347. Fillastre JP, Leroy A, Borsa-Lebas F, Etienne I, Gy C, Humbert G. Lack of effect of ketoprofen on the pharmacokinetics of pefloxacin and ofloxacin [letter]. J Antimicrob Chemother 1993;31:805,806.
348. Fillastre JP, Leroy A, Borsa-Lebas F, Etienne I, Gy C, Humbert G. Effects of ketoprofen (NSAID) on the pharmacokinetics of pefloxacin and ofloxacin in healthy volunteers. Drugs Exp Clin Res 1992;18:487–492.
349. Iqbal Z, Khan A, Naz A, et al. Pharmacokinetic interaction of ciprofloxacin with diclofenac: a single-dose, two-period crossover study in healthy adult volunteers. Clin Drug Invest 2009; 29:275–281.
350. Halliwell RF, Lambert JJ, Davey PG. Actions of quinolones and nonsteroidal anti-inflammatory drugs on γ-aminobutyric acid currents of rat dorsal root ganglion neurons. Rev Infect Dis 1989;11(suppl 5):S1398,S1399.
351. Halliwell RF, Davey PG, Lambert JJ. The effects of quinolones and NSAIDs upon GABA-evoked currents recorded from rat dorsal root ganglion neurones. J Antimicrob Chemother 1991;27:209–218.
352. Akahane K, Sekiguchi M, Une T, Osada Y. Structure-epileptogenicity relationship of quinolones with special reference to their interaction with γ-aminobutyric acid receptor sites. Antimicrob Agents Chemother 1989;33:1704–1708.
353. Segev S, Rehavi M, Rubinstein E. Quinolones, theophylline, and diclofenac interactions with the γ-aminobutyric acid receptor. Antimicrob Agents Chemother 1988;32:1624–1626.
354. Hori S, Shimada J, Saito A, Matsuda M, Miyahara T. Comparison of the inhibitory effects of new quinolones on γ-aminobutyric acid receptor binding in the presence of antiinflammatory drugs. Rev Infect Dis 1989;11(suppl 5):S1397,S1398.
355. Motomura M, Kataoka Y, Takeo G, et al. Hippocampus and frontal cortex are the potential mediatory sites for convulsions induced by new quinolones and non-steroidal anti-inflammatory drugs. Int J Clin Pharmacol Ther Toxicol 1991;29:223–227.
356. Kawakami J, Shimokawa M, Yamamoto K, et al. Inhibition of GABAA receptor-mediated current responses by enoxacin (new quinolone) and felbinac (non-steroidal antiinflammatory drug) in Xenopus oocytes injected with mouse-brain messenger RNA. Biol Pharm Bull 1993;16:726–728.
357. Christ W, Gindler K, Gruene S, et al. Interactions of quinolones with opioids and fenbufen, a nonsteroidal antiinflammatory drug: involvement of dopaminergic neurotransmission. Rev Infect Dis 1989;11(suppl 5):S1393,S1394.
358. Kawakami J, Yamamoto K, Asanuma A, Yanagisawa K, Sawada Y, Iga T. Inhibitory effect of new quinolones on GABAA receptor-mediated response and its potentiation with felbinac in Xenopus oocytes injected with mouse-brain mRNA: correlation with convulsive potency in vivo. Toxicol Appl Pharmacol 1997;145:246–254.
359. Imanishi T, Akahane K, Akaike N. Attenuated inhibition by levofloxacin, l-isomer of ofloxacin, on GABA response in the dissociated rat hippocampal neurons. Neurosci Lett 1995;193:81–84.
360. Akahane K, Tsutomi Y, Kimura Y, Kitano Y. Levofloxacin, an optical isomer of ofloxacin, has attenuated epileptogenic activity in mice and inhibitory potency in GABA receptor binding. Chemotherapy 1994;40:412–417.
361. Yakushiji T, Shirasaki T, Akaike N. Non-competitive inhibition of GABAA responses by a new class of quinolones and non-steroidal anti-inflammatories in dissociated frog sensory neurones. Br J Pharmacol 1992;105:13–18.
362. Kim J, Ohtani H, Tsujimoto M, at al. Quantitative comparison of the convulsive activity of combinations of twelve fluoroquinolones with five nonsteroidal antiinflammatory agents. Drug Metab Pharmacokinet 2009;24:167–174.
363. Halliwell RF, Davey PG, Lambert JJ. A patch clamp study of the effects of ciprofloxacin and biphenyl acetic acid on rat hippocampal neurone GABAA and ionotropic glutamate receptors. Neuropharmacology 1995;34:1615–1624.
364. Tsuji A, Sato H, Okezaki E, Nagata O, Kato H. Effect of the anti-inflammatory agent fenbufen on the quinolone-induced inhibition of γ−aminobutyric acid binding to rat brain membranes in vitro. Biochem Pharmacol 1988;37:4408–4411.

365. Ito T, Miura Y, Kadokawa T, Hori S, Shimada J, Migahara T. Effects of enoxacin and its combination with 4-biphenylacetate, an active metabolite of fenbufen, on population spikes in rat hippocampal slices. Pharmacol Toxicol 1991;68:220–225.
366. Ito Y, Ishige K, Aizawa M, Fukuda H. Characterization of quinolone antibacterial-induced convulsions and increases in nuclear AP-1 DNA- and CRE-binding activities in mouse brain. Neuropharmacology 1999;38:717–723.
367. Marchand S, Pariat C, Bouquet S, Courtois P, Couet W. Pharmacokinetic-pharmacodynamic modelling of the convulsant interaction between norfloxacin and biphenyl acetic acid in rats. Br J Pharmacol 2000;129:1609–1616.
368. Marchand S, Pariat C, Boulanger A, Bouquet S, Couet W. A pharmacokinetic/pharmacodynamic approach to show that not all fluoroquinolones exhibit similar sensitivity toward the proconvulsant effect of biphenyl acetic acid in rats. J Antimicrob Chemother 2001;48:813–820.
369. Smolders I, Gousseau C, Marchand S, Couet W, Ebinger G, Michotte Y. Convulsant and subconvulsant doses of norfloxacin in the presence and absence of biphenylacetic acid alter extracellular hippocampal glutamate but not gamma-aminobutyric acid levels in conscious rats. Antimicrob Agents Chemother 2002;46:471–477.
370. Kohno K, Niwa M, Nozaki M, et al. Role of nitric oxide in the convulsive seizures induced by fluoroquinolones coadministered with 4-biphenylacetic acid. Gen Pharmacol 1997;29:767–770.
371. Masukawa T, Nakanishi K, Natsuki R, et al. Role of nitric oxide in the convulsions following the coadministration of enoxacin with fenbufen in mice. Jpn J Pharmacol 1998;76:425–429.
372. Jaillon P, Morganroth J, Brumpt I, Talbot G. Overview of electrocardiographic and cardiovascular safety for sparfloxacin. Sparfloxacin Safety Group. J Antimicrob Chemother 1996;37(suppl A):161–167.
373. Demolis JL, Charransol A, Funck-Bretano C, Jaillon P. Effects of a single oral dose of sparfloxacin on ventricular repolarization in healthy volunteers. Br J Clin Pharmacol 1996;41:499–503.
374. Morganroth J, Talbot GH, Dorr MB, Johnson RD, Geary W, Magner D. Effect of single ascending, supratherapeutic doses of sparfloxacin on cardiac repolarization (QTc interval). Clin Ther 1999;21:818–828.
375. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. Clin Infect Dis 1999;28:352–364.
376. Lode H, Vogel F, Elies W. Grepafloxacin: a review of its safety profile based on clinical trials and postmarketing surveillance. Clin Ther 1999;21:61–74.
377. Springsklee M, Reiter C, Meyer JM. Safety and tolerability profile of moxifloxacin. Proceedings of the 13th European Congress of Clinical Microbiology and Infectious Diseases, Berlin, Germany, March, 1999. Abstract P-0208.
378. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy 2001;21:1468–1472.
379. Samaha FF. QTC interval prolongation and polymorphic ventricular tachycardia in association with levofloxacin [letter]. Am J Med 1999;107:528,529.
380. Owens RC Jr, Ambrose PG. Torsades de pointes associated with fluoroquinolones. Pharmacotherapy 2002;22:663–672.
381. Bertino JS Jr, Owens RC Jr, Carnes TD, Iannini PB. Gatifloxacin-associated corrected QT interval prolongation, torsades de pointes, and ventricular fibrillation in patients with known risk factors. Clin Infect Dis 2002;34:861–863.
382. Amankwa K, Krishnan SC, Tisdale JE. Torsades de pointes associated with fluoroquinolones: importance of concomitant risk factors. Clin Pharmacol Ther 2004;75:242–247.
383. Nair MK, Patel K, Starer PJ. Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient. Addiction 2008;103:2062–2064.
384. Keivanidou A, Arnaoutoglou C, Krommydas A, et al. Ciprofloxacin induced acquired long QT syndrome in a patient under class III antiarrhythmic therapy. Cardiol J 2009;16:172–174.
385. Knorr JP, Moshfeghi M, Sokoloski MC. Ciprofloxacin-induced Q-T interval prolongation. Am J Health-Syst Pharm 2008;65:547–551.
386. Altin T, Ozcan O, Turhan S, et al. Torsade de pointes associated with moxifloxacin: a rare but potentially fatal adverse event. Can J Cardiol 2007,23:907,908.

387. Kazmierczak J, Peregud-Pogorzelska M, Rzeuski R. QT interval prolongation and torsades de pointes due to a coadministration of ciprofloxacin and azimilide in a patient with implantable cardioverter-defibrillator. Pacing Clin Electrophysiol 2007;30:1043–1046.
388. Dupont H, Timsit JF, Souweine B, et al. Torsades de pointes probably related to sparfloxacin [letter]. Eur J Clin Microbiol Infect Dis 1996;15:350,351.
389. Nykamp DL, Blackmon CL, Schmidt PE, et al. QTc prolongation associated with combination therapy of levofloxacin, imipramine, and fluoxetine. Ann Pharmacother 2005;39:543–546.
390. Letsas KP, Sideris A, Kounas SP, et al. Drug-induced QT interval prolongation after ciprofloxacin administration in a patient receiving olanzapine [letter]. Int J Cardiol 2006;109:273,274.
391. Paltoo B, O'Donoghue S, Mousavi MS. Levofloxacin induced polymorphic ventricular tachycardia with normal QT interval. Pacing Clin Electrophysiol 2001;24:895–897.
392. Zambon A, Polo Friz H, Contiero P, et al. Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. Drug Safety 2009; 32:159–167.
393. Paran Y, Mashav N, Henis O, et al. Drug-induced torsades de pointes in patients aged 80 years or more. Anagolu Kardiyol Derg 2008;8:260–265.
394. Kang J, Wang L, Chen XL, Triggle DJ, Rampe D. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+channel HERG. Mol Pharmacol 2001;59:122–126.
395. Anderson ME, Mazur A, Yang T, Roden DM. Potassium current antagonist properties and proarrhythmic consequences of quinolone antibiotics. J Pharmacol Exp Ther 2001; 296:806–810.
396. Hagiwara T, Satoh S, Kasai Y, Takasuna K. A comparative study of the fluoroquinolone antibacterial agents on the action potential duration in guinea pig ventricular myocardia. Jpn J Pharmacol 2001;87:231–234.
397. Bischoff U, Schmidt C, Netzer R, Pongs O. Effects of fluoroquinolones on HERG currents. Eur J Pharmacol 2000;406:341–343.
398. Patmore L, Fraser S, Mair D, Templeton A. Effects of sparfloxacin, grepafloxacin, moxifloxacin, and ciprofloxacin on cardiac action potential duration. Eur J Pharmacol 2000;406:449–452.
399. Lacroix P, Crumb WJ, Durando L, et al. Prulifloxacin: in vitro (HERG current) and in vivo (conscious dog) assessment of cardiac risk. Eur J Pharmacol 2003;477:69–72.
400. Akita M, Shibazaki Y, Izumi M, et al. Comparative assessment of prulifloxacin, sparfloxacin, gatifloxacin, and levofloxacin in the rabbit model of proarrhythmia. J Toxicol Sci 2004; 29:63–71.
401. Satoh Y, Sugiyama A, Chiba K, Tamura K, Hashimoto K. QT-prolonging effects of sparfloxacin, a fluoroquinolone antibiotic, assessed in the in vivo canine model with monophasic action potential monitoring. J Cardiovasc Pharmacol 2000;36:510–515.
402. Chiba K, Sugiyama A, Satoh Y, Shiina H, Hashimoto K. Proarrhythmic effects of fluoroquinolone antibacterial agents: in vivo effects as physiologic substrate for torsades. Toxicol Appl Pharmacol 2000;169:8–16.
403. Morganroth J, Hunt T, Dorr MB, Magner D, Talbot GH. The cardiac pharmacodynamics of therapeutic doses of sparfloxacin. Clin Ther 1999;21:1171–1181.
404. Morganroth J, Hunt T, Dorr MB, Magner D, Talbot GH. The effect of terfenadine on the cardiac pharmacodynamics of sparfloxacin. Clin Ther 1999;21:1514–1524.
405. Iannini PB, Doddamani S, Byazrova E, Curciumara I, Kramer H. Risk of torsades de pointes with non-cardiac drugs. prolongation of QT interval is probably a class effect of fluoroquinolones [letter]. BMJ 2001;322:46,47.
406. Demolis JL, Kubitza D, Tenneze L, Funck-Brentano C. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. Clin Pharmacol Ther 2000;68:658–666.
407. Noel GJ, Goodman DB, Chien S, Solanki B, Padmanabhan M, Natarajan J. Measuring the effects of supratherapeutic doses of levofloxacin on healthy volunteers using four methods of QT correction and periodic and continuous ECG recordings. J Clin Pharmacol 2004;44:464–473.

408. Noel GJ, Natarajan J, Chien S, Hunt TL, Goodman DB, Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. Clin Pharmacol Ther 2003;73: 292–303.
409. Doig JC. Drug-induced cardiac arrhythmias: incidence, prevention and management. Drug Safety 1997;17:265–275.
410. Roden DM. A practical approach to torsades de pointes. Clin Cardiol 1997;20:285–290.
411. Janeira LF. Torsades de pointes and long QT syndromes. Clin Fam Phys 1995;52:1447–1453.
412. Yu C-C, Kelly PA, Burckart GJ, Zeevi A. Sirolimus inhibition of lymphocyte proliferation is not antagonized by ciprofloxacin and other quinolone antibiotics. Transplant Proc 2001;33:2989–2991.
413. Kelly PA, Burckart GJ, Anderson D, Shapiro R, Zeevi A. Ciprofloxacin does not block the antiproliferative effect of tacrolimus [letter]. Transplantation 1997;63:172,173.
414. Garbel SM, Pound MW, Miller SM. Hypoglycemia associated with the use of levofloxacin. Am J Health-Sys Pharm 2009;66:1014–1019.
415. Roberge RJ, Kaplan R, Frank R, Fore C. Glyburide–ciprofloxacin interaction with resistant hypoglycemia. Ann Emerg Med 2000;36:160–163.
416. Lin G, Hays DP, Spillane L. Refractory hypoglycemia from ciprofloxacin and glyburide interaction. J Toxicol Clin Toxicol 2004;42:295–297.
417. Menzies DJ, Dorsainvil PA, Cunha BA, Johnson DH. Severe and persistent hypoglycemia due to gatifloxacin interaction with oral hypoglycemic agents. Am J Med 2002;113: 232–234.
418. LeBlanc M, Belanger C, Cossette P. Severe and resistant hypoglycemia associated with concomitant gatifloxacin and glyburide therapy. Pharmacotherapy 2004;24:926–931.
419. Bobba RK, Arsura EL. Hyperglycemia in an elderly diabetic patient: drug-drug or drug-disease interaction? [letter] South Med J 2006;99:94,95.
420. Khovidhunkit W, Sunthornyothin S. Hypoglycemia, hyperglycemia, and gatifloxacin. Ann Intern Med 2004;141:969.
421. Happe MR, Mulhall BP, Maydonovitch CL, Holtzmuller KC. Gatifloxacin-induced hyperglycemia. Ann Intern Med 2004;141:968,969.
422. Tequin® (gatifloxacin) package insert. Princeton, NJ: Bristol Myers-Squibb, October 2002.
423. Frothingham R. Glucose homeostasis abnormalities associated with the use of gatifloxacin. Clin Infect Dis 2005;41:1269–1276.
424. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med 2006;354:1352–1361.
425. Aspinall SL, Good CB, Jiang R, et al. Severe dysglycemia with fluoroquinolones: a class effect? Clin Infect Dis 2009;49:402–408.
426. Onyenwenyi AJ, Winterstein AG, Hatton RC. An evaluation of the effects of gatifloxacin on glucose homeostasis. Pharm World Sci 2008;30:544–549.
427. Grasela D, Lacreta F, Kollia G, Randall D, Stoltz R, Berger S. Lack of effect of multipledose gatifloxacin (GAT) on oral glucose tolerance (OGTT), glucose and insulin homeostasis, and glyburide pharmacokinetics (PK) in patients with type II non-insulin-dependent diabetes mellitus (NIDDM). Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1999. Abstract 196.
428. Zheng HX, Huang Y, Frassetto LA, et al. Elucidating rifampin's inducing and inhibiting effects on glyburide pharmacokinetics and blood glucose in healthy volunteers: unmasking the differential effects of enzyme induction and transporter inhibition for a drug and its primary metabolite. Clin Pharmacol Ther 2009;85:78–85.
429. Gajjar DA, LaCreta FP, Uderman HD, et al. A dose-escalation study of the safety, tolerability, and pharmacokinetics of intravenous gatifloxacin in healthy adult men. Pharmacotherapy 2000;20(6 pt 2):49S–58S.
430. Gajjar DA, LaCreta FP, Kollia GD, et al. Effect of multiple-dose gatifloxacin or ciprofloxacin on glucose homeostasis and insulin production in patients with noninsulin dependent diabetes mellitus maintained with diet and exercise. Pharmacotherapy 2000;20(6 pt. 2): 76S–86S.

431. Bristol-Myers Squibb. Dear Healthcare Provider Letter. February 15, 2006. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm.150760.htm (accessed 8/10/10).
432. FDA. Determination that Tequin (gatifloxacin) was withdrawn from sale for reasons of safety or effectiveness. Fed Reg 2008;73:52357,52358.
433. Trissel LA. Handbook on Injectable Drugs. 14th ed. Bethesda, MD: American Society of Health-System Pharmacists, 2007.
434. Szentmary N, Kraszni M, Nagy ZZ. Interaction of indomethacin and ciprofloxacin in the cornea following phototherapeutic keratectomy. Graefes Arch Clin Exp Ophthalmol 2004;242:614–616.

Chapter 10
Glycopeptides, Lipopeptides, and Lipoglycopeptides

Mary A. Ullman and John C. Rotschafer

Abstract Due to increasing resistance in Gram-positive organisms, use of glycopeptides, lipopeptides, and lipoglycopeptides will steadily increase. These three classes of drugs are primarily renally eliminated; therefore, CYP 450 interactions are not of concern. Daptomycin, the only agent in the class of lipopeptides, should be closely monitored with other drugs that are likely to cause muscle damage, especially HMG CoA reductase inhibitors, due to adverse events related to increases in creatinine phosphokinase levels, a marker of muscle injury. The newest class, lipoglycopeptides, includes three agents: telavancin, oritavancin, and dalbavancin. Telavancin, the only agent of this class approved in the United States, is known to affect the QT_c interval and should be used cautiously with other agents known to have similar effects. Drug interactions with the glycopeptide, vancomycin, are likely to involve other renally eliminated drugs; renal function should be closely monitored when vancomycin, daptomycin, or telavancin is prescribed concurrently with other nephrotoxic agents. As use of these lipoglycopeptides increases, more information regarding possible drug interactions will be available to clinicians.

10.1 Introduction

While glycopeptide antibiotics have been available in practice for over 50 years, lipopetides and lipoglycopeptide antibiotics are relatively new. Vancomycin is the only glycopeptide antibiotic currently available in the U.S.A. Teicoplanin is a glycopeptide that is only available in Europe and will not be discussed in this chapter.

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Table 10.1 Pharmacokinetic properties of vancomycin, daptomycin, and telavancin

	Vancomycin	Daptomycin	Telavancin
Class	Glycopeptide	Lipopeptide	Lipoglycopeptide
Molecular weight	1485.71	1620.67	1792.1
Oral bioavailability	–	–	–
% Renal elimination	95%	78%	72%
Serum half-life	6–12 h	8 h	7.5 h
%Protein binding	10–50%	>90%	>90%
Pregnancy class	C	B	C

However, teicoplanin does not have any significant drug-drug interactions. Daptomycin is the only available lipopeptide and telavancin, a lipoglycopeptide was approved by the Food and Drug Administration in 2009 [1]. Oritavancin and dalbavancin are lipoglycopeptides awaiting governmental approval. Both dalbavancin and oritavancin have a serum half-life profile quite different than currently available products (150–300 h vs. 6–12 h) and a typical course of therapy with these new agents would be ~2 doses of drug [1]. Possible adverse reaction with having a half-life of this magnitude would be of significant concern should oritavancin and/or dalbavancin be marketed.

While these three antibiotic classes are chemically different there are many similarities among these compounds. The drugs tend to be large molecules which limits or delays antibiotic penetration to various sites in the body [2–4]. This large molecular weight (Table 10.1) also contributes to a low bioavailability when these compounds are administered orally. All of these compounds with the exception of vancomycin are extensively protein bound (>90%, Table 10.1) leaving but a small free fraction of antibiotic that can cross biological barriers and interact with bacteria [2, 3]. High levels of protein binding can be theoretically associated with drug-drug binding displacement interactions. However, clinically significant protein binding displacement has not been reported with these compounds. The kidneys are primarily responsible for the elimination of these three classes of antibiotics [2–4] (Table 10.1). Thus adjustments in dose are warranted when age related or biologic induced renal dysfunction is present. Many of these agents have been associated with nephrotoxicity directly or when used in conjunction with other nephrotoxic agents such as aminoglycosides, non-steroidal anti-inflammatory agents, ACE inhibitors, loop diuretics, etc. (Table 10.2). Because these agents are primarily renally eliminated there is generally modest concerns with the need for dose adjustment in liver failure, liver enzyme induction, or drug-drug interactions associated with CYP liver enzyme metabolism. Another common concern among glyco/lipo/lipoglyco class members is the possibility of infusion reactions, the so-called red man or red neck syndrome (Table 10.2).

As with all class compounds, differences do exist with respect to individual pharmacokinetic parameters particularly in terms of the length of half-live and the size of distribution volume (Table 10.1). Generally speaking however, these three

Table 10.2 Potential drug-drug interactions of vancomycin, daptomycin, and telavancin

	Vancomycin	Daptomycin	Telavancin
Liver CYP enzyme induction	–	–	–
Drug-drug CYP interaction with metabolism	–	–	–
Other drug-drug interactions	Nephrotoxic Agents[a]	Nephrotoxic Agents[a] Statins	Nephrotoxic Agents[a] Formulated with Hydroxyl-propyl-Beta-cyclodextrin[b]
Protein binding displacement	–	–	–
Antibiotic antagonism	–	–	–
QTc prolongation	–	–	5 ms[c]
Laboratory test interference			Anticoagulation tests[d] Protein dipstick
Infusion reactions[e]	Definite	Possible	Possible

[a] Concomitant use of Loop Diuretics, ACE inhibitors, Aminoglycosides, Amphotericin B, NSAID's, Polymyxins could contribute to the development of nephrotoxicity; reduced drug elimination of adefovir, cisplatin, cyclosporine, methotrexate, tacrolimus, telbivudine, tenofivir with concomitant vancomycin are cautioned in individual drug package inserts [49]

[b] Can accumulate in renal dysfunction. Use caution when in combination with other agents using this solubilizer

[c] In itself not likely an issue but used with other agents capable of increasing the QTc interval or in a patient with a QTc interval >500 msec, concomitant use could be a problem

[d] Can artificially alter PT, INR, APTT, Activated Clotting Time, and Factor Xa based test results – draw blood for these test as close to next telavancin dose as possible

[e] Redman or Redneck syndrome

antibiotic classes are relatively free of typical CYP drug-drug interactions. We will review each member of these three antibiotic classes differentiating each drug in terms of their pharmacokinetic parameters and likely drug interaction potential.

10.2 Vancomycin (Glycopeptide)

Vancomycin has been and remains to date the gold standard antibiotic for the management of methicillin/oxacillin resistant *S. aureus* (MRSA/ORSA) infections [5]. While this agent has been available clinically for over 60 years the vast majority of our clinical experience has been at substantially lower doses than what are currently recommended. The IDSA/ASHP/SIDP published a position paper on the therapeutic monitoring of vancomycin in January 2009 [5]. In this consensus opinion and in accordance with previously published treatment guidelines recommending clinicians obtain trough concentrations two to four times the previous standard (5–10 mg/L), a loading doe of 25–30 mg/kg (actual body weight) and maintenance doses of 15–20 mg/kg (actual body weight) are to be used when treating patients for serious gram positive infections. Because of the substantially larger doses currently being used, clinicians should monitor patients carefully for infusion reactions and nephrotoxicity.

10.2.1 Absorption

Because of the large molecular size of vancomycin, very little absorption occurs after oral administration. In patients with normal renal function who received vancomycin 500 mg orally every 6 h, resulted in vancomycin serum concentrations of 2.4–3.0 mcg/mL [6]. Therefore, to treat systemic infections, vancomycin must be administered intravenously. However, in the management of *Clostridium difficile* infections, oral administration is the preferred route as the drug remains in the intestinal lumen at the site of infection [7, 8]. In the rare cases of a patient with both pseudomembranous colitis and severe renal failure, therapeutic concentrations were achieved in the serum secondary to increased oral absorption due decreased integrity of the intestinal lumen [9, 10].

10.2.2 Distribution

The pharmacokinetics of vancomycin distribution has been characterized using one-, two-, three and non-compartment models. Protein binding is generally estimated to be approximately 50%. Vancomycin binds to albumin and appears to have a low affinity for alpha-1-acid-glycoprotein [4].

10.2.3 Metabolism

Vancomycin does not undergo significant hepatic metabolism and thus is not a source for CYP drug interactions either by induction or competitive metabolism [4].

10.2.4 Elimination

Vancomycin is primarily eliminated renally (95%), and drug clearance correlates well with creatinine clearance [4]. Conventional hemodialysis methods do not extensively remove vancomycin from the serum. However, high flux dialysis methods have been reported to clear vancomycin much more effectively [11]. Additionally, clinicians should be aware concomitant use of drugs that affect a patient's hemodynamics (e.g., dopamine, dobutamine, furosemide) may also result in higher clearance of vancomycin. Patients who continue on vancomycin after discontinuation of these agents may require adjustments due to decreased clearance.

10.2.5 Scope of Problem

Vancomycin has been associated with nephrotoxicity, although the incidence decreased since the drug's initial introduction as the purity of the drug formulation

has improved. However, with current clinical practice recommending much larger loading and maintenance doses of vancomycin plus the almost exclusive use of generic products with potentially higher concentrations of impurities, there may be a greater risk of nephrotoxicity than reported in years past where lower doses were used and the product was branded. In cases of renal dysfunction, vancomycin does accumulate. Monitoring of serum trough concentrations is recommended to prevent nephrotoxicity in patients at high risk of toxicity either due to pre-existing renal impairment, use of aggressive dosing strategies to achieve troughs of 15–20 mg/L, or prolonged courses of vancomycin of 5 days or greater [5]. Potential drug interactions involve the use of vancomycin in conjunction with other nephrotoxic agents, most commonly aminoglycosides. Vancomycin degradation products (VDP) have been reported to accumulate in patients with renal dysfunction. VDP have also resulted in the reporting of falsely high concentrations of vancomycin with some assays as VDP are falsely interpreted as vancomycin (factor B vancomycin) [12]. Additionally, vancomycin can rarely cause and/or contribute to neutropenia; neutrophil counts should be monitored when used with other agents that may cause neutropenia.

10.3 Daptomycin (Lipopeptide)

10.3.1 Pharmacology

Much of our clinical experience to date with daptomycin has been at daily doses of 4 mg/kg (skin and soft tissue infection) and 6 mg/kg (right sided endocarditis and bacteremia) [2]. However, many infectious diseases consultants and critical care physicians choose to go off label using daily doses of up to 12 mg/kg so our experience with daptomycin adverse events could change as we explore the upper daily dosing limit for daptomycin [13–19].

While there would theoretically exist the potential for a variety of drug-drug interactions, daptomycin has remained relatively free of such problems. Like vancomycin and other lipoglycopeptides, daptomycin is primarily cleared renally avoiding induction of CYP liver enzymes or competing with other drugs for metabolism [20]. Even in terms of the drug's antibacterial action combining daptomycin with other antibiotics may result in synergy, an additive effect or indifference [21]. Only rarely is any type of antagonism demonstrated although use with tobramycin has been reported to reduce area under the serum concentration time curve (AUC) by 15% [2].

Concomitant use of daptomycin with other known nephrotoxic agents may increase the risk of nephrotoxicity and the use of "statins" in conjunction with daptomycin may increase the risk of muscle enzyme (creatine phosphokinase-CPK) elevation [2, 22–24]. While infusion reactions should be a concern with any of the glycopeptide, lipopeptide, and lipoglycopeptide classes, there are published studies using 2 min intravenous push doses of daptomycin compared to traditional 30 min

intravenous infusions demonstrating the bolus dosing method are as well tolerated by patients as the 30 min infusion [25].

10.3.2 Absorption

Because of the large molecular size of daptomycin, oral absorption would not likely result in therapeutic serum concentrations.

10.3.3 Distribution

The volume of distribution is small for daptomycin, and daptomycin is highly protein bound (90–95%) in a concentration independent manner. Hepatic dysfunction did not alter the rate of protein binding. Studies indicate a slow distribution of daptomycin into the tissues from the serum [2].

10.3.4 Metabolism

The exact metabolism of daptomycin is not completely understood. Induction or inhibition of cytochrome P450 isoforms has not been demonstrated with daptomycin. While metabolites are detected in the urine, no metabolites are detected in serum, suggesting the possibility of renal metabolism of daptomycin [2].

10.3.5 Elimination

Daptomycin is eliminated renally, with approximately 50–60% excreted as unchanged. Dose adjustments in renal dysfunction are recommended by the manufacturer [2].

10.3.6 Scope of Problem

Theoretically, because daptomycin is a highly protein bound drug, concomitant use of other highly protein bound drugs could result in displacement of drug. While alpha-1 glycoprotein has been identified as one of the proteins that bind daptomycin, other protein targets have not been identified. Alternatively, in critically ill patients who may have reduced levels of serum proteins, higher free drug concentrations of daptomycin may be present.

10.4 Telavancin (Lipoglycopeptide)

10.4.1 Pharmacology

Telavancin attacks the cell wall by inhibiting polymerization of the bacterial cell wall, The drug also interferes with transpeptidation by binding to the d-ala-d-ala terminal sequence. Lastly like daptomycin, telavancin causes depolarization of the outer membrane of the gram positive cell wall. Telavancin is primarily a gram positive antibiotic active against staphylococci, streptococci, and enterococci. The drug has no gram negative activity and has limited activity against anaerobes [1, 3, 26].

10.4.2 Absorption

Similar to vancomycin, telavancin and other lipopeptides and lipoglycopeptides are not systemically absorbed following oral administration.

10.4.3 Distribution

Similar to daptomycin, telavancin is highly protein bound (approximately 90%). Albumin is the main protein responsible for binding telavancin; hepatic or renal impairment does not affect the rate of binding. The volume of distribution is small at 0.1 L/kg [3]. In difficult to treat infections such as meningitis limited animal studies have demonstrated the superior performance of telavancin vs. vancomycin in clearing bacteria causing meningitis and sterilizing CSF [27]. Comparable performance has been demonstrated in animal models of osteomyelitis comparing telavancin and vancomycin. Telavancin also appears to penetrate and demonstrate biologic activity in bacterial biofilms [28, 29].

10.4.4 Metabolism

Telavancin has not demonstrated CYP450 3A4 activity following a midazolam probe [30]. Approximately 3–6% of the telavancin dose is converted to a 7-hydroxy metabolite which is excreted in the urine. The mechanism of telavancin's metabolism is unknown at this time. Mild to moderate hepatic impairment does not affect the pharmacokinetics of telavancin and no dosage adjustment is recommended [3].

10.4.5 Elimination

Two-thirds to three-quarters of telavancin is eliminated renally unchanged. Dose adjustments are recommended in patients with a creatinine clearance of less than 50 mL/min [3]. Clinical outcome in patients with reduced renal function as well as elderly patients (>65 years) who may have age related renal impairment have not done as well in terms of clinical outcome compared to patients with normal renal function [3]. Current dosage adjustment for renal failure possibly may not be providing the required amount of telavancin to overcome clinical infection keeping in mind that the drug is a concentration dependent killer. Additionally, one of the excipients in the intravenous solution is hydroxypropyl-beta-cyclodextrin, known to accumulate in patients with renal dysfunction [3]. Hemodialysis has been found to remove ~6% of a single dose of 7.5 mg/kg in patients with end stage renal disease undergoing hemodialysis. Continuous venovenous hemofiltration is much more efficient at removing telavancin from the bloodstream. The amount of telavancin removal is dependent on the rate of ultrafiltration [3].

10.4.6 Scope of Problem

While not extensively studied, there does not appear to be any antibiotic-antibiotic antagonistic combinations reported to date with telavancin.

Because of the highly protein bound nature of telavancin, the potential exists for drug interaction in patients also receiving other drugs that are highly bound to proteins, especially albumin. Although no reports of clinically significant protein binding displacement events have been reported to date. Clinicians should be aware of the potential interaction and monitor patients accordingly. A higher incidence of side effects has been reported with telavancin in clinical trials as compared to vancomycin [3]. The most common adverse events with this new agent include nausea, emesis, foamy urine, and a metallic after taste following parenteral administration.

Care should be used in patients with renal dysfunction to monitor for drug accumulation but also because the drug is formulated with hydroxypropyl-beta-cyclodextrin, this agent may also accumulate in patients with renal failure. Two other antimicrobials that carry warning about cyclodextrin use in renal impairment are itraconazole and voriconazole. In clinical trials telavancin has been shown to cause more nephrotoxicity than the comparator, vancomycin (15 vs 7%) [31–33]. However, vancomycin dosages were 2 g/day in patients with normal renal function. These differences may not be present at higher, more contemporary dosing of vancomycin. Concern should also be directed at concomitant use of telavancin and other drugs known to contribute to nephrotoxicity.

Telavancin has also been show to increase QTc intervals [34]. On average the increase is relatively small, i.e. ~5 msec but if used in conjunction with other agents or in the background of conditions known to increase QTc there could be an adverse

clinical outcome. Telavancin is also not recommended in pregnancy and is a category C drug [3]. Current dosage recommendations for telavancin call for a daily dose of 10 mg/kg to be determined based on actual body weight. Possible red man or red neck infusion related reactions are clearly a risk with the use of telavancin.

Because telavancin binds to phospholipids there are some significant drug-laboratory test interactions [3]. Telavancin artificially interferes with the determination of prothrombin time, internal normalization ratio, activated partial thromboplastin time, activated clotting time, and coagulation studies based on factor Xa test. A clear distinction needs to be made that the drug interferes with the test result of various coagulation studies but does not actually alter the coagulation state. As telavancin is administered every 24 h, the easiest maneuver to avoid this interaction is to obtain blood for these studies in the terminal 6 h of the dosing interval (i.e., 6 h or less before the next telavancin dose). Telavancin can also interfere with qualitative dipstick protein assay methods.

10.5 Important Drug Interactions

10.5.1 Vancomycin

10.5.1.1 Aminoglycosides

Mechanism: Both aminoglycosides and vancomycin are known to cause damage to similar sites in the renal tubules. The use of these two agents concomitantly can result in additive toxicity.

Literature: Several studies have demonstrated the toxicities encountered when using the combination vancomycin and aminoglycosides. In a prospective study with 34 patients and 39 courses of vancomycin performed by Mellor and colleagues, six courses of vancomycin alone were compared with 27 courses of vancomycin plus aminoglycoside, either concurrently or within 3 weeks of the first dose of vancomycin [35]. The mean total dose and duration of vancomycin therapy was 28.3 ± 18.1 g and 15.3 ± 9.3 days, respectively, approximately 1.8 g/day. Nephrotoxicity was defined as a rise of ≥0.5 mg/dL if initial creatinine was 3 g/dL or less; if initial creatinine was greater than 3 g/dL, a rise of ≥1.0 mg/dL was indicative of nephrotoxicity. Three patients developed acute nephrotoxicity (7.1%); 9.1% of patients developed nephrotoxicity within the 2 weeks following vancomycin therapy. All cases of nephrotoxicity demonstrated an abrupt rise in creatinine following septicemia or gastrointestinal hemorrhage. Additionally, two patients reported tinnitus and dizziness. One patient was diagnosed with acute hearing loss, but the authors concluded this was not due to drug toxicity.

In an retrospective evaluation of 229 courses of antibiotic therapy, Cimino and colleagues examined the relationship of serum vancomycin and aminoglycoside concentrations to nephrotoxicity [36]. Antibiotic courses were divided into

three groups: aminoglycoside alone (148 cases), vancomycin alone (41 cases), and vancomycin concurrently with aminoglycoside (40). Nephrotoxicity was defined as a rise of >0.5 mg/dL in serum creatinine, when compared to baseline. Normal values for vancomycin and aminoglycosides were peak: 20–40 mg/L, trough: <10 mg/L; and peak: 4–9 mg/L, trough: <2 mg/L, respectively. Overall, a 17% incidence of nephrotoxicity was noted. When broken down in the three groups, 18% of patients developed nephrotoxicity with aminoglycosides alone, 15% with vancomycin alone, and 15% with concurrent vancomycin and aminoglycosides. While higher serum creatinine concentrations were associated with increased nephrotoxicity in patients with aminoglycosides alone and higher daily doses of vancomycin (36.3 ± 4.8 mg/kg/day versus 24.0 ± 1.1 mg/kg/day) were associated with nephrotoxicity in patients with vancomycin alone, the only significant relationship of concurrent vancomycin and aminoglycoside therapy to higher incidence of nephrotoxicity was found to be serum drug concentrations which exceeded the normal values.

Rybak et al. studied the nephrotoxicity of vancomycin alone and in combination with an aminoglycoside in 231 courses of antibiotic therapy in 224 patients (168 – vancomycin alone, 63 – vancomycin and aminoglycoside, 103 – aminoglycoside alone) [37]. Nephrotoxicity was defined as an increase of 0.5 mg/dL of serum creatinine or 50% increase above baseline, whichever was greater. Targeted vancomycin peak and trough concentrations were 30–40 mg/L and <15 mg/L, respectively. Targeted aminoglycoside peak and trough concentrations were 4–10 mg/L and <2 mg/L, respectively. The incidence of nephrotoxicity was 5% in the vancomycin alone group, 11% in aminoglycoside alone group, and 22% in patients receiving both vancomycin and an aminoglycoside; these differences were all found to statistically different. Following a multivariate analysis, increased incidence of nephrotoxicity was found to be associated with concurrent vancomycin and aminoglycoside therapy, treatment with vancomycin of greater than 10 days, and vancomycin serum trough concentrations greater than 10 mg/L.

A recent clinical trial compared daptomycin with standard therapy, either antistaphylococcal penicillin or vancomycin in combination with an aminoglycoside, for the treatment of bacteremia and endocarditis [38]. Cosgrove and colleagues utilized patient information collected during the trial to specifically analyze the incidence of nephrotoxicity in relation of use of low dose gentamicin (mean daily dose of 3.1 mg/kg). A total of 236 patients were analyzed for adverse event data related to kidney function: 120 received daptomycin; 53 received vancomycin, of which 49 also received low-dose gentamicin; and 63 received antistaphylococcal penicillins, of which 59 also received low-dose gentamicin. A clinically significant decrease in creatinine clearance (CrCl) was defined as a decrease in CrCl to <50 mL/min if baseline CrCl was ≥50 mL/min. In patients with a baseline CrCl < 50 mL/min, a significant decrease in CrCl occurred if CrCl decrease to <10 mL/min. A sustained decrease in CrCl was defined if ≥2 sequential decreased CrCl measurements. CrCl was calculated by the Cockroft-Gault equation. After data evaluation, 8% in the daptomycin arm, 22% in the vancomycin arm, and 25% in the antistaphylococcal penicillin arm were found to have a decreased creatinine clearance. The median length of aminoglycosides therapy with vancomycin and antistaphylococcal penicillins was only 5 and 4 days, respectively. Twenty-two percent of patients who

received low dose gentamicin experienced decreased creatinine clearance versus only 8% of patients who did not, a statistically significant difference. After multivariate analysis, only age greater than 65 and receipt of any gentamicin were individual risk factors for nephrotoxicity. No differences were noted in the incidence of nephrotoxicity when comparing antistaphylococcal penicillins and vancomycin other than nephrotoxicity with antistaphylococcal penicillins occurred earlier in therapy when compared to vancomycin. The authors suggest this finding may indicate that nephrotoxicity seen with vancomycin and gentamicin is more sustained.

Clinical Importance: Guidelines for the treatment of endocarditis recommend the use of low-dose aminoglycosides with vancomycin for treatment with cases due to penicillin resistant gram-positive strains, particularly MRSA [39]. Some clinicians may also expand the synergistic use of aminoglycosides with vancomycin in other types of infections involving MRSA, based on recommendations for endocarditis. For most of these infections, vancomycin trough concentrations of 15-20 mg/L will be targeted, based on new guidelines released [5].

Management: If possible, patients should be evaluated as to whether the use of an aminoglycoside is essential with vancomycin therapy. Patients receiving concurrent therapy of vancomycin and aminoglycosides should be carefully monitored for development of nephrotoxicity, especially in cases where vancomycin trough concentrations of 15-20 mg/L are targeted and in patients with possibly impaired baseline renal function. If nephrotoxicity develops, switching to alternative agents should be considered.

10.5.1.2 Indomethacin

Mechanism: In infants, indomethacin has been shown to lead to decreased renal elimination of vancomycin.

Literature: In a study of 11 neonates with patent ductus arteriosus (PDA) who received vancomycin, six infants received indomethacin while the five others did not and served as controlled [40]. The pharmacokinetics of vancomycin in these two groups was compared. In the neonates who received both indomethacin and vancomycin, the volume of distribution was 0.71 L/kg (control 0.48 L/kg), the half-life was 24.6 h (control 7.0 L/kg), and the serum clearance was 23 mL/kg/h (control 54 mL/kg/h).

Clinical Importance: The authors of the study recommended, based on these results, neonates with PDA receiving indomethacin should be adequately treated with once-daily doses of vancomycin. Additionally, maintenance dosing of vancomycin should be approximately half of the dose used in neonates not receiving indomethacin.

Management: While these findings have not been confirmed on a larger scale in the neonatal population or in other patient populations, care should be used when administering vancomycin with other renally eliminated drugs, especially in patients demonstrating impaired renal function. Appropriate dose adjustments for all renally eliminated drugs, including vancomycin, should be employed when renal impairment is present.

10.5.1.3 Vecuronium

Mechanism: Vancomycin can depress neuromuscular function as well as skeletal muscle function.

Literature: A case report of a 34-kg patient received vancomycin as surgical prophylaxis during an exploratory laparoscopy [41]. Prior to the administration of the vancomycin, tracheal intubation was performed using vecuronium, and the patient's muscular response was appropriately monitored using the train-of-four (electrical stimulation of the ulnar nerve). T1 function had returned to 35% and T4 was barely perceptible 20 min after induction of anesthesia. When the infusion of 1 g vancomycin was started, a rapid decrease of T1 to less than 10% and absence of a T4 response was noted. Within 3 min of the completion of the vancomycin infusion, the T1 and T4 response recovered steadily. Neuromuscular function continued to increase after reversal of the vecuronium with atropine and edrophonium after completion of surgery. Five minutes after administration of the edrophonium, responses decreased to levels prior to administration. While the patient was awake and able to control breathing, she was not able to sustain head lift. Twenty minutes after the injection of edrophonium, the patient regained adequate muscle tone response. No other side effects were noted. The serum concentration of the vancomycin 25 min after the start of infusion was found to be 70 mg/L.

Clinical Importance: Given the patient's smaller weight in addition to administration of 1 g of vancomycin over 35 min, the peak concentration is larger than what has typically be encountered clinically. However, given new recommendations of aggressive vancomycin dosing, larger serum concentrations are likely to be seen with vancomycin. The authors of the case report also note several papers that also supported evidence of vancomycin having an effect on neuromuscular function occurring at typical vancomycin peak concentrations of 40–50 mg/L.

Management: Clinicians should be aware of the potential interaction of vancomycin with neuromuscular blockers. Strategies to prevent large peaks of vancomycin such as infusing over at least an hour or more (dependent on the dose) and carefully evaluating the appropriate dose based on patient's actual body weight and renal functions will help to reduce the possibility of vancomycin-related neuromuscular blockade. In patients receiving surgical neuromuscular blockade use or in patients in intensive care units receiving neuromuscular blockers, neuromuscular function should be appropriately monitored when used in conjunction with vancomycin.

10.5.1.4 Heparin

Mechanism: Heparin and vancomycin are incompatible in admixtures or y-sites due the concentration-dependent acid–base reaction that leads to precipitation and inactivation of vancomycin.

Literature: Barg and colleagues present a case of persistent staphylococcal bacteremia in an intravenous drug abuser [42]. The patient presented with fever, shaking chills, and diaphoresis; he admitted to intravenous heroin use for the past 3 years, with the femoral veins as a frequent place of injection. Upon presentation, swelling and tenderness at the injection site in the right groin was noted. A subclavian venous line was placed due to lack of peripheral venous access. Antibiotic treatment was initiated with vancomycin and tobramycin, with the tobramycin being soon discontinued after *Staphylococcus aureus* was identified as the causative pathogen. Additionally, continuous heparin anticoagulation was initiated after the discovery of deep vein thrombosis, confirmed by venogram. Both heparin and vancomycin were infused in the same line. Fevers and positive blood cultures persisted for 7 days despite antibiotic treatment. On the seventh day, another intravenous line was placed. With the availability of two intravenous lines, heparin and vancomycin were administered in separate lines. Within 24 h of the second line placement, fevers dispersed and blood cultures became (and remained) negative. Further investigations performed by the authors of the case examined the effects of co-administering vancomycin and heparin *in vitro*. At higher vancomycin concentrations of 1–5 mg and heparin concentrations of 1–1,000 units/mL (concentrations similar to what would be seen if administered through the same line), a white precipitate was immediately formed. Concentrations of vancomycin similar to those seen in the serum (5, 50, and 100 μg/mL) when combined with less than 1 unit/mL of heparin did not demonstrate the formation of any precipitate.

Clinical Importance: Because of the high incidence of both staphylococcal infections and deep vein thrombosis in intravenous drug users, the likelihood of the co-administration of both of these drugs is high.

Management: Clinicians should be appropriately educated that vancomycin and heparin should not be administered through the same intravenous line. While using sodium chloride for admixtures (instead of dextrose) may reduce the likelihood of precipitation, these two drugs should be administered via separate lines whenever possible.

10.5.1.5 Bile Acid Sequestrants

Mechanism: Agents such as cholestyramine and colestipol are used to treat hyperlipidemia by utilizing their ability to bile acids in the intestines. These agents are also able to bind other materials in the intestines such as co-administered drugs and cytotoxins.

Literature: Taylor and Barlett studied the binding of *Clostridium difficile* cytotoxins and vancomycin by cholestyramine and colestipol using an *in vitro* and hamster model of *C. difficile* colitis [43]. The use of cholestyramine and colestipol alone displayed extreme reductions in toxin to below assay sensitivity *in vitro*. When vancomycin was combined with either of the agents, less than 25% of the vancomycin

concentration was detectable. Colestipol bound a greater amount of vancomycin than cholestyramine, but vancomycin was more strongly bound to cholestyramine. In the hamster model, the use of cholestyramine alone, vancomycin alone, and cholestyramine plus vancomycin resulted in a smaller percentage of mortality during the treatment period of 5 days. When following these animals for an additional 11 days, all three treatment arms prevented death longer than controls alone. Vancomycin prevented 100% cumulative mortality for a longer time period than use of cholestyramine alone or cholestyramine plus vancomycin. The authors speculate that the 100% mortality reported after the additional 11 days was likely due to reacquisition of *C. difficile* from the environment rather from the ability of the drug(s) to adequately treat the infection.

Clinical Importance: Cholestyramine and colestipol are not recommended as alternative treatments for the treatment of persistent *C. difficile* colitis [7], primarily due to the likelihood that these agents will bind the two medications recommended for treatment, i.e., vancomycin and metronidazole.

Management: Because of the dosing schedule of vancomycin (usually every 6–8 h initially), attempts to avoid interactions by creative scheduling to separate administration times as far apart as possible (at least 1–2 h before administration or 4–6 h after administration) are likely to fail. Use of oral vancomycin for treatment of *C. difficile* should not be in combination with oral binding agents. In cases where patients have been prescribed cholestyramine for the treatment of hyperlipidemia while also need to use vancomycin to treat *C. difficile* infections, alternative agents for hyperlipidemia should be used during the duration of vancomycin treatment.

10.5.2 Daptomycin

10.5.2.1 HMG CoA Reductase Inhibitors

Mechanism: Both daptomycin and HMG CoA reductase inhibitors are known to cause increase levels of creatine phosphokinase (CPK), a marker of muscle injury.

Literature: Literature has been published on each agent's individual ability to increase CPK and possible cause rhabdomyolysis and has been included in each product's labeling [2, 44]. Odero and colleagues published a case report of rhabdomyolysis and acute renal failure associated with the administration of daptomycin, simvastatin, niacin, and esomeprazole [22]. Daptomycin was initially started at 7.2 mg/kg q24h; 4 days after initiation, the dose was changed to 7.2 mg/kg q48h, after noting a serum creatinine of 1.5 mg/dL. After 16 days of treatment with daptomycin, patient complaints included muscle weakness and pains in the proximal thighs and arms. Daptomycin was discontinued and linezolid initiated; simvastatin and niacin were still continued. A maximal serum CPK level of 8,995 Units/L and serum creatinine of 3.4 mg/dL were noted. Creatinine levels returned to baseline

levels 6 days after daptomycin discontinuation; CPK concentrations were noted to be 125 Units/L on the seventh day after daptomycin discontinuation. While the authors note that simvastatin and niacin both have the potential to cause rhabdomyolysis, they also note that the patient had tolerated simvastatin and niacin previously, with no complaints.

Clinical Importance: Given the high prevalence of HMG CoA reductase inhibitor use among patients and the increasing incidence of methicillin-resistant *Staphylococcus aureus*, these two agents will be likely used together more often. Clinicians should be aware of the potential interaction and be prepared to monitor these patients frequently who require co-administration of these two agents, especially when daptomycin is used for longer periods of time and/or maximal doses of the HMG CoA reductase inhibitor are used.

Management: Weekly measurements of CPK levels are recommended in the use of daptomycin alone. More frequent CPK monitoring (two to three times a week) during the concomitant use of these two agents is recommended, particularly in patients who also have renal impairment when receiving both medications [2]. Additionally, patients should be evaluated for unexplained muscle pain and/or weakness, especially in the distal extremities.

When used alone, in patients who have a CPK elevation of greater than 1,000 Units/L with signs and symptoms or greater than 2,000 Units/L without signs or symptoms, daptomycin should be discontinued, per manufacturer's recommendations. Furthermore, other drugs associated with rhabdomyolysis, like HMG CoA reductase inhibitors, should be discontinued temporarily until CPK levels return to baseline.

10.5.2.2 Aminoglycosides

Mechanism: Not fully known

Literature: While the mechanism is unknown, studies of co-administration of daptomycin and tobramycin showed that daptomycin helped protect against tobramycin-induced nephrotoxicity in rats [45, 46]. In this same experiment, the use of vancomycin and tobramycin demonstrated greater damage to the proximal tubular cells. A further investigation into this phenomenon alluded to the possibility of daptomycin directly interacting with the tobramycin molecule to prevent tobramycin-induced changes in the proximal tubular cells.

Clinical Importance: Daptomycin has been studied *in vitro* and *in vivo* in animals in combination with aminoglycosides; large scale trials of the combination of these two drugs in humans have not been performed. The antimicrobial and clinical benefits gained from the addition of an aminoglycoside to a daptomycin regimen have not been fully elucidated. The small number of patients that did receive daptomycin with gentamicin in a large scale trial comparing daptomycin to vancomycin and antistaphylococcal penicillins demonstrated a smaller cumulative percentage of

patients who experienced a significant decrease in creatinine clearance when compared to daptomycin or vancomycin/antistaphylococcal penicillins with or without aminoglycosides.

Management: Administration of both of these drugs should not cause significant negative effects in terms of renal function. Because the antimicrobial benefits (such as synergy) of this combination of drugs have not been fully studied in human trials, the use of both of these agents together should be evaluated on an individual basis [47].

10.5.2.3 PT/INR Laboratory Results

Mechanism: Daptomycin may interact with recombinant thromboplastin reagents, leading to a prolongation of PT and increase in INR due to laboratory artifacts [2].

Literature: Package insert

Clinical Importance: Because of the likelihood of interaction, in patients who are started on daptomycin and need PT and/or INR laboratory results, clinicians should note any unexpected changes in PT and/or INR results. Daptomycin has not been found to interact with warfarin; therefore, the clinician should suppose the interaction to be due to a lab assay interaction and not drug-drug interaction.

Management: In cases where an abnormal PT and/or INR measurement is documented, the clinicians should schedule another assessment of PT and INR just prior to the next dose of daptomycin. Additionally, other sources of interactions should be evaluated as relevant.

10.5.3 Telavancin

10.5.3.1 QT_c Prolonging Drugs

Mechanism: Because telavancin has been shown to prolong the QT_c interval during clinical trials, the possibility exists that concomitant use with other drugs known to prolong the QT_c interval would have additive effects. Prolonged QT_c intervals can lead to torsades de points, ventricular arrhythmias, and sudden cardiac death.

Literature: A large body of literature exists on the potential for arrhythmias following administration of one or more drugs known to prolong the QT_c intervals [48] (Table 10.3). For telavancin, a randomized, multi-dose clinical study conducted in healthy subjects found that mean changes in QT_c intervals were 4.1 and 4.5 msec following administration of 7.5 and 15 mg/kg doses, respectively [3, 48]. None of the study subjects demonstrated any significant ECG abnormalities or clinical symptoms beyond the interval changes. Change in QT_c intervals were not found to correlate to concentrations of telavancin.

Table 10.3 QTc prolonging agents [50, 51]

Select agents with risk of QT_c prolongation	Select agents with possible risk of QT_c prolongation
Amiodarone	Alfuzosin
Astemizole[a]	Amantadine
Bepridil[b]	Atazanavir
Chlorpromazine	Azithromycin
Cisapride[b,c]	Clozapine
Clarithromycin	Dronedarone[b]
Dofetilide	Flecanide
Droperidol	Foscarnet
Erythromycin	Fosphenytoin
Haloperidol	Gatifloxacin
Levomethadyl[b]	Gemifloxacin
Mesoridazine[b]	Levofloxacin
Methadone	Lithium
Pentamidine	Moxifloxacin
Pimozide[b]	Ondansetron
Procainamide	Paliperidone
Quinidine	Risperidone
Sotalol	Tacrolimus
Sparfloxacin[a,b]	Tamoxifen
Terfenadine[a]	Telithromycin
Thioridazine[b]	Venlafaxine
	Voriconazole
	Ziprasadone

[a] No longer available in the United States
[b] Co-comittant use with telavancin is contraindicated
[c] Only available through a restricted access program

Clinical Importance: Given that telavancin has only recently been approved, no clinical reports of substantial effects of QT_c interval prolongation following the use of telavancin for treatment of infections have been published as of now.

Management: Interactions of this type are best managed by using alternative treatments that do not carry the QT_c prolongation risk, if possible. If no alternatives exist, clinicians should consider cardiac monitoring for patients who require treatment with one or more drugs known to prolong the QT_c interval. Clinicians should also use caution with telavancin in patients who already exhibits QT_c prolongation prior to treatment.

10.5.3.2 Coagulation Panels

Mechanism: Because of the nature of telavancin to bind artificial phospholipid surfaces, telavancin will bind these types of surfaces which are commonly used in anticoagulation tests [3].

Literature: Package insert

Clinical Importance: The degree of binding is dependent upon the commercial assay used, as reagents differ among these assays. False elevations of PT, INR, aPTT, and ACT have been noted, and, in patients where monitoring of these levels is used to dose antithrombotic agents, clinicians should be aware of this possibility and should attempt to schedule telavancin doses and lab draws at times so not as to interfere.

Management: The likelihood of the interaction decreases as the plasma concentrations decrease; therefore, in cases for patients who need to daily monitor these lab values, the ideal time for these lab draws to take place is just prior to the administration of the next telavancin dose. In cases, where multiple lab draws are needed per day, as in the case of adjustment of heparin by aPTT values, use of another antimicrobial agent might be preferred.

10.6 Summary and Conclusions

Use of these agents is likely to increase as the incidence of methicillin-resistant *S. aureus* infections increases. In general, few drug interactions exist for these classes of drugs. The key drug interaction to consider with vancomycin is the concomitant use of other nephrotoxic agents, especially in those patients who may already exhibit decreased renal function. Use of daptomycin with HMG CoA reductase inhibitors should be limited and monitored closely due to the possibility of rhabdomyolysis. More information regarding possible drug interactions with telavancin will likely be available as the drug becomes more widely used; caution should be used when administering telavancin with other QT_c prolonging drugs or in patients who present with a QT_c prolongation.

References

1. Guskey MT and Tsuji BT. A comparative review of the lipoglycopeptides: oritavancin, dalbavancin, and telavancin. Pharmacotherapy 2010;30:80–94.
2. Cubicin (daptomycin) product information, Cubist Pharmaceuticals, Inc: Lexington, MA.
3. Vibativ (telavancin) product information, Theravance, Inc.: South San Francisco, CA.
4. Vancomycin product information, Hospira, Inc.: Lake Forest, IL.
5. Rybak M, Lomasestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66:82–98.
6. Vancocin (vancomycin) product information, ViroPharma Incorporated: Exton, PA.
7. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol 2010;31: 431–455.

8. Gerding DN, Muto CA, and Owens RC, Jr. Treatment of Clostridium difficile infection. Clin Infect Dis 2008; 46 Suppl 1:S32–42.
9. Dudley MN, Quintiliani R, Nightingale CH, and Gontarz N. Absorption of vancomycin. Ann Intern Med 1984;101:144.
10. Tedesco F, Markham R, Gurwith M, Christie D, and Bartlett JG. Oral vancomycin for antibiotic-associated pseudomembranous colitis. Lancet 1978;2:226–228.
11. Boereboom FT, Ververs FF, Blankestijn PJ, Savelkoul TJ, and van Dijk A. Vancomycin clearance during continuous venovenous haemofiltration in critically ill patients. Intensive Care Med 1999;25:1100–1104.
12. Somerville AL, Wright DH, and Rotschafer JC. Implications of vancomycin degradation products on therapeutic drug monitoring in patients with end-stage renal disease. Pharmacotherapy 1999;19:702–707.
13. Cunha BA, Eisenstein LE, and Hamid NS. Pacemaker-induced Staphylococcus aureus mitral valve acute bacterial endocarditis complicated by persistent bacteremia from a coronary stent: Cure with prolonged/high-dose daptomycin without toxicity. Heart Lung 2006;35: 207–211.
14. Cunha BA, Krol V, and Kodali V. Methicillin-resistant Staphylococcus aureus (MRSA) mitral valve acute bacterial endocarditis (ABE) in a patient with Job's syndrome (hyperimmunoglobulin E syndrome) successfully treated with linezolid and high-dose daptomycin. Heart Lung 2008;37:72–75.
15. Cunha BA, Mickail N, and Eisenstein L, E. faecalis vancomycin-sensitive enterococcal bacteremia unresponsive to a vancomycin tolerant strain successfully treated with high-dose daptomycin. Heart Lung 2007;36:456–461.
16. Figueroa DA, Mangini E, Amodio-Groton M, et al. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. Clin Infect Dis 2009; 49:177–180.
17. Katz DE, Lindfield KC, Steenbergen JN, et al. A pilot study of high-dose short duration daptomycin for the treatment of patients with complicated skin and skin structure infections caused by gram-positive bacteria. Int J Clin Pract 2008;62:1455–1464.
18. Lichterfeld M, Ferraro MJ, and Davis BT. High-dose daptomycin for the treatment of endocarditis caused by Staphylococcus aureus with intermediate susceptibility to glycopeptides. Int J Antimicrob Agents 2010;35:96.
19. Moise PA, Hershberger E, Amodio-Groton MI, and Lamp KC. Safety and clinical outcomes when utilizing high-dose (> or =8 mg/kg) daptomycin therapy. Ann Pharmacother 2009;43: 1211–1219.
20. Oleson FB, Berman CL, and Li AP. An evaluation of the P450 inhibition and induction potential of daptomycin in primary human hepatocytes. Chem Biol Interact 2004;150:137–147.
21. Steenbergen JN, Mohr JF, and Thorne GM. Effects of daptomycin in combination with other antimicrobial agents: a review of in vitro and animal model studies. J Antimicrob Chemother 2009;64:1130–1138.
22. Odero RO, Cleveland KO, and Gelfand MS. Rhabdomyolysis and acute renal failure associated with the co-administration of daptomycin and an HMG-CoA reductase inhibitor. J Antimicrob Chemother 2009;63:1299,1300.
23. Schriever CA, Fernandez C, Rodvold KA, and Danziger LH. Daptomycin: a novel cyclic lipopeptide antimicrobial. Am J Health Syst Pharm 2005;62:1145–1158.
24. Stein GE. Safety of newer parenteral antibiotics. Clin Infect Dis 2005; 41 Suppl 5:S293–302.
25. Chakraborty A, Roy S, Loeffler J, and Chaves RL. Comparison of the pharmacokinetics, safety and tolerability of daptomycin in healthy adult volunteers following intravenous administration by 30 min infusion or 2 min injection. J Antimicrob Chemother 2009;64:151–158.
26. Saravolatz LD, Stein GE, and Johnson LB. Telavancin: a novel lipoglycopeptide. Clin Infect Dis 2009;49:1908–1914.
27. Stucki A, Gerber P, Acosta F, Cottagnoud M, and Cottagnoud P. Efficacy of telavancin against penicillin-resistant pneumococci and Staphylococcus aureus in a rabbit meningitis model and determination of kinetic parameters. Antimicrob Agents Chemother 2006;50:770–773.

28. Gander S, Kinnaird A, and Finch R. Telavancin: in vitro activity against staphylococci in a biofilm model. J Antimicrob Chemother 2005;56:337–343.
29. LaPlante KL and Mermel LA. In vitro activities of telavancin and vancomycin against biofilm-producing Staphylococcus aureus, S. epidermidis, and Enterococcus faecalis strains. Antimicrob Agents Chemother 2009;53:3166–3169.
30. Wong SL, Goldberg MR, Ballow CH, Kitt MM, and Barriere SL. Effect of Telavancin on the pharmacokinetics of the cytochrome P450 3A probe substrate midazolam: a randomized, double-blind, crossover study in healthy subjects. Pharmacotherapy 2010;30:136–143.
31. Stryjewski ME, Chu VH, O'Riordan WD, et al. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 study. Antimicrob Agents Chemother 2006;50:862–867.
32. Stryjewski ME, Graham DR, Wilson SE, et al. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. Clin Infect Dis 2008;46:1683–1693.
33. Stryjewski ME, O'Riordan WD, Lau WK, et al. Telavancin versus standard therapy for treatment of complicated skin and soft-tissue infections due to gram-positive bacteria. Clin Infect Dis 2005;40:1601–1607.
34. Barriere S, Genter F, Spencer E, et al. Effects of a new antibacterial, telavancin, on cardiac repolarization (QTc interval duration) in healthy subjects. J Clin Pharmacol 2004;44:689–695.
35. Mellor JA, Kingdom J, Cafferkey M, and Keane CT. Vancomycin toxicity: a prospective study. J Antimicrob Chemother 1985;15:773–780.
36. Cimino MA, Rotstein C, Slaughter RL, and LJ Emrich LJ. Relationship of serum antibiotic concentrations to nephrotoxicity in cancer patients receiving concurrent aminoglycoside and vancomycin therapy. Am J Med 1987;83:1091–1097.
37. Rybak MJ, Albrecht LM, Boike SC, and Chandrasekar PH. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. J Antimicrob Chemother 1990;25:679–687.
38. Cosgrove SE, Vigliani GA, Fowler VG, Jr., et al. Initial low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 2009;48:713–721.
39. Nishimura RA, Carabello BA, Faxon DP, et al. ACC/AHA 2008 Guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:676–685.
40. Spivey JM and Gal P. Vancomycin pharmacokinetics in neonates. Am J Dis Child 1986;140:859.
41. Huang KC, Heise A, Shrader AK, and Tsueda K. Vancomycin enhances the neuromuscular blockade of vecuronium. Anesth Analg 1990;71:194–196.
42. Barg NL, Supena RB, and Fekety R. Persistent staphylococcal bacteremia in an intravenous drug abuser. Antimicrob Agents Chemother 1986;29:209–211.
43. Taylor NS and Bartlett JG. Binding of Clostridium difficile cytotoxin and vancomycin by anion-exchange resins. J Infect Dis 1980;141:92–97.
44. Chatzizisis YS, Koskinas KC, Misirli G, et al. Risk factors and drug interactions predisposing to statin-induced myopathy: implications for risk assessment, prevention and treatment. Drug Saf 2010;33:171–187.
45. Beauchamp D, Pellerin M, Gourde P, Pettigrew M, and Bergeron MG. Effects of daptomycin and vancomycin on tobramycin nephrotoxicity in rats. Antimicrob Agents Chemother 1990; 34:139–147.
46. Couture M, Simard M, Gourde P, et al. Daptomycin may attenuate experimental tobramycin nephrotoxicity by electrostatic complexation to tobramycin. Antimicrob Agents Chemother 1994;38:742–749.
47. Miro JM, Garcia-de-la-Maria C, Armero Y, et al. Addition of gentamicin or rifampin does not enhance the effectiveness of daptomycin in treatment of experimental endocarditis due to methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 2009;53: 4172–4177.

48. Cubeddu LX. QT prolongation and fatal arrhythmias: a review of clinical implications and effects of drugs. Am J Ther 2003;10:452–457.
49. Baxter K. Stockley's Drug Interactions. [online] London: Pharmaceutical Press. Available at: www.medicinescomplete.com. Date accessed: July 28, 2010.
50. ArizonaCERT. Available at: www.qtdrugs.org. Date accessed: May 21, 2010.
51. Micromedex. Available at: www.thomsonhc.com/hcs/librarian. Date accessed: February 24, 2010.

Chapter 11
Miscellaneous Antibiotics

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Abstract The chapter on miscellaneous antibiotics reviews the drug interactions with antibiotics such as chloramphenicol, tetracycline and the aminoglycosides which are older agents that are less frequently prescribed, so many clinicians may not be familiar with their interactions with other medications. It also reviews the interactions with tigecycline and quinupristin-dalfopristin, two agents that are the only available agents from classes of antibiotics that are used clinically today. Many of the interactions reviewed such as with linezolid are based on single case reports or a limited series of patients. This chapter serves as a convenient resource for the drug interactions associated with these older antibiotics and as a compilation of the multiple case reports of drug interactions with antibiotics such as linezolid.

11.1 Introduction

This chapter discusses the interactions of antibiotics that may be the only available agents from a class of antibiotics that is used clinically today. Chloramphenicol and tetracycline are older agents that are less frequently prescribed; so many clinicians may not be familiar with their interactions with other medications. Many of the interacting agents also are less frequently prescribed, such as first-generation oral hypoglycemic agents. Since many of the interactions in this chapter are based on single case reports, it is often difficult to determine the mechanism of the interaction and if a true interaction exists. The existence of some interactions may be questioned because of other potential causes that may have been present when the interaction was discovered.

The interactions described in this chapter are summarized in Table 11.1.

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Table 11.1 Antibiotics Interaction

Primary drug	Interacting drug	Mechanism	Effects	Comments/management
Chloramphenicol	Acetaminophen	Increased chloramphenicol clearance	Reduced chloramphenicol concentrations Potential for therapeutic failure	Monitor chloramphenicol concentrations and adjust dose as needed Use alternative agent for antipyresis or analgesia
	Anticonvulsants	Increased chloramphenicol clearance	Reduced chloramphenicol concentrations Potential for therapeutic failure	Monitor chloramphenicol concentrations and adjust dose as needed Patients should be monitored for clinical and microbiologic response to therapy
	Anticonvulsants	Decreased metabolism of phenytoin and phenobarbital	Increased serum concentrations of these anticonvulsants with increased CNS toxicity	Monitor phenytoin and phenobarbital concentrations and adjust does as needed
	Oral hypoglycemic agents	Decreased metabolism of tolbutamide and excretion of chlorpropamide	Increased half-life of tolbutamide and chlorpropamide with increased risk of hypoglycemia	Monitor blood glucose and adjust dose of oral hypoglycemic agents as needed Monitor for clinical signs and symptoms of hypoglycemia
	Penicillins	Antagonism of bacteriocidal agents	Potential risk of therapeutic failure when both agents are administered concurrently	Monitor clinical and microbiologic response to therapy Monitor MIC and MBC of antibiotic combination and each antibiotic along Use alternative class of antibiotic
	Rifampin	Increased chloramphenicol clearance	Reduced chloramphenicol concentrations Potential for therapeutic failure	Monitor chloramphenicol concentrations and adjust dose as needed Patients should be monitored for clinical and microbiologic response to therapy

	Oral anticoagulants	Enhanced metabolism of warfarin Decreased gut production of vitamin K Altered production of prothrombin by hepatic cell	Increased risk of major and minor bleeding	Monitor PT/INR when beginning or discontinuing chloramphenicol therapy Monitor for clinical signs of bleeding
	Immunosuppressive agents	Decreased cyclosporine and tacrolimus clearance	Increased cyclosporine and tacrolimus concentrations Potential for cyclosporine and tacrolimus toxicity	Monitor cyclosporine and tacrolimus concentrations and adjust dose as needed
	Voriconazole	Decreased voriconazole clearance	Increased voriconazole concentrations	Use alternative class of antibiotic Monitor voriconazole concentrations as appropriate
Clindamycin	Nondepolarizing neuromuscular blocking agents	Local anesthetic effect on myelinated muscle Stimulates nerve terminal and blocks postsynaptic cholinergic receptor Direct depressant action on muscle	Prolonged duration of neuromuscular blockade	Patients receiving this combination of medications should have their neuro-muscular function monitored with peripheral nerve stimulation to access the degree paralysis induced by these agents Patients should be monitored for the potential development of respiratory failure
	Aminoglycosides	No clear evidence to support the hypothesis that clindamycin leads to an increased risk of nephrotoxicity when prescribed concurrently with aminoglycoside antibiotics		

(continued)

Table 11.1 (continued)

Primary drug	Interacting drug	Mechanism	Effects	Comments/management
	Paclitaxel	No clear evidence to support that clindamycin any clinically significant effect on paclitaxel pharmacokinetic parameters when prescribed concurrently		
Sulfonamides	Oral anticoagulants	Some sulfonamides appear to impair the hepatic metabolism of oral anticoagulants Competition for plasma protein binding sites may play an additional roll	An enhanced hypoprothrombinemic response to warfarin with an increased risk of minor and major bleeding	Monitor PT/INR when beginning or discontinuing sulfonamide therapy Monitor for clinical signs of bleeding
Tetracycline	Heavy metals, trivalent cations	Chelate tetracycline products in the gastrointestinal tract	Impair their absorption and decrease bioavailability Potential for therapeutic failure	Tetracycline products should be administered 2 h before or 6 h after an antacid H2-receptor antagonists and proton pump inhibitors may be prescribed in place of antacids Alternative antibiotics may be prescribed in place of a tetracycline Patients should be monitored for clinical and microbiologic response to therapy
	Colestipol	Bind tetracycline products in the gastrointestinal tract	Impair their absorption and decrease bioavailability Potential for therapeutic failure	Tetracycline products should be administered 2 h before or 3 h after an colestipol Alternative antibiotics may be prescribed in place of a tetracycline Patients should be monitored for clinical and microbiologic response to therapy

Digoxin	Tetracycline can suppress the gut flora responsible for metabolizing digoxin in the GI tract	Increased digoxin absorption and bioavailability may result in toxicity	Serum digoxin concentrations should be monitored and the dose adjusted with initiating or discontinuing antibiotic therapy
Anticonvulsants	Anticonvulsants increase the hepatic metabolism of doxycycline reducing its serum concentration	Increased potential for therapeutic failure	Patients should be monitored for clinical and microbiologic response to therapy Renally eliminated tetracycline or other classes of antibiotics should be prescribed to avoid this interaction Doxycycline should be administered twice a day in patients on chronic anticonvulsant therapy
Warfarin	Doxycycline enhances the anticoagulation response to oral anticoagulants	An enhanced hypoprothrombinemic response to warfarin with an increase risk of minor and major bleeding	Patients should be monitored for clinical signs and symptoms of bleeding when these drugs are used concurrently PT and/or INR should be monitored when these drugs are used concurrently Alternative antibiotics should be prescribed in patients on oral anticoagulants
Lithium	It is unclear if there is a direct interaction between lithium and tetracycline	Potential for increased serum lithium concentrations and lithium toxicity	Patients should be monitored for signs and symptoms of lithium toxicity when receiving lithium and tetracycline concurrently Monitor serum lithium concentrations when patients receiving lithium and tetracycline

(continued)

Table 11.1 (continued)

Primary drug	Interacting drug	Mechanism	Effects	Comments/management
	Theophylline	A reduction in theophylline metabolism	The reduction in clearance appears to be quite variable so that it may be difficult to predict how much the theophyline concentration will increase following the addition of tetracycline to the medication regimen	Patients should be monitored clinically for signs and symptoms of theophylline toxicity Serum theophylline concentration should be closely monitored in patients at high risk for developing theophylline toxicity
	Oral contraceptives	Prospective trials have failed to documented a consistent effect	Unexpected pregnancies	It is not know if noncompliance played a role in some of these unplanned pregnancies Women should be counseled to use other methods of birth control during tetracycline therapy
	Psychotropic agents	In is unclear as to the exact mechanism of the interaction	Possible potential for acute psychotic behavior	Monitor for signs and symptoms of acute psychotic behavior Use alternative class of antibiotic
	Methotrexate	Decreased methotrexate clearance	Increased methotrexate concentration Potential for methotrexate toxicity	Monitor methotrexate concentrations Maintain leucovorin rescue until methotrexate concentrations below the desired range
	Rifampin	Increased doxycycline clearance	Increased potential for therapeutic failures in patients with *Brucellosis* infections	Monitor clinical and microbiologic response to therapy Use alternative class of antibiotic
Tigecycline	Warfarin	Decreased warfarin clearance and increased warfarin AUC and half-life	Potential for prolongation of INR and risk of bleeding	Monitor INR and adjust warfarin dose as needed Use alternative antibiotic class

Aminoglycosides	Amphotericin B	Additive direct nephro-toxicity effects on kidney	The concurrent administration of aminoglycoside antibiotics and amphotericin B may increase the risk of developing renal failure	Aminoglycoside concentrations should be monitored and the dosage regimen adjusted to maintain serum concentrations within the desired therapeutic range Attempts should be made to avoid other conditions that increase the risk for developing nephrotoxicity (i.e. hypotension, IV contrast media) Avoid prescribing other agents that cause nephrotoxicity
	Neuromuscular blocking agents	Aminoglycosides have been shown to interfere with acetylcholine release and exert a postsynaptic curare-like action These agents have membrane stabilizing properties and exert their effect on acetylcholine release by interfering with calcium-ion fluxes at the nerve terminal, an action similar to magnesium ions Aminoglycosides also possess a smaller but significant decrease in postjunctional receptor sensitivity and spontaneous release	These drugs may cause postoperative respiratory depression when administered before or during operations and may also cause a transient deterioration in patents with myasthenia gravis	Patient should be monitored for prolonged postoperative paralysis if they received neuromuscular blocking agents and aminoglycoside antibiotics during the perioperative or immediate postoperative period.

(continued)

Table 11.1 (continued)

Primary drug	Interacting drug	Mechanism	Effects	Comments/management
	Indomethacin	Nonsteroidal anti-inflammatory agents may cause renal failure	Increased concentrations of renally eliminated medications	Serum concentrations of medications should be monitored when possible and dosage regimens adjusted to maintain serum concentrations within the accepted therapeutic ranges
	Cyclosporine	Additive direct nephrotoxicity effects on kidney	Concurrent administration of aminoglycoside antibiotics and cyclosporine may increase the risk of developing renal failure	Aminoglycoside and cyclosporine concentrations should be monitored and the dosage regimen adjusted to maintain serum concentrations within the desired therapeutic range Attempts should be made to avoid other conditions that increase the risk for developing nephrotoxicity (i.e. hypotension, IV contrast media) Avoid prescribing other agents that cause nephrotoxicity
	Cisplatin	Additive direct nephrotoxicity effects on kidney	Concurrent administration of aminoglycoside antibiotics and cisplatin based chemotherapy regimens may increase the risk of developing renal failure	Aminoglycoside concentrations should be monitored an the dosage regimen adjusted to maintain serum concentrations within the desired therapeutic range Attempts should be made to avoid other conditions that increase the risk for developing nephrotoxicity (i.e. hypotension, IV contrast media) Avoid prescribing other agents that cause nephrotoxicity

Loop diuretics	Ethacrynic may cause direct additive ototoxic effects on the ear	When ethacrynic acid is used alone or in combination with aminoglycosides, it should be used in low doses and titrated to maintain adequate urine output or fluid balance It is unclear whether furosemide directly increases the nephrotoxicity and ototoxicity of aminoglycosides	Aminoglycoside concentrations should be monitored and the dosage regimens adjusted to maintain concentrations within the terpaeutic range Furosemide should be used with caution in patients receiving aminoglycoside antibiotics; careful attention should be paid to the patients' weight, urine output, fluid balance and indices of renal function
Vancomycin	Unclear if vancomycin increases the nephrotoxicity of aminoglycosides	The development of nephrotoxicity	Aminoglycoside and vancomycin concentrations should be monitored and the dosage regimen adjusted to maintain serum concentrations within the desired therapeutic range Attempts should be made to avoid other conditions that increase the risk for developing nephrotoxicity (i.e. hypotension, IV contrast media) Avoid prescribing other agents that cause nephrotoxicity

(continued)

Table 11.1 (continued)

Primary drug	Interacting drug	Mechanism	Effects	Comments/management
	Anti-Pseudomonas penicillins	Penicillins combine with aminoglycoside antibiotics in equal molar concentrations at a rate dependent on the concentration, temperature and medium composition The greater the concentration of the penicillin, the greater the inactivation of the aminoglycoside The inactivation is thought to occur by way of a nucleophilic opening of the beta-lactam ring, which then combines with an amino group of the aminoglycoside, leading to the formation of a microbiologically inactive amide	Unexpected low serum aminoglycoside concentrations for a given dose	Blood samples for aminoglycosides concentrations should be sent to the laboratory within 1–2 h so that the sample can be spun down and frozen if not assayed immediately The two antibiotics should never to be given at the same time; schedule administration time of the antibiotic so that the administration of the aminoglycoside occurs toward the end of the penicillin dosing interval If a patient is receiving this antibiotic combination and unusually low aminoglycoside concentrations occur, the above factors should be checked
Linezolid	Selective Serotonin Reuptake Inhibitors	Decreased serotonin metabolism by inhibition of monoamine oxidase	Development of the Serotonin Syndrome	Review patient profile before prescribing linezolid Use alternative class of antibiotic If necessary, treat Serotonin Syndrome with serotonin antagonist cyproheptadine

	Systemic decongestants	Decreased metabolism by inhibition of monoamine oxidase	Increased blood pressure	Review patient profile before prescribing linezolid Use alternative class of antibiotic Consider using topical nasal decongestants
	Meperidine	Decreased metabolism by inhibition of monoamine oxidase	Development of serotonin Syndrome	Review patient profile before prescribing meperidine Use alternative class of analgesic If necessary, treat Serotonin Syndrome with serotonin antagonist cyproheptadine
	Rifampin	Increased linezolid clearance	Unexpected low serum linezolid concentrations Development of therapeutic failures	Use alternative class of anitibiotic
Quinupristin-dalfopristin	Medications metabolized by cytochrome P450 3A4 enzyme	Decreased metabolism of medications metabolism by cytochrome P450 3A4 enzyme	Prolonged therapeutic effects or increased adverse reactions	Review patient profile before prescribing quinupristin-dalfopristin Use alternative class of antibiotic Monitor patients closely for signs of adverse effects

11.2 Chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic that has been shown to interact with a number of medications, including analgesics-antipyretics, other antibiotics, oral hypoglycemic agents, anticoagulants, and anticonvulsants. Most of these interactions are limited to case reports with small numbers of patients. The mechanism of the interaction for several of the interactions is unknown or is limited to speculation. Five to fifteen percent of chloramphenicol is excreted as free chloramphenicol in the urine, the remainder of a dose is metabolized in the liver to inactive metabolites, principally the glucuronide metabolite.

11.2.1 Acetaminophen

Chloramphenicol has been reported to increase, decrease, and have no effect on the half-life of acetaminophen. Spika and colleagues evaluated the effect of multiple doses of acetaminophen on chloramphenicol metabolism in patients with bacterial meningitis [1]. Significant differences in chloramphenicol peak serum concentration, volume of distribution, half-life, and clearance occurred between samples obtained before and during treatment with acetaminophen. Peak serum concentrations fell; volume of distribution and clearance increased, and half-life became shorter. The greatest change was in clearance, which increased by more than 300% from baseline values. During treatment with acetaminophen, the percent of chloramphenicol excreted unchanged in the urine decreased; its succinate metabolite remained unchanged, while the glucuronide metabolite increased by approximately 300%. Kearns also evaluated the effect of acetaminophen in acutely ill pediatric patients [2]. Chloramphenicol pharmacokinetic parameters were compared between a group of patients receiving acetaminophen and a group not receiving acetaminophen. There was no statistical difference in the chloramphenicol pharmacokinetic parameters between the two groups. However, there was a clinically significant increase in chloramphenicol clearance and decrease in half-life between the initial dose and final dose in the patients receiving acetaminophen. Following acetaminophen therapy, the chloramphenicol half-life decreased by approximately 33%, from 3.4 to 2.2 h, while its clearance increased by more than 50%, from 5.5 to 8.9 mL/min/kg. The peak chloramphenicol serum concentrations were lower after the final dose than at steady state, 15.7 versus 22.7 mg/L, respectively. Stein was unable to document any effect of acetaminophen on chloramphenicol metabolism in hospitalized adult patients [3]. In a randomized crossover design, patients received either chloramphenicol or chloramphenicol with acetaminophen for 48 h. There was no significant difference in peak and trough chloramphenicol concentrations, half-life, or area under the concentration-time curve between the two treatment periods.

Although the mechanism of this interaction is unclear, it appears to be an alteration in clearance. This interaction may take several days to manifest its full effect, and in some studies patients may not have been studied for a long enough period of time to

evaluate fully the effects of acetaminophen on chloramphenicol pharmacokinetic parameters. Although Spika suggested that the increase in chloramphenicol clearance was due to an increased in glucuronidation, other investigators have not confirmed this.

This interaction may be important in patients receiving chloramphenicol for the treatment of central nervous system infections or infections due to organisms that are resistant to more traditional antibiotics. Reduced peak concentrations or increases in clearance without appropriate adjustments in dosage regimens to account for these changes may result in therapeutic failures. Patients receiving chloramphenicol and acetaminophen should have chloramphenicol serum concentrations monitored every 2–3 days during a course of therapy, especially during the later part of therapy when it appears that chloramphenicol levels may begin to decline. Dosage regimens should be adjusted to maintain chloramphenicol concentrations within the desired therapeutic range. Other agents such as aspirin or ibuprofen may be used as alternatives to acetaminophen for antipyresis and analgesia.

11.2.2 Anticonvulsants

Anticonvulsants have been shown to increase the metabolism of chloramphenicol by increasing its hepatic metabolism. Phenobarbital has been shown to stimulate the metabolism of chloramphenicol in several case reports [4, 5]. In addition, chloramphenicol has been shown to reduce the metabolism of phenytoin and phenobarbital when both agents are administered concurrently [6–10]. The onset of these interactions appears to be rapid and may persist for several days after chloramphenicol is discontinued.

The reduction in phenytoin and phenobarbital metabolism is mostly likely due to a competition for metabolic enzymes. The clinical significance of the interaction is the potential for patients to develop phenytoin and/or phenobarbital toxicity after beginning chloramphenicol therapy. Patients may show signs of lethargy, excessive sedation, nystagmus, hallucinations, or other mental status changes. Because phenytoin undergoes nonlinear metabolism, toxic serum concentrations may not occur for several days after starting chloramphenicol. After the maximum rate of phenytoin metabolism is exceeded, serum concentrations will rise rapidly and may remain elevated for a period of time after the chloramphenicol is discontinued. Due to phenobarbital's long half-life, its sedative effects can be expected to resolve slowly as the serum concentration falls.

Patients receiving chloramphenicol with either phenytoin or phenobarbital must have their anticonvulsant serum concentrations monitored frequently, preferably every 3–5 days if possible, to detect increases in the concentrations. Patients also should be monitored clinically for the development of signs and symptoms of phenytoin and/or phenobarbital toxicity.

Phenobarbital has been shown to increase the metabolism of chloramphenicol, resulting in a reduction in its peak serum concentrations. Bloxham reported two

patients who received chloramphenicol and phenobarbital for the treatment of meningitis [4]. In one patient, peak chloramphenicol serum concentrations fell from 31 mg/L on day 2 and day 3 to less than 5 mg/L on day 5. Patients receiving concurrent therapy with chloramphenicol and phenobarbital should have chloramphenicol concentrations monitored daily to monitor for reductions in the serum concentration. The chloramphenicol dosage regimen needs to be adjusted to maintain therapeutic concentrations and prevent therapeutic failures.

11.2.3 Oral Hypoglycemic Agents

Several investigators have documented chloramphenicol's ability to decrease the hepatic metabolism of tolbutamide, resulting in increases in its half-life and serum concentrations [10, 11]. Patients receiving tolbutamide and chloramphenicol concurrently may experience greater reductions in their serum glucose values and hypoglycemia with its associated complications. However, frank hypoglycemia has not been reported when this combination has been given together.

Petitpierre and Fabre reported the ability of chloramphenicol to inhibit the renal excretion of chlorpropamide [12]. They reported that five patients taking these agents together experienced an increase in their chlorpropamide half-lives from 30 to 36 h to up to 40–146 h. Hypoglycemia was not documented in these patients.

Patients taking oral hypoglycemic agents should monitor their blood glucose frequently when taking chloramphenicol. The oral hypoglycemic dosage regimen may need to be adjusted to maintain the blood glucose within a desirable range. Patients should also be instructed to monitor for signs of hypoglycemia and to carry glucose-containing products to reverse any episodes of hypoglycemia that may develop. If possible, alternative antibiotics should be selected to avoid this interaction. Since a patient's blood glucose may be controlled on a stable oral hypoglycemic dose, switching oral hypoglycemic agents to avoid this interaction is not recommended.

11.2.4 Antibiotics

11.2.4.1 Penicillins

Chloramphenicol has been reported to antagonize the effect of beta-lactam antibiotics. A number of reports have been published suggesting that bacteriostatic and bactericidal antibiotics may antagonize each other in vitro [13, 14] and in vivo [15, 16]. Despite this information, many authorities do not believe that this is a clinically significant interaction and have used this combination of antibiotics as a standard of practice for many years for the treatment of bacterial meningitis.

French and colleagues described a case in which chloramphenicol and ceftazidime were used together to treat an infant with *Salmonella* meningitis [16]. The combination failed to eradicate the infection, but subsequent treatment with ceftazidime alone

was successful. In vitro tests of serum and cerebrospinal fluid taken at that time showed that the serum could inhibit the growth of an inoculum of the salmonella at a dilution of 1:2, and the cerebrospinal fluid at a dilution of 1:16, but that neither fluid could kill the organism at any dilution. A specimen of cerebrospinal fluid taken during treatment with ceftazidime alone inhibited and killed the standard inoculum of salmonella in vitro at a dilution of 1:32.

Minor degrees of antagonism have been demonstrated in occasional laboratory experiments between almost any pair of drugs, but generally the most consistent interfering drugs are bacteriostatic agents such as chloramphenicol, tetracyclines, and macrolides [14]. All these agents appear to act predominantly as inhibitors of protein synthesis in microorganisms. They actively antagonize agents such as the penicillins, which primarily block the synthesis of cell-wall mucopeptides. It is believed that protein synthesis must proceed actively in order to permit active mucopeptide synthesis; therefore, inhibitors of protein synthesis can antagonize inhibitors of cell-wall synthesis.

11.2.4.2 Rifampin

Prober [17] and Kelly [18] each reported two cases in which the coadministration of rifampin and chloramphenicol resulted in significantly lower chloramphenicol serum concentrations. Two patients were treated with chloramphenicol for *H. influenzae*. During the last 4 days of treatment, the patients received 20 mg/kg/day of rifampin. After 12 doses of chloramphenicol, the peak serum concentrations of chloramphenicol in these two patients were 21.5 and 38.5 mg/L, respectively, and trough concentrations were 13.7 and 28.8 mg/L. After the administration of rifampin, peak chloramphenicol concentrations progressively declined. By day 3 of rifampin coadministration, the peak concentration of chloramphenicol was reduced by 85.5%, to 3.1 mg/L in one patient, and by 63.8%, to 8 mg/L in the second patient. Serum concentrations increased back into the therapeutic range after the daily dose of chloramphenicol was increased to 125 mg/kg/day. The reduction in serum concentrations was most likely due to rifampin stimulating the hepatic metabolism of chloramphenicol, increasing its clearance and decreasing its serum concentrations.

Patients should have chloramphenicol concentrations monitored daily while they are receiving rifampin. The chloramphenicol dosage regimen may need to be adjusted to maintain concentrations within the therapeutic range, since subtherapeutic concentrations may result in therapeutic failure. Patients also should be monitored clinically for their response to therapy.

11.2.5 Anticoagulants

Chloramphenicol may enhance the hypoprothrombinemic response to oral anticoagulants. Christensen documented a two- to fourfold increase in dicumarol half-life when coadministered with chloramphenicol [10].

Several potential mechanisms may be responsible for this interaction. Chloramphenicol has been shown to inhibit the metabolism of dicumarol, probably by inhibiting hepatic microsomal enzymes [10]. Some investigators have proposed that chloramphenicol decreases vitamin K production by gastrointestinal bacteria [19, 20]; however, bacterial production of vitamin K appears to be less important than dietary intake. Moreover, chloramphenicol does not usually have much effect on bowel flora [21]. Vitamin K depletion by chloramphenicol may affect the production vitamin K-dependent clotting factors in the hepatocyte [22].

The clinical consequences of an increased prothrombin time (PT) or international normalized ratio (INR) would be increased risk of bleeding. This includes minor bleeding such as nosebleeds and bleeding from the gums, but also major bleeding into the gastrointestinal tract, central nervous system, or retroperitoneal space. The PT/INR should be monitored daily when chloramphenicol is started or discontinued in patients taking oral anticoagulants. There may be an increase in clot formation and thromboembolic complications if the warfarin dose is not increased after the chloramphenicol is stopped.

11.2.6 Immunosuppressive Agents

11.2.6.1 Cyclosporine and Tacrolimus

Several reports have appeared in the literature describing an interaction between chloramphenicol and immunosuppressive agents, specifically cyclosporine and tacrolimus. Bui and Huang reported the interaction in a renal transplant patient receiving cyclosporine [23]. The patient required cyclosporine 50–75 mg twice daily to maintain trough concentrations in the 100–150 μg/L prior to hospital admission. The patient's cyclosporine dose required increasing to 300 mg twice daily during her hospital admission to maintain similar trough concentrations because of rifampin therapy for the treatment of line sepsis. Ten days after the rifampin was stopped, chloramphenicol 875 mg 6 h was started for the treatment of an *Enterococcus* sinusitis. The trough cyclosporine concentration on the following day increased to 280 μg/L. Despite stepwise lowering of the cyclosporine dose to 50–100 mg/day, the concentrations continued to rise for the next 2 weeks, reaching a plateau of 600 μg/L. After stopping the chloramphenicol, the cyclosporine concentration stabilized between 100 and 150 μg/L on a dose of 50 mg twice daily. Steinfort and McConachy reported a similar experience in a heart transplant patient receiving chloramphenicol and cyclosporine [24]. Mathis reported a 41.3% increase in trough cyclosporine concentration in 3 renal transplant patients following the addition of chloramphenicol to their medication regimens [25]. Mean cyclosporine doses were reduced by 44–49% in order to maintain therapeutic cyclosporine concentrations.

Several reports have documented a similar interaction between chloramphenicol and tacrolimus in transplant patients [26–28]. Schulman and colleagues reported a 7.5-fold increase in tacrolimus dose-adjusted AUC, 22.7 vs 171 μg*h/L and an

increased in tacrolimus half-life from 9.1 to 14.7 h following the addition of chloramphenicol to a stable tacrolimus regimen [26]. Taber and colleagues documented the chloramphenicol-tacrolimus interaction in a liver transplant patient. The patient was stabilized on an outpatient tacrolimus dose of 5 mg twice daily with trough concentrations ranging between 9 and 11 ng/mL. The tacrolimus 12-h trough concentration increased to more than 60 ng/mL after 3 days of chloramphenicol 1,850 mg every 6 h. The patient complained of lethargy, fatigue, headaches, and tremors. The tacrolimus concentration decreased to 8.2 ng/mL 7 days after the chloramphenicol was stopped. The tacrolimus regimen was restarted at 5 mg twice daily resulting in stable trough concentrations between 6.7 and 11.0 ng/mL [27]. Bakri reported an approximately fourfold increase in the tacrolimus blood concentration of a renal transplant patient after the initiation of chloramphenicol 750 mg 4 times daily [28]. The tacrolimus concentration ranged between 5 and 11 ng/mL on stable regimen of 4 mg twice daily but increased to >30 ng/mL within 3 days after starting chloramphenicol. The patients also experienced a slight rise in serum creatinine and a significant increase in his serum potassium level during this time. The tacrolimus dose was reduced to 1.5 mg twice daily and the blood concentration fell to 18–25 ng/mL. Chloramphenicol was stopped after 15 days of therapy and the patient's tacrolimus blood concentration stabilized between 8 and 15 mg/mL on a regimen of 3 mg twice daily. Mathis also reported up to a 207% increase in trough tacrolimus concentration in another 3 renal transplant patients following the addition of chloramphenicol to their medication regimens [25]. Mean tacrolimus doses were reduce by 25–34% in order to maintain therapeutic cyclosporine concentrations.

11.2.7 Antifungal Agents

11.2.7.1 Voriconazole

Chloramphenicol was shown to inhibit the metabolism of voriconazole in a pediatric patient with fungal ventriculitis [29]. A voriconazole dose of approximately 4 mg/kg twice daily resulted in plasma voriconazole trough concentrations of 2.2 and 3.5 mcg/mL while the patient was also receiving chloramphenicol. The voriconazole dose had to be increased to 9 mg/kg twice in order to maintain concentrations within the range to treat *Aspergillus* infections.

The mechanism of the interaction is most likely due to chloramphenicol's inhibition of the cytochrome P450 3A4 enzyme that is responsible for the metabolism of cyclosporine and tacrolimus. If chloramphenicol has to be used in a patient receiving cyclosporine or tacrolimus, a prospective decrease in dose may be warranted. Cyclosporine and tacrolimus concentrations should be closely monitored with appropriate dose adjustments while patients are receiving chloramphenicol. Cyclosporine and tacrolimus administration should be stopped in patients with elevated trough concentrations, especially in patients slowing signs of cyclosporine or tacrolimus toxicity until the concentrations returned to the normal therapeutic

range. The agents may be restarted at appropriately adjusted doses to maintain the trough concentrations within the therapeutic range. Chloramphenicol inhibits voriconazole metabolism by inhibiting P450 3A4 and possibly 2C19 isoenzymes. Voriconazole doses will need to be adjusted with the initiation and discontinuation of chloramphenicol therapy. Monitoring voriconazole concentrations may be warranted in order concentration within the range need to effectively treat serious fungal infections.

11.3 Clindamycin

11.3.1 Nondepolarizing Neuromuscular Blocking Agents

Clindamycin has been shown to interact with nondepolarizing neuromuscular blocking agents and aminoglycoside antibiotics. Becker and Miller investigated the neuromuscular blockade induced by clindamycin alone and when mixed with d-tubocurarine or pancuronium in an in vitro guinea pig lumbrical nerve-muscle preparation [30]. Clindamycin initially increased twitch tension, but with higher concentrations twitch tensions subsequently decreased. With 15–20% twitch depression induced by clindamycin, neostigmine or calcium slightly but not completely antagonized the blockade. Clindamycin at a dose that did not depress twitch tension potentiated d-tubocurarine- and pancuronium-induced neuromuscular blockade.

Several clinical reports document clindamycin's ability to prolong neuromuscular blockade following depolarizing and nondepolarizing neuromuscular blocking agents [31–33]. Best and colleagues reported on a patient who received clindamycin 300 mg IV 30 min before surgery to repair a nasal fracture [31]. Succinylcholine 120 mg was administered to facilitate intubation with no additional nondepolarizing neuromuscular blocking agents administered during the surgery. Approximately 5 h after surgery and 20 min after receiving clindamycin 600 mg intravenously, the patient complained of profound overall body weakness and was noted to have bilateral ptosis, difficulty speaking, and rapid shallow respirations. After several minutes her weakness rapidly became more profound, with 1/5 muscle strength noted in all extremities. Nerve stimulation showed marked neuromuscular blockade with the train-of-four (TOF) stimulation noted to be 0/4. The patient was treated with neostigmine 4 mg IV and glycopyrrolate 0.8 mg IV enabling the patient to move all extremities and develop a more normal respiratory pattern. Follow-up nerve stimulation showed a TOF of 4/4 and within 20 min of the reversal agent the patient returned to baseline muscle strength (5/5) in all extremities.

Clindamycin-induced neuromuscular blockade is difficult to reverse. No reversal could be obtained by using either calcium or neostigmine [34]. The mode of action of clindamycin on neuromuscular function is complex. Although it has a local anesthetic effect on myelinated nerves, it also stimulates the nerve terminal and simultaneously blocks the postsynaptic cholinergic receptor. It appears that its major

neuromuscular blocking effect is a direct depressant action on the muscle by the un-ionized form of clindamycin [35]. Clindamycin also has been shown to decrease the quantal content of acetylcholine released with presynaptic stimulation in-vitro [36], possibly the result of effects on presynaptic voltage gated Ca^{+2} channels [37].

This interaction may be of clinical significance in patients receiving clindamycin and depolarizing or nondepolarizing neuromuscular blocking agent during the perioperative period or in an intensive-care unit. This interaction may result in a prolonged period of neuromuscular blockade, resulting in recurarization with respiratory failure and an extended period of mechanical ventilation.

Patients receiving this combination of agents should be monitored clinically with peripheral nerve stimulation using train-of-four or other mode of nerve stimulation to assess neuromuscular function and degree of neuromuscular blockade.

11.3.2 Aminoglycosides

One report suggests that clindamycin may increase the risk of nephrotoxicity when administered concurrently with aminoglycoside antibiotics. Butkus and colleagues reported three patients who developed acute renal failure when gentamicin and clindamycin were administered concurrently [38]. The evidence for combined nephrotoxicity consisted of the temporal relationship between administration of the antibiotics and the development of acute renal failure with rapid recovery after the antibiotics were stopped.

11.3.3 Paclitaxel

The pharmacokinetics of paclitaxel 175 mg/m^2 was studied in 16 patients with ovarian cancer [39]. Paclitaxel was administered alone and with clindamycin doses of 600 and 1,200 mg/dose. There was a slight reduction in paclitaxel C_{max} and AUC with increasing doses of clindamycin. The baseline paclitaxel C_{max} and AUC were 3.25 ± 1.22 μg/mL and 8.40 ± 2.88 μg h/mL, respectively but fell progressively with the coadministration of clindamycin 600 mg/dose (3.02 ± 0.81 μg/mL and 7.49 ± 1.94 μg h/mL) and 1,200 mg/dose (2.87 ± 0.89 μg/mL and 7.45 ± 2.24 μg h/mL).

This interaction is supported by circumstantial evidence. Although both agents were administered concurrently, none of the patients had gentamicin concentrations monitored during therapy. The reversible renal failure is consistent with that seen with aminoglycosides. It occurs during the course of therapy and resolves rapidly once the aminoglycoside antibiotic is stopped. There is no evidence to suggest that the administration of clindamycin in the setting of appropriately dosed aminoglycoside antibiotics leads to an increased risk of nephrotoxicity. The changes in paclitaxel concentrations following the coadministration of clindamycin are minimal and probably not clinical relevant. No alterations in the paclitaxel dose are recommended when it is coadministered with clindamycin.

11.4 Sulfonamides

11.4.1 Warfarin

Several reports have described an enhanced hypoprothrombinemic response to warfarin when sulfamethoxazole, usually in combination with trimethoprim, was added to a patient's therapy [40–43]. Two pharmacokinetic studies in healthy adults confirmed that sulfamethoxazole enhances the hypoprothrombinemic response to warfarin in most people [43, 44]. Although the sulfamethoxazole seems more likely to have been responsible than the trimethoprim, a trimethoprim effect cannot be ruled out.

O'Reilly conducted two studies evaluating the stereoselective interaction between trimethoprim-sulfamethoxazole (TMP-SMX) and warfarin. In one study, patients received 1.5 mg/kg of racemic warfarin with and without 320 mg trimethoprim-1,600 mg sulfamethoxazole beginning 7 days before warfarin and continuing daily throughout the period of hypoprothrombinemia [45]. There was a significant increase in the areas of the one-stage prothrombin time, from 53 to 83 units, during the administration of TMP-SMX. In a follow-up study, O'Reilly studied the effects of TMP-SMX on each of the warfarin enantiomers [46]. Subjects received each enantiomer alone and in combination with 80 mg trimethoprim-400 mg sulfamethoxazole. TMP-SMX had no effect on the R-isomer. The areas of the one-stage prothrombin time increased by approximately 70%, from 40 to 67 units, when the S-isomer and TMP-SMX were given together. Additional case reports describe the prolongation in PT following the addition of TMP-SMX to medication regimens containing warfarin [40–43]. Penning-van Beest and colleagues analyzed a retrospective group of approximately 60,000 patients taking coumarin anticoagulants identified in the PHARMO Record Linkage System in the Netherlands [47]. The relative risk of bleeding was calculated for a variety of antibiotics co-administered with the coumarin anticoagulants with the relative risk of bleeding being 3–5 for TMP-SMX.

Some sulfonamides appear to impair the hepatic metabolism of oral anticoagulants. Competition for plasma protein–binding sites may play an additional role. Although sulfonamides reportedly decrease vitamin K production by the gastrointestinal bacteria, evidence for such an effect is lacking.

Patients should be monitored closely for an increase in PT/INR when sulfamethoxazole-containing products are coadministered with warfarin. Two reports suggest that a preemptive warfarin dose reduction of approximately 10–20% when initiating TMP-SMX therapy is effective in maintaining INR in the therapeutic range [45, 48]. Patients should be monitored clinically for signs of bleeding with initiating TMP-SMX and decreased effects upon discontinuing TMP-SMX or when preemptively reducing the warfarin dose. Other antibiotics may be prescribed to avoid this interaction, or other forms of anticoagulation such as unfractionated or low-molecular-weight heparin may be used as alternatives to warfarin.

11.5 Tetracyclines

Tetracyclines have been documented to interact with a number of medications. The most common interaction is with heavy metals that chelate tetracyclines and impair their absorption from the gastrointestinal tract. Although somewhat controversial, interactions may occur with oral contraceptives, where tetracycline may reduce their effectiveness and increase the risk of pregnancy.

11.5.1 Heavy Metals

Numerous studies have documented the ability of heavy metals to chelate tetracycline products and impair their absorption [49–51]. These products contain divalent and trivalent cations such as aluminum, magnesium, and calcium. Antacids also may impair the dissolution of tetracyclines. Bismuth subsalicylate, a common ingredient in antidiarrheal medications, also has been shown to impair the absorption of tetracyclines through a similar chelation mechanism [52, 53].

This is a pharmacokinetic interaction because it impairs absorption and reduces oral bioavailability. The clinical consequences of this interaction could be the potential of a therapeutic failure because of inadequate tetracycline serum and tissue concentrations.

Oral tetracycline products should be taken 2 h before or 6 h after antacids. This may not completely avoid the interaction, but should minimize it. Since this interaction is not based on an alteration in pH, H_2-receptor antagonists and proton pump inhibitors may be alternative medications. Additionally, other antibiotics may be prescribed to avoid the interaction.

Bismuth can reduce the bioavailability of tetracycline, similar to heavy metals. Ericsson and colleagues evaluated the influence of a 60-mL dose of bismuth subsalicylate on the absorption of doxycycline [52]. Doxycycline bioavailability was reduced by 37% and 51% when given simultaneously and as a multiple-dose regimen before doxycycline. Peak serum concentrations of doxycycline were significantly decreased when bismuth subsalicylate was give 2 h before doxycycline but not when given 2 h after doxycycline. Albert and co-workers documented a 34% reduction in doxycycline bioavailability when the two products were administered simultaneously [53]. A further discussion on the effect of various food containing divalent cations is given in Chap. 10.

11.5.2 Colestipol

Colestipol reduces the bioavailability of tetracycline by impairing its absorption in the gastrointestinal tract. Friedman et al. showed that when colestipol and tetracycline were given together, there was a 50% reduction in tetracycline bioavailability [54].

In a single dose, three-way crossover study, subjects ingested 500 mg tetracycline with 180 mL of water, 180 mL of water and 30 g colestipol, and 180 mL of orange juice and 30 g colestipol. There were significant differences in the 48-h urinary excretion of tetracycline. More than 50% of the dose was recovered in the urine when the tetracycline was administered with water. Only 23–24% was recovered in the urine when it was administered with colestipol. There was no significant difference among the three groups in the mean-value excretion half-life.

This interaction impairs absorption and reduces oral bioavailability as a result of tetracycline adsorbing onto colestipol-binding sites. The clinical consequences of this interaction could be the potential of a therapeutic failure because of inadequate tetracycline serum and tissue concentrations.

Oral tetracycline should be taken 2 h before or at least 3 h after a dose of colestipol. Additionally, other antibiotics may be prescribed to avoid the interaction.

11.5.3 Digoxin

Tetracycline can reduce the gastrointestinal bacterial flora responsible for metabolizing digoxin in the gastrointestinal tract and increase digoxin absorption and bioavailability in some patients. Lindenbaum and colleagues administered digoxin to healthy volunteers for 22–29 days. After 10 days, 500 mg tetracycline q6h for 5 days was started [55]. During the period of antibiotic administration, digoxin reduction products fell, urine digoxin output rose, and digoxin steady-state serum concentrations increased by as much as twofold in some subjects. Preantibiotic serum digoxin serum concentrations ranged between 0.37 and 0.76 μg/L and increased to 0.8–1.33 μg/L following antibiotic therapy. It also was noted that these effects persisted for several months after the antibiotics were stopped. There were no reports of digoxin toxicity in the patients who experienced an increase in their digoxin concentrations.

The mechanism of this interaction appears to be the inhibition of digoxin metabolism by suppressing gut bacteria. The clinical implications of this interaction are the possibility that therapy with antibiotics in subjects producing large amounts of digoxin reduction products may precipitate toxicity. Unrecognized changes in gut flora might result in variability in digoxin response, in the direction of either drug toxicity or therapeutic failure.

11.5.4 Anticonvulsants

Phenobarbital and phenytoin have been shown to reduce the serum concentrations of doxycycline [56–58]. Penttilla and Neuvonen conducted three trials to evaluate the effect of anticonvulsants on doxycycline metabolism [56]. In one study they compared the half-life of doxycycline in patients taking long-term phenytoin and/or carbamazepine therapy to a control group of patients not receiving anticonvulsants. The doxycycline half-life in the patients receiving chronic anticonvulsants ranged

between 7 and 7.5 h compared to 15 h in the control subjects. In a second crossover trial, they determined the half-life of doxycycline in five patients after 10 days of phenobarbital therapy and in another five patients taking phenobarbital chronically [57]. The half-life of doxycycline was 15 h in the control patients before phenobarbital therapy was begun. After 10 days of therapy the half-life was reduced to 11 h. The doxycycline half-life was 7 h in the patients taking phenobarbital chronically. In a third trial, they evaluated the effect of chronic anticonvulsant therapy on a variety of tetracycline products and compared this to results in control patients [58]. The doxycycline half-life averaged 7 h and the peak concentrations were lower in the patients on chronic anticonvulsant therapy compared to the control group. There was no difference in the half-lives of oxytetracycline, methacycline, chlortetracycline, and demethylchlortetracycline between the patients on anticonvulsants and control patients.

Although doxycycline is primarily eliminated in the feces, the enhanced hepatic metabolism of doxycycline appears to be the mechanism of this interaction. The clinical consequences of this interaction could be a reduction in serum doxycycline concentrations and the potential for therapeutic failure. An alternative class of antibiotics should be selected for these patients because they may be receiving anticonvulsants for the control of a seizure disorder and it would not be wise to switch anticonvulsants to avoid this interaction.

11.5.5 Warfarin

Tetracyclines may be associated with an increased hypoprothrombinemic response in patients taking oral anticoagulants. Several case reports describe patients stabilized on chronic warfarin therapy who experienced increases in PT after the addition of doxycycline to their medication regimens [59, 60]. Westfall described a patient maintained on warfarin therapy with stable PT values approximately two times the control value [59]. After the initiation of 100 mg of doxycycline twice a day, the patient's PT increased to 51 s and was associated with an unusually heavy menstrual flow. Upon medical evaluation her hemoglobin and hematocrit had dropped to 5.7 g/dL and 18.9%, respectively.

Caraco and Rubinow described two patients taking chronic oral anticoagulation who presented with severe hemorrhage and disturbed anticoagulation tests after the addition of doxycycline to their medication regimens [60]. In the first patient, the PT ratio increased from 1.49 to 3.82 following the addition of 100 mg of doxycycline daily. In the second patient, the PT ratio increased from between 1.5 and 2.5–4.09 following the addition of 100 mg of doxycycline twice daily.

Penning-van Beest estimated the relative risk of bleeding in patients taking coumarin anticoagulants and a tetracycline in the PHARMO Record Linkage System in the Netherlands [47]. The relative risk of bleeding was calculated to be 3–5 for doxycycline and 9 for tetracycline.

The mechanism of this interaction is unclear but may involve a reduction in the plasma prothrombin activity by impairing prothrombin utilization or decreasing vitamin K production by the gastrointestinal tract.

The clinical significance of this interaction is the increased anticoagulant effect, which may result in an increased risk of bleeding. Patients should be closely monitored for clinical signs of bleeding such as nosebleeds or bleeding from the gums, and the PT monitored and warfarin dose adjusted to maintain the PT/INR in the therapeutic range. Other antibiotics may be prescribed to avoid this interaction, or other forms of anticoagulation such as unfractionated or low-molecular-weight heparin may be used as alternatives to warfarin.

11.5.6 Lithium

One case report described the increase in lithium concentrations following a course of tetracycline [61]. However, a prospective trial documented small decreases in the serum lithium concentration when both agents were administered concurrently [62].

McGennis reported a patient taking lithium chronically for a history of manic depression [61]. Two days after starting tetracycline, it was noted that her serum lithium level increased from 0.81 to 1.7 mmol/L. The patient exhibited slight drowsiness, slurred speech, and a fine tremor of both hands consistent with lithium toxicity. At the time lithium and tetracycline were stopped, the serum lithium concentration was 2.74 mmol/L. The concentration declined to within the therapeutic range 5 days after stopping both agents.

Fankhauser evaluated the effect of tetracycline on steady-state serum lithium concentrations in healthy volunteers and compared the frequency and severity of adverse effects in the lithium and lithium-tetracycline treatment phases [62]. There was a significant decrease in the serum lithium concentration between the control and treatment phases (0.51 versus 0.47 mEq/L, $p = 0.01$). It is unclear whether this is a clinically significant decrease in the serum lithium concentration. There was no difference in adverse effects between the control and treatment phases of the trial.

The mechanism of this interaction is not known. One possibility may be that tetracycline-induced renal failure may reduce urinary lithium excretion. Although it is unlikely that a significant interaction exists, patients should be monitored for signs of lithium toxicity when this combination is prescribed. Renal function should also be monitored to prevent increases in the serum lithium concentrations secondary to reductions in renal function. Another class of antibiotics should be prescribed to avoid this interaction.

11.5.7 Psychotropic Agents

Steele and Couturier reported the possible interaction between tetracycline and respiradone and or sertraline in a 15-year-old male with Asperger's disorder, Tourette's Disorder and obsessive-compulsive disorder [63]. Tetracycline was added to a respiradone-sertraline treatment regimen resulting in an acute exacerbation of motor and vocal tics. The authors postulated that the increase in

tics may have resulted from either a tetracycline-respiradone interaction leading to a reduction in respiradone levels or a tetracycline-sertraline interaction leading to increased levels of sertraline or the natural course of Tourette's disorder. The sertraline dose was increased with no concomitant increase in tics and subsequent discontinuation of tetracycline resulted in an improvement in tics, which suggests the possibility of an interaction between tetracycline and respiradone. The mechanism of this potential interaction is unknown, but the author recommended that the addition of antibiotics to psychotropic medications require close monitoring due to the potential for the interaction.

11.5.8 Theophylline

Several case reports describe increases in theophylline serum concentrations during a course of tetracycline administration [64, 65]. However, prospective trials have failed to document a consistent effect [66–69].

Four prospective studies have evaluated the interaction between theophylline and tetracycline. Pfeifer gave nine patients tetracycline for 48 h and did not observe a statistically significant interaction [66]. However, six subjects had a decrease in theophylline clearance during the combined tetracycline-theophylline period, and in four of the subjects the decrease was greater than 15%. Mathis studied eight healthy volunteers by giving them a single IV injection of aminophylline before and after 7 days of tetracycline [67]. Theophylline clearance decreased by an average of 9%, but four patients had greater than 15% decrease in clearance and one patient had a 32% decrease in clearance. Gotz and Ryerson evaluated the interaction between tetracycline and theophylline in five patients with chronic obstructive airways disease [68]. Theophylline clearance decreased by an average of 11% following the 5-day course of tetracycline. Jonkman evaluated the effects of doxycycline on theophylline pharmacokinetic parameters in healthy volunteers during a 9-day course of theophylline alone and with the coadministration of doxycycline [69]. There was no influence of doxycycline on absorption, elimination, and volume of distribution of theophylline. Mean steady-state plasma concentrations were not significantly different between the two treatment periods.

The mechanism for the interaction in unknown but appears to be a reduction in the hepatic metabolism of theophylline. The reduction in metabolism appears to be quite variable. It may take several days for the interaction to occur, so increases in serum theophylline may not be clinically significant after short courses of tetracycline. Patients taking longer courses of tetracycline may be at risk for developing theophylline toxicity.

Patients should be closely monitored when tetracycline is added to a medication regimen containing theophylline. Although short courses may not result in clinically significant increases in the serum theophylline concentration, patients maintained in the upper end of the therapeutic range may be at risk of developing theophylline toxicity even with modest increases in the serum theophylline concentration.

Also, the reduction in clearance appears to be quite variable, so it may be difficult to predict how much the theophylline will increase following the addition of tetracycline to the medication regimen. All patients should be monitored clinically for signs and symptoms of theophylline toxicity. Serum theophylline concentration should be monitored every 2–3 days in patients at high risk for developing theophylline toxicity.

11.5.9 Oral Contraceptives

Several case reports suggest that tetracycline can reduce the effectiveness of oral contraceptives [70, 71]. One retrospective study should that the oral contraceptive failure rate was within the expected range associated with the typical pattern of use [72]. However, prospective trials have failed to document a consistent effect [73, 74]. These case reports of unintended pregnancies have occurred following the concurrent administration of tetracycline and other antibiotics with oral contraceptives. Two small controlled studies evaluated the effect of tetracycline on the serum levels of ingredients contained in commonly prescribed oral contraceptives. Neely et al. compared the serum concentrations of ethinyl estradiol, norethindrone, and endogenous progesterone during a control period and after a 7-days course of doxycycline starting on day 14 of their cycle [73]. There were no statistically significant differences in serum concentrations of ethinyl estradiol, norethindrone, and endogenous progesterone between the control and treatment phases. Murphy et al. studied the effect of tetracycline on ethinyl estradiol, norethindrone after 24 h and 5–10 days of therapy with tetracycline [74]. There was no significant decrease in ethinyl estradiol, norethindrone concentrations after 24 h or after 5–10 days of therapy. A pharmacokinetic study was performed to investigate whether there was any interaction between etonogestrel or ethinylestradiol released from the combined contraceptive vaginal ring NuvaRing and concomitant treatment with orally administered doxycycline. Healthy women were randomised to receive either NuvaRing alone for 21 days or NuvaRing for 21 days doxycycline The doxycycline study measured AUC values over the initial 24 h on days 1 and 10 and the whole of days 1–11 and 1–22. There were no differences in the etonogestrel or ethinylestradiol serum concentrations between subjects using NuvaRing alone versus those receiving the ring plus doxycycline. Calculation of etonogestrel and ethinylestradiol interaction/control ratios confirmed the absence of an interaction between these medications [75].

The mechanism for the interaction is unknown but may be due to interference with the enterohepatic circulation of estrogens in the intestines, making this a pharmacokinetic interaction. Other antibiotics have also been reported to reduce the effectiveness of oral contraceptives when administered concurrently. It is not known if noncompliance played a role in some of these unplanned pregnancies. Other more extensive reviews on the interaction between tetracyclines and oral contraceptives have concluded that this interaction is not supported by pharmacokinetic data [76].

Although the evidence of the interaction between tetracycline and oral contraceptives is limited to case reports, women should be counseled to use other methods of birth control during tetracycline therapy.

11.5.10 Methotrexate

Tortajada-Ituren and colleagues reported an interaction between doxycycline and high-dose methotrexate [77]. A 17-year female was receiving high-dose methotrexate as part of a chemotherapy regimen. The patient had undergone 10 cycles of the regimen without complications. Her mean methotrexate pharmacokinetic parameters following the 10 cycles were a methotrexate clearance of 2.95 L/h; half-life, 2.96 h; mean residence time, 4.27 h; and volume of distribution, 12.53 l. On admission to the hospital for the eleventh cycle of chemotherapy, the patient was noted to have a palpebral abscess in her left eye which was treated with doxycycline 100 mg twice daily. The high-dose methotrexate, 18 g was administered according to her usual protocol. During the first 24 h after the methotrexate infusion, the patient developed facial erythema, malaise and vomiting that had not occurred during the first 10 cycles. The doxycycline was stopped 48 h after chemotherapy. The pharmacokinetic monitoring was prolonged for 168 h revealing a significant decrease in methotrexate clearance (1.29 L/h) and significant increase in half-life (6.26 h) and mean residence time (9.03 h) compared to the values obtained during the first 10 cycles. Her hospital stay was prolonged to 11 days compared to an average of 7.7 days during the first 10 cycle.

Although the mechanism of the interaction is unknown, one proposed theory suggests that tetracyclines may displace methotrexate from plasma protein binding sites [78]. In an attempt to validate this mechanism in their patient, the authors determined the degree of methotrexate plasma protein binding in two plasma samples with similar methotrexate concentrations from the seventh and eleventh cycles. The unbound methotrexate concentrations were determined with an ultrafiltration process. The unbound methotrexate fractions during the seventh and eleventh cycles were 53% and 41% respectively.

Although case reports of a tetracycline-methotrexate interaction are limited, tetracyclines should be avoided in patients receiving high-dose methotrexate therapy. If therapy with a tetracycline is required, pharmacokinetic monitoring should be continued until the methotrexate concentrations are below the desired range and the leucovorin rescue should be continued, if necessary until all signs and symptoms of methotrexate toxicity disappear.

11.5.11 Rifampin

Colmenero and colleagues studied the possible interaction between rifampin and doxycycline in 20 patients with brucellosis [79]. Patients were treated with either doxycycline and streptomycin or doxycycline and rifampin. The doxycycline levels in the patients treated with rifampin were significantly lower than those patients treated

with doxycycline and streptomycin. The doxycycline clearance in patients treated with rifampin was significantly higher than in the patients treated with doxycycline and streptomycin 3.59 and 1.55 L/h, respectively. The elimination half-life (4.32 h vs 10.59 h) and area under the concentration-time curve were significantly lower in patients in the rifampin treated patients (30.4 vs 72.6 μg*h/mL). Additionally, there were lower doxycycline levels in the rifampin treatment group who were rapid acetylators. There were no treatment failures in the patients receiving doxycycline and streptomycin, while there were two treatment failures in the doxycycline-rifampin group.

Rifampin is a potent inducer of hepatic microsomal enzymes. Although doxycycline is only partially metabolized, the effect of rifampin may be significant enough to lower doxycycline concentrations to subtherapeutic levels. Caution should be used when treating patients with combined rifampin and doxycycline therapy. If possible, alternative antibiotic should be prescribed to avoid potential treatment failures.

11.6 Tigecycline

The interaction between tigecycline and warfarin was studied in 19 healthy males subjects [80]. On day 1, the subjects received a single warfarin 25 mg dose. On day 8, they received a 100 mg loading dose of IV tigecycline followed by 50 mg every 12 h for eight additional doses. On day 12 they received another warfarin 25 mg dose with their last tigecycline dose. After 8 dose of tigecycline, R- and S- warfarin AUCs were increased by 68% and 29%, respectively, and clearance decreased by 40% and 23% respectively. There was an approximately 50% increase in the R-warfarin half-life from 42.4 to 68.7 h, but less than a 20% increase in the S-warfarin half-life from 32 to 37 h. There was no significant effect on INR.

The reductions in clearance and half-life suggest that this effect was due to an increase in warfarin protein binding. Although there was no effect on the INR after single doses in healthy volunteers, all patients on chronic warfarin therapy receiving broad-spectrum antibiotics should have their INR closely monitored and doses adjusted as needed.

11.7 Aminoglycosides

Aminoglycoside antibiotics are involved in a number of drug interactions, many of which result in an increased risk of nephrotoxicity.

11.7.1 Amphotericin B

The concurrent use of aminoglycoside antibiotics may lead to an increased risk of developing nephrotoxicity. Churchill and Seely reported four patients that developed nephrotoxicity when both agents were administered together [81]. All of the

patients received amphotericin B at an approximate dose of 0.5 mg/kg/day. Two of the four patients had documented gentamicin trough concentrations of 5 mg/L. All patients developed progressive renal failure during the first several days of combined therapy. In the patients who survived, renal function returned to baseline values after both agents were discontinued.

The mechanism of this is the potential of additive nephrotoxicity from both agents. Amphotericin B is associated with a predictable rise in creatinine within the first several days of therapy. Aminoglycoside antibiotics are associated with acute tubular necrosis, especially in the setting of elevated serum concentrations. In the case report, three patients had documented gentamicin concentrations significantly higher than the desired 2 mg/L. This mostly likely contributed to the development of nephrotoxicity in these patients.

Patients receiving aminoglycoside antibiotics and amphotericin B should be closely monitored for the development of renal failure. The aminoglycoside serum concentrations should be monitored every 2–3 days and the dosage regimen adjusted to maintain peak and trough concentrations within the desired therapeutic range. Every attempt should be made to avoid other conditions that might increase the risk of developing renal failure (i.e. hypotension) and avoiding administering other medications that might increase the risk of developing renal failure (i.e. iv contrast media, loop diuretics).

11.7.2 Neuromuscular Blocking Agents

Aminoglycoside agents are known to potentiate paralysis from neuromuscular blocking agents [82–85]. Often this has occurred in the setting of the instillation of aminoglycoside-containing irrigation solutions into the intraabdominal cavity during surgery. Dupuis et al. evaluated prospectively the interaction between aminoglycosides and atracurium and vecuronium in 44 patients [86]. Twenty-two patients had therapeutic concentrations of gentamicin or tobramycin and 22 patients served as controls. Onset time, clinical duration, and time to spontaneous recovery T_1/T_4 ratio of 0.7 after atracurium or vecuronium injection were measured. Although no statistically significant differences were found in onset time, clinical duration was longer in patients receiving tobramycin or gentamicin and paralyzed with vecuronium than in controls. The neuromuscular blockade produced by atracurium was not significantly influenced by the presence of therapeutic serum concentrations of tobramycin or gentamicin. The clinical duration of patients receiving atracurium alone or in the presence of an aminoglycoside was approximately 40 min in each group, and the time to recovery of a T_1/T_4 ratio >0.7 approximately 60–70 min. The clinical duration was significantly longer in the vecuronium patients receiving aminoglycosides than in the vecuronium control patients, 30 versus 55 min, respectively. The time to recovery of a T_1/T_4 ratio >0.7 in the patients receiving vecuronium with aminoglycosides also was longer in the patients receiving an aminoglycoside, 55 versus 105 min, respectively.

Aminoglycosides have been shown to interfere with acetylcholine release and exert a postsynaptic curare-like action [87]. These agents have membrane-stabilizing properties and exert their effect on acetylcholine release by interfering with calcium-ion fluxes at the nerve terminal, an action similar to magnesium ions. Aminoglycosides also possess a smaller but significant decrease in postjunctional receptor sensitivity and spontaneous release.

These drugs may cause postoperative respiratory depression when administered before or during operations and may also cause a transient deterioration in patients with myasthenia gravis. Patients should be monitored for prolonged postoperative paralysis if they received neuromuscular blocking agents and aminoglycoside antibiotics during the perioperative or immediate postoperative period.

11.7.3 Indomethacin

Zarfin et al. evaluated the effect of indomethacin on gentamicin and amikacin serum concentration in 22 neonates with patent ductus arteriosus treated with indomethacin and aminoglycosides [88]. The aminoglycoside doses were held stable before the initiation of indomethacin therapy. After the addition of indomethacin, there was a significant rise in aminoglycoside trough and peak concentrations, a reduction in urine output, and a significant rise in serum creatinine. This may have been due to the ability of nonsteroidal anti-inflammatory agents to cause reversible renal failure. In this setting the elimination of all renally eliminated medications would be expected to be reduced with elevation in serum concentrations.

Renal function should be closely monitored in patients receiving nonsteroidal anti-inflammatory agents. If renal failure develops, the doses of all renally eliminated medications should be adjusted to the level of remaining renal function. Serum concentrations of medications should be monitored when possible and dosage regimens adjusted to maintain serum concentrations within the accepted therapeutic ranges.

11.7.4 Cyclosporine

Cyclosporine and aminoglycosides are both nephrotoxic and produce additive renal damage when administered together. Termeer et al. reported that the combined use of gentamicin and cyclosporine in renal transplant patients increased the incidence of acute tubular necrosis to 67%, compared with 5–10% when gentamicin was used alone or when cyclosporine was used with other, non-nephrotoxic antibiotics [89]. Animal studies have also documented the additive nephrotoxicity of aminoglycosides when administered with cyclosporine.

The mechanism appears to be additive injury to the renal tubule. Aminoglycosides induce renal failure by inhibiting the intracellular phospholipases in lysosomes of

tubular cells in the proximal tubule. Cyclosporine-induced acute renal failure is related primarily to its effects on the renal blood vessels. Cyclosporine acutely reduces renal blood flow, with a corresponding increase in renal vascular resistance and a reduction in glomerular filtration rate.

Patients receiving aminoglycoside antibiotics and cyclosporine should be closely monitored for the development of renal failure. The aminoglycoside and cyclosporine serum concentrations should be monitored every 2–3 days and the dosage regimen adjusted to maintain peak and trough concentrations within the desired therapeutic range. Every attempt should be made to avoid other conditions that might increase the risk of developing renal failure (i.e. hypotension) and avoiding administering other medications that might increase the risk of developing renal failure (i.e. iv contrast media, loop diuretics).

11.7.5 Chemotherapeutic Agents

Numerous reports have documented the additive nephrotoxicity when aminoglycosides are administered to patients receiving cisplatin-type chemotherapeutic agents [90–96]. Cisplatin-type chemotherapeutic agents have been shown to be associated with a reduction in renal function. Patients who received aminoglycoside antibiotics during or after a course of cisplatin-based chemotherapy regimens have demonstrated additional reductions in renal function.

The mechanism appears to be direct injury to the renal tubule. Aminoglycosides induce renal failure by inhibiting the intracellular phospholipases in lysosomes of tubular cells in the proximal tubule. Cisplatin-induced renal failure is mediated by a toxic effect on the renal tubular cells, resulting in acute tubular necrosis.

Prior administration of cisplatin is not an absolute contraindication to the use of aminoglycoside antibiotics. When clinically indicated, patients who have previously received cisplatin and have apparently normal renal function should be treated cautiously with standard doses of aminoglycoside antibiotics and pharmacokinetic monitoring should be performed routinely, with the dosage regimens adjusted to maintain serum concentrations within the normal therapeutic range.

11.7.6 Loop Diuretics

Several reports describe the increased risk of nephro- and ototoxicity when aminoglycosides and loop diuretics are administered together [97, 98]. Although some case reports suggest there is increased ototoxicity when ethacrynic acid is given in combination with aminoglycosides [99]. The data supporting the association between furosemide and aminoglycosides are controversial [100].

11.7.6.1 Ethacrynic Acid

High doses of ethacrynic given alone have been shown to produce hearing loss in patients with renal failure [99, 101]. Hearing loss can range between partial and full deafness and is usually irreversible. When patients receiving ethacrynic acid have been given an aminoglycoside such as kanamycin or streptomycin, hearing loss has been reported to occur within 15 min after an injection of the diuretic and lasting for several hours. Some patients had reduced hearing loss, while others remained deaf [99].

The mechanism of this pharmacodynamic interaction is not known. Ethacrynic is thought to produce hearing loss by an alteration in the formation of perilymph in the cochlea. This may be disputed because not all patients experience vertigo or nausea. Other possible causes of deafness may be the cysteine adduct of ethacrynic acid, a substance known to be ototoxic, or a direct toxicity to the auditory nerves by ethacrynic acid. Aminoglycosides produce ototoxicity by destroying the sensory hair cells in the cochlea and vestibular labyrinth.

Ethacrynic acid and the older-generation aminoglycosides are rarely used in clinical practice. However, some patients may be unable to take loop diuretics such as furosemide or bumetanide, so ethacrynic acid may be their only available option. When ethacrynic acid is used alone or in combination with aminoglycosides, it should be used in the lowest dose that maintains adequate urine output or fluid balance. Aminoglycoside concentrations should be monitored and the dosage regimens adjusted to maintain concentrations within the therapeutic range. Patients should be monitored with audiograms if therapy is to be continued for an extended duration, and audiograms should be performed in patients who complain of hearing loss.

11.7.6.2 Furosemide

Kaka et al. reported a suspected case of furosemide increasing the peak and trough concentrations of tobramycin in a 72-year-old women [97]. The patient received intermittent doses of furosemide for the management of congestive heart failure. The patient developed a Gram-negative aspiration pneumonia. Tobramycin was started, with serum concentrations drawn after the loading dose followed by a maintenance dose of 180 mg IV q8h. Twelve hours after an intravenous dose of 120 mg of furosemide, the tobramycin trough and peak concentrations around the fourth dose were 5.3 and 16.2 mg/L, respectively. The authors concluded that moderate doses of furosemide could increase tobramycin concentrations, thus increasing the risk of ototoxicity and nephrotoxicity in some patients.

It is unclear whether furosemide was the cause of the increased tobramycin concentrations in this patient. Although furosemide has been reported to both increase and decrease the clearance of gentamicin, there are other possible explanations for the elevated tobramycin concentrations in these patients. The authors determined the patient's tobramycin pharmacokinetic parameters after the initial dose and

used these parameters to determine the patient's maintenance dosage regimen. The maintenance regimen may have been overly aggressive for the patient's age, weight, and underlying renal function. There was extreme variability in the tobramycin pharmacokinetic parameters between the first and fourth doses, suggesting errors in drug administration or sampling technique rather than changes in the patient's clinical status or the administration of furosemide.

Smith and Liftman analyzed the data from three prospective, controlled, randomized, double-blind clinical trials to determine whether furosemide increased the nephrotoxicity and ototoxicity of aminoglycosides. There was no difference in the incidence of nephrotoxicity or ototoxicity between the groups receiving aminoglycosides alone and the group receiving aminoglycosides and furosemide [100].

It is unclear whether furosemide directly increases the nephrotoxicity and ototoxicity of aminoglycosides. Furosemide may increase the risk of developing nephrotoxicity by causing excessive diuresis, hypovolemia, and a reduction in renal blood flow. Furosemide should be used with caution in patients receiving aminoglycoside antibiotics. Careful attention should be paid to the patient's weight, urine output, fluid balance, and indices of renal function. Aminoglycosides concentrations should be monitored and the dosage regimen adjusted to maintain concentrations within the therapeutic range.

11.7.7 Vancomycin

Several reports have been published evaluating the potential of vancomycin to increase the nephrotoxicity of aminoglycoside antibiotics. Two studies were retrospective reviews and two studies were prospective evaluations. Cimino retrospectively evaluated 229 courses of therapy in 229 oncology patients [102]. Forty patients received vancomycin alone, 148 patients received aminoglycosides alone, and 40 patients received vancomycin and an aminoglycoside antibiotic. The incidence of nephrotoxicity in patients administered an aminoglycoside was 18%; vancomycin, 15%; and an aminoglycoside and vancomycin, 15%. They could not show that the concurrent administration of vancomycin had an additive effect on the incidence of nephrotoxicity. Pauly et al. retrospectively evaluated the incidence of nephrotoxicity in 105 patients who received at least 5 days of combined therapy [103]. Twenty-eight (27%) patients developed nephrotoxicity during combined vancomycin-aminoglycoside therapy. However, 22 patients had other insults such as amphotericin B, sepsis, or liver disease that could account for the increase in nephrotoxicity. There were no control groups of patients receiving vancomycin or aminoglycosides alone to provide a comparative incidence of nephrotoxicity between these groups. The results of these two studies are limited by their retrospective design, the small number of patients who received vancomycin and an aminoglycoside, and the patients who had other potential causes for developing nephrotoxicity.

Mellor et al. prospectively evaluated 39 courses of vancomycin therapy in 34 patients [104]. Twenty-seven courses were associated with aminoglycoside administration either concurrently or within 2 weeks of the first dose of vancomycin.A reduction in renal function was seen during (7%) and after (9%) vancomycin therapy. There was no evidence of synergistic toxicity between vancomycin and aminoglycosides. One feature of the patients with renal dysfunction was the severity of their underlying disease. Each case of nephrotoxicity occurred in association with either sepsis or gastrointestinal hemorrhage.

Ryback and colleagues prospectively evaluated the incidence of nephrotoxicity in patients receiving vancomycin alone or in combination with an aminoglycoside, following 224 patients receiving 231 courses of therapy [105]. One hundred and sixty-eight patients received vancomycin alone, 63 patients received vancomycin with an aminoglycoside, and 103 patients received an aminoglycoside alone. Eight patients (5%) receiving vancomycin alone, 14 patients (22%) receiving vancomycin with an aminoglycoside, and 11 patients (11%) receiving an aminoglycoside alone were found to have nephrotoxicity. Factors thought to be associated with an increased risk of nephrotoxicity in patients receiving vancomycin were concurrent therapy with an aminoglycoside, length of treatment with vancomycin (>21 days), and vancomycin trough concentrations (>10 mg/L).

Both of these studies are small prospective studies. Although they had control groups, it is unclear how well matched the control groups were to the group of patients receiving vancomycin and an aminoglycoside for underlying disease states and renal function. The risk of an increased risk of nephrotoxicity when vancomycin is administered with an aminoglycoside antibiotic is controversial. The clinical studies published to date do not show a clear association between the combination use of these agents and an increased risk of nephrotoxicity. Patients receiving vancomycin and aminoglycoside antibiotics should be closely monitored for the development of renal failure. The aminoglycoside and vancomycin serum concentrations should be monitored and the dosage regimen adjusted to maintain peak and trough concentrations within the desired therapeutic range. Every attempt should be made to avoid other conditions that might increase the risk of developing renal failure (i.e. hypotension) and to avoid administering other medications that might increase the risk of developing renal failure (i.e. iv contrast media, loop diuretics).

11.8 Linezolid

Linezolid is a synthetic oxazolidinone antibiotic that selectively inhibits bacterial protein synthesis. As a class, oxazolidinones are known to inhibit monoamine oxidase (MAO). Two forms of MAO exit in humans: Type A and Type B. MAO-A preferentially deaminates noradrenaline, adrenaline, and serotonin, while Type-B deaminates dopamine. Linezolid has been shown to be a weak, competitive inhibitor of MAO-A.

11.8.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

Numerous reports have documented the development of the Serotonin Syndrome following the coadministration of linezolid and SSRIs and this interaction has been extensively reviewed in the literature [106–108]. SSRIs that have been documented to have been associated with the development of there serotonin syndrome following the coadministration with linezolid include paroxetine [106, 109], sertraline [110–113], mirtazepine [114, 115], venlafaxine [116–120], Fluoxetine [121], citalopram [115, 119, 122] and escitalopram [122]. A wide range of complications associated with the Serotonin Syndrome has been reported involving the central nervous system (altered mental status, paranoia, hallucinations, myoclonus, seizures, dizziness, confusion, delirium, hostility, anger, fatigue, ataxia, tremors), cardiovascular system (hypertension, tachycardia, palpitations syncope, cardiac arrest) and gastrointestinal tract (diarrhea). Death has also been reported as a complication of the serotonin syndrome. Symptoms can develop anywhere from 1 h to several days after the addition of an SSRI [106].

11.8.2 Meperidine

The Serotonin Syndrome was reported in a leukemia patient following the coadministration of linezolid and meperidine [123]. The patient had been receiving meperidine as a pretreatment to prevent amphotericin-associated rigors. The patient received meperidine 90 min after his third dose of linezolid and 30 min later developed tremulousness with myoclonus, paranoid ideation with visual hallucinations. The meperidine was stopped and the patient was treated with methotrimeprazine 4 mg resulting in the resolution of neuropsychiatric symptoms within 2 h.

11.8.3 Rifampin

Two reports have described an interaction between linezolid and rifampin resulting in decreased linezolid serum concentration [124, 125]. Gebhart reported a patient who received rifampin and linezolid for 19 days. Ten days after rifampin was discontinued, the patient's trough linezolid level was reported as a trace and the linezolid dose was increased to 600 mg every 8 h. Rifampin was restarted 11 days after it was initially discontinued and administered for an additional 8 days. Six days after rifampin was discontinued for the second time, linezolid peak and trough concentrations were reported as 7.29 and 2.04 μg/mL, respectively. Follow up peak and trough levels obtained 2 days later 12.46 and 5.03 μg/mL, respectively [124]. Egle administered a single linezolid 600 mg IV dose to 8 healthy males [125]. The following day he administered linezolid 600 mg IV with rifampin 600 mg IV. The pooled serum levels of linezolid were lower after co-administration with rifampin compared to when linezolid was administered alone.

Serotonin is removed from the nerve synapse by reuptake into the nerve terminal or degradation by MAO. Linezolid's ability to inhibit MAO degradation of serotonin results in increased serotonin levels and the development of the Serotonin Syndrome. Patient medication profiles should be reviewed for medications that are metabolized by MAO before linezolid is prescribed. When possible, alternative antibiotics should be prescribed to avoid the risk of the development of the Serotonin Syndrome in susceptible individuals. Due to the long half-lives of some of the SSRIs, the Serotonin Syndrome may develop in patients whose SSRI was discontinued several days before initiating linezolid therapy. Alternative analgesics such as morphine or hydromorphone should be prescribed in place of meperidine. Management of the serotonin syndrome is primarily supportive with removal of the offending agent with symptoms typically resolve within 24–48 h but may last up to 7–10 days if the agents has a long half-life or active metabolites. If necessary, cyproheptadine appears to be an effective antiserotonin agent. It usually relieves symptoms after the first dose, but may be administered every 1–4 h until a therapeutic response is obtained. The mechanism of the interaction between rifampin and linezolid is not known. Linezolid is not metabolized through cytochrome P450 pathways. Egle has suggested that rifampin may stimulate the induction of P-glycoprotein expression leading to increased linezolid clearance by up regulation of linezolid intestinal secretion [125]. Careful consideration should be used when selecting antibiotics to treat resistant gram-positive infections. In the event that rifampin and linezolid should be used together, the monitoring of linezolid serum concentrations should be considered.

11.8.4 Cough and Cold Preparations

Many over-the-counter (OTC) cough and cold preparations contain ingredients that are metabolized by MAO or are selective serotonin reuptake inhibitors. Decongestants such as pseudoephedrine and phenylpropanolamine are metabolized by MAO. The cough suppressant, dextromethorphan, has been shown to block serotonin reuptake and has been implicated in precipitating the Serotonin Syndrome when co-ingested with MAO inhibitors. Hendershot and colleagues reviewed the data from three linezolid clinical trials to evaluate the pharmacokinetic and pharmacodynamic responses to the coadministration of linezolid with pseudoephedrine, phenylpropanolamine, and dextromethorphan [126]. Significant increases in systolic blood pressure (SBP) were observed following the coadministration of linezolid with either pseudoephedrine or phenylpropanolamine. The mean maximum increase from baseline in SBP was 32 and 38 mmHg with the co-administration with pseudoephedrine and phenylpropanolamine, respectively. Treatment emergent SBP greater than 160 mmHg was observed following the co-administration of linezolid with pseudoephedrine in 5 subjects and in 2 patients in the linezolid -phenylpropanolamine treated group. Dizziness was the most frequent adverse event when linezolid and pseudoephedrine were given concomitantly and headache was the most

frequent adverse event when linezolid and phenylpropanolamine were given together. There were no statistically or clinically significant effects on heart rate in either treatment group.

There were no statistically or clinically significant changes in blood pressure, heart rate, or temperature and no abnormal neurological examination results in the dextromethorphan-linezolid treatment group.

Linezolid's ability to inhibit the MAO degradation of pseudoephedrine and phenylpropanolamine resulted in the significant increases in blood pressure that was seen when linezolid was coadministered with the decongestants. Patients should be counseled to consult with their pharmacist or physician before taking systemic decongestants while taking linezolid. Topical nasal decongestants such as sodium chloride or oxymetazoline maybe alternative agents for patients requiring decongestants while receiving linezolid.

11.9 Quinupristin-Dalfopristin

11.9.1 Cytochrome P450 3A4 Metabolized Drugs

In-vitro drug interaction studies have demonstrated that quinupristin-dalfopristin significantly inhibits cytochrome P450 3A4 metabolism. There are no published drug interaction studies in normal volunteers and only limited reports of interactions in patients receiving quinupristin-dalfopristin for therapeutic indications. The manufacturers package insert indicates that it is reasonable to expect that the concomitant administration of quinupristin-dalfopristin and other drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may likely result in increased plasma concentrations of these drugs that could increase or prolong their therapeutic effect or and/or increase adverse reactions [127].

In health volunteers, the coadministration of quinupristin-dalfopristin with midazolam increased midazolam C_{max} and AUC by 14% and 33% respectively. Also in healthy volunteers the C_{max} and AUC of nifedipine was increased by 18% and 44% when the two agents were coadministered. Additional studies in transplant patients indicate that quinupristin-dalfopristin can inhibit the metabolism of cyclosporine and tacrolimus. Stamatakis and Richards reported an interaction between cyclosporine and quinupristin-dalfopristin in a renal transplant patient [128]. The patient's baseline cyclosporine levels ranged from 80 to 105 ng/mL. Two and three days after the initiation of quinupristin-dalfopristin therapy, trough cyclosporine trough concentrations increased to 261 and 291 ng/mL, respectively. Following the discontinuation of quinupristin-dalfopristin, the cyclosporine blood concentrations decreased and the dosage was increased to the previous regimen.

Medications know to be metabolized through the cytochrome P450 3A4 pathway, especially those with a narrow therapeutic index, should be administered with caution and closely monitored for adverse effects.

11.10 Antipseudomonal Penicillins

Aminoglycosides and penicillins are often administered in combination for their additive or synergistic effects in the treatment of serious Gram-negative infections. Numerous reports have been published documenting the ability of commonly used anti-pseudomonal penicillins to inactivate aminoglycoside antibiotics in vivo [129–136] and in vitro [137–143]. These have usually documented unusually low aminoglycoside concentrations in patients receiving this combination, despite high doses of aminoglycosides. Carbenicillin inactivates all aminoglycosides at faster rates and to a greater extent than ticarcillin, mezlocillin, and piperacillin. Tobramycin is the least stable and amikacin is the most stable aminoglycoside. Gentamicin has intermediate stability. Pickering and Gearhart evaluated the effect of time on the in vitro interaction between mixtures of four aminoglycosides at two concentrations with carbenicillin, piperacillin, mezlocillin, azlocillin, and mecillinam at three concentrations [139]. The inactivation of the aminoglycoside was shown to be directly proportional to the concentration of the penicillin. Aminoglycoside inactivation was greater at 72 h of incubation with the penicillins than after 24 h of incubation. Inactivation by each penicillin was greater for tobramycin and gentamicin than for netilmicin and amikacin, especially at higher penicillin concentrations. At concentrations of 500 μg/mL, significantly less inactivation of amikacin occurred compared to netilmicin. No significant change in aminoglycoside activity occurred when the aminoglycosides were stored with the penicillins at –70°C for 30 days.

There are several reports of in vivo inactivation of aminoglycosides by ticarcillin and carbenicillin. These have occurred in the patients with renal failure, where the penicillin concentrations would expected to be high. Thompson and colleagues studied the inactivation of gentamicin by piperacillin and carbenicillin in patients with end-stage renal disease [135]. Patients received a single dose of gentamicin, 4 g piperacillin every 12 h for four doses, or 2 g carbenicillin every 8 h for six doses and gentamicin plus piperacillin or carbenicillin. Subjects were studied on off-dialysis days. Gentamicin was inactivated to a greater extent by carbenicillin than by piperacillin. In the subjects in the carbenicillin group, the terminal elimination half-life of gentamicin was 61.6 h when gentamicin was administered alone and 19.4 h when gentamicin was administered with carbenicillin. In the subjects in the piperacillin group, the mean gentamicin half-life when gentamicin was given alone was 53.9 h, and it was 37.7 h when it was administered with piperacillin. Control samples verified that no in vitro inactivation occurred.

Penicillins combine with aminoglycoside antibiotics in equal molar concentrations at a rate dependent on the concentration, temperature, and medium composition. The greater the concentration of the penicillin, the greater is the inactivation of the aminoglycoside. The inactivation is thought to occur by way of a nucleophilic opening of the beta-lactam ring, which then combines with an amino group of the aminoglycoside, leading to the formation of a microbiologically inactive amide. The inactivation occurs less in pooled human sera than in other media, including whole blood. Spinning down whole blood can help slow the inactivation. Significant

serum inactivation occurs at room temperature and under refrigeration. Only when the blood sample is centrifuged and frozen is the inactivation arrested.

Rich reviewed the procedure for handling aminoglycoside concentrations in patients receiving this combination of antibiotics [144]. Blood samples for aminoglycosides concentrations drawn from patients receiving the combination should be sent on ice to the laboratory within 1–2 h so that the sample can be spun down and frozen to arrest any inactivation. Samples left exposed at room temperature will decay 10% in 1 h. The two antibiotics should not be given at the same time. The administration times should be scheduled so that the administration of the aminoglycoside occurs at the end of the penicillin-dosing interval, when its concentrations are the lowest. If a patient is receiving this antibiotic combination and unusually low aminoglycoside concentrations occur, the above factors should be checked. Inactivation with beta lactam antibiotics is further described in Chap. 7.

References

1. Spika JS, Davis DJ, Martin SR, et al. Interaction between chloramphenicol and acetaminophen. Arch Dis Child 1986;61:1211–1124.
2. Kearns GL, Bocchini JA, Brown RD, et al. Absence of a pharmacokinetic interaction between chloramphenicol and acetaminophen in children. J Pediatr 1985;107:134–139.
3. Stein CM, Thornhill DP, Neill P, et al. Lack of effect of paracetamol on the pharmacokinetics of chloramphenicol. Br J Clin Pharmacol 1989;27:262–264.
4. Bloxham RA, Durbin GM, Johnson T, et al. Chloramphenicol and phenobarbitone Na drug interaction. Arch Dis Child 1979;54:76–77.
5. Powell DA, Nahata MC, Durrell DC, et al. Interactions among chloramphenicol, phenytoin, and phenobarbital in a pediatric patient. J Pediatr 1981;98:1001–1003.
6. Koup JR, Gibaldi M, McNamara P, et al. Interaction of chloramphenicol with phenytoin and phenobarbital. Clin Pharmacol Ther 1987;24:571–575.
7. Ballek RE, Reidenberg MM, Orr L. Inhibition of diphenylhydantoin metabolism by chloramphenicol. Lancet 1973;1:150.
8. Greenlaw CW. Chloramphenicol-phenytoin interaction. Drug Intell Clin Pharm 1979; 13:609,610.
9. Saltiel M, Stephens NM. Phenytoin-chloramphenicol interaction. Drug Intell Clin Pharm 1980;14:221.
10. Christensen LK, Skovsted L. Inhibition of metabolism by chloramphenicol. Lancet 1969;2:1397–1399.
11. Brunova E, Slabochova Z, Platilova H, et al. Interaction of tolbutamide and chloramphenicol in diabetic patients. Int J Clin Pharmacol 1977;15:7–12.
12. Petitpierre B, Fabre J. Chlorpropamide and chloramphenicol. Lancet 1970;1:789.
13. Wallace JF, Smith RH, Garcia M, et al. Studies on the pathogenesis of meningitis. VI. Antagonism between penicillin and chloramphenicol in experimental pneumococcal meningitis. J Lab Clin Med 1967;70:408–418.
14. Jawetz E. The use of combinations of antimicrobial drugs. Annu Rev Pharmacol 1968;8:151–170.
15. Deritis F, Giammanco G, Manzillo G. Chloramphenicol combined with ampicillin in treatment of typhoid. Br Med J 1972;4:17,18.

16. French GL, Ling TKW, Davies DP, et al. Antagonism of ceftazidime by chloramphenicol in vitro and in vivo during treatment of gram negative meningitis. Br Med J 1985;291: 636,637.
17. Prober C. G. Effect of rifampin on chloramphenicol levels. N Engl J Med 1985;312: 788,789.
18. Kelly HW, Couch RC, Davis RL, et al. Interaction of chloramphenicol and rifampin. J Pediatr 1988;112:817–820.
19. Koch-Weser J, Sellars EM. Drug interactions with coumarin anticoagulants (first of two parts). N Engl J Med 1971;285:487–498.
20. Koch-Weser J, Sellars EM. Drug interactions with coumarin anticoagulants (second of two parts). N Engl J Med 1971;285:547–558.
21. Finegold SM. Interaction of antimicrobial therapy and intestinal flora. Am J Clin Nutr 1970;23:1466–1471.
22. Klippel AP, Pitsinger B. Hypoprothrombinemia secondary to antibiotic therapy and manifested by massive gastrointestinal hemorrhage. Arch Surg 1968;96:266-268.
23. Bui LL, Huang DD. Possible interaction between cyclosporine and chloramphenicol. Ann Pharmacother 1999;33:252–253.
24. Steinfort CL, McConachy KA. Cyclosporin-chloramphenicol drug interaction in a heart-lung transplant patient. Med J Aust 1994;161:455.
25. Mathis AS, Shah N, Knipp GT, et al. Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant patients. Transplant Infect Dis 2002;4:169–174.
26. Schulman SL, Shaw LM, Jabs K, et al. Interaction between tacrolimus and chloramphenicol in a renal transplant recipient. Transplantation 1998;65:1397–1398.
27. Taber DJ, Dupuis RE, Hollar KD, et al. Drug-drug interaction between chloramphenicol and tacrolimus in a liver transplant recipient. Transplant Proc 2000;32:660–662.
28. Bakri R, Breen C, Maclean D, et al. serious interaction between tacrolimus FK506 and chloramphenicol in a kidney-pancreas transplant recipient. Transpl Int 2003;16:441–443.
29. Hafner V, Albermann N, Haefeli WE, et al. Inhibition of voriconazole metabolism by chloramphenicol in a adolescent with central nervous system aspergillosis. Antimicrob Agents Chemother 2008;52:4172–4174.
30. Becker LD, Miller RD. Clindamycin enhances a nondepolarizing neuromuscular blockade. Anesthesiology 1976;45:84–87.
31. Best JA, Marashi AH, Pollan LD. Neuromuscular blockade after clindamycin administration: a case report. J Oral Maxillofac Surg 1999;57:600–603
32. al Ahdal O, Bevan DR. Clindamycin-induced neuromuscular blockade. Can J Anaesth 1995;42:614–617.
33. Sloan PA, Rasul M. Prolongation of rapacuronium neuromuscular blockade by clindamycin and magnesium. Anesth Analg 2002;94:123–124.
34. Rubbo JT, Sokoll MD, Gergis SD. Comparative neuromuscular effects of lincomycin and clindamycin. Anesth Analg 1977;56:329–332.
35. Wright JM, Collier B. Characterization of the neuromuscular block produced by clindamycin and lincomycin. Can J Physiol Pharmacol 1976;54:937–944.
36. Fiekers J, Henderson F, Marshall I, et al. Comparative effects of clindamycin and lincomycin on end-plate currents and quantal content at the neuromuscular junction. J Pharmacol Exp Ther 1983;227:308–315.
37. Atchinson W, Adgate L, Beaman C. Effects of antibiotics on the uptake of calcium into isolated nerve terminals. J Pharmacol Exp Ther 1988;245:394–401.
38. Butkus DE, de Torrente A, Terman DS. Renal failure following gentamicin in combination with clindamycin. Nephron 1976;17:307–313.

39. Fruscio R, Lissoni AA, Frapolli R, et al. Clindamycin-paclitaxel pharmacokinetic interaction in ovarian cancer patients. Cancer Chemother Pharmacol 2006;58:319–325.
40. Tilstone WJ, Gray JM, Nimmo-Smith RH, et al. Interaction between warfarin and sulphamethoxazole. Postgrad Med J 1977;53:388–390.
41. Kaufman JM, Fauver HE. Potentiation of warfarin by trimethoprim-sulfamethoxazole. Urology 1980;16:601–603.
42. Greenlaw CW. Drug interaction between co-trimoxazole and warfarin. Am J Hosp Pharm 1979;36:1155.
43. Errick JK, Keys PW. Co-trimoxazole and warfarin: case report of an interaction. Am J Hosp Pharm 1978;35:1399–1401.
44. O'Reilly RA, Motley CH. Racemic warfarin and trimethoprim-sulfamethoxazole interaction in humans. Ann Intern Med 1979;91:34–36.
45. Schalekamp T, van Geest-Daalderop JHH, Kramer MHH, et al. Coumarin anticoagulants and co-trimoxazole: avoid the combination rather than manage the interaction. Eur J Clin Pharmacol 2007;63:335–343.
46. O'Reilly RA. Stereoselective interaction of trimethoprim-sulfamethoxazole with the separated enantiomorphism of racemic warfarin in man. N Engl J Med 1980;302:33–35.
47. Penning-van Beest, Koerselman J, Herings RMC. Risk of major bleeding during concomitant use of antibiotic drugs and coumarin anticoagulants. J Thromb Haemost 2008;6:284–290.
48. Ahmed A, Stephens JC, Kaus CA, et. al. Impact of preemptive warfarin dose reduction on anticoagulation after initiation of trimethoprim-sulfamethoxazole or levofloxacin. J Throm Thrombolysis 2008;26:44–48.
49. Jaffe JM, Colonize JL, Pouts RI, et al. Effect of altered urinary pH on tetracycline and doxycycline excretion in humans. J Pharmacokinet Bipolar 1973;1:267–282.
50. Jaffe JM, Pouts RL, Fled SL, et al. Influence of repetitive dosing and altered pH on doxycycline excretion in humans. J Pharm Sci 1974;63:1256–1260.
51. Chin TF, Latch JL. Drug diffusion and bioavailability: tetracycline metallic chelation. Am J Hosp Pharm 1975;32:625–529.
52. Ericsson CD, Feldman S, Pickering LK, et al. Influence of subsalicylate bismuth on absorption of doxycycline. JAMA 1982;247:2266,2267.
53. Albert KS, Welch RD, Descanted KA, et al. Decreased tetracycline bioavailability caused by a bismuth subsalicylate antidiarrheal mixture. J Pharm Sci 1979;68:586–588.
54. Friedman H, Greenbelt DJ, Leduc BW. Impaired absorption of tetracycline by colestipol is not reversed by orange juice. J Clin Pharmacol 1989;29:748–751.
55. Lindenbaum J, Round DG, Butler VP, et al. Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. N Engl J Med 1981;305:789–794.
56. Penttilla O, Neuvonen PJ, Ahoy K, et al. Interaction between doxycycline and some ant epileptic drugs. Br Med J 1974;2:470–472.
57. Neuvonen PJ, Penttilla O, Lehtovaara R, et al. Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. Eur J Clin Pharmacol 1975;9:147–154.
58. Neuvonen PJ, Penttila O. Interaction between doxycycline and barbiturates. Br Med J 1974;1:535,536.
59. Westfall LK, Mintzer DL, Wiser TH. Potentiation of warfarin by tetracycline. Am J Hosp Pharm 1980;37:1620–1625.
60. Caraco Y, Rubinow A. Enhanced anticoagulant effect of coumarin derivatives induced by doxycycline coadministration. Ann Pharmacother 1992;26:1084–1086.
61. McGennis AJ. Lithium carbonate and tetracycline interaction. Br Med J 1978;1:1183.

62. Fankhauser MP, Lindon JL, Connolly B, et al. Evaluation of lithium-tetracycline interaction. Clin Pharm 1988;7:314–317.
63. Steele M, Couturier J. A possible tetracycline-respiradone-sertraline interaction in an adolescent. Can J Clin Pharmacol 1999;6:15–17.
64. McCormack JP, Reid SE, Lawson LM. Theophylline toxicity induced by tetracycline. Clin Pharm 1990;9:546–549.
65. Kawai M, Honda A, Yoshida H, et al. Possible theophylline-minocycline interaction. Ann Pharmacother 1992;26:1300,1301.
66. Pfeifer HJ, Greenblatt DJ, Friedman P. Effects of three antibiotics on theophylline kinetics. Clin Pharmacol Ther 1979;26:36–40.
67. Mathis JW, Prince RA, Weinberger MM, et al. Effect of tetracycline hydrochloride on theophylline kinetics. Clin Pharm 1982;1:446–448.
68. Gotz VP, Ryerson GG. Evaluation of tetracycline on theophylline disposition in patients with chronic obstructive airways disease. Drug Intell Clin Pharm 1986;20:694–697.
69. Jonkman JHG, van der Boon WJV, Schoenmaker R, et al. No influence of doxycycline on theophylline pharmacokinetics. Ther Drug Monit 1985;7:92–94.
70. Bacon JF, Shenfield GM. Pregnancy attributable to interaction between tetracycline and oral contraceptives. Br Med J 1980;280:293.
71. DeSano EA, Hurley SC. Possible interactions of antihistamines and antibiotics with oral contraceptive effectiveness. Fertil Steril 1982;37:853–854.
72. Helms SE, Bredle DL, Zajic J, et al. Oral contraceptive failure rates and oral antibiotics. J Am Acad Dermatol 1997;36:705–710.
73. Neely JL, Abate M, Swinkler M, et al. The effect of doxycycline on serum levels of ethinyl estradiol, norethindrone, and endogenous progesterone. Obstet Gynecol 1991;77:416–420.
74. Murphy AA, Zacur HA, Charache P, et al. The effect of tetracycline on levels of oral contraceptives. Am J Obstet Gynecol 1991;164:28–33.
75. Dogterom P, van den Heuvel MW, Thomsen T. Absence of pharmacokinetic interactions of the combined contraceptive vaginal ring NuvaRing with oral amoxicillin or doxycycline in two randomized trials. Clin Pharmacokinet 2005;44:429–38.
76. Archer JS, Archer DF. Oral contraceptive efficacy and antibiotic interaction; a myth debunked. J Am Acad Dermatol 2002;46:917–23.
77. Tortajada-Ituren JJ, Ordovas-Baines JP, Llopis-Salvia P, et al. High-dose methotrexate-doxycycline interaction. Ann Pharmacother 1999;33:804–808.
78. Turck M. Successful psoriasis treatment then sudden “cytotoxicity.” Hosp Pract 1984;19:175–6.
79. Colmenero JD, Fernandez-Gallardo LC, Agundez JAG, et al. Possible implications of doxycycline-rifampin interaction for treatment of brucellosis. Antimicrob Agents Chemother 1994;38:2798–2802.
80. Zimmerman JJ, Raible DG, Harper DM, et al. Evaluation of potential tigecycline-warfarin drug interaction. Pharmacotherapy 2008;28:895–905.
81. Churchill DN, Seely J. Nephrotoxicity associated with combined gentamicin-amphotericin B therapy. Nephron 1977;19:176–181.
82. Kroenfeld MA, Thomas SJ, Turndorf H. Recurrence of neuromuscular blockade after reversal of vecuronium in a patient receiving polymyxin/amikacin sternal irrigation. Anesthesiology 1986;65:93–94.
83. Warner WA, Sanders E. Neuromuscular blockade associated with gentamicin therapy. JAMA 1971;215:1153–1154.
84. Levanen J, Nordman R. Complete respiratory paralysis caused by a large dose of streptomycin and its treatment with calcium chloride. Ann Clin Res 1975;7:47–49.

85. Lippmann M, Yang E, Au E, et al. Neuromuscular blocking effects of tobramycin, gentamicin, and cefazolin. Anesth Analg 1982;61:767–770.
86. Duouis JY, Martin R, Tetrault JP. Atracurium and vecuronium interaction with gentamicin and tobramycin. Can J Anaesth 1989;36:407–411.
87. Singh YN, Marshall IG, Harvey AL. Pre- and postjunctional blocking effects of aminoglycoside, polymyxin, tetracycline and lincosamide antibiotics. Br J Anaesth 1982;54:1295–1306.
88. Zarfin Y, Koren G, Maresky D, et al. Possible indomethacin-aminoglycoside interaction in preterm infants. J Peds 1985;106:511–513.
89. Termeer A, Hoitsma AJ, Koene RAP. Severe nephrotoxicity caused by the combined use of gentamicin and cyclosporine in renal allograft recipients. Transplantation 1986;42: 220–221.
90. Christensen ML, Stewart CF, Crom WR. Evaluation of aminoglycoside disposition in patients previously treated with cisplatin. Ther Drug Monit 1989;11:631–636.
91. Gonzalez-Vitale JC, Hayes DM, Cvitkovic E, et al. Acute renal failure after cis-dichlorodiammineplatinum(II) and gentamicin-cephalothin therapies. Cancer Treat Rep 1978;62:693–698.
92. Salem PA, Jabboury KW, Khalil MF. Severe nephrotoxicity: a probable complication of cis-dichlorodiammineplatinum (II) and cephalothin-gentamicin therapy. Oncology 1982;39:31,32.
93. Kohn S, Fradis M, Podoshin L, et al. Ototoxicity resulting from combined administration of cisplatin and gentamicin. Laryngoscope 1997;107:407,408.
94. Dentino M, Luft F. C, Yum M. N, et al. Long-term effect of cis-diamminedichloride platinum (CDDP) on renal function and structure in man. Cancer 1978;41:1274–1281.
95. Lee EJ, Egorin MJ, Van Echo DA, et al. Phase I and pharmacokinetic trial of carboplatin in refractory adult leukemia. J Natl Cancer Inst 1988;80:131–135.
96. Bregman CL, Williams PD. Comparative nephrotoxicity of carboplatin and cisplatin in combination with tobramycin. Cancer Chemother Pharmacol 1986;18:117–123.
97. Kaka JS, Lyman C, Kilarski DJ. Tobramycin-furosemide interaction. Drug Intell Clin Pharm 1984;18:235-238.
98. Mathog RH, Klein WJ. Ototoxicity of ethacrynic acid and aminoglycoside antibiotics in uremia. N Engl J Med 1969;280:1223–1224.
99. Pillay VKG, Schwartz FD, Aimi K, et al. Transient and permanent deafness following treatment with ethacrynic acid in renal failure. Lancet 1969;1:77–79.
100. Smith CR, Lietman PS. Effect of furosemide on aminoglycoside-induced nephrotoxicity and auditory toxicity in humans. Antimicrob Agents Chemother 1983;23:133–137.
101. Meriweather WD, Mangi RJ, Serpick AA. Deafness following standard intravenous doses of ethacrynic acid. JAMA 1971;216:795–798.
102. Cimino MA, Rotstein C, Slaughter RL, et al. Relationship of serum antibiotic concentrations to nephrotoxicity in cancer patients receiving concurrent aminoglycoside and vancomycin therapy. Am J Med 1987;83:1091–1097.
103. Pauly DJ, Musa DM, Lestico MR, et al. Risk of nephrotoxicity with combination vancomycin-aminoglycoside antibiotic therapy. Pharmacotherapy 1990;10:378382.
104. Mellor JA, Kingdom J, Cafferkey M, et al. Vancomycin toxicity: a prospective study. J Antimicrob Chemother 1985;15:773–780.
105. Ryback MJ, Albrecht LM, Boike SC, et al. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. J Antimicrob Chemother 1990;25:679–687.
106. Huang V, Gortney JS. Risk of serotonin syndrome with concomitant administration of linezolid and serotonin agonists. Pharmacotherapy 2006;26:1784–1793.

107. Taylor JJ, Wilson JW, Estes LL. Linezolid and serotonergic drug interactions: a retrospective study. Clin Infect Dis 2006;43:180–187.
108. Narita M, Tsuji BT, Yu V. Linezolid-associated peripheral and optic neuropathy, lactic acidosis, and serotonin syndrome. Pharmacotherapy 2007;27:1189–1197.
109. Wigen CL, Goetz MB. Serotonin syndrome and linezolid. Clin Infect Dis 2002 ;34:1651,1652.
110. Hachem RY, Hicks K, Huen A, et al. Myelosuppression and serotonin syndrome associated with concurrent use of linezolid and selective serotonin reuptake inhibitors in bone marrow transplant recipients. Clin Infect Dis 2003;37:e8–11.
111. Lavery S, Ravi H, McDaniel WW, et al. Linezolid and serotonin syndrome. Psychosomatics 2001;42:432–434.
112. Clark DB, Andrus MR, Byrd DC. Drug interactions between linezolid and selective serotonin reuptake inhibitors: case report involving sertraline and review of the literature. Pharmacotherapy 2006;26:269–276.
113. Sola CL, Bostwick JM, Hart DA, et al. Anticipating potential linezolid-SSRI interactions in the general hospital setting an MAOI in disguise. Mayo Clin Proc 2006;81:330–334.
114. Aga VM, Barklage NE, Jefferson JW. Linezolid, a monoamine oxidase inhibiting antibiotic, and antidepressants. J Clin Psychiatry 2003;64:609–611.
115. Debellas RJ, Schaefer OP,Liquori M, et al. Linezolid-associated serotonin syndrome after concomitant treatment with citalopram and mirtazapine in a critically ill bone marrow transplant recipient. J Intens Care Med 2005;20:303–305.
116. Hammerness P, Parada H, Abrams A. Linezolid:maoi activity and potential drug interactions. Psychosomatics 2002;43:248,249.
117. Packer S, Berman SA. Serotonin syndrome precipitated by the monoamine oxidase inhibitor linezolid. Am j Psychiatry 2007;164:346–347.
118. Mason LW, Randhawa KS, Carpenter EC. Serotonin toxicity as a consequence of linezolid use in revision hip arthroplasty. Orthopedics 2008;31:1140.
119. Bergeron L, Boule M, Perreault S. serotonin toxicity associated with concomitant use of linezolid. Ann Pharmacother 2005;39:956–961.
120. Jones SL, Athan E, OBrien D. Serotonin syndrome due to co-administration of linezolid and venlafaxine. J Antimicrob Chemother 2004;54:289–90.
121. Steinberg M, Morin A. mild serotonin syndrome associated with concurrent linezolid and fluoxetine. Am J Health Sys Pharm 2007;64;5962.
122. Lorenz RA, Vandenberg AM, Canepa EA. Serotonergic antidepressants and linezolid: a retrospective chart review and presentation of cases. Int J Psychiatry Med 2008;38:81–90.
123. Das PK, Warkentin DI, Hewko R, et al. Serotonin syndrome after concomitant treatment with linezolid with meperidine. Clin Infect Dis 2008;46:264–265.
124. Gebhart BC, Barker BC, Markewitz BA. Decreased serum linezolid levels in a critically ill patient receiving concomitant linezolid and rifampin. Pharmacotherapy 2007;27:476–479.
125. Egle H, Trittler R, Kummerer K, et al. Linezolid and rifampin: drug interaction contrary to expectations? Clin Pharmacol Ther 2005;77:451–452.
126. Hendershot PE, Antal EJ, Welshman IR. Linezolid: pharmacokinetic and pharmacodynamic evaluation of coadministration with pseudoephedrine hcl, phenylpropanolamine hcl, and dextromethorphan hbr. J Clin Pharmacol 2002;41:563–572.
127. Synercid IV. (quinupristin-dalfopristin) product information. Bristol, TN: King Pharmaceutical, 2003.
128. Stamatakis MK, Richards JG. Interaction between quinupristin-dalfopristin and cyclosporine. Ann Pharmacother 1997;31:576–578.

129. Lampasona V, Crass RE, Reines HD. Decreased serum tobramycin concentrations in patient with renal failure. Clin Pharm 1983;2:6–9.
130. Russo M. Penicillin-aminoglycoside inactivation: another possible mechanism of interaction. Am J Hosp Pharm 1980;37:702–704.
131. Chow MSS, Quintiliani R, Nightingale CH. In vivo inactivation of tobramycin by ticarcillin. JAMA 1982;247:658,659.
132. Kradjan WA, Burger R. In vivo inactivation of gentamicin by carbenicillin and ticarcillin. Arch Intern Med 1980;140:1668–1670.
133. Schentag JJ, Simons GW, Schultz RW, et al. Complexation versus hemodialysis to reduce elevated aminoglycoside serum concentrations. Pharmacotherapy 1984; 4:374–380.
134. Uber WE, Brundage RR, White RL, et al. In vivo inactivation of tobramycin by piperacillin. Ann Pharmacother 1991;25:357–359.
135. Thompson MIB, Russo ME, Saxon BJ, et al. Gentamicin inactivation by piperacillin or carbenicillin in patients with end-stage renal disease. Antimicrob Agents Chemother 1982;21:268–273.
136. Ervin FR, Bullock WE, Nuttall CE. Inactivation of gentamicin by penicillins in patients with renal failure. Antimicrob Agents Chemother 1976;9:1004–1031.
137. Wallace SM, Chan LY. In vitro interaction of aminoglycosides with □-lactam penicillins. Antimicrob Agents Chemother 1985;28:274–281.
138. Henderson JL, Polk RE, Kline BJ. In vitro inactivation of gentamicin, tobramycin, and netilmicin by carbenicillin, azlocillin, or mezlocillin. Am J Hosp Pharm 1981;38:1167–1170.
139. Pickering LK, Gearhart P. Effect of time and concentration upon interaction between gentamicin, tobramycin, netilmicin, or amikacin and carbenicillin or ticarcillin. Antimicrob Agents Chemother 1979;15:592–596.
140. Pickering LK, Rutherford I. Effect of concentration and time upon inactivation of tobramycin, gentamicin, netilmicin, and amikacin by azlocillin, carbenicillin, mecillinam, mezlocillin, and piperacillin. J Pharmacol Exp Ther 1981;217:345–349.
141. Hold HA, Broughall JM, McCarthy M, et al. Interactions between aminoglycoside antibiotics and carbenicillin or ticarcillin. Infection 1976;4:107–109.
142. Davies M, Morgan JR, Anand C. Interaction of carbenicillin and ticarcillin with gentamicin. Antimicrob Agents Chemother 1975;7:431–434.
143. Mclaughlin JE, Reeves DS. Clinical and laboratory evidence of inactivation of gentamicin by carbenicillin. Lancet 1971;1:261–264.
144. Rich DS. Recent information about inactivation of aminoglycosides by carbenicillin, and ticarcillin: clinical implications. Hosp Pharm 1983;18:41–43.

Chapter 12
Drugs for Tuberculosis

Rocsanna Namdar and Charles A. Peloquin

Abstract Clinically significant drug interactions can occur when using drugs to treat tuberculosis. The following chapter reviews the most common infectious disease drug interactions with drugs used for tuberculosis and other nontuberculosis mycobacterial infections. The management of drug interactions in the treatment of tuberculosis and human immunodeficiency virus is discussed. Most drug interactions with antituberculosis drugs are a result of effects on hepatic enzyme metabolism. Interactions with drugs affecting absorption are also reviewed.

12.1 Introduction

Tuberculosis (TB) remains a leading infectious killer, particularly in the developing world [1]. Given the high rates of co-infection with TB and HIV, drug interactions are frequent occurrences. In particular, rifamycins commonly produce significant drug interactions that can decrease the effectiveness of highly active antiretroviral therapy in patients with HIV. This chapter assesses drug interactions in patients with TB, and briefly in patient's with nontuberculous mycobacterial infections (NTM).

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12.2 Standard Treatment for Tuberculosis

The published treatment guidelines for TB generally produce successful outcomes, even in HIV-positive patients [1, 2]. These references are recommended to all practitioners dealing with such patients. For suspected drug-susceptible disease, a regimen of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) is used. Rifabutin (RBN) is an alternative to RIF to reduce cytochrome P450 (CYP) enzyme induction in both the liver and the intestine. When full drug susceptibility is confirmed, EMB can be discontinued. PZA can be discontinued in patients who respond normally to treatment after 8 weeks [1, 2]. INH and either RIF or RBN are continued for an additional 4 months, or longer if the patient is slow to respond, or has extensive pulmonary cavitary, bone, or central nervous system (CNS) disease. Multidrug-resistant tuberculosis (MDR-TB, defined as resistance to at least INH and RIF) and extensively drug resistant (XDR-TB, defined as MDR-TB plus resistance to a quinolone and an injectable agent) are much more difficult to treat [1, 2]. The drugs used for DR-TB are less effective and more toxic than INH and RIF, and the duration of treatment for DR-TB is much longer (often 24 months or more).

12.3 Oral Absorption

12.3.1 Interactions with Food

INH and RIF show marked decreases in the maximum serum concentration (C_{max}, 51% and 36%, respectively), and lesser decreases in area under the serum concentration versus time curve (AUC, 12% and 6%, respectively) when given with high-fat meals (Table 12.1) [3–5]. EMB shows modest decreases in C_{max} (17%) but not AUC, while PZA only shows a modest delay in absorption when these drugs are given with high-fat meals [6, 7]. High-fat meals do not adversely affect the absorption of ethionamide (ETA), but decrease the C_{max} of cycloserine (CS) by 16% (but does not change AUC) [8, 9]. Orange juice also decreases the C_{max} of cycloserine by about 7% (increases AUC by 5%), and presumably this would occur other acidic beverages [9]. In contrast, high-fat meals increase the C_{max} of clofazimine (CF) and p-aminosalicylic acid (PAS) granules [10, 11].

12.3.2 Interactions with Antacids

Of the four most frequently used TB drugs, only EMB appears to be significantly affected by co-administration with antacids (Mylanta®, Table 12.1) [4, 6, 7]. Conflicting data exist for INH; our investigation showed no significant effect when

Table 12.1 Effects of food and antacids on the absorption of antituberculous drugs

Drug	Effect of food	Effect of antacids	Clinical implications
Para-Aminosalicylic acid (PAS) granules	Acidic beverage or yogurt prevent release in stomach, thus reducing nausea; food increases absorption	Small decrease in absorption	Give PAS granules with acidic beverage or with food. Avoid antacids if possible.
Ciprofloxacin	Delayed T_{max}, but minimal effect on AUC	Large decrease in C_{max} and AUC	Do not coadminister with di- and trivalent cations, including antacids
Cycloserine	Food decreases C_{max} 16%, no effect on AUC	Antacids slightly increase C_{max}	Do not coadminister with food if possible
Ethambutol	Delayed T_{max}, 16% decrease in C_{max}, but minimal effect on AUC	28% decrease in C_{max} and 10% decrease in AUC	May be given with food. Do not coadminister with antacids
Ethionamide	No significant effect	No significant effect	Can be coadministered with food and antacids
Isoniazid	Food, especially carbohydrate-based meals, significantly reduce isoniazid C_{max} and AUC	0–19% decrease in AUC	Do not coadminister with meals; do not coadminister with antacids whenever possible
Levofloxacin	No significant effect	Large decreases in C_{max} and AUC	Do not coadminister with di- and trivalent cations; including antacids
Pyrazinamide	Delayed T_{max}, no effect on AUC	No significant effect	May be given with food or antacids
Rifabutin	No significant effect	Unknown, not affected by didanosine	May be given with food; do not coadminister with antacids until studied
Rifampin	Delayed T_{max}, 15–36% decrease in C_{max} and 4–23% decrease in AUC	No significant change in serum concentrations, 30% decrease in 24-h urinary excretion	Do not coadminister with food; may be given with ranitidine; avoid coadministration with antacids whenever possible

Adapted from [3]. With permission

T_{max} = time from drug ingestion to peak (maximal) serum concentration, *AUC* area under the serum concentration-time curve, C_{max} = peak (maximal) serum concentration

Mylanta® was given 9 h before INH, at the time of dosing, and then with lunch and dinner following dosing. Antacids produced little change in the absorption of CS, ETA, PAS, and CF [8–11].

12.3.3 Interactions with H_2 Antagonists

RIF is not affected by the co-administration of ranitidine [4]. Data are not available for the other TB drugs.

12.3.4 Malabsorption in Selected Patient Populations

Patients with known or suspected gastroenteropathies may have difficulty absorbing the TB drugs. INH, RIF and EMB appear to be more prone to malabsorption, with lower C_{max} and AUC [12–18]. Recent studies suggest that the dose of RBN is too low, and minimal data exist for rifapentine [19–21]. Studies show that INH and RBN malabsorption may lead to treatment failures and the selection of drug resistance, especially among AIDS patients [22, 23]. PZA generally is well absorbed [12, 13]. Reasons for drug malabsorption may include HIV-related achlorhydria, HIV enteropathy, and opportunistic infections of the gastrointestinal tract, such as cryptosporidiosis [3, 24–27]. Other populations to observe carefully include patients with cystic fibrosis and diabetes mellitus. Therapeutic drug monitoring (TDM) may be used to identify problems and to guide dose adjustments [18].

12.4 Drug and Disease Interactions

12.4.1 Isoniazid Interactions

INH is cleared by N-acetyltransferase 2 (NAT2) to the microbiologically inactive metabolite acetylisoniazid, and subsequently to mono- and di-acetyl-hydrazine [22, 28]. INH is not substantially removed by hemodialysis [29]. INH interacts significantly with phenytoin (a CYP2C9 substrate) and carbamazepine (CYP3A4 and either CYP2C8 or CYP2C9), increasing concentrations of both [30, 31]. INH also may inhibit the clearance of valproic acid [32] diazepam (CYP3A4 and CYP2C19), primidone, chlorzoxazone (CYP2E1), theophylline (CYP1A2), warfarin (CYP1A2, CYP2C9, CYP2C19, CYP3A4) and clozapine [33–39]. More recently, Desta and colleagues showed that INH inhibits CYP2C19 and CYP3A4 in a concentration dependent manner [40]. Significant inhibition of CYP2C9 and CYP1A2 in their human liver microsome system was not shown; however, INH

was considered a weak noncompetitive inhibitor of CYP2E1 and a competitive inhibitor of CYP2D6 [40]. INH can also act as a monoamine oxidase inhibitor, with a potential for interaction with antidepressants. Excess catecholamine stimulation resulting in increased blood pressure has been reported with INH and levodopa therapy [41].

INH causes an initial inhibition, followed by induction of CYP2E1 [37]. Therefore, INH can alter the clearance of ethanol. INH may inhibit or promote the conversion of acetaminophen to its putative toxic intermediate metabolite, N-acetyl-p-benzoquinone imine (NAPQI), depending on the timing of the doses [37]. Therefore, high-dose acetaminophen should be avoided with INH [37, 42–45]. The absorption of INH can be affected by drugs. Coadministration of ciprofloxacin and INH results in a delay (but not a reduction in the extent) of INH absorption [46].

12.4.2 Rifamycin Interactions

The available rifamycins include rifampin (RIF), rifabutin (RBN), and rifapentine (RPNT). They share a similar mechanism of action, and generally show cross-resistance. They are cleared by esterases to their 25-desacetyl derivatives, which have roughly half of the parent drugs' activity. Most of the parent drug and metabolite are cleared through the biliary tract, with small amounts through the urine [4, 28, 43]. For 25-desacetyl-RBN, subsequent metabolism occurs via CYP3A4. RIF is not substantially removed by hemodialysis [29]. Rifamycins are potent inducers of the P450 enzyme system, especially CYP3A4 and 2C8/9 [3, 47]. Further, rifampin also induces the activity of the phase II enzymes uridine glucuronosyl transferase and sulphotransferase, and the efflux transporter P-glycoprotein (P-gp) [47].

Single doses of rifampin can inhibit P-gp and MRP2 *in vitro* and in animals. However, continued doses of rifampin appear to induce MRP2. Rifampin, like cyclosporine and gemfibrozil, inhibits OATP1B1, an uptake transporter protein for many drugs and endogenous substances [48, 49]. At pharmacological concentrations, rifampin induces the expression of MRP transporters both at the apical (MRP2) and basolateral (MRP3) membrane of hepatocytes while, at higher concentrations, it was shown to exert *in vitro* a competitive inhibitory effect on MRP2 [50] Caution should be exercised when reading this literature, since the effects may depend on whether the experiment was done in vitro or in vivo, and for the latter, if the experiment was single-dose or multi-dose. For example, rifampin can inhibit OATPs, which correlates with the initial rise in serum bilirubin at the start of rifampin treatment [51]. However, it is well known that these values return to normal early in treatment. So, it is possible that some of these effects of rifampin on OATP are not sustained over time. Further, compensatory effects across different OATP receptors may be seen. For example, data suggest that SLCO1B1 gene polymorphisms do not affect the extent of induction of hepatic CYP3A4 by rifampicin, probably because other uptake transporters, such as OATP1B3, can compensate for reduced uptake of rifampicin by OATP1B1 [52]. This is an active area of research.

RIF intracellular concentrations and CYP3A induction are strongly correlated with P-gp levels, encoded on the multidrug resistance gene (MDR1) [53, 54]. Polymorphic expression of MDR1 may partially explain the wide inter-patient variability in CYP3A induction by RIF. RPNT is about 85% as potent an inducer as RIF, and RBN is about 40% as potent [55]. The AUC of RIF may be lower in patients with active tuberculosis, those with the solute carrier organic anion transporter (OATP) 1B1 SLCO1B1 gene, and in TB patients from Africa versus North America [56]. The extent of induction by rifamycins may change with dosing frequency (daily versus intermittently) [57]. For 600 mg RIF daily, maximum induction occurs in about 7 days. Larger doses may shorten the time to, but not the extent of, induction, which lasts for 7–14 days after the rifamycin is stopped [57, 58]. CYP3A4, and to a lesser degree, CYP2C9, CYP2C19, and CYP2D6, are most affected, leading to shorter half-lives and lower plasma concentrations for many co-administered drugs.

RBN induces and is metabolized by CYP3A, leading to complex bi-directional interactions [3, 47]. RBN decreases concentrations of other drugs, while CYP3A inhibitors increase the concentrations of RBN and especially 25-O-desacetyl RBN, sometimes leading to toxicity [3, 47]. In contrast, RPNT is very similar to RIF regarding drug interactions. Unlike RBN, RPNT does not offer any advantage in sparing the drug interactions. Like RIF, RPNT is not a substrate for CYP enzymes, and concentrations of RIF and RPNT do not increase with concurrent enzyme inhibitors.

Significant inter-patient variability in the extent of rifamycin drug interactions can be seen [3, 18, 47, 59]. Most data come from small studies of healthy volunteers, and focus on bi-directional interactions. Clinically, complex interactions involving 3, 4, or more drugs cannot be predicted, especially when factoring in erratic drug absorption in some patients [18, 59]. For such patients, therapeutic drug monitoring (TDM) is available. TDM should be considered early in treatment for complicated multidrug interactions involving TB drugs, azoles, HIV protease inhibitors, NNRTI, and macrolides [18, 59]. A review of rifamycin drug interactions with antimicrobials is described below. A summary is provided in Table 12.2 [12, 60–62].

12.4.2.1 Azoles

RIF reduces itraconazole AUC 64–88% in both healthy volunteers and in AIDS patients, often resulting in undetectable concentrations [63, 64]. Likewise, RIF reduces the AUC of ketoconazole by 82% in healthy volunteers [65]. Based on these data, the concurrent use of RIF and itraconazole or ketoconazole should be avoided due to the risk of therapeutic failure.

RIF may reduce fluconazole's AUC by 23–52% and may cause treatment failures [66–68]. Higher doses of fluconazole may be required if used concomitantly with RIF [1, 69]. There is no significant effect of fluconazole on RIF pharmacokinetics [70]. As noted, RBN demonstrates bi-directional interactions. Fluconazole increases

Table 12.2 Rifamycin drug interactions with antimicrobials

Drug class	Drugs whose concentrations are substantially decreased by rifamycins	Comments
Antiinfectives	HIV-1 protease inhibitors (saquinavir, indinavir, nelfinavir, amprenavir, ritonavir, lopinavir/ritonavir)	Can be used with rifabutin. Ritonavir, 400–600 mg twice daily, probably can be used with rifampin. The combination of saquinavir and ritonavir can also be used with rifampin.
	Nonnucleoside reverse transcriptase inhibitors (Delavirdine, Nevirapine, Efavirenz, Etravirine)	Delavirdine should not be used with any rifamycin. Doses of nevirapine and efavirenz may need to be increased if given with rifampin; no dose increase needed if given with rifabutin. Etravirine and rifampin should not be used together. Marked decrease of etravirine with RBN is predicted.
	Macrolide antibiotics (clarithromycin, erythromycin)	Either avoid concomitant administration of clarithromycin and rifampin or rifabutin, or use cautiously. Azithromycin has no significant interaction with rifamycins.
	Fluoroquinolones (moxifloxacin)	Plasma concentrations of moxifloxacin can guide therapy.
	Doxycycline	May require use of a drug other than doxycycline.
	Azole antifungal agents (ketoconazole, itraconazole, voriconazole)	Itraconazole, ketoconazole, and voriconazole concentrations may be subtherapeutic with any of the rifamycins. Fluconazole can be used with rifamycins, but the dose of fluconazole may have to be increased.
	Atovaquone, dapsone	Consider alternative *Pneumocystis carinii* treatment or prophylaxis
	Chloramphenicol	Consider an alternative antibiotic.

Adapted from [60]:45–50 and Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (online) 2007. URL: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm

RBN's AUC by 76%, and further increased the 25-desacetyl metabolite [71]. Caution, and TDM, should be exercised during concurrent use of fluconazole with RBN. In cases of coexisting mycobacterial and fungal infections, careful drug selection and therapeutic monitoring of drug concentrations can allow for combined use of these drugs. Schwiesow et al. report the use of voriconazole and RBN together to successfully treat a combined mycobacterial and *Aspergillus* infection [72].

12.4.2.2 Chloramphenicol

Several case reports have described low chloramphenicol serum concentrations in patients treated concomitantly with RIF. The dose of chloramphenicol could be increased to maintain serum concentrations; however, this may put the patient at greater risk for aplastic anemia. Alternative therapies should be considered in patients taking RIF [73, 74].

12.4.2.3 Dapsone

RIF and RBN have been associated with a significant increase (50–70%) in the clearance of dapsone [20, 75], resulting in lower dapsone AUC values. Since lower dapsone exposures may increase the risk of *Pneumocystis jiroveci* pneumonia (PCP), higher dapsone doses may be needed when used with RBN or RIF [75]. Patients should be monitored closely and TDM should be considered.

12.4.2.4 Doxycycline

Treatment failures have been reported in patients with brucellosis being treated with doxycycline and RIF. Patients receiving RIF and doxycycline had decreased doxycycline AUC values (59%) and higher clearances compared to those receiving doxycycline plus streptomycin. An alternative to doxycycline should be considered in patients taking RIF [76].

12.4.2.5 Fluoroquinolones

Limited data exist regarding the interactions between fluoroquinolones and rifamycins. Quinolone clearance may be increased by RIF [77, 78]. Weiner et al. evaluated the effects of rifampin on concentrations of moxifloxacin. The AUC of moxifloxacin was decreased by 27%, but peak concentrations were unchanged, secondary to rifampin's inductive effect on phase II clearance pathways noted above [79]. Similar results were seen by Nijland et al. [80]. Currently, there are not enough data to support routine dosage adjustments. Where available, moxifloxacin plasma concentrations can guide therapy.

12.4.2.6 Isoniazid

The oral bioavailability of RIF was reduced by an average of 32% in volunteers who were administered an INH-RIF fixed dose combination (FDC) product, compared with RIF alone [81]. This appears to be a function of the FDC formulation, and not directly due to an interaction between INH and RIF. This is compensated by giving a slightly higher dose of RIF (in milligrams) as in the FDC product.

12.4.2.7 Macrolides

The combination of clarithromycin and RIF resulted in reduced mean peak clarithromycin concentrations (87%) when compared to clarithromycin monotherapy [82]. Overall, concentration of the active metabolite of clarithromycin, 14-OH clarithromycin, was not affected, although the usual ratio of parent to metabolite was inverted. Based on current data, RIF can decrease the efficacy of clarithromycin by reducing serum concentrations.

Macrolide drug interactions with RBN are complex. RBN decreases macrolide concentrations, while the macrolides, CYP3A inhibitors, increase the concentration of RBN and its active metabolite, occasionally leading to RBN toxicity. The pharmacokinetics of clarithromycin plus RBN has been evaluated in healthy volunteers and in HIV positive patients [71, 82, 83]. Concomitant administration resulted in increased serum concentration (76%) and AUC (99%) of RBN and it's partially active metabolite, 25-O-desacetyl rifabutin. Rifabutin reduced clarithromycin's AUC by 44% and increased concentrations of 14-OH clarithromycin. Reports of significant adverse reactions, including neutropenia, fever, myalgia and uveitis have been associated with the combination of clarithromycin plus RBN [82, 83]. Based on current data, the combination of RBN and clarithromycin should be avoided. Despite azithromycin's reduced affinity for CYP, studies evaluating the combination of azithromycin and RBN also resulted in unusually high rates of neutropenia [82]. Azithromycin may be preferred if RBN + macrolide therapy is necessary. TDM should be used to achieve the desired concentrations.

12.4.2.8 Metronidazole

Limited data has shown that RIF increases the clearance of metronidazole and decreases the AUC [84].

12.4.2.9 Non-nucleoside Reverse Transcriptase Inhibitors

Table 12.3 summarizes the effects of RIF and RBN on the AUC of non-nucleoside reverse transcriptase inhibitors [3, 85]. Due to the bi-directional interaction with RBN and the significant reduction in AUC caused by RIF, delavirdine should not be used with any rifamycin [1, 69, 86, 87]. Etravirine should not be used together with RIF; but can be used with RBN, However dosage [88] adjustments may be necessary. Nevirapine and efavirenz can be used with either RIF or RBN. Dosage adjustments need to be made if given with RIF [89]. RBN doses should be adjusted to 600 mg/dose when used together with efavirenz [90]. Rilpivirine is a substrate and inducer of CYP3A4. Drug interactions similar to other NNRTI's are expected. Studies indicate rilpivirine is a mild inducer at doses of 300 mg [91].

12.4.2.10 Nucleoside Reverse Transcriptase Inhibitors

Zidovudine and lamivudine are not metabolized by the CYP450 enzymes. The efficacy of these drugs is correlated with the intracellular concentrations of the active derivative. The coadministration of RIF with zidovudine resulted in a decrease (43%) in C_{max} and AUC (47%) of zidovudine. Decreased plasma concentrations have not been shown to reduce the concentration of the intracellular metabolite [92]. Therefore, RIF is expected to have little impact on the clinical effect and antiviral activity of zidovudine [58].

Table 12.3 Co-administration rifabutin and rifampin with currently approved non-nucleoside reverse transcriptase inhibitors (NNRTI's)

	Rifabutin		Rifampin[a]		
NNRTI (references)	Effect of rifabutin on NNRTI	Effect of NNRTI on rifabutin (predicted)[b]	Effect of rifampin on NNRTI	Effect of NNRTI on rifampin (predicted)[b]	Comment
Nevirapine (AUC)	↓ 16%	NR (↓)	↓ 37%	NR (unchanged)	No dosage change
Delavirdine (AUC)	↓ 80%	↑ 342%	↓ 96%	Unchanged	Do not use
Efavirenz (AUC)	↓ 10%	↓ 38%	↓ 13%	Unchanged	No dosage change with RIF. Increase RBN dose.
Etravirine (C_{min})		↓45%			No dosage change

Adapted from: Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (online) 2007. URL: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm and [3]. With Permission
NR not reported
[a]Rifapentine produces approximately 85% of the effects seen with rifampin
[b]Predicted using existing knowledge regarding metabolic pathways for the two drugs

12.4.2.11 Protease Inhibitors

The protease inhibitors are CYP3A substrates and inhibitors, therefore exhibiting a bi-directional interaction. Table 12.4 summarizes the effects of RIF and RBN on the AUC of protease inhibitors [3, 85]. Due to the profound effects of RIF and RPNT on the AUC's of saquinavir, indinavir, nelfinavir, and amprenavir, concomitant administration is discouraged, and standard doses would be ineffective [69, 92–96]. RBN should be used if combination therapy is necessary [97, 98]. However, due to the bi-directional interaction and the potential for intolerance, RBN and/or protease inhibitor dosage adjustments may warranted [92, 95, 99]. The combination of daily nelfinavir with RBN twice-weekly resulted in reasonable RBN AUC's [100]. However, a related study, by the same research group, found 5% failure or relapse with the selection of acquired rifamycin resistance (ARR) with twice-weekly TB treatment, including RBN [101]. Lopinavir-ritonavir used in combination with RBN three times weekly also lead to the selection of ARR, and requires RBN dosage adjustments based on plasma concentration monitoring [102]. RIF profoundly reduces saquinavir concentrations when saquinavir is used alone, but RIF has lesser effects on it when co-administered with higher doses of ritonavir; RIF has modest effects on ritonavir as well [103]. Tipranavir, like the other protease inhibitors both inhibits and induces the cytochrome P450 enzyme system; when used in combination with ritonavir, its net effect on CYP3A4 is inhibition. Tipranavir also induces p-glycoprotein transporter. Thus, tipranavir may alter the concentrations of many other drugs metabolized by these pathways, in ways that may be complex and difficult to predict. Rifampin induces tipranavir metabolism and decreases tipranavir

Table 12.4 Co-administration of rifabutin and rifampin with HIV-1 protease inhibitors (PI): effect on the area-under-the-curve (AUC) of each drug

	Rifabutin		Rifampin[a]		
Protease inhibitor (PI)	Effect of rifabutin on PI	Effect of PI on rifabutin	Effect of rifampin on PI	Effect of PI on rifampin	Comment
Saquinavir	↓ 45%	↑ 44%	↓ 80%	NR	Do not use with RIF
Ritonavir[b]	NR	↑ 293%	↓ 35%	Unchanged	Use with caution
Indinavir	↓ 34%	↑ 173%	↓92%	NR	Do not use with RIF. Decrease dose with RBN.
Nelfinavir	↓ 32%	↑ 207%	↓ 82%	NR	Do not use with RIF. Decrease dose with RBN.
Amprenavir	↓ 14%	↑ 200%	↓ 82%	Unchanged	Do not use with RIF. Decrease dose with RBN.
Atazanavir	NR	↑ 250%	NR (↓ predicted)	NR	Do not use with RIF. Decrease dose with RBN.
Lopinavir/ Ritonavir	NR	↑ 303%	↓ 75%	NR	Use with caution
Darunavir	↑57%	↑66%	NR	NR	Do not use with RIF. Decrease dose with RBN.
Tipranavir/ Ritonavir	Unchanged	↑640%	NR	NR	Do not use with RIF RBN use with caution

Adapted from: Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (online) 2007. URL: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm and [3]. With Permission

Notes:

- These are average changes, but the effect of these interactions in an individual patient may be substantially different
- Rifampin is a potent inducer of CYP3A, but is not itself a CYP3A substrate. For example, concomitant delavirdine, a moderate CYP3A inhibitor, does not change serum concentrations of rifampin. Therefore, although there are very few data at present, it is likely that protease inhibitors will not substantially increase the serum concentrations of rifampin (the same is true of rifapentine)
- There are no data regarding the magnitude of these bi-directional interactions when the rifamycin is administered twice- or thrice-weekly

NR not reported

[a] Rifapentine produces approximately 85% of the effects seen with rifampin

[b] Data from only 2 subjects

levels; rifampin should not be given concomitantly with tipranavir. Combining tipranavir with rifabutin should be done with caution, while toxicity and rifabutin drug levels should be monitored [104]. Darunavir is metabolized by CYP3A4. Rifampin induces darunavir metabolism and decreases darunavir concentrations; rifampin should not be given concomitantly with darunavir. Similar to other ritonavir boosted protease inhibitors, coadministration of darunavir and ritonavir is expected to increase rifabutin concentrations and decrease darunavir concentrations. Rifabutin should be dosed as 150 mg every other day, and TDM performed. [105].

Based on current data, ritonavir or saquinavir and ritonavir should be used with caution in combination with RIF [1, 69]. TDM may help to optimize regimens for the co-administration of these agents.

12.4.2.12 CCR-5 Receptor Antagonists

Maraviroc is the first drug to be approved in the class of CCR-5 receptor antagonists. It is primarily and extensively metabolized by CYP3A4. In the presence of CYP3A4 inducers, such as RIF, the dosage of maraviroc should be increased [106]. Current clinical experience with RBN is limited.

12.4.2.13 Integrase Inhibitors

In-vitro and in-vivo studies indicate raltegravir does not have any significant induction or inhibitory effects on the CYP enzymes [107]. Interactions have been observed with RIF; however, efficacy data is required [108]. Raltegravir is metabolized by glucuronidation. The enzyme responsible for the metabolite of raltegravir appears to be the UDP-glucuronosyltransferase (UGT) 1A1 subtype. Rifampin is a potent UGT inducer. A 40% reduction in raltegravir AUC occurred when it was dosed as 400 mg twice daily with rifampin 600 mg daily. An increased dose of raltegravir (800 mg twice daily) demonstrated that the negative effect of rifampin on raltegravir exposure could be reversed [109]. Caution is warranted if the combination of raltegravir and RIF is selected.

Drug doses for persons with HIV co-infection who are being treated with combination anti-retroviral therapy (CART) often must be adjusted when rifamycins are used concurrently. Many interaction effects are drug-specific, and an effort should be made to obtain expert consultation and the latest available information to guide dosing. Note that plasma concentrations changes seen in 2-way interaction studies may be very different from those seen clinically when 3 or more interacting drugs are used concurrently.

12.4.2.14 Sulfamethoxazole and Trimethoprim

The effect of RIF on concentrations of sulfamethoxazole/trimethoprim (SMZ/TMP) was evaluated in HIV positive patients [110]. A decrease (23%) in mean AUC of SMZ/TMP was observed. The clinical significance of this interaction has not been established but reduced efficacy of SMZ/TMP may be of concern.

Rifamycins interact with several other classes of drugs beyond those listed above. Additional information regarding rifamycin interactions can be found in the article by Niemi et al. and in several other papers [111–113].

12.4.3 Pyrazinamide Interactions

Pyrazinamide (PZA) is metabolized to pyrazinoic acid and 5-hydroxypyrazinoic acid, which are subsequently cleared renally [7, 28, 43]. PZA is removed by hemodialysis [29]. It is not associated with a large number of drug interactions. Because PZA can compete with uric acid for excretion, patients will accumulate uric acid while on PZA. In most cases, this is not a clinically significant problem, but may precipitate a flare-up of the disease. Allopurinol inhibits the clearance of PZA's primary metabolite, pyrazinoic acid, thereby exacerbating the metabolite's inhibition of uric acid secretion [114, 115]. Further, probenecid may be significantly less effective as a uricosuric agent in the presence of PZA [116]. Thus, the most effective management of PZA-induced elevations of uric acid and arthralgias may be to hydrate the patient and withhold PZA.

The combination of RIF and PZA in the absence of INH leads to an unexpectedly high incidence of hepatotoxicity in HIV-negative patients [117–120]. It is important to stress this was in the context of 2 month regimens of RIF and PZA for latent TB infection (LTBI), and not during the treatment of active TB disease with INH, RIF, PZA and EMB. Therefore, this 2 month combination of RIF and PZA for LTBI generally should no longer be used [119]. PZA combined with ofloxacin or levofloxacin for LTBI due to multidrug-resistant TB also is poorly tolerated [121–123]. It is possible that PZA or its metabolites compete with quinolones for renal tubular secretion, although this has not been proven. This regimen also cannot be recommended at this time.

12.4.4 Ethambutol Interactions

EMB is cleared both hepatically and renally [6, 28, 43]. EMB is not significantly removed by hemodialysis [29]. The specific pathways involved in its hepatic clearance are not known. EMB has few documented interactions. The affect of concurrent antacids was described above. Because EMB can cause optic neuritis, patients receiving other potential ocular toxins (RBN, cidofovir) should be monitored carefully. While RBN and cidofovir are associated with uveitis and not optic neuritis, additive effects may adversely affect vision [35, 124, 125].

12.4.5 Aminoglycoside and Polypeptide Interactions

The aminoglycosides amikacin, kanamycin, streptomycin, as well as the polypeptides capreomycin and viomycin, are all primarily cleared renally [28, 126, 127]. Aminoglycosides are removed by hemodialysis [28, 128]. However, under clinical

conditions, especially in the intensive care setting, traditional hemodialysis removal may be limited. Other methods of renal replacement can also substantially remove drug. Aminoglycosides can adversely affect vestibular, auditory, and renal function. Reported differences in the incidence of these toxicities among the agents reflect, in part, differences in doses and frequencies used. Elevated serum creatinine values due to non-oliguric acute tubular necrosis are usually reversible; renal wasting of cations also may occur [28, 43, 126]. Periodic monitoring (every 2–4 weeks) of the serum blood urea nitrogen, creatinine, calcium, potassium, and magnesium should be considered, especially if other nephrotoxins (such as amphotericin B) are being used [1]. Vestibular changes may be noted on physical exam, and may occur independently of, or in conjunction with, tinnitus and auditory changes [128]. Auditory changes are best detected by monthly audiograms for those patients requiring prolonged treatment, or those receiving concurrent potential ototoxins (clarithromycin, ethacrynic acid, furosemide) [1, 128]. Aminoglycosides and polypeptides can potentiate the neuromuscular blocking agents, or may precipitate neuromuscular blockade in patients with myasthenia gravis [43, 126]. Therefore, these drugs should be used cautiously in those settings.

12.4.6 Cycloserine Interactions

There is little known regarding the potential for drug interactions with cycloserine (CS) [129]. This drug is renally cleared, and there are no known metabolites [28, 129]. CS is cleared by hemodialysis [130]. It can cause a variety of central nervous system disturbances, including anxiety, confusion, memory loss, dizziness, lethargy, and depression, including suicidal tendencies [28]. Therefore, other agents associated with any of these effects (INH, ethionamide, and quinolones) may have additive CNS toxicities. CS should be used cautiously in patients with a history of depression or psychosis, or those receiving treatment for these conditions. It is not clear if cycloserine can alter the potential for seizures in patients predisposed to these events. Caution is advised, as is TDM to insure that concentrations do not exceed the recommended range of 20–35 mcg/ml [18, 129]. Older literature suggests that CS may decrease the clearance of phenytoin, possibly leading to toxicity [43].

12.4.7 Ethionamide Interactions

ETA is extensively metabolized, including reversibly to a sulfoxide metabolite that appears to be active against mycobacteria [28, 131]. The specific hepatic microsomal enzymes responsible for this metabolism are not known. Little unchanged drug is excreted in the urine, or cleared by hemodialysis [130, 131].

ETA causes significant gastrointestinal (GI) distress. ETA may cause CNS effects, including headache, drowsiness, depression, psychosis, and visual changes. And additive effects with INH, CS or fluoroquinolones are possible [43, 131]. ETA may cause peripheral neuritis, so caution should be exercised in patients receiving other agents, such as nucleoside reverse transcriptase inhibitors, that share this toxicity. ETA can cause hepatotoxicity and goiter, with or without hypothyroidism; the latter is worsened by the concurrent use of PAS [131]. Thyroid-stimulating hormone (TSH) concentrations should be monitored periodically in patients receiving ETA.

12.4.8 Para-aminosalicylic acid Interactions

PAS is metabolized by N-acetyltransferase 1 (NAT1) to acetyl-PAS, that is subsequently cleared renally [10, 28, 130, 132]. Little PAS is cleared by hemodialysis, but some of the acetyl-PAS is cleared by hemodialysis [130]. PAS can cause diarrhea, and this can affect the pharmacokinetics of other drugs. Various types of malabsorption with PAS have been described, including steatorrhea, vitamin B_{12}, folate, xylose and iron. With the possible exception of digoxin, it is not known if PAS can cause specific drugs to be malabsorbed [132]. Hypersensitivity reactions with fever, including hepatitis, can occur, and desensitization to PAS-induced hypersensitivity is not recommended [132]. PAS is known to produce goiter, with or without myxedema, and this is more frequent with concomitant ETA therapy. This can be prevented or treated with thyroxine. Older tablet forms of PAS that contained bentonite reduced serum RIF concentrations; this should not occur with the granule form [132]. Due to the reported greater risk of crystalluria, the concurrent use of ammonium chloride with PAS is not recommended [133].

12.4.9 Clofazimine Interactions

Clofazimine (CF) is a weak anti-TB drug, and has a very unusual pharmacokinetic profile [11, 28, 43, 127]. It is highly tissue-tropic, and as a result, displays a very long elimination half-life. It is primarily excreted non-renally, but the precise mechanisms have not been described. CF is negligibly removed by hemodialysis [130]. As noted above, oral absorption is improved when CF is given with a high-fat meal. The most serious adverse reactions associated with CF are dose-related gastrointestinal (GI) toxicities, and these can be additive with other drugs' effects [28, 43, 127]. Skin discoloration may also occur, and other drugs, including amiodarone and RBN, may worsen discoloration. CF can produce a statistically significant increase in RIF's Tmax, but this interaction is unlikely to be clinically significant. The large accumulation of CF in macrophages may affect the function of these cells, but this has not been well defined. It is at least

theoretically possible that such affects can contribute to the poor outcome seen in some AIDS patients who received CF as part of their regimen for disseminated MAC infection (DMAC).

12.5 Management of Patients Co-infected with HIV and TB

The Centers for Disease Control and Prevention has published guidelines for the management of TB in patients co-infected with HIV [1, 69]. First, clinicians should look for a paradoxical worsening of TB symptoms upon the introduction of combination anti-retroviral therapy (CART) as a consequence of immune reconstitution inflammatory syndrome (IRIS) [1, 69]. Next, the guidelines generally recommend the use of RBN instead of RIF for patients receiving CART in an attempt to minimize drug interactions. It is very important to bear in mind that most interaction studies involving RIF or RBN and CART were performed in small numbers of healthy volunteers. Results seen in HIV-positive patients can be very different. For example, combinations of RIF and ritonavir are very poorly tolerated in healthy subjects, with high rates of hepatic enzyme elevations. This is not nearly as common in patients with HIV, based on available information. Table 12.5 summarizes the current data available on drug interactions between protease inhibitors and anti-tuberculosis drugs other than rifamycins [3, 134]. It is our practice to measure the serum concentrations of the various interacting drugs (antimycobacterial drugs, oral azole antifungals, and anti-HIV protease inhibitors) in order to verify adequate dosing [3, 18]. As noted, low RBN plasma concentrations have been associated with acquired rifamycin resistant (ARR) mycobacteria in patients with HIV [101]. Intermittent dosing of TB drugs in patients with HIV may become a thing of the past. However, the best daily dose of RBN for patients receiving CART requires further study.

Table 12.5 Predicted potential for drug-drug interaction between HIV protease inhibitors and antituberculosis drugs other than rifamycins

Drug	Metabolism	Effect on CYP3A	Effect of drug X on PI (predicted)[a]	Effect of PI on drug X (predicted)[a]
Isoniazid	Acetylation	Mild inhibitor	No change in indinavir	None
Pyrazinamide	Deamidase > xanthine oxidase	None known	(None)	(None)
Ethambutol	Renal > CYP	None known	(None)	(None)
Ethionamide	CYP	None known	Unknown	(Increase)
PAS	Acetylation	None known	(None)	(None)
Quinolones	Renal transferases	None known	(None)	(None)
Aminoglycosides	Renal	None known	(None)	(None)

Adapted from [3]. With permission

[a] Predicted using existing knowledge regarding metabolic pathways for the two drugs

12.6 Nontuberculous Mycobacterial (NTM) Infections

The NTM comprise a substantial list of infections caused by various slow growing and rapid growing mycobacteria. The management of such infections has been summarized elsewhere [135, 136]. Clinicians should be aware that there are differences between HIV-infected and non-infected hosts as far as disease presentation and management. It is important to consider the drug interactions described above for TB, as many of these same drugs are used to treat NTM. Advanced generation macrolides (azithromycin, clarithromycin) are frequently used to treat NTM, such as *M. avium* complex, and clarithromycin has been associated with many CYP3A4 interactions [34, 43, 112, 136]. In particular, bi-directional interactions involving RBN and clarithromycin should be anticipated [137]. RIF causes a more pronounced decline in clarithromycin concentrations than RBN [138, 139].

12.7 Future Considerations

Several new TB drugs are under development, including PA-824, OPC-67683, SQ109, and TMC-207 [140–145]. SQ109 is metabolized by CYP2D6 and CYP2C19 and up to 58% of parent is metabolized in 10-minute incubation with microsomes. Insignificant metabolism is found in the presence of CYP3A4 [146]. Therefore, interactions with rifamycins may be expected. TMC-207 is a substrate for CYP3A4, and serum concentrations of TMC-207 are reduced by 50% when given with rifampin [141]. The optimal dosing for combined use of these new TB drugs with rifampin or other rifamycins in humans has not been studied to date.

12.8 Conclusion

The above discussion highlights the need for the careful introduction of the TB drugs into existing drug regimens. In particular, rifamycins can seriously disrupt ongoing treatment, with potentially serious consequences. While the role of TDM remains to be better defined for these situations, it does offer the potential to untangle multi-directional drug interactions.

References

1. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America. Treatment of Tuberculosis. Am J Respir Crit Care Med 2003;167: 603–662.
2. Peloquin CA Tuberculosis. In DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, Eds. Pharmacotherapy: A pathophysiologic approach, 8th ed., McGraw Hill, New York, 2011, p 1931–1949.

3. Burman WJ, Gallicano K, Peloquin, C. Therapeutic implications of drug interactions in the treatment of HIV-related tuberculosis. Clin Infect Dis 1999;28:419–30.
4. Peloquin CA, Namdar R, Dodge AA, Nix DE. Pharmacokinetics of isoniazid under fasting conditions with food, and with antacids. Inter Tuber Lung Dis 1999;3:703–710.
5. Peloquin CA, Namdar R, Singleton MD, Nix DE. Pharmacokinetics of rifampin under fasting conditions, with food, and with antacids. Chest 1999;115:12–18.
6. Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, Childs JM, Nix DE. Pharmacokinetics of ethambutol under fasting conditions, with food, and with antacids. Antimicrob Agents Chemother 1999;43:568–572.
7. Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, James GT, Nix DE. Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. Pharmacotherapy 1998; 18:1205–1211.
8. Auclair B, Nix DE, Adam RD, James GT, Peloquin CA. Pharmacokinetics of ethionamide under fasting conditions, with orange juice, food, and antacids. Antimicrob Agents Chemother 2001;45:810–14.
9. Zhu M, Nix DE, Adam RD, Childs JM, Peloquin CA. Pharmacokinetics of cycloserine under fasting conditions, with orange juice, food, and antacids. Pharmacotherapy 2001;21: 891–897.
10. Peloquin CA, Zhu M, Adam RD, Godo, PG, Nix DE. Pharmacokinetics of p-aminosalicylate under fasting conditions, with orange juice, food, and antacids. Ann Pharmacother 2001;35: 1332–8.
11. Nix DE, Zhu M, Adam RD, Godo PG, Peloquin CA. Pharmacokinetics of Clofazimine under Fasting Conditions, with Orange Juice, Food, and Antacids. Tuberculosis (in press).
12. Sahai J, Gallicano K, Swick L, et al. Reduced plasma concentrations of antiturberculous drugs in patients with HIV infection. Ann Intern Med 1997;127:289–293.
13. Peloquin CA, Nitta AT, Burman WJ, et al. Low antituberculosis drug concentrations in patients with AIDS. Ann Pharmacother 1996;30:919–925.
14. Berning SE, Huitt GA, Iseman MD, Peloquin CA. Malabsorption of antituberculosis medications by a patient with AIDS (letter). N Engl J Med. 1992;327:1817–1818.
15. Patel KB, Belmonte R, Crowe HM. Drug malabsorption and resistant tuberculosis in HIV-infected patients (letter). N Engl J Med 1995;332:336–337.
16. Peloquin CA, MacPhee AA, Berning SE. Malabsorption of antimycobacterial medications (letter). N Engl J Med 1993;329:1122–1123.
17. Gordon SM, Horsburgh CR Jr, Peloquin CA, et al. Low serum levels of oral antimycobacterial agents in patients with disseminated mycobacterium avium complex disease. J Infect Dis 1993;168:1559–1562.
18. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs 2002;62: 2169–2183.
19. Colborn D, Lewis R, Narang P. HIV disease does not influence rifabutin absorption. Abstract. 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. Orlando, FL, 1994.
20. Gatti G, Di Biagio A, De Pascalis CR, Guerra M, Bassetti M, Bassetti D. Abstract Pharmacokinetics of rifabutin in HIV-infected patients with or without wasting syndrome. Br J Clin Pharmacol 1999;48:704–711.
21. Keung AC, Owens RC Jr, Eller MG, Weir SJ, Nicolau DP, Nightingale CH. Pharmacokinetics of rifapentine in subjects seropositive for the human immunodeficiency virus: a phase I study. Antimicrob Agents Chemother 1999;43:1230–1233.
22. Weiner M, Burman W, Vernon A, Benator D, Peloquin CA, Khan A, Weis S, King B, Shah N, Hodge T and the Tuberculosis Trials Consortium. Low isoniazid concentration associated with outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. Am J Respir Crit Care Med 2003;167:1341–1347
23. Weiner M, Burman B, Khan A, Peloquin C, Benator D, Vernon A, Zhao Z, Weis S, Tuberculosis Trials Consortium. The Effect of HIV Serostatus on Isoniazid Pharmacokinetics among Patients with Active Tuberculosis. ATS 2004, Orlando FL.

24. Ehrenpreis ED, Ganger DR, Kochvar GT, Patterson BK, Craig RM. D-xylose malabsorption: characteristic finding in patients with the AIDS wasting syndrome and chronic diarrhea. J Acquir Immune Defic Syndr 1992;5:1047–1050.
25. Kotler DP, Francisco A, Clayton F, Scholes JV, Orenstein JM. Small intestinal injury and parasitic diseases in AIDS. Ann Intern Med 1990;113:444–449.
26. Kotler DP, Giang TT, Thiim M, Nataro JP, Sordillo EM, Orenstein JM. Chronic bacterial enteropathy in patients with AIDS. J Infect Dis 1995;171:552–558.
27. Blum RA, D'Andrea DT, Florentino BM, et al. Increased gastric pH and the bioavailability of fluconazole and ketoconazole. Ann Intern Med 1991;114:755–757.
28. Peloquin CA, Antituberculosis Drugs: Pharmacokinetics. In Heifets, L, ed. Drug susceptibility in the chemotherapy of mycobacterial infections. CRC Press, Boca Raton, 1991, p 59–88.
29. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on isoniazid, rifampin, pyrazinamide, and ethambutol. Am J Respir Crit Care Med 1999;159: 1580–1584.
30. Murray FJ. Outbreak of unexpected reactions among epileptics taking isoniazid. Am Rev Respir Dis 1962;86:729–732.
31. Valsalan VC, Cooper GI. Carbamazepine intoxication caused by interaction with isoniazid. BMJ 1982;285:261–262.
32. Dockweiler U. Isoniazid induced valproic acid toxicity, or vice versa. Lancet 1987;2:152.
33. Angelini MC, MacCormack-Gagnon J, Dizio S. Increase in plasma levels of clozapine after the addition of isoniazid. J Clin Psychopharm 2009;29(2):190.
34. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmacokinet 1997;32:210–258.
35. Ochs HR, Greenblatt DJ, Roberts GM, Dengler HJ. Diazepam interaction with antituberculosis drugs. Clin Pharmacol Ther 1981;29:671–678.
36. Sutton G, Kupferberg HJ. Isoniazid as an inhibitor of primidone metabolism. Neurology 1975;25:1179–1181.
37. Zand R, Nelson SD, Slattery JT, Thummel KE, Kalhorn TF, Adams SP, Wright JM. Inhibition and induction of cytochrome P4502E1-catalyzed oxidation by isoniazid in humans. Clin Pharmacol Ther 1993;54:142–149.
38. Baciewicz AM, Self TH. Isoniazid interactions. Southern Med J 1985;78:714–718.
39. Rosenthal AR, Self TH, Baker ED, et al. Interaction of isoniazid and warfarin. JAMA 1977;238:2177.
40. Desta Z, Soukhova NV, Flockhart DA. Inhibition of cytochrome P450 (CYP450) isoforms by isoniazid: potent inhibition of CYP2C19 and CYP3A4. Antimicrob Agent Chemother 2001; 45:382–392.
41. Wenning GK, O'Connell MT, Patsalos PN, et al. A clinical and pharmacokinetic case study of an interaction of levodopa and antituberculous therapy in Parkinson's disease. Mov Disord 1995;10:664–667.
42. Nolan CM, Sandblom RE, Thummel KE, Slattery JT, Nelson SD. Hepatotoxicity associated with acetaminophen usage in patients receiving multiple drug therapy for tuberculosis. Chest 1994;105:408–411.
43. McEvoy GK, Ed. AHFS Drug Information 2010. American Society of Health-Systems Pharmacists, Bethesda, MD, 2010.
44. Murphy R, Swartz R, Watkins PB. Severe acetaminophen toxicity in a patient receiving isoniazid. Ann Intern Med 1990;113:799–800.
45. Moulding TS, Redeker AG, Kanel GC. Acetaminophen, isoniazid and hepatic toxicity. Ann Intern Med 1991;114:431.
46. Ofoefule SI, Obodo CE, Orisakwe OE, Ilondu NA, Afonne OJ, Maduka SO, Anusiem CA, Agbassi PU. Some plasma pharmacokinetic parameters of isoniazid in the presence of a fluoroquinolone antibacterial agent. Am J Ther 2001;8:243–6.
47. Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. Clin Pharmacokinet 2001;40:327–341.

48. Oswald S, Giessmann T, Luetjohann D, Wegner D, Rosskopf D, Weitschies W, Siegmund W. Disposition and sterol-lowering effect of ezetimibe are influenced by single-dose coadministration of rifampin, an inhibitor of multidrug transport proteins. Clin Pharmacol Ther 2006; 80(5):477–85.
49. Payen L, Sparfel L, Courtois A, Vernhet L, Guillouzo A, Fardel O. The drug efflux pump MRP2: regulation of expression in physiopathological situations and by endogenous and exogenous compounds. Cell Biol Toxicol 2002;18(4):221–33.
50. Corpechot C, Ping C, Wendum D, Matsuda F, Barbu V, Poupon R. Identification of a Novel 974 C→G Nonsense Mutation of the MRP2/ABCC2 Gene in a Patient with Dubin-Johnson Syndrome and Analysis of the Effects of Rifampicin and Ursodeoxycholic Acid on Serum Bilirubin and Bile Acids. Am J Gastroenterol 2006;101:2427–2432.
51. Vavricka SR, Van Montfoort J, Ha HR, Meier PJ, Fattinger K. Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. Hepatology 2002; 36(1):164–72.
52. Niemi M, Kivistö KT, Diczfalusy U, Bodin K, Bertilsson L, Fromm MF, Eichelbaum M. Effect of SLCO1B1 polymorphism on induction of CYP3A4 by rifampicin. Pharmacogenet Genomics 2006;16(8):565–8.
53. Schuetz EG, Schinkel AH, Relling MV, Schuetz JD. P-glycoprotein: a major determinant of rifampicin inducible expression of cytochrome P4503A in mice and humans. Proc Natl Acad Sci USA. 1996;93:4001–4005.
54. Hoffmeyer S, Burk O, von Richter O. Functional polymorphisms of the human multidurg resistance gene:multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci USA 2000;97:3473–3478.
55. Li AP, Reith MK, Rasmussen A Gorski JC, Hall SD, Xu L, Kaminski DL, Cheng LK. Primary human hepatocytes as a tool for the evaluation of structure-activity relationship in a cytochrome P450 induction potential of xenobiotics: evaluation of rifampin, rifapentine, and rifabutin. Chem Biol Interact 1997;107:17–30.
56. Weiner M, Peloquin C, Burman MD, et al., Tuberculosis Trials Consortium. The effects of tuberculosis, race and human gene SLCO1B1 polymorphisms on rifampin concentrations. 2010.
57. Keung AC, Reith K, Eller MG. Enzyme induction observed in healthy volunteers after repeated administration of rifapentine and its lack of effect on steady-state rifapentine pharmacokinetics. Int J Tuber Lung Dis 1999;3:426–36.
58. Gallicano KD, Sahai J, Shukla VK, Seguin I, Pakuts A, Kwok D, Foster BC, Cameron DW. Induction of zidovudine glucuronidation and amination pathways by rifampicin in HIV-infected patients. Br J Clin Pharmacol 1999;48:168–79.
59. Peloquin CA. What is the right dose of rifampin? Int J Tuberc Lung Dis 2003;7:3–5.
60. CDC. Treatment of tuberculosis. MMWR 2003;52:1–77.
61. Indinavir pharmacokinetics study group. Indinavir (MK 639) drug interactions studies [Abstract no. MoB174]. In: Program and abstracts of the XI International AIDS Conference. Vancouver, Canada 1996:18.
62. Grub S, Bryson H, Goggin T, Ludin E, Jorga K. The interaction of saquinavir with ketoconazole, erythromycin and rifampin: comparison of the effect in healthy volunteers and in HIV-infected patients. Eur J Clin Pharmacol 2001;57:115–121.
63. Jaruratanasirikul S, Sriwiriyajan S. Effect of rifampicin on the pharmacokinetics of itraconazole in normal volunteers and AIDS patients. Eur J Clin Pharmacol 1998;54:155–158.
64. Drayton J, Dickenson G, Rinaldi MG. Coadministration of rifampin and itraconazole leads to undetectable levels of serum itraconazole. Clin Infect Dis 1994;18:266.
65. Doble N, Shaw R, Rowland-Hill C, Lush M, Warnock DW, Keal EE. Pharmacokinetic study of the interaction between rifampicin and ketoconazole. J Antimicrob Chemother 1998;21:633–635.
66. Nicolau DP, Crowe HM, Nightingale CH, Quintiliani R. Rifampin-fluconazole interaction in critically ill patients. Ann Pharmacother 1995;29:994–6.

67. Apseloff G, Hilligoss DM, Gardner MJ, Henry EB, Inskeep PB, Gerver N. Induction of fluconazole metabolism by rifampin : in vivo study in humans. J Clin Pharmacol 1991;31:358–61.
68. Coker RJ, Tomlinson DR, Prakin J, Harris JRW, Pinching AJ. Interaction between fluconazole and rifampicin. BMJ 1990;301:818.
69. Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR 2004;53:37.
70. Jaruratanasirikul S, Kleepkaew A. Lack of effect of fluconazole on the pharmacokinetics of rifampicin in AIDS patients. J Antimicrob Chemother 1996;38:877–880.
71. Jordan MK, Polis MA, Kelly G, Narang PK, Masur H, Piscitelli SC. Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. Antimicrob Agents Chemother 2000;44:2170–2172.
72. Schwiesow JN, Iseman MD, Peloquin CA. Concomitant use of voriconazole and rifabutin in a patient with multiple infections. Pharmacother 2008;28(8):1076–1080.
73. Kelly HW, Couch RC, Davis RL, Cushing AH, Knott R. Interaction of chloramphenicol and rifampin. J Pediatr 1988;112:817–820.
74. Prober CG. Effect of rifampin on chloramphenicol levels. N Engl J Med 1985;312:788.
75. Mirochnick M, Cooper E, Capparelli E, McIntosh K, Lindsey J, Xu J, Jacobus D, Mofenson L, Bonagura VR, Nachman S, Yogev R, Sullivan JL, Spector SA. Population pharmacokinetics of dapsone in children with human immunodeficiency virus infection. Clin Pharmacol Ther 2001;70:24–32.
76. Colmenero JD, Fernandez-Gallardo LC, Agundez JAG, Sedeno J, Benitez J, Valverde E. Possible implications of doxycycline-rifampin interaction for treatment of brucellosis. Antimicrob Agents Chemother 1994;38:2798–2802.
77. Temple ME, Nahata MC. Interaction between ciprofloxacin and rifampin. Ann Pharmacother 1999;33:868–70.
78. Chandler MH, Toler SM, Rapp RP, Muder RR, Korvick JA. Multiple dose pharmacokinetics of concurrent oral ciprofloxacin and rifampin therapy in elderly patients. Antimicrob Agents Chemother 1990;34:442–7.
79. Weiner M, Burman W, Luo CC, et al. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. AAC 2007;51:2861–2866.
80. Nijland HM, Ruslami R, Suroto AJ, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. Clin Infect Dis 2007;45(8):1001–1007.
81. Shishoo CJ, Shah SA, Rathod IS, Savale SS, Vora MJ. Impaired bioavailability of rifampicin in presence of isoniazid from fixed dose combination (FDC) formulation. Int J Pharm 2001;228:53–67.
82. Apseloff G, Foulds G, LaBoy-Goral L, Willavize S, Vincent J. Comparison of Azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. J Clin Pharmacol 1998;38:830–835.
83. Hafner R, Bethel J, Power M, Landry B, Banach M, Mole L, Standiford HC, Follansbee S, Kumar P, Raasch R, Cohn D, Mushatt D, Drusano G. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. Antimicrob Agents Chemother 1998;42:631–639.
84. Djojosaputro M, Mustofa S, Donatus IA, Santoso B. The effects of doses and pre-treatment with rifampicin on the elimination kinetics of metronidazole. Eur J Pharmacol 1990;183:1870.
85. CDC. Updated guidelines for use of rifamycins for the treatment of tuberculosis among HIV infected patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. MMWR 2004;53(2):37.
86. Borin MT, Chambers JH, Carel BJ, Gagnon S, Freimuth WW. Pharmacokinetic study of the interaction between rifampin and delavirdine mesylate. Clin Pharmacol Ther 1997;61:544–553.
87. Borin MT, Chambers JH, Carel BJ, Freimuth WW, Aksentijevich S, Piergies AA. Pharmacokinetic study of the interaction between rifabutin and delavirdine mesylate in HIV1 infected patients. Antiviral Res 1997;35:53–63.

88. Scholler-Gyure M, Woodfall B, De Marez T, et al., Pharmacokinetic interaction between TMC125 and rifabutin. In : 44th Annual Meeting of the Infectious Disease Society of America, Toronto, Canada (Abstract 1059).
89. Lopez-Cortes LF, Ruiz-Valderas R, Viciana P, Alarcon-Gonzalez A, Gomez- Mateos J, Leon-Jimenez E, Sarasanacenta M, Lopez-Pua Y, Pachon J. Pharmacokinetic interactions between efavirenz and rifampicin in HIV infected patients with tuberculosis. Clin Pharmacokinet 2002;41:681–90.
90. Weiner M, Benator D, Peloquin CA, et al. Evaluation of the drug interaction between rifabutin and efavirenz in patients with HIV infection and tuberculosis. CID 2005;41(1): 1343–1349.
91. Crauwels HM, Kakuda TN. Drug interactions with new investigational antiretrovirals. Clin Pharmacokin 2010;49(1):67–68.
92. Polk RE, Brophy DF, Israel DS, Patron R, Sadler BM, Chittick GE, Symonds WT, Lou Y, Kristoff D, Stein DS. Pharmacokinetic interaction between amprenavir and rifabutin or rifampin in healthy males. Antimicrob Agents Chemother 2001;45:502–8.
93. Cato A, Cavanaugh J, Shi H, Hsu A, Leonard J, Granneman GR. The effect of multiple doses of ritonavir on the pharmacokinetics of rifabutin. Clin Pharmacol Ther 1998;63:414–421.
94. Kerr BM, Daniels R, Cledeninn N. Pharmacokinetic interaction of nelfinavir with half-dose rifabutin. Can J Infect Dis 1999;10:21B.
95. Moyle J, Buss NE, Goggin T, Snell P, Higgs C, Hawkins DA. Interaction between saquinavir soft-gel and rifabutin in patients infected with HIV. Br J Clin Pharmacol 2002;54:178–182.
96. Moreno S, Podzamczer D, Blazquez R, Tribarren JA, Ferror B, Reparez J, Pena JM, Carero E, Usan L. Treatment of tuberculosis in HIV-infected patients: safety and antiretroviral efficacy of the concomitant use of ritonavir and rifampin. AIDS 2001;15:1185–7.
97. Narita M, Stambaugh JJ, Hollender ES, Jones D, Pitchenik AE, Ashkin D. Use of rifabutin with protease inhibitors for human immunodeficiency virus-infected patients with tuberculosis. Clin Infect Dis 2000;30:779–83.
98. Peloquin CA. Tuberculosis Drug Serum Levels (letter). Clin Infect Dis 2001;33:584–5.
99. Hamzeh FM, Benson C, Gerber J, Currier J, McCrea J, Deutsch P, Ruan P, Wu H, Lee J, Flexner C, AIDS clinical trials group 365 study team. Steady-state pharmacokinetic interaction of modified-dose indinavir and rifabutin. Clin Pharmacol Ther 2003;73:159–69.
100. Benator D, Weiner M, Burman W, et al. for the Tuberculosis Trials Consortium. Clinical Evaluation of the Nelfinavir – Rifabutin Interaction in Patients with HIV Infection and Tuberculosis. Pharmacotherapy 2007;27:793–800.
101. Weiner M, Benator D, Burman W, et al., for the Tuberculosis Trials Consortium. Association Between Acquired Rifamycin Resistance and the Pharmacokinetics of Rifabutin and Isoniazid among Patients with HIV and Tuberculosis. Clinical Infectious Diseases 2005;40: 1481–1491
102. Boulaner C, Hollender E, Farrell K, et al., Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. CID 2009;49:1305–1311.
103. Ribera E, Azuaje C, Lopez RM. Pharmacokinetic interaction between rifampicin and the once daily combination of saquinavir and low dose ritonavir in HIV infected patients with tuberculosis. J Antimicrob Chemother 2007;59:690–697.
104. Tipranavir [package insert]. US prescribing information: Boehringer Ingelheim, Germany: 2006.
105. Darunavir [package insert]. East Bridgewater, NJ: Tibotec Therapeutics: July 2006.
106. Abel S, Back DJ, Vourvahis M. Maraviroc: pharmacokinetics and drug interactions. Antivir Ther 2009;14(5):607–618.
107. Iwamoto M, Kassahun K, Troyer MD. Lack of a pharmacokinetic effect of raltegravir on midazolam; in vitro/in vivo correlation. J Clin Pharmacol 2008;48:209–214.
108. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug metabolizing enzymes, on the pharmacokinetics of raltegravir. Antimicrob Agents Chemother 2009;53:2852–2856.

109. Wenning LA, Hanley WD, Brainard DM, Petry AS, Ghosh K, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. Antimicrob Agents Chemother 2009;53(7):2852–6.
110. Ribera E, Pou L, Fernandez-Sola A, Campos F, Lopez RM, Ocana I, Ruiz I, Pahissa A. Rifampin reduces concentrations of trimethoprim and sulfamethoxazole in serum in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2001;45: 3238–3241.
111. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampin: clinical relevance. Clin Pharmcokinet 2003;42:815–50.
112. Lin JH, Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. Clin Pharmacokinet 1998;35:361–390.
113. Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacother 1998;18:84–112.
114. Lacroix C, Guyonnaud C, Chaou M, Duwoos H, Lafont O. Interaction between allopurinol and pyrazinamide. Eur Respir J 1988;1:807–811.
115. Urban T, Maquarre E, Housset C, Chouaid C, Devin E, Lebeua B. Allopurinol hypersensitivity. A possible cause of hepatitis and mucocutaneous eruptions in a patient undergoing antitubercular treatment. Revue des Maladies Respiratoires 1995;12:314–316.
116. Yu TF, Perel J, Berger L, Roboz J. The effect of the interaction of pyrazinamide and probenecid on urinary uric acid excretion in man. Am J Med 1977;63:723–728.
117. Burman WJ, Reves RR. Hepatotoxicity from rifampin plus pyrazinamide: lessons for policymakers and messages for care providers. Am J Respir Crit Care Med 2001;164: 1112–1113.
118. Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, King MD, Kawamura LM, Hopewell PC; Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection (SCRIPT) Study Investigators. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med 2002;137:640–7.
119. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection--- United States, 2003. MMWR 2003:52;735–739.
120. Kunimoto D, Warman A, Beckon A, et al. Severe hepatotoxicity associated with rifampin-pyrazinamide preventative therapy requiring transplantation in an individual at low risk for hepatotoxicity. Clin Infect Dis 2003;36:158–161.
121. Ridzon R, Meador J, Maxwell R, Higgins K, Weismuller P, Onorato IM. Asymptomatic hepatitis in persons who received alternative preventive therapy with pyrazinamide and ofloxacin. Clin Infect Dis 1997;24:1264–5.
122. Papastavros T, Dolovich LR, Holbrook A, Whitehead L, Loeb M. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. CMAJ 2002;167:131–6.
123. Lou HX, Shullo MA, McKaveney TP. Limited tolerability of levofloxacin and pyrazinamide for multidrug-resistant tuberculosis prophylaxis in a solid organ transplant population. Pharmacotherapy 2002;22:701–4.
124. Tseng AL, Walmsley SL. Rifabutin-associated uveitis. Ann Pharmacother 1995;29: 1149–1155.
125. Tseng AL, Mortimer CB, Salit IE. Iritis associated with intravenous cidofovir. Ann Pharmacother 1999;33:167–71.
126. Nicolau DP, Quintiliani R. Aminoglycosides. In Yu VL, Merigan TC, Barriere S, White NJ, Eds. Antimicrobial Chemotherapy. Williams and Wilkins, Baltimore, MD, 1998, p 621–37.
127. Kucers A, Bennett N McK, Eds. The use of antibiotics. 4th ed. JB Lippincott Co, Philadelphia, PA, 1988.
128. Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, Iseman MD, Cook JL, Curran-Everett D. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis 2004;38:1538–1544.

129. Berning SE, Peloquin CA. Antimycobacterial agents: cycloserine. In Yu VL, Merigan TC, Barriere S, White NJ, Eds. Antimicrobial Chemotherapy. Williams and Wilkins, Baltimore, MD, 1998, p 638–42.
130. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on cycloserine, ethionamide, para-aminosalicylate, and clofazimine. Chest 1999; 116(4): 984–90.
131. Berning SE, Peloquin CA. Antimycobacterial agents: ethionamide. In Yu VL, Merigan TC, Barriere S, White NJ, Eds. Antimicrobial Chemotherapy. Williams and Wilkins, Baltimore, MD, 1998, p 650–4.
132. Berning SE, Peloquin CA. Antimycobacterial agents: para-aminosalicylic acid. In Yu VL, Merigan TC, Barriere S, White NJ, Eds. Antimicrobial Chemotherapy. Williams and Wilkins, Baltimore, MD, 1998, p 663–8.
133. Jacobus Pharmaceutical Co. Paser® granules (aminosalicylic acid granules) prescribing information, 1996. In: Physicians' desk reference. 57th ed. Montvale, NJ: Medical Economics Company Inc; 2003:1770–1.
134. Burman WJ, Peloquin CA. Antimycobacterial Agents: Isoniazid. In Yu VL, Merigan TC, Barriere S, White NJ, Eds. Antimicrobial Chemotherapy and Vaccines, 2nd edition (in press).
135. Yu VL, Merigan TC, Barriere S, White NJ, Eds. Antimicrobial chemotherapy. Williams and Wilkins, Baltimore, MD, 2003.
136. American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med 1997;156:S1–S25.
137. Amsden GW. Macrolides versus azalides: a drug interaction update. Ann Pharmacother 1995; 29:906–17.
138. Wallace RJ, Brown BA, Griffith DE. Reduced serum levels of clarithromycin in patients treated with multidrug regimens including rifampin or rifabutin for Mycobacterium avium-intracellulare infection. J Infect Dis 1995;171:747–50.
139. Peloquin CA, Berning SE. Evaluation of the drug interaction between clarithromycin and rifampin. J Infect Dis Pharmacother 1996;2:19–35.
140. Lalloo UG, Ambaram A. New antituberculous drugs in development. Curr HIV/AIDS Rep 2010;7(3):143–51.
141. Burman WJ. Rip Van Winkle wakes up: development of tuberculosis treatment in the 21st century. Clin Infect Dis 2010;50(Suppl 3):S165–72.
142. [No authors listed] PA-824.Tuberculosis (Edinb). 2008;88(2):134–6.
143. [No authors listed] OPC-67683. Tuberculosis (Edinb). 2008;88(2):132–3.
144. [No authors listed] SQ109 Tuberculosis (Edinb). 2008;88(2):159–61.
145. [No authors listed] TMC-207 Tuberculosis (2008);88(2):168–169.
146. Jia L, Noker PE, Coward L, Gorman GS, Protopopova M, Tomaszewski JE. Interspecies pharmacokinetics and *in vitro* metabolism of SQ109. Br J Pharmacol 2006;147:476–85.

Chapter 13
Drug Interactions with Antiretrovirals for HIV Infection

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Abstract Despite great strides in human immunodeficiency virus (HIV) drug development, the management of drug interactions remains a key component of patient care. A number of new drugs have been approved in the past 5 years, including two new classes of antiretrovirals: CCR5 antagonists and integrase inhibitors. HIV treatment is complex, generally requiring at least three antiretrovirals in addition to medications for supportive care and concomitant infections. Many antiretrovirals have clinically significant drug interactions that require dosage adjustment. This chapter reviews important drug interactions for the newest antiretrovirals and provides detailed tables to guide clinicians on patient management.

13.1 Introduction

Numerous advances have been made in the management of the HIV-infected patients over the past 5–10 years. This period has brought forth more antiretrovirals with once daily dosing, improved side effect profiles and fewer restrictions on food. Despite these strides, drug interactions remain an important part in the management of a patient's treatment regimen and play a critical role in the selection of which drugs are prescribed.

Several new therapies were approved since the last edition of **Drug Interactions in Infectious Disease** and two new drug classes are now available to prescribers (Chemokine Receptor 5 (CCR5) antagonists and integrase inhibitors). With a wide variety of antiretrovirals available for clinicians to choose from, the overall profile of a drug must now be considered. Long term safety and efficacy are still the primary

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determinants of treatment choice, but other factors including tolerability, dosing convenience and drug interactions are involved in the decision. Agents with a low potential for drug interactions have significant advantages in complex regimens and also may find usage in special patient populations such as co-infection with tuberculosis or hepatitis C virus, epilepsy, women of child bearing potential, and methadone maintenance programs. The ability to administer a drug without dosage adjustments or a substitution of the patient's regimen is a significant advantage.

Treatment of HIV infection has come full circle in terms of complexity. In the early years of the disease, zidovudine monotherapy was the only available treatment. The 1980s saw treatment efficacy improve dramatically with the use of protease inhibitors and drug "cocktails" comprised of multiple agents, with a focus on putting together the most effective regimen and with less emphasis on patient convenience and tolerability. Treatment regimens today are moving back toward simplification with protease inhibitor monotherapy and two-drug treatment regimens under evaluation (i.e. raltegravir and atazanavir) [1, 2]. Throughout this remarkable 25 year period, the management of drug interactions remains a key component of patient care.

There are a number of complex issues relating to drug interactions with antiretroviral agents. The extensive tables in this chapter provide a reference for clinicians to use in managing their patients' regimens, while the text will address interactions with new FDA-approved antiretrovirals and key issues relating to drug interactions in the HIV-infected patient. Additional data can be obtained at a number of internet sites that also provide detailed information on antiretroviral combinations [3–6].

13.2 Integrase Inhibitors

13.2.1 Raltegravir

Raltegravir is the first approved inhibitor of HIV integrase, a key enzyme in the HIV lifecycle that incorporates the DNA of the virus into the host genome. Drug interactions with raltegravir are shown in Tables 13.1 and 13.2. Raltegravir is metabolized by UDP-glucuronosyltransferase (UGT) 1A1 and thus does not have the complex interaction profile of the protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) that are primarily metabolized through cytochrome P450 (CYP) 3A [18]. Raltegravir also has a low propensity to cause interactions with other drugs because it does not induce or inhibit any of the CYP isozymes or UGTs 1A1 or 2B7, and has no significant effect on p-glycoprotein (p-gp) [18]. Importantly, a pharmacokinetic/pharmacodynamic (PK/PD) analysis from Phase 3 clinical trials did not show a strong relationship between raltegravir exposure and virologic response [19]. One reason for this finding is the large variability in raltegravir plasma concentrations observed in Phase 3 studies combined with the favorable clinical response rates, resulting in a wide therapeutic index. The lack of correlation between plasma concentrations and efficacy make it difficult to interpret drug

Table 13.1 Interactions between NNRTIs, Maraviroc, Raltegravir and PIs [7–14]

		Efavirenz	Etravirine	Nevirapine	Maraviroc	Raltegravir
Atazanavir (ATV)	**Exposure**	ATV without RTV	ATV without RTV	With ATV 300 mg ± RTV 100 mg QD	ATV without RTV	ATV without RTV
		↔ EFV ↓ ATV	↑ ETR ↓ ATV	↑ NVP ↓ ATV	↑ MVC	↑ RAL
		With ATV 300 mg ± RTV 100 mg QD with food	With (ATV 300 mg ± RTV 100 mg) QD		With ATV 300 mg ± RTV 100 mg QD	With ATV 300 mg ± RTV 100 mg QD
		ATV concentrations similar to ATV without RTV and without EFV	↑ ETR ↓ ATV		↑ MVC	↑ RAL
	Dose	**Do not coadminister with unboosted ATV.** In treatment-naïve patients ATV 400 mg QD + RTV 100 mg QD + standard dose EFV **Do not coadminister in treatment-experienced patients.**	**Do not coadminister with ATV +/– RTV.**	**Do not coadminister with ATV +/– RTV** because NVP substantially decreases ATV exposure and potential risk for NVP associated toxicity due to increased NVP exposures	MVC 150 mg BID with standard doses of ATV +/– RTV	No dose adjustments needed

(continued)

Table 13.1 (continued)

		Efavirenz	Etravirine	Nevirapine	Maraviroc	Raltegravir
Darunavir (DRV)	**Exposure**	With DRV 300 mg ± RTV 100 mg BID	ETR 100 mg BID with DRV 600 mg ± RTV 100 mg BID	With DRV 400 mg ± RTV 100 mg BID	With DRV 600 mg ± RTV 100 mg BID	With DRV 600 mg ± RTV 100 mg BID
		↓ DRV	↔ DRV	↑ DRV	↑ MVC	↓ RAL
		↑ EFV	↓ ETV	↑ NVP	With DRV 600 mg ± RTV 100 mg BID ± ETR	
					↑ MVC	
	Dose	No dose adjustments needed; use with caution and monitor for increased risk of EFV related side effects	No dose adjustments needed, despite decreased ETR, because safety and efficacy established with this combination in a clinical trial	No dose adjustments needed	MVC 150 mg BID + standard doses of DRV/RTV	No dose adjustments needed
Efavirenz (EFV)	**Exposure**	•	↓ ETR possible	↔NVP ↓ EFV	MVC: AUC ↓ 45%	↓ EFV
	Dose		**Combining two NNRTIs has not shown to be beneficial; therefore, do not co-administer**	**Combining two NNRTIs has not shown to be beneficial; therefore, do not co-administer**	MVC 600 mg BID + EFV 600 mg QD	No dose adjustments needed

Etravirine (ETR)	**Exposure**	↓ ETR possible	•	↓ ETR possible	With ETR 200 mg BID ↓ MCV ↔ ETR With DRV 600 mg ± RTV 100 mg BID ↑ MCV ↔ ETR or DRV	↑ ETR ↓RAL
	Dose	**Combining two NNRTIs has not shown to be beneficial; therefore, do not co-administer**		**Combining two NNRTIs has not shown to be beneficial; therefore, do not co-administer**	With ETR 200 mg BID MCV 600 mg BID With DRV 600 mg ± RTV 100 mg BID MCV 150 mg BID	No dose adjustments needed
Fosamprenavir (FPV)	**Exposure**	With FPV 1,400 mg ± RTV 200 mg QD ↓ APV	With FPV 700 mg ± RTV 100 mg BID ↑ APV	FPV 1,400 mg BID without RTV ↓ APV ↑ NVP With FPV 1,400 mg ± RTV 100 mg BID ↑ NVP	↑ MVC possible	No data
	Dose	FPV 1,400 mg + RTV 300 mg QD + standard dose of EFV or FPV 700 mg + RTV 100 mg BID + standard dose of EFV	**Do not coadminister with FPV +/– RTV due to significant increase in systemic exposure of amprenavir.**	FPV 700 mg + RTV 100 mg BID + standard dose of NVP	MVC 150 mg BID + standard doses of FPV/RTVTV	No data

(continued)

Table 13.1 (continued)

		Efavirenz	Etravirine	Nevirapine	Maraviroc	Raltegravir
Indinavir (IDV)	**Exposure**	↓ IDV	↓ IDV	↓ IDV ↔ NVP	↑ MVC possible	No data
	Dose	**Do not coadminister.** Increasing indinavir dose to 1,000 mg Q8H may not be sufficient to compensate for interaction	**Do not coadminister.**	IDV 1,000 mg q8h, or IDV 800 mg + RTV 100–200 mg BID NVP standard	MVC 150 mg BID + standard dose of IDV	No data
Lopinavir/ Ritonavir (LPV/r)	**Exposure**	With LPV/RTV tablets 500/125 mg BID‡ ± EFV 600 mg	With LPV/RTV tablets	With LPV/RTV capsules		
		LPV levels similar to LPV/RTV 400/100 mg BID without EFV	↓ ETR (comparable to the decrease with DRV/RTV)	↓ LPV	↑ MVC	↓ RAL
			↓ LPV		With LPV/RTV ± EFV ↑ MVC	↔ LPV/RTV
	Dose	LPV/RTV tablets 500/125 mg + standard dose of EFV	No dose adjustments needed	LPV/RTV tablets 500/125 mg + standard dose of EFV	MVC 150 mg BID + standard dose of LPV/RTV	No dose adjustments needed
		LPV/RTV oral solution 533/133 mg BID + standard dose of EFV		LPV/RTV oral solution 533/133 mg BID + standard dose of EFV	With LPV/RTV ± EFV MVC 150 mg + standard doses of LPV/RTV and EFV	

Nelfinavir (NFV)	**Exposure**	↑ NFV ↔ EFV	No data	↓ NFV ↔ NVP	Unknown, possibly ↑ MVC concentration	No data
	Dose	No dose adjustments needed	**Do not coadminister.**	No dose adjustments needed	MVC 150 mg BID + standard dose of NFV	No data
***Nevirapine* (NVP)**	**Exposure**	↔ NVP ↓ EFV	↓ ETR possible	•	↑ MCV	No data
	Dose	**Combining two NNRTIs has not shown to be beneficial; therefore, do not co-administer**	**Combining two NNRTIs has not shown to be beneficial; therefore, do not co-administer**		Without PI MVC 300 mg BID With PI (except TPV/RTV) MVC 150 mg BID	No data
Raltegravir (RAL)	**Exposure**	↓ RAL	↑ ETV ↓ RAL	No data	↓ RAL ↓ MVC	•
	Dose	No dose adjustments needed	No dose adjustments needed	No data	No dose adjustments needed	
Ritonavir (RTV)	**Exposure**	Refer to information for PI with RTV	Refer to information for PI wtih RTV	Refer to information for PI with RTV	With RTV 100 mg BID ↑ 161%	With RTV 100 mg BID ↓ RAL
	Dose				MVC 150 mg BID	No dose adjustments needed

(continued)

Table 13.1 (continued)

		Efavirenz	Etravirine	Nevirapine	Maraviroc	Raltegravir
Saquinavir (SQV)	**Exposure**	With SQV 1,200 mg TID ↓ SQV ↓ EFV	With SQV 1,000 mg ± RTV 100 mg BID ↓ SQV ↓ ETR Reduced ETR levels similar to reduction with DRV/RTV	With SQV 600 mg TID ↓ SQV ↔ NVP	With SQV 1,000 mg ± RTV 100 mg BID ↑ MCV With SQV 1,000 mg ± RTV 100 mg BID ± EFV ↑ MCV	No data
	Dose	SQV 1,000 mg + RTV 100 mg BID + standard dose of EFV	SQV 1,000 mg + RTV 100 mg BID + standard dose of ETR	SQV 1,000 mg + RTV 100 mg BID + standard dose of NVP	MVC 150 mg BID + standard dose of SQV	No data

Tipranavir (TPV)	**Exposure**	With TPV 500 mg ± RTV 100 mg BID	With TPV 500 mg ± RTV 200 mg BID	With TPV 250 mg ± RTV 200 mg BID and with TPV 750 mg ± RTV 100 mg BID	With TPV 500 mg ± RTV 200 mg BID	With TPV 500 mg ± RTV 200 mg BID
		↓ TPV ↔ EFV	↓ ETR ↑ TPV	↔NVP TPV: no data	↔ MVC TPV: no data	↓ RAL
	Dose	No dose adjustments needed	**Do not coadminister due to significant decrease in ETR plasma concentrations and possible loss of therapeutic effect of ETR**	No dose adjustments needed	MVC 300 mg BID + standard dose of TPV/RTV	No dose adjustments needed. TPV/RTV reduces RAL exposures; however, comparable efficacy was observed for TPV/RTV + RAL combination relative to other RAL containing regimens in phase 3 treatment-experienced trials

Table 13.2 Drug interactions between Maraviroc or Raltegravir and other drugs [15–17]

Drug affected	Maraviroc (MVC)	Raltegravir (RAL)
ACID REDUCERS		
H_2-receptor Antagonists	No dose adjustments needed	↓ RAL
Proton Pump Inhibitors		No dose adjustments needed
ANTIFUNGALS		
Itraconazole	Possible ↑ MVC Use MVC 150 mg BID	No data; interaction is not expected
Ketoconazole	↑ MVC Use MVC 150 mg BID	No data; interaction is not expected
Voriconazole	Possible ↑ MVC Use MVC 150 mg BID	No data; interaction is not expected
ANTICONVULSANTS		
Carbamazepine, Phenobarbital, Phenytoin	Possible ↓ MVC Use MVC 600 mg BID (if no concomitant strong CYP3A inhibitor)	No data; possible ↓ RAL
ANTI-MYCOBACTERIALS		
Clarithromycin	Possible ↑ MVC Use MVC 150 mg BID	No data; interaction is not expected
Rifampin	↓ MVC Coadministration not recommended; if necessary, increase MVC dose to 600 mg BID. If coadministering with a strong CYP3A inhibitor, use MVC 300 mg BID	↓ RAL Increase RAL dose to 800 mg BID
Rifabutin	Possible ↓ MVC Use MVC 300 mg BID	↑ RAL No dose adjustments needed
BENZODIAZEPINES		
Midazolam	No dose adjustments needed	No dose adjustments needed
Hormonal contraceptives		
Combined Oral Contraceptives	No dose adjustments needed	No dose adjustments needed
Opioid replacement		
Methadone	No data	↔ Methadone No dose adjustments needed
Other agents		
St. John's wort	Avoid combination	No data; possible ↓ RAL

interaction data. While it is assumed that an exposure-response relationship exists, there are no specific guidelines or recommendations for target concentrations that need to be achieved for a successful outcome. Population PK/PD analyses performed on data collected from Phase 3 trials demonstrated that increases or decreases in raltegravir concentrations due to concomitant medications do not appear to result in a loss of efficacy or untoward toxicity.

In general, raltegravir has very few clinically relevant drug-drug interactions due to its route of metabolism and wide therapeutic index. Potent inducers of UGT1A1

such as rifampin can significantly decrease raltegravir plasma exposures [20]. When combined with rifampin, the recommendation is to double the raltegravir dose from 400 to 800 mg BID. In healthy subjects, etravirine decreased the area under the concentration-time curve (AUC) of raltegravir by only 10%, and similarly raltegravir had no significant effect on etravirine [21]. This decrease was not considered clinically significant: however, case reports of subjects having virologic failure on this combination have been reported [22]. Modest decreases in exposure of raltegravir were also observed with tipranavir/ritonavir and efavirenz [7, 23]. Based on the lack of clear exposure-response or exposure-toxicity relationship, dose adjustments are not needed.

The UGT1A1 inhibitor, atazanavir, increases raltegravir AUC by 72% by blocking its primary metabolic pathway [24]. The magnitude of the interaction is lower when raltegravir is combined with atazanavir/ritonavir (41% increase in AUC), likely due to the induction of glucuronidation by ritonavir. However, this increase is not considered clinically significant because clinical trials demonstrated no safety issues with this combination, and no dose adjustment is necessary. A cross-sectional study found that darunavir trough concentrations were lower in HIV-infected subjects taking raltegravir compared to those who were not; however, these differences did not affect virologic outcome [25]. When fosamprenavir, either ritonavir-boosted or not, and raltegravir were co-administered in healthy subjects, both drugs demonstrated decreases in exposure, although each agent still achieved minimum concentration (C_{min}) values considered to be therapeutic [26].

13.3 Entry Inhibitors

13.3.1 Maraviroc

Maraviroc is the only approved CCR5 antagonist, and the only HIV medication that targets a host receptor. The envelope glycoprotein of HIV binds to CD4 cells and causes a conformational change that allows binding to one of two co-receptors, CCR5 or CXC Chemokine Receptor 4 (CXCR4) [27]. This binding initiates conformational changes that ultimately lead to membrane fusion with the host cell. Maraviroc inhibits the binding of HIV to CCR5, thus preventing entry of the virus into the cell. Maraviroc is a substrate of CYP3A and p-gp and has numerous drug interactions with inhibitors and inducers of these mechanisms (Tables 13.1 and 13.2). Because of its sensitivity to CYP3A inhibitors and inducers, maraviroc is dosed differently depending on the concomitant therapy.

Ritonavir-boosted protease inhibitors generally increase the AUC of maraviroc and result in the need for a dosage adjustment. In HIV-infected subjects, maraviroc AUC was increased by a mean of 2.6-fold and maximum concentration (C_{max}) increased 1.8-fold when given with lopinavir/ritonavir compared to a maraviroc alone control group [28]. Atazanavir and atazanavir/ritonavir also significantly increased maraviroc AUC by 3.6-fold and 4.9-fold respectively [29]. The combination with ritonavir

boosted saquinavir is generally considered the worst case scenario for increases in maraviroc exposure. A study in healthy volunteers with saquinavir/ritonavir 1,000/100 mg BID resulted in increases of 832% for AUC and 423% for C_{max} [29]. Concomitant use with these protease inhibitors requires a decrease in the dose from 300 to 150 mg twice daily. When efavirenz is given with either lopinavir/ritonavir or saquinavir/ritonavir, the AUC of maraviroc remains significantly increased, also requiring a dosage reduction to 150 mg twice daily, although the magnitude of the increase is smaller due to the induction effects of efavirenz [30].

Potent CYP3A inducers significantly decrease maraviroc exposure and result in the need for a dosage increase. Etravirine (200 mg twice daily) alone was shown to decrease the AUC of maraviroc by 53% in healthy volunteers [31]. However, when maraviroc and etravirine were co-administered with darunavir/ritonavir, the AUC was increased 210% compared to maraviroc alone [31]. Thus, the maraviroc dose should be increased to 600 mg twice daily with etravirine, but no dose adjustment is needed if also given with darunavir/ritonavir. Maraviroc had no effect on etravirine or darunavir exposure.

In a study in healthy volunteers, using a maraviroc dose of 100 mg twice daily, concomitant administration with efavirenz led to a 51% decrease in the AUC of maraviroc [30]. This exposure returned to near pre-induction values by doubling the dose to 200 mg twice daily of maraviroc. A study in HIV-infected patients evaluated the pharmacokinetics of maraviroc when given with efavirenz and two nucleoside reverse transcriptase inhibitors. The maraviroc AUC was decreased 53% compared to a historical maraviroc monotherapy group in HIV-infected patients [28]. Maraviroc dose should be increased to 600 mg twice daily when used with efavirenz or other potent CYP3A inducers. In a separate cohort where maraviroc was administered with nevirapine and two nucleoside reverse transcriptase inhibitors (NRTIs), the exposure of maraviroc was not significantly different than the monotherapy group [28]. These data suggest that nevirapine does not demonstrate a similar decrease in maraviroc exposure compared to efavirenz and no dose adjustment is required.

An unexpected interaction was observed between raltegravir and maraviroc. A cross-over study in healthy volunteers demonstrated a decrease in the exposure of both drugs. While the maraviroc AUC was only modestly decreased by 14%, the raltegravir AUC was decreased by 38% [32]. The decrease in raltegravir was also not considered clinically significant based on review of efficacy data and trough concentrations in Phase 3 from subjects receiving the combination and no dose adjustment in raltegravir is recommended [32].

13.3.2 Enfuvirtide

Enfuvirtide (ENF) is an entry inhibitor that exerts in action by binding to the gp41 subunit of the HIV envelope glycoprotein, preventing critical conformation changes needed for viral entry into the cell. Prior to the development of potent oral agents such as darunavir and raltegravir, ENF was an option for treatment-experienced

patients with few options, but is rarely used today. ENF is a peptide and must be administered twice daily by subcutaneous injection. Since ENF undergoes catabolism and not metabolism by CYP450, ENF does not demonstrate drug interactions with other antiretrovirals. Clinical trials showed no clinically relevant interactions with saquinavir and ritonavir, ritonavir alone (200 mg BID), or rifampin, one of the most potent inducers of the CYP3A4 [8, 33]. ENF also was shown not to affect the exposure of darunavir in HIV-infected patients in an analysis of data from Phase 3 clinical trials comparing darunavir pharmacokinetics with and without ENF [34]. However, tipranavir and ritonavir concentrations were unexpectedly higher in subjects receiving this protease inhibitor and ENF compared to subjects on ENF alone [35].

13.4 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

13.4.1 Pharmacology

NRTIs are still the most commonly used agents in HIV treatment and remain a key component of most treatment regimens despite the approval of many new drugs in recent years. NRTIs are not metabolized via the CYP450 pathway, nor do they induce or inhibit these pathways. Thus, they may be used concomitantly at standard doses with all other drug classes. NRTIs are prodrugs that must be phosphorylated intracellularly to their active forms. While it is possible to measure intracellular concentrations in specialized laboratories, the clinical significance of these concentrations remains to be validated, and most NRTI drug interactions are of limited clinical importance [36].

13.4.2 Tenofovir

Tenofovir is the one NRTI for which unpredictable drug interactions have been reported. This drug is a nucleotide reverse transcriptase inhibitor that undergoes two phosphorylation steps intracellularly, compared to three steps for other NRTIs. Although this compound is eliminated renally, a number of interesting drug interactions are observed, even with drugs that are hepatically metabolized.

Tenofovir decreases the AUC of atazanavir by approximately 25%, whether atazanavir is given alone or in combination with ritonavir [37]. Therefore, tenofovir is not recommended to be give with atazanavir unless the atazanavir is boosted with ritonavir. The mechanism of this interaction is currently unknown. Conversely, atazanavir, lopinavir/ritonavir, and saquinavir/ritonavir have been shown to increase tenofovir exposure [38]. The mechanism may be related to the effect of intestinal p-gp by protease inhibitors or possibly through inhibition of renal transporters [39, 40].

Tenofovir increases didanosine plasma AUC by 40–60% with the EC (delayed-release, enteric coated) formulation [41]. Furthermore, the interaction was observed

in either the fed or fasted state. The mechanism is thought to be tenofovir's inhibition of the enzyme responsible for didanosine catabolism. A reduction in the dose of didanosine EC from 400 to 250 mg QD is recommended and the reduced dose achieves similar exposures to didanosine EC 400 mg [42].

13.4.3 Competition for Metabolic Pathways

Other clinically significant drug interactions for NRTIs occur between agents that compete for the intracellular activation pathways. A number of NRTI combinations should be avoided, including zidovudine/stavudine and tenofovir/abacavir/lamivudine [43]. The use of these combinations has been demonstrated to lead to virologic failure.

13.5 Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

13.5.1 Pharmacology

The NNRTIs are widely used agents based on their convenient dosing, durability of response, and track record of long-term safety. NNRTIs are also important components of fixed dose combinations allowing for the administration of a three-drug regimen in a once daily tablet. Drug interactions with NNRTIs are shown in Tables 13.1 and 13.3. Nevirapine and efavirenz are potent inducers of CYP3A and thus decrease concentrations of drugs which are primarily metabolized through this pathway. Efavirenz also has mixed induction/inhibition and can increase exposure of certain agents such as warfarin [56]. NNRTIs can demonstrate clinically significant induction even when a potent CYP3A inhibitor is co-administered. Plasma lopinavir concentrations are modestly decreased with efavirenz and nevirapine, despite the presence of co-formulated ritonavir. A dosage increase from 400 mg lopinavir/100 mg ritonavir to 500 mg lopinavir/125 mg ritonavir is recommended [57].

13.5.2 Etravirine

Etravirine is a second generation NNRTI with activity against efavirenz-resistant strains and has become an important agent for treatment-experienced patients. Etravirine has a complex metabolic profile as it is a substrate of CYP3A4, 2C9, and 2C19, an inhibitor of CYP2C9, 2C19 and P-gp, and an inducer of CYP3A4 [44]. Etravirine likely also induces UGT1A1 based on the decrease in raltegravir exposure when these drugs are co-administered [21, 22].

Table 13.3 Drug interactions between NNRTIs and other drugs [44–55]

	Efavirenz (EFV)	Etravirine (ETR)	Nevirapine (NVP)
ANTIFUNGALS			
Fluconazole	No dose adjustments needed	↑ ETR No dosage adjustments needed; use with caution	↑ NVP Use with caution and monitor for NVP-related toxicities
Itraconazole	↓ itraconazole and OH-itraconazole ↔ EFV	Possible ↓ itraconazole Possible ↑ ETR	Possible ↓ itraconazole
Ketoconazole	Possible ↓ ketoconazole	Possible ↓ ketoconazole Possible ↑ ETR	↓ ketoconazole Possible ↑ NVP Do not coadminister
Posaconazole	↓ posaconazole ↔ EFV Avoid concomitant use unless benefit outweighs risk	Possible ↑ ETR	No data; possible ↓ posaconazole
Voriconazole	↓ voriconazole ↑ EFV Increase voriconazole to 400 mg Q12h and decrease EFV dose to 300 mg QD	↑ ETR No dose adjustments needed; use with caution	No data; possible ↓ voriconazole and possible ↑ NVP
ANTICONVULSANTS			
Carbamazepine (CBZ)	EFV + CBZ: ↓ EFV and ↓ CBZ	No data; may result in significant ↓ ETR and ↓ anticonvulsant	No data; possible ↓ NVP and ↓ anticonvulsant
Phenobarbital	No data for phenytoin or phenobarbital, but ↓ EFV and anticonvulsant exposure is expected. Avoid combination or	Do not coadminister	Use with caution and monitor anticonvulsant and NVP levels
Phenytoin	monitor anticonvulsant and EFV levels.		
Valproic Acid	No dose adjustments needed	No data	No data

(continued)

Table 13.3 (continued)

	Efavirenz (EFV)	Etravirine (ETR)	Nevirapine (NVP)
ANTIDEPRESSANTS			
Bupropion	↓ bupropion Titrate dose to effect	No data	No data; possible ↓ bupropion
Sertraline	↓ sertraline Titrate dose to effect	No data	No data; possible ↓ sertraline
ANTI-MYCOBACTERIALS			
Clarithromycin	↓ clarithromycin and ↑ OH-clarithromycin Consider alternatives (e.g. azithromycin)	↓ clarithromycin and ↑ OH-clarithromycin ↓ ETR AUC Consider alternatives (e.g. azithromycin)	↓ clarithromycin and ↑ OH-clarithromycin Consider alternatives (e.g. azithromycin)
Rifabutin	↔ EFV ↓ Rifabutin Increase rifabutin dose to 450–600 mg QD or 600 mg 3×/week	↓ Rifabutin and metabolite ↓ ETR Rifabutin 300 mg QD if ETR is **not** coadministered with a RTV-boosted PI	No dose adjustments needed
Rifampin	↓ EFV Consider increase in EFV dose to 800 mg QD in patients >60 kg	No data; possible ↓ ETR Use of this combination is not recommended	↓ NVP Use of this combination is not recommended
BENZODIAZEPINES			
Alprazolam	No data; possible ↓ alprazolam	No data; possible ↓ alprazolam	No data; possible ↓ alprazolam
Diazepam	No data; possible ↓ diazepam	No data	No data; possible ↓ diazepam
Lorazepam	No dose adjustments needed	No data	No data
Midazolam	No data; avoid combination	No data; possible ↓ midazolam	No data; possible ↓ midazolam
Triazolam	No data; avoid combination	No data; possible ↓ triazolam	No data; possible ↓ triazolam
CALCIUM CHANNEL BLOCKERS			
Diltiazem	↓ diltiazem Titrate diltiazem dose based on response	No data; possible ↓ diltiazem Titrate diltiazem dose based on response	No data; possible ↓ diltiazem Titrate diltiazem dose based on response

HORMONAL CONTRACEPTIVES			
Combined Oral Contraceptives	↔ ethinyl estradiol ↓ norgestromin Use alternative or additional methods of contraception	↑ Ethinyl estradiol No dose adjustments needed	↓ ethinyl estradiol ↓ norethindrone Use alternative or additional methods of contraception
Depomedroxyprogesterone acetate	No dose adjustment necessary	No data	No dose adjustment necessary
Levonorgestrel	↓ levonorgestrel Effectiveness of emergency postcoital contraception may be diminished	No data; possible ↓ levonorgestrel	No data; possible ↓ levonorgestrel
LIPID LOWERING AGENTS			
Atorvastatin	↓ Atorvastatin Higher atorvastatin doses may be necessary; adjust dose according to response. Do not exceed maximum recommended dose.	↓ Atorvastatin Higher atorvastatin doses may be necessary; adjust dose according to response. Do not exceed maximum recommended dose.	No data
Lovastatin Simvastatin	↓ Simvastatin Higher simvastatin doses may be necessary; adjust dose according to response. Do not exceed maximum recommended dose.	No data	No data
Pravastatin Rosuvastatin	↓ pravastatin Higher pravastatin doses may be necessary; adjust dose according to response. Do not exceed maximum recommended dose.	No data	No data

(continued)

Table 13.3 (continued)

	Efavirenz (EFV)	Etravirine (ETR)	Nevirapine (NVP)
OPIOID REPLACEMENT			
Methadone	↓ methadone Monitor for withdrawal and consider ↑ methadone dose if needed	↔ Methadone ↔ Etravirine No dose adjustments needed	↓ Methadone (↓ R-methadone) Monitor for withdrawal and consider ↑ methadone dose if needed
Buprenorphine	↓ buprenorphine Monitor for withdrawal and consider increase in buprenorphine dose if needed	No data	No dose adjustments needed
Oral anticoagulants/anti-platelet drugs			
Clopidogrel	No data	Possible decrease in activation of clopidogrel; avoid combination or use alternative	No data
Warfarin	No data; possible ↓ or ↑ in warfarin Monitor INR closely	No data; possible ↑ warfarin Monitor INR closely	No data; possible ↓ or ↑ in warfarin Monitor INR closely
Phosphodiesterase 5 (pde5) inhibitors			
Sildenafil	No data; possible ↓ PDE5-inhibitor	↓ Sildenafil	No data; possible ↓ PDE5-inhibitor
Tadalafil		No data for tadalafil & vardenafil	
Vardenafil		May require higher dose of sildenafil; do not exceed maximum recommended dose	

Etravirine has a number of clinically significant interactions with the protease inhibitors. Etravirine cannot be combined with unboosted protease inhibitors, nor with boosted combinations of atazanavir/ritonavir, fosamprenavir/ritonavir or tipranavir/ritonavir, due to clinically significant alterations in exposures of both agents. Co-administration with atazanavir 400 mg once daily resulted in a decrease in atazanavir AUC of 17% and C_{min} decrease of 47%, with a 50% increase in etravirine AUC [58]. With ritonavir-boosted atazanavir, the decrease in atazanavir C_{min} was only 38% with an increase in etravirine of approximately 30% [58]. The combination of lower atazanavir exposures and higher etravirine exposures warrants avoidance of concomitant therapy.

In HIV-infected subjects, the addition of etravirine to a stable fosamprenavir/ritonavir regimen led to an increase in amprenavir AUC and C_{min} of 69% and 77%, respectively [59]. Due to the magnitude of the increase, the combination should not be co-administered.

Induction of CYP3A has been well described for tipranavir/ritonavir [60]. Co-administration with etravirine resulted in a decrease in the etravirine AUC by 76% while tipranavir and ritonavir exposures were only modestly increased by approximately 20% [61]. This combination should be avoided due to the potential for a loss of therapeutic effect of etravirine. Full dose ritonavir (600 mg BID) also decreased etravirine concentrations approximately 45% due to induction of glucuronidation [62]. However, the unboosted dose of ritonavir is generally not used clinically.

Etravirine can be given with saquinavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir, NRTIs and raltegravir without dose adjustment [63]. Darunavir/ritonavir and etravirine are frequently used in combination in treatment-experienced patients. In a healthy volunteer study, etravirine 100 and 200 mg twice daily were co-administered with darunavir/ritonavir. Etravirine AUC was decreased 37% and darunavir exposures were not significantly altered [64]. No dose adjustment is necessary based on safety and efficacy from Phase 3 clinical trials [63]. Since saquinavir/ritonavir and lopinavir/ritonavir reduce etravirine exposure to a similar extent as darunavir/ritonavir, no dose adjustment is therefore needed for these protease inhibitors.

13.6 Protease Inhibitors

13.6.1 Pharmacology

The protease inhibitors are widely used in HIV-infected patients due to their potency, durability, and high genetic barrier to resistance. These drugs act at a late stage in the life cycle of HIV, preventing the formation and release of infectious virions from the cell [65]. All protease inhibitors are metabolized primarily by CYP3A4 and have inhibitory effects on this metabolic pathway [45]. Some of them act on other pathways as well, including atazanavir which is an inhibitor of UGT1A1 and ritonavir which modulates multiple CYP isozymes and UGT1A1. Clinically significant interactions with the protease inhibitors are shown in Tables 13.4 and 13.5.

Table 13.4 Drug interactions between protease inhibitors and other drugs [55, 58, 66–83]

Drug affected	Atazanavir (ATV) (± Ritonavir)	Darunavir (DRV) + Ritonavir (RTV)	Fosamprenavir (FPV) (± Ritonavir)	Indinavir (IDV) (± Ritonavir)	Lopinavir (LPV)/ Ritonavir (RTV)	Nelfinavir (NFV)	Saquinavir (SQV) + Ritonavir (RTV)	Tipranavir (TPV) + Ritonavir (RTV)
ACID REDUCERS								
Antacids	Possible ↓ ATV (+/− RTV) Administer ATV 2 h before or 1 h after antacids	No dose adjustments needed	FPV (without RTV): slight ↓ APV May be given together or separated by 2 h	No data; possible ↓ IDV	No dose adjustments needed	No dose adjustments needed	No dose adjustments needed	↓ TPV Give tipranavir either 2 h before or 1 h after antacids
H_2-receptor antagonists (H_2RA)	Sig. ↓ ATV exposure, especially without RTV. Avoid H_2RA + ATV (without RTV), if possible. Do not exceed H_2RA dose equiv. of 40 mg BID famotidine in tx-naïve pts receiving ATV/RTV and 20 mg BID if receiving ATV. Do not exceed equiv. of 20 mg BID famotidine in tx-experienced pts. Give ATV/RTV simultaneously with and/or ≥ 10 h after the H_2RA; without RTV, give ATV ≥ 2 h before and ≥ 10 h after H_2RA.	No dose adjustments needed	FPV (without RTV): ↓ APV Use with caution; consider boosting with RTV	No data; possible ↓ IDV	No dose adjustments needed	No data	No data	No data
Proton pump inhibitors	Sig. ↓ ATV exposure when co-administered, especially without RTV. Do not use PPI if ATV is unboosted or in tx-experienced. Do not exceed PPI dose equiv. of 20 mg omeprazole, and separate by 12 h.	No dose adjustments needed	No dose adjustments needed (+/− RTV)	↓ IDV Avoid combination if possible or boost with RTV	No dose adjustments needed	↓ NFV Avoid combination	↑ SQV Use with caution and monitor for SQV-related toxicities	↓ omeprazole Omeprazole dose may need to be increased; titrate to effect

ANTICOAGULANTS								
Warfarin	Possible ↑ warfarin	↓ warfarin	Possible ↑ or ↓ warfarin	No data; however, warfarin may be affected by IDV (±RTV).	Possible ↑ or ↓ warfarin	Possible ↑ or ↓ warfarin	No data; however, possible ↑ or ↓ warfarin	Possible ↑ or ↓ warfarin
	Monitor INR closely when starting or stopping ATV (+/– RTV)	Monitor INR closely when starting or stopping DRV/RTV	Monitor INR closely when starting or stopping FPV (±RTV)	Monitor INR closely when starting or stopping therapy.	Monitor INR closely when starting or stopping LPV/RTV	Monitor INR closely when starting or stopping NFV	Monitor INR closely when starting or stopping therapy.	Monitor INR closely when starting or stopping TPV/RTV
ANTICONVULSANTS								
Carbamazepine	Possible ↑ carbamazepine & ↓ ATV, especially without RTV Avoid combination if possible	No dose adjustments needed; monitor carbamazepine concentrations and titrate dose based on response	Possible ↓ FPV without RTV Avoid combination if unable to boost with RTV	Possible ↓ IDV Avoid combination if unable to boost with RTV	Possible ↓ LPV Avoid combination if possible. Do not use LPV/RTV once daily.	Possible ↓ NFV Avoid combination if possible	Possible ↓ SQV Avoid combination if possible	Possible ↓ TPV Avoid combination if possible
Phenobarbital	Possible ↓ ATV, especially without RTV	Possible ↓ DRV and ↓ phenobarbital	Possible ↓ FPV, especially without RTV	Possible ↓ IDV, especially without RTV	Possible ↓ LPV	Possible ↓ NFV	Possible ↓ SQV	Possible ↓ TPV
	Avoid combination if possible	Avoid combination if possible, or monitor levels and titrate based on response	Avoid combination if possible.	Avoid combination if possible.	Avoid combination if possible. Do not use LPV/RTV once daily.	Avoid combination if possible	Avoid combination if possible	Avoid combination if possible
Phenytoin	Possible ↓ ATV, especially without RTV	Possible ↓ phenytoin	↓ Phenytoin with FPV/RTV	Possible ↓ IDV, especially without RTV	↓ LPV and ↓ phenytoin	↓ phenytoin	Possible ↓ SQV	Possible ↓ TPV
	Avoid combination if possible	Monitor levels and titrate based on response	Monitor levels and adjust dose accordingly. No dose adjustment for FPV/RTV. No data for FPV (without RTV).	Avoid combination if possible.	Avoid combination if possible. Do not use LPV/RTV once daily.	Monitor levels of phenytoin and adjust dose accordingly	Avoid combination if possible	Avoid combination if possible

(continued)

Table 13.4 (continued)

Drug affected	Atazanavir (ATV) (± Ritonavir)	Darunavir (DRV) + Ritonavir (RTV)	Fosamprenavir (FPV) (± Ritonavir)	Indinavir (IDV) (± Ritonavir)	Lopinavir (LPV)/ Ritonavir (RTV)	Nelfinavir (NFV)	Saquinavir (SQV) + Ritonavir (RTV)	Tipranavir (TPV) + Ritonavir (RTV)
ANTIDEPRESSANTS								
Bupropion	No data	No data	No data	No data	↓ bupropion and ↓OH-bupropion (active metabolite) Titrate bupropion dose based on response; monitor closely for efficacy	No data	No data	↓ bupropion Titrate bupropion dose based on response; monitor closely for efficacy
Paroxetine	No data	↓ paroxetine Dose titrate carefully based on response	↓ paroxetine Dose titrate carefully based on response	No data	No data	No data	No data	No data
Sertraline	No data	↓ sertraline Dose titrate carefully based on response.	No data; possible ↓ sertraline Dose titrate carefully based on response	No data	No data	No data	No data	No data
Trazodone	Possible ↑ trazodone; monitor closely and consider lower dose of trazodone.	Possible ↑ trazodone; monitor closely and consider lower dose of trazodone.	Possible ↑ trazodone (±RTV); monitor closely and consider lower dose of trazodone.	Possible ↑ trazodone (±RTV); monitor closely and consider lower dose of trazodone.	Possible ↑ trazodone; monitor closely and consider lower dose of trazodone.	Possible ↑ trazodone; monitor closely and consider lower dose of trazodone.	Possible ↑ trazodone; monitor closely and consider lower dose of trazodone.	Possible ↑ trazodone; monitor closely and consider lower dose of trazodone.
ANTIFUNGALS								
Fluconazole	No dose adjustments needed	No data; no significant interaction is expected	No data; no significant interaction is expected	No dose adjustments needed	No dose adjustments needed	No dose adjustments needed	No dose adjustments needed	↑ tipranavir Dose adjustments not needed; however, fluconazole doses greater than 200 mg/day not recommended

Itraconazole	No dose adjustments needed in combination with ATV; do not exceed itraconazole doses of 200 mg/day with ATV/RTV	No dose adjustments needed for DRV/RTV; do not exceed itraconazole dose of 200 mg/day	Possible ↑ itraconazole Use with caution with FPV (without RTV) and do not exceed 200 mg/day with FPV/RTV	↑ IDV Reduce IDV dose to 600 mg Q8h	Possible ↑ itraconazole Use with caution and do not exceed 200 mg/day with FPV/RTV	No dose adjustments needed	↑ itraconazole Use with caution and do not exceed 200 mg/day of ketoconazole	Possible ↑ itraconazole Use with caution and do not exceed 200 mg/day of ketoconazole
Ketoconazole	No dose adjustments needed in combination with ATV; use ketoconazole with caution and avoid doses >200 mg/day with ATV/RTV	No dose adjustments needed for DRV/RTV; do not exceed ketoconazole dose of 200 mg/day	↑ ketoconazole with FPV/RTV Use with caution with FPV (without RTV) and do not exceed 200 mg/day with FPV/RTV	↑ indinavir Reduce IDV dose to 600 mg Q8h	↑ ketoconazole Use with caution and do not exceed 200 mg/day of ketoconazole	No dose adjustments needed	↑ ketoconazole Use with caution and do not exceed 200 mg/day of ketoconazole	Possible ↑ ketoconazole Use with caution and do not exceed 200 mg/day of ketoconazole
Posaconazole	↑ ATV Monitor for ATV-related toxicities	No data	↓ APV (without RTV) and ↓ posaconazole Avoid coadministration if possible	No dose adjustments needed	No data	No data	No data	No data
Voriconazole	No data for voriconazole + ATV (without RTV) Avoid with ATV/RTV unless benefit outweighs risk due to expected ↓ voriconazole	↓ voriconazole with low-dose RTV Coadministration should be avoided unless benefit outweighs risk	No data for FPV (without RTV) ↓ voriconazole with low-dose RTV Coadministration should be avoided unless benefit outweighs risk	No dose adjustments needed with IDV (without RTV) ↓ voriconazole with low-dose RTV Coadministration should be avoided unless benefit outweighs risk	↓ voriconazole with low-dose RTV Coadministration should be avoided unless benefit outweighs risk	No data	↓ voriconazole with low-dose RTV Coadministration should be avoided unless benefit outweighs risk	↓ voriconazole with low-dose RTV Coadministration should be avoided unless benefit outweighs risk

(continued)

Table 13.4 (continued)

Drug affected	Atazanavir (ATV) (± Ritonavir)	Darunavir (DRV) + Ritonavir (RTV)	Fosamprenavir (FPV) (± Ritonavir)	Indinavir (IDV) (± Ritonavir)	Lopinavir (LPV)/ Ritonavir (RTV)	Nelfinavir (NFV)	Saquinavir (SQV) + Ritonavir (RTV)	Tipranavir (TPV) + Ritonavir (RTV)
Anti-mycobacterials								
Clarithromycin (clari)	↑ clarithromycin	No dose adjustments needed in patients with normal renal function. If CrCl 30–60 mL/min, ↓ clari dose by 50%. If CrCl < 30 mL/min, ↓ clari dose by 75%	No dose adjustments needed with FPV (without RTV). No data with FPV/RTV, but ↑ clarithromycin expected. If CrCl 30–60 mL/min, ↓ clari dose by 50%. If CrCl < 30 mL/min, ↓ clari dose by 75%	↑ clarithromycin with IDV (+/− RTV)	Possible ↑ clarithromycin	No data	Possible ↑ clarithromycin	Possible ↑ clarithromycin and ↑ TPV
	Decrease clarithromycin dose by 50% with ATV (± RTV) or consider alternative treatment			No dose adjustment in patients with normal renal function. If CrCl 30–60 mL/min, ↓ clari dose by 50%. If CrCl < 30 mL/min, ↓ clari dose by 75%	No dose adjustments needed in patients with normal renal function. If CrCl 30–60 mL/min, ↓ clari dose by 50%. If CrCl < 30 mL/min, ↓ clari dose by 75%		No dose adjustments needed in patients with normal renal function. If CrCl 30–60 mL/min, ↓ clari dose by 50%. If CrCl < 30 mL/min, ↓ clari dose by 75%	No dose adjustments needed in patients with normal renal function. If CrCl 30–60 mL/min, ↓ clari dose by 50%. If CrCl < 30 mL/min, ↓ clari dose by 75%
Rifampin	Possible significant ↓ ATV	Possible significant ↓ DRV	Significant ↓ APV	Significant ↓ IDV	Significant ↓ LPV	Significant ↓ NFV	Significant ↓ SQV	Significant ↓ TPV
	Do not coadminister	Do not coadminister	Do not coadminister	Do not coadminister	Do not coadminister	Do not coadminister	Do not coadminister	Do not coadminister
Rifabutin[b]	↑ rifabutin	↑ rifabutin	↑ Rifabutin	↓ IDV, ↓ Rifabutin	↑ rifabutin	↑ rifabutin	↑ rifabutin	↑ rifabutin
	Decrease rifabutin dose to 150 mg QOD or 3×/week	Decrease rifabutin dose to 150 mg QOD or 3×/week	Decrease rifabutin dose by at least 50% with FPV (without RTV) and decrease by 75% to 150 mg QOD or 3×/week with FPV/RTV	Decrease Rifabutin dose to 150 mg QOD or 3×/week Increase IDV dose to 1,000 mg TID	Decrease rifabutin dose to 150 mg QOD or 3 times per week	Decrease rifabutin dose to one-half the usual dose	Decrease rifabutin dose to 150 mg QOD or 3 times per week	Decrease rifabutin dose to 150 mg QOD or 3 times per week
Benzodiazepines								
Midazolam	↑ midazolam with all PIs							
	Use single doses of IV midazolam with caution and close monitoring for prolonged sedation and possible respiratory depression.							
	Do not use oral midazolam.							

Cardiac drugs								
Antiarrhythmics (Amiodarone, bepridil, flecainide, systemic lidocaine, quinidine)	Possible ↑ antiarrhythmic exposure Use with caution with close monitoring.	Possible ↑ antiarrhythmic exposure Use with caution with close monitoring.	Possible ↑ antiarrhythmic exposure Use with caution with close monitoring.	Possible ↑ antiarrhythmic exposure Use with caution with close monitoring Amiodarone is contraindicated	Possible ↑ antiarrhythmic exposure Use with caution with close monitoring	Possible ↑ antiarrhythmic exposure Use with caution with close monitoring Amiodarone is contraindicated	Possible ↑ antiarrhythmic exposure Use with caution with close monitoring Amiodarone, flecainide, propafenone, bepridil, and quinidine are contraindicated	Possible ↑ antiarrhythmic exposure Use with caution with close monitoring Amiodarone, flecainide, propafenone, bepridil, and quinidine are contraindicated
Beta-Blockers (atenolol, metoprolol, etc.)	↑ atenolol Use with caution with increased monitoring; dose reduction of beta-blocker may be needed	Use with caution with increased monitoring; dose reduction of beta-blocker may be needed	Use with caution with increased monitoring; dose reduction of beta-blocker may be needed	Use with caution with increased monitoring; dose reduction of beta-blocker may be needed	Use with caution with increased monitoring; dose reduction of beta-blocker may be needed	Use with caution with increased monitoring; dose reduction of beta-blocker may be needed	Use with caution with increased monitoring; dose reduction of beta-blocker may be needed	Use with caution with increased monitoring; dose reduction of beta-blocker may be needed
Bosentan	Do not coadminister without RTV. For patients maintained on ATV/RTV for ≥10 days, start bosentan 62.5 mg QD or QOD based on tolerability; For patients maintained on bosentan, d/c bosentan ≥36 h before starting ATV/RTV and resume at 62.5 mg QD or QOD based on tolerability	For patients maintained on DRV/RTV for ≥10 days, start bosentan 62.5 mg QD or QOD based on tolerability; For patients maintained on bosentan, d/c bosentan ≥36 h before starting DRV/RTV and resume at 62.5 mg QD or QOD based on tolerability	For patients maintained on FPV (±RTV) for ≥10 days, start bosentan 62.5 mg QD or QOD based on tolerability; For patients maintained on bosentan, d/c bosentan ≥36 h before starting FPV (±RTV) and resume at 62.5 mg QD or QOD based on tolerability	For patients maintained on IDV or patients maintained on bosentan and starting IDV, start bosentan 62.5 mg QD or QOD based on tolerability	For patients maintained on LPV/RTV for ≥10 days, start bosentan 62.5 mg QD or QOD based on tolerability; For patients maintained on bosentan, d/c bosentan ≥36 h before starting LPV/RTV and resume at 62.5 mg QD or QOD based on tolerability	For patients maintained on NFV or patients maintained on bosentan and starting NFV, start bosentan 62.5 mg QD or QOD based on tolerability	For patients maintained on SQV/RTV for ≥10 days, start bosentan 62.5 mg QD or QOD based on tolerability; For patients maintained on bosentan, d/c bosentan ≥36 h before starting SQV/RTV and resume at 62.5 mg QD or QOD based on tolerability	For patients maintained on TPV/RTV for ≥10 days, start bosentan 62.5 mg QD or QOD based on tolerability; For patients maintained on bosentan, d/c bosentan ≥36 h before starting TPV/RTV and resume at 62.5 mg QD or QOD based on tolerability

(continued)

Table 13.4 (continued)

Drug affected	Atazanavir (ATV) (± Ritonavir)	Darunavir (DRV)+ Ritonavir (RTV)	Fosamprenavir (FPV) (± Ritonavir)	Indinavir (IDV) (± Ritonavir)	Lopinavir (LPV)/ Ritonavir (RTV)	Nelfinavir (NFV)	Saquinavir (SQV)+ Ritonavir (RTV)	Tipranavir (TPV)+ Ritonavir (RTV)
Digoxin	No data; possible ↑ digoxin	↑ digoxin	No data; possible ↑ digoxin with FPV/ RTV.	No data; possible ↑ digoxin	No data; possible ↑ digoxin	No data; possible ↑ digoxin	↑ digoxin	↓ digoxin
	Monitor levels closely and adjust dose accordingly	Monitor levels closely and adjust dose accordingly	Monitor levels closely and adjust dose accordingly	Monitor levels closely and adjust dose accordingly	Monitor levels closely and adjust dose accordingly	Monitor levels closely and adjust dose accordingly	Monitor levels closely and adjust dose accordingly	Monitor levels closely and adjust dose accordingly
Dihydropyridine CCBs (e.g., felodipine, nifedipine, nicardipine)	Use with caution due to possible ↑ CCB exposure	Use with caution due to possible ↑ CCB exposure	Use with caution due to possible ↑ CCB exposure	Use with caution due to possible ↑ CCB exposure	Use with caution due to possible ↑ CCB exposure	Use with caution due to possible ↑ CCB exposure	Use with caution due to possible ↑ CCB exposure	Use with caution due to possible ↑ CCB exposure
Diltiazem	Consider 50% dose reduction of diltiazem	Use with caution due to possible ↑ diltiazem exposure	Use with caution due to possible ↑ diltiazem exposure	↑ diltiazem with IDV/RTV Use low starting dose of diltiazem and titrate with caution	Use with caution due to possible ↑ diltiazem exposure	Use with caution due to possible ↑ diltiazem exposure	Use with caution due to possible ↑ diltiazem exposure	Use with caution due to possible ↑ diltiazem exposure
Hormonal contraceptives								
Combined Oral Contraceptives	COC should contain ≥35 mcg of ethinyl estradiol with ATV/RTV; COC should contain ≤30 mcg of ethinyl estradiol with ATV (without RTV)	↓ ethinyl estradiol	↓ ethinyl estradiol	↑ ethinyl estradiol	↓ ethinyl estradiol	↓ ethinyl estradiol	↓ ethinyl estradiol	↓ ethinyl estradiol
	Long-term effects of ↑ progesterone exposure are unknown.	↓ norethindrone Alternative methods of nonhormonal contraception are recommended	Alternative methods of nonhormonal contraception are recommended	↑ norethindrone No dose adjustments needed	↓ norethindrone Alternative methods of nonhormonal contraception are recommended	↓ norethindrone Alternative methods of nonhormonal contraception are recommended	Alternative methods of nonhormonal contraception are recommended	Alternative methods of nonhormonal contraception are recommended

HMG-CoA reductase inhibitors								
Atorvastatin	Caution when exceeding doses >20 mg/day atorvastatin with ATV/RTV. Use with caution and low starting dose with ATV.	Caution when exceeding doses of 20 mg/day of atorvastatin	Caution when exceeding atorvastatin doses >20 mg/day with FPV/RTV	Use with caution and low starting dose of atorvastatin	Caution when exceeding doses >20 mg/day atorvastatin	Use with caution and low starting dose	Caution when exceeding doses >20 mg/day atorvastatin	↑ atorvastatin; use with caution and low starting dose of atorvastatin
Pitavastatin	No data for ATV/RTV; no dosage adjustments needed with ATV	No data	No data	No data	No data; avoid this combination due to possible ↑ pitavastatin and increased risk of rhabdomyolitis	No data	No data	No data
Pravastatin	No data; significant interaction not expected	Use lowest starting dose of statin with careful monitoring	No data; significant interaction not expected	No data; significant interaction not expected	Coadminister with no dose adjustment	↓ pravastatin; titrate pravastatin doses	No data; significant interaction not expected	No data; significant interaction not expected
Rosuvastatin	Do not exceed 10 mg/day rosuvastatin with ATV/RTV; use with caution and low starting dose with ATV (without RTV)	Possible ↑ rosuvastatin Start with low dose and titrate cautiously	Possible ↑ rosuvastatin Start with low dose and titrate cautiously	Possible ↑ rosuvastatin Start with low dose and titrate cautiously	Do not exceed 10 mg/day rosuvastatin	Possible ↑ rosuvastatin Start with low dose and titrate cautiously	Possible ↑ rosuvastatin Start with low dose and titrate cautiously	↑ rosuvastatin and ↑ tipranavir Use lowest starting dose of statin with careful monitoring
Simvastatin	Do not coadminister.	Do not coadminister.	Do not coadminister.	Do not coadminister.	Do not coadminister.	Do not coadminister.	Do not coadminister.	Do not coadminister.
Lovastatin	Possible for serious adverse events due to large ↑ statin levels	Possible for serious adverse events due to large ↑ statin levels	Possible for serious adverse events due to large ↑ statin levels	Possible for serious adverse events due to large ↑ statin levels	Possible for serious adverse events due to large ↑ statin levels	Possible for serious adverse events due to large ↑ statin levels	Possible for serious adverse events due to large ↑ statin levels	Possible for serious adverse events due to large ↑ statin levels
Immunosupressants								
Cyclosporin	Possible ↑ immunosuppressants	Possible ↑ immunosuppressants	Possible ↑ immunosuppressants	Possible ↑ immunosuppressants	Possible ↑ immunosuppressants	Possible ↑ immunosuppressants	Possible ↑ immunosuppressants	Possible ↑ immunosuppressants

(continued)

Table 13.4 (continued)

Drug affected	Atazanavir (ATV) (± Ritonavir)	Darunavir (DRV) + Ritonavir (RTV)	Fosamprenavir (FPV) (± Ritonavir)	Indinavir (IDV) (± Ritonavir)	Lopinavir (LPV)/ Ritonavir (RTV)	Nelfinavir (NFV)	Saquinavir (SQV) + Ritonavir (RTV)	Tipranavir (TPV) + Ritonavir (RTV)
Sirolimus Tacrolimus	Therapeutic drug monitoring (TDM) is recommended	Therapeutic drug monitoring (TDM) is recommended	Therapeutic drug monitoring (TDM) is recommended	Therapeutic drug monitoring (TDM) is recommended	Therapeutic drug monitoring (TDM) is recommended	Therapeutic drug monitoring (TDM) is recommended	Therapeutic drug monitoring (TDM) is recommended	Therapeutic drug monitoring (TDM) is recommended
Opioid replacement								
Buprenorphine	Consider dose reduction of buprenorphine with ATV/RTV based on symptoms of sedation and cognitive effects. Avoid with ATV (without RTV) due to possible ↓ ATV.	No dose adjustments needed; however, clinical monitoring is recommend as buprenorphine dose may need adjustment in some patients	No data	No data	No dose adjustment required	No data	No data	No dose adjustments needed
Methadone	No dose adjustments needed with ATV (without RTV). No data for ATV/RTV; monitor closely as methadone dose may need adjustment in some patients	No dose adjustment required; however, clinical monitoring is recommend as methadone dose may need adjustment in some patients	Slight ↓ R-methadone (active form) No dose adjustments needed, but monitor for symptoms of withdrawal and adjust dose accordingly	No dose adjustments needed	↓ methadone Monitor for symptoms of withdrawal and adjust dose accordingly	↓ methadone Monitor for symptoms of withdrawal and adjust dose accordingly	↓ methadone Monitor for symptoms of withdrawal and adjust dose accordingly	↓ methadone Monitor for symptoms of withdrawal and adjust dose accordingly
Phosphodiesterase 5 (pde5) inhibitors								
Sildenafil	Pulmonary arterial hypertension (PAH): Contraindicated	PAH: Contraindicated	PAH: Contraindicated	PAH: Contraindicated	PAH: Contraindicated	PAH: Contraindicated	PAH: Contraindicated	PAH: Contraindicated
	Erectile dysfunction (ED): Use with caution and do not exceed 25 mg in 48 h	ED: Use with caution and do not exceed 25 mg in 48 h	ED: Use with caution and do not exceed 25 mg in 48 h	ED: Use with caution and do not exceed 25 mg in 48 h	ED: Use with caution and do not exceed 25 mg in 48 h	ED: Use with caution and do not exceed 25 mg in 48 h	ED: Use with caution and do not exceed 25 mg in 48 h	ED: Use with caution and do not exceed 25 mg in 48 h

Tadalafil	PAHL: Tadalafil 20 mg QD; increase to 40 mg QD based on tolerability. If maintained on tadalafil and starting ATV (±RTV), stop tadalafil ≥24 h before starting ATV (±RTV); after at least 1-week later, resume at 20 mg QD. Increase to 40 mg QD based on tolerability.	PAHL: Tadalafil 20 mg QD; increase to 40 mg QD based on tolerability. If maintained on tadalafil and starting DRV/RTV, stop tadalafil ≥24 h before starting DRVRTV; after at least 1-week later, resume at 20 mg QD. Increase to 40 mg QD based on tolerability.	PAHL: Tadalafil 20 mg QD; increase to 40 mg QD based on tolerability. If maintained on tadalafil and starting FPV (±RTV), stop tadalafil ≥24 h before starting FPV (±RTV); after at least 1-week later, resume at 20 mg QD. Increase to 40 mg QD based on tolerability.	PAH: Tadalafil 20 mg QD; increase to 40 mg QD based on tolerability.	PAH: Tadalafil 20 mg QD; increase to 40 mg QD based on tolerability. If maintained on tadalafil and starting LPV/RTV, stop tadalafil ≥24 h before starting LPV/RTV; resume ≥1-week later at lower tadalafil dose	PAH: Tadalafil 20 mg QD; increase to 40 mg QD based on tolerability.	PAH: Tadalafil 20 mg QD; increase to 40 mg QD based on tolerability. If maintained on tadalafil and starting SQV/RTV, stop tadalafil ≥24 h before starting SQV/RTV; resume ≥1-week later at lower tadalafil dose	PAH: Tadalafil 20 mg QD; increase to 40 mg QD based on tolerability. If maintained on tadalafil and starting TPV/RTV, stop tadalafil ≥24 h before starting TPV/RTV; resume ≥1-week later at lower tadalafil dose
	ED: Do not exceed 10 mg in a 72-h period	ED: Do not exceed 10 in a 72-h period	ED: Do not exceed a maximum single dose of tadalafil 10 mg once every 72 h	ED: Do not exceed a maximum single dose of tadalafil 10 mg once every 72 h	ED: Do not exceed a maximum single dose of tadalafil 10 mg once every 72 h	ED: Do not exceed a maximum single dose of tadalafil 10 mg once every 72 h	ED: Do not exceed a maximum single dose of tadalafil 10 mg once every 72 h	ED: Do not exceed a maximum single dose of tadalafil 10 mg once every 72 h
Vardenafil	Possible ↑ vardenafil	Possible ↑ vardenafil	Possible ↑ vardenafil	↑ vardenafil	Possible ↑ vardenafil	Possible ↑ vardenafil	Possible ↑ vardenafil	Possible ↑ vardenafil
	Do not exceed 2.5 mg in a 24 h period with ATV (without RTV). Do not exceed 2.5 mg in a 72-h period with ATV/RTV	Do not exceed 2.5 mg in a 72-h period	Do not exceed 2.5 mg in a 24-h period with FPV (without RTV). Do not exceed 2.5 mg in a 72-h period with FPV/RTV	Do not exceed 2.5 mg in a 24-h period	Do not exceed 2.5 mg in a 72-h period	Do not exceed 2.5 mg in a 24-h period	Do not exceed 2.5 mg in a 72-h period	Do not exceed 2.5 mg in a 72-h period

(continued)

Table 13.4 (continued)

Drug affected	Atazanavir (ATV) (± Ritonavir)	Darunavir (DRV) + Ritonavir (RTV)	Fosamprenavir (FPV) (± Ritonavir)	Indinavir (IDV) (± Ritonavir)	Lopinavir (LPV)/ Ritonavir (RTV)	Nelfinavir (NFV)	Saquinavir (SQV) + Ritonavir (RTV)	Tipranavir (TPV) + Ritonavir (RTV)
Steroids								
Inhaled/nasal fluticasone	Possible ↑ systemic fluticasone with ATV/RTV; no data with ATV (without RTV)	Possible ↑ systemic fluticasone	Possible ↑ systemic fluticasone with FPV/RTV	Possible ↑ systemic fluticasone with IDV/RTV	Possible ↑ systemic fluticasone	Possible ↑ systemic fluticasone	Possible ↑ systemic fluticasone	Possible ↑ systemic fluticasone
	Avoid if possible.	Avoid if possible	Avoid if possible. Use with caution with FPV (without RTV)	Avoid if possible. Use with caution with IDV (without RTV)	Avoid if possible	Avoid if possible	Avoid if possible	Avoid if possible
Other agents								
Salmeterol	Possible ↑ salmeterol	Possible ↑ salmeterol	Possible ↑ salmeterol	Possible ↑ salmeterol	Possible ↑ salmeterol	Possible ↑ salmeterol	Possible ↑ salmeterol	Possible ↑ salmeterol
	Avoid combination due to risk of QT prolongation associated with salmeterol	Avoid combination due to risk of QT prolongation associated with salmeterol	Avoid combination due to risk of QT prolongation associated with salmeterol	Avoid combination due to risk of QT prolongation associated with salmeterol	Avoid combination due to risk of QT prolongation associated with salmeterol	Avoid combination due to risk of QT prolongation associated with salmeterol	Avoid combination due to risk of QT prolongation associated with salmeterol	Avoid combination due to risk of QT prolongation associated with salmeterol
Colchicine	All RTV-boosted PIs and unboosted ATV and unboosted IDV:							
	Treatment of gout flares: 0.6 mg colchicine × 1, then 0.3 mg 1-h later.							
	Prophylaxis of gout flares: reduce regimen from 0.6 mg BID to 0.3 mg QD, or from 0.6 mg QD to 0.3 mg QOD.							
	Treatment of familial Mediterranean fever (FMF): Max dose 0.6 mg/day.							
	Do not give combination in patients with impaired renal or hepatic function.							
	FPV (without RTV):							
	Treatment of gout flares: 1.2 mg colchicine × 1; repeat dose no earlier than 3 days.							
	Prophylaxis of gout flares: reduce regimen from 0.6 to 0.3 mg BID or 0.6 mg QD, or reduce 0.6–0.3 mg QD.							
	Treatment of FMF: Max dose 1.2 mg/day.							

[a]Increases or decreases in concentrations refer to AUC unless otherwise stated

[b]Rifabutin 150 mg QOD or 3×/week is recommended based on results of DDI studies conducted in healthy volunteers. Acquired rifamycin resistance has been reported in HIV patients on boosted PI regimens treated with this dose. Therapeutic drug monitoring (TDM) of rifabutin is recommended

Table 13.5 Interactions between PIs [43, 57, 65, 66, 79–89]

Drug affected	Atazanavir	Fosamprenavir	Indinavir	Lopinavir/Ritonavir	Nelfinavir	Ritonavir	Saquinavir	Tipranavir
Darunavir (DRV)	Dose: ATV 300 mg QD+DRV 600 mg BID+RTV 100 mg BID	No data	Dose: Not established.	Dose: Not established.	No data	Dose: *Treatment-naïve:*	Dose: Not established.	Combining a protease inhibitor, other than RTV, with TPV/RTV is not recommended
	↔ DRV		↑ DRV	↓ DRV		DRV 800 mg QD+RTV 100 mg QD		
	↔ ATV			↔ LPV		*Treatment experienced:* DRV 600 mg BID+RTV 100 mg BID		
						↑ DRV		
Fosamprenavir (FPV)	Dose: Not established	•	See FPV+IDV cell	Appropriate doses of the combination not established. An increased rate of adverse events has been observed with this combination	See FPV+NFV cell.	Dose: *Treatment-naïve:* FPV 1,400 mg BID or FPV 1,400 mg QD+RTV 200 mg QD or FPV 1,400 mg QD+RTV 100 mg QD or FPV 700 mg BID+RTV 100 mg BID	Dose: Not established	Combining a protease inhibitor, other than RTV, with TPV/RTV is not recommended
	↔ FPV			↓ FPV		*Treatment-experienced:* FPV 700 mg BID+RTV 100 mg BID		
	↓ ATV			↓LPV		↑ FPV		

(continued)

Table 13.5 (continued)

Drug affected	Atazanavir	Fosamprenavir	Indinavir	Lopinavir/Ritonavir	Nelfinavir	Ritonavir	Saquinavir	Tipranavir
Indinavir (IDV)	**Should not be coadministered because of potential for additive hyperbilirubine-mia**	Dose: Not established	•	Dose: IDV 600 mg BID + LPV/RTV 400/100 mg BID	Dose: Limited data for IDV 1,200 mg BID + NFV 1,250 mg BID with low fat snack and on an empty stomach	Dose: Not established. Limited data on the following regimens: IDV 800 mg BID + RTV 100–200 mg BID	Dose: Not established	Combining a protease inhibitor, other than RTV, with TPV/RTV is not recommended
				↔ LPV	↑ IDV	Caution renal events may be increased with higher IDV exposures	INVIRASE/RTV, interaction has not been evaluated.	
				↑ IDV C_{min}; ↓IDV AUC	↑ NFV	↑ IDV	SQV effect on IDV is not well established	
Lopinavir/ **Ritonavir (LPV/RTV)**	Dose: ATV 300 mg QD + LPV/RTV 400/100 mg BID	See LPV/r + FPV cell	See LPV/r + FPV cell	•	See LPV/RTV + NFV cell.	Lopinavir is coformu-lated with ritonavir as Kaletra.	See LPV/RTV + SQV cell.	Combining a protease inhibitor, other than RTV, with TPV/RTV is not recommended
Nelfinavir (NFV)	No data	Dose: Not established.	See NFV + IDV cell.	Dose: Do not administer LPV/RTV once daily with nelfinavir. Increase LPV/RTV dose to 500/125 mg BID and decrease NFV dose to 1,000 mg BID, when coadministered	•	See NFV + RTV cell.	See NFV + SQV cell.	Combining a protease inhibitor, other than RTV, with TPV/RTV is not recommended
				↓ LPV/RTV				
				↑ NFV C_{min}				

Ritonavir (RTV)	Dose: ATV 300 mg + RTV 100 mg QD ↑ ATV	See RTV + FPV cell	See RTV + FPV cell	Lopinavir is coformulated with ritonavir as Kaletra.	Dose: Not established	•	Dose:SQV 1,000 mg BID + RTV 100 mg BID	Dose:TPV 500 mg + RTV 200 mg BID
Saquinavir (SQV)	Dose: Not established	Dose: Not established	See SQV + IDV cell	Dose: SQV 1,000 mg BID + LPVRTV 400/100 mg BID	Dose: SQV 1,200 mg BID + NFV 1,250 mg BID results in adequate plasma drug concentrations for both protease inhibitors	See SQV + RTV cell.	•	Combining a protease inhibitor, other than RTV, with TPV/RTV is not recommended
	ATV/SQV resulted in inadequate efficacy compared to ATV/RTV and LPV/RTV in experienced subjects ↑ ATV ↑ SQV			↑ SQV	INVIRASE/RTV interaction has not been evaluated			
Tipranavir/ Ritonavir (TPV/RTV)	Combining a protease inhibitor, other than RTV, with TPV/RTV is not recommended	See TPV/ RTV + FPV cell	See TPV/ RTV + IDV cell	See TPV/RTV + IDV cell	See TPV/ RTV + LPV/RTV cell	See TPV/RTV + RTV cell	See TPV/ RTV + SQV cell	•

13.6.2 Contraindications

Because of their effects on CYP3A4, a number of drugs are contraindicated with protease inhibitors due to the potential for serious or life-threatening toxicity (Table 13.6). Use with cisapride, pimozide, bepridil and some antiarrhythmics should be avoided due to the potential for cardiac arrhythmia [43]. The use of protease inhibitors with ergot derivatives can lead to serious peripheral ischemia because of the potent vasoconstricting effects of this drug class [90]. As most protease inhibitors cause increases in triglyceride and cholesterol, many HIV-infected individuals require lipid-lowering agents.

Simvastatin and lovastatin are contraindicated with protease inhibitors due to the risk of myopathy, including rhabdomyolysis. Some interactions between protease inhibitors and statins are mediated through transport proteins such as rosuvastatin, an organic anion-transporting polypeptide (OATP) 1B1 substrate, in which exposure is increased 2–3-fold with lopinavir/ritonavir and atazanavir/ritonavir [46]. Only modest increases are observed with ritonavir-boosted tipranavir and fosamprenavir. Pitavastatin is another OATP1B1 substrate which has a narrow therapeutic index and its use is not recommended with protease inhibitors until exposure data are available. Pravastatin is not metabolized primarily by CYP3A4, however darunavir increases pravastatin AUC by 81% demonstrating protease inhibitors have differential effects on this statin [66]. Atorvastatin is an option for HIV-infected subjects if low doses are used and patients are closely monitored.

Over sedation is a potential complication when protease inhibitors are administered with certain benzodiazepines (midazolam, triazolam), particularly when orally administered. However, many clinicians will give one to two doses of IV midazolam prior to a surgical procedure as long as the patient is being closely monitored. The long acting beta agonist, salmeterol, should also be avoided with the boosted protease inhibitors, due to the risk of cardiovascular adverse events secondary to elevated salmeterol concentrations.

Other contraindications are due to the effect of the concomitant drug on plasma protease inhibitor concentrations. Rifampin and products containing St. John's wort markedly reduce protease inhibitor exposure and should be avoided [91, 92]. While not contraindicated, many anti-epilepsy drugs (phenytoin, phenobarbital, carbamazepine) could also reduce protease inhibitor concentrations and require close monitoring [93].

13.6.3 Drug Interactions to Improve Bioavailability and Dosing

Protease inhibitors demonstrate the best example of how a drug interaction can be used for patient benefit. The addition of low-dose ritonavir to increase the exposure of another protease inhibitor has been used since the late 1990s [94]. "Boosting" with ritonavir allows for other protease inhibitors to be used once daily and with lower doses. In the case of lopinavir, tipranavir and darunavir, the protease inhibitor alone cannot be prescribed without co-administration of ritonavir because they would not achieve effective concentrations at the doses approved for use. Atazanavir

Table 13.6 Drugs that are contraindicated or not recommended for use with protease inhibitors and NNRTIs [43, 57, 65, 66, 79–83, 88][a,b]

Drug class/drug name	Drugs that should not be coadministered	Clinical comment
Alpha 1-adrenoreceptor antagonist: Alfuzosin	Atazanavir (+/– ritonavir), Darunavir/ritonavir, Fosamprenavir (+/– ritonavir), Indinavir Lopinavir/ritonavir, Nelfinavir, Saquinavir/ritonavir Tipranavir/ritonavir	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as hypotension
Antiarrhythmics: Amiodarone	Indinavir	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmia's secondary to increases in plasma concentrations of antiarrhythmics
Antiarrhythmics: Amiodarone, quinidine	Nelfinavir Saquinavir/ritonavir Tipranavir/ritonavir	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmia's secondary to increases in plasma concentrations of antiarrhythmics
Antiarrhythmics: Flecainide, propafenone	Fosamprenavir (+/–ritonavir) Saquinavir/ritonavir Tipranavir/ritonavir	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmia's secondary to increases in plasma concentrations of antiarrhythmics
Anticonvulsants: Carbamazepine Phenobarbital	Etravirine	May lead to loss of virologic response and possible resistance to each agent or to the class
Phenytoin	Lopinavir/ritonavir	Do not administer lopinavir/ritonavir once daily with carbamazepine, phenobarbital or phenytoin
Ketoconazole	Nevirapine	May lead to loss of antifungal response
Antimycobacterials: Rifabutin	Etravirine if used with ritonavir boosted PI	May lead to loss of virologic response and possible resistance to each agent or to the class
Antimycobacterials: Rifampin	Atazanavir (+/– ritonavir), Darunavir/ritonavir, Fosamprenavir (+/– ritonavir), Indinavir, Lopinavir/ritonavir, Nelfinavir, Saquinavir/ritonavir Tipranavir/ritonavir Efavirenz, Etravirine, Nevirapine	May lead to loss of virologic response and possible resistance to each agent or to the class
Anti-cancer: Irinotecan	Atazanavir	ATV inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities

(continued)

Table 13.6 (continued)

Drug class/drug name	Drugs that should not be coadministered	Clinical comment
Calcium channel blocker: Bepridil	Efavirenz	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias
Corticosteroid: Inhaled/Nasal Fluticasone	Atazanavir/ritonavir, Darunavir/ritonavir, Fosamprenavir/ritonavir, Lopinavir/ritonavir, Saquinavir/ritonavir, Tipranavir/ritonavir	Coadministration with any boosted PI regimen or ritonavir 600 mg bid is not recommended unless potential benefit outweighs risk of systemic corticosteroid adverse effects
Disulfiram Metronidazole	Lopinavir/ritonavir oral solution Tipranavir capsules	Lopinavir/ritonavir oral solution and tipranavir capsules contain alcohol which can produce disulfiram-like reactions when coadministered with disulfiram or other drugs which produce this reaction (e.g., metronidazole)
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Atazanavir (+/– ritonavir) Darunavir/ritonavir, Fosamprenavir (+/– ritonavir) Indinavir Lopinavir/ritonavir, Nelfinavir, Saquinavir/ritonavir, Tipranavir/ritonavir Efavirenz	CONTRAINDICATED due to potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues
Garlic capsules	Saquinavir	Coadministration is not recommended due to the potential for garlic capsules to induce the metabolism of saquinavir which may result in sub-therapeutic saquinavir concentrations
GI: Cisapride	Atazanavir (+/– ritonavir) Darunavir/ritonavir, Fosamprenavir (+/– ritonavir) Indinavir Lopinavir/ritonavir, Nelfinavir, Saquinavir/ritonavir, Tipranavir/ritonavir Efavirenz	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias

(continued)

Table 13.6 (continued)

Drug class/drug name	Drugs that should not be coadministered	Clinical comment
Herbal Products:	Atazanavir (+/− ritonavir)	May lead to loss of virologic response and possible resistance to each agent or to the class
St. John's wort (Hypericum perforatum)	Darunavir/ritonavir, Fosamprenavir (+/− ritonavir)	
	Indinavir	
	Lopinavir/ritonavir, Nelfinavir, Saquinavir/ritonavir, Tipranavir/ritonavir	
	Efavirenz, Etravirine, Nevirapine	
	Maraviroc	
HMG Co-Reductase Inhibitors:	Atazanavir (+/− ritonavir),	Potential for serious reactions such as risk of myopathy including rhabdomyolysis
Lovastatin, simvastatin Rosuvastatin	Darunavir/ritonavir, Fosamprenavir (+/− ritonavir),	
	Indinavir	
	Lopinavir/ritonavir, Nelfinavir, Saquinavir/ritonavir, Tipranavir/ritonavir	
Long-acting beta agonist:	Atazanavir (+/− ritonavir),	May result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia
Salmeterol	Darunavir/ritonavir, Fosamprenavir (+/− ritonavir)	
	Indinavir	
	Lopinavir/ritonavir, Nelfinavir, Saquinavir/ritonavir	
	Tipranavir/ritonavir	
Neuroleptic:	Atazanavir (+/− ritonavir)	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias
Pimozide	Darunavir/ritonavir, Fosamprenavir (+/− ritonavir),	
	Indinavir	
	Lopinavir/ritonavir, Nelfinavir, Saquinavir/ritonavir, Tipranavir/ritonavir	
	Efavirenz	
Opiods:	Atazanavir without ritonavir	My decrease atazanavir concentrations and may lead to loss of virologic response and possible resistance
Buprenorphine		

(continued)

Table 13.6 (continued)

Drug class/drug name	Drugs that should not be coadministered	Clinical comment
Oral contraceptives: Ethinyl estradiol/ norethindrone	Fosamprenavir (+/– ritonavir)	May lead to loss of virologic response and possible resistance to amprenavir. Increased risk of transaminase elevations. Alternative methods of non-hormonal contraception is recommended
	Atazanavir	Do not use oral contraceptive with more than 30 mcg of ethinyl estradiol
	Atazanavir/ritonavir	Do not use oral contraceptive containing less than 35 mcg of ethinyl estradiol
	Darunavir/ritonavir Indinavir Lopinavir/ritonavir, Nelfinavir, Saquinavir/ ritonavir, Tipranavir/ ritonavir	Alternative methods of non-hormonal contraception are recommended.
PDE-5 inhibitor: Sildenafil (Revatio) [for treatment of pulmonary arterial hypertension]	Atazanavir (+/– ritonavir)	Increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection and syncope)
	Darunavir/ritonavir, Fosamprenavir (+/– ritonavir) Indinavir Lopinavir/ritonavir, Nelfinavir, Saquinavir/ ritonavir, Tipranavir/ ritonavir	
Sedative/hypnotics: Midazolam (oral), triazolam	Atazanavir (+/– ritonavir)	CONTRAINDICATED due to potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression
	Darunavir/ritonavir, Fosamprenavir (+/– ritonavir) Indinavir Lopinavir/ritonavir, Nelfinavir, Saquinavir/ ritonavir, Tipranavir/ ritonavir Efavirenz Indinavir	Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation
Alprazolam		CONTRAINDICATED due to potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression

[a]Ritonavir given at approved dose for treatment of HIV-1 infection (600 mg bid) and delavirdine are not included in this table. Please refer to the FDA package inserts for information regarding delavirdine and ritonavir contraindications

[b]See Table 13.1 for full details on coadministration of NNRTIs and PIs, including those combinations which are contraindicated or not recommended

can be administered alone at a dose of 400 mg once daily or with ritonavir at a dose of 300 mg atazanavir/100 mg ritonavir once daily. The majority of clinical atazanavir use is in combination with ritonavir since it provides higher plasma levels. While early pharmacoenhancement efforts evaluated higher ritonavir doses, research over time have generally led to doses of 100 mg once or twice daily, except for tipranavir which is dosed at tipranavir 500 mg/ritonavir 200 mg twice daily. These low doses still provide significant increase in the exposure of the co-administered protease inhibitor and improve the tolerability of ritonavir [95].

13.6.4 Darunavir

Darunavir is the most recently-approved protease inhibitor and became available in 2006. It has become one of the most commonly used protease inhibitors due to its potency and resistance profile. After its introduction, darunavir was primarily used in treatment-experienced subjects but has now also been increasing prescribed in those who are treatment-naïve. Darunavir cannot be administered alone and requires co-administration with ritonavir to increase its exposure. Both darunavir and ritonavir are inhibitors of CYP3A4 and therefore darunavir therapy shares the drug interactions, precautions, and contraindications of all protease inhibitors as well as those specific only to ritonavir [84]. Darunavir also induces CYP3A4 but the net result of the mixed inhibition/induction is generally inhibition.

While not widely used, combinations of three protease inhibitors have been studied as part of NRTI-sparing regimens. Darunavir 1,200 mg/ritonavir 100 mg bid was studied with lopinavir 400 mg/ritonavir 100 in HIV-infected subjects. While lopinavir exposures were not significantly altered, darunavir AUC decreased by 38% [85]. A second study evaluated 1,200 mg bid of darunavir with lopinavir 533/ritonavir 133 mg twice daily. The darunavir AUC was similarly decreased by 41% [85]. Based on the decreased concentrations of darunavir, co-administration with lopinavir/ritonavir is not recommended. Darunavir was also studied at a dose of 400 mg darunavir/100 mg ritonavir with saquinavir 1,000 mg twice daily in healthy subjects. Darunavir AUC was decreased 26% and C_{min} was decreased 42% [86]. An increase in adverse events was also observed and this combination should be avoided. However a study with atazanavir 300 mg and darunavir/ritonavir (400 mg/100 mg) did not demonstrate significant changes in the AUC of either protease inhibitor, although atazanavir trough concentrations were increased by 52% [87].

13.7 Issues with Antiretroviral Drug Interactions

13.7.1 Timing of Co-Administered Drugs

The potential for drug interactions must be considered prior to and during antiretroviral therapy. In certain situations, the timing of the addition or removal of co-administered drugs can lead to significant safety issues due to drug interactions.

Ritonavir-boosted protease inhibitors cause large increases in the first few days of therapy compared to steady-state when the inductive of effects of ritonavir result in lower concentrations.

Clinicians should be aware of new recommendations for the use of bosentan, a treatment for pulmonary arterial hypertension, when combined with protease inhibitors [96]. If a patient is already receiving a protease inhibitor for at least 10 days, bosentan co-administration should be initiated at 62.5 mg once daily or every other day based upon individual tolerability. However, the recommendation is different for subjects already on bosentan but needing to add a protease inhibitor. In this situation, the bosentan needs to be discontinued for at least 36 h prior to initiation of protease inhibitor. After at least 10 days following the initiation of the protease inhibitor, the patient may resume the bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Although indinavir and nelfinavir are no longer commonly used, patients on these agents need only to start at or adjust bosentan to 62.5 mg once daily or every other day based upon individual tolerability.

A similar situation exists for tadalafil, another agent for the treatment of pulmonary arterial hypertension [96]. If already on a protease inhibitor for at least 1 week, tadalafil should be initiated at 20 mg once daily and increased to 40 mg once daily based upon individual tolerability. For a patient already on tadalafil and requiring protease inhibitor therapy, the tadalafil should be discontinued for at least 24 h prior to starting the protease inhibitor. After at least 1 week following initiation of the protease inhibitor, tadalafil can be resumed at 20 mg once daily and increased to 40 mg once daily based upon individual tolerability. Patients on indinavir or nelfinavir can start at or adjust tadalafil to 20 mg daily and increase to 40 mg once daily based upon individual tolerability.

13.7.2 Interactions with pH Altering Agents

HIV-infected patients commonly use proton pump inhibitors (PPIs), histamine-H2 receptor (H2)-antagonists and antacids in combination with their antiretrovirals. Certain antiretrovirals that do not interact with pH-altering drugs can have a significant advantage in terms of patient convenience. Most protease inhibitors do not require dose adjustments with acid reducers. However, the solubility of atazanavir is pH dependent and decreases with increasing pH. Thus, clinically significant interactions occur with antacids, PPIs and H2-antagonists.

Atazanavir should be administered 2 h before or 1 h after antacids [88]. With PPIs, there is a significant reduction in atazanavir exposure and a PPI should not be co-administered if atazanavir is unboosted with ritonavir or in treatment-experienced patients [88]. Subjects should avoid a PPI dose greater than the equivalent of 20 mg of omeprazole and they should separate the PPI and atazanavir by 12 h.

Atazanavir should also be given boosted with ritonavir in combination with H2-antagonists. The atazanavir/ritonavir should be given simultaneously with or >10 h after the H2-antagonist. For patients unable to tolerate ritonavir, the atazanavir

should be given at least 2 h before and at least 10 h after the H2-antagonist [88]. Table 13.4 outlines the doses of the H2-antagonist that are recommended with combination therapy depending on the patient population.

The solubility of raltegravir increases with increasing pH and omeprazole was demonstrated to increase AUC by approximately 3-fold in healthy subjects [97]. However, a population PK analysis from Phase 3 studies showed that HIV-infected patients receiving a PPI had only marginally higher plasma concentrations than patients without a PPI [97]. The concomitant use of a PPI with raltegravir in clinical studies did not lead to clinically significant adverse events compared to placebo and no dose adjustment is needed with proton pump inhibitors or H2 antagonists.

13.7.3 Interactions with Oral Contraceptives

Most oral contraceptives contain an estrogen and a progesterone component. Estrogens are generally metabolized via CYP3A4 while progesterones also are metabolized by glucuronidation. With darunavir, fosamprenavir, and lopinavir/ritonavir, there is a decrease in ethinyl estradiol concentrations that could lead to failure of the contraceptive, likely due to induction of CYP3A4 or glucuronidation [98]. Thus, alternative methods of nonhormonal contraception are recommended. The amount of ethinyl estradiol is important in combination use depending on how atazanavir is being used, due to differing effects of atazanavir and ritonavir on glucuronidation. The oral contraceptive should contain ≥35 mcg of ethinyl estradiol with atazanavir/ritonavir and ≤30 mcg with atazanavir alone [88]. Efavirenz and nevirapine also require use of alternative contraception methods due to decreases in the estrogen or progesterone components; however, no dose adjustments are required for etravirine, maraviroc and raltegravir. Efavirenz also decreases levonorgestrel exposure and the effectiveness of emergency postcoital contraception may be diminished [56].

13.8 Summary

The availability of potent treatment regimens for HIV-infected patients has led to dramatic increases in survival and quality of life. Great strides in drug development have resulted in therapies with once daily dosing, lack of significant food effects, and improved safety and tolerability. However, the management of drug interactions remains an area where clinicians must have an active role in patient care to avoid a loss of efficacy or increased adverse effects.

In no other disease area does the sheer volume of data exist for drug interactions than HIV disease. The standard of care for the HIV-infected patient commonly involves three or more antiretrovirals, but HIV-infected subjects also receive many other medications for co-morbidities such as pain, depression, gastrointestinal disorders, and opportunistic infections. Keeping up to date with this information can be overwhelming, but websites, reviews, and tables are available to clinicians.

Despite this challenge, our knowledge and understanding of drug interactions in HIV-infection have greatly increased. In vitro tests and probe cocktail studies can provide early knowledge on new drugs and reduce the number of clinical pharmacology studies that are required. Investigational drugs that inhibit CYP3A4, do not have antiviral activity, and have the potential for fewer side effects than ritonavir are being explored as potential pharmacoenhancers to replace ritonavir. Other investigational drugs with favorable drug interaction profiles are being evaluated in clinical studies. We have also gained a better understanding of mechanisms and the ability to predict the magnitude of drug interactions. These advances will lead to safer and more effective treatment regimens for HIV-infected patients.

References

1. Bermúdez PE, Domingo P, Gutierrez M, et al. Saquinavir/Ritonavir Monotherapy as a New Nucleoside-Sparing Maintenance Strategy in Long-Term Virologically Suppressed HIV-Infected Patients. Curr HIV Res. 2010 Jul 19. [Epub ahead of print].
2. JR Arribas, A Horban, J Gerstoft, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. AIDS, 2010;24:1057–9.
3. www.hiv-druginteractions.org.
4. www.clinicaloptions.com/hiv.
5. http://hivinsite,ucsf.edu.
6. www.medscape.com.
7. Iwamoto M, Wenning LA, Petry AS, et al. Minimal effects of ritonavir and efavirenz on the pharmacokinetics of raltegravir. Antimicrob Agents Chemother. 2008;52:4338–43.
8. Crownover P, Tressler R, Damle B. Ruxrungtham K, Boyd M, Bellibas SE, et al. Lack of interaction between enfuvirtide and ritonavir or ritonavir-boosted saquinavir in HIV-1-infected patients. J Clin Pharmacol. 2004;44:793–803.
9. Wire MB, Ballow C, Preston SL, et al. Pharmacokinetics and safety of GW433908 and ritonavir, with and without efavirenz, in healthy volunteers. AIDS 2004;18:897–907.
10. Wire MB, Ballow C, Preston SL, et al. An assessment of plasma amprenavir (APV) pharmacokinetics (PK) following administration of two GW433908 (908) and ritonavir (ritonavir) regimens in combination with efavirenz (EFV) in healthy adult subjects (APV10010). 9th Conference on Retroviruses and Opportunistic Infections; 2002 Feb 24–28; Seattle, Washington. Abstract #431.
11. DeJesus E, Piliero P, Summers K, et al. Evaluation of the pharmacokinetic drug interaction between fosamprenavir, fosamprenavir plus ritonavir and nevirapine in HIV-infected patients. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2004 Oct 30-Nov 2; Washington, D.C. Abstract A-447.
12. Rhame F, Long M, Acosta A. RAL-KAL: pharmacokinetics of coadministered raltegravir and lopinavir-ritonavir in healthy adults. 17th International AIDS Conference, August 3–8, 2008; Mexico City, Mexico. Abstract TuPE0075.
13. Brainard DM, Petry AS, Fang L, et al. Lack of a clinically important effect of rifabutin on raltegravir pharmacokinetics. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2009 September 12–15; San Francisco, California. Abstract A1-1296.
14. Selzentry (maraviroc) package insert. New York, NY: Pfizer Inc; November 2009.
15. Isentress (raltegravir) package insert. Whitehouse Station, NJ: Merck and Co., Inc; March 2010.
16. Orrell CJ, Geel J, Pitt JA, et al. Effect of fluconazole on nevirapine pharmacokinetics. XV International AIDS Conference; 2004 July 11–16; Bangkok, Thailand. Abstract TuPeB4606.

17. Robertson S, Maldarelli F, Natarajan V, et al. Efavirenz induces CYP450 2B6 activity as measured by bupropion hydroxylation in healthy subjects. J Acquir Immune Defic Syndr 2008;49:513–9.
18. Croxtall JD, Keam SJ. Raltegravir: a review of its use in the management of HIV infection in treatment-experienced patients. Drugs. 2009;69:1059–75.
19. Wenning LA, Hwang E, Nguyen B-Y, et al. Pharmacokinetic/pharmacodynamic analysis for raltegravir in Phase III studies in treatment experienced HIV-infected following 48 weeks of treatment. 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct 25–28, 2008. Washington, DC. Abstract H-4054.
20. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. Antimicrob Agents Chemother. 2009;53:2852–6.
21. Anderson MS, Kakuda TN, Hanley W, et al. Minimal pharmacokinetic interaction between the human immunodeficiency virus nonnucleoside reverse transcriptase inhibitor etravirine and the integrase inhibitor raltegravir in healthy subjects. Antimicrob Agents Chemother. 2008;52:4228–32.
22. Menard A, et al. Etravirine-raltegravir, a marked interaction in HIV-1-infected patients: about four cases. AIDS. 2009;23:869–871.
23. Hanley WD, Wenning LA, Moreau A, et al. Effect of tipranavir-ritonavir on pharmacokinetics of raltegravir. Antimicrob Agents Chemother. 2009;53:2752–5.
24. Iwamoto M, Wenning LA, Mistry GC, et al. Atazanavir modestly increases plasma levels of raltegravir in healthy subjects. Clin Infect Dis. 2008;47:137–40.
25. Fabbiani M, Di Giambenedetto S, Ragazzoni E, et al. Unexpected drug interaction between darunavir and raltegravir. 12th European AIDS Conference. November 11–13, 2009. Cologne, Germany. Abstract PE4.3/4.
26. Luber A, Slowinski PD, Acosta E, et al. Steady-state pharmacokinetics of fosamprenavir and raltegravir alone and combined with unboosted and ritonavir-boosted fosamprenavir. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2009 September 12–15; San Francisco, California. Abstract A1-1297.
27. Berger EA, Murphy PM, Farber JM. Chemokine Receptors As HIV-1 Coreceptors: Roles in Viral Entry, Tropism, and Disease. Annu Rev Immunol 1999;17:657–700.
28. Pozniak AL, Boffito M, Russell D, Ridgway CE, Muirhead GJ. A novel probe drug interaction study to investigate the effect of selected antiretroviral combinations on the pharmacokinetics of a single oral dose of maraviroc in HIV-positive subjects. Br J Clin Pharmacol. 2008;65 Suppl 1:54–9.
29. Abel S, Russell D, Taylor-Worth RJ, Ridgway CE, Muirhead GJ. Effects of CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. Br J Clin Pharmacol. 2008;65 Suppl 1:27–37.
30. Abel S, Jenkins TM, Whitlock LA, Ridgway CE, Muirhead GJ. Effects of CYP3A4 inducers with and without CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. Br J Clin Pharmacol. 2008;65 Suppl 1:38–46.
31. Davis J, Scholler-Gyure M, Kakuda TN, et al. An open randomized two-period crossover study in 2 cohorts to investigate the effect of steady-state TMC125 and the combination of TMC125/darunavir/ritonavir on the steady-state pharmacokinetics of oral maraviroc in healthy subjects. 11th European AIDS Conference;, Oct 24–27, 2007, Madrid, abstract P4-3.02.
32. Andrews E, Glue P, Fang J, et al. Assessment of the pharmacokinetics of co-administered maraviroc and raltegravir. Br J Clin Pharmacol. 2010;69:51–7.
33. Boyd MA, Zhang X, Dorr A, et al, Lack of enzyme-inducing effect of rifampicin on the pharmacokinetics of enfuvirtide. J Clin Pharmacol. 2003;43:1382–91.
34. Sekar V, De Paepe E, Vangeneugden T, et al. Absence of an interaction between the potent HIV protease inhibitor TMC114 and the fusion inhibitor enfuvirtide in the POWER 3 analysis. 7th International Workshop on Clinical Pharmacology of HIV Therapy. April 20–222, 2006, Lisbon. Abstract 54.

35. González de Requena D, Calcagno A, et al. Unexpected drug-drug interaction between tipranavir/ritonavir and enfuvirtide. AIDS. 2006;20:1977–9.
36. Bazzoli C, Jullien V, Le Tiec C, et al. Intracellular pharmacokinetics of antiretroviral drugs in HIV-infected patients and their correlation with drug action. Clin Pharmacokinet. 2010;49:17–45.
37. Kaul S, Bassi K, Damle B, et al. Pharmacokinetic evaluation of the combination of atazanavir, enteric coated didanosine, and tenofovir disoproxil fumarate for a once-daily antiretroviral regimen. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, September 14–17, 2003, abstract A-1616.
38. Kearney BP, Flaherty JF, Shah J. Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. Clin Pharmacokinet. 2004;43:595–612.
39. Tong L, Phan TK, Robinson KL, et al. Effects of human immunodeficiency virus protease inhibitors on the intestinal absorption of tenofovir disoproxil fumarate in vitro. Antimicrob Agents Chemother. 2007;51:3498–504.
40. Kiser JJ, Aquilante CL, Anderson PL, et al. Clinical and genetic determinants of intracellular tenofovir diphosphate concentrations in HIV-infected patients. J Acquir Immune Defic Syndr. 2008;47:298–303.
41. Flaherty J, Kearney B, Wolf J, et al. Coadministration of tenofovir DF and didanosine: a pharmacokinetic and safety evaluation. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, Dec 16–19, 2001, abstract 1729.
42. Kearney BP, Sayre JH, Flaherty JF, et al. Drug-drug and drug-food interactions between tenofovir disoproxil fumarate and didanosine. J Clin Pharmacol. 2005;45:1360–7.
43. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Office of AIDS Research Advisory Council. December 1, 2009. (www.aidsinfo.nih.gov).
44. Schöller-Gyüre M, Kakuda TN, Raoof A, et al. Clinical pharmacokinetics and pharmacodynamics of etravirine. Clin Pharmacokinet. 2009;48:561–74.
45. Piscitelli SC, Gallicano KD. Interactions among drugs for HIV and opportunistic infections. N Engl J Med. 2001;344:984–96.
46. Crestor (rosuvastatin) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals; March 2010.
47. Kaul S, Ji P, Xie J, et al. A 2-way pharmacokinetic interaction between efavirenz and carbamazepine. 13th Conference on Retrovirus and Opportunistic Infections; 2006 Feb 5–8; Denver, Colorado. Abstract 575a.
48. Carten M, Kiser J, Kwara A, et al. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel and efavirenz. 17th Conference on Retroviruses and Opportunistic Infections; 2010 Feb 16–18; San Francisco, California. Abstract 934.
49. Mildvan D, Yarrish R, Marshak A, et al. Pharmacokinetic interaction between nevirapine and ethinyl estradil/norethindrone when administered concurrently to HIV-infected women. J Acq Immune Def Syn 2002;29:471–7.
50. Stocker H, Kruse G, Kreckel P, et al. Nevirapine significantly reduces the levels of racemic methadone and (R)-methadone in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2004;48:4148–53.
51. Altice FL, Cooney E, Friedland GH. Nevirapine induced methadone withdrawal: Implications for antiretroviral treatment of opiate dependent HIV infected patients. 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4; Chicago, Illinois. Abstract 372.
52. McCance-Katz E, Pade P, Friedland G, et al. Efavirenz decreases buprenorphine exposure, but is not associated with opiate withdrawal in opiod dependent individuals. 12th Conference on Retroviruses and Opportunistic Infections; 2005 February 22–25; Boston, Massachusetts. Abstract 653.
53. McCance-Katz EF, Moody DE, Morse GD, et al. Lack of clinically significant drug interactions between nevirapine and buprenorphine. Am J Addict 2010;19:30–7.
54. Viramune (nevirapine) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; January 2010.

55. Lipitor (atorvastatin) package insert. New York, NY: Pfizer Inc; June 2009.
56. Sustiva (efavirenz) package insert. Princeton, NJ: Bristol Myers Squibb, 2010.
57. Kaletra (lopinavir/ritonavir) package insert. Abbott Park, IL: Abbott Laboratories, 2010.
58. Schöller-Gyüre M, Woodfall B, De Marez T, et al. Pharmacokinetics of TMC125 with atazanavir and atazanavir/ritonavir. 8th International Congress of Drug Therapy in HIV Infection. Glasgow, UK, 2006. Abstract P278.
59. Schöller-Gyüre M, Woodfall B,Bollen S, et al. Pharmacokinetics of amprenavir and TMC125in HIV-infected volunteers receiving TMC125 with fosamprenavir/ritonavir. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy. Sep 27–20, 2006, San Francisco, CA. Abstract A-370.
60. King JR, Acosta EP. Tipranavir: a novel nonpeptidic protease inhibitor of HIV. Clin Pharmacokinet. 2006;45:665–82.
61. Scholler M, Kraft M, Hoetelmans R, et.al. Significant decrease in TMC125 exposures when co-administered with tipranavir boosted with ritonavir in healthy subjects. 13th Conference on Retroviruses and Opportunistic Infections. Feb 25–27, 2007. Los Angeles, CA. Abstract 563.
62. Baede P, Piscitelli S, Graham N, et.al. Drug interactions with TMC125, a potent, next generation NNRTI. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Sep 27–30, 2002, San Diego, CA. Abstract A-1827.
63. Intelence (etravirine) package insert. Raritan, NJ; Tibotec Therapeutics, 2008.
64. Schöller-Gyüre M, Kakuda TN, Sekar V. Pharmacokinetics of darunavir/ritonavir and TMC125 alone and coadministered in HIV-negative volunteers. Antivir Ther. 2007;12: 789–96.
65. Flexner C. HIV-protease inhibitors. N Engl J Med. 1998 Apr 30;338(18):1281–92.
66. Prezista (darunavir) package insert. Raritan, NJ: Tibotec Therapeutics; April 2010.
67. McCance-Katz EF, Farber S, Selwyn PA, et al. Decrease in methadone levels with nelfinavir mesylate. Am J Psychiatry 2000;157:481.
68. Rublein JC, Donovan BJ, Hollowell SB, et al. Effect of omeprazole (OMP) on the plasma concentrations of indinavir (IDV) in HIV-negative subjects. 43 rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2003 September 14–17; Chicago, Illinois. Abstract A-1611.
69. Burger DM, Hugen PWH, Kroon FP, et al. Pharmacokinetic interaction between the proton pump inhibitor omeprazole and the HIV protease inhibitor indinavir. [correspondence] AIDS. 1998;12:2080–2082.
70. Hugen PWH, Burger DM, ter Hofstede HJM, Koopmans PP. Concomitant use of indinavir and omeprazole: risk of antiretroviral subtherapy. AIDS 1998;12 (Suppl. 4): S29.
71. Beique L, Giguere P, la Porte C, Angel J. Interactions between protease inhibitors and acid-reducing agents: a systematic review. HIV Medicine 2007;8:335–345.
72. Bruggemann RJM, van Luin M, van den Dungen MW, et al. Bidirectional pharmacokinetic interaction between posaconazole and fosamprenavir [abstract 621]. 17th Conference on Retroviruses and Opportunistic Infections; 2010 Feb 16–18; San Francisco, California.
73. Noxafil (posaconazole) package insert]. Kenilworth, NJ: Schering-Plough; February 2009.
74. Vfend (voriconazole) package insert]. New York: NY, Pfizer, 2008.
75. Glesby MJ, Aberg JA, Kendall MA, et al. Pharmacokinetic interactions between indinavir plus ritonavir and calcium channel blockers. Clin Pharmacol Ther 2005;78:143–153.
76. Hogeland GW, Swindells S, McNabb JC, et al. Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. Clin Pharmacol Ther. 2007;81:69–75.
77. Aberg JA, Rosenkranz SL, Fichtenbaum CJ, et al. Pharmacokinetic interaction between nelfinavir and pravastatin in HIV-seronegative volunteers: ACTG Study A5108. AIDS 2006;20:725–9.
78. Pham PA, Lee L, Fuchs E, et al. Pharmacokinetic interaction between tipranavir/ritonavir and rosuvastatin. 13th Conference on Retroviruses and Opportunistic Infections; 2008 February 3–6; Boston, Massachusetts. Abstract 767.
79. Lexiva (fosamprenavir) package insert. Research Triangle Park, NC: GlaxoSmithKline; April 2010.
80. Crixivan (indinavir) package insert. Whitehouse Station, NJ: Merck and Co., Inc; April 2010.

81. Invirase (saquinavir) package insert. Nutley, NJ: Roche Laboratories Inc; April 2010.
82. Aptivus (tipranavir) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; April 2010.
83. Viracept (nelfinavir) package insert. La Jolla, CA. Agouron Pharmaceuticals; April 2010.
84. Back D, Sekar V, Hoetelmans RM. Darunavir: pharmacokinetics and drug interactions. Antivir Ther. 2008;13:1–13.
85. Sekar VJ, Lefebvre E, Boogaerts G, et al. Pharmacokinetic interaction between the protease inhibitors TMC114 and lopinavir/ritonavir. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy. Sep 27–30, 2006, San Diego, CA. Abstract A-367.
86. Sekar VJ, Lefebvre E, Mariën K, et al. Pharmacokinetic interaction between darunavir and saquinavir in HIV-negative volunteers. Ther Drug Monit. 2007;29:795–801.
87. Sekar VJ, Lefebvre E, De Marez T, et al. Pharmacokinetics of darunavir (TMC114) and atazanavir during coadministration in HIV-negative, healthy volunteers. Drugs R D. 2007;8:241–8.
88. Reyataz (atazanavir) package insert. Princeton, NJ; Bristol Myers Squibb, 2010.
89. Pham PA, Flexner C, Parsons T, et al. Beneficial pharmacokinetic interaction between atazanavir and lopinavir/ritonavir. J Acquir Immune Defic Syndr. 2007;45:201–5.
90. Richardson JD, Sorenson S. Rifampin to treat ritonavir-ergotamine drug interaction. Clin Infect Dis 1999;29:1002.
91. Moreno S, Hernández B, Dronda F. Antiretroviral therapy in AIDS patients with tuberculosis. AIDS Rev. 2006;8:115–249.
92. Piscitelli SC, Burstein AH, Chaitt D, et al. Indinavir concentrations and St. John's Wort. Lancet. 2000;355:547,548.
93. Romanelli F, Jennings HR, Nath A, Ryan M, Berger J. Therapeutic dilemma: the use of anticonvulsants in HIV-positive individuals. Neurology. 2000;54:1404–7.
94. Kempf DJ, Marsh KC, Kumar G, et al. Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. Antimicrob Agents Chemother. 1997;41:654–60.
95. Gallant JE. Protease-inhibitor boosting in the treatment-experienced patient. AIDS Rev. 2004;6:226–33.
96. US Food and Drug Administration. New label information affecting all approved protease inhibitors for treatment of HIV. April 27, 2010. http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/hivandaidsactivities/ucm209920.htm.
97. Iwamoto M, Wenning LA, Nguyen BY, et al. Effects of omeprazole on plasma levels of raltegravir. Clin Infect Dis. 2009;48:489–92.
98. El-Ibiary SY, Cocohoba JM. Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives. Eur J Contracept Reprod Health Care. 2008;13:123–32.

Chapter 14
Non-HIV Antiviral Agents

Douglas N. Fish

Abstract During the past several decades, viruses have been increasingly recognized as frequent and important pathogens. Critically ill and immunocompromised patients, particularly within the transplant and human immunodeficiency virus (HIV)-infected populations, are at particularly high risk for severe viral infections such as those caused by cytomegalovirus (CMV), adenovirus, disseminated herpes simplex virus (HSV), and infections with hepatitis B virus (HBV) and hepatitis C virus (HCV). Influenza continues to be a significant public and global health problem as well. Many of the currently available antiviral agents have been in clinical use for many years and clinical data related to important drug interactions often concern the use of older drugs with which significant interactions were likely to frequently occur (e.g., zidovudine, didanosine). Unfortunately, however, interaction data are often unavailable for drugs such as the newer antiretroviral and immunosuppressant agents which are now considered standards of care for management of populations at high risk for serious viral infections. Some of the non-HIV antiviral drugs such as acyclovir, famciclovir, oseltamivir, and amantadine are associated with relatively few clinically significant drug interactions. However, there are a number of significant interactions which must be considered for the safe and effective use of drugs such as ganciclovir, foscarnet, cidofovir, ribavirin, and the interferons. This chapter summarizes available data regarding pharmacokinetic and toxic interactions with the current non-HIV antiviral agents.

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14.1 Introduction

During the past several decades, viruses have been increasingly recognized as frequent and important pathogens. Critically ill and immunocompromised patients, particularly within the transplant and human immunodeficiency virus (HIV)-infected populations, are at particularly high risk for severe viral infections such as those caused by cytomegalovirus (CMV), adenovirus, and disseminated herpes simplex virus (HSV). Infections caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) are also quite prevalent, and influenza continues to be a significant public and global health problem. Despite the increasing need for effective management of such infections, the development of new antiviral agents for the prophylaxis and/or treatment of non-HIV viral infections has been relatively sluggish. Few novel agents have been introduced to the marketplace in recent years; the anti-influenza drugs oseltamivir and zanamivir were first marketed in the United States in 1999 and are still among the newest non-HIV antivirals available. Since many of the currently available antiviral agents have been in clinical use for many years, specific clinical data related to important drug interactions are often related to older drugs with which significant interactions were likely to frequently occur (e.g., zidovudine, didanosine). Unfortunately, interaction data are often unavailable for drugs such as the newer antiretroviral and immunosuppressant agents which are now considered standards of care for management of populations at high risk for serious viral infections. This chapter summarizes currently available data regarding interactions with non-HIV antiviral agents; relevant drug interactions are summarized in Tables 14.1–14.4. There is a great need for additional studies related to interactions with this small yet clinically important group of drugs.

14.2 Drugs for Treatment of Herpes Simplex Virus and Varicella Zoster Virus Infections

14.2.1 Acyclovir/Valacyclovir

Potentially important drug interactions with acyclovir and valacyclovir are summarized in Table 14.1. Although the effects of administration with food as described below will differ depending on whether acyclovir is administered as the parent drug or the valacyclovir prodrug, other potential drug interactions involving systemic acyclovir would be assumed to generally apply, and would be likely to occur, after administration of either compound. Studies evaluating the effect of administering acyclovir and valacyclovir with food have shown no significant changes in the areas under the plasma concentration vs. time curve (AUC) compared to administration of the drugs in the fasted state. Since these changes were not considered to be clinically relevant, both oral acyclovir and valacyclovir may be administered without regard to meals [1, 2]. The concurrent administration of a single dose of aluminum- or

Table 14.1 Interactions with drugs used for treatment of herpes simplex and varicella zoster virus infections

Primary drug	Interacting drug	Effects	Mechanisms	Comments/management
Acyclovir	Food	AUC ↓ 18%	Decreased absorption	Not clinically significant, may administer without regard to meals
	Cytarabine	ACV C_{max} ↓ 43%, F ↓ 38%	Decreased absorption caused by mucosal damage	Clinical significance unknown, monitor antiviral response for effectiveness of therapy
	Phenytoin, valproic acid	↓ serum concentrations of AEDs	Decreased absorption, unknown mechanism	Clinical significance unknown, monitor for effectiveness of AED therapy
	Probenecid	ACV AUC ↑ 40%	Decreased renal tubular secretion	May be clinically significant, consider reduction in ACV dose
	Lithium	300% ↑ lithium concentration	Competitive renal tubular secretion	Clinical significance unknown, additional monitoring of lithium concentrations recommended
	Cyclosporine	No effect		No additional monitoring necessary
	Mycophenolate mofetil	ACV C_{max} ↑ 18%; MMF AUC ↑ 9%	Competitive renal tubular secretion	Not likely to be clinically significant
	Nephrotoxins (aminoglycosides, amphotericin B, cidofovir, foscarnet, intravenous pentamidine, vancomycin, etc.); also reports of nephrotoxicity during ceftriaxone therapy	Additive renal toxicity	Overlapping adverse effects	Avoid combination if possible; otherwise close clinical monitoring of renal function is required
	Theophylline	THEO CL ↓ 30%, AUC ↑ 45%	Decreased oxidative metabolism	Clinical significance unknown, additional monitoring of theophylline concentrations recommended

(continued)

Table 14.1 (continued)

Primary drug	Interacting drug	Effects	Mechanisms	Comments/management
	Zidovudine	Improved survival in HIV-infected patients	Synergistic anti-HIV activity	Not consistently demonstrated, clinical significance unknown; may be less relevant with HAART
Valacyclovir	High-fat meal	No effect		May administer without regard to meals
	Al^{3+}/Mg^{2+} antacids	No effect		Not significant
	Probenecid	ACV C_{max} ↑ 22%, AUC ↑ 49%	Decreased renal tubular secretion	May be clinically significant, consider reduction in VACV dose
	Cimetidine	ACV C_{max} ↑ 8%, AUC ↑ 32%	Decreased renal tubular secretion	May be clinically significant
	Probenecid + cimetidine	ACV C_{max} ↑ 30%, AUC ↑ 78%	Decreased renal tubular secretion	May be clinically significant
	Digoxin	No effect		No additional monitoring necessary
	Mycophenolate mofetil	ACV C_{max} ↑ 40%, AUC ↑ 31%; MMF ↔	Competitive renal tubular secretion	Not likely to be clinically significant but monitor antiviral therapy
	Nephrotoxins (aminoglycosides, amphotericin B, cidofovir, foscarnet, intravenous pentamidine, vancomycin, etc.)	Additive renal toxicity	Overlapping side effects	Avoid combination if possible; otherwise close clinical monitoring of renal function is required
Famciclovir/ penciclovir	Food	PCV C_{max} ↓ 53%, ↑ T_{max}, AUC ↔	Decreased rate of absorption	Not clinically significant, may administer without regard to meals
	Digoxin	No effect		No additional monitoring necessary

ACV acyclovir, *AED* antiepileptic drug, *AUC* area under the plasma concentration vs. time curve, *CL* total systemic clearance, C_{max} maximum plasma concentration, *F* bioavailability, *HAART* highly-active antiretroviral therapy, *MMF* mycophenolate, *PCV* penciclovir, *THEO* theophylline, T_{max} time to maximum plasma concentration, *VACV* valacyclovir

magnesium-containing antacids was also shown to have no significant effects on the pharmacokinetics of valacyclovir after oral administration of a 1 g dose [2].

Acyclovir is commonly administered for suppression of HSV disease during remission-induction chemotherapy in patients with acute myelogenous leukemia (AML); standard chemotherapy regimens usually consist of high doses of an anthracycline, usually daunorubicin, and cytarabine. Malabsorption of D-xylose as a probable result of damage to the intestinal mucosa has previously been observed after cytarabine therapy. A study was therefore conducted to evaluate whether similar changes in the absorption of acyclovir occurred after receipt of chemotherapy and whether these changes would pose a potential problem for the effective use of acyclovir in this population [3]. Pharmacokinetics of intravenously administered acyclovir were unchanged after chemotherapy. However, both the peak plasma concentration (C_{max}) and bioavailability of oral acyclovir were substantially decreased after chemotherapy compared to pre-chemotherapy values [3]. It is not known whether these changes are clinically important or whether such pharmacokinetic alterations are also seen with valacyclovir; however, effectiveness of antiviral therapy should be carefully monitored when these agents are orally administered in similar clinical scenarios.

Two case reports have described the possibly decreased oral absorption of phenytoin and valproic acid after the use of oral acyclovir in children; the subsequently decreased serum concentrations of the antiepileptic drugs were associated with increased seizure frequency in previously stable patients [4]. The mechanisms underlying this potential interaction are unknown.

Acyclovir is primarily eliminated by the kidneys through a combination of glomerular filtration and active renal tubular secretion. Potential drug interactions involving drugs which may inhibit the tubular secretion of acyclovir have therefore been evaluated. The AUC of acyclovir was increased by approximately 40% after concomitant administration of probenecid, with renal clearance and urinary excretion of acyclovir also correspondingly decreased [1, 5]. Similar results have not unexpectedly been observed with valacyclovir [2]. The C_{max} and AUC of acyclovir were also increased by 8% and 32%, respectively, in subjects receiving valacyclovir 1 g orally after concomitant administration of a single 800 mg dose of cimetidine [2]. Additionally, acyclovir C_{max} and AUC were increased to an even greater extent after concomitant administration of valacyclovir 1 g orally along with the combination of both probenecid and cimetidine [2]. Although both probenecid and cimetidine caused substantial alterations in acyclovir pharmacokinetics, these changes are unlikely to be clinically relevant unless using high doses of acyclovir where accumulation to excessively high concentrations may increase the risk of drug-related adverse effects. Conversely, although acyclovir is not otherwise known to inhibit the renal secretion of other drugs, one case report described a fourfold increase in lithium serum concentrations following the addition of high-dose intravenous acyclovir to a chronic lithium carbonate regimen [6].

No significant pharmacokinetic alterations were observed when valacyclovir was administered together with multiple doses of thiazide diuretics [2]. Likewise, the

pharmacokinetics of neither acyclovir nor digoxin were significantly altered when valacyclovir was administered concomitantly [2].

The pharmacokinetics of neither acyclovir nor cyclosporine were significantly affected when the two drugs were administered concomitantly [1]. However, studies assessing the possible interaction of acyclovir and mycophenolate mofetil have had conflicting results [7–9]. One study found that the AUC of mycophenolate and its primary glucuronide conjugate metabolite, MPAG, were increased by 9% and 10%, respectively, while the acyclovir C_{max} was also increased by 18% [7]. A second study found that the pharmacokinetics of neither mycophenolate nor acyclovir were significantly affected [8]. In a final study, 15 patients were randomized to receive oral acyclovir alone, valacyclovir alone, mycophenolate mofetil alone, acyclovir plus mycophenolate, or valacyclovir plus mycophenolate in a single-dose, cross-over study [9]. After co-administration with mycophenolate, acyclovir C_{max}, time to peak plasma concentration (T_{max}), and AUC were significantly increased compared to those parameters after administration of acyclovir alone. The mean renal clearance of acyclovir was also reduced by 19%, possibly due to competition with MPAG for renal tubular secretion. Valacyclovir T_{max} was also significantly increased by 0.5 h when co-administered with mycophenolate, and alterations in C_{max}, T_{max}, and AUC were similar to those seen with oral acyclovir. Mycophenolate pharmacokinetics were not significantly altered after co-administration with either acyclovir or valacyclovir, with the exception that the AUC of MPAG was decreased by 12% after concomitant administration of valacyclovir. Overall, the interactions between acyclovir, valacyclovir, and mycophenolate mofetil were felt by the authors to not be clinically significant in otherwise healthy subjects with good renal function [9].

Because high-dose acyclovir and valacyclovir have been associated with adverse renal effects including acute tubular necrosis, crystalluria, and acute renal failure, caution should be exercised when using these antivirals in combination with other drugs that also have potential for additive nephrotoxicity, e.g., aminoglycosides, amphotericin B products, cidofovir, foscarnet, intravenous pentamidine, vancomycin, and others [1]. The concomitant use of ceftriaxone has also been reported to increase the nephrotoxicity of acyclovir [10].

A study conducted in five healthy subjects demonstrated a mean 30% reduction in total systemic clearance and 45% increase in theophylline AUC when theophylline was administered together with acyclovir [11]. The results of this study suggest that acyclovir interferes with the oxidative metabolism of theophylline, although such metabolic interactions with acyclovir have not been previously reported and the clinical significance is unknown.

The combination of acyclovir and zidovudine has been suggested to have synergistic antiviral effects and to be associated with improved survival in HIV-infected patients. However, the benefits of this combination have not been consistently demonstrated, and no pharmacokinetic or *in vitro* pharmacologic interactions between these two drugs have been demonstrated [12–17]. The clinical significance of this interaction is therefore unknown and may be less relevant with the current use of highly active antiretroviral therapy (HAART) for treatment of HIV infection.

14.2.2 Famciclovir/Penciclovir

Famciclovir is the diacetyl, 6-deoxy ester prodrug of penciclovir. Dideacetylation of famciclovir occurs in the blood and possibly in the intestinal wall, followed by 6-oxidation of the intermediary metabolite to form the active antiviral agent penciclovir. Conversion of 6-deoxy-penciclovir to penciclovir is catalyzed by the aldehyde oxidase enzyme. Cimetidine and promethazine are both *in vitro* inhibitors of aldehyde oxidase, but interaction studies have not shown any relevant effects of these drugs on the formation of penciclovir [18]. Raloxifene is also a potent *in vitro* inhibitor of aldehyde oxidase but has not been studied for potential effects on penciclovir formation [18].

The effects of food on the pharmacokinetics of famciclovir were evaluated in two studies [19, 20]; the results of these studies are summarized in Table 14.1. The administration of oral famciclovir with food was associated with a decrease in penciclovir C_{max} of 53% and an increase in T_{max} of approximately 2 h compared to the fasting state. However, the penciclovir AUC was not significantly altered, indicating that the rate of famciclovir absorption was altered but the overall bioavailability was not affected. Famciclovir may thus be administered without regard to meals [18–20].

The potential for clinically significant drug interactions with famciclovir appears to be very low overall. Like acyclovir, probenecid may affect the renal tubular excretion of penciclovir but this interaction is not considered to be clinically relevant under most circumstances [18]. An *in vitro* study using human liver microsomes found no inhibition of cytochrome (CYP) 3A4 enzymes by penciclovir [18]. In other studies, no clinically significant effects on penciclovir pharmacokinetics were observed after pre-treatment with multiple doses of allopurinol, magnesium/aluminum hydroxide antacids, cimetidine, promethazine, theophylline, thiazides, emtricitabine, or zidovudine (either the parent drug or the zidovudine glucuronide metabolite) followed by administration of single doses of famciclovir [18]. Finally, the steady-state pharmacokinetics of digoxin were also not affected by either single or multiple doses of famciclovir [18].

14.3 Drugs Used for Treatment of Cytomegalovirus Infections

14.3.1 Ganciclovir and Valganciclovir

Potentially important drug interactions with ganciclovir and valganciclovir are summarized in Table 14.2. Although the effects of administration with food as described below will differ depending on whether ganciclovir is administered as the parent drug or the valganciclovir prodrug, other potential drug interactions involving systemic ganciclovir would generally apply, and would be likely to occur, after administration of either compound. The C_{max} and AUC of oral ganciclovir were

Table 14.2 Interactions with drugs used for treatment of cytomegalovirus infections

Primary drug	Interacting drug	Effects	Mechanisms	Comments/management
Ganciclovir	High-fat meal	C_{max} ↑ 15%, AUC ↑ 20%	Increased absorption	Administer oral ganciclovir with high-fat meal
Valganciclovir	High-fat meal	GCV C_{max} ↑ 14%, AUC ↑ 23–57%	Increased absorption	Administer oral valganciclovir with high-fat meal
Ganciclovir/ valganciclovir	Probenecid	GCV AUC ↑ 53%	Decreased renal tubular secretion	Avoid combination if possible due to increased risk of GCV toxicities; otherwise consider empiric reduction of GCV dose, close patient monitoring required
	Zidovudine	GCV AUC ↓ 17%, ZDV AUC ↑ 19%	Unknown, may involve competition for renal secretion	Pharmacokinetic changes not clinically significant, but potential for increased hematologic toxicities requires close patient monitoring
	Zidovudine	Increased myelosuppression	Overlapping adverse effects	Potential for increased hematologic toxicities requires close patient monitoring; avoid combination if possible
	Zidovudine	Decreased survival in AIDS patients	Unknown	Clinical significance unknown; may be less relevant with HAART
	Myelosuppressives (dapsone, flucytosine, antineoplastics, amphotericin B, intravenous pentamidine, TMP/SMX, pyramethamine, trimetrexate, zidovudine, etc.)	Increased myelosuppression	Overlapping adverse effects	Avoid combination if possible; otherwise close patient monitoring is required due to potential for increased hematologic toxicities
	Didanosine	GCV AUC ↑ 21%; ddI C_{max} ↑ 36–49%, AUC ↑ 50–115%	Unknown, does not appear to involve tubular secretion	Avoid combination if possible; otherwise consider ddI dose reduction, close monitoring of both drugs required due to potential for increased toxicities

	Didanosine	Pancytopenia, persistently decreased CD4+ count	Decreased ddI metabolism, ↑ toxicity	Avoid combination if possible; otherwise consider ddI dose reduction, close monitoring for increased ddI toxicities
	Cyclosporine	No effect		No additional monitoring required
	Valproic acid	Decreased antiviral activity of GCV, foscarnet, cidofovir against CMV	VPA stimulation of viral replication	Clinical significance unknown
	Imipenem	Seizures	Overlapping adverse effects	
Cidofovir	Probenecid	CDV C_{max} ↑ 35–70%, AUC ↑ 29–45%	Decreased renal tubular secretion	Interaction used therapeutically to increase CDV exposure and improve efficacy; recommended probenecid dose is 2 g orally 3 h prior to CDV, then 1 g orally 2 and 8 h after completion of CDV infusion
	Zidovudine	ZDV AUC ↑ in presence of probenecid	Decreased renal tubular secretion	Temporarily discontinue ZDV or reduce dose by 50%
	Nephrotoxins (aminoglycosides, amphotericin B, acyclovir, NSAIDS, foscarnet, intravenous pentamidine, vancomycin, etc.)	Additive renal toxicity	Overlapping adverse effects	Close clinical monitoring of renal function is required; discontinue other agents prior to starting CDV if possible
	Rifabutin	Additive ocular toxicity, uveitis	Overlapping adverse effects	Avoid combination if possible; otherwise close clinical monitoring for ocular toxicities is required

(continued)

Table 14.2 (continued)

Primary drug	Interacting drug	Effects	Mechanisms	Comments/management
Foscarnet	Probenecid	Not well described	Decreased renal tubular secretion	Avoid combination if possible; otherwise close clinical monitoring of renal function is required
	Nephrotoxins (aminoglycosides, amphotericin B, acyclovir, cidofovir, cyclosporine, intravenous pentamidine, vancomycin, etc.)	Additive renal toxicity	Overlapping adverse effects	Avoid combination if possible; otherwise close clinical monitoring of renal function is required
	Ciprofloxacin	Seizures	Enhanced ciprofloxacin inhibition of GABA receptors	Clinical significance unknown; avoid combination if possible, otherwise close clinical monitoring recommended
	Pentamidine (IV)	Severe hypocalcemia	Additive nephrotoxicity, enhanced renal calcium wasting	Avoid combination if possible; otherwise close clinical monitoring is required
	Zidovudine	Synergistic effects against HIV and CMV *in vitro*	Unknown	Clinical significance unknown

AUC area under the plasma concentration vs. time curve, *CDV* cidofovir, C_{max} maximum plasma concentration, *CMV* cytomegalovirus, *ddI* didanosine, *GABA* gamma-aminobutyric acid, *GCV* ganciclovir, *HAART* highly-active antiretroviral therapy, *HIV* human immunodeficiency virus, *IV* intravenous, *NSAID* non-steroidal anti-inflammatory drug, *PO* oral, *TMP/SMX* trimethoprim/sulfamethoxazole, *ZDV* zidovudine

increased by 15% and 20%, respectively, when the drug was administered with a high-fat meal [21]. Although the commercial availability of the better-absorbed valganciclovir prodrug makes this interaction of little relevance, similar results have also been observed with valganciclovir; C_{max} of ganciclovir was increased by 14% and the AUC increased by 23–57% when valganciclovir was administered with standard or high fat meals [22, 23]. Based on these studies, valganciclovir tablets should be administered with food [22–24].

As with acyclovir and penciclovir, ganciclovir is approximately 90% eliminated as unchanged drug through a combination of glomerular filtration and active renal tubular secretion. When oral ganciclovir was administered concomitantly with probenecid, the steady-state AUC was increased by 53 ± 91% (range −14% to 299%) and the ganciclovir renal clearance was decreased by 22 ± 20% (range −54% to −4%). The results of this study are consistent with a probenecid-induced decrease in renal tubular transport [24]. The potential for acyclovir to competitively inhibit ganciclovir secretion was also assessed, but no interaction was found [23–25].

Because of the high incidence of CMV disease in HIV-infected patients and the overlapping myelosuppressive toxicities (i.e., anemia, leucopenia, thrombocytopenia) of ganciclovir and zidovudine, potential interactions between these two drugs have been assessed [25]. In a specific interaction study in which oral ganciclovir was administered concomitantly with zidovudine, the steady-state ganciclovir AUC was decreased by 17 ± 25% (range −52% to 23%) while the steady-state zidovudine AUC was increased by 19 ± 27% (range −11% to 74%). Neither of these alterations was considered to be clinically significant [25]; no studies have been conducted with intravenous ganciclovir.

Although studies did not indicate a high risk for serious pharmacokinetic interactions, the overlapping myelosuppressive toxicities of ganciclovir and zidovudine are still of concern. The combination of ganciclovir with zidovudine was found to be associated with high rates of drug intolerance and hematologic toxicity [26–30]. The combination of zidovudine plus intravenous ganciclovir was associated with hematologic toxicity in 82% of 40 AIDS patients and with severe neutropenia in 55% of patients. These toxicities required dose reduction or drug discontinuation to effectively manage the adverse effects [26]. In a second open-label clinical study, 113 patients with AIDS or AIDS-related complex received zidovudine for a median duration of 152 days. Statistical analysis revealed that the concomitant use of ganciclovir was associated with significantly increased risk of anemia and thrombocytopenia [27]. Similar high rates of anemia and neutropenia have been reported in other studies as well [31]. Because of the high risk of hematologic toxicities and the current availability of a number of other antiretroviral agents, the use of zidovudine in combination of ganciclovir or valganciclovir should be avoided if possible. If such a combination must be used for clinical reasons, frequent monitoring of complete blood counts is required. Caution should also be exercised in combining ganciclovir or valganciclovir with other drugs with myelosuppressive potential; such drugs include dapsone, flucytosine, various antineoplastic agents, intravenous pentamidine, pyramethamine, amphotericin B products, trimethoprim/sulfamethoxazole (TMP/SMX), and trimetrexate [25, 32].

Although the product information for ganciclovir states that ganciclovir pharmacokinetics were not affected by didanosine [25], one study reported a minor pharmacokinetic interaction when oral ganciclovir was administered after didanosine [33]. In a multiple-dose cross-over study in 13 HIV-positive patients, oral ganciclovir was administered together with didanosine; didanosine was administered either simultaneously with ganciclovir or sequentially, i.e., 2 h before ganciclovir. Significantly increased AUC was reported for didanosine during both simultaneous and sequential administration [115% and 108% increased AUC, respectively ($P<0.001$)]. In addition, the AUC of ganciclovir was also decreased by 21% when administered 2 h after didanosine ($P=0.002$) [33]. In a second study, intravenous ganciclovir plus didanosine resulted in significant increases in didanosine AUC (70 ± 40%, range 3–121%) and C_{max} (49 ± 48%, range −28% to 125%) [25, 34]. In a third study, ganciclovir combined with didanosine resulted in the steady-state didanosine AUC being increased by 50 ± 26% (range 22–110%) and C_{max} being increased by 36 ± 36% (range −27% to 94%) [25, 35]. The mechanism for the apparent two-way pharmacokinetic interaction between ganciclovir and didanosine is unknown, but does not appear to involve competition for renal tubular excretion of either drug [35]. Because of the potential for increased toxicities of didanosine in association with a significantly increased drug exposure, this interaction should be approached with caution and the concomitant use of ganciclovir and didanosine avoided. If this combination is required for clinical reasons, careful monitoring for adverse effects of both drugs is required. Whether a similar interaction exists with the use of oral valganciclovir is unknown.

Beyond pharmacokinetic interactions, a case report has also described pancytopenia and persistently decreased CD4+ lymphocyte counts in an HIV-infected patient receiving the combination of valganciclovir and didanosine. The proposed mechanism is a ganciclovir-induced inhibition of purine nucleoside phosphorylase, an enzyme responsible for catalyzing the breakdown of didanosine and endogenous purines [36, 37].

In vitro models have previously suggested that ganciclovir has antagonistic effects on the anti-HIV effects of zidovudine and didanosine, while foscarnet plus zidovudine has synergistic activity [30]. Studies evaluating the use of ganciclovir and foscarnet in the treatment of CMV retinitis in 234 patients with AIDS found that patients receiving foscarnet had a 3-month relative survival advantage compared to patients receiving ganciclovir, and that this difference in survival could not be attributed solely to differences in drug exposures or toxicities [38, 39]. Although these clinical data provide some support for potential antagonistic or synergistic anti-HIV effects of ganciclovir and foscarnet, it is difficult to prove that the observed mortality differences were due to pharmacological effects of the drugs alone. The clinical relevance of these findings is unknown.

Serum creatinine elevations to greater than 2.5 mg/dL have reportedly occurred in up to 20% of bone marrow transplant and heart transplant patients during ganciclovir therapy [40, 41]. Most of these patients were also receiving cyclosporine, and in many cases amphotericin B as well. Whether ganciclovir played a role in increasing the nephrotoxicity of these other drugs through pharmacokinetic

interactions or additive toxicities is unknown. However, a retrospective study of 93 liver transplant patients receiving ganciclovir concomitantly with oral cyclosporine found no evidence of effects on cyclosporine whole blood concentrations which may have predisposed to enhanced toxicities [25].

Valproic acid, an inhibitor of histone deacetylase (HDAC), has been shown in *in vitro* studies to stimulate the replication of CMV and to significantly impair the antiviral activity of ganciclovir, cidofovir, and foscarnet through mechanisms probably related to HDAC-related stimulatory effects on CMV itself [42]. Effects were most pronounced in cells that had been pretreated with valproic acid; when added during or after infection, VPA did not inhibit antiviral actions of the other drugs. The clinical relevance of these findings is unknown. Finally, seizures have been reported in patients receiving ganciclovir together with imipenem [25, 43]. Whether these seizures were related to the combination therapy or were attributable solely to imipenem is unclear.

14.3.2 Cidofovir

Potential drug interactions involving cidofivir are summarized in Table 14.2. Cidofovir is approximately 90% renally excreted with a high degree of active renal tubular secretion. Not surprisingly, probenecid has been shown to significantly inhibit the tubular secretion of cidofovir with marked decreases in cidofovir clearance and corresponding increases in AUC. This significant interaction serves as the basis for the Food and Drug Administration (FDA)-approved use of cidofovir in combination with probenecid in the treatment of CMV infection. The recommended dose of probenecid is 2 g orally 3 h prior to the cidofovir dose, followed by 1 g orally at 2 and 8 h after completion of the cidofovir infusion [44]. Although cidofovir is routinely used in combination with probenecid for purposes of improving the pharmacokinetic disposition of cidofovir and enhancing clinical efficacy, the use of probenecid also appears to increase the overall incidence of drug-related adverse effects observed during cidofovir therapy [45–47]. Up to half of patients receiving cidofovir plus probenecid may develop constitutional symptoms of fever, chills, nausea, vomiting, fatigue, headache, GI upset, and rash; serious reactions including systemic hypotension may occur in 3% of patients and often result in discontinuation of cidofovir/probenecid therapy. Although difficult to determine whether such adverse effects are primarily due to cidofovir or probenecid, they seem to be most closely related to the administration of probenecid [48, 49].

In addition to cidofovir and other antiviral agents, probenecid is known to interact with the renal tubular secretion of many other drugs including acetaminophen, angiotensin-converting enzyme inhibitors, aminosalicylic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide, nonsteroidal anti-inflammatory drugs, theophylline, and zidovudine. Concomitant medications should be carefully evaluated as part of the overall assessment and monitoring of cidofovir/probenecid therapy [44]. Although no consistent change in

zidovudine AUC has been observed when combined with cidofovir [50], and although the combination of cidofovir plus zidovudine did not appear to increase the incidence of drug-related myelosuppression [28], the manufacturer of cidofovir recommends that zidovudine should either be temporarily discontinued or the dose decreased by 50% when co-administered with probenecid on the day of cidofovir dosing [44].

Due to the risk of additive nephrotoxicity during cidofovir therapy, the combination of cidofovir with other potentially nephrotoxic agents such as aminoglycosides, acyclovir, amphotericin B products, foscarnet, intravenous pentamidine, vancomycin, and nonsteroidal anti-inflammatory drugs should be avoided whenever possible [44]. The manufacturer of cidofovir recommends that other potential nephrotoxins be discontinued at least 7 days prior to starting therapy with cidofovir [44]. If the use of other potentially nephrotoxic agents cannot be avoided due to clinical considerations, serum creatinine and other markers of renal function should be carefully monitoring before and after each dose of cidofovir.

A number of case reports have described the occurrence of ocular toxicities during the administration of cidofovir concomitantly with rifabutin [51–54]. Both agents have been associated with uveitis, but whether the combination substantially increases the risk of ocular toxicities is unknown. Nevertheless, caution should be exercised when using these two agents together.

14.3.3 Foscarnet

Important drug interactions involving foscarnet are summarized in Table 14.2. Like many other antiviral agents, foscarnet undergoes a high degree of active renal tubular secretion. Although the potential interaction between foscarnet and probenecid has not actually been well described, there is also potential for competition between foscarnet and certain other drugs such as didanosine and zalcitabine which are also actively secreted through the kidney. However, no pharmacokinetic alterations with didanosine or zalcitabine have been observed [55, 56]. While the need for the combination of foscarnet plus ganciclovir should rarely be required, no alterations in the pharmacokinetics of either drug were noted when the combination was studied in 13 patients [55].

Pharmacokinetic interactions involving foscarnet have not been well described; however, the risk of overlapping and potentially additive toxicity with other drugs is a major consideration during foscarnet therapy. The concomitant use of foscarnet and other potentially nephrotoxic agents such as aminoglycosides, acyclovir, amphotericin B products, cidofovir, cyclosporine, intravenous pentamidine, and vancomycin should be approached with caution and avoided whenever possible [55, 57]. Abnormal renal function has also been noted with combinations of foscarnet plus ritonavir, as well as combined foscarnet, ritonavir, plus saquinavir [55]. The potential mechanisms or significance of observed renal dysfunction during combined therapy with these antiretroviral drugs is unknown.

Additive central nervous system toxicity resulting in seizures in two patients has been reported with the concomitant use of foscarnet and ciprofloxacin [58]. Although both of the patients in whom these seizures occurred were receiving multiple medications and a direct causal effect is unclear, a study in mice has also reported increased seizure potential with the combination of foscarnet plus ciprofloxacin (but not enoxacin) [59]. Although this interaction appears to involve alteration of gamma-aminobutyric acid (GABA) activity in the central nervous system, it has not been commonly reported with either ciprofloxacin or other fluoroquinolones and the clinical importance is unknown.

Severe hypocalcemia has been reported during combined therapy of foscarnet and intravenous pentamidine [55]. Post-marketing surveillance by the manufacturer found that four patients in the United Kingdom who were treated with the combination of foscarnet and pentamidine may have developed drug-related hypocalcemia; one of these patients reportedly died of severe hypocalcemia. This potential additive toxicity would be expected to occur only with intravenous pentamidine since the systemic absorption of pentamidine after aerosolized administration is negligible. The combination of foscarnet and intravenous pentamidine should be avoided when possible; close patient monitoring is required if concomitant therapy with these drugs is required.

In vitro models have demonstrated additive or synergistic activity against HIV and CMV when the combination of foscarnet and zidovudine was studied at clinically relevant concentrations [60, 61]. The mechanisms of such enhanced effects are unknown, and no pharmacokinetic interactions between the two drugs have been observed [62]. Although the clinical significance of these potential interactions is unknown, it is likely of low clinically relevance given the use of multiple-drug antiretroviral combinations during HAART.

14.4 Drugs Used for Prevention and Treatment of Influenza

14.4.1 Amantadine and Rimantadine

Potentially important drug interactions with amantadine and rimantadine are summarized in Table 14.3. Pharmacokinetic studies of amantadine and rimantadine have demonstrated that administration of these drugs with food has no significant effects on their bioavailability compared to administration in the fasting state [63, 64]. Amantadine and rimantadine may thus be administered without regard to meals.

As with many other antiviral agents, amantadine and rimantadine undergo active renal tubular secretion [65, 66]. A number of drugs have been associated with decreased renal clearance and increased adverse effects of amantadine. Concomitant use of amantadine with the diuretic triamterene/hydrochlorothiazide was associated with a 50% increase in amantadine concentrations and the occurrence of central nervous system toxicity. The mechanism of this interaction is assumed to be due to

Table 14.3 Interactions with drugs used for prevention and treatment of influenza

Primary drug	Interacting drug	Effects	Mechanisms	Comments/management
Amantadine	Food	No effect		May administer without regard to meals
	Triamterene/ hydrochlorothiazide	AMA AUC ↑ 50%	Decreased renal tubular secretion	Clinical monitoring of patients for enhanced CNS toxicities advised
	TMP/SMX	Decreased AMA clearance, increased CNS toxicity	Decreased renal tubular secretion by TMP	Clinical monitoring of patients for enhanced CNS toxicities advised
	Quinine, quinidine	AMA renal clearance ↓ 30%	Decreased renal tubular secretion	Clinical monitoring of patients for enhanced CNS toxicities advised
	Agents with CNS toxicities (antihistamines, psychotropics, anticholinergics, buproprion, phenylpropanolamine)	Additive CNS toxicity	Overlapping adverse effects	Clinical monitoring of patients for enhanced CNS toxicities advised; consider avoiding combination if possible
	LAIV intranasal vaccine	Potential for reduced vaccine efficacy	Inhibition of viral replication	LAIV vaccine should not be administered within 2 weeks before, or 48 h after, administration of AMA
Rimantadine	Food	No effect		Administer without regard to meals
	LAIV intranasal vaccine	Potential for reduced vaccine efficacy	Inhibition of viral replication	LAIV vaccine should not be administered within 2 weeks before, or 48 h after, administration of RIM
Oseltamivir	Food	C_{max} ↓ 16%, AUC ↓ 2%		Not clinically significant, may administer without regard to meals
	Al^{3+}/Mg^{2+} or calcium carbonate antacids	No effect		No significant interaction
	Clopidogrel	Conversion of oseltamivir to active oseltamivir carboxylate ↓ 90%	Competitive inhibition of hepatic carboxyl-esterase 1 enzyme	Probably not clinically significant due to methodological problems with the *in vitro* studies

	Probenecid	Oseltamivir AUC ↑ 100%	Decreased renal tubular secretion	Probably not clinically significant due to favorable side effect profile of oseltamivir; may allow for alternative dosing regimens to reduce daily dosing requirements of oseltamivir
	Methotrexate	Interaction not evaluated but potential for ↑ AUC of MTX	Potential for decreased renal tubular secretion	Caution with use of oseltamivir during MTX therapy; close patient monitoring advised
	Warfarin	No effects on warfarin kinetics or coagulation parameters		No additional monitoring required
	Amantadine	No significant effects on either oseltamivir or AMA		No significant interaction
	LAIV intranasal vaccine	Potential for reduced vaccine efficacy	Inhibition of viral replication	LAIV vaccine should not be administered within 2 weeks before, or 48 h after, administration of oseltamivir
Zanamivir	LAIV intranasal vaccine	Potential for reduced vaccine efficacy	Inhibition of viral replication	LAIV vaccine should not be administered within 2 weeks before, or 48 h after, administration of zanamivir

AMA amantadine, *AUC* area under the plasma concentration vs. time curve, C_{max} maximum plasma concentration, *CNS* central nervous system, *LAIV* live attenuated influenza virus, *MTX* methotrexate, *RIM* rimantadine, *TMP* trimethoprim, *TMP/SMX* trimethoprim/sulfamethoxazole

decreased renal clearance through inhibition of tubular secretion, although it is unknown which component of the diuretic combination was responsible [67]. The combination antibiotic TMP/SMX was also reported to cause decreased renal clearance and neurologic toxicity when administered concomitantly with amantadine, presumably due to trimethoprim-induced reduction in the tubular secretion of amantadine [68]. Co-administration of quinine or quinidine also reportedly reduces the renal clearance of amantadine by approximately 30% [65]. Other cationic drugs with active tubular secretion could theoretically compete with the renal tubular secretion of rimantadine, but no other cases have been reported [69].

Increased central nervous system toxicities, particularly of amantadine, have been reported when the antiviral agents are used concomitantly with a number of other agents with overlapping toxicity profiles. The neurotoxic effects of amantadine may reportedly be increased by antihistamines, psychotropic agents including thioridazine, and drugs with pronounced anticholinergic activity. Reports have been particularly frequent among patients taking anticholinergic agents for treatment of Parkinson's disease [65, 66, 70–72]. Neurotoxicity has also been reported with combinations of amantadine with either phenylpropanolamine [73] or buproprion [74]. In the case of toxic interactions with buproprion, reversible central nervous system toxicity was reported to occur in six of eight patients receiving buproprion within 1 week of beginning amantadine treatment; the mechanism of toxicity is believed to be related to the dopamine stimulating effects of the two drugs [74]. In general, caution should be used when amantadine is combined with other central nervous system stimulants and patients carefully monitored for evidence of neurologic toxicities [65].

Amantadine and rimantadine exert their effects against the influenza virus by inhibiting viral replication. There is a theoretical potential for these antiviral drugs to reduce the efficacy of the live attenuated influenza virus (LAIV) intranasal vaccine by inhibiting replication of the live virus after vaccine administration. It is therefore recommended that the LAIV intranasal vaccine should not be administered within 2 weeks before, or 48 h after, administration of amantadine. The use of amantadine or rimantadine should not affect administration of the injectable vaccines containing the inactivated influenza virus [65, 66].

14.4.2 Oseltamivir

Potential drug interactions involving oseltamivir are shown in Table 14.3. Compared to administration in the fasting state, co-administration of oral oseltamivir with food has no significant effect on either the C_{max} or AUC of oseltamivir carboxylate, the active compound which is rapidly formed after administration of oseltamivir phosphate [75]. In addition, the rate and extent of oseltamivir absorption were not affected by either magnesium hydroxide/aluminum hydroxide or calcium carbonate antacids after concomitant administration to healthy volunteers [76].

Oseltamivir has low potential for drug interactions based on the characteristics of low protein binding, lack of hepatic metabolism, and renal elimination through

glomerular filtration and anionic tubular secretion [75, 77]. The conversion of oseltamivir to oseltamivir carboxylate occurs via carboxylesterases which are located predominantly in the liver. Drug interactions involving competition for, or inhibition of, these esterases have not been extensively reported in literature. *In vitro* studies also suggest that neither oseltamivir nor oseltamivir carboxylate are good substrates for CYP450 mixed-function oxidases or glucuronyl transferases.

Hydrolytic activation of oseltamivir to oseltamivir carboxylate is catalyzed by human carboxylesterase1 (HCE1). The hydrolysis of oseltamivir was reportedly inhibited by as much as 90% in the presence of the antiplatelet drug clopidogrel, which is also hydrolyzed by HCE1 but has a greater affinity for the enzyme than does oseltamivir [78]. The inhibition of oseltamivir carboxylation *in vitro* was dependent on the clopidogrel dose/concentration used [79], and studies describing clopidogrel interactions have been criticized in part because the relative concentrations of oseltamivir and clopidogrel evaluated (50 μM and 2.5–50 μM) were approximately 240 and 400–8,000 fold higher, respectively, than plasma concentrations achieved with typical oseltamivir and clopidogrel dosing regimens. The true significance of this potential clopidogrel interaction is unknown, but is not likely to be clinical important based on methodological problems with the *in vitro* studies [80].

Systemic clearance of oseltamivir carboxylate primarily occurs through active renal secretion via the organic anion transport systems in the renal tubules, specifically hOAT-1. Clinically important drug interactions involving oseltamivir could thus potentially occur with other drugs that inhibit renal tubular secretion through this pathway [77]. Cimetidine is a potent inhibitor of O-carboxylate 1 and 2, two active pathways for transport and secretion of cationic drugs by renal tubular epithelial cells. Not surprisingly because of the difference in transporter systems affected, no interaction was observed when cimetidine was administered concomitantly with oseltamivir [77, 81]. However, probenecid reduced the renal clearance of oseltamivir carboxylate by 50% from 15.7 to 7.5 L/min and correspondingly increased the AUC by 100% [75, 77]. No interaction was noted between oseltamivir and concomitant administration of amoxicillin (also secreted into urine by anionic renal tubular transporters) in healthy volunteers [77, 81]. Even though oseltamivir has only weak inhibitory effects on renal tubular anionic secretory transporters, it is recommended that care be exercised with co-administration of methotrexate because of common secretory pathways and potential for increased methotrexate toxicities [81].

The interaction between oseltamivir and probenecid has been suggested as likely not clinically important because these two drugs are seldom used together and because oseltamivir lacks serious toxicities [77]. However, in response to concerns regarding potential influenza pandemics and limited supplies of oseltamivir, it has been suggested to take advantage of the probenecid interaction by combining it with oseltamivir as a means of reducing oseltamivir dosing requirements [82, 83]. At least two pharmacokinetic studies have evaluated the feasibility of oseltamivir/probenecid combinations [84, 85]. In the first study, 48 healthy volunteers were randomized to receive either oseltamivir 75 mg once daily, oseltamivir 75 mg every 48 h plus probenecid 500 mg 4 times daily, or oseltamivir 75 mg every 48 h plus probenecid 500 mg twice daily [84]. Oseltamivir and oseltamivir carboxylate C_{max} and T_{max} did

not significantly differ between the three groups. However, total 48-h oseltamivir carboxylate AUCs within the three groups were not found to be bioequivalent based on differences in geometric mean ratios. The steady-state apparent oral clearances of oseltamivir carboxylate were significantly decreased ($P<0.05$) in the probenecid groups compared to oseltamivir alone, confirming inhibitory effects of probenecid on oseltamivir renal excretion. Arithmetic mean concentrations at 48 h were not significantly different between the oseltamivir and oseltamivir plus four-times-daily probenecid group (42 ± 76 ng/mL vs. 81 ± 54 ng/mL, respectively, $P=0.194$); however, concentrations in the twice-daily probenecid group were significantly decreased compared to the oseltamivir-alone group (23 ± 26 ng/mL vs. 81 ± 54 ng/mL, respectively, $P=0.012$). The results of this study suggested that co-administration of oseltamivir 75 mg every 48 h plus probenecid 500 mg 4 times daily was bioequivalent to every-day dosing of oseltamivir and that this regimen might be a feasible way of allowing for reduction of oseltamivir doses without compromising clinical efficacy [84]. A second study found that reducing oseltamivir doses to 45 mg twice daily plus probenecid maintained oseltamivir exposures which were comparable to the typical 75 mg twice daily regimen without probenecid [85]. Although the daily dose of oseltamivir could potentially be reduced from 150 to 90 mg/day through combination therapy with probenecid, the authors of the study noted that the potential for increased adverse effects and nonadherence related to probenecid use requires careful consideration prior to routine recommendations for such a dosing strategy [85]. The combination of oseltamivir plus probenecid has also recently been associated with thrombocytopenia, lending some credence to the concerns regarding toxicity expressed by the authors of this latter study [86].

No interactions have been observed between oseltamivir and either single-dose acetaminophen or single-dose aspirin [81, 87, 88]. In addition, no interactions have been observed between oseltamivir and cyclosporine, mycophenolate mofetil, or tacrolimus [81].

In a study evaluating potential interactions between oseltamivir and warfarin, subjects received oseltamivir 75 mg twice daily for a total of 9 doses either with or without warfarin with an appropriate wash-out period of 4–8 days between treatment periods. No statistical differences in international normalized ratio (INR), Factor VIIa levels, or vitamin K1 concentrations were found when the drugs were administered concomitantly. Also, no effects of oseltamivir on warfarin pharmacokinetics were noted [75, 77, 89].

Due to concerns regarding severe pandemics with novel influenza strains such as H5N1, combination therapy with amantadine plus oseltamivir has also been suggested to increase the potential for increased antiviral efficacy with decreased potential for resistance. A study was thus conducted to evaluate any pharmacokinetic interactions between the two drugs [90]. A randomized, cross-over trial was conducted in which 17 subjects received amantadine alone or in combination with oseltamivir for 5 days. Co-administration with oseltamivir had no significant effects on amantadine AUC or C_{max}. Similarly, amantadine co-administration had no significant effects on the pharmacokinetics of either oseltamivir or oseltamivir carboxylate. No evidence of increased adverse effects of either drug were noted in this study [90].

As with amantadine/rimantadine, there is a theoretical potential for oseltamivir to reduce the efficacy of the LAIV intranasal vaccine by inhibiting replication of the live virus after vaccination. It is therefore recommended that the LAIV intranasal vaccine not be administered within 2 weeks before, or 48 h after, administration of oseltamivir. The use of oseltamivir should not affect administration of the injectable vaccine containing the inactivated influenza virus [75].

14.4.3 Zanamivir

Like oseltamivir, zanamivir has a low potential for significant drug interactions due to its low degree of protein binding, lack of hepatic metabolism, and elimination primarily by glomerular filtration and tubular secretion [91]. Zanamivir does not appear to serve as a substrate or otherwise affect CYP450 enzymes (i.e., 1A1/2, 2A6, 2C9, 2C18, 2D6, 2E1, or 3A4) in human liver microsomes [92]. Few specific pharmacokinetic drug interactions have been evaluated or observed because of the use of aerosolized zanamivir with its resultant minimal systemic exposure. However, the recent availability of intravenous zanamivir may prompt additional interaction studies in the future.

Beyond pharmacokinetic interactions, several drugs have been assessed for their potential affects on the antiviral activity of zanamivir. Aspirin, ibuprofen, acetaminophen, promethazine, oxymetazoline, phenylephrine, and amoxicillin/clavulanate were all shown to have no effect on the antiviral activity of zanamivir against influenza A *in vitro* [91]. Although codeine and diphenhydramine have been shown to enhance zanamivir's antiviral activity in vitro through direct antiviral effects of some unknown mechanism, the concentrations of codeine and diphenhydramine used in the *in vitro* studies were many times higher than would be achieved with typical doses of these agents and the clinical relevance is therefore unlikely to be important [91, 92].

As with oseltamivir, LAIV intranasal vaccine should not be administered within 2 weeks before or 48 h after zanamivir administration in order to avoid the theoretical concern regarding decreased vaccine efficacy with close temporal administration of zanamivir (Table 14.3) [92].

14.5 Miscellaneous Antiviral Agents

14.5.1 Ribavirin

A large number of potential drug interactions involving ribavirin exist and are summarized in Table 14.4. The prevalence of infection with HCV is a growing problem worldwide, particularly among HIV-infected patients in whom rates of

Table 14.4 Interactions with ribavirin and the interferons

Primary drug	Interacting drug	Effects	Mechanisms	Comments/management
Ribavirin	Food	C_{max} ↑ 66%, T_{max} ↑ 100%, AUC ↑ 42%	Increased absorption	Oral ribavirin should be administered with meals
	Interferon-α	Enhanced efficacy in treatment of HCV	Synergistic antiviral activity, primary mechanism unknown but seems to be pharmacologically rather than immunologically or pharmacokinetically based	Combination therapy with pegylated interferon is current standard of care; no role for ribavirin monotherapy
	Interferon-α	Increased hemolytic anemia	Overlapping adverse effects	Close patient monitoring required
	Al^{3+}/Mg^{2+} plus simethicone antacids	AUC ↓ 14%	Decreased absorption	No significant interaction
	Myelosuppressives (dapsone, flucytosine, antineoplastics, amphotericin B, intravenous pentamidine, TMP/SMX, pyramethamine, trimetrexate, zidovudine, etc.)	Increased myelosuppression	Overlapping adverse effects; with azathioprine, ribavirin causes alteration in metabolic pathways leading to increase in toxic metabolites	Avoid combination if possible; otherwise close patient monitoring is required due to potential for increased hematologic toxicities
	Zidovudine	Reduced anti-HIV activity of ZDV; may also effect other nucleoside analogues including lamivudine, stavudine, emtricitabine, and tenofovir	Decreased intracellular phosphorylation of nucleoside analogues through competitive inhibition by RIB	Clinical significance unknown; *in vitro* findings have not been confirmed by clinical data in humans
	Didanosine	Increased ddI toxicities including lactic acidosis and pancreatitis; may also effect stavudine and abacavir	RIB inhibition of intracellular enzyme leading to accumulation of dideoxyadenosine-5′-triphosphate, increased mitochondrial toxicity	Avoid combination if possible; otherwise close patient monitoring is required due to potential for increased mitochondrial toxicities of antiretrovirals

	Atazanavir	Increased hyperbilirubinemia	RIB-induced hemolysis in combination with ATV inhibition of bilirubin conjugation pathways	Discontinuation of ATV, change to different antiretroviral if possible
	Warfarin	Decreased warfarin activity	Unknown mechanism	Clinical significance unknown
Interferon-α (including pegylated interferons)	Drugs metabolized by CYP1A (theophylline, caffeine, antipyrine, TCAs, olanzapine, clozapine) and CYP3A (azole antifungals, macrolide antibiotics, many antiretroviral agents, some immunosuppressants, SSRIs, TCAs, statins, antipsychotics, benzodiazepines, barbiturates, calcium channel antagonists)	Theophylline AUC ↑ 25–100%; erythromycin AUC ↑ 15–35%, hexobarbital CL ↓ 7%; antipyrine CL ↓ 16–22%; caffeine less effected	IFN-related downregulation/ inhibition of CYP activity	Changes highly variable and may be dose-related; alterations not always clinically significant, but patients should nevertheless be monitored for enhanced adverse effects of concomitant drugs
	Drugs metabolized by CYP2C8/9 (warfarin, phenytoin, NSAIDs, angiotensin receptor blockers, certain statins, sulfonylureas) or CYP2D6 (β-blockers, lidocaine, flecainide, TCAs, SSRIs, opiate analgesics, antipsychotics)	Enzyme activity increased by 28–66%; effects on warfarin, phenytoin, and flecainide specifically mentioned by drug manufacturers	IFN-related upregulation/ induction of CYP activity	Changes highly variable and may be dose-related; alterations not always clinically significant, but patients should nevertheless be monitored for altered activity or enhanced adverse effects of concomitant drugs
	Methadone	Methadone AUC ↑ 16%	Inhibition of hepatic CYP3A4 metabolism	Clinical significance unknown, but patients should be closely monitored for enhanced methadone side effects

(continued)

Table 14.4 (continued)

Primary drug	Interacting drug	Effects	Mechanisms	Comments/management
	Ribavirin	Increased hemolytic anemia	Overlapping adverse effects	Close patient monitoring required
	Myelosuppressives (clozapine, dapsone, flucytosine, antineoplastics (including 5-fluorouracil, hydroxyurea, melphalan), amphotericin B, intravenous pentamidine, TMP/SMX, pyramethamine, thalidomide, trimetrexate, zidovudine, etc.)	Increased myelosuppression	Overlapping adverse effect s	Avoid combination if possible; otherwise close patient monitoring is required due to potential for increased hematologic toxicities
	Ethanol	Decreased clinical response of HCV infection to interferon	Ethanol-mediated ↑ viral replication, ↑ inflammation/fibrosis; inhibition of intracellular signaling pathways and ↓ expression of interferon-induced antiviral gene products	Avoid ethanol consumption during treatment with interferon

ATV atazanavir, *AUC* area under the plasma concentration vs. time curve, *CL* total systemic clearance, C_{max} maximum plasma concentration, *CYP* cytochrome P450, *ddI* didanosine, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *IFN* interferon, *NSAID* non-steroidal anti-inflammatory drug, *RIB* ribavirin, *SSRI* serotonin-specific reuptake inhibitor, *TCA* tricyclic antidepressant, T_{max} time to maximum plasma concentration, *TMP/SMX* trimethoprim/sulfamethoxazole, *ZDV* zidovudine

coinfection with HIV and HCV may be as high as 90% [93, 94]. Ribavirin monotherapy is ineffective in the chronic treatment of HCV infections with a sustained virological response rate (SVR) of close to 0% in clinical studies, while the SVR of interferon-α alone is approximately 20% [94–97]. However, the combination of ribavirin plus interferon-α is associated with SVR rates of approximately 40% [94, 95, 97]. The synergistic SVR associated with ribavirin plus interferon-α combination therapy occurs through mechanisms which are not completely understood, but which may involve drug-induced stimulation of an anti-HCV immune response and/or direct antiviral effects of the drugs. *In vitro* models indicate that direct, synergistic antiviral effects of the drugs occur at physiologically relevant concentrations [98]. Whether interferon-α stimulation of infected cells renders them more susceptible to the effects of ribavirin or *vice versa* is not clear and the exact mechanisms involved are unknown. Regardless of the mechanisms, the combination of ribavirin with pegylated interferon-α has become a standard of care [98].

No pharmacokinetic interactions have been noted with combined administration of ribavirin and interferon alfa-2b or peginterferon alfa-2b [99, 100]. However, hemolytic anemia with hemoglobin values of less than 10 gm/dL was reported in approximately 10% of patients receiving combination therapy with ribavirin and interferon alfa-2b, usually occurring within 1–2 weeks of initiating ribavirin therapy [101].

No studies have specifically evaluated the potential for interactions involving inhaled ribavirin; however, the manufacturer recommends that inhaled ribavirin not be administered together with other drugs given by the inhaled route [102]. The remainder of this section deals only with drug interactions involving orally or intravenously administered ribavirin.

When single oral doses of ribavirin were co-administered with a high-fat meal, T_{max} of ribavirin was doubled, the AUC was increased by 42%, and the C_{max} was increased by 66% compared to parameters obtained in the fasting state. Ribavirin should thus be routinely administered with food in order to maximize oral absorption [99, 100]. Concomitant administration of magnesium, aluminum, and simethicone antacids reduced the AUC of oral ribavirin by 14% [99, 100]. This reduction in bioavailability may be related to either increases in intestinal transit time or a change in gastrointestinal pH; however, it is not considered to be clinically relevant [99, 100].

Ribavirin elimination is accomplished through a mixture of hepatic and renal processes including reversible phosphorylation, degradation by deribosylation and amide hydrolysis, and elimination of unchanged drug through the kidneys with evidence of both glomerular filtration and renal tubular secretion [103]. Ribavirin does not appear to be influenced by, nor be a substrate of, CYP450 enzyme systems based on *in vitro* human and rat microsomal liver preparations; there is furthermore no evidence for induction or inhibition of 2C9, 2C19, 2D6, or 3A4 enzymes [99, 100].

Due to ribavirin's potential for hematologic toxicities, concomitant therapy with other agents that may also cause myelosuppression should be used only with caution and carefully monitored [99, 100, 104]. Several case reports describe severe myelosuppression with the combination of ribavirin plus azathioprine in the treatment of inflammatory bowel diseases and coexistent HCV infection. The proposed mechanism is interference with the normal clearance of azathioprine intermediate

metabolites through ribavirin-induced inhibition of inosine monophosphate dehydrogenase (IMPDH). Inhibition of IMPDH leads to increased levels of methylated azathioprine metabolites, e.g., 6-methylthioinosine monophosphate (6-MTIMP), which have been associated with myelotoxicity [105–108]. Patients with HIV/HCV coinfection who were administered zidovudine in combination with pegylated interferon-α plus ribavirin developed severe neutropenia (ANC < 500) and anemia (hemoglobin <8 gm/dL) more frequently than did patients not receiving zidovudine. This increased incidence of hematologic toxicity with ribavirin plus zidovudine is apparently due to overlapping toxicities rather than pharmacokinetic alterations and are usually able to be clinically managed through dose reduction or drug discontinuation [99, 100, 109, 110].

Ribavirin is a guanosine analogue and may compete with zidovudine, lamivudine, stavudine, emtricitabine, and other nucleosides for intracellular phosphorylation [99, 100, 110]. *In vitro* studies indicate that ribavirin induces an increase in deoxythymidine triphosphate which results in feedback inhibition of thymidine kinase and decreased intracellular formation of phosphorylated zidovudine [111, 112]. These effects of ribavirin may potentially increase zidovudine toxicities while also reducing clinical efficacy of the drug in HIV-infected patients [113].

Although myelosuppression with the combination of ribavirin and zidovudine has been noted as previously described, several published studies of HCV in the setting of HIV coinfection showed no evidence of adverse clinical outcomes related to antiviral drug failure with combination therapy [114–116]. Another recent pharmacokinetic study of 14 subjects receiving zidovudine also found no significant impact on zidovudine triphosphate AUC, plasma zidovudine AUC, or the ratio of zidovudine triphosphate to zidovudine AUC after the addition of ribavirin [117]. Since the clinical pharmacology of zidovudine does not appear to be altered despite *in vitro* findings, dosage adjustment does not appear to be needed with concomitant ribavirin therapy. Likewise, although *in vitro* studies indicate that the anti-HIV activity of tenofovir may be antagonized by ribavirin [118], no interaction between oral ribavirin and tenofovir was observed in a multiple-dose interaction study in 23 healthy subjects [119]. Other studies have also failed to find evidence of adverse clinical outcomes in patients receiving ribavirin for anti-HCV treatment along with HAART regimens, so the clinical significance of *in vitro* studies remain unknown but does not appear to be highly relevant [109, 120, 121].

Ribavirin is also a potent inhibitor of inosine monophosphate dehydrogenase, a key enzyme necessary for guanosine nucleotide biosynthesis. Inhibition of this enzyme in patients receiving didanosine for treatment of HIV infection promotes formation of dideoxyadenosine-5′-triphosphate, elevated levels of which are in turn associated with the mitochondrial toxicity of didanosine. There are a number of reports describing lactic acidosis and pancreatitis in patients receiving concomitant ribavirin and didanosine therapy [100, 109, 122–124]. In one study, the incidence of symptomatic lactic acidosis was 33/1,000 patient years in those patients treated for HCV with ribavirin and receiving HAART versus 13.5/1,000 patient years in those receiving HARRT only. In this study, both didanosine and stavudine were significantly associated with increased risk of symptomatic lactic acidosis

($P<0.01$ and $P=0.04$) [115]. Since no pharmacokinetic interactions have been observed between ribavirin and didanosine [125], toxicities are presumed to be caused by ribavirin-induced enhanced mitochondrial toxicity [94, 126–129]. It has been stated that didanosine-related lactic acidosis and pancreatitis occurs more rapidly in the presence of ribavirin than with didanosine alone, usually within the first 3 months of therapy [99, 100]. Finally, this toxic interaction may persist for up to 1–2 months based on the very long half-life of ribavirin (approximately 120–170 h) [99, 100]. Based on all of these considerations, extreme caution should be used in combining ribavirin with didanosine and concomitant use of the two drugs should be avoided if possible. Combination therapy with stavudine and abacavir should be approached with caution as well [99, 100, 109]. There is no indication of risk with other antiretroviral drugs such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors [99, 100].

The addition of ribavirin plus pegylated interferon for HCV treatment in HIV-infected patients receiving the protease inhibitor atazanavir has been associated with a significantly increased incidence of hyperbilirubinemia [130]. A total of 72 patients who were co-infected with HIV and HCV were evaluated following the addition of HCV therapy to existing antiretroviral drug regimens. By 4 weeks, patients also receiving atazanavir had a significantly greater increase in total bilirubin levels ($P=0.003$). The proportion of patients experiencing increases of more than 1 mg/dL was also significantly greater in patients receiving atazanavir (45% vs. 3%, $P=0.001$). The proposed mechanism of toxicity is ribavirin-induced hemolysis of red blood cells and increased production of bilirubin, followed by an inhibitory competition by atazanavir of uridinglucuronosyltransferase (UGT) 1A1, an enzyme which is normally responsible for bilirubin conjugation. This combination of effects thus leads to increased serum bilirubin levels and jaundice [130].

Finally, the use of ribavirin in patients receiving chronic warfarin therapy has reportedly cause a decrease in prothrombin time. Although the mechanism involved is unknown, the interaction was clinically significant in the reported case [131].

14.5.2 The Interferons

Very few formal studies of potential drug interactions have been conducted for most interferon drugs [132–137]. Despite this, a considerable amount of information (although often conflicting) is available regarding potential interactions with the interferons, particularly related to interferon-induced alterations in CYP450-related drug metabolism; these potential interactions are summarized in Table 14.4. The effects of the various interferons on CYP450 activity as reported from various sources is highly variable and probably depends on use of specific interferons, specific CYP enzyme families studied, and interferon doses. The following summaries will therefore focus on peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (PegIntron®), two interferon products specifically FDA-indicated for use in the treatment of chronic HCV infection.

The interferons as a whole have long been associated with reduced CYP450 activity after it was determined that CYP downregulation during acute viral infections was primarily mediated by interferons [138–141]. Interferon effects on CYP450 metabolism occur through unclear mechanisms and may be attributed to either increased degradation, suppressed synthesis, or direct inhibition of the enzymes [132, 133, 137].

With few exceptions, the interferons have consistently demonstrated decreased clearance of various drugs metabolized by CYP1A and CYP 3A subfamilies. Studies which failed to show significant changes in hepatic drug metabolism were using low doses of interferon-α in metastatic cancer and HCV (e.g., three million units three times per week) [142–144]. Chronic administration of low-dose interferon-α was associated with a moderate decrease in theophylline metabolism, minimal effect on antipyrine clearance, and minimal effect on hexobarbital metabolism [142–145]. However, larger doses of interferons have been associated with more pronounced reductions in theophylline and antipyrine metabolism, suggesting that the effects of interferons on CYP1A2 drug metabolism are likely to be dose-dependent [132, 146]. Once-weekly administration of interferon-α for 4 weeks in healthy subjects resulted in inhibition of CYP450 1A2 and a 25% increase in theophylline AUC [132], while other studies have reported 100% increases in theophylline concentrations after interferon treatment [147, 148]. Interferon-α has also been shown to inhibit CYP3A4 metabolism using the ^{14}C-erythromycin breath test as a marker of CYP3A4 activity in healthy volunteers and patients with HCV [149]. Despite data indicating alterations in CYP1A2 and CYP3A4 activity, these changes are not always consistently reported [132] and/or may not always be considered clinically significant with required changes in drug dosing [133]. In light of potentially variable and dose-related effects, patients receiving drugs metabolized by CYP1A2 (e.g., theophylline, caffeine, antipyrine, tricyclic antidepressants [TCAs], olanzapine, clozapine) or CYP3A (e.g., azole antifungals, macrolide antibiotics, many antiretroviral agents, some immunosuppressants, some serotonin-specific reuptake inhibitors [SSRIs], TCAs, certain statins, opiate analgesics, benzodiazepines, antipsychotics, barbiturates, calcium channel antagonists) should be carefully monitored during interferon therapy.

Although it has been stated that interferon-α has no effect on the pharmacokinetics of drugs metabolized by CYP 2C9, CYP2C11, CYP2C19, or CYP2D6 [132, 150], it has elsewhere been reported that the activities of CYP2C8/9 and CYP2D6 were actually induced by an average of 28–66% in 22 patients with chronic HCV who received interferon-α for 4 weeks [133]. These effects were highly variable, however, with 40% of patients exhibiting either inhibition of CYP activity or no change rather than increased activity [133]. Close monitoring is therefore recommended during interferon therapy with the concomitant use of drugs metabolized by CYP2C8/9 (e.g., warfarin, phenytoin, NSAIDS, angiotensin receptor blockers, certain statins, sulfonylureas) or CYP2D6 (e.g., β-blockers, lidocaine, flecainide, TCA, SSRIs, opiate analgesics, antipsychotics) as the therapeutic effects of these drugs may be either decreased, increased, or unchanged [133]. As a case in point, increased effects of warfarin during interferon therapy have been previously described in two case reports [151, 152].

The pharmacokinetics of methadone were assessed in 18 patients with chronic HCV who received concomitant administration of interferon-α2b [133]. All patients were stable on chronic methadone treatment at the time of interferon initiation. A mean 16% increase in methadone AUC was observed after 4 weeks of interferon therapy, but the AUC was increased by 100% in two patients. This interaction is probably related to inhibition of CYP3A4 metabolism. The clinical significance of this interaction is unknown and likely highly variable; cautious monitoring of sedative and respiratory effects of methadone is warranted during the first few weeks of combined therapy [133].

Although ribavirin plus pegylated interferon-α is considered first-line therapy for chronic HCV infection, this combination has the potential for increased incidence and/or severity of myelosuppression due to overlapping potentials for hematologic toxicity [99, 100, 132, 133]. As previously described, hemolytic anemia occurred in 10% of patients receiving combination therapy with ribavirin and interferon alfa-2b within 1–2 weeks of initiating ribavirin therapy [133]. Such interactions between ribavirin and the interferons have not been not consistently reported [99, 100], however close monitoring for hematologic toxicities is required during therapy with ribavirin and interferon.

Caution should also be exercised during combined use of interferons with other potentially myelosuppressive drugs. As previously described, the administration of zidovudine in combination with pegylated interferon-α plus ribavirin was associated with increased rates of severe neutropenia and anemia [109]. Interferon has been associated with significant alterations in zidovudine pharmacokinetics [153]; decreased zidovudine clearance and increased AUC was found in 8 patients with AIDS who were started on interferon-β after 8 weeks of zidovudine monotherapy. Interferon has also been associated with significant changes in zidovudine metabolic rates, plasma elimination rates, and decreased ratio of parent drug to glucuronide metabolite after initiation of interferon; such metabolic alterations may contribute to the increased risk of myelosuppression with the combination of interferon and zidovudine. In contrast to the significant effects on zidovudine metabolism, no interaction was found between interferon-α and didanosine [154]. Severe and irreversible granulocytopenia has also been reported in several patients during concomitant use of interferon alfa-2a and angiotensin converting enzyme (ACE) inhibitors including both captopril and enalapril [155, 156]. Potential drug interactions resulting in increased drug toxicities have been reported during concomitant use of interferon-α and antineoplastic agents including 5-fluorouracil (myelosuppression) [157], hydroxyurea (myelosuppression, vasculitis) [158], and melphalan (myelosuppression) [159, 160]. Studies have not consistently shown alterations in pharmacokinetic parameters such as C_{max} or AUC and the mechanisms behind these potential interactions with certain antineoplastic agents are unknown [161–166]. However, the potential for severe toxicities necessitates careful patient monitoring during combined use of these agents. Suspected additive myelosuppression during combined peginterferon and thalidomide therapy has also been reported [167]. Finally, hematologic toxicity has also been reported in a patient receiving combined interferon-α and clozapine; although the specific mechanisms for this interaction were not defined, clozapine is known to be a CYP1A2 substrate [168].

A number of studies have demonstrated a decreased response to interferon-α therapy in the treatment of HCV infection among patients who consume alcohol [169–173]. Rates of SVR during interferon therapy have been shown to be directly related to the level of ethanol consumption. In one study non-drinkers had a 53.3% response rate to interferon, while responses were 42.9% among light drinkers (<70 g of ethanol/day, or approximately 2.5 oz) and 0% among heavy drinkers (>70 g ethanol/day); the difference between non-drinkers and heavy drinkers was statistically significant ($P < 0.01$) [169]. In another study, only 10.7% of patients failing to respond to interferon therapy were non-drinkers compared to 63.1% of patients with any level of alcohol consumption; furthermore, overall non-response rates directly increased according to the level of alcohol consumption [172]. While the association between ethanol consumption and response of HCV infection to treatment with interferon-α is clear, the actual cause is unclear. Alcohol has been shown to accelerate the course of HCV disease through increased HCV replication, enhanced oxidative stress, increased inflammatory and fibrotic effects, and modulation of the immune response to HCV infection, therefore indicating that the effects of alcohol on interferon response are more attributable to effects on the underlying infectious process [174]. However, *in vitro* data also suggest that alcohol may directly inhibit the actions of interferon-α through effects on intracellular signaling pathways which are activated after binding of interferon to cellular receptors. Specifically, alcohol has been shown *in vitro* to inhibit phosphorylation and activation of specific cytoplasmic transcription factors (signal transducers and activators of transcription, or STATs); the inhibition of these STATs then results in downstream decreases in expression of antiviral interferon-stimulated genes (ISGs) which are responsible for the efficacy of interferon against HCV [174]. The effects of alcohol on interferon response rates are thus multifactorial and likely involve both direct inhibition of interferon's pharmacologic activity as well as indirect disease state-mediated effects on HVC infection. Patients infected with HCV should thus abstain from any level of alcohol consumption while receiving therapy with interferon-α.

References

1. Zovirax (acyclovir) product information. Research Triangle Park, NC: GlaxoSmithKline, 2007.
2. Valtrex (valacyclovir) product information. Research triangle park, NC: GlaxoSmithKline, 2010.
3. Sitar D, Aoki FY, Bow EJ. Acyclovir bioavailability in patients with acute myelogenous leukemia treated with daunorubicin and cytarabine. J Clin Pharmacol 2008;48:995–998.
4. Parmeggiani A, Riva R, Posar A, Rossi PG. Possible interaction between acyclovir and antiepileptic treatment. Ther Drug Monit 1995;17:312–315.
5. Laskin OL, de Miranda P, Kinh DH, et al. Effects of probenecid on the pharmacokinetics and elimination of acyclovir in humans. Antimicrob Agents Chemother 1982;21:691–715.
6. Sylvester RK, Leitch J, Granum C. Does acyclovir increase serum lithium levels? Pharmacotherapy 1996;16:466–468.
7. Bullingham R, Nicholls A, Kamm B. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharmacokinet 1998;34:429–455.

8. Shah J, Juan D, Bullingham R. A single dose drug interaction study of mycophenolate mofetil and acyclovir in normal subjects [abstract]. J Clin Pharmacol 1994;34:1029–1033.
9. Gimenez F, Foeillet E, Bourdon O, et al. Evaluation of pharmacokinetic interactions after oral administration of mycophenolate mofetil and valacyclovir or acyclovir to healthy subjects. Clin Pharmacokinet 2004;43:685–692.
10. Vomiero G, Carpenter B, Robb I, Filler G. Combination of ceftriaxone and acyclovir – an underestimated nephrotoxic potential? Pediatr Nephrol 2002;17:633–637.
11. Maeda Y, Konishi T, Omoda K, et al. Inhibition of theophylline metabolism by aciclovir. Biol Pharm Bull 1996;19:1591–1595.
12. Tartaglione TA, Collier AC, Opheim K, Gianola FG, Benedetti J, Corey L. Pharmacokinetic evaluations of low-and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. Antimicrob Agents Chemother 1991;35:2225–2231.
13. Cooper DA, Pedersen C, Aiuti F, et al. The efficacy and safety of zidovudine with or without acyclovir in the treatment of patients with AIDS-related complex. The European-Australian Collaborative Group. AIDS 1991;5:933–943.
14. Pedersen C, Cooper DA, Brun-Vezinet F, et al. The effect of treatment with zidovudine with or without acyclovir on HIV p24 antigenaemia in patient with AIDS or AIDS-related complex. AIDS 1992;6:821–825.
15. Cooper DA, Pehrson PO, Pedersen C, et al. The efficacy and safety of zidovudine alone or as cotherapy with acyclovir for the treatment of patients with AIDS and AIDS-related complex: a double-blind randomized trial. European-Australian Collaborative Group. AIDS 1993;7:197–207.
16. Stein DS, Graham NM, Park LP, et al. The effect of the interaction of acyclovir with zidovudine on progression to AIDS and survival. Analysis of data in the Multicenter AIDS Cohort Study. Ann Intern Med 1994;121:100–108.
17. Gallant JE, Moore RD, Keruly J, Richman DD, Chaisson RE. Lack of association between acyclovir use and survival in patients with advanced acquired immunodeficiency virus disease treated with zidovudine. Zidovudine Epidemiology Study Group. J Infect Dis 1995;172:346–352.
18. Famvir (famciclovir) product information. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2009.
19. Fowles SE, Pierce MC, Prince WT, et al. Effect of food on the bioavailability and pharmacokinetics of penciclovir, a novel antiherpes agent, following oral administration of the prodrug, famciclovir. Br J Clin Pharmacol 1990;29:620P,621P.
20. Fowles SE, Fairless AJ, Pierce DM, et al. A further study of the effect of food on the bioavailability and pharmacokinetics of penciclovir after oral administration of famciclovir. Br J Clin Pharmacol 1991;32:657P.
21. Lavella J, Follansbee S, Trapnell CB, et al. Effect of food on the relative bioavailability of oral ganciclovir. J Clin Pharmacol 1996;36:238–241.
22. Brown F, Banken L, Saywell K, et al. Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. Clin Pharmacokinet 1999;37:167–176.
23. Markham A, Faulds D. Ganciclovir: an update of its therapeutic use in cytomegalovirus infection. Drugs 1994;48:455–484.
24. Valcyte (valganciclovir) product information. Nutley, NJ: Roche laboratories, Inc, 2001.
25. Cytovene (ganciclovir) product information. South San Francisco, CA: Genentech USA, Inc, 2010.
26. Hochster H, Dieterich D, Bozzette S, et al. Toxicity of combined ganciclovir and zidovudine for cytomegalovirus disease associated with AIDS: an AIDS clinical trials group study. Ann Intern Med 1990;113:111–117.
27. Pinching AJ, Helbert M, Peddle B, Robinson D, Janes K, Gor D. Clinical experience with zidovudine for patients with acquired immune deficiency syndrome and acquired immune deficiency syndrome-related complex. J Infect 1989;18(Suppl1):33–40.

28. Snoeck R, Lagneaux L, Delforge A, et al. Inhibitory effects of potent inhibitors of human immunodeficiency virus and cytomegalovirus on the growth of human granulocyte-macrophage progenitor cells in vitro. Eur J Clin Micro Infect Dis 1990;9:615–618.
29. Causey D. Concomitant ganciclovir and zidovudine treatment for cytomegalovirus retinitis in patients with HIV infection: an approach to treatment. J Acquir Immune Defic Synd 1991; 4(Suppl 1):S16–21.
30. Burger DM, Meenhorst PL, Koks CHW, Beijnen JH. Drug interactions with zidovudine. AIDS 1993;7:445–460.
31. Millar AB, Miller RF, Patou G, Mindel A, Marsh R, Semple SJG. Treatment of cytomegalovirus retinitis with zidovudine and ganciclovir in patients with AIDS: outcome and toxicity. Genitourin Med 1990;66:156–158.
32. Freitas VR, Fraser-Smith EB, Matthews TR. Efficacy of ganciclovir in combination with other antimicrobial agents against cytomegalovirus *in vitro* and *in vivo*. Antiviral Res 1993;20:1–12.
33. Cimoch PJ, Lavelle J, Pollard R, et al. Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. J Acquir Immune Defic Syndr Hum Retrovirol 1998;17:227–234.
34. Frascino RJ, Gaines Griffy K, Jung D, Yu S. Multiple dose crossover study of IV ganciclovir induction dose (5 mg/kg IV q12h) and didanosine (200 mg po q12h) in HIV-infected persons. In: Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 17–20, 1995, Abstract A-27.
35. Jung D, Griffy K, Dorr A, et al. Effect of high-dose oral ganciclovir on didanosine disposition in human immunodeficiency virus (HIV)-positive patients. J Clin Pharmacol 1998; 38:1057–1062.
36. Tseng AL, Salit IE. CD4+ cell count decline despite HIV suppression: a probable didanosine-valganciclovir interaction. Ann Pharmacother 2007;41:512–517.
37. Ray AS, Olson L, Fridland A. Role of purine nucleoside phosphorylase in interactions between 2′,3′-dideoxyinosine and allopurinol, ganciclovir, or tenofovir. Antimicrob Agents Chemother 2004;48:1089–1095.
38. Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. Mortality in patients with the acquired immune deficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. N Engl J Med 1992;326:213–220.
39. Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. Morbidity and toxic effects associated with ganciclovir or foscarnet therapy in a randomized cytomegalovirus retinitis trial. Arch Intern Med 1995;155:65–74.
40. Merigan TC, Renlund DG, Keay S, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. N Engl J Med 1992;326:1182–1186.
41. Schmidt GM, Horak DA, Niland JC, et al. A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplants. N Engl J Med 1991;324:1005–1011.
42. Michaelis M, Ha TAT, Doerr HW, Cinati J Jr. Valproic acid interferes with antiviral treatment in human cytomegalovirus-infected endothelial cells. Cardiovasc Res 2008;77:544–550.
43. Faulds D, Heel RC. Ganciclovir – a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. Drugs 1990;39:597–638.
44. Vistide (cidofovir) product information. Foster City, CA: Gilead Sciences, Inc., 2000.
45. Lalezari J, Jaffe HS, Schaker T, et al. A randomized, double-blind placebo controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. J Infect Dis 1997;176:892–898.
46. Lalezari JP, Stagg RJ, Kuppermann BD, et al. Intravenous cidofovir for peripheral cytomegalovirus retinitis in patients with AIDS. Ann Intern Med 1997;126:257–263.
47. Studies of Ocular Complications of AIDS Research Group in Collaboration with the AIDS Clinical Trials Group. Parenteral cidofovir for cytomegalovirus retinitis in patients with AIDS: the HPMPC peripheral cytomegalovirus retinitis trial. Ann Intern Med 1997;126:264–274.

48. Lalezari JP, Drew WL, Glutzer E, et al. (*S*)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl] cytosine (cidofovir): results of a phase I/II study of a novel antiviral nucleoside analogue. J Infect Dis 1995;171:788–796.
49. Polis MA, Spooner KM, Baird BF, et al. Anticytomegaloviral activity and safety of cidofovir in patients with human immunodeficiency virus infection and cytomegalovirus viruria. Antimicrob Agents Chemother 1995;39:882–886.
50. Wachsman M, Petty BG, Cundy KC, et al. Pharmacokinetics, safety and bioavailability of HPMPC (cidofovir) in human immunodeficiency virus-infected subjects. Antiviral Res 1996;29:153–161.
51. Tseng AL, Walmsley SL. Rifabutin-associated uveitis. Ann Pharmacother 1995;29:1149–1155.
52. Davis JL, Taskintuna I, Freeman WR, Weinberg DV, Feuer WR, Leonard RE. Iritis and hypotony after treatment with intravenous cidofovir for cytomegalovirus retinitis. Arch Ophthalmol 1997;115:733–737.
53. Palau LA, Tufty GT, Pankey GA. Recurrent iritis after intravenous administration of cidofovir. Clin Infect Dis 1997;25:337,338.
54. Tseng AL, Mortimer CB, Salit IE. Iritis associated with intravenous cidofovir. Ann Pharmacother 1999;33:167–171.
55. Foscavir (foscarnet sodium) product information. Wilmington, DE: AstraZeneca, 2006.
56. Aweeka FT, Brody SR, Jacobson M, Botwin K, Martin-Munley S. Is there a pharmacokinetic interaction between foscarnet and zalcitabine during concomitant administration? Clin Ther 1998;20:232–243.
57. Morales JM, Muñoz MA, Fernandez Zatarain G, et al. Reversible acute renal failure caused by the combined use of foscarnet and cyclosporin in organ transplanted patients. Nephrol Dial Transplant 1995;10:882,883.
58. Fan-Havard P, Sanchorawala V, Oh J, Moser EM, Smith SP. Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. Ann Pharmacother 1994;28:869–872.
59. Matsuo H, Ryu M, Nagata A, et al. Neurotoxicodynamics of the interaction between ciprofloxacin and foscarnet in mice. Antimicrob Agents Chemother 1998;42:691–694.
60. Koshida R, Vrang L, Gilljam G, Harmenberg J, Oberg B, Wahren B. Inhibition of human immunodeficiency virus in vitro by combinations of 3′-azido-3′-deoxythymidine and foscarnet. Antimicrob Agents Chemother 1989;33:778–780.
61. Eriksson BF, Schinazi RF. Combinations of 3′-azido-3′-deoxythymidine (zidovudine) and phosphonoformate (foscarnet) against human immunodeficiency virus type 1 and cytomegalovirus replication in vitro. Antimicrob Agents Chemother 1989;33:778–780.
62. Aweeka FT, Gambertoglio JG, van der Horst C, Raasch R, Jacobson MA. Pharmacokinetics of concomitantly administered foscarnet and zidovudine for treatment of human immunodeficiency virus infection (AIDS Clinical Trials Group protocol 053). Antimicrob Agents Chemother 1992;36:1773–1778.
63. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. Clin Pharmacokinet 1988;14:35–51.
64. Wills RJ, Rodriguez LC, Choma N, Oakes M. Influence of meal on the bioavailability of rimantadine HCL. J Clin Pharmacol 1987;27:821–823.
65. Symmetrel (amantadine) product information. Chadds Ford, PA: Endo Pharmaceuticals, 2007.
66. Flumadine (rimantadine hydrochloride) product infection. St. Louis, MO: Forest Pharmaceuticals, Inc, 2010.
67. Wilson TW, Rajput AH. Amantadine-dyazide interaction. Can Med Assoc J 1983;12:974,975.
68. Speeg KV, Leighton JA, Maldonado AL. Toxic delirium in a patient taking amantadine and trimethoprim-sulfamethoxazole. Am J Med Sci 1989;29:410–412.
69. Wills RJ. Update on rimantadine's clinical pharmacokinetics. J Resp Dis 1989;10:S20-S25.
70. Millet VM, Dreisbach M, Bryson YJ. Double-blind controlled study of central nervous system side effects of amantadine, rimantadine, and chlorpheniramine. Antimicrob Agents Chemother 1982;211:1–4.
71. Harper RW, Knothe BU. Coloured Lilliputian hallucinations with amantadine. Med J Aust 1973;19:444,445.

72. Postma JU, Tilburg WV. Visual hallucinations and delirium during treatment with amantadine (Symmetrel). J Am Geriatr Soc 1975;23:212–215.
73. Stroe AE, Hall J, Amin F. Psychotic episode related to phenylpropanolamine and amantadine in a healthy female. Gen Hosp Psych 1995;17:457,458.
74. Trappler B, Miyashiro AM. Buproprion-amantadine-associated neurotoxicity. J Clin Psych 2000;61:61,62.
75. Tamiflu (oseltamivir) product information. South San Francisco, CA: Genentech USA, Inc., 2010.
76. Snell P, Oo C, Dorr A, Barrett J. Lack of pharmacokinetic interaction between the oral anti-influenza neuraminidase inhibitor prodrug oseltamivir and antacids. Br J Clin Pharmacol 2002;544:372–377.
77. Hill G, Cihlar T, Oo C, et al. The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion – correlation of in vivo and in vitro studies. Drug Metab Disposit 2002;301:13–19.
78. Tang M, Mukundan M, Yang J et al. Antiplatelet agents aspirin and clopidogrel are hydrolyzed by distinct carboxylesterases and the hydrolyses are markedly altered with certain polymorphistic variants. J Pharmacol Exp Ther 2006;319:1467–1476.
79. Shi D, Yang J, Yang D, et al. Anti-influenza prodrug oseltamivir is activated by carboxylesterase human carboxyesterase 1, and the activation is inhibited by antiplatelet agent clopidogrel. J Pharmacol Exp Ther 2006;319:1477–1484.
80. Fowler S, Lennon SM, Hoffmann G, Rayner C. Comments on "Anti-influenza prodrug oseltamivir is activated by carboxylesterase human carboxyesterase 1, and the activation is inhibited by antiplatelet agent clopidogrel" [letter]. J Pharmacol Exp Ther 2006;322:422,423.
81. Davies BE. Pharmacokinetics of oseltamivir: an oral antiviral for the treatment and prophylaxis of influenza in diverse populations. J Antimicrob Chemother 2010;65(Suppl 2):ii5–10.
82. Butler D. Wartime tactic doubles power of scarce bird-flu drug. Nature 2005;438:6.
83. Howton JC. Probenecid with oseltamivir for human influenza A (H5N1) virus infection? N Engl J Med 2006;354:879,880.
84. Holodniy M, Penzak SR, Stright TM, et al. Pharmacokinetics and tolerability of oseltamivir combined with probenecid. Antimicrob Agents Chemother 2008;52:3013–3021.
85. Rayner CR, Chanu P, Gieschke R, Boak LM, Jonsson EN. Population pharmacokinetics of oseltamivir when coadministered with probenecid. J Clin Pharmacol 2008;48:935–947.
86. Raisch DW, Straight TM, Holodniy M. Thrombocytopenia from combination treatment with oseltamivir and probenecid: case report, MedWatch data summary, and review of the literature. Pharmacotherapy 2009;29:988–992.
87. He G, Massarella J, Aitken M, et al. The safety and pharmacokinetics of the neuraminidase inhibitor RO 64-0796 when administered concurrently with paracetamol. Clin Microbiol Infect 1999;5:150 [abstract P.247].
88. Oo C, Barrett J, Dorr A, Liu B, Ward P. Lack of pharmacokinetic interaction between the oral anti-influenza prodrug oseltamivir and aspirin. Antimicrob Agents Chemother 2002;466:1993–1995.
89. Davies BE, Aceves BP, Brewster M. Effect of oseltamivir on anticoagulation: a crossover study in patients stabilized on warfarin. In: Abstracts of the 49th Interscience Conference on Antimicrobiao Agents and Chemotherapy, San Francisco, CA, September 12–15, 2009, Abstract A1-596.
90. Morrison D, Roy S, Rayner C, et al. A randomized, crossover study to evaluate the pharmacokinetics of amantadine and oseltamivir administered alone and in combination. PLoS ONE 2007;2:e1305.
91. Daniel MJ, Barnett JM, Pearson BA. The low potential for drug interactions with zanamivir. Clin Pharmacokinet 1999;36:41–50.
92. Relenza (zanamivir) product information. Research Triangle Park, NC: GlaxoSmithKline, 2010.
93. Rockstroh JK. Management of hepatitis B and C in HIV co-infected patients. J Acquir Immune Defic Syndr 2003;34:S59–S65.
94. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatol 2009;49:1335–1374.

95. Gutfreund KS, Bain VC. Chronic viral hepatitis C: management update. Can Med Assoc J 2000;162:827–833.
96. Bodenheimer HC Jr, Lindsay KL, Davis GL, et al. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. Hepatol 1997;26:473–477.
97. Buckwold VE. Implications of finding synergistic *in vitro* drug-drug interactions between of interferon-α and ribavirin for the treatment of chronic hepatitis C. J Antimicrob Chemother 2004;53:413,414.
98. Buckwold VE, Wei J, Wenzel-Mathers M, et al. Synergistic in vitro interactions between alpha interferon and ribavirin against bovine viral diarrhea virus and yellow fever virus as surrogate models of hepatitis C viral replication. Antimicrob Agents Chemother 2003;47:2293–2298.
99. Rebetol (ribavirin) product information. Kenilworth, NJ: Schering Corporation, 2009.
100. Copegus (ribavirin) product information. Nutley, NJ: Roche Laboratories, Inc., 2010.
101. Intron A (interferon alfa-2b) product information. Kenilworth, NJ: Schering Corporation, 2009.
102. Virazole (ribavirin for inhalation) product information. Costa Mesa, CA: Valeant Pharmaceuticals North America, 2006.
103. Paroni R, Del Puppo M, Borghi C, Sirtori CR, Galli Kienle M. Pharmacokinetics of ribavirin and urinary excretion of the major metabolite 1,2,4-triazole-3-carboxamide in normal volunteers. Int J Clin Pharmacol Ther Toxicol 1989;27:302–307.
104. Huggins JW. Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug. Rev Infect Dis 1989;2:S750-S761.
105. Chaparro M, Trapero-Marugan M, Moreno-Otero R, Gisbert JP. Azathioprine plus ribavirin treatment and pancytopenia [letter]. Aliment Pharmacol Ther 2009;30:962,963.
106. Peyrin-Biroulet L, Cadranel JF, Nousbaum JB, et al. Interaction of ribavirin with azathioprine metabolism potentially induces myelosuppression. Aliment Pharmacol Ther 2008;28:984–993.
107. Hindorf U, Lindqvist M, Peterson C, et al. Pharmacogenetics during standardized initiation of thiopurine treatment in inflammatory bowel disease. Gut 2006;55:1423–1431.
108. Gilissen LP, Derijks LJ, Verhoeven HM, et al. Pancytopenia due to high 6-methylmercaptopurine levels in a 6-mercaptopurine treated patient with Crohn's disease. Dig Liver Dis 2007;39:182–186.
109. Perronne C. Antiviral hepatitis and antiretroviral drug interactions. J Hepatol 2006;44: 119–125.
110. Retrovir (zidovudine) package insert. Research Triangle Park, NC: GlaxoWellcome; Sept 2005.
111. Vogt MW, Hartshorn KL, Furman PA, et al. Ribavirin antagonizes the effect of azidothymidine on HIV replication. Science 1987;235:1376–1379.
112. Sim SM, Hoggard PG, Sales SD, Phiboonbanakit D, Hard CA, Back DJ. Effect of ribavirin on zidovudine efficacy and toxicity in vitro: a concentration-dependent interaction. AIDS Res Hum Retrovir 1998;14:1661–1667.
113. Tornevik Y, Ullman B, Balzarini J, Wahren B, Eriksson S. Cytotoxicity of 3′-azido-3′deoxythymidine correlates with 3′-azidothymidine-5′-monophosphate (AZTMP) levels, whereas anti-human immunodeficiency virus (HIV) activity correlates with 3′-azidothymidine-5′-triphosphate (AZTTTP) levels in cultured CEM T-lymphoblastoid cells. Biochem Pharmacol 1995;49:829–837.
114. Chung RT,, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med 2004;351:451–459.
115. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004;351: 438–450.
116. Gries J-M, Torriani FJ, Rodriguez-Torres M, et al. Effect of ribavirin on intracellular and plasma pharmacokinetics of nucleoside reverse transcriptase inhibitors in patients with human immunodeficiency virus-hepatitis C coinfection: results of a randomized clinical study. Antimicrob Agents Chemother 2005;49:3997–4008.

117. Aweeka FT, Kang M, Yu J-Y, et al. Pharmacokinetic evaluation of the effects of ribavirin on zidovudine triphosphate formation: ACTG 5092 s Study Team. HIV Medicine 2007; 8:288–294.
118. Margot NA, Miller MD. *In vitro* combination studies of tenofovir and other nucleoside analogues with ribavirin against HIV-1. Antiviral Therapy 2006;10:343–348.
119. Ramanathan S, Cheng A, Mittan A, Ebrahimi R, Kearney BP. Absence of clinically relevant pharmacokinetic interaction between ribavirin and tenofovir in healthy subjects. J Clin Pharmacol 2006;46:559–566.
120. Morsica G, De Bona A, Foppa CU, Sitia G, Finazzi R, Lazzarin A. Ribaviring therapy for chronic hepatitis C does not modify HIV viral load in HIV-1 positive patients under antiretroviral treatment. AIDS 2000;154:1656–1658.
121. Landau A, Batisse D, Piketty C, Jian R, Kazatchkine MD. Lack of interference between ribavirin and nucleoside analogues in HIV/HCV co-infected individuals undergoing concomitant antiretroviral and anti-HCV combination therapy. AIDS 2000;14:1857,1858.
122. Balzarini J, Naesens L, Robins MJ, DeClercq E. Potentiating effects of ribavirin on the in vitro and in vivo antiretrovirus activities of 2′,3′-dideoxyinosine and 2′,3′-dideoxy-2,6-diaminiopurine riboside. J AIDS 1990;3:1140–1147.
123. Videx (didanosine) product information. Princeton, NJ: Bristol-Myers Squibb Company, 2010.
124. Butt AA. Fatal lactic acidosis and pancreatitis associated with ribavirin and didanosine therapy. AIDS Reader 2003;13:344–348.
125. Japour AJ, Lertora JJ, Meehan PM, et al. A phase-1 study of the safety, pharmacokinetics, and antiviral activity of combination didanosine and ribavirin in patients with HIV-1 disease. J AIDS 1996;13:235–246.
126. Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. Lancet 2001;357:280,281.
127. Salmon-Ceron D, Chauvelot-Moachon L, Abad S, Silbermann B, Sogni P. Mitochondrial toxic effects and ribavirin [letter]. Lancet 2001;357:1803,1804.
128. Kakuda TN, Brinkman K. Mitochondrial toxic effects and ribavirin [letter]. Lancet 2001;357:1802,1803.
129. Soriano V, Sulkowski M, Bergin C, et al. Care of patients with chronic hepatitis C and HIV co-infection: recommendations from the HIV-HCV International Panel. AIDS 2002;16:813–828.
130. Rodriguez-Novoa S, Morello J, Gonzalez M, et al. Increase in serum bilirubin in HIV/hepatitis-C virus co-infected patients on atazanavir therapy following initiation of pegylated-interferon and ribavirin [letter]. AIDS 2008;22:2535–2537.
131. Schulman S. Inhibition of warfarin activity by ribavirin. Ann Pharmacother 2002;36:72–74.
132. Pegasys (peginterferon alfa-2a) product information. Nutley, NJ: Hoffman-LaRoche, Inc., 2002.
133. PegIntron (peginterferon alfa-2b) product information. Kenilworth, NJ: Schering Corporation, 2010.
134. Alferon N (interferon alfa-n3, human leukocyte derived). Philadelphia, PA: Hemispherx Biopharma, Inc, 2010.
135. Rebif (interferon beta-1a) product information. Rockland, MA: Serono, Inc., 2003.
136. Avonex (interferon beta-1a) product information. Cambridge, MA: Biogen, Ind., 2003.
137. Actimmune (interferon gamma-1b) product information. Brisbane, CA: InterMune, Inc., 2009.
138. Bleau AM, Levitchi MC, Maurice H, du Souich P. Cytochrome P450 inactivation by serum from humans with a viral infection and serum from rabbits with a turpentine-induced inflammation: the role of cytokines. Br J Pharmacol 2000;130:1777–1784.
139. Renton KW. Mannering GJ. Depression of hepatic cytochrome P-450-dependent monoxygenase systems with administered interferon inducing agents. Biochem Biophys Res Commun 1976;2:343–348.
140. Singh G, Renton KW. Interferon-mediated depression of ctyochrome P450-dependent drug biotransformation. Mol Pharmacol 1981;20:681–684.

141. Okuno H, Kitao Y, Takasu M, et al. Depression of drug-metabolizing activity in the human liver by interferon-α. Eur J Clin Pharmacol 1990;39:365–367.
142. Israel BC, Blouin RA, McIntyre W, Shedlofsky SI. Effects of interferon-α monotherapy on hepatic drug metabolism in cancer patients. Br J Clin Pharmacol 1993;36:229–235.
143. Pageaux GP, LeBricquir Y, Berthou F, et al. Effects of interferon-α on cytochrome P-450 isoforms 1A2 and 3A activities in patients with chronic hepatitis C. Eur J Gastro Hepatol 1998;10:491–495.
144. Carlson TJ, Billings RE. Role of nitric oxide in the cytokine-mediated regulation of cytochrome P-450. Mol Pharmacol 1996;49:796–801.
145. Brockmeyer NH. Barthel B. Mertins L. Goos M. Changes in antipyrine pharmacokinetics during influenza and after administration of interferon-alpha and –beta. Int J Clin Pharmacol Ther 1998;36:309–311.
146. Williams SJ, Farrell GC. Inhibition of antipyrine metabolism by interferon. Br J Clin Pharmacol 1986;22:610–612.
147. Williams SJ, Baird-Lambert JA, Farrell GC. Inhibition of theophylline metabolism by interferon. Lancet 1987;2:939–941.
148. Okuno H, Takasu M, Kano H, et al. Depression of drug-metabolizing activity in the human liver by interferon-β. Hepatology 1993;17:65–69.
149. Craig PI, Tapner M, Farrell GC. Interferon suppresses erythromycin metabolism in rats and human subjects. Hepatology 1993;17:230–235.
150. Sewer MB, Morgan ET. Nitric oxide-independent suppression of P450 2CII expression by interleukin-1β and endotoxin in primary rat hepatocytes. Biochem Pharmacol 1997;54: 729–737.
151. Adachi Y, Yokoyama Y, Nanno T, Yamamoto T. Potentiation of warfarin by interferon. BMJ 1995;311:292.
152. Serratrice J, Durand JM, Morange S. Interferon-alpha 2b interaction with acenocoumarol. Am J Hematol 1998;57:89.
153. Nokta M, Loh JP, Douidar SM, Ahmed AE, Pollard RE. Metabolic interaction of recombinant interferon-β and zidovudine in AIDS patients. J Interferon Res 1991;11:159–164.
154. Piscitelli SC, Amantea MA, Vogel S, et al. Effects of cytokines on antiviral pharmacokinetics: an alternative approach to assessment of drug interactions using bioequivalence guidelines. Antimicrob Agents Chemother 1996;40:161–165.
155. Casato M, Pucillo LP, Leoni M, et al. Granulocytopenia alter combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. Am J Med 1995;99:386–391.
156. Jacquot C, Caudwell V, Belenfant X. Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. Am J Med 1996;101:235,236.
157. Raderer M. Scheithauer W. Treatment of advanced colorectal cancer with 5-fluorouracil and interferon-alpha: an overview of clinical trials. Eur J Cancer 1995;31:1002–1008.
158. Al-Zahrani H, Gupta V, Minden MD, Messner HA, Lipton JH. Vascular events associated with alpha interferon therapy. Leuk Lymphoma 2003;44:471–475.
159. Österborg A, Björkholm M, Björeman M, et al. Natural interferon-α in combination with melphalan/prednisone versus melphalan/prednisone in the treatment of multiple myeloma stages II and III: a randomized study from the Myeloma Group of Central Sweden. Blood 1993;81:1428–1434.
160. Cooper MR, Dear K, McIntyre OR, et al. A randomized clinical trial comparing melphalan/ prednisone with or without interferon alfa-2b in newly diagnosed patients with multiple myeloma: a Cancer and Leukemia Group B study. J Clin Oncol 1993;11:155–160.
161. Pittman K, Perren T, Ward U, et al. Pharmacokinetics of 5-fluorouracil in colorectal cancer patients receiving interferon. Ann Oncol 1993;4:515,516.
162. Seymour MT, Patel N, Johnston A, Joel SP, Slevin ML. Lack of effect of interferon α2a upon fluorouracil pharmacokinetics. Br J Cancer 1994;70:724–728.

163. Schueller J, Czejka MJ, Schernthaner G, Fogl U, Jaeger W, Micksche M. Influence of interferon alfa-2b with or without folinic acid on pharmacokinetics of fluorouracil. Semin Oncol 1992;19(Suppl 2):93–97.
164. Danhauser LL, Freimann JH, Gilchrist TL, et al. Phase I and plasma pharmacokinetic study of infusional fluorouracil combined with recombinant interferon alfa-2b in patients with advanced cancer. J Clin Oncol 1993;11:751–761.
165. Schueller J, Czejka M. Pharmacokinetic interaction of 5-fluorouracil and interferon alpha-2b with or without folinic acid. Med Oncol 1995;12:47–53.
166. Ehrsson H, Eksborg S, Wallin I, Österborg A, Mellstedt H. Oral melphalan pharmacokinetics: influence of interferon-induced fever. Clin Pharmacol Ther 1990;47:86–90.
167. Gomez-Rangel JD, Ruiz-Delgado GJ, Ruiz-Arguelles GJ. Pegylated-interferon induced severe bone marrow hypoplasia in a patient with multiple myeloma receiving thalidomide. Am J Hematol 2003;74:290,291.
168. Hoffmann RM, Ott S, Parhofer KG, Batrl R, Pape GR. Interferon-a induced agranulocytosis in a patient on long-term clozapine therapy. J Hepatol 1998;29:170–175.
169. Okazaki K, Yoshihara H, Suzuki K, et al. Efficacy of interferon therapy in patients with chronic hepatitis C. Scand J Gastroenterol 1994;29:1039–1043.
170. Mochida S, Ohnishi K, Matsuo S, Kakihara K, Fujiwara K. Effect of alcohol intake on the efficacy of interferon therapy in patients with chronic hepatitis C as evaluated by multivariate logistic regression analysis. Alcohol Clin Exp Res 1996;20:A371-A377.
171. Ohnishi K, Matsuo S, Matsutani K, et al. Interferon therapy for chronic hepatitis C in habitual drinkers: comparison with chronic hepatitis C in infrequent drinkers. Am J Gastroenterol 1996;91:1374–1379.
172. Loguercio C, Di Pierro M, Di Marino MP, et al. Drinking habits of subjects with hepatitis C virus-related chronic liver disease: prevalence and effect on clinical, virological and pathological aspects. Alcohol Alcohol 2000;35:296–301.
173. Safdar K, Schiff ER. Alcohol and hepatitis C. Semin Liver Dis 2004;24:305–315.
174. McCartney EM, Beard MR. Impact of alcohol on hepatitis C virus replication and interferon signaling. World J Gastroenterol 2010;16:1337–1343.

Chapter 15
Antifungal Agents

Paul O. Gubbins and Jarrett R. Amsden

Abstract Antifungal agents are often prescribed in critically ill patients who receive many other concomitant medications. Antifungal agents have the potential to interact with a significant number of drugs. Interactions involving amphotericin B are a function of its adverse effects. The azoles primarily inhibit the biotransformation or transport of other medicines, which affects their distribution and elimination. The echinocandins have the lowest propensity to interact with other medicines. The clinical relevance of antifungal-drug interactions varies substantially. This chapter reviews the pharmacokinetic properties of antifungal agents and their clinically relevant drug interactions.

15.1 Introduction

Clinicians have multiple antifungal treatment options when managing systemic mycoses. Clear differences in the spectrum of activity, toxicity, and drug interaction potential exist between, and in some cases, within the antifungal therapeutic class. These differences can be exploited to tailor therapy against a specific pathogen. When choosing systemic antifungal therapy clinicians often consider available susceptibility data, the drug's spectrum of activity, and potential toxicities. However the significant potential for a systemic antifungal agent to interact with other medicines may be easily overlooked. Failure to recognize a drug-drug interaction involving systemic antifungal agents may lead to enhanced toxicity of the concomitant medication(s) or ineffective antifungal treatment. Therefore, clinicians must understand the drug interaction profile of antifungal agents.

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15.1.1 Amphotericin B Pharmacology

Amphotericin B binds to ergosterol, a key component of the fungal cell membrane, which disrupts the integrity of the fungal cell membrane and allows cellular components to leak out and ultimately cell death. Amphotericin B produces infusion-related toxicities, including hypotension, fever, rigors, and chills, and dose-dependent adverse effects, such as nephrotoxicity, azotemia, renal tubular acidosis, electrolyte imbalance, cardiac arrhythmias, and anemia [1]. Infusion-related adverse effects rarely limit the use amphotericin B or other agents, but dose-dependent adverse effects often do.

15.1.1.1 Distribution

Amphotericin B distributes to the liver and, to a lesser extent, other tissues (i.e. spleen, kidneys, and heart) [1]. Amphotericin B deoxycholate is protein bound (>95%), primarily to albumin and α_1-acid glycoprotein [2]. The apparent volume of distribution (Vd) of amphotericin B deoxycholate is 2–4 L/kg, which suggests extensive tissue distribution [2, 3]. The formulation of amphotericin B in a lipid vehicle alters its distribution by increasing drug uptake by the reticuloendothelial system. This reduced distribution into the kidneys decreases the propensity for acute kidney injury with lipid formulated amphotericin B compared to amphotericin B deoxycholate [2–4].

15.1.1.2 Elimination

Amphotericin B deoxycholate is cleared slowly from its distribution sites [3]. More than 90% of a dose can be recovered up to 1 week after administration [3]. Amphotericin B deoxycholate is mostly excreted as unchanged drug in the urine (20.6%) and feces (42.5%) [3]. The formulation of amphotericin B with lipids significantly alters its elimination [3].

15.1.2 5-Fluorocytosine (5-FC) Pharmacology

The oral absorption of 5-Fluorocytosine (5-FC) is rapid and complete. In the fasting state 5-FC bioavailability is approximately 90% [5]. 5-FC is minimally bound to plasma proteins and its Vd approximates total body water [5]. Approximately 90% of a 5-FC dose is renally excreted as unchanged drug [5]. Renal clearance (CL_R) correlates highly with creatinine clearance (CL_{CR}). 5-FC half-life ($t_{1/2}$) increases as CL_{CR} declines [5]. The deamination of 5-FC to 5-fluorouracil (5-FU) contributes to myelosuppression, the primary toxicity of 5-FC [5].

15.1.3 Azole Pharmacology

Commonly prescribed systemic azoles (itraconazole, fluconazole, voriconazole, and posaconazole) inhibit fungal cytochrome P450 (CYP)-dependent C-14 α-demethylase, which converts lanosterol to ergosterol. This inhibition depletes ergosterol, the essential sterol of the fungal cell membrane, and compromises cell membrane integrity. With the exception of fluconazole, the azoles are lipophilic weak bases that have poor water solubility or are insoluble.

The systemic azoles are CYP substrates and inhibitors to varying degrees. Certain azoles are also substrates and inhibitors of the MDR-1 gene product, P-glycoprotein (P-gp), and other transporter proteins [6–8]. P-gp, a large transmembrane efflux protein, shares substrate specificity and is extensively co-localized with CYP3A in the intestine, liver, kidney [8, 9].

15.1.3.1 Oral Absorption of the Systemic Azoles

Itraconazole is marketed as a capsule and solubilized in a 40% hydroxypropyl-β-cyclodextrin (HP-βCD) solution for oral and intravenous (i.v.) use. The i.v. solution is no longer available in the United States. Absorption from the capsule is slow, variable, and optimal under acidic gastric conditions or in the fed state [10]. To be absorbed the capsule must undergo dissolution. The concentration of drug in solution in gastric fluid varies depending on gastric pH and gastric emptying. Consequently, the amount of drug delivered to the intestinal epithelium may be insufficient to saturate intestinal CYP3A4. Therefore, the capsule undergoes significant intestinal and hepatic ("first-pass") metabolism before reaching the systemic circulation [11, 12]. Unlike the capsule, itraconazole in the oral solution requires no dissolution so its absorption is rapid and unaffected by alterations in gastric pH [13]. The oral solution delivers high itraconazole concentrations to the intestinal epithelium that may transiently saturate intestinal CYP3A4, and minimize "first-pass" metabolism [11, 12]. The absorption of itraconazole from the oral solution is optimal in the fasted state [11]. The formulations are bioequivalent, but the absolute bioavailability of the oral solution is higher than that of the capsule [10, 14].

Fluconazole is more hydrophilic than the other systemic azoles, and so it requires no solubilizing agent to formulate as an i.v. solution. Moreover, it undergoes less hepatic metabolism than the other azoles. Oral fluconazole is rapidly and nearly completely absorbed [15]. Fluconazole absorption is not dependent on gastric acidity or the presence of food [15].

Voriconazole is available in both i.v and oral formulations. Intravenous voriconazole is formulated with the solubilizing agent sulfobutyl ether β-cyclodextrin (SEβCD). Oral voriconazole absorption is rapid and nearly complete [16]. Voriconazole dissolution is unaffected by changes in gastric pH, but fatty foods and enteral feedings decrease its bioavailability by up to 22% and the Cmax by 34% [16, 17].

Posaconazole is marketed solely as an oral suspension and exhibits saturable absorption at doses exceeding 800 mg daily [18]. Posaconazole absorption and exposure are optimized by administering the total daily dose in divided dosages [19, 20]. Administering posaconazole with or shortly after a meal, or with a liquid nutritional supplement also significantly increases exposure [20–22]. Posaconazole absorption is influenced by gastric pH and is optimal in acidic gastric conditions [20].

15.1.3.2 Protein Binding and Distribution of the Systemic Azoles

Itraconazole and posaconazole are highly protein bound (95–99%) [10, 23]. Unbound concentrations of these compounds in body fluids are much lower than their plasma concentration. Voriconazole moderately binds (58%) to plasma proteins [13]. Fluconazole minimally binds (11%) to proteins, circulates mostly as free drug [15]. Itraconazole, posaconazole and voriconazole distribute widely throughout the body [10, 13, 23]. Fluconazole distributes extensively into a variety of body fluids, hepatic, and renal tissues [15]. Unlike itraconazole, fluconazole and voriconazole adequately distribute into the cerebrospinal fluid (CSF), and central nervous system (CNS) tissues [15, 16, 24]. Whether posaconazole distributes to the CSF and CNS tissue is unknown.

15.1.3.3 Metabolism/Elimination of the Systemic Azoles

Itraconazole exhibits dose-dependent elimination, and is extensively metabolized by CYP3A4 to many metabolites. Very little (≈ 2%) of an itraconazole dose is excreted unchanged in the urine [10, 25]. Marketed itraconazole formulations are a mixture of four stereoisomers. Itraconazole biotransformation involves stereoselective sequential CYP3A4 metabolism of only one of the pair of stereoisomers to three metabolites (hydroxy-itraconazole, keto-itraconazole, and *N*-desalkyl-itraconazole) [26–28]. These metabolites circulate in sufficient concentrations to contribute to drug interactions involving itraconazole [28].

Approximately 91% of oral fluconazole is excreted in the urine. Most (80%) is excreted as unchanged drug; two metabolites account for the remaining 11% [29]. Less than 2% of a voriconazole dose is excreted unchanged in the urine [16, 30]. Voriconazole is extensively metabolized by hepatic CYP enzymes to eight metabolites [31]. The hepatic metabolism of voriconazole involves CYP2C19, CYP3A4, and CYP2C9 [16, 30]. CYP2C19 and CYP2C9 exhibit genetic polymorphism. The primary pathway (CYP2C19) for voriconazole has eight known variant alleles, which if expressed, result in deficient or absent enzyme activity that manifests as a poor metabolizing phenotype. This phenotype is expressed among Polynesians and Micronesians, and less frequently among Asians, Caucasian, and African Americans populations [30, 32]. Populations exhibiting the homozygous poor metabolizing phenotype have nearly a fourfold increase in drug exposure compared to those with

the homozygous efficient metabolizing phenotype. Furthermore, drug exposure in the heterozygous efficient metabolizing phenotype are nearly double compared to the homozygous efficient metabolizing phenotype [16]. CYP2C9 metabolism has six known variant alleles, of which two are associated with reduced enzyme activity. The variant alleles are expressed among Caucasians, and less frequently among African-Americans, but they are not expressed in Asian populations [32, 33]. CYP3A4 expression varies widely and likely contributes to interindividual variability in voriconazole pharmacokinetics.

Posaconazole is primarily eliminated unchanged in the feces (77%) and urine (13%) [34]. Only 17% of a dose undergoes biotransformation, of which little (2%) is metabolized by CYP [34, 35]. Most metabolites are glucuronide conjugates formed by uridine diphosphate glucuronosyltransferase (UGT) pathways [35]. The primary posaconazole metabolite is formed by UGT1A4 [35].

15.1.4 Echinocandins Pharmacology

The echinocandins disrupt cell wall synthesis by inhibiting 1,3,-β-D-glucan synthase. These compounds are large molecular weight semisynthetic lipopeptides that are administered intravenously.

15.1.4.1 Distribution of the Echinocandins

Caspofungin binds extensively to albumin and has multiphasic distribution. The drug first distributes to plasma and extracelluar fluid [36]. Then, via active transport by organic anion transport proteins (OATP), including OATP1B1, caspofungin distributes slowly into the liver and, to a lesser extent, other tissues [36, 37]. This slow active transport influences the caspofungin $t_{1/2}$ [37]. Micafungin and anidulafungin distribution in humans is not fully understood. Micafungin binds extensively to albumin and, to a lesser extent, α1-acid glycoprotein. Comparatively, anidulafungin binds plasma proteins less, has a larger volume of distribution and achieves lower peak (C_{max}) serum concentrations [38].

15.1.4.2 Elimination of the Echinocandins

The echinocandins exhibit linear pharmacokinetics. However, echinocandins differ in how they are metabolized or degraded, but are not appreciably metabolized by CYP. Less than 2% of a caspofungin dose is excreted unchanged in the urine [39]. Caspofungin is slowly metabolized in the liver via *N*-acetylation and peptide hydrolysis to several metabolites, which are excreted in the bile and feces [40]. Less than 1% of a micafungin dose is eliminated unchanged in the urine. Micafungin is hepatically metabolized to several metabolites that are formed by arylsulfatase,

catechol-O-methyltransferase and, to a minor extent, ω-1 hydroxylation via CYP, which are eliminated with the parent drug in feces [38, 41, 42]. Less than 10% of an anidulafungin dose is excreted in the feces or urine as unchanged drug [43, 44]. Anidulafungin is not hepatically metabolized. Rather, in the plasma it undergoes slow non-enzymatic chemical degradation to a peptide breakdown product [43, 44].

15.2 Drug Interaction Potential of Antifungal Agents

The potential for drug interactions involving amphotericin B formulations is related to its associated nephrotoxicity, and whether the concomitant medication is eliminated renally or shares other toxicities. This potential is high when amphotericin B formulations are administered with other nephrotoxic or renally eliminated medications. Because 5-FC is often used with amphotericin B, the potential for an interaction is high. The azoles cause drug interactions at various sites (intestine, liver, blood brain barrier, kidneys, etc.) via several mechanisms (alterations in pH, interference with transport proteins, and oxidative or conjugative enzymatic drug metabolism processes). Many of the azole–drug interactions occur class-wide, thus the potential for azoles to cause an interaction is high. The echinocandins are relatively devoid of significant drug interactions. Thus, their potential to interact with other drugs is low.

15.3 Amphotericin B

Drug interactions involving amphotericin B formulations are summarized in Table 15.1.

15.3.1 Amphotericin B Interactions Involving Synergistic/Additive Nephrotoxicity

Amphotericin B causes nephrotoxicity via direct cytotoxicity to the renal tubules, which impairs proximal and distal reabsorption of electrolytes. Indirectly it reduces renal blood flow that causes ischemic damage and reduces glomerular filtration [1]. Other commonly administered medicines (i.e., aminoglycosides, cyclosporine, foscarnet, tacrolimus, etc.) share these nephrotoxic effects with amphotericin B, and if co-administered may produce additive or synergistic nephrotoxicity. Amphotericin B-induced nephrotoxicity causes renally eliminated drugs with a narrow therapeutic index (i.e., 5-fluorocytosine) to accumulate in toxic concentrations that produce secondary extrarenal adverse effects.

Table 15.1 Drug interactions caused by amphotericin B formulations

Interaction	Drugs	Comments
Additive/synergistic effects		
Direct or indirect nephrotoxicity	Cyclosporine	Monitor serum creatinine
	Tacrolimus	Blood urea nitrogen
	Aminoglycosides	Electrolytes, consider lipid
	Foscarnet	Amphotericin B formulations or other antifungal agents
Fluid and electrolyte disturbance (i.e. water retention, hypokalemia hypomagnesemia)	Thiazide and loop diuretics aminoglycosides, corticosteroids	Monitor Scr, BUN, electrolytes. Supplement electrolytes as needed
Secondary non-renal toxicity		
Myelosuppression	5-Flucytosine (5-FC)	Effect due to diminished renal clearance of 5-FC secondary to amphotericin B-associated nephrotoxicity
Miscellaneous electrolyte disturbances		
Increase cardiac automaticity and inhibition of $Na^{+-}K^{+}$ ATPase pump	Digoxin	Effects secondary to amphotericin B-induced hypokalemia

15.3.1.1 Clinical Importance of Amphotericin B Interactions Involving Synergistic/Additive Nephrotoxicity

Amphotericin B is commonly used in patients who are severely immunocompromised and at high risk for renal failure and electrolyte disturbances. Interactions involving amphotericin B complicate the use of renally eliminated concomitant medications.

15.3.1.2 Management of Amphotericin B Interactions Involving Synergistic/Additive Nephrotoxicity

Drug interactions involving amphotericin B are somewhat unavoidable. Clinicians should focus on limiting the risk or severity of these interactions. The lipid amphotericin B formulations should be used in patients with, or at high risk for nephrotoxicity. These formulations may also cause nephrotoxicity with concomitant nephrotoxic drugs [45, 46]. Depending upon the case, other intravenous, non-nephrotoxic antifungal agents (i.e. caspofungin, fluconazole) should be considered. Voriconazole is available intravenously, but the potential accumulation of SEβCD in patients with diminished renal function is a concern.

Amphotericin B deoxycholate and cyclosporine cause hypomagnesemia, but the effect is not synergistic when they are given together [47]. Frank drug interactions with amphotericin B should be rare or recognized early because frequent laboratory

monitoring is the standard of care in patients receiving it. Additionally therapeutic drug monitoring of the nephrotoxic drugs (aminoglycosides, cyclosporine, or tacrolimus) should be routinely performed.

15.3.2 Amphotericin B Interactions Involving Secondary Nonrenal Toxicities

Amphotericin B reduces the CL_R of renally eliminated drugs with a narrow therapeutic index, such as 5-FC. The reduced CL_R of such drugs leads to their accumulation and an increased risk of secondary toxicities associated with their use. Flucytosine induced myelosuppression, hepatic necrosis, and diarrhea are associated with elevated plasma 5-FC concentrations and often occur with reduced renal function [5]. Amphotericin B-associated nephrotoxicity reduces 5-FC elimination, which increases its serum concentrations [48]. When administered orally 5-FC is deaminated by intestinal microflora, resulting in elevated 5-FU serum concentrations, which can cause myelosuppression and gastrointestinal mucosa toxicity [5]. The incidence of this interaction is approximately 20–40% [49, 50]. The clinical importance of this interaction is outweighed by the efficacy of this combination in the treatment of cryptococcal meningitis [51].

15.3.2.1 Management of Amphotericin B Interactions Involving Secondary Nonrenal Toxicities

Often, in the treatment of cryptococcal meningitis, this combination cannot be avoided, so renal function and 5-FC blood concentrations should be monitored. Ideally, 5-FC serum concentrations should be maintained between 25 and 100 μg/mL [52]. Several 5-FC dosing nomograms for patients with renal dysfunction exist. These methods should not be used unless the renal dysfunction is chronic in nature, and they should be used cautiously in elderly patients.

15.3.3 Interactions Involving Amphotericin B Formulations – Miscellaneous Electrolyte Disturbances

Amphotericin B-associated electrolyte disturbances may be an overlooked source of drug–drug interactions. Amphotericin B-associated hypokalemia can lead to cardiopathy, which concomitant medications (Table 15.1) can compound. Amphotericin B-induced hypokalemia can increase cardiac automaticity and facilitate inhibition of the $Na^{+-}K^{+}$ ATPase pump by digoxin. Co-administration of drugs that cause hypokalemia and fluid retention (i.e., corticosteroids) can augment amphotericin B-associated hypokalemia, and contribute to reversible cardiomegaly or congestive heart failure [53].

15.3.3.1 Clinical Importance of Amphotericin B Interactions Involving Miscellaneous Electrolyte Disturbances

Hydrocortisone is frequently added to the amphotericin B admixtures to prevent infusion-related toxicity. Given the potential to augment amphotericin B-induced hypokalemia, the use of hydrocortisone to prevent infusion-related toxicity should be employed only after careful consideration of the patient's clinical condition.

15.4 5-Fluorocytosine (5-FC)

15.4.1 5-Fluorocytosine (5-FC) Interactions Involving Secondary Nonrenal Toxicities

Concomitantly administered nephrotoxic drugs (i.e., amphotericin B, aminoglycosides) will prolong 5-FC elimination. Without 5-FC dosage adjustment, accumulation of toxic concentrations can occur. Although not described, the same potential interaction exists when 5-FC is administered to patients receiving calcineurin inhibitors.

15.4.2 5-Fluorocytosine (5-FC) Interactions Involving Additive/Synergistic Myelosuppression & Cytotoxicity

5-FC co-administration with myelosuppressive or cytotoxic drugs (i.e. zidovudine, ganciclovir) may increase the risk of blood dyscrasias. Clinicians are overly hesitant to use 5-FC in AIDS patients because of the concern over the potential myelotoxicity. However, consensus guidelines for the treatment of cryptococcosis support the use of 5-FC in combination with amphotericin B with close monitoring for myelosuppression [51].

15.5 Systemic Azoles

15.5.1 Interaction Mechanisms

Drug interactions involving the systemic azoles primarily affect the pharmacokinetic processes of the concomitantly administered drug(s), the systemic azole, or both. Itraconazole, voriconazole and posaconazole are lipophilic agents that cannot be formulated as an i.v. dosage form without the use of a solubilizing agent. Fluconazole differs physicochemically from other azoles and overall, is less prone to drug interactions. All systemic azoles undergo hepatic, and perhaps intestinal, oxidative CYP-mediated metabolism.

15.5.1.1 Interactions Affecting Solubility and Absorption (pH Interactions)

Drug dissolution rate determines the intestinal lumen concentration of drug in solution available for absorption [54]. Therefore, intraluminal pH can indirectly affect absorption. Weakly basic drugs such as itraconazole and posaconazole dissolve more slowly at higher pH, whereas weakly acidic drugs dissolve faster at higher pH. Itraconazole and posaconazole are highly lipophilic weak bases with high pK_a values and their dissolution and subsequent absorption is optimal at pH 1–4 [21, 55]. Itraconazole and posaconazole absorption is impaired above these pH values. Fluconazole and voriconazole are also weak bases, with lower pKa values and thus their dissolution is unaffected by increases in gastric pH.

15.5.1.2 Interactions Affecting CYP-Mediated Biotransformation

Itraconazole, voriconazole and posaconazole cannot be excreted into the urine without conversion to hydrophilic metabolites. In contrast, fluconazole is hydrophilic and requires less biotransformation prior to excretion in urine. All the azoles are CYP inhibitors and substrates, although their affinities for specific isoforms differ. As CYP inhibitors the systemic azoles generally exhibit rapidly reversible binding [56]. As reviewed in previous chapters, this type of binding to CYP by an inhibitor or its metabolite results in either competitive or noncompetitive inhibition. The azoles primarily exert competitive inhibition [56]. However, fluconazole has also demonstrated noncompetitive or mixed-type inhibition of CYP [56, 57]. Whether voriconazole or posaconazole also exhibit noncompetitive or mixed-type inhibition has not been described.

All the systemic azoles inhibit CYP3A4, which is extensively expressed in the liver and intestine. The itraconazole stereoisomers inhibit only CYP3A4 [28]. Furthermore, itraconazole metabolites circulate at concentrations sufficient to inhibit CYP3A4 and contribute to drug interactions involving itraconazole [28]. Fluconazole undergoes minimal CYP-mediated metabolism, it inhibits CYP3A4, albeit much more weakly than other systemic azoles [58]. However, fluconazole is a comparatively stronger inhibitor of several other isoforms, (i.e. CYP2C9, and perhaps CYP2C19) [58]. Fluconazole binds noncompetitively to CYP, and in vivo it circulates largely as free drug. Thus, greater inhibition may occur with elevated concentrations achieved with higher doses. Even though only a small percentage of fluconazole undergoes CYP-mediated metabolism, this percentage may greatly increase in the presence of a potent CYP-inducer. Fluconazole also interacts with enzymes involved in glucuronidation [15]. Voriconazole is a potent competitive inhibitor of CYP2B6, CYP2C9, and CYP2C19 [59, 60]. In addition voriconazole is a potent competitive and noncompetitive CYP3A4 inhibitor [59, 60]. Therefore, it has the potential to interact with many medicines [59, 60]. Although very little posaconazole is metabolized by CYP, like all azoles, it inhibits CYP3A4 [61]. However, in humans, posaconazole has no effect on the activity of CYP2C8/9, CYP1A2, CYP2D6, or CYP2E1 [61].

15.5.1.3 Interactions Affecting P-Glycoprotein (P-gp)-Mediated Efflux and Other Transporters

Transport proteins are key determinants of drug disposition. Expressed in a variety of tissues, they allow for the efficient uptake or efflux of many drugs. While there are likely many transport proteins involved in drug disposition, most research has focused on the role of the efflux transporter P-gp. P-gp, functions as a transmembrane efflux pump for a broad range of substrates and is expressed on cells of the blood-brain barrier, intestine, liver, and kidney [8]. In the intestine P-gp reduces drug absorption, whereas in the liver and kidney it helps eliminate endogenous and exogenous compounds from the systemic circulation. At the blood–brain barrier P-gp limits distribution into the CNS [56]. P-gp is extensively co-localized with CYP3A, and the two proteins exhibit significant overlap in substrate specificity [8]. Although many P-gp inhibitors are substrates and/or inhibitors of CYP3A4, the inhibitory potency of a compound towards the two proteins can differ [62]. Breast Cancer Resistance Protein (BCRP) belongs to the same transporter superfamily as P-gp and it is expressed in the placenta, small intestine, and liver. BCRP functions like P-gp in the transport of its substrates [7].

The organic anion-transporting polypeptide (OATP) family of transport proteins are uptake transporters that also determine drug disposition. Like P-gp, the OATP transporters are expressed in the intestine, liver, kidney and at the blood-brain barrier and transport many structurally diverse compounds [63].

The systemic azoles vary in how they interact with various transport proteins. Fluconazole may be a P-gp substrate but it is not a P-gp inhibitor [8, 64, 65]. However, itraconazole is a substrate and inhibitor of P-gp, and a potent inhibitor of BCRP [6–8, 65, 66]. Voriconazole is neither a substrate nor an inhibitor of P-gp, nor does it inhibit BCRP [7, 66]. Data suggest that posaconazole is a P-gp substrate and inhibitor [34, 67]. To date the interaction between the azoles and OATP transporters has not been fully elucidated.

15.6 Drug Interactions Involving Itraconazole

Drug interactions involving itraconazole are summarized in Tables 15.2–15.4.

15.6.1 Itraconazole Interactions Involving Gastric pH

Itraconazole is a lipophilic, weak base that is virtually water insoluble, and ionized at low pH [21, 25]. The dissolution and subsequent absorption of itraconazole capsules depends on gastric pH, retention time and the fat content of a meal; it is optimal in acidic gastric conditions [99]. Increased gastric pH decreases absorption of the itraconazole capsule, but does not affect the absorption of the oral solution [13].

Table 15.2 Itraconazole interactions affecting CYP-mediated biotransformation of other drugs

Drug	Effect on drug (% Change)	Inhibition site	Reference(s)
"Statins"			
Lovastatin	↑C_{max} (≈1,157%); ↑$AUC_{(0-\infty)}$ (≈1,380%); ↑$t_{1/2}$(42.3%)	Hepatic CYP3A; perhaps intestinal CYP3A or P-gp	[68]
Simvastatin	↑C_{max} (175%); ↑$AUC_{(0-\infty)}$ (417%); ↑$t_{1/2}$ (25%)	Hepatic CYP3A; perhaps intestinal CYP3A or P-gp	[69]
Atorvastatin	↑C_{max} (20–38%); ↑$AUC_{(0-\infty)}$ (150–231%); ↑$t_{1/2}$ (29–190%)	Hepatic CYP3A; perhaps intestinal CYP3A or P-gp	[70, 71]
Fluvastatin			[68]
Pravastatin	None		[69]
Rosuvastatin			[72]
Benzodiazepines			
Midazolam (oral)		Hepatic CYP3A; perhaps intestinal CYP3A	[73]
+ ITZ Day 1	↑C_{max} (75%); ↑$AUC_{(0-\infty)}$ (242%); ↑$t_{1/2}$ (104%)		
+ ITZ Day 6	↑C_{max} (151%); ↑$AUC_{(0-\infty)}$ (564%); ↑$t_{1/2}$ (259%)		
Midazolam (i.v.)		Hepatic CYP3A	[73]
+ ITZ Day 4	↓CL (69%); ↑$t_{1/2}$ (141%)		
Triazolam	↑C_{max} (41–76%); ↑T_{max} (11–94%); ↑$AUC_{(0-\infty)}$ (210–348%);↑ $t_{1/2}$ (155–210%)	Hepatic CYP3A; perhaps intestinal CYP3A	[74]
Diazepam	↑$AUC_{(0-\infty)}$ (31.8%); ↑$t_{1/2}$ (34%)	Hepatic CYP3A	[75]
Estazolam			
Bromazepam			
Temazepam	None		[76–78]
Oxazepam			
Other anxiolytics, sedatives and hypnotics			
Buspirone	↑ C_{max} (1,240%); ↑$AUC_{(0-\infty)}$ (1,815%),	Hepatic CYP3A; perhaps intestinal CYP3A	[79]
Zolpidem	None		[80]
Antipsychotic agents			
Haloperidol	↑C_{max} (14%); ↑$AUC_{(0-\infty)}$ (82%); ↑$t_{1/2}$ (115%); ↓CL/F (33%)	Hepatic CYP3A	[81, 82]
Clozapine	None		[83]
Calcineurin Inhibitors			
Cyclosporine	↑C_{ss} (80%) (range 24–149%)	Hepatic CYP3A; perhaps intestinal CYP3A/P-gp	[84]
Tacrolimus	↑C_{ss} (83%) (range 49–117%)	Hepatic CYP3A; perhaps intestinal CYP3A/P-gp	[84]

(continued)

Table 15.2 (continued)

Drug	Effect on drug (% Change)	Inhibition site	Reference(s)
Corticosteroids			
Methylprednisolone			
Oral	↑C_{max} (57–87%); ↑$AUC_{(0-\infty)}$ (279%);↑$t_{1/2}$ (71–132%);	Hepatic and intestinal CYP3A4/P-gp	[85, 86]
i.v	↑$AUC_{(0-\infty)}$ (143%); ↑$t_{1/2}$ (129%): ↓CL (62%); ↓Vd (15%)	Hepatic CYP; perhaps biliary P-gp	[87]
Dexamethasone		Primarily hepatic CYP3A4	[88]
Oral	↑$AUC_{(0-\infty)}$ (269%); ↑C_{max} (58%); ↑$t_{1/2}$ (172%); F (14.7%)		
i.v.	↑$AUC_{(0-\infty)}$ (223%); ↑$t_{1/2}$ (197%); ↓CL (69%)		
Prednisolone	↑C_{max} (2–14%); ↑$t_{1/2}$ (14–29%); ↑$AUC_{(0-\infty)}$ (24%)	Hepatic and intestinal CYP3A4	[86, 89]
Budesonide	↑C_{max} (64%); ↑$AUC_{(0-\infty)}$ (321%); ↑$t_{1/2}$ (287%); ↑T_{max} (150%)	Hepatic and intestinal CYP3A4	[90]
Calcium-channel blockers			
Felodipine	↑C_{max} (675%); ↑$AUC_{(0-\infty)}$ (534%); ↑$t_{1/2}$ (71%)	Hepatic and intestinal CYP3A4	[91]
Miscellaneous			
Oxybutynin	↑C_{max} (89%); ↑$AUC_{(0-t)}$ (85%)	Hepatic and intestinal CYP3A4	[92]
Busulfan	↑C_{ss} (25%); ↑CL/F (20%)	Hepatic CYP3A; perhaps intestinal CYP3A4	[25]
Meloxicam	↓$AUC_{(0-72)}$ (37%); ↓C_{max} (63%); ↑$t_{1/2}$ (55%); ↑T_{max} (500%)	Perhaps intestinal CYP3A4 and intestinal transport	[93]
Oxycodone		Hepatic and intestinal CYP3A4	[94]
Oral	↑C_{max} (43%); ↑$AUC_{(0-\infty)}$ (125%); ↑$t_{1/2}$ (48%);↓CL/F (58%); ↑F (49%)		
i.v.	↓CL (33%); ↑$AUC_{(0-\infty)}$ (51%); ↑$t_{1/2}$ (44%)		

H_2-receptor antagonists, proton pump inhibitors, and antacids reduce the exposure, C_{max}, or oral availability of the itraconazole capsule up to 67% [100–103]. Generally pH interactions reduce itraconazole C_{max}, AUC, T_{max}, and lower serum concentrations of hydroxyitraconazole. The antiretroviral didanosine (ddI) buffered oral tablet significantly reduced absorption of the itraconazole capsule [104].

Table 15.3 Interactions that induce itraconazole biotransformation or inhibit its absorption

Drug	Effect on itraconazole (% change)	Mechanism	Reference(s)
Gastric pH			
Modifiers			
Famotidine	$\downarrow C_{max}$ (30–52%); $\downarrow C_{min}$ (35%); $AUC_{(0-48)}$(51%)	↑ gastric pH and ↓ absorption	[100, 101]
Omeprazole			
Itraconazole caps	$\downarrow C_{max}$ (67%); $\downarrow AUC_{(0-24)}$ (65%); $\uparrow T_{max}$ (27%)	↑ gastric pH and ↓ absorption	[102]
Itraconazole soln	None		[13]
Didanosine			
Buffered formulation	Undetectable serum concentrations	↑ gastric pH and ↓ absorption	[104]
Enteric coated formulation	None		[105]
Inducing agents			
Phenobarbital	Subtherapeutic serum concentrations	CYP3A induction	[126]
Carbamazepine	Undetectable serum concentrations	CYP3A induction	[126]
Phenytoin	$\downarrow C_{max}$ (83%); $\downarrow AUC_{(0-\infty)}$ (93%); $\downarrow T_{1/2}$ (82%); ↑CL/F (1,384%)	Hepatic and intestinal CYP3A induction	[127]
Rifampin	$\downarrow C_{max}$ (67%); $\downarrow AUC_{(0-24)}$ (67%); $\downarrow T_{max}$ (35%)	CYP3A induction	[128]
Nevirapine	$\downarrow C_{max}$ (38%); $\downarrow AUC_{(0-96)}$ (61%); $\downarrow AUC_{(0-\infty)}$ (62%); $^{\downarrow}t_{1/2}$ (31%)	Hepatic CYP3A4 induction; P-gp induction	[129]

Table 15.4 Itraconazole interactions affecting P-gp-mediated transport of other drugs

Drug	Effect on drug (% change)	Inhibition site	Reference(s)
Cardiac			
Glycoside			
Digoxin	$\uparrow C_{max}$ (31%); $\uparrow AUC_{(0-\infty)}$ (68%); $\uparrow t_{1/2}$ (38%); $\downarrow CL_R$ (20%)	Renal P-gp; possibly hepatic/biliary P-gp	[95]
Alkaloids			
Quinidine	$\uparrow C_{max}$ (32–59%); $\uparrow t_{1/2}$ (35–67%); $\uparrow AUC_{(0-\infty)}$ (142%); $\uparrow T_{max}$ (150%);$\downarrow CL_R$ (49–60%)		
Quinidine metabolites		Inhibition of hepatic CYP3A; renal P-gp	[96, 97]
3-hydroxyquinidine	$\downarrow AUC_{(0-24)}$ (78%); $\downarrow CL_{(partial)}$ (84%)		
N-oxide	$\downarrow CL_{(partial)}$ (73%)		
Miscellaneous drugs			
Morphine	$\uparrow C_{max}$ (25%); $\uparrow AUC_{(0-9)}$ (27%);$\uparrow AUC_{(0-48)}$ (19%)	Inhibition of intestinal P-gp	[98]

Subsequently, the non-buffered enteric coated ddI formulation did not interact with the itraconazole capsule [105].

15.6.1.1 Clinical Importance of Itraconazole Interactions Involving Gastric pH Interactions

Reduced itraconazole absorption may lead to therapeutic failure. However, elevated gastric pH interactions with the itraconazole capsule are unavoidable in patients who require high-dose corticosteroid therapy (i.e. transplant recipients). In these instances the oral solution may be preferred.

15.6.1.2 Management of Itraconazole Interactions Involving Gastric pH Interactions

In patients requiring acid suppression therapy and short courses of itraconazole, the solution should be employed. The solution being somewhat dilute may be impractical for protracted courses of therapy, so alternative antifungal agents should be considered. If no suitable alternative agent exists, the itraconazole capsule can be employed with the understanding that absorption will be reduced and variable. In these cases therapeutic drug monitoring should be performed to document adequate oral availability. In general, for optimal effectiveness, investigators advocate maintenance of an itraconazole plasma trough concentration of at least 0.25 μg/mL (measured by HPLC) [25]. Nonetheless, clinical response should guide judgments on the adequacy of the concentrations achieved.

15.6.2 Itraconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

15.6.2.1 The 3-Hydroxy-3 Methylglutaryl (HMG) Coenzyme a Reductase Inhibitors (the "Statins")

The statins are primarily CYP and/or P-gp substrates, and one, pravastatin, is a hepatic OATP-C substrate, while another, pitavastatin is a hepatic OATP1B1 and OATP2 substrate [62, 106, 107]. Itraconazole inhibits both P-gp and CYP3A4, thus it is difficult to attribute its interactions with certain statins solely to CYP3A4 inhibition. Nonetheless, CYP3A inhibition is primarily involved. Itraconazole co-administration with certain statins can elevate their systemic concentrations, which may result in rare, but severe, life-threatening toxicities [25]. Lovastatin, simvastatin, and atorvastatin are CYP3A4 substrates; fluvastatin is a CYP2C9

substrate [108]. In contrast, pravastatin, and rosuvastatin are negligibly metabolized by CYP and excreted primarily in the urine as unchanged drug [108].

The inhibitory effects of itraconazole on the CYP3A4-metabolized statins varies. It significantly increases the exposure and C_{max} of lovastatin or simvastatin, but it affects atorvastatin pharmacokinetics considerably less [69–71, 109, 110]. Quantitative prediction models based upon parameters obtained from the *in vitro* inhibition experiments and *in vivo* pharmacokinetic analysis predict that the maximum competitive inhibition of simvastatin metabolism by itraconazole increases simvastatin exposure up to 100 times [110]. Using this method also predicts that itraconazole increases lovastatin exposure up to 240 times, which is approximately 2.5 times that observed with simvastatin [110]. Data from clinical evaluations demonstrate interactions that are much smaller in magnitude (Table 15.4). Nonetheless this method is a reasonable approach for identifying the potential extent of itraconazole inhibition [110] In contrast, itraconazole has no significant effect on fluvastatin, pravastatin, and rosuvastatin pharmacokinetics [68, 69, 71, 72, 108, 110].

15.6.2.2 Benzodiazepines

Itraconazole co-administration with triazolam, midazolam, or diazepam can produce significant pharmacokinetic interactions that enhance their pharmacologic effects. The most notable alterations are observed with triazolam and midazolam, which are metabolized only by CYP3A4 [73, 111]. The oral administration of either benzodiazepine with itraconazole increases their systemic availability and decreases their clearance (CL). This interaction produces significant changes in triazolam or midazolam exposure, C_{max}, t_{max}, and $t_{1/2}$ [73, 111]. The effect of itraconazole on the systemic clearance (CL) of triazolam cannot be determined because an i.v. formulation of this benzodiazepine does not exist. Therefore, further characterizing the mechanism of this interaction (intestinal, hepatic, etc.) is not possible. However, itraconazole does not affect the steady-state volume of distribution (Vss) of i.v. midazolam, but it substantially reduces its plasma CL as reflected by a prolongation in $t_{1/2}$ [111].

The itraconazole – triazolam interaction occurs even if triazolam is administered up to 24 h after itraconazole and can persist for several days after discontinuing the azole [74, 112]. The itraconazole metabolites, which *in vitro* are potent CYP3A4 inhibitors, likely contribute to the persistence of the interactions [26, 28]. The N-desalkyl-itraconazole metabolite has a much longer half-life than the other metabolites or the parent compound and contributes substantially to CYP3A4 inhibition for at least 24 h [28].

The interaction between itraconazole and either benzodiazepine produces long-lasting pharmacological effects, including prolonged amnesia, significantly reduced psychomotor performance, and severe sedation [73, 111]. These effects can occur with a single or multiple itraconazole doses. Given the nonlinear stereoselective sequential metabolism of itraconazole, and prolonged elimination of itraconazole

and its metabolites, the affect on the benzodiazepines' pharmacokinetics and pharmacological effects will likely be greater and more prolonged with repeated or increased itraconazole doses [73, 111].

Diazepam undergoes minimal first-pass metabolism, and is metabolized by CYP2C19 [75]. Concomitant itraconazole produces a small yet statistically significant increase in diazepam exposure, and slightly prolongs its $t_{1/2}$, but it does not enhance the pharmacological effects of this benzodiazepine [75]. Estazolam is a short-acting – triazolobenzodiazepine derivative that is extensively metabolized by CYP3A4 [113]. Itraconazole inhibits estazolam metabolism *in vitro*, but co-administration with itraconazole capsules (100 mg/day) for 3 days did not alter the pharmacokinetics or enhance the effects of single dose estazolam [76, 113]. The lack of *in vitro* to *in vivo* correlation of this drug interaction may have been a result of the low dose of itraconazole used in this clinical study [76]. Itraconazole does not affect the pharmacokinetics or enhance the effects of benzodiazepines that are not appreciably metabolized by CYP3A4 (i.e. bromazepam, temazepam, oxazepam) [77, 78].

15.6.2.3 Other Anxiolytics, Sedatives, and Hypnotics

Buspirone undergoes extensive first-pass metabolism [79]. Itraconazole co-administration significantly increases buspirone exposure and C_{max}. The interaction does not alter the buspirone $t_{1/2}$, which suggests it involves intestinal CYP3A4 inhibition. Itraconazole co-administration moderately enhances the pharmacological effects of buspirone [79]. Zolpidem is a substrate of CYP3A4, and to a lesser extent CYP1A2. Unlike midazolam, triazolam, and buspirone, it undergoes minimal first-pass metabolism and possesses good oral availability. Itraconazole minimally affects zolpidem pharmacokinetics or its pharmacological effects [80].

15.6.2.4 Antipsychotic Agents

Haloperidol undergoes first-pass metabolism, but has good oral availability. The drug is hepatically metabolized by CYP2D6 and CYP3A4 [81]. The CYP2D6 gene is highly polymorphic; certain alleles (CYP2D6*3, *4, and *5) are associated with complete loss of activity, and significantly influence haloperidol disposition [81]. Other alleles (CYP2D6*10) are only associated with diminished but not complete loss of activity, and moderately influence haloperidol disposition [81]. Itraconazole significantly increases plasma concentrations of haloperidol and its metabolite (reduced haloperidol), which demonstrates the critical role CYP3A4 plays in haloperidol disposition [81, 82]. CYP3A4 inhibition by itraconazole also enhances the contribution of minor CYP2D6 alleles to haloperidol metabolism [81]. Itraconazole co-administration also augments the neurological side effects of haloperidol [81, 82]. The atypical antipsychotic agent clozapine is primarily metabolized by CYP1A2, but CYP3A4 and

CYP2D6 catalyze secondary metabolic pathways [83]. Because CYP3A4 has only a minor influence on clozapine disposition, its pharmacokinetics or activity are unaffected by itraconazole co-administration [83].

15.6.2.5 Calcineurin Inhibitors and Proliferation Signal Inhibitors

Pharmacokinetic interactions between tacrolimus or cyclosporine and the azoles are well known. Regardless of route of administration, itraconazole increases cyclosporine concentrations 40–200% [84, 114]. Itraconazole interacts with tacrolimus even more substantially and raises "trough" (C_{min}) tacrolimus concentrations up to sevenfold [84, 115]. The interaction between itraconazole and the calcineurin inhibitors persists even after itraconazole is discontinued. The itraconazole metabolites likely contribute to the persistence of the interaction [28]. All the azoles apparently interact with sirolimus, but the interaction between sirolimus and itraconazole has only been reported in several cases [116, 117]. An anecdotal observation from a large population pharmacokinetic analysis of everolimus demonstrated that itraconazole co-administration in a single patient reduced everolimus clearance 74% [118].

15.6.2.6 Corticosteroids

Itraconazole inhibits the metabolism of oral or i.v. methylprednisolone (i.e., two-threefold increases in exposure, C_{max}, and $t_{1/2}$) [85, 87]. The interaction can reduce morning plasma cortisol concentration 80–90% [85–87]. The metabolism of methylprednisolone has not been elucidated, but these data suggest CYP3A4 is primarily involved.

Dexamethasone is a CYP3A4 substrate, and like methylprednisolone, itraconazole increases its systemic exposure after i.v. or oral administration, approximately three and fourfold, respectively [88]. The interaction can also significantly reduce morning plasma cortisol concentrations. Dexamethasone is also a P-gp substrate, and thus this efflux protein may be involved in this interaction. In contrast to methylprednisolone and dexamethasone, itraconazole co-administration increases prednisolone exposure and $t_{1/2}$ 13–30%, but produces only minimal changes in prednisolone C_{max} or morning plasma cortisol concentrations [86, 89].

Itraconazole also interacts with inhaled corticosteroids. Depending on the inhalation device and patient technique, approximately 33% of an inhaled corticosteroid dose reaches the lungs and is absorbed into the systemic circulation, where it can undergo hepatic metabolism [90]. The remaining fraction is inadvertently swallowed and can undergo intestinal and/or hepatic metabolism [90]. Oral itraconazole significantly inhibits the metabolism of inhaled budesonide and leads to 1.5–4-fold increases in exposure, C_{max}, and $t_{1/2}$ [90]. This interaction enhances the adrenal suppressive effects of budesonide and should be considered when coadministering other similar corticosteroids with itraconazole [90, 119].

15.6.2.7 Calcium Channel Blockers

Felodipine, is a CYP3A4 substrate that undergoes extensive first-pass metabolism [91]. Itraconazole co-administration increases felodipine exposure approximately sixfold; C_{max} eightfold, and $t_{1/2}$ approximately twofold [91]. These pharmacokinetic changes significantly reduce systolic and diastolic blood pressure and increase heart rate considerably [91].

15.6.2.8 Miscellaneous Drugs

Itraconazole interacts with several other medicines including oxybutynin (increases exposure and C_{max}) [92], and busulfan (increases steady-state busulfan concentrations and lowers apparent oral clearance (CL/F)) [25]. A case report has noted that concomitant itraconazole therapy also substantially enhances warfarin's effect. The pharmacologically active *S* enantiomer of warfarin (*S*-warfarin) is a CYP2C9 substrate. However, itraconazole does not inhibit CYP2C9 activity. A well controlled, rigorous pharmacokinetic evaluation of these drugs administered in combination is needed [120].

In healthy volunteers oral itraconazole co-administration significantly reduced the exposure, and C_{max}, and delayed the absorption of the COX-2 inhibitor meloxicam [93]. The mechanism behind this interaction is unknown, but investigators ruled out protein displacement of meloxicam. Rather, they hypothesize that itraconazole decreases meloxicam exposure by impairing its gastrointestinal absorption, perhaps by inhibiting a yet to be characterized intestinal transport system for meloxicam absorption [93]. Oxycodone undergoes extensive hepatic metabolism via CYP3A to noroxycodone and via CY2D6 to oxymorphone. Both metabolites are further metabolized via CYP3A4 to noroxymorphone [121, 122]. Itraconazole co-administration affected the metabolism of oxycodone administered i.v. and even more so orally. Itraconazole reduced i.v. oxycodone CL and prolonged its $t_{1/2}$ [94]. Itraconazole co-administration increased oral oxycodone exposure, C_{max}, and bioavailability, and decreased CL/F and prolonged its $t_{1/2}$ [94]. These changes resulted from itraconazole inhibition of hepatic and intestinal CYP3A4-mediated pathways of oxycodone metabolism [94]. This can produce small compensatory changes in oxymorphone pharmacokinetics, via a minor pathway mediated by CYP2D6, which itraconazole does not inhibit [94]. Itraconazole did not change the pharmacological effects of i.v. oxycodone, but did so with oral oxycodone [94].

15.6.2.9 Clinical Importance of Itraconazole Interactions Affecting CYP Biotransformation of Other Drugs

Many interactions involving itraconazole are clinically important. Myopathy (skeletal muscle toxicity), a rare, but potentially severe side effect of elevated statin concentrations can progress to rhabdomyolysis [109]. The incidence of rhabdomyolysis

associated with the CYP3A4-metabolized statins is nearly five-times greater than that of the statins that are not metabolized by CYP3A4 [123]. The risk of rhabdomyolysis associated with the CYP3A4-metabolized statins increases significantly when they are administered with potent CYP3A4 inhibitors [124]. Rhabdomyolysis has been reported when lovastatin or simvastatin is co-administered with itraconazole and may occur with atorvastatin [69–71]. Concomitant itraconazole therapy may increase the risk of dose-dependent adverse effects (i.e., hepatotoxicity) associated with the CYP3A4-metabolized statins [125].

Co-administration of itraconazole with midazolam, triazolam, or buspirone severely impairs intellectual capacity and psychomotor skills even when low doses of these benzodiazepines (particularly midazolam and triazolam) are used for prolonged periods. The interaction between the azoles, such as itraconazole and the calcineurin inhibitors is largely unavoidable, and if not properly managed can lead to calcineurin associated nephrotoxicity. Itraconazole interacts significantly with orally, i.v. or inhaled corticosteroids and the interaction can produce significant suppression of endogenous cortisol production. There have been approximately 20 cases of Cushing's syndrome or adrenal insufficiency reported literature attributed to itraconazole co-administration with either fluticasone or budesonide [119].

Itraconazole co-administration with felodipine produces clinically significant cardiovascular effects. In addition, although there are no data indicating that itraconazole inhibits CYP2C9, the interaction between itraconazole and warfarin produces excessive anticoagulation and is considered clinically significant.

15.6.2.10 Management of Itraconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

Patients receiving lovastatin, simvastatin, or atorvastatin, with itraconazole should be closely monitored for clinical and laboratory signs of skeletal muscle toxicity (myalgia, arthralgia, CK elevations) and hepatotoxicity (transaminase elevations). Pravastatin, fluvastatin, and rosuvastatin are alternatives for patients receiving concurrent itraconazole therapy.

Itraconazole and its metabolites are slowly eliminated therefore the interaction between triazolam, and midazolam, cannot be avoided by adjusting itraconazole dosing [8]. The benzodiazepines temazepam, oxazepam, and lorazepam are not appreciably metabolized by CYP3A4 and are alternatives to triazolam and midazolam for patients receiving concurrent itraconazole therapy. Other alternatives include diazepam, estazolam and zolpidem.

Management of the itraconazole-calcineurin inhibitor interaction necessitates monitoring calcineurin inhibitor blood concentrations; adjusting calcineurin inhibitor dosages, or switching antifungal therapy. Calcineurin inhibitor blood concentrations should be obtained before, during, and after azole use and dosages adjusted accordingly. The use of itraconazole is not recommended with the proliferation signal inhibitors.

In patients requiring concomitant itraconazole and oral or i.v. corticosteroid therapy, prednisolone should be considered for immunosuppressive or anti-inflammatory agent.

If patients are receiving dexamethasone or methylprednisolone (dosed chronically or as pulse therapy), corticosteroid dose reduction may be needed during concomitant itraconazole therapy.

Co-administration of itraconazole with felodipine, or other chemically-related calcium channel blockers (i.e., amlodipine, isradipine, nifedipine, etc.) should be avoided given the considerable clinical significance of the interaction. If these combinations cannot be avoided, then the dose of the calcium channel blocker should be reduced, and the patient's heart rate and blood pressure should be closely monitored until stable. Termination of the interaction between itraconazole and warfarin requires discontinuation of itraconazole, and perhaps infusion of fresh-frozen plasma and administration of vitamin K to reverse excessive anticoagulation [120]. The combination of itraconazole and warfarin should be avoided. If antifungal therapy is needed, an amphotericin B formulation or an echinocandin should be used.

15.6.3 Interactions that Induce Itraconazole Biotransformation

Phenytoin, phenobarbital, carbamazepine, rifampin, and nevirapine are CYP3A4 inducers. Itraconazole co-administration with these agents results in a pharmacokinetic interaction that markedly reduces its serum concentrations [126–129]. The onset of induction varies with each drug, and may not be detectable for up to 2 weeks [126–129]. After discontinuation of these agents, induction may persist for up to 2 weeks [126–129].

Phenytoin significantly reduces itraconazole and hydroxyitraconazole exposure, $t_{1/2}$, C_{max} and C_{min}. In addition itraconazole CL/F is increased approximately 14-fold [127]. Rifampin and nevirapine also induce itraconazole metabolism lowering its serum concentrations [128, 129].

15.6.3.1 Clinical Importance of Interactions that Induce Itraconazole Biotransformation

Interactions between CYP3A inducers and itraconazole lead to undetectable or subtherapeutic serum itraconazole concentrations, which can result in therapeutic failure.

15.6.3.2 Management of Interactions that Induce Itraconazole Biotransformation

These interactions likely cannot be circumvented by increasing the itraconazole dose. If possible, these combinations should be avoided. However, this is often not possible, especially in HIV patients receiving rifampin or rifabutin. In these cases, if alternative antifungal therapy (i.e., amphotericin B, echinocandins) cannot be

used, then itraconazole serum concentrations and the patient's clinical condition should be closely monitored for therapeutic failure. If alternative antifungal agents cannot be used, then antimycobacterial regimens without rifampin or rifabutin should be considered. Similarly, gabapentin, or levetiracetam may represent alternatives devoid of CYP3A-inducing properties for patients needing anticonvulsant therapy.

15.6.4 Itraconazole Interactions Affecting P-Glycoprotein-Mediated Efflux of Other Drugs

15.6.4.1 Digoxin

Initially the interaction between itraconazole was somewhat enigmatic. Digoxin is not metabolized by CYP, undergoes little hepatic metabolism and is renally eliminated primarily as unchanged drug, through P-gp-mediated renal tubular secretion [130]. Therefore, the interaction results from inhibition of P-gp-mediated digoxin renal secretion by itraconazole. The reduced P-gp-mediated efflux causes decreases CL_R and increases serum digoxin concentrations [95].

15.6.4.2 Quinidine

Quinidine is primarily metabolized by CYP3A4 to form 3-hydroxyquinidine and CYP2C9 and perhaps CYP3A4 to form quinidine N-oxide [96, 97]. Quinidine is also actively secreted by the renal tubules, which most likely involves P-gp. Itraconazole co-administration significantly increases quinidine exposure 2.5-fold; C_{max} nearly twofold; prolongs elimination $t_{1/2}$ and significantly reduces its CL_R [96, 97]. Itraconazole co-administration also significantly reduces the partial CL of both metabolites [97]. This interaction likely results from inhibition of intestinal and hepatic CYP3A4 metabolism, and P-gp-mediated tubular secretion of quinidine by itraconazole [96, 97, 131].

15.6.4.3 Vinca Alkaloids and Opiates

Itraconazole reduces CYP3A4 metabolism and P-gp efflux of vincristine. The subsequent accumulation and distribution of vincristine produces neurological toxicities (seizures, paresthesia, sensory deficits, muscle weakness, neuropathy), gastrointestinal disturbances (abdominal pain/distention, constipation, ileus) hyponatremia, and SIADH [132]. Itraconazole also interacts to a similar degree with vinblastine [133]. Itraconazole produces subtle increases in oral morphine plasma concentrations, but does not alter its pharmacological effects [98]. The interaction probably involves inhibition of intestinal P-gp [98].

15.6.4.4 Clinical Importance of Itraconazole Interactions Involving P-Glycoprotein-Mediated Efflux of Other Drugs

Case reports document that interactions between itraconazole and digoxin or the vinca alkaloids are clinically significant [98, 132–134]. Quinidine has a relatively narrow therapeutic index, and elevated concentrations can produce life-threatening toxicity. Therefore, the interaction is considered clinically significant [96].

15.6.4.5 Management of Itraconazole Interactions Involving P-Glycoprotein-Mediated Efflux of Other Drugs

Patients receiving itraconazole and digoxin should be questioned about nonspecific symptoms of digoxin toxicity and have their serum digoxin concentrations closely monitored [134]. Similarly, plasma quinidine concentrations should be closely monitored in patients receiving quinidine and itraconazole [96]. Due to the severity of the interaction itraconazole, or any azole should not be co-administered with vincristine or vinblastine containing regimens. If a vinca alkaloid is started in a patient receiving an azole, the azole should be discontinued [132].

15.7 Interactions Involving Fluconazole

Drug interactions involving fluconazole are summarized in Table 15.5.

15.7.1 Fluconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

15.7.1.1 The 3-Hydroxy-3 Methylglutaryl (HMG) Coenzyme a Reductase Inhibitors (the "Statins")

Fluconazole significantly increases fluvastatin exposure, $C_{max,}$ and $t_{1/2}$ [98]. Pravastatin, and rosuvastatin are not CYP2C9 or CYP2C19 substrates, thus fluconazole does not significantly affect their pharmacokinetics [135, 136]. Case reports suggest even a moderate CYP3A4 inhibitor like fluconazole can inhibit the metabolism of CYP3A-metabolized statins (simvastatin, atorvastatin, lovastatin) [150–152].

15.7.1.2 Benzodiazepines

Fluconazole co-administration with triazolam or midazolam significantly alters the pharmacokinetics and enhances the pharmacological effect of both. Fluconazole

Table 15.5 Fluconazole interactions affecting CYP-mediated biotransformation of other drugs

Drug	Effect on drug (% change)	Inhibition site	Reference(s)
Statins			
Fluvastatin	↑C_{max} (44%); ↑$AUC_{(0-\infty)}$ (84%); $t_{1/2}$ (80%)	Hepatic CYP2C9	[135]
Pravastatin	None		[135]
Rosuvastatin	None		[136]
Benzodiazepines			
Midazolam (oral)			
+ FCZ po Day 1	↑C_{max} (130–150%); ↑$AUC_{(0-\infty)}$ (251–273%); ↑$t_{1/2}$ (71–123%)	Hepatic and intestinal CYP3A4	[73, 137]
+ FCZ po Day 6	↑C_{max} (74%); ↑$AUC_{(0-\infty)}$ (259%); ↑$t_{1/2}$ (71%)	Hepatic and intestinal CYP3A4	[73]
+ FCZ iv Day 1	↑C_{max} (79%); ↑T_{max} (100%); ↑$AUC_{(0-\infty)}$ (244%); ↑$t_{1/2}$ (123%)	Hepatic CYP3A4	[137]
Midazolam (i.v.)		Hepatic CYP3A4	[73]
+ FCZ po Day 4	↓CL (51%); ↑$t_{1/2}$ (52%)		
α-OH-midazolam		Hepatic CYP3A4	[137]
+ FCZ po Day 1	↓C_{max} (19%); ↑$AUC_{(0-17)}$ (50%); ↑$t_{1/2}$ (142%); ↓Ratio (54%)		
+ FCZ iv Day 1	↓C_{max} (10%); ↑$AUC_{(0-17)}$ (56%); ↑$t_{1/2}$ (157%); ↓Ratio (56%)		
Triazolam		Hepatic and possibly intestinal CYP3A4	
+ FCZ po 50 mg	↓C_{max} (47%); ↑$AUC_{(0-\infty)}$ (63%); ↑$t_{1/2}$ (29%); ↑T_{max} (15%)		[138]
+ FCZ po 100 mg	↓C_{max} (25–40%); ↑$AUC_{(0-\infty)}$ (105–145%); ↑$t_{1/2}$ (77–83); ↑T_{max} (11–92%)		[138, 139]
+ FCZ po 200 mg	↓C_{max} (133%); ↑$AUC_{(0-\infty)}$ (342%); ↑$t_{1/2}$ (126%); ↑T_{max} (54%)		[138]
Diazepam	↑$AUC_{(0-48)}$ (51%); ↑$AUC_{(0-\infty)}$ (174%); ↑$t_{1/2}$ (135%); ↓CL/F (59%)	Hepatic CYP2C19 and CYP3A4	[140]
N-Desmethyldiazepam	↓$C_{48\,h}$ (60%); ↓$AUC_{(0-48)}$ (70%); ↓AUC_{ratio} (71%)	Hepatic CYP2C19	[140]
Calcineurin inhibitors			
Cyclosporine			
Day 4	↑C_{max} (39%); ↑C_{min} (38%); ↑AUC (87%); ↓CL (18%)	Hepatic intestinal CYP3A and P-gp	[141]

(continued)

Table 15.5 (continued)

Drug	Effect on drug (% change)	Inhibition site	Reference(s)
Tacrolimus	C_{min}, $AUC_{(0–12)}$ similar pre- and post- fluconazole with 40% ↓dose		[142]
Anticonvulsants			
Phenytoin	*↑C_{min} (∪25%); ↑$AUC_{(0–24)}$ (75%)*	*Hepatic CYP3A4*	[143]
Anticoagulants			
Warfarin	Inhibits S-warfarin metabolic pathway ≈ 70%	Hepatic CYP2C9	[58, 120]
Miscellaneous drugs			
Fentanyl	↓CL (17%); ↓norfentanyl $AUC_{(0-\infty)}$ (56%); ↓Ratio (67%)	Hepatic CYP3A4	[144]
Alfentanil		Hepatic CYP3A4	[145]
FCZ po	↑$AUC_{(0–10)}$ (96%); ↑$t_{1/2}$ (67%); ↓CL (54%); ↓V_{ss} (19%)		
FCZ i.v.	↑$AUC_{(0–10)}$ (107%); ↑$t_{1/2}$ (80%); ↓CL (58%); ↓V_{ss} (19%)		
Methadone	↑$AUC_{(0–24)}$ (35%); ↑C_{max} (27%); ↑C_{min} (48%);↓CL/F (24%)	Hepatic CYP	[146]
Cyclophosphamide	↑$AUC_{(0–24)}$ (79%); ↑C_{max} (33–36%)	Hepatic CYP	[147]
4-OH-cyclophosphamide	↓C_{max} (33–36%)		
Nevirapine	↑$AUC_{(0–8)}$ (29%); ↑C_{max} (28%); ↓CL/F (22%)	Hepatic CYP3A4	[148]
Ibuprofen (*S-enantiomer*)	↑$AUC_{(0–24)}$ (83%); ↑C_{max} (16%); ↑$t_{1/2}$ (34%)	Hepatic CYP2C9	[149]

increases the oral availability and decreases the CL (i.e., increases exposure, C_{max} and $t_{1/2}$,) of both benzodiazepines [73, 137–139]. Fluconazole has no affect on Vss of i.v. midazolam, but does substantially reduce its plasma CL thereby prolonging its $t_{1/2}$ [72]. The interaction significantly enhances and prolongs the pharmacological effects of these benzodiazepines [72, 137–139]. The inhibition of CYP-mediated midazolam metabolism is greater with orally rather than i.v. administered fluconazole [73, 137]. The effects of fluconazole on midazolam did not increase with repeated dosing [73], but with increasing dose, the extent of the interaction with triazolam increased accordingly [138]. Fluconazole significantly increases diazepam exposure, but the interaction minimally changes its pharmacological effects [140].

15.7.1.3 Calcineurin Inhibitors and Proliferation Signal Inhibitors

Fluconazole interacts with calcineurin inhibitors in a dose-related manner, with interaction occurring at higher (≥200 mg) doses [57, 141, 153–156]. The maximum

effect occurs approximately 4 days after starting fluconazole [156]. The magnitude of the interaction is influenced by route of fluconazole administration and is less with i.v. dosing [157]. A case report describes a significant interaction between fluconazole and sirolimus [158]. The interaction manifests rapidly, and results in toxic sirolimus concentrations [158]. Similarly, a case report describing the management of a pharmacokinetic drug interaction between everolimus and fluconazole suggest that the dose of everolimus should be reduced to avoid overexposure, and that reduction should probably be less when administered with fluconazole than other triazoles (e.g. voriconazole) [159].

15.7.1.4 Phenytoin

In a study of healthy volunteers fluconazole significantly increased phenytoin exposure and C_{min} [143]. For ethical and safety reasons the study limited the phenytoin dose and its duration [143]. Therefore, phenytoin did not induce fluconazole, but in practice it likely will.

15.7.1.5 Warfarin

Therapeutic plasma fluconazole concentrations exceed its in vitro inhibitory constant for CYP2C9-mediated warfarin metabolism [58].Therefore fluconazole interacts with warfarin in a predictable manner. Fluconazole inhibits *S*-warfarin metabolism approximately 70%, which results in a 38% increase in the INR in previously stabilized patients [58, 120].

15.7.1.6 Miscellaneous Drugs

Oral fluconazole (400 mg) significantly decreased fentanyl plasma CL and the exposure of its primary active metabolite, norfentanyl [144]. The interaction did not affect fentanyl V_{ss} or $t_{1/2}$, which suggests it was due to inhibition of CYP3A-mediated norfentanyl formation. Oral or i.v. fluconazole significantly reduces alfentanil CL and nearly doubles its $t_{1/2}$ [145]. The increased alfentanil concentrations were associated with enhance pharmacological effects [145]. Fluconazole (200 mg daily) reduced methadone CL/F and increased its exposure in patients receiving a mean daily methadone dose of 55 mg [146].

Cyclophosphamide undergoes extensive metabolism including one pathway involving activation by several CYPs including CYP2C9, and CYP3A4, which produces the cytotoxic alkylating agent 4-hydroxycyclophosphamide. Fluconazole reduces cyclophosphamide CL and increases its $t_{1/2}$ in children [147]. Data also indicate that fluconazole increases cyclophosphamide exposure and C_{max}, and reduces 4-hydroxycyclophosphamide C_{max} [160]. In HIV patients, the co-administration of fluconazole and rifabutin increased the rifabutin C_{max} 91% and the AUC 76%.

This interaction also extended to the primary rifabutin metabolite, 25-O-desacetyl-rifabutin, in which the C_{max} and C_{min} were increased by 3.6-fold and 2.3-fold, respectively [161]. Drug interactions involving antiretroviral agents are discussed in detail elsewhere. However, fluconazole (200 mg three times/week) co-administration significantly increases nevirapine exposure [148].

Ibuprofen, is a chiral compound and the pharmacologically active *S*-enantiomer, which produces most of its analgesic effect, is metabolized primarily by CYP2C9. Fluconazole significantly increases the *S*-enantiomer C_{max}, exposure, and its $t_{1/2}$ [149].

15.7.1.7 Clinical Importance of Fluconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

Several interactions involving fluconazole are clinically significant. For example, the interaction between fluconazole and midazolam or triazolam produces significant and prolonged changes in these benzodiazepines' pharmacological effects. Unless properly monitored interactions between fluconazole-cyclosporine, phenytoin and warfarin can produce significant toxicity. A case report with fatal outcome of patient administered fluconazole while receiving transdermal fentanyl illustrates the clinical significance of this interaction [162]. By reducing metabolite formation, the fluconazole-cyclophosphamide may exert a protective effect against toxicities associated with cyclophosphamide regimens, however further study is needed to determine the impact of this interaction on efficacy of such regimens [160]. In certain patient populations the potential for fluconazole to be co-administered with rifabutin is high. Thus, it is important that clinicians monitor for, and recognize rifabutin toxicities (uveitis, flu-like symptoms, and liver enzymes) [161]. Fluconazole co-administration with ibuprofen may increase the risk of concentration-dependent ibuprofen toxicity, including renal, cardiovascular, or gastrointestinal adverse effects [149].

15.7.1.8 Management of Fluconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

The interaction between fluconazole and triazolam, and perhaps midazolam, occurs with low doses of fluconazole, thus these combinations should be avoided. In patients receiving fluconazole, temazepam, oxazepam, and lorazepam may be alternatives to triazolam and midazolam. Other possible alternatives including diazepam and zolpidem require further study to determine their potential to interact with fluconazole.

When used with the calcineurin inhibitors, the lowest effective fluconazole dose should be employed and calcineurin inhibitor blood concentrations and renal function monitored accordingly. Phenytoin serum concentrations should be monitored prospectively with the addition of fluconazole therapy. If the two are used together for prolonged times, clinicians should monitor for breakthrough fungal infections. The interaction

between fluconazole and warfarin cannot be avoided by reducing the fluconazole dose. Termination this interaction requires azole discontinuation and perhaps infusion of fresh-frozen plasma and administration of vitamin K to reverse excessive anticoagulation [120].Therefore, amphotericin B or an echinocandin should be used.

When using fluconazole and fentanyl concomitantly, respiratory depression may occur if the i.v. or transdermal fentanyl dose is not reduced and the patients are not monitored closely [144]. The use of rifabutin therapy in *Mycobacterium avium* infections is often unavoidable, therefore careful monitoring will be necessary [161]. Similar to fentanyl, a reduced ibuprofen dose should be used in patients receiving fluconazole. If the fluconazole-phenytoin interaction cannot be overcome by adjusting the fluconazole dose, or the patient is not responding to antifungal therapy, echinocandins or amphotericin B formulations should be considered.

15.7.2 Interactions that Induce Fluconazole Biotransformation

Although fluconazole undergoes minimal metabolism, co-administration with CYP3A4 inducers markedly reduce its exposure [163].

15.7.2.1 Clinical Importance of Interactions that Induce Fluconazole Biotransformation

Rifampin co-administration with fluconazole produces a clinically significant interaction [163]. Without adjusting fluconazole dosage, the resulting induction leads to undetectable or subtherapeutic serum fluconazole concentrations that could lead to therapeutic failure.

15.7.2.2 Management of Interactions that Induce Fluconazole Biotransformation

Often the induction of fluconazole CYP-mediated metabolism cannot be overcome by increasing its dose. However, in patients receiving rifampin, the dose of fluconazole should be doubled [163].

15.7.3 Fluconazole Interactions Affecting Conjugative Biotransformation of Other Drugs

Fluconazole lowers concentrations of the conjugative enzyme, uridine diphosphate glucuronosyl transferase (UDPGT) in rats [15]. In humans UDPGT catalyzes zidovudine metabolism to its major metabolite, zidovudine glucuronide [164]. Fluconazole (400 mg daily) co-administration significantly decreased zidovudine

CL/F and formation of zidovudine glucuronide, which increased zidovudine exposure, C_{max}, and $t_{1/2}$ [164].

15.7.3.1 Clinical Importance and Management of Fluconazole Interactions Affecting Conjugative Biotransformation of Other Drugs

The clinical significance of the fluconazole-zidovudine interaction is undetermined. Patients receiving this combination should be monitored for zidovudine toxicity.

15.8 Interactions Involving Voriconazole

Drug interactions involving voriconazole are summarized in Tables 15.6 and 15.7.

Table 15.6 Voriconazole interactions affecting CYP-mediated biotransformation of other drugs

Drug	Effect on drug (% change)	Inhibition site	Reference(s)
Benzodiazepines			
Midazolam (oral)		Hepatic and intestinal CYP3A4	[165]
+ VCZ po	↑C_{max} (259%); ↑$AUC_{(0-\infty)}$ (840%) ↑$t_{1/2}$ (252%); ↓CL/F (91%)		
α-OH-midazolam			
+ VCZ po	↓C_{max} (6%); ↑$AUC_{(0-\infty)}$ (149%); ↓Ratio(77%)		
Midazolam (i.v.)		Hepatic CYP3A4	[165]
+ VCZ po	↑$AUC_{(0-\infty)}$ (253%);↓CL (72%); ↑$t_{1/2}$ (196%)		
α-OH-midazolam			
+ VCZ po	↓C_{max} (18%); ↑$AUC_{(0-\infty)}$ (68%); ↑T_{max} (168%); ↓Ratio (54%)		
Diazepam	↑$AUC_{(0-48)}$ (39%); ↑$AUC_{(0-\infty)}$ (123%); ↑$t_{1/2}$ (97%); ↓CL/F (47%)	Hepatic CYP2C19 and CYP3A4	[140]
N-Desmethyldiazepam	↓$C_{48\,h}$ (48%); ↓$AUC_{(0-48)}$ (64%); ↓AUC_{ratio} (71%)	Hepatic CYP2C19	[140]
Calcineurin inhibitors			
Cyclosporine	↑C_{min} (248%); ↑$AUC_{(0-12)}$ (70%)	Hepatic and intestinal CYP3A and P-gp	[166]
Tacrolimus	↑C_{min} great than predicted	Hepatic intestinal CYP3A	[167, 168]
Analgesics and anti-inflammatory agents			
Ibuprofen (*S-enantiomer*)	↑$AUC_{(0-24)}$ (103%); ↑C_{max} (19%); ↑$t_{1/2}$ (33%)	Hepatic CYP2C9	[149]

(continued)

Table 15.6 (continued)

Drug	Effect on drug (% change)	Inhibition site	Reference(s)
Alfentanil	$\uparrow AUC_{(0\text{–}10)}$ (264%);$\uparrow AUC_{(0\text{-}\infty)}$ (444%) $\uparrow t_{1/2}$ (340%);$\downarrow$CL (85%); $\downarrow V_{ss}$ (28%)	Hepatic CYP3A4	[169]
Fentanyl	$\downarrow$CL (24%); $\uparrow AUC_{(0\text{-}\infty)}$ (39%);	Hepatic CYP3A4	[144]
Norfentanyl	$\downarrow AUC_{(0\text{-}\infty)}$ (56%); $\downarrow$Ratio (67%)		
Methadone	$\uparrow AUC_{(0\text{–}24)}$ (44%); $\uparrow C_{max}$ (30%)	Hepatic CYP2B6, 3A, 2C9 and 2C19	[170]
Oxycodone	$\uparrow C_{max}$ (69%); $\uparrow AUC_{(0\text{-}\infty)}$ (257%); $\downarrow$CL/F (71%); $\uparrow t_{1/2}$ (102%)	Hepatic CYP3A4	[171]
Noroxycodone	$\downarrow C_{max}$ (87%); $\downarrow AUC_{(0\text{-}\infty)}$ (67%); $\downarrow$Ratio(92%); $\uparrow t_{1/2}$ (106%)		
Oxymorphone	$\uparrow C_{max}$ (104%); $\uparrow AUC_{(0\text{-}\infty)}$ (597%); $\uparrow$Ratio(100%); $\uparrow t_{1/2}$ (541%)		
Noroxymorphone	$\downarrow C_{max}$ (88%); $\downarrow AUC_{(0\text{-}\infty)}$ (49%); $\downarrow$Ratio(87%); $\uparrow t_{1/2}$ (218%)		
Meloxicam	$\uparrow AUC_{(0\text{–}72)}$ (46%); $\uparrow t_{1/2}$ (50%)	HepaticCYP2C9 and CYP3A4	[93]
Diclofenac	$\uparrow AUC_{(0\text{-}\infty)}$ (77%); $\uparrow C_{max}$ (114%)	HepaticCYP2C9/19 and CYP3A4	[172]
Etoricoxib	$\uparrow AUC_{(0\text{-}\infty)}$ (49%)	Hepatic CYP3A	[173]
Miscellaneous drugs			
Warfarin	Inhibits *S-warfarin* metabolic pathway ≈ 41%	Hepatic CYP2C9	[174]
Phenytoin	$\uparrow AUC_{(0\text{–}24)}$ (80%); $\uparrow C_{max}$ (70%)	Hepatic CYP2C9 and CYP3A4	[175]
Efavirenz (400 mg/day)		Hepatic CYP2B6	[176]
+ VCZ 200 mg B.I.D	$\uparrow AUC_{(0\text{–}24)}$ (44%); $\uparrow C_{max}$ (37%)		
Efavirenz (300 mg/day)[a]		Less inhibition with lower efavirenz dose and higher voriconazole dose	[177]
+ VCZ 300 mg Q12 h	$\downarrow AUC_{(0\text{–}24)}$ (8%); $\downarrow C_{max}$ (18%)		
+ VCZ 400 mg Q12 h	$\uparrow AUC_{(0\text{–}24)}$ (6%); $\downarrow C_{max}$ (10%)		
Ritonavir			
400 mg B.I.D	None		
100 mg B.I.D	$\downarrow AUC_{(0\text{–}12)}$ (18%); $\downarrow C_{max}$ (30%); $\downarrow C_{min}$ (22%)	Unknown	[178]

[a] Values compared to Efavirenz 600 mg/day

Table 15.7 Interactions that induce voriconazole biotransformation

Drug	Effect on voriconazole (% change)	Comments	Reference(s)
Phenytoin		CYP 3A4, 2 C9/19 induction	[175]
+ VCZ 200 mg B.I.D	↓$AUC_{(0–12)}$ (64%); ↓C_{max} (39%)		
+ VCZ 400 mg B.I.D[a]	↑$AUC_{(0–12)}$ (39%); ↑C_{max} (34%)	Doubling dose compensated induction	
Ritonavir (Chronic dose study)		CYP2C19 and CYP2C9 induction	[178]
400 mg B.I.D	↓$AUC_{(0–12)}$ (84%); ↓C_{max} (66%)		
100 mg B.I.D	↓$AUC_{(0–12)}$ (27%); ↓C_{max} (16%)		
Ritonavir (Acute dose study)	↑$AUC_{(0-\infty)}$ (354%); ↑C_{max} (17%);↓CL/F (43%)	CYP 3A4 inhibition	[179]
Efavirenz (400 mg/day)	↓$AUC_{(0–24)}$ (78%); ↓C_{max} (62%)	CYP2C19/9 and CYP3A4 induction; greater effect with standard 600 mg dose?	[176]
+ VCZ 200 mg B.I.D			
Efavirenz (300 mg/day)[b]		Less induction with lower efavirenz dose and higher voriconazole dose	[177]
+ VCZ 300 mg Q12 h	↓$AUC_{(0–12)}$ (48%); ↓C_{max} (27%)		
(VCZ-N-oxide)	None		
+ VCZ 400 mg Q12 h	↑$AUC_{(0–24)}$ (4.5%); ↑C_{max} (28%)		
(VCZ-N-oxide)	↑$AUC_{(0–24)}$ (41%); ↑C_{max} (45%)		

[a] Values compared to Voriconazole 200 mg
[b] Values compared to Voriconazole 400 mg/day

15.8.1 Voriconazole Interactions Involving Gastric pH and Motility

Voriconazole co-administration with high fat meals reduces the absolute bioavailability by 22%, and C_{max} by 34% [17].

15.8.1.1 Clinical Importance of Voriconazole Interactions Involving Gastric pH or Motility Interactions

When considered alone, the clinical significance of the impact of food on voriconazole disposition is minimal.

15.8.1.2 Management of Voriconazole Interactions Involving Gastric pH Interactions and Motility

The voriconazole-food interaction can be managed by separating the doses from meals or by therapeutic drug monitoring. Separating the voriconazole dose by more than 1 h pre – or post a meal, should maintain its high oral bioavailability [17].

15.8.2 Voriconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

15.8.2.1 Benzodiazepines

Voriconazole co-administration significantly reduces i.v. midazolam CL and nearly triples its $t_{1/2}$ [165]. Voriconazole co-administration also significantly increases oral midazolam exposure, $C_{max,}$ and bioavailability [165]. Voriconazole profoundly enhanced the pharmacological effects oral midazolam, more so than intravenous midazolam. Voriconazole co-administration significantly increases diazepam exposure, but does not enhance the pharmacological effects of this benzodiazepine [140].

15.8.2.2 Calcineurin Inhibitors and Proliferation Signal Inhibitors

Voriconazole co-administration significantly increases cyclosporine exposure and C_{min} [166].The magnitude of this interaction is similar to that observed with tacrolimus and voriconazole [142, 166]. However, the interaction between voriconazole and tacrolimus observed *in vivo* is much greater than that predicted by *in vitro* studies [167, 168]. Whether administered orally or via i.v., voriconazole interacts with the calcineurin inhibitors with considerable interpatient variability [142]. In healthy adults voriconazole reportedly increases systemic sirolimus exposure 11-fold [180]. A case report describing the management of a pharmacokinetic drug interaction between everolimus and voriconazole suggest that the dose of everolimus should be reduced to avoid overexposure, and that reduction should probably be more when administered with voriconazole than other triazoles (e.g. fluconazole) [159].

15.8.2.3 Analgesics and Anti-inflammatory Agents

Voriconazole co-administration with ibuprofen produces effects on the pharmacokinetics of the pharmacologically active ibuprofen *S*-enantiomer similar to those observed with fluconazole co-administration (significantly increases in plasma

S-ibuprofen C_{max}, exposure, and $t_{1/2}$) [149]. Alfentanil, a short-acting, synthetic opioid analgesic used as anesthesia during painful diagnostic and therapeutic procedures, is a CYP3A4 substrate. Voriconazole co-administration significantly decreases the mean alfentanil plasma CL; increases exposure (sixfold) and prolongs its $t_{1/2}$ [169]. Similar to fluconazole, oral voriconazole significantly increases fentanyl exposure, and decreases its CL, and norfentanyl exposure [144]. Voriconazole likely inhibits CYP3A-mediated norfentanyl formation. Methadone hydrochloride, is a chiral compound with a pharmacologically active *R*-enantiomer. The oxidative metabolism of methadone involves multiple CYP enzymes including, but not limited to, CYP2B6, CYP3A4, CYP2C19, and CYP2C9. Voriconazole significantly increases *R*-methadone exposure (47.2%) and C_{max} (30.7%) [170]. Voriconazole co-administration with oxycodone can significantly decrease first-pass metabolism of oxycodone by inhibiting its CYP3A4-mediated pathway of metabolism [171].This can produce compensatory changes in oxymorphone pharmacokintetics mediated by CYP2D6, which voriconazole does not inhibit [171]. Despite these changes, the interaction only modestly enhances the pharmacological effects of oxycodone [171].

Meloxicam is extensively metabolized by hepatic CYP2C9, and somewhat by CYP3A4 [93]. Voriconazole co-administration markedly increases meloxicam exposure and prolongs its $t_{1/2}$, but does not affect its C_{max} [93]. Diclofenac is extensively metabolized by hepatic CYP2C9, and somewhat by CYP2C19 and CYP3A4 [172]. Voriconazole co-administration can significantly increase diclofenac exposure, and C_{max}, but does not affect its $t_{1/2}$ [172]. The interaction likely results from inhibition of the first-pass metabolism of diclofenac [172]. Etoricoxib, undergoes negligible first pass metabolism. However it is extensively metabolized by hepatic CYP, primarily by CYP3A4, but CYP2C9, 2 C19, 2D6, and 1A2 also contribute to a lesser extent. Voriconazole co-administration can moderately increase single dose etoricoxib exposure, C_{max}, and $t_{1/2}$ [173].

15.8.2.4 Miscellaneous Drugs

Voriconazole interacts with several other medicines including warfarin, phenytoin, efavirenz. Voriconazole co-administration significantly enhances the pharmacological effects of warfarin [174]. The interaction can increase prothrombin time by 100% from baseline and can persist for upto 6 days [174]. Steady state plasma phenytoin concentrations and exposure increase dramatically following repeated administration of oral voriconazole (400 mg twice daily for 10 days) [175]. However, as discussed below, this interaction is bi-directional. Efavirenz is a CYP3A4 and CYP2B6 substrate and it undergoes glucuronidation. In addition, it inhibits CYP2C9, CYP2C19 and CYP3A4 and induces CYP3A4 in a concentration-dependent manner [181, 182]. Drug interactions involving antiretroviral agents are discussed in detail elsewhere. However, in healthy volunteers co-administration of voriconazole (400 mg daily in divided doses) with efavirenz (400 mg daily), can moderately increase efavirenz exposure and C_{max} [176]. Doubling the voriconazole dose (800 mg daily in divided

doses) and lowering the efavirenz dose 25% (300 mg daily) minimizes changes in efavirenz pharmacokinetic values [177]. This interaction is likely due to voriconazole inhibition of CYP2B6 [59]. However, as discussed below, efavirenz produced more significant changes in voriconazole disposition [176, 177]. Voriconazole had no apparent effect on steady-state high-dose (400 mg twice daily) ritonavir exposure, but did slightly reduce C_{max} of low-dose (100 mg twice daily). The mechanism of this effect is not clear [178]. Voriconazole may also interact with other antiretrovirals, calcium channel blockers, omeprazole, quinidine, rifabutin, the statins, sulfonylureas, and vinca alkaloids, and but data describing these interactions are lacking [183].

15.8.2.5 Clinical Importance of Voriconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

Voriconazole interactions with midazolam, the calcineurin inhibitors, sirolimus ibuprofen, alfentanil, fentanyl and warfarin are clinically significant. Voriconazole increases and prolongs the effects of commonly used hypnotic doses of oral midazolam to the extent that its pharmacological effects are no longer considered "short acting". The use of voriconazole with oral midazolam should be avoided. The interaction between i.v. midazolam and oral voriconazole is also significant. If high doses of i.v. midazolam are co-administered with voriconazole, the doses should be adjusted and the patients should be monitored closely.

The impact of voriconazole on cyclosporine and tacrolimus pharmacokinetics are qualitatively similar and are likely to become clinically significant if appropriate dose modifications are not made with the use of therapeutic drug monitoring.

Voriconazole co-administration with ibuprofen may increase the risk of concentration-dependent ibuprofen toxicity, including renal, cardiovascular, or gastrointestinal adverse effects [149]. The interaction between voriconazole and alfentanil is probably only significant when larger alfentanil doses are given either by intermittent bolus or continuous infusion. In these cases extubation procedures may be delayed, more nausea and vomiting may be observed, and respiratory depression can occur. Although there have been no case reports, the voriconazole-fentanyl interaction is as clinically significant as that of fluconazole and fentanyl. Given the danger of prolonged and excessive anticoagulation, the voriconazole–warfarin interaction is clinically significant.

15.8.2.6 Management of Voriconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

The use of oral midazolam with voriconazole should be avoided, or substantially lower doses should be used. To manage the voriconazole-calcineurin inhibitors interactions, uniform dose reduction of calcineurin inhibitors 50–66% has been recommended. However, given the substantial interpatient variability associated with this interaction, dosage adjustments should be individualized [142]. The concomitant use of fluconazole and sirolimus is contraindicated. Even though there are

retrospective data, including a moderately sized (n = 31 cases) medical record review, that suggest this significant interaction may be clinically manageable, the combination should be avoided until there are prospective data further characterizing the interaction [183].

Caution should be exercised when using alfentanil with voriconazole. Alfentanil dosage adjustments are not needed if only small bolus alfentanil doses are administered during voriconazole treatment. However, patients receiving larger alfentanil doses as repetitive bolus or continuous infusion, may require 70–90% reductions in alfentanil dosage for the maintenance of analgesia [169]. In patients receiving warfarin who require voriconazole therapy, the warfarin dose should be reduced according to INR and prothrombin time values.

15.8.3 Interactions that Induce Voriconazole Biotransformation

Co-administration of voriconazole with CYP inducers (i.e. phenytoin, ritonavir, efavirenz) can significantly reduce its serum concentrations, which could lead to therapeutic failure [16, 24, 184].

15.8.3.1 Phenytoin

The interaction between voriconazole and phenytoin is bi-directional. Initially, repeated administration of oral voriconazole increases steady-state phenytoin concentrations and exposure [172]. However, phenytoin (300 mg/day) co-administration for 2 weeks significantly reduces steady state voriconazole C_{max}, and exposure for up to 12 h postdose [175].

15.8.3.2 Antiretroviral Agents

Voriconazole plasma concentrations increase with acute co-administration of ritonavir, particularly among the CYP2C19 PM phenotype [179]. The increase results from CYP3A4 inhibition by ritonavir [179]. However, with chronic co-administration, ritonavir significantly reduces voriconazole exposure in a dose dependent fashion [178]. This interaction likely results from ritonavir induction of CYP2C19/2C9.

Efavirenz (400 mg daily) co-administration with voriconazole (400 mg daily in divided doses) decreases voriconazole exposure and C_{max} [176]. However, this complex interaction is mitigated by doubling the voriconazole dose (800 mg daily in divided doses) and lowering the efavirenz 25% (300 mg daily) [177]. The interaction is caused by efavirenz induction of CYP3A4, and possibly CYP2C19 or CYP2C9 [176, 177].

15.8.3.3 Miscellaneous Drugs

Voriconazole may also be induced by co-administration with phenobarbital, carbamazepine, rifampin, or other CYP inducers, but data from well controlled studies describing these interactions are lacking.

15.8.3.4 Clinical Importance of Interactions that Induce Voriconazole Biotransformation

Interactions that reduce voriconazole serum concentrations are clinically significant because they can precipitate therapeutic failure.

15.8.3.5 Management of Interactions that Induce Voriconazole Biotransformation

In many cases, given the magnitude of the interaction, induction of voriconazole cannot be completely overcome by increasing the voriconazole dose or reducing the dose of the CYP inducer. Therefore, the concomitant use of certain drugs (rifabutin, rifampin, phenobarbital, and carbamazepine) are contraindicated. While doubling the voriconazole dose may compensate for the effect of phenytoin on plasma voriconazole levels in healthy volunteers [175], this may not work in clinical practice [185].

15.9 Interactions Involving Posaconazole

Drug interactions involving posaconazole are summarized in Tables 15.8 and 15.9.

15.9.1 Posaconazole Interactions Involving Gastric pH and Motility

Antacid co-administration with an unmarketed form of posaconazole suggested that elevations in gastric pH did not impact posaconazole absorption [190]. However, a well designed study using the currently marketed suspension, and esomeprazole clearly demonstrates that posaconazole absorption is significantly impacted by changes in pH, and by food [20]. Co-administration with esomeprazole reduces posaconazole C_{max} and exposure [20]. Regardless of fat content, solid or liquid food significantly increases posaconazole systemic availability [21, 22, 190]. Increases in gastric emptying caused by metoclopramide may result in clinically insignificant reductions in C_{max} and exposure [20].

Table 15.8 Posaconazole interactions affecting CYP-mediated biotransformation of other drugs

Drug	Effect on drug (% change)	Inhibition site	Reference(s)
Benzodiazepines			
Midazolam (oral)		Hepatic CYP3A; perhaps intestinal CYP3A	[186]
+ PCZ 200 mg B.I.D	↑C_{max} (120%); ↑$AUC_{(0-\infty)}$ (398%); ↑$t_{1/2}$ (112%); ↓CL/F (81%)		
+ PCZ 400 mg B.I.D	↑C_{max} (133%); ↑$AUC_{(0-\infty)}$ (426%); ↑$t_{1/2}$ (162%); ↓CL/F (82%)		
Midazolam (i.v.)		Hepatic CYP3A	[186]
+ PCZ 200 mg B.I.D	↑C_{max} (30%); ↑$AUC_{(0-\infty)}$ (342%); ↑$t_{1/2}$ (130%); ↓CL/F (76%)		
+ PCZ 400 mg B.I.D	↑C_{max} (68%); ↑$AUC_{(0-\infty)}$ (523%); ↑$t_{1/2}$ (130%); ↓CL/F (83%)		
Calcineurin Inhibitors			
Tacrolimus	↑C_{max} (114%); ↑$AUC_{(0-\infty)}$ (323%); ↑$t_{1/2}$ (24%); ↓CL/F (80%)	Hepatic CYP3A; perhaps intestinal CYP3A/P-gp	[187]
Miscellaneous Drugs			
Sirolimus	↑C_{max} (537%); ↑$AUC_{(0-\infty)}$ (690%); ↑$t_{1/2}$ (52%); ↓CL/F (89%); ↓Vd/F (80%)	Hepatic CYP3A4	[188]
Atazanavir		Hepatic CYP3A4	[189]
+ PCZ	↑C_{max} (115%); ↑$AUC_{(0-24)}$ (209%); ↑$t_{1/2}$ (90%); ↓CL/F (81%); ↓Vd/F (56%)		
+ PCZ + RTV	↑C_{max} (47%); ↑$AUC_{(0-24)}$ (140%);↓CL/F (60%)		
Ritonavir (+ Atazanavir)		Hepatic CYP3A4	[189]
+ PCZ	↑C_{max} (27%); ↑$AUC_{(0-24)}$ (63%); ↑$t_{1/2}$ (30%);↓CL/F (51%) ↓Vd/F (31%)		

Table 15.9 Interactions that induce posaconazole biotransformation or inhibit its absorption

Drug	Effect of Itraconazole (% change)	Mechanism	Reference(s)
Gastric pH Modifiers			
Esomeprazole	↓C_{max} (49%); AUC (34%)	↑ gastric pH and ↓ absorption	[20]
Inducing agents			
Efavirenz	↓C_{max} (40%); ↓$AUC_{(0-24)}$ (46%); ↑CL/F (99%)	Induction of UGT-mediated Glucuronidation	[189]

15.9.1.1 Clinical Importance of Posaconazole Interactions Involving Gastric pH Interactions

Reduced posaconazole absorption may lead to therapeutic failure. However, elevated gastric pH interactions with posaconazole are unavoidable in certain patients.

15.9.1.2 Management of Posaconazole Interactions Involving Gastric pH Interactions

Posaconazole interactions involving alterations in gastric pH may be managed by administering posaconazole in three or four divided doses; with or after a high-fat meal or any meal; or with a nutritional supplement, or an acidic beverage [20].

15.9.2 Posaconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

15.9.2.1 Benzodiazepines

Posaconazole significantly inhibits CYP3A metabolism of intravenous or oral midazolam [186]. Posaconazole (200 or 400 mg BID) co-administration significantly increases oral midazolam (2 mg) exposure, C_{max}, more than doubles its $T_{1/2}$ and prolongs its T_{max} [186]. Similar changes were seen when posaconazole (200 or 400 mg BID) was co-administration i.v. midazolam [186]. Posaconazole likely interacts with other benzodiazepines that are CYP3A4 substrates (triazolam, alprazolam, etc.), but data regarding such interactions are lacking.

15.9.2.2 Calcineurin Inhibitors and Proliferation Signal Inhibitors

Posaconazole significantly interacts with the calcineurin inhibitors. However, the magnitude of the interaction with cyclosporine is much less than with the other azoles [187]. However, these data are derived from a small number of patients (n = 4), using an unmarketed posaconazole tablet rather than the marketed suspension, and a lower dose (200 mg once daily) given less frequently than is currently recommended [187]. However, a simulation to predict what the interaction with cyclosporine would be at a clinically relevant dose (600 mg/divided in three doses) revealed cyclosporine concentrations would increase 50% [187]. A significant interaction (increased exposure, C_{max}, $t_{1/2}$, and reduced CL/F) between posaconazole suspension and single-dose tacrolimus has also been reported [187].

Posaconazole suspension (400 mg twice daily) significantly altered the single dose pharmacokinetics of sirolimus in 12 healthy adults. Posaconazole increased sirolimus exposure, C_{max}, and $t_{1/2}$ [188]. In addition, the interaction reduced sirolimus apparent volume of distribution (Vd/F), and CL/F, 80% and 88%, respectively [188]. The interaction is likely due to posaconazole inhibition of CYP3A-mediated sirolimus metabolism [188]. Whether, P-gp inhibition by posaconazole contributed to this interaction is unknown.

15.9.2.3 Phenytoin

One parallel-designed interaction study demonstrated a bi-directional interaction between posaconazole and phenytoin. Posaconazole co-administration produced modest, but not statistically significant increases in steady state phenytoin C_{max} (24%), exposure (25%), and relative bioavailability (15.5%) which are not considered clinically significantly [191]. However, this study used a small number of healthy volunteers (three groups, n = 12/group), who did not serve as their own controls and received substandard doses of posaconazole tablets (200 mg/day), and phenytoin (200 mg/day). Whether these limitations impacted the magnitude of the observed interaction is unclear. How posaconazole produces these modest changes in phenytoin disposition is unknown.

15.9.2.4 Miscellaneous Drugs

Posaconazole interacts with several other medicines including atazanavir, ritonavir and rifabutin. Drug interactions involving antiretroviral agents are discussed in detail in elsewhere. However, healthy volunteers in part 1 of a 2-part crossover study received the protease inhibitor atazanavir alone, and then co-administered with either ritonavir or posaconazole. In addition subjects received all three concomitantly [189]. Atazanavir and ritonavir are CYP3A4 substrates and inhibitors. When administered concomitantly with atazanavir, ritonavir and posaconazole each increased the protease inhibitor's concentration and exposure via CYP3A4 inhibition [189]. Compared to when atazanavir was administered alone, posaconazole co-administration (400 mg twice daily for 7 days) increased atazanavir exposure, C_{max}, and $t_{1/2}$ [189]. In addition, the interaction reduced atazanavir Vd/F, and CL/F [189]. However, because both ritonavir and posaconazole inhibit CYP3A4, when all three were administered together no additional increases in the concentrations and exposure of atazanavir were observed compared with ritonavir and atazanavir administration together [189]. In this study, posaconazole co-administration modestly increased ritonavir exposure and C_{max} compared with ritonavir and atazanavir administration alone [189].

Steady state plasma rifabutin exposure and C_{max} increase 72% and 31%, respectively following repeated administration of an unmarketed posaconazole

tablet (200 mg once daily for 10 days) in healthy volunteers [192]. However, as discussed below, this interaction is bi-directional.

Posaconazole may also interact with other antiretrovirals, calcium channel blockers, omeprazole, the statins, and vinca alkaloids, but data describing these interactions are lacking.

15.9.2.5 Clinical Importance of Posaconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

Posaconazole interactions with midazolam, the calcineurin inhibitors, and sirolimus are clinically significant. Similar to the other azole, the posaconazole-calcineurin inhibitor interactions are clinically significant when clinicians fail to properly monitor blood concentrations and make dosage adjustments accordingly. More importantly, all of these interactions illustrate that even drugs like posaconazole that are minimally metabolized by CYP3A4 can potently inhibit this important enzyme. Clinicians may miss or confuse this point and mistakenly believe that because posaconazole is a poor CYP3A4 substrate, it will be relatively devoid of drug interactions.

15.9.2.6 Management of Posaconazole Interactions Affecting CYP-Mediated Biotransformation of Other Drugs

Data regarding the management of patients receiving benzodiazepines, other than midazolam, and concomitant posaconazole therapy are lacking. Clinicians should consider empirical dose adjustments, and monitoring of benzodiazepine adverse events in patients receiving midazolam or other benzodiazepines that are metabolized by CYP3A4 (e.g., triazolam, alprazolam).

Depending on the suspected pathogen, the interaction between the azoles and calcineurin inhibitors may be unavoidable. Management of these interactions necessitates monitoring, adjusting, or substituting calcineurin inhibitor therapy. Empirically derived dose adjustments are a good starting point to manage these interactions. A small retrospective study of lung transplant recipients receiving posaconazole and tacrolimus suggests the interaction may be safely managed by an empirical reduction in the tacrolimus dose by a factor of 3, with subsequent tapering to a mean of 2 mg daily [193]. However, to adequately manage these interactions, blood concentrations of the calcineurin inhibitors should be obtained before, during, and after azole use. Any dose adjustment should be based upon the objective results of these blood concentration data. The combination of posaconazole and sirolimus should be avoided until this interaction is more thoroughly characterized in a larger study in patients.

15.9.3 Interactions that Induce Posaconazole Biotransformation

Co-administration of posaconazole with CYP inducers (i.e. phenytoin, ritonavir, efavirenz) can significantly reduce its serum concentrations, which could potentially lead to therapeutic failure. As discussed above, one study demonstrated that posaconazole interacts with phenytoin. Despite the limitations of that study, which were previously mentioned, steady state posaconazole exposure and C_{max} were significantly reduced by phenytoin co-administration. There was also a 57% reduction in posaconazole $t_{1/2}$ and a 90% increase in its steady-state CL [191]. Rifabutin reduces the posaconazole tablets C_{max} and AUC_{τ} by 43% and 49%, respectively [192]. Co-administration of efavirenz (400 mg once daily for 10 days) decreased posaconazole exposure and C_{max} [189]. Posaconazole undergoes glucuronidation via UGT1A4 and phenytoin, rifabutin and efavirenz all induce UGT activity [189]. Therefore, in all these interactions are believed to result from or be due in part to induction of UGT-mediated posaconazole glucuronidation [189, 191, 192].

15.9.3.1 Clinical Importance of Interactions that Induce Posaconazole Biotransformation

Interactions that induce posaconazole biotransformation are potentially clinically significant because they may precipitate therapeutic failure. In addition, these interactions are often bi-directional and may at times increase the risk of toxicity associated with the inducer.

15.9.3.2 Management of Interactions that Induce Posaconazole Biotransformation

Because these interactions are bi-directional, increased plasma concentrations of phenytoin, rifabutin and efavirenz should be expected when these drugs are co-administered with posaconazole. Thus, frequent adverse events and toxicity monitoring is recommended. However, if possible avoid these combinations due to the decreased posaconazole exposure and subsequent risk for therapeutic failure.

15.10 Echinocandins

There have been very few reported drug-drug interactions with this class. The interactions reported to date have involved caspofungin and micafungin, but not anidulafungin. The mechanism(s) behind those that have been reported are largely unknown.

15.10.1 Interactions Involving Echinocandins

15.10.1.1 Calcineurin Inhibitors

Early studies involving very few patients raised concerns about the potential for the co-administration of caspofungin and cyclosporine to produce additive or synergistic hepatotoxicity. However, with more widespread use experience with this combination has demonstrated that the combination is well tolerated and these concerns have dissipated. There are few published data describing drug interactions with micafungin. Data suggest that micafungin does not significantly interact with tacrolimus [194]. Micafungin does interact with cyclosporine. In most individuals micafungin mildly inhibits cyclosporine metabolism, but the interaction varies in magnitude, and in rare cases a clinically significant increase in cyclosporine concentrations can occur [195].

15.10.1.2 Miscellaneous Drugs

Caspofungin, is not a CYP substrate or inhibitor, and at concentrations achieved clinically, it does not inhibit P-gp [37]. However, co-administration of rifampin produces both an inhibitory and an induction effect on caspofungin disposition, with an overall effect being slight induction at steady state [196]. In the initial days of concomitant therapy rifampin produced a transient increase in caspofungin plasma concentration [196]. This interaction occurred during the β distribution phase of caspofungin, which suggests that rifampin inhibits the uptake of caspofungin into tissues. The mechanism for this interaction is believed to involve OATP. Caspofungin and rifampin are OATP1B1 substrates and rifampin is an inhibitor of this transport protein [37]. Inhibition of OATP1B1 could reduce caspofungin distribution and lead to increases in concentrations of and exposure to this agent [36, 37, 196]. Ultimately, continued rifampin co-administration produced continually declining C_{min} over a 2 week period. This part of the interaction may have been due to induction of tissue uptake of caspofungin by rifampin [196].

15.10.1.3 Clinical Importance of Interactions Involving Echinocandins

The interaction between cyclosporine and micafungin is significant only in those individuals with a very high cyclosporine CL/F. These individuals cannot be identified by obtaining a single cyclosporine blood concentration.

It is unlikely that the initial transient increase in serum caspofungin concentrations produced by rifampin co-administration are clinically important. However, the continuing decline in caspofungin concentrations as therapy continued, could precipitate therapeutic failure [196].

15.10.1.4 Management of Interactions Involving Caspofungin

When micafungin is co-administered with cyclosporine, it is difficult to identify patients in who will have a clinically significant interaction. Therefore, in these patients careful monitoring of cyclosporine blood concentrations, and dosage adjustment as needed are recommended upon initiating or discontinuing micafungin therapy.

A reduction in caspofungin dose is not necessary for the transient elevation in caspofungin plasma concentrations when rifampin and caspofungin are initiated on the same study day. When rifampin is added to caspofungin therapy, an increase in the daily caspofungin maintenance dose from 50 to 70 mg should be considered [196].

15.11 Summary

The myriad of potential drugs that antifungal agents can interact with is daunting and can be confusing. Antifungal agents differ markedly in their pharmacokinetic properties and in how the interact with other medicines. The clinical relevance of antifungal-drug interactions varies substantially. While certain interactions are benign and result in little or no untoward clinical outcomes, others can produce significant toxicity or compromise efficacy if not properly managed. However, certain interactions produce significant toxicity or compromise efficacy to such an extent that they cannot be managed and the particular combination of antifungal and interacting medicine should be avoided. The amphotericin B formulations interact with other medicines by reducing their renal elimination or producing additive toxicities. However, among the several classes of antifungal agents, drug interactions are most common with the triazole class (fluconazole, itraconazole, voriconazole and posaconazole), due primarily to their ability to inhibit CYP. As a class these agents inhibit several CYP isoforms including CYP2C9, and CYP2C19 (fluconazole and voriconazole), and CYP3A4 (all agents). In addition, while they all inhibit CYP3A4, they do so to different degrees (e.g. itraconazole and voriconazole are the strong CYP3A4 inhibitors, whereas fluconazole is a moderate inhibitor). Therefore, collectively this class interacts with a vast array of medicines and the degree of interaction is often triazole specific. While the potential drug interaction profile of this class is vast, the most clinically significant interactions with the triazoles involve benzodiazepines and anxiolytics, immunosuppressants (i.e. calcineurin inhibitors, proliferation signal inhibitors, corticosteroids), the “statins”, certain types of calcium channel blockers, phenytoin and warfarin. The echinocandins have the lowest propensity to interact with other medicines.

References

1. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. Rev Infect Dis 1990;12:308–329.
2. Bekersky I, Fielding RH, Dressler DE, et al. Plasma protein binding of amphotericin B and pharmacokinetics of bound versus unbound amphotericin B after administration of intravenous liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate. Antimicrob Agents Chemother 2002;46:834–840.
3. Bekersky I, Fielding RH, Dressler DE, et al. Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. Antimicrob Agents Chemother 2002;46:828–833.
4. Wong-Berringer A, Jacobs RA, Guglielmo BJ. Lipid formulations of amphotericin B: clinical efficacy and toxicities. Clin Infect Dis 1998;27:603–618.
5. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal drugs. Clin Pharmacokinet 1983;8:17–42.
6. Wang E, Lew K, Casciano CN, et al. Interaction of common azole antifungals with p-glycoprotein. Antimicrob Agents Chemother 2002;46:160–165.
7. Gupta A, Unadkat JD, Mao Q. Interactions of azole antifungal agents with the human breast cancer resistance protein (BCRP). J Pharm Sci 2007; 96;3226–3235.
8. Wacher VJ, Wu CJ, Benet LZ. Overlapping substrate specificities and tissue distribution of cytochrome P450 3A and P-glycoprotein: implications for drug delivery and activity in cancer chemotherapy. Mol Carcinogen 1995;13:129–134.
9. Wacher VJ, Silverman JA, Zhang Y, et al. Role of P-glycoprotein and cytochrome P450 in limiting oral absorption of peptides and peptidomimetics. J Pharm Sci 1998;87:1322–1330.
10. Heykants J, Van Peer A, Van de Velde V, et al. The clinical pharmacokinetics of itraconazole: an overview. Mycoses 1989;32(suppl 1):67–87.
11. Van de Velde VJ, Van Peer AP, Heykants JJ, et al. Effect of food on the pharmacokinetics of a new hydroxypropyl-β-cyclodextrin formulation of itraconazole. Pharmacotherapy 1996;16: 424–428.
12. Barone JA, Moskovitz BL, Guarnieri J, et al. Food interaction and steady-state pharmacokinetics of itraconazole oral solution in healthy volunteers. Pharmacotherapy 1998;18: 295–301.
13. Johnson MD, Hamilton CD, Drew RH, et al. A randomized comparative study to determine the effect of omeprazole on the peak serum concentration of itraconazole oral solution. J Antimicrob Chemother 2003;51:453–457.
14. Barone JA, Moskovitz BL, Guarnieri J, et al. Enhanced bioavailability of itraconazole in hydroxypropyl-β-cyclodextrin solution versus capsules in healthy volunteers. Antimicrob Agents Chemother 1998;42:1862–1865.
15. Debruyne D, Ryckelynk JP. Clinical Pharmacokinetics of fluconazole. Clin Pharmacokinet 1993;24:10–27.
16. Johnson LB, Kauffman CA. Voriconazole: A new triazole antifungal agent. Clin Infect Dis 2003;36:630–637.
17. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/Pharmacodynamic Profile of Voriconazole. Clin Pharmacokinet 2006;45:649–663.
18. Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother 2003; 47:2788–2795.
19. Ezzet F, Wexler D, Courtney R, Krishna G, Lim J, Laughlin M. Oral bioavailability of posaconazole in fasted healthy subjects: comparison between three regimens and basis for clinical dosage recommendations. Clin Pharmacokinet 2005;44:211–220.
20. Krishna G, Moton A, MaL, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother 2009;53:958–966.

21. Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. Br J Clin Pharmacol 2003;57:218–222.
22. Sansone-Parsons A, Krishna G, Calzetta A, et al. Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers. Antimicrob Agents Chemother 2006;50:1881–1883.
23. Nagappan V, Deresinski S. Posaconazole: a broad-spectrum triazole antifungal agent. Clinical Infect Dis 2007;45:1610–1617.
24. Schwartz S, Milatovic D, Eckhard T. Successful treatment of cerebral aspergillosis with a novel triazole (voriconazole) in a patient with acute leukemia. Brit J Haematol 1997;97:663–665.
25. Poirier JM, Cheymol G. Optimization of itraconazole therapy using target drug concentrations. Clin Pharmacokinet 1998;35:461–473.
26. Isoherranen N, Kunze KL, Allen KE, et al. Role of itraconazole metabolites in CYP3A4 inhibition. Drug Metab Dispos 2004;32:1121–1131
27. Kunze KL, Nelson WL, Kharasch ED, Thummel KE, Isoherranen N. stereochemical aspects of itraconazole metabolism in vitro and in vivo. Drug Metab Dispos 2006;34:583–590.
28. Templeton IE, Thummel KE, Kharasch ED, et al. Contribution of itraconazole metabolites to inhibition of CYP3A4 in vivo. Clin Pharmacol Ther 2008;83:77–85.
29. Brammer KW, Coakley AJ, Jezequel SG, et al. The disposition and metabolism of [^{14}C] fluconazole in humans. Drug Metab Disp 1991;19:764–767.
30. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the *N*-oxidation of voriconazole. Drug Metab Disp 2003;31:540–547.
31. Sabo JA, Abdel-Rahman SM. Voriconazole: A new triazole antifungal. Ann Pharmacotherapy 2000;34:1032–1043.
32. Goldstein JA. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. Br J Clin Pharmacol 2001;52:349–355.
33. Lee CR. Goldstein JA. Pieper JA. Cytochrome P450 2 C9 polymorphisms: a comprehensive review of the in-vitro and human data. Pharmacogenetics 2002;12:251–263.
34. Krieter P, Flannery B, Musick T, Gohdes M, Martinho M, Courtney R. Disposition of posaconazole following single-dose oral administration in healthy subjects. Antimicrob Agents Chemother 2004;48:3543–3551.
35. Ghosal A, Hapangama N, Yuan Y, et al. Identification of human UDP-glucuronosyltransferase enzyme(s) responsible for the glucuronidation of posaconazole (Noxafil). Drug Metab Dispos 2004;32:267–271.
36. Stone JA, Xu X, Winchell GA, et al. Disposition of caspofungin: Role of distribution in determining pharmacokinetics in plasma. Antimicrob Agents Chemother 2004;48:815–823.
37. Sandhu P, Lee W, Xu X, et al. Hepatic uptake of the novel antifungal agent caspofungin. Drug Metab Disp 2005;33:676–682.
38. Cappelletty D, Eiselstein-McKitrick K. The echinocandins. Pharmacotherapy 2007;27: 369–388.
39. Stone JA, Holland SD, Wickersham PJ, et al. Single- and multiple-dose pharmacokinetics of caspofungin in healthy men. Antimicrob Agents Chemother 2002;46:739–745.
40. Balani SK, Xu X, Arison BH, et al. Metabolites of caspofungin acetate, a potent antifungal agent, in human plasma and urine. Drug Metab Disp 2000;28:1274–1278.
41. Hebert MF, Smith HE, Marbury TC, et al. Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. J Clin Pharmacol 2005;45:1145–1152.
42. Joseph JM, Jain R, Danziger LH. Micafungin: A new echinocandin antifungal. Pharmacotherapy 2007;27:53–67.
43. Damle BD, Dowell JA, Walsky RL, Weber GL, Stogniew M, Inskeep PB. In vitro and in vivo studies to characterize the clearance mechanism and potential cytochrome p450 interactions of anidulafungin. Antimicrob Agent Chemother 2009;53:1149–1156.
44. Estes KE, Penzak SR, Calis KA, Walsh TJ. Pharmacology and antifungal properties of anidulafungin, a new echinocandin. Pharmacotherapy 2009;29:17–30.

45. White MH, Bowden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. Clin Infect Dis 1998;27:296–302.
46. Ringdén O, Andström E, Remberger M, et al. Safety of liposomal amphotericin B (AmBisome) in 187 transplant recipients treated with cyclosporine. Bone Marrow Transplant 1994;14(suppl 5):S10–S14.
47. June CH, Thompson CB, Kennedy MS, et al. Profound hypomagnesemia associated with the use of cyclosporine for marrow transplantation. Transplantation 1985;39:620–624.
48. Block ER, Bennett JE. Pharmacological studies with 5-fluorocytosine. Antimicrob Agents Chemother 1972;1:476–482.
49. Stamm AM, Diaso RB, Dismukes WE, et al. Toxicity of amphotericin B plus flucytosine in 194 patients with cryptococcal meningitis. Am J Med 1987;83:236–242.
50. Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. N Engl J Med 1979; 301:126–131.
51. Perfect JR, Dismukes WE, Dromer F, et al. Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2010;50: 291–322.
52. Viviani MA. Flucytosine—what is its future? J Antimicrob Chemother 1995;35:241–244.
53. Chung DK, Koenig MG. Reversible cardiac enlargement during treatment with amphotericin B and hydrocortisone. Am Rev Respir Dis 1971;103:831–841.
54. Fleisher D, Li C, Zhou Y, et al. Drug, meal and formulation interactions influencing drug absorption after oral administration: clinical implications. Clin Pharmacokinet 1999;36: 233–254.
55. Lange D, Pavao JH, Wu J, et al. Effect of a cola beverage on the bioavailability of itraconazole in the presence of H_2 blockers. J Clin Pharmacol 1997;37:535–540.
56. Thummel KE, Wilkinson GR. In vitro and in vivo drug interactions involving human CYP3A. Annu Rev Pharmacol Toxicol 1998;38:389–430.
57. Omar G, Whiting PH, Hawksworth GM, et al. Ketoconazole and fluconazole inhibition of the metabolism of cyclosporin A by human liver in vitro. Ther Drug Monit 1997;19:436–445.
58. Black DJ, Kunze KL, Wienkers LC, et al. Warfarin-fluconazole II. A metabolically based drug interaction: in vivo studies. Drug Metab Disp 1996;24:422–428.
59. Jeong S, Nguyen PD, Desta Z. Comprehensive in vitro analysis of voriconazole inhibition of eight cytochrome P450 (CYP) enzymes: Major effect on CYPs 2B6, 2 C9, 2 C19, and 3A. Antimicrob Agents Chemother 2009;53:541–551.
60. Niwa T, Shiraga T, Takagi A. Effect of antifungal drugs on cytochrome P450 (CYP) 2 C9, CYP2C19, and CYP3A4 activities in human liver microsomes. Biol Pharm Bull 2005;28: 1805–1808.
61. Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. Eur J Pharm Sci 2004;21:645–653.
62. Wandel C, Kim RB, Kajiji S, et al. P-glycoprotein and cytochrome P-450 3A inhibition: dissociation of inhibitory potencies. Cancer Res 1999;59:3944–3948.
63. Kim RB. Organic anion-transporting polypeptide (OATP) transporter family and drug disposition. Eur J Clin Invest 2003;33(Suppl. 2):1–5.
64. Eytan GD, Regev R, Oren G, et al. The role of passive transbilayer drug movement in multidrug resistance and its modulation. J. Biol Chem 1996;271:12897–12902.
65. Ferté J. Analysis of tangled relationships between P-glycoprotein-mediated multidrug resistance and the lipid phase of the cell membrane. Eur J Biochem 2000;267;277–294.
66. Purkins L, Wood N, Kleinermans D, et al. Voriconazole does not affect the steady-state pharmacokinetics of digoxin. Br J Clin Pharmacol 2003;56:45–50.
67. Sansone-Parsons A, Krishna G, Simon J, et al. Effects of Age, gender, race/ethnicity on the pharmacokinetics of posaconazole in healthy volunteers. Antimicrob Agents Chemother 2007;51:495–502.

68. Kivistö KT, Kantola T, Neuvonen PJ. Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. Br J Clin Pharmacol 1998;46:49–53.
69. Neuvonen PJ, Kantola T, Kivistö KT. Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. Clin Pharmacol Ther 1998;63: 332–341.
70. Kantola T, Kivistö KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atorvastatin. Clin Pharmacol Ther 1998;64:58–65.
71. Mazzu AL, Lasseter KC, Shamblin EC, et al. Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin. Clin Pharmacol Ther 2000;68:391–400.
72. Cooper KJ, Martin PD, Dane AL, et al. Effect of itraconazole on the pharmacokinetics of rosuvastatin. Clin Pharmacol Ther 2003;73:322–329.
73. Olkkola KT, Ahonen J, Neuvonen PJ. The effect of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. Anesth Analg 1996;82:511–516.
74. Neuvonen PJ, Varhe A, Olkkola KT. The effect of ingestion time interval on the interaction between itraconazole and triazolam. Clin Pharmacol Ther 1996;60:326–331.
75. Ahonen J, Olkkola KT, Neuvonen PJ. The effect of the antimycotic itraconazole on the pharmacokinetics and pharmacodynamics of diazepam. Fundam Clin Pharmacol 1996;10: 314–318.
76. Otsuji Y, Okuyama N, Aoshima T, et al. No effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of estazolam. Ther Drug Monit 2002;24:375–378.
77. Oda M, Kotegawa T, Tsutsumi K, et al. The effect of itraconazole on the pharmacokinetics and pharmacodynamics of bromazepam in healthy volunteers. Eur J Clin Pharmacol 2003;59: 615–619.
78. Ahonen J, Olkkola KT, Neuvonen PJ. Lack of effect of the antimycotic itraconazole on the pharmacokinetics or pharmacodynamics of temazepam. Ther Drug Monit 1996;18:124–127.
79. Kivistö KT, Lamberg TS, Kantola T, et al. Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. Clin Pharmacol Ther 1997;62:348–354.
80. Luurila H, Kivistö KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics and pharmacodynamics of zolpidem. Eur J Clin Pharmacol 1998;54:163–166.
81. Park JY, Shon JH, Kim KA, et al. Combined effects of itraconazole and CYP2D6*10 genetic polymorphism on the pharmacokinetics and pharmacodynamics of haloperidol in healthy subjects. J Clin Psychopharm 2006;26:135–142.
82. Yasui N, Kondo T, Otani K, et al. Effects of itraconazole on the steady-state plasma concentrations of haloperidol and its reduced metabolite in schizophrenic patients: in vivo evidence of the involvement of CYP3A4 for haloperidol metabolism. J Clin Psychopharmacol 1999;19: 149–154.
83. Raaska K, Neuvonen PJ. Serum concentrations of clozapine and N-desmethylclozapine are unaffected by the potent CYP3A4 inhibitor itraconazole. Eur J Clin Pharmacol 1998;54(2): 167–170.
84. Leather H, Boyette RM, Tian L, Wingard JR. Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant 2006;12:325–334.
85. Varis T, Kaukonen KM, Kivistö KT, et al. Plasma concentrations and effects of oral methylprednisolone are considerably increased by itraconazole. Clin Pharmacol Ther 1998;64: 363–368.
86. Lebrun-Vignes B, Corbrion Archer V, Diquet B, et al. Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. Br J Clin Pharmacol 2001;51:443–450.
87. Varis T, Kivistö KT, Backman JT, et al. Itraconazole decreases the clearance and enhances the effects of intravenously administered methylprednisolone in healthy volunteers. Pharmacol Toxicol 1999;85:29–32.

88. Varis T, Kivistö KT, Backman JT, et al. The cytochrome P450 3A4 inhibitor itraconazole markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect. Clin Pharmacol Ther 2000;68:487–494.
89. Varis T, Kivistö KT, Neuvonen PJ. The effect of itraconazole on the pharmacokinetics and pharmacodynamics of oral prednisolone. Eur J Clin Pharmacol 2000;56:57–60.
90. Raaska K, Niemi M, Neuvonen M, et al. Plasma concentrations of inhaled budesonide and its effects on plasma cortisol are increased by the cytochrome P4503A4 inhibitor itraconazole. Clin Pharmacol Ther 2002;72:362–369.
91. Jalava KM, Olkkola KT, Neuvonen PJ. Itraconazole greatly increases plasma concentrations and effects of felodipine. Clin Pharmacol Ther 1997;61:410–415.
92. Lukkari E, Juhakoski A, Aranko K, et al. Itraconazole moderately increases serum concentrations of oxybutynin but does not affect those of the active metabolite. Eur J Clin Pharmacol 1997;52:403–406.
93. Hynninen VV, Olkkola KT, Bertilsson L, et al. Voriconazole increases while itraconazole decreases plasma meloxicam concentrations. Antimicrob Agent Chemother 2009;53;587–592.
94. Saari TI, Grönlund J, Hagelberg NM, et al. Effects of itraconazole on the pharmacokinetics and pharmacodynamics of intravenously and orally administered oxycodone. Eur J Clin Pharmacol 2010;66:387–397.
95. Jalava KM, Partanen J, Neuvonen PJ. Itraconazole decreases renal clearance of digoxin. Ther Drug Monit 1997;19:609–613.
96. Kaukonen KM, Olkkola KT, Neuvonen PJ. Itraconazole increases plasma concentrations of quinidine. Clin Pharmacol Ther 1997;62:510–517.
97. Demkier P, Hansen LL, Brøsen K. Effect of diclofenac, disulfram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. Br J Clin Pharmacol 1999;48:829–838.
98. Heiskanen T, Backman JT, Neuvonen M, Kontinen VK, Neuvonen PJ, Kalso E. Itraconazole, a potent inhibitor of P-glycoprotein increases plasma concentrations of oral morphine. Acta Anaestesiol Scand 2008;52:1319–1326.
99. Zimmerman NT, Yeates RA, Laufen H, et al. Influence of concomitant food intake on the oral absorption of two triazole antifungal agents, itraconazole and fluconazole. Eur J Clin Pharmacol 1994;46:147–150.
100. Kanda Y, Kami M, Matsuyama T, et al. Plasma concentrations of itraconazole in patients receiving chemotherapy for hematological malignancies: the effect of famotidine on the absorption of itraconazole. Hematol Oncol 1998;16:33–37.
101. Lim SG, Sawyerr AM, Hudson M, et al. Short report: the absorption of fluconazole and itraconazole under conditions of low intragastric acidity. Aliment Pharmacol Ther 1993;7: 317–321.
102. Jaruratanasirikul S, Sriwiriyajan S. Effect of omeprazole on the pharmacokinetics of itraconazole. Eur J Clin Pharmacol 1998;54:159–161.
103. Lohinavy M, Lohitnavy O, Thangkeattiyanon O, Srichai W. Reduced oral itraconazole bioavailability by antacid suspension. Journal Clin Pharmacy Ther 2005;30:201–206.
104. May DB, Drew RH, Yedinak KC, et al. Effect of simultaneous didanosine administration on itraconazole absorption in healthy volunteers. Pharmacotherapy 1994;14:509–513.
105. Damle B, Hess H, Kaul S, et al. Absence of clinically relevant drug interactions following simultaneous administration of didanosine-encapsulated, enteric-coated bead formulation with either itraconazole or fluconazole. Biopharm Drug Disp 2002;23:59–66.
106. Christians U, Jacobsen W, Floren LC. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in transplant patients: are the statins mechanistically similar? Pharmacol Ther 1998;80:1–34.
107. Wensel TM, Waldrop BA, Wensel B. Pitavastatin: A New HMG-CoA Reductase Inhibitor. Ann Pharmacother 2010;44:507–514.
108. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: Mechanisms and clinical relevance. Clin Pharmacol Ther 2006;80:565–581.

109. Neuvonen PJ, Jalava KM. Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. Clin Pharmacol Ther 1996;60:54–61.
110. Ishigam M, Uchiyama M, Kondo T, et al. Inhibition of in vitro metabolism of simvastatin by itraconazole in humans and predictions of in vivo drug-drug interactions. Pharm Res 2001;18:622–631.
111. Varhe A, Olkkola KT, Neuvonen PJ. Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther 1994;56: 601–607.
112. Backman JT, Kivistö KT, Olkkola KT, et al. The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. Eur J Clin Pharmacol 1998;54:53–58.
113. Miura M, Otani K, Ohkubo T. Identification of human cytochrome P450 enzymes involved in the formation of 4-hydroxyestazolam from estazolam. Xenobiotica 2005;35:455–465.
114. Kramer MR, Marshall SE, Denning DW, et al. Cyclosporine and itraconazole in heart and lung transplant recipients. Ann Intern Med 1990;113:327–329.
115. Billaud EM, Guillemain R, Tacco F, Chevalier P. Evidence for a pharmacokinetic interaction between itraconazole and tacrolimus in organ transplant patients. Br J Clin Pharmacol 1998;46:271–272.
116. Kuypers DR, Claes K, Evenepoel P, et al. Drug interaction between itraconazole and sirolimus in a primary renal allograft recipient. Transplantation 2005;79:737.
117. Said A, Garnick JJ, Dieterle N, Peres E, Abidi MH, Ibrahim RB. Sirolimus-itraconazole interaction in a hematopoietic stem cell transplant recipient. Pharmacotherapy 2006;26:289–295.
118. Kovarik JM, Hsu CH, McMahon L, et al. Population pharmacokinetics of everolimus in de novo renal transplant patients: Impact of ethnicity and comedications. Clin Pharmacol Ther 2001;70:247–254.
119. Daveluy A, Raignoux C, Miremont-Salamé, et al. Drug interactions between inhaled corticosteroids and enzymatic inhibitors. Eur J Clin Phamacol 2009;65:743–745.
120. Lomaestro BM, Piatek MA. Update on drug interactions with azole antifungal agents. Ann Pharmacotherapy 1998;32:915–928.
121. Lalovic B, Phillipis B, Risler LL et al. Quantitative contribution of CYP2D6 and CYP3A to oxycodone metabolism in human liver and intestinal microsomes. Drug Metab Disp 2004;32:447–454.
122. Lalovic B, Kharasch E, Hoffer C et al. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. Clin Pharmacol Ther 2006;79:461–479.
123. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006;97:S52–60.
124. Jacobsen W, Kirchner G, Hallensleben K, et al. Comparison of cytochrome P-450-dependent metabolism and drug interactions of the 3-hydroxy-3-methylglutaryl-COA-reductase inhibitors lovastatin and pravastatin in the liver. Drug Metab Disp 1999;27:173–179.
125. McCormick AD, McKillop D, Butters CJ, et al. ZD4522- An HMG-CoA reductase inhibitor free of metabolically mediated drug interactions: Metabolic studies in human in vitro systems [abstract]. J Clin Pharmacol 2000;40:1055.
126. Bonay M, Jonville-Bera AP, Diot P, et al. Possible interaction between phenobarbital, carbamazepine and itraconazole. Drug Safety 1993;9:309–311.
127. Ducharme MP, Slaughter RL, Warbasse LH, et al. Itraconazole and hydroxyitraconazole serum concentrations are reduced more than tenfold by phenytoin. Clin Pharmacol Ther 1995;58:617–624.
128. Jaruratanasirikul S, Sriwiriyajan S. Effect of rifampicin on the pharmacokinetics of itraconazole in normal volunteers and AIDS patients. Eur J Clin Pharmacol 1998;54:155–158.
129. Jaruratanasirikul S, Sriwiriyajan S. Pharmacokinetic study of the interaction between itraconazole and nevirapine. Eur J Clin Pharmacol 2007;63:451–456.
130. de Lannoy IAM, Silverman M. The mdr-1 gene product P-glycoprotein mediates transport of the cardiac glycoside, digoxin. Biochem Biophys Res Comm 1992; 189:551–557.

131. de Lannoy IAM, Koren G, Klein J, et al. Cyclosporin and quinidine inhibition of renal digoxin excretion: evidence for luminal secretion of digoxin. Am J Physiol 1992;263:F613–F622.
132. Burmúdez M, Fuster JL, Llinares E, Galera A, Gonzalez C. Itraconazole-related increased vincristine neurotoxicity: Case report and review of literature. J Pediatr Hematol Oncol 2005;27:389–392.
133. Bashir H, Motl S, Metzger ML, et al. Itraconazole-enhanced chemotherapy toxicity in a patient with hodgkin lymphoma. J Pediatr Hematol Oncol 2006;28:33–35.
134. Sachs MK, Blanchard LM, Green PJ. Interaction of itraconazole and digoxin. Clin Infect Dis 1993;16:400–403.
135. Kantola T, Backman JT, Niemi M, Kivistö KT, Neuvonen PJ. Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. Eur J Clin Pharmacol 2000;56:225–229.
136. Cooper KJ, Martin PD, Dane AL, Warwick MJ, Schneck DW, Cantarini MV. Effect of fluconazole on the pharmacokinetics of rosuvastatin. Eur J Clin Pharmacol 2002;58: 527–531.
137. Ahonen J, Olkkola KT, Neuvonen PJ. Effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. Eur J Clin Pharmacol 1997;51:415–419.
138. Varhe A, Olkkola KT, Neuvonen PJ. Effect of fluconazole dose on the extent of fluconazole-triazolam interaction. Br J Clin Pharmacol 1996;42:465–470.
139. Varhe A, Olkkola KT, Neuvonen PJ. Fluconazole, but not terbinafine, enhances the effects of triazolam by inhibiting its metabolism. Br J Clin Pharmacol 1996;41:319–323.
140. Saari TI, Laine K, Bertilsson L, Neuvonen PJ Olkkola KT. Voriconazole and fluconazole increase the exposure to oral diazepam. Eur J Clin Pharmacol 2007;63:941–949.
141. Lopez-Gil JA. Fluconazole-cyclosporine interaction: a dose-dependent effect? Ann Pharmacotherapy 1993;27:427–430.
142. Mori T, Asia Y, Kato J, Nakamura Y, Ikeda Y, Okamoto S. Drug Interaction between calcineurin inhibitors in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplantation 2009;44:371–374.
143. Blum RA, Wilton JH, Hilligoss DM, et al. Effect of fluconazole on disposition of phenytoin. Clin Pharmacol Ther 1991;49:420–425.
144. Saari TI, Laine K, Neuvonen M, Neuvonen PJ, Olkkola KT. Effect of voriconazole and fluconazole on the pharmacokinetics of intravenous fentanyl. Eur J Clin Phamacol 2008;64:25–30.
145. Palkama VJ, Isohanni MH, Neuvonen PJ, et al. The effect of intravenous and oral fluconazole on the pharmacokinetics and pharmacodynamics of intravenous alfentanil. Anesth Analg 1998;87:190–194.
146. Cobb MN, Desai J, Brown LS, Jr., Zannikos PN, Rainey PM. The effect of fluconazole on the clinical pharmacokinetics of methadone. Clin Pharmacol Ther 1998;63:655–662.
147. Yule SM, Walker D, Cole M, et al. The effect of fluconazole on cyclophosphamide metabolism in children. Drug Metab Disp 1999;27:417–421.
148. Wakeham K, Ratanshi RP, Watson V, Ggayi AB, Khoo S, Lalloo DG. Co-administration of fluconazole increases nevirapine concentrations in HIV-infected Ugandans. J Antimicrob Chemother 2010;65:316–319.
149. Hynninen VV, Olkkola KT, Leino K et al. Effects of the antifungals voriconazole and fluconazole on the pharmacokinetics of S-(+)- and R-(−)-ibuprofen. Antimicrob Agents Chemother 2006;50:1967–1972.
150. Shaukat A, Benekli M, Vladutiu GD, Slack JL, Wetzler M, Baer MR. Simvastatin-fluconazole causing rhabdomyolysis. Ann Pharmacother 2003;37:1032–1035.
151. Hazin R, Abuzetun JY, Suker M, Porter J. Rhabdomyolysis induced by simvastatin-fluconazole combination. J Natl Med Assoc 2008;100:444–446.
152. Kahri J, Valkonen M, Bäcklund T, Vuoristo M, Kivistö KT. Rhabdomyolysis in a patient receiving atorvastatin and fluconazole. Eur J Clin Pharmacol 2005;60:905–907.
153. Krüger HU, Schuler U, Zimmermann R, et al. Absence of significant interaction of fluconazole with cyclosporin. J Antimicrob Chemother 1989;24:781–786.

154. Canafax DM, Graves NM, Hilligoss DM, et al. Interaction between cyclosporine and fluconazole in renal allograft recipients. Transplantation 1991;51:1014–1018.
155. Mañez R, Martin M, Raman D, et al. Fluconazole therapy in transplant recipients receiving FK506. Transplantation 1994;57:1521–1523.
156. Sud K, Baljinder S, Krishna VS, et al. Unpredictable cyclosporine-fluconazole interaction in renal transplant recipients. Nephrol Dial Transplant 1999;14:1698–1703.
157. Mihara A, Mori T, Yamazaki R, et al. Greater impact of oral fluconazole on drug interaction with intravenous calcineurin inhibitors as compared with intravenous fluconazole. Eur J Clin Pharmacol 2008;64:89–91.
158. Cervelli MJ. Fluconazole-sirolimus drug interaction. Transplantation 2002;27:1477–1478.
159. Pea F, Baccarani U, Tavio M. Pharmacokinetic interaction between everolimus and antifungal triazoles in a liver transplant patient. Ann Pharmacother 2008;42:1711–1716.
160. Upton A, McCune JS, Kirby KA, et al. Fluconazole co-administration concurrent with cyclophosphamide conditioning may reduce regimen-related toxicity postmyeloablative hematopoietic cell transplantation. Biol Blood Marrow Transplant 2007;13:760–764.
161. Jordan MK, Polis MA, Kelly G, Narang PK, Masur H, Piscitelli SC. Effects of fluconazole and clarithromycin on rifabutin and 25-O-Desacetylrifabutin pharmacokinetics. Antimicrob Agents Chemother 2000;44:2170–2172.
162. Hallberg P, Marten L, Wadelius M. Possible fluconazole fentanyl interaction-a case report. Eur J Clin Pharmacol 2006;62(2):491–492.
163. Apseloff G, Hilligoss DM, Gardner MJ, et al. Induction of fluconazole metabolism by rifampin: in vivo study in humans. J Clin Pharmacol 1991;31:358–361.
164. Sahai J, Gallicano K, Pakuts A, et al. Effect of fluconazole on zidovudine pharmacokinetics in patients infected with Human Immunodeficiency Virus. J Infect Dis 1994;169: 1103–1107.
165. Saari TI, Laine K, Leino K Valtonen M, Neuvonen PJ, Olkkola KT. Effect of voriconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. Clin Pharmacol Ther 2006;79:362–370.
166. Romero AJ, Le Pogamp P, Nilsson LG, et al. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant recipients. Clin Pharmacol Ther 2002;71:226–234.
167. Venkataramanan R, Zang S, Gayowski T, et al. Voriconazole inhibition of the metabolism of tacrolimus in a liver transplant recipient and in human liver microsomes. Antimicrob Agents Chemother 2002;46:3091–3093.
168. Tintillier M, Kirch L, Goffin E, Cuvelier C, Pochet JM. Interaction between voriconazole and tacrolimus in a kidney-transplanted patient. Nephrol Dial Transplant 2005;20: 664–665.
169. Saari TL, Laine K, Leino K et al. Voriconazole, but not terbinafine, markedly reduces alfentanil clearance and prolongs its half-life. Clin Pharmacol Ther 2006;80:502–508.
170. Liu P, Foster G, LaBadie R et al. Pharmacokinetic interaction between voriconazole and methadone at steady state in patients on methadone therapy. Antimicrob Agents Chemother 2007;51:110–118.
171. Hagelberg NM, Nieminen TH, Saari TI, et al. Voriconazole drastically increases exposure to oral oxycodone. Eur J Clin Pharmacol 2009;65:263–271.
172. Hynninen VV, Olkkola KT, Leino K, et al. Effect of voriconazole on the pharmacokinetics of diclofenac. Fundamental Clin Pharmacol 2007;21:651–656.
173. Hynninen VV, Olkkola KT. Neuvonen PJ, Laine KT. Oral voriconazole and miconazole oral gel produce comparable effects on the pharmacokinetics and pharmacodnamics of etoricoxib. Eur J Clin Pharmacol 2009;65:89–95.
174. Purkins L, Wood N, Kleinermans D, et al. Voriconazole potentiates warfarin-induced prothrombin time prolongation. Br J Clin Pharmacol 2003;56(Suppl 1):24–29.
175. Purkins L, Wood N Ghahramani P, et al. Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. Br J Clin Pharmacol 2003;56 (Suppl 1):37–44.

176. Liu P, Foster G, Labadie RR, Gutierrez MJ, Sharma A. Voriconazole and efavirenz at steady state in healthy male subjects. J Clin Phamacol 2008;48:73–84.
177. Damle B, LaBadie R, Crownover P, Glue P. Pharmacokinetic interactions of efavirenz and voriconazole in healthy volunteers. Br J Clin Pharmacol 2008;65:523–530.
178. Liu P, Grover F, Gandelman K, et al. Steady-state pharmacokinetic and safety profiles of voriconazole and ritonavir in healthy male subjects. Antimicrob Agent Chemother 2007;51:3617–3626.
179. Mikus G, Schöwel V, Drzewinska M, et al. Potent cytochrome P450 2 C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. Clin Pharmacol Ther 2006;80:126–135.
180. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. Pharmacotherapy 2006;26:1730–1744.
181. von Moltke LL, Greenblatt DJ, Granda BW, et al. Inhibition of human cytochrome P450 isoforms by nonnucleoside reverse transcriptase inhibitors. J Clin Pharmacol 2001;41: 85–91.
182. Mouly S, Lown KS, Kornhauser D, et al. Hepatic but not intestinal CYP3A4 displays dose-dependent induction by efavirenz in humans. Clin Pharmacol Ther 2002;72:1–9.
183. Gubbins PO, Heldenbrand SD. Clinically relevant drug interactions of current antifungal agents. Mycoses 2010;53:95–113.
184. Muijser RBR, Goa KL, Scott LJ. Voriconazole in the treatment of invasive aspergillosis. Drugs 2002;18:2655–2664.
185. Alffenaar JWC, van der Elst KCM, Uges DRA, Kosterink JGW, Daenen SMGJ. Phenytoin-induced reduction of voriconazole serum concentration is not compensated by doubling the dosage. Br J Clin Pharmacol 2009;68:462–463.
186. Krishna G, Moton A, Ma L, et al. Effects of oral posaconazole on the pharmacokinetics of oral and intravenous midazoloam: A phase I randomized, open-label, crossover study in healthy volunteers. Clin Ther 2009;31:286–298.
187. Sansone-Parsons A, Krishna G, Martinho M, Kantesaria B, Gelone S, Mant TG. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. Pharmacotherapy 2007;27:825–834.
188. Moton A, Ma L, Krishna G, Martinho M, Seiberling M, McLeod J. Effects of oral posaconazole on the pharmacokinetics of sirolimus. Curr Med Res Opin 2009;25:701–707.
189. Krishna G, Moton A, Ma L, Martinho M, Seiberling M, McLeod J. Effects of oral posaconazole on the pharmacokinetics of atazanavir alone and with ritonavir or with efavirenz in healthy adult volunteers. J Acquir Immune Defic Syndr 2009;51:437–444.
190. Courtney R, Radwanski E, Lim J, Laughlin M. Pharmacokinetics of posaconazole coadministered with antacid in fasting or nonfasting healthy men. Antimicrob Agents Chemother 2004;48:804–808.
191. Krishna G, Sansone-Parsons A, Kantesaria B. Drug interaction assessment following concomitant administration of posaconazole and phenytoin in healthy men. Curr Med Res Opin 2007;23:1415–1422.
192. Krishna G, Parsons A, Kantesaria B, Mant T. Evaluation of the pharmacokinetics of posaconazole and rifabutin following co-administration to healthy men. Curr Med Res Opin 2007; 23:545–552.
193. Berge M, Chevalier P, Benammer M, et al. Safe management of tacrolimus together with posaconazole in lung transplants with cystic fibrosis. Ther Drug Monit 2009;31:396–399.
194. Hebert MF, Blough DK, Townsend RW et al. Concomitant tacrolimus and micafungin pharmacokinetics in healthy volunteers. J Clin Pharmacol 2005;45:1018–1024.
195. Hebert MF, Townsend RW, Austin S et al. Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. J Clin Pharmacol 2005;45:954–960.
196. Stone JA, Migoya EM, Hickey L, et al. Potential for interactions between caspofungin and nelfinavir or rifampin. Antimicrob Agents Chemother 2004;48:4306–4314.

Chapter 16
Antimalarial Agents

Sunil Parikh, Ming-Na Tina Lee, and Francesca T. Aweeka

Abstract Malaria is one of the most important infectious diseases in the world. Disease caused by Plasmodium falciparum, the most virulent human malaria parasite, is responsible for approximately 243 million cases of malaria yearly, accounting for ~863,000 deaths. Artemisinin combination therapy (ACT) is the mainstay of treatment for malaria today due to resistance to older drugs and is now recommended by the World Health Organization for treatment of uncomplicated malaria. ACT drugs are very effective clinically; include two drug combinations of a short acting artemisinin drug coupled with a long acting partner drug and exhibit complex pharmacology making them susceptible to drug-drug interactions, especially during treatment for coinfections including HIV and tuberculosis. Alterations in ACT exposure may impact response to malaria therapy and increase risk for development of drug resistance. If resistance were to arise for ACT, this would have devastating consequences in regions such as sub-Saharan Africa. This chapter will discuss pharmacokinetic and pharmacodynamic interactions involving current ACTs: artemether-lumefantrine, dihydroartemisinin-piperaquine, artesunate in combination with amodiaquine as well as summarize data relevant to older antimalarial drugs include mefloquine and sulfadoxine–pyrimethamine. In addition, drug interactions involving other antimalarials (atovaquone, proguanil, chloroquine, mefloquine, quinine) recommended for prophylactic use and for treatment of malaria will also be discussed.

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16.1 Malaria and Its Treatment

Malaria is a serious and sometimes fatal disease with over 243 million new cases and up to 1 million deaths annually worldwide [1]. Transmitted by *Anopheles* mosquitoes, malaria primarily afflicts young children in sub-Saharan Africa and South Asia, leading to fever and nonspecific symptoms [2]. Malaria has a devastating economic impact on already impoverished countries. Increasing predominance and expanding geographical distribution of resistant strains of *Plasmodium falciparum* malaria has led to a demand for novel antimalarial treatment.

Up until recently, the management of malaria has relied upon the use of antimalarial agents such as chloroquine, sulfadoxine/pyrimethamine (SP) and mefloquine. Chloroquine and SP are inexpensive but their use has been limited by the development and spread of drug resistance [3]. Chloroquine became widely used in 1946. In 1957, the emergence of chloroquine resistant *P. falciparum* was identified in Southeast Asia which led to its diminishing use over the next several decades [4]. Resistance to SP was reported in 1967 in the Thai-Cambodia border, within the same year after the drug was introduced [5]. Mefloquine resistance, although comparatively more rare, was identified in 1982 after 5 years of use clinically [6].

In 2001, due to increasing resistance to the mainstays of antimalarial therapy, chloroquine and SP, the World Health Organization (WHO) recommended artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria [7]. ACTs are very potent drugs that include two drug components; a short-acting artemisinin derivative that rapidly diminishes parasite burden and fever, partnered with a longer-acting, less potent drug responsible for eradicating residual parasites and protecting against artemisinin resistance [8]. The two most widely adopted ACTs in Africa are artemether-lumefantrine (AL) and artesunate-amodiaquine (AS/AQ) [9]. A third and promising ACT is dihydroartemisinin-piperaquine (DP) [10]. The partner drug piperaquine (PQ) has a uniquely long half-life of ~21–28 days, longer than most other current partner drugs (lumefantrine t ½ approximately 3–4 days) [11]. While all three regimens display unique PK/PD, all have proven to be highly effective through numerous clinical trials [12].

The extent of exposure to ACT may impact clinical outcomes [13]. For example, significantly diminished ACT exposure during acute treatment may increase risk for malaria treatment failure (recrudescence or relapse due to the original infecting strain). Low ACT exposure may also increase risk for new infection due to low exposure of the long-acting partner drug limiting "post-treatment prophylaxis". Recent studies evaluating exposure-outcome relationships have focused primarily on artemether-lumefantrine and evaluated the predictive value of single day 7 drug levels of lumefantrine with treatment outcomes [14]. The rationale for this approach is that by day 7, following rapid elimination of the artemisinins, residual parasites are exposed only to the partner drug, and this exposure is critical to both clearing the current infection and potentially providing "post-treatment prophylaxis" against newly infecting strains. Day 7 levels also serve as a surrogate for the area under the plasma concentration versus time curve (AUC), as has been recently reported for AQ and lumefantrine (LR), and has been reported for SP [13, 15, 16]. In 201 patients,

aged 2–70 years, the median day 7 LR level was 528 ng/ml, and patients with levels <175 ng/mL were more likely to experience treatment failure [17]. Other studies have also correlated LR PK exposure with clinical outcomes in adults [18–20].

16.1.1 Pharmacology of Artemisinin Combination Therapy

The pharmacology of ACTs is interesting and highly complex. Nearly all drug components of ACTs require pharmacological activation and/or undergo metabolism, making these drugs highly prone to clinically relevant drug-drug interactions [11]. For example in the case of AL, artemether (AR) undergoes rapid demethylation, by cytochrome p450 3A4/5 (CYP3A4/5) and possibly CYP2B6 [21, 22]. The resulting metabolite, dihydroartemisinin (DHA), undergoes further metabolism via UDP-glucuronosyltransferases (UGT) [23]. Both AR and DHA are potent antimalarials. Intriguingly, artemether also enhances its own metabolism through autoinduction, possibly of CYP2B6, although the clinical significance of this remains unclear [24–26]. Lumefantrine, the partner drug, is metabolized via CYP3A4, to marginally active or inactive metabolites [27]. Lumefantrine also demonstrates significant CYP2D6 inhibition *in vitro* [28]. A number of studies described in detail below document drug-drug interactions between AL and concomitant therapies including ART and antifungal drugs such as ketoconazole [29, 30]. As ACT prescribing continues to rise, specific information on antimalarial drug interactions will become increasingly relevant for clinicians managing third-world populations where polypharmacy is the norm for treatment of patients with co-infections.

16.1.2 Antiretroviral Therapy and ACT Drug Interactions

As malaria treatment is common in the setting of expanded access to ART, potential drug-drug interactions must be assessed (Table 16.1). Significant alterations in antimalarial levels in the context of daily ART may impact malaria treatment efficacy or toxicity. Conversely, the effect of 3 days of ACT on antiretroviral efficacy is less of a concern. The standard first-line ART regimens used in resource limited settings generally consist of a non-nucleoside reverse transcriptase inhibitor (NNRTI) given with two nucleoside reverse transcriptase inhibitors (NRTI) [31]. The predominant NNRTI in these settings is nevirapine, followed by efavirenz. Second-line ART regimens include use of protease inhibitors (PI), especially lopinavir/ritonavir, given with 2 NRTIs. Knowledge of the metabolism of enzyme-inducing or inhibiting antiretrovirals (ARVs) and AL suggests that there is potential for PK drug–drug interactions. HIV PIs and NNRTIs (particularly efavirenz, EFV and nevirapine, NVP) have opposing effects on CYP3A4 and may inhibit and induce, respectively, the metabolism of artemether and lumefantrine. For example, the protease inhibitor ritonavir, given in combination at a low-dose with several other protease inhibitors, is among the most potent known inhibitors of CYP3A4 metabolism [32]. Additional interactions may arise through metabolism or induction of CYP2B6 by NNRTIs and artemether [22, 26, 33, 34] (Table 16.1).

Table 16.1 Routes of metabolism for artemether-lumefantrine and selected ARTs

	Substrates	Induces	Inhibits
Antimalarial			
Lumefantrine	CYP3A4	–	CYP2D6
Artemether	CYP3A4, CYP2B6	CYP3A4/2B6/2C19	–
DHA	UGT1A9, UGT2B7	–	–
Antiretroviral			
LPV/r	CYP3A4	–	CYP3A4
Nevirapine	CYP2B6, CYP3A4	CYP3A4	–
Efavirenz	CYP2B6>CYP3A4	CYP3A4	CYP3A4 (rare)

16.1.3 Antituberculosis and ACT Drug Interactions

Malaria and tuberculosis (TB) co-infection is also of paramount importance in endemic countries causing more than 3 million deaths worldwide annually, TB and malaria are two of the leading diseases contributing to morbidity and mortality in countries with limited resources [35]. The complexity of co-treatment of these diseases also lies in the potential drug-drug interactions between TB treatment and ACT. Rifamycins, potent P450 inducers, are prescribed in combination with ethambutol and isoniazid for the treatment of TB [36]. Co-administration of rifamycins, in particular rifampin, with antimalarials is likely to lead to decreased levels and efficacy of antimalarial treatment.

This chapter will discuss pharmacokinetic and pharmacodynamic interactions involving current artemisinin combination therapies (ACTs): artemether-lumefantrine, dihydroartemisinin-piperaquine, artesunate in combination with amodiaquine as well as summarize data relevant to older antimalarial drugs include mefloquine and sulfadoxine–pyrimethamine. In particular, clinically relevant drug interactions, between ACT, ART and TB treatment will be summarized. In addition, drug interactions involving other antimalarials (atovaquone, proguanil, chloroquine, mefloquine, quinine) recommended for prophylactic use and for treatment of malaria will also be discussed.

16.2 Pharmacokinetic Interactions

16.2.1 Drug Interactions with Antiretrovirals

16.2.1.1 Interactions Between AS/AQ and Antiretrovirals

NNRTIs are known substrates and inducers of P450, particularly CYP3A4, but occasionally efavirenz inhibits certain P450 isoforms (Table 16.2). Amodiaquine (AQ), a component of the ACT AS/AQ, has been shown to undergo metabolism

Table 16.2 Pharmacokinetic interaction of antimalarials and concomitant drugs

Antimalarial	Interacting drug	Effects on antimalarial PK	Clinical comment	Reference
Artesunate-amodiaquine	Efavirenz	AQ: AUC, C_{max}, $t_{1/2}$ increased DEAQ: AUC decreased	Avoid	[40]
Lumefantrine	Lopinavir/RTV	LR: AUC +125%, C_{max} +39%	Likely safe	[29]
	Ketoconazole	LR: AUC +61%, C_{max} +28%	Likely safe	[30]
Artemether	Lopinavir/RTV	AR: AUC −35%, C_{max} −22% DHA: AUC −45%, C_{max} −37%	Likely safe	[29]
	Ketoconazole	AR: AUC +131%, C_{max} +116% DHA: AUC +51%, C_{max} +37%	Likely safe	[30]
Atovaquone-proquanil	Efavirenz	Proguanil: AUC +113%, C_{max} +47% Cycloguanil: AUC −37%, C_{max} -31% ATQ: AUC −75%, C_{max} −44% Proguanil: AUC −43%, C_{max} N/S	Potential reduced efficacy	[45]
	Lopinavir/RTV	ATQ: AUC −74% C_{max} −44% Proguanil: AUC −38%, C_{max} N/S	Potentially reduced efficacy	[44]
	Atazanavir/RTV	ATQ: AUC −46% C_{max} −49% Proguanil: AUC −41%, C_{max} N/S		
	Rifampin	ATQ: AUC −50%	Avoid	[58]
	Rifabutin	ATQ: AUC −34%		
Quinine	RTV	Q: AUC +340%, C_{max} +284% 3-HQ: AUC −59% C_{max} −47%	Consider dose adjustment	[48]
	Nevirapine	AUC −33%, C_{max} −36%	Caution	[47]
	Rifampin	Clearance +521%, $t_{1/2}$ −50% $AUC_{(day\ 0–7)}$ −75%	Avoid	[56] [110]
Mefloquine	RTV	No significant change	Safe	[49]
	Nelfinavir	No significant change	Safe	[50]
	Indinavir	No significant change	Safe	
	Rifampin	MQ: AUC −68%, C_{max} −19%, $t_{1/2}$ −63%	Avoid	[55]
	Tetracycline	MQ: AUC no significant change, C_{max} +38%	Safe	[59]
	Ampicillin	MQ: AUC no significant change, C_{max} +34%	Safe	[60]
	Ketoconazole	AUC + 79%, C_{max} + 64%, $t_{1/2}$ +39%	Caution	[61]
Halofantrine	Tetracycline	HF: AUC +99%, C_{max} +147%, $t_{1/2}$ +73%	Avoid	[62]
	Fluconazole	HF: no significant change DHF: AUC −46%, C_{max} −37%	Caution	[63]

AUC area under the curve, *Cl* clearance, *AQ* amodiaquine, *DEAQ* desethylamodiaquine, *LR* lumefantrine, *RTV* ritonavir, *AR* artemether, *DHA* dihydroartemisinin, *ATQ* atovaquone, *Q* quinine, *3-HQ* 3-hydroxyquinine, *MQ* mefloquine, *HF* halofantrine, *DHF* desbutylhalofantrine

primarily through CYP2C8, into the active metabolite desethylamodiaquine (DEAQ), while artesunate (AS) undergoes hydrolysis by plasma esterases and metabolism through CYP2A6 and CYP2B6 [37, 38]. Most recently, *in vitro* studies have shown both that efavirenz, lopinavir, saquinavir, and tipranavir inhibit CYP2C8 at clinically relevant concentrations (10). Metabolism of both debrisoquine, a CYP2D6 substrate, and losartan, a CYP2C9 substrate, has been shown to be inhibited *in vivo* after a single AQ dose given to healthy volunteers [39].

The potential for *in vivo* interactions between AS/AQ and efavirenz has been studied in healthy volunteers. In two participants, hepatoxicity was observed with notable increases in alanine and aspartate transferase levels above the upper limit of normal. Exposure to AQ was increased in these two individuals (AUC +300% and +100%, respectively), while exposure to the metabolite, DEAQ, was decreased by 24% and 9%, respectively, a finding possibly partly related to CYP2C8-mediated drug drug interactions [40, 41]. This pivotal study led to recommendations that AQ-AS should be avoided in patients receiving EFV [42]. Studies examine the clinical relevance of protease inhibitor-mediated CYP2C8 inhibition have not been done.

16.2.1.2 Interactions Between AL and ART

Artemether-lumefantrine (AL) is predominantly metabolized by CYP3A4, making drug interactions between AL and both PIs and NNRTIs highly likely [30]. In the case of AL with PI, a study in healthy volunteers found that co-administration of lopinavir/ritonavir (LPV/r, Kaletra®) with AL resulted in a two- to threefold increase in lumefantrine AUC [29]. However, co-administration with LPV/r modestly decreased the AUC and C_{max} of artemether and active DHA, without change in the DHA:artemether AUC ratio [29]. A second study evaluated the effect of 3A4 inhibitor ketoconazole on the bioavailability of AL; coadministration increased AUC and C_{max} of artemether (mean +131% and +116%, respectively), DHA AUC and C_{max} (mean +51% and +37%, respectively) and lumefantrine AUC and C_{max} (mean +61% and +28%, respectively) compared to AL alone [30]. These increases were not associated with increased incidence of serious side-effects or changes in ECG parameters. Therefore, the increases in exposure of lumefantrine were determined as not significant enough to require dose adjustment of AL or avoid coadministration with PIs. Clinical studies currently underway in malaria-endemic are addressing safety of AL and PI co-administration. AL is also suspectible to drug-drug interactions with NNRTIs, potentially resulting in the opposite effect than seen with PI. One report has shown unexpected increases in lumefantrine levels in HIV-infected females treated with NVP [43]. Studies of AL in combination with both efavirenz and with nevirapine are currently underway.

16.2.1.3 Interactions Between Atovaquone-Proguanil and ART

Recent studies have evaluated the pharmacokinetics of atovaquone/proguanil, an antimalarial primarily used in prophylaxis for travelers, in combination with

ARTs [44, 45]. The mean ratio of AUC of atovaquone in those on ART compared to those not on ART was 0.25, 0.26, and 0.54 for efavirenz, lopinavir/ritonavir, and atazanavir/ritonavir, respectively [44]. Similarly, proguanil concentrations were decreased by 38–43%. Thus, although not a contraindication, concern has been raised regarding atovaquone-proguanil prophylaxis in HIV-infected patients on ART.

16.2.1.4 Interactions Between Quinine and ART

Quinine, metabolized through CYP3A4 and P-glycoprotein (P-gp), remains a mainstay for the treatment of severe malaria. Although little resistance has been reported, side effects such as cardiotoxicity and cinchonism are not unusual [46]. Two studies in healthy volunteers have recently shown that coadministation of ART impacts upon quinine levels [47, 48]. Ritonavir, which both inhibits CYP3A4 and P-gp, when administered with quinine, resulted in a nearly fourfold increase in quinine Cmax and AUC, raising concerns that quinine may need to be downward dose adjusted [48]. Consideration of more extensive safety studies and studies with routinely used ritonavir dosage (100 mg bid or qd, not 200 mg bid) may help to formalize these recommendations. A second study evaluated the concomitant use of nevirapine, typically a CYP3A4 inducer, and quinine [47]. Concurrent administration of nevirapine led to an approximately 33% decrease in quinine AUC and Cmax [47]. As above, further studies are required, but this study raises concern that conventional dosing of quinine may be insufficient in the setting of nevirapine usage.

16.2.1.5 Interactions Between Mefloquine and ART

A final antimalarial that has been evaluated with ART is mefloquine. Similar to quinine, mefloquine use has been associated with a number of side effects, most notably neuropsychiatric disturbances. Its interaction with ritonavir was evaluated in a healthy control study, and revealed that despite using a relatively high dose of ritonavir (200 mg bid), mefloquine AUC and Cmax were minimally altered [49]. Similarly, a study involving two patients taking either nelfinavir or indinavir, found no significant increase or decrease in mefloquine levels [50].

16.2.2 Antimalarials and Antituberculous Therapy

In vivo studies have unveiled the potential drug interactions of administering antimalarials concomitantly with rifamycins [51]. Rifamycins are potent P450 inducers, particularly CYP3A4, and rifampin also induces P-gp [36]. Rifabutin, a newer rifamycin, is a weaker enzyme inducer than rifampin [52].

16.2.2.1 Interactions Between Quinoline Antimalarials and Rifamycins

A study in infected mice reported that the concurrent administration of rifampin and CQ decreased survival rate and clearance of parasitaemia and increased the rate of recrudescence [53]. These findings support a pregnane X receptor upregulating CYP3A4 expression [54]. Rifampin (600 mg dose) has also been shown to lower mefloquine AUC (−68%) and $t_{1/2}$ (−63%); and increase mefloquine metabolite AUC and clearance (+30% and +25%, respectively) after a single mefloquine dose in healthy Thai volunteers [55]. Even though the results did not reach statistical significance, the study authors recommended avoiding the co-administration of MQ and rifampin due to increased risk for antimalarial resistance. Rifampin has also been studied in combination with quinine. When administered with rifampin, quinine clearance increased (0.87 vs. 0.14 L/h/kg), as did the elimination half-life of quinine (5.5 vs. 11.1 h) [56]. A second study evaluated the clinical impact of rifampin and quinine coadminstration in the setting of acute malaria [57]. Results showed that patients receiving rifampin had significantly greater metabolism of quinine and thus considerably lower concentrations of quinine in their plasma after the second day of treatment ($AUC_{0\text{-}7day} = 11.7$ versus 47.5 μg/ml/day, $P < 0.001$). Most strikingly, recurrence rates were 5 times higher in those receiving rifampin. Thus, coadministration of these two drugs should be avoided.

16.2.2.2 Interactions Between Atovaquone-Proguanil and Rifamycins

A similar risk is posed in prescribing hepatically metabolized antimalarials with rifamycins in the treatment of TB and malaria co-infected patients. Atovaquone metabolism is characterized by enterohepatic circulation. In a study of 13 subjects treated for *Toxoplasma gondii*, atovaquone AUC decreased (−50%) with rifampin and to a lesser extent with rifabutin (−34%) [58]. Co-administration of atovaquone and rifampin is not recommended, while the clinical significance of the moderate decrease in atovaquone concentrations in the presence of rifabutin remains unclear. Data on proguanil and rifampin is not available. Theoretically, since rifampin is a potent inducer of CYP2C19, and proguanil is metabolized to the active metabolite cycloguanil, it is possible that proguanil levels may be reduced in the setting of rifampin coadminstration.

16.2.2.3 Antimalarials and Other Antimicrobials

Mefloquine (MQ) has also been evaluated in combination with tetracycline in 20 healthy Thai male volunteers. There was no significant change in the MQ $AUC_{0\text{-}\infty}$, but $AUC_{0\text{-}7days}$ was significantly increased with tetracycline without an apparent increase in side-effects [59]. In the case of ampicillin, there were no significant changes in MQ $AUC_{0\text{-}\infty}$, but C_{max} of MQ was increased by 34% [60]. Increases in the MQ AUC, elimination t ½, and C_{max} have been seen when administered with ketoconazole in healthy Thai males [61].

Artemether-lumefantrine has been evaluated after a single dose in the setting of ketoconazole [30]. In this study, exposure (AUC) to artemether, DHA, and

lumefantrine increased by 131%, 51%, and 61%, respectively. These increases were not felt substantial enough to warrant dose adjustment.

Halofantrine, although rarely in use clinically, remains an alternative option for antimalarial treatment or prophylaxis. The rarity of its usage is due to concerns of cardiotoxicity, including QT interval prolongation, torsades de pointes, and fatal cardiac arrests [46]. Since halofantrine is predominantly metabolized by CYP3A4, inhibition of substrate metabolism could potentially potentiate cardiotoxicity. Several crossover studies have evaluated the effect of CYP3A4 inhibitors on the pharmacokinetics of halofantrine. The co-administration of tetracycline (500 mg twice daily for 7 days) and halofantrine (500 mg single doses) in 8 healthy participants resulted in a significant increase in the plasma halofantrine C_{max} (mean +147%), AUC (mean +199%), $t_{1/2}$ (mean +73%) compared with halofantrine alone ($P<0.05$) [62]. The effect of the 3A4 inhibitor fluconazole on the PK of halofantrine was evaluated in healthy participants. Co-administration of fluconazole significantly altered the metabolite (desbutylhalofantrine)/drug ratio through a reduction in metabolite C_{max}, and AUC by 37% and 46%, respectively ($P<0.05$), presumably due to inhibition of CYP3A4-mediated metabolism of halofantrine by fluconazole [63]. Given the narrow therapeutic index of this drug, the manufacturer's Summary of Product Characteristics advises that coadministration of CYP 3A4 inhibitors such as PIs are contraindicated [64]. The therapeutic consequences of 3A4 inhibition on halofantrine are not clear but caution should be exercised when co-administering azoles, tetracycline, PIs, and NNRTIs to avoid accumulation and subsequent cardiotoxic effects of halofantrine.

16.2.3 Interactions at the Level of Drug Absorption

Among the most significant interactions reported with ACTs has been the impact of food upon lumefantrine bioavailability. Absorption of lumefantrine may be increased by 16-fold with food as compared to a fasting state [65, 66]. Thus, to improve bioavailability, it is recommended to take AL with fatty food. Similar, although less significant findings, have been seen with piperaquine, a component of DP. In one study, in the fed state, piperaquine C_{max} increased by 213% and $AUC_{0-\infty}$ increased by 98% [67]. However, no effect with food intake was seen in a study of Vietnamese [68].

The effect of multivalent cations decreasing the oral bioavailability of the quinoline, chloroquine, was first reported in 1982 [69]. The pharmacokinetic study revealed that magnesium trisilicate and kaolin decreased chloroquine AUC by (mean +18.2% and +28.6%, respectively). The mechanism of the interaction is postulated as chelation of quinolines to the antacids/adsorbents. Tetracycline absorption is also reduced in the setting of concomitant cation administration. It is unclear to what extent such interactions exist for ACTs. Although clinical use of chloroquine is at an all time low, if used, the antimalarial should not be taken with gastrointestinal medications of this type or its administration with these drugs should be separated by at least 4 h to prevent loss of systemic availability.

16.2.4 Impact of Clinical Malaria Upon Antimalarial Pharmacokinetics

Acute malaria also has been shown to influence the metabolism and distribution of certain antimalarials. Plasma concentrations of quinine following oral administration in 11 Africans during acute uncomplicated malaria revealed that mean plasma quinine concentrations were significantly higher during the acute illness than after recovery (5.2 ± 0.9 ug/ml versus 3.6 ± 0.4 ug/ml) [70]. The apparent oral clearance and volume of distribution of quinine was also significantly lower during the acute illness than after recovery. These and other data suggest that the disposition of quinine is significantly altered by acute malaria [70–73]. Artesunate and dihydroartemisinin PK following intra-rectal dosing of artesunate has also been found to vary during acute malaria [74]. These changes in antimalarial PK are felt to largely be due to alterations in drug absorption and/or disease-induced hepatic dysfunction occurring during malaria which impairs drug metabolism.

16.2.5 Impact of Pharmacogenetic Variation upon Antimalarial Pharmacokinetics

Proguanil is metabolized through CYP2C19 into the active metabolite cycloquanil. Studies of poor metabolizers (PM) and extensive metabolizers (EM) have revealed that genetic variants in CYP2C19 do impact upon substrate:metabolite ratios [75]. However, no impact upon clinical efficacy has been seen, possibly due to intrinsic activity of proguanil against malaria parasites [75–77].

AQ metabolism may be impaired by common CYP2C8 polymorphisms; CYP2C8(*)2, allele frequency 0.155 in Africans, showed defective metabolism of AQ (threefold higher K(m) and sixfold lower intrinsic clearance); CYP2C8(*)3, allele frequency of up to 0.15 in Caucasians, had markedly decreased activity [78]. The *in vivo* relevance of these findings has yet to be explored.

16.3 Pharmacodynamic Interactions

16.3.1 Neutropenia in HIV and Malaria Co-infection

Patients with HIV and malaria co-infection are prone to increased rates of drug toxicity especially neutropenia. High rates of neutropenia have been reported in HIV-infected children, aged 5–13 years of age who were receiving artesunate-amodiaquine (AS/AQ) in Kampala, Uganda [79]. Specifically, the risk of neutropenia 14 days after treatment with AS/AQ was higher (45% vs 6%, $p<0.001$) and more severe in HIV infected children compared to HIV uninfected children. In addition, children

receiving ART were more likely to experience neutropenia compared to those not receiving ART (75% vs. 26%, p = 0.001) with 16% of cases rated severe or life threatening (grade 3 or 4, absolute neutrophil count (ANC), <750 cells/mm^3).

Increased rate of neutropenia have also been seen in a cohort of HIV infected children in Tororo, Uganda randomized to either AL or DP for episodes of malaria (Jamal Harris, personal communication). In children aged 4–22 months, ART was an independent risk factor for grade 3–4 neutropenia. Similar results linking ART use and neutropenia have also been observed for older HIV-infected children also residing in Tororo.

Multiple factors may contribute to neutropenia in the context of HIV and malaria co-infection making it difficult to decipher the primary cause. Potential contributors include the direct effects of malaria, prophylactic therapy with trimethoprim-sulfamethoxazole, ART and drug-drug interactions between ART and ACT. Trimethoprim-sulfamethoxazole has been directly associated with neutropenia in multiple studies [80, 81]. Specifically in one study, a 34% rate of neutropenia was reported in children receiving an oral 10-day course of drug [80].

For ART, the nucleoside analogues including zidovudine (ZDV) in particular, have been associated with high rates of neutropenia with rates ranging from 10% to 50% reported through multiple studies [82–84]. In HIV infected children managed with ZDV rates of neutropenia range from 1% to 20% from previously published studies, rates lower than observed recently in Uganda [85–87] (unpublished). One study from Thailand reported increased rates of neutropenia in children switching from stavudine to zidovudine [88].

Zidovudine has a direct effect on bone marrow suppression with some studies suggesting this correlates directly with plasma ZDV exposure [89–91]. However, ZDV requires intracellular phosphorylation to ZDV-triphosphate in order to exert pharmacological activity. ZDV-monophosphate has been directly linked to bone marrow suppression through in vitro studies [92, 93]. Whether or not treating malaria and HIV concomitantly leads to a worsening of ZDV associated neutropenia is a focus of ongoing studies in Tororo, Uganda.

Specific components of ACT have also been linked to neutropenia. A recent study reported an increased rate of neutropenia in the setting of high-dose artesunate monotherapy [94]. AQ has also been directly linked to neutropenia where severe neutropenia was reported during prophylactic use in several patients from two travel clinics in the United Kingdom where frequency was estimated as one case of severe neutropenia for every 2000 patients receiving prophylactic drug [95]. This report is consistent with multiple case studies reported for amodiaquine associated neutropenia over 4 decades of use for malaria prophylaxis. Amodiaquine has also been associated with neutropenia when used in combination with artesunate in healthy volunteers to determine the pharmacokinetics of this ACT regimen. Following administration of only 3 doses of AS/AQ over 28 days to 13 healthy volunteers in Africa, 2 of the 13 volunteers developed neutropenia [96]. The mechanism of the neutropenia has been postulated that AQ and its metabolites exhibit cytotoxic effects on mononuclear leukocytes and inhibit granulocyte-monocyte colony formation [97].

16.3.2 Hepatotoxicity with ACT and ART Use

Additional toxicities can be exacerbated during ACT and ART coadministration. As noted earlier, a study in healthy volunteers, designed to evaluate the pharmacokinetic interaction between AS/AQ and efavirenz was terminated early due to unexpected drug toxicity [40]. Hepatitis induced by EFV therapy is uncommon and has not been associated with AS therapy [98]. However, AQ therapy has resulted in hepatitis when used for chronic malaria chemoprophylaxis but 3-day treatment courses of AQ/AS therapy have not been linked to hepatotoxicity [99, 100].

16.3.3 Cardiotoxicity of Antimalarials

Although there is a lack of available large scale clinical studies, the co-administration of QT prolonging agents with halofantrine poses a theoretical increased risk of QT-prolongation and Torsades de Pointes [101–103]. Therefore an alternative antimalarial should be selected for patients currently taking QT prolonging agents: antipsychotics (haloperidol, risperadone, pimozide, quetiapine, clozapine, ziprasidone), appetite suppressants (sibutramine, phentermine), cardiac agents (flecanide, mexiletine, quinidine, dofetilide, ibutilide, amiodarone, sotalol, ranolazine, nicardipine), azoles, decongestants (pseudoephedrine, phenylephrine), methadone, 5HT3 antagonists (dolasetron, ondansetron). Similarly, quinine should be avoided with halofantrine. As CQ also increases the risk of QT prolongation, chloroquine should not be used in combination with halofantrine.

16.3.4 Neuropsychiatric Side Effects of Quinolines

Seizures have been reported in patients taking quinolines (chloroquine and mefloquine) for malaria prophylaxis [104]. Generalized convulsions have been reported rarely in travelers taking weekly chloroquine prophylaxis. Four case studies of women who developed tonic-clonic seizures after taking chloroquine all had either a previous history of seizures and/or electroencephalogram (EEG) remarkable for lower seizure threshold [105]. Conversely, a prospective study conducted in 5,120 Italian soldiers evaluated for compliance and tolerability of long-term malaria chemoprophylaxis using mefloquine or chloroquine with proguanil; no seizures were reported in either group [106]. Even though further evidence is needed for a formal recommendation, precautions should be taken when prescribing mefloquine or chloroquine with drugs that can induce seizures, lower the seizure thresholds, or lead to increased antimalarial levels: clozapine, enflurane, theophylline, foscarnet, ganciclovir, ritonavir, conventional antipsychotics (olanzapine or risperidone), bupropion, tricyclic antidepressants/selective serotonin reuptake inhibitors, cyclosporin, interferon, corticosteroids, propofol, imipenem especially in epileptic

patients. Caution should also be taken when prescribing mefloquine with chloroquine or quinine due to possible increased risk of seizures.

Mefloquine has also been associated more generally with several neuropsychiatric effects. Approximately 1/200 European travelers and 1/1,754 ethnic Karen develop dose related neuropsychiatric effects during treatment of malaria with mefloquine [107]. The risk of serious adverse neuropsychiatric events is estimated to be 1 in 10,600 patients taking mefloquine for prophylaxis [107]. Even though no formal correlation has been established, confusion, depressed mood, panic attacks, sleep disturbances, anorexia, tremor, ataxia, fatigue and rarely suicide have also been reported in patients taking mefloquine. Caution should be taken when prescribing concomitant use of mefloquine with agents known to cause neuropsychiatric side effects (steroids, dopamine agonists in addition to the agents listed that increase the risk of seizure) until clinical findings evaluate the safety of additive neuropsychiatric effects.

16.3.5 Hematologic Toxicity of Antifolates

Several case reports have suggested that the coadministration of sulfadoxine-pyrimethamine and trimethoprim-sulfamethoxasole should be avoided [108, 109]. Reports of megaloblastic anemia are postulated to be due to additive inhibition of folate synthesis.

16.4 Perspective

In recent years, the treatment of malaria has rapidly evolved towards the use of newer artemisinin combination therapies. Importantly, regions undergoing this shift in antimalarial therapy are also facing widespread HIV and TB epidemics. As access to therapy for malaria, HIV, and TB is expanded, it will be important for practitioners to familiarize themselves with potential drug interactions, as many of these drugs share common metabolic pathways. Notably, these concerns are not limited to co-endemic regions, as recent studies have highlighted potentially important interactions in the setting of antimalarial prophylaxis.

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References

1. World Health Organization, *World Malaria Report*, WHO, Editor. 2009: Geneva.
2. Snow, R.W., C.A. Guerra, A.M. Noor, H.Y. Myint, and S.I. Hay, *The global distribution of clinical episodes of Plasmodium falciparum malaria.* Nature, 2005. **434**: p. 214–7.

3. D'Alessandro, U. and H. Buttiens, *History and importance of antimalarial drug resistance.* Tropical Medicine and International Health, 2001. **6**: p. 845–8.
4. Harinasuta, T., P. Suntharasamai, and C. Viravan, *Chloroquine-resistant falciparum malaria in Thailand.* Lancet, 1965. **2**: p. 657–60.
5. Verdrager, J., A. Richie, and C.M. Chheang, *[The effect of diaphenylsulfone-pyrimethamine association on malaria caused by Plasmodium falciparum in Cambodia].* Bulletin of the World Health Organization, 1969. **40**: p. 319–24.
6. Nosten, F., F. ter Kuile, T. Chongsuphajaisiddhi, C. Luxemburger, H.K. Webster, M. Edstein, et al., *Mefloquine-resistant falciparum malaria on the Thai-Burmese border.* Lancet, 1991. **337**: p. 1140–3.
7. World Health Organization, *Antimalarial drug combination therapy: Report of WHO technical consultation,*. 2001, World Health Organization: Geneva.
8. Eastman, R.T. and D.A. Fidock, *Artemisinin-based combination therapies: a vital tool in efforts to eliminate malaria.* Nat Rev Microbiol, 2009. **7**: p. 864–74.
9. World Health Organization. *Facts on ACTs. January 2006 update*. 2006 January 12, 2009]; Available from: http://www.searo.who.int/LinkFiles/Drug_Policy_RBMInfosheet_9.pdf.
10. Myint, H.Y., E.A. Ashley, N.P. Day, F. Nosten, and N.J. White, *Efficacy and safety of dihydroartemisinin-piperaquine.* Transactions of the Royal Society of Tropical Medicine and Hygiene, 2007. **101**: p. 858–66.
11. German, P.I. and F.T. Aweeka, *Clinical pharmacology of artemisinin-based combination therapies.* Clinical Pharmacokinetics, 2008. **47**: p. 91–102.
12. Nosten, F. and N.J. White, *Artemisinin-based combination treatment of falciparum malaria.* Am J Trop Med Hyg, 2007. **77**: p. 181–92.
13. Barnes, K.I., W.M. Watkins, and N.J. White, *Antimalarial dosing regimens and drug resistance.* Trends Parasitol, 2008. **24**: p. 127–34.
14. White, N.J., K. Stepniewska, K. Barnes, R.N. Price, and J. Simpson, *Simplified antimalarial therapeutic monitoring: using the day-7 drug level?* Trends Parasitol, 2008. **24**: p. 159–63.
15. Mwesigwa, J., S. Parikh, B. McGee, P. German, T. Drysdale, J.N. Kalyango, et al., *Pharmacokinetics of artemether-lumefantrine and artesunate-amodiaquine in children in Kampala, Uganda.* Antimicrobial Agents and Chemotherapy, 2010. **54**: p. 52–9.
16. Barnes, K.I., F. Little, P.J. Smith, A. Evans, W.M. Watkins, and N.J. White, *Sulfadoxine-pyrimethamine pharmacokinetics in malaria: pediatric dosing implications.* Clin Pharmacol Ther, 2006. **80**: p. 582–96.
17. Price, R.N., A.C. Uhlemann, M. van Vugt, A. Brockman, R. Hutagalung, S. Nair, et al., *Molecular and pharmacological determinants of the therapeutic response to artemether-lumefantrine in multidrug-resistant Plasmodium falciparum malaria.* Clin Infect Dis, 2006. **42**: p. 1570–7.
18. Ezzet, F., M. van Vugt, F. Nosten, S. Looareesuwan, and N.J. White, *Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria.* Antimicrob Agents Chemother, 2000. **44**: p. 697–704.
19. Denis, M.B., R. Tsuyuoka, P. Lim, N. Lindegardh, P. Yi, S.N. Top, et al., *Efficacy of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in northwest Cambodia.* Trop Med Int Health, 2006. **11**: p. 1800–7.
20. Price, R.N., A.C. Uhlemann, M. van Vugt, A. Brockman, R. Hutagalung, S. Nair, et al., *Molecular and pharmacological determinants of the therapeutic response to artemether-lumefantrine in multidrug-resistant Plasmodium falciparum malaria.* Clinical Infectious Diseases, 2006. **42**: p. 1570–7.
21. Asimus, S., D. Elsherbiny, T.N. Hai, B. Jansson, N.V. Huong, M.G. Petzold, et al., *Artemisinin antimalarials moderately affect cytochrome P450 enzyme activity in healthy subjects.* Fundamental and Clinical Pharmacology, 2007. **21**: p. 307–16.
22. Navaratnam, V., S.M. Mansor, N.W. Sit, J. Grace, Q. Li, and P. Olliaro, *Pharmacokinetics of artemisinin-type compounds.* Clin Pharmacokinet, 2000. **39**: p. 255–70.
23. Ilett, K.F., B.T. Ethell, J.L. Maggs, T.M. Davis, K.T. Batty, B. Burchell, et al., *Glucuronidation of dihydroartemisinin in vivo and by human liver microsomes and expressed*

UDP-glucuronosyltransferases. Drug Metabolism and Disposition: The Biological Fate of Chemicals, 2002. **30**: p. 1005–12.
24. Ashton, M., D.S. Nguyen, V.H. Nguyen, T. Gordi, N.H. Trinh, X.H. Dinh, et al., *Artemisinin kinetics and dynamics during oral and rectal treatment of uncomplicated malaria.* Clinical Pharmacology and Therapeutics, 1998. **63**: p. 482–93.
25. Ashton, M., T.N. Hai, N.D. Sy, D.X. Huong, N. Van Huong, N.T. Nieu, et al., *Artemisinin pharmacokinetics is time-dependent during repeated oral administration in healthy male adults.* Drug Metabolism and Disposition: The Biological Fate of Chemicals, 1998. **26**: p. 25–7
26. Simonsson, U.S., B. Jansson, T.N. Hai, D.X. Huong, G. Tybring, and M. Ashton, *Artemisinin autoinduction is caused by involvement of cytochrome P450 2B6 but not 2 C9.* Clinical Pharmacology and Therapeutics, 2003. **74**: p. 32–43.
27. Lefevre, G., M. Bindschedler, F. Ezzet, N. Schaeffer, I. Meyer, and M.S. Thomsen, *Pharmacokinetic interaction trial between co-artemether and mefloquine.* European Journal of Pharmaceutical Sciences, 2000. **10**: p. 141–51.
28. Novartis Pharma AG (1999) *Product Monograph: Coartem*.
29. German, P., S. Parikh, J. Lawrence, G. Dorsey, P.J. Rosenthal, D. Havlir, et al., *Lopinavir/ritonavir affects pharmacokinetic exposure of artemether/lumefantrine in HIV-uninfected healthy volunteers.* Journal of Acquired Immune Deficiency Syndromes, 2009. **51**: p. 424–9.
30. Lefevre, G., P. Carpenter, C. Souppart, H. Schmidli, M. McClean, and D. Stypinski, *Pharmacokinetics and electrocardiographic pharmacodynamics of artemether-lumefantrine (Riamet) with concomitant administration of ketoconazole in healthy subjects.* British Journal of Clinical Pharmacology, 2002. **54**: p. 485–92.
31. World Health Organization, *Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach*. 2010: Geneva.
32. Zeldin, R.K. and R.A. Petruschke, *Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients.* Journal of Antimicrobial Chemotherapy, 2004. **53**: p. 4–9.
33. Ward, B.A., J.C. Gorski, D.R. Jones, S.D. Hall, D.A. Flockhart, and Z. Desta, *The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity.* Journal of Pharmacology and Experimental Therapeutics, 2003. **306**: p. 287–300.
34. Riska, P., M. Lamson, T. MacGregor, J. Sabo, S. Hattox, J. Pav, et al., *Disposition and biotransformation of the antiretroviral drug nevirapine in humans.* Drug Metabolism and Disposition: The Biological Fate of Chemicals, 1999. **27**: p. 895–901.
35. Vitoria, M., R. Granich, C.F. Gilks, C. Gunneberg, M. Hosseini, W. Were, et al., *The global fight against HIV/AIDS, tuberculosis, and malaria: current status and future perspectives.* American Journal of Clinical Pathology, 2009. **131**: p. 844–8.
36. Niemi, M., J.T. Backman, M.F. Fromm, P.J. Neuvonen, and K.T. Kivisto, *Pharmacokinetic interactions with rifampicin : clinical relevance.* Clinical Pharmacokinetics, 2003. **42**: p. 819–50.
37. Dai, D., D.C. Zeldin, J.A. Blaisdell, B. Chanas, S.J. Coulter, B.I. Ghanayem, et al., *Polymorphisms in human CYP2C8 decrease metabolism of the anticancer drug paclitaxel and arachidonic acid.* Pharmacogenetics, 2001. **11**: p. 597–607.
38. Li, X.Q., A. Bjorkman, T.B. Andersson, L.L. Gustafsson, and C.M. Masimirembwa, *Identification of human cytochrome P(450)s that metabolise anti-parasitic drugs and predictions of in vivo drug hepatic clearance from in vitro data.* Eur J Clin Pharmacol, 2003. **59**: p. 429–42.
39. Wennerholm, A., A. Nordmark, M. Pihlsgard, M. Mahindi, L. Bertilsson, and L.L. Gustafsson, *Amodiaquine, its desethylated metabolite, or both, inhibit the metabolism of debrisoquine (CYP2D6) and losartan (CYP2C9) in vivo.* European Journal of Clinical Pharmacology, 2006. **62**: p. 539–46.
40. German, P., B. Greenhouse, C. Coates, G. Dorsey, P.J. Rosenthal, E. Charlebois, et al., *Hepatotoxicity due to a drug interaction between amodiaquine plus artesunate and efavirenz.* Clinical Infectious Diseases, 2007. **44**: p. 889–91.

41. Parikh, S., J.B. Ouedraogo, J.A. Goldstein, P.J. Rosenthal, and D.L. Kroetz, *Amodiaquine metabolism is impaired by common polymorphisms in CYP2C8: implications for malaria treatment in Africa.* Clin Pharmacol Ther, 2007. **82**: p. 197–203.
42. World Health Organization, *Guidelines for the treatment of malaria/World Health Organization*, P. Olumese, Editor. 2010, World Health Organization: Geneva.
43. Kredo, T., J. Van der Walt, K. Mauff, L. Wiesner, G. Maartens, K. Cohen, et al. *Nevirapine Increases Lumefantrine Exposure in HIV-infected Patients*. in *Conference on Retroviruses and Opportunistic Infections*. 2010. San Francisco, California, February 16–19, Abstract N-140.
44. Van Luin, M., M.E. Van der Ende, C. Richter, M. Visser, D. Faraj, A. Van der Ven, et al., *Lower atovaquone/proguanil concentrations in patients taking efavirenz, lopinavir/ritonavir or atazanavir/ritonavir.* AIDS, 2010.
45. Soyinka, J.O. and C.O. Onyeji, *Alteration of pharmacokinetics of proguanil in healthy volunteers following concurrent administration of efavirenz.* European Journal of Pharmaceutical Sciences, 2010. **39**: p. 213–8.
46. AlKadi, H.O., *Antimalarial drug toxicity: a review.* Chemotherapy, 2007. **53**: p. 385–91.
47. Soyinka, J.O., C.O. Onyeji, S.I. Omoruyi, A.R. Owolabi, P.V. Sarma, and J.M. Cook, *Effects of concurrent administration of nevirapine on the disposition of quinine in healthy volunteers.* Journal of Pharmacy and Pharmacology, 2009. **61**: p. 439–43.
48. Soyinka, J.O., C.O. Onyeji, S.I. Omoruyi, A.R. Owolabi, P.V. Sarma, and J.M. Cook, *Pharmacokinetic interactions between ritonavir and quinine in healthy volunteers following concurrent administration.* British Journal of Clinical Pharmacology, 2010. **69**: p. 262–70.
49. Khaliq, Y., K. Gallicano, C. Tisdale, G. Carignan, C. Cooper, and A. McCarthy, *Pharmacokinetic interaction between mefloquine and ritonavir in healthy volunteers.* Br J Clin Pharmacol, 2001. **51**: p. 591–600.
50. Schippers, E.F., P.W. Hugen, J. den Hartigh, D.M. Burger, R.M. Hoetelmans, L.G. Visser, et al., *No drug-drug interaction between nelfinavir or indinavir and mefloquine in HIV-1-infected patients.* AIDS, 2000. **14**: p. 2794–5.
51. Sousa, M., A. Pozniak, and M. Boffito, *Pharmacokinetics and pharmacodynamics of drug interactions involving rifampicin, rifabutin and antimalarial drugs.* Journal of Antimicrobial Chemotherapy, 2008. **62**: p. 872–8.
52. Reinach, B., G. de Sousa, P. Dostert, R. Ings, J. Gugenheim, and R. Rahmani, *Comparative effects of rifabutin and rifampicin on cytochromes P450 and UDP-glucuronosyl-transferases expression in fresh and cryopreserved human hepatocytes.* Chemico-Biological Interactions, 1999. **121**: p. 37–48.
53. Hou, L.J., S.S. Raju, M.S. Abdulah, N.M. Nor, and M. Ravichandran, *Rifampicin antagonizes the effect of choloroquine on chloroquine-resistant Plasmodium berghei in mice.* Jpn J Infect Dis, 2004. **57**: p. 198–202.
54. Chen, J. and K. Raymond, *Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor.* Ann Clin Microbiol Antimicrob, 2006. **5**: p. 3.
55. Ridtitid, W., M. Wongnawa, W. Mahatthanatrakul, P. Chaipol, and M. Sunbhanich, *Effect of rifampin on plasma concentrations of mefloquine in healthy volunteers.* Journal of Pharmacy and Pharmacology, 2000. **52**: p. 1265–9.
56. Wanwimolruk, S., W. Kang, P.F. Coville, S. Viriyayudhakorn, and S. Thitiarchakul, *Marked enhancement by rifampicin and lack of effect of isoniazid on the elimination of quinine in man.* British Journal of Clinical Pharmacology, 1995. **40**: p. 87–91.
57. Pukrittayakamee, S., S. Prakongpan, S. Wanwimolruk, R. Clemens, S. Looareesuwan, and N.J. White, *Adverse effect of rifampin on quinine efficacy in uncomplicated falciparum malaria.* Antimicrobial Agents and Chemotherapy, 2003. **47**: p. 1509–13.
58. Sadler, B., P. Caldwell, J. Scott, M. Rogers, and M. Blum, *Drug interaction between rifampin and atovaquone in HIV + asymptomatic volunteers*, in *35th Interscience Conference of Antimicrobial Agents and Chemotherapy*. 1995: San Francisco.

59. Karbwang, J., K. Na Bangchang, D.J. Back, D. Bunnag, and W. Rooney, *Effect of tetracycline on mefloquine pharmacokinetics in Thai males.* European Journal of Clinical Pharmacology, 1992. **43**: p. 567–9.
60. Karbwang, J., K. Na Bangchang, D.J. Back, and D. Bunnag, *Effect of ampicillin on mefloquine pharmacokinetics in Thai males.* European Journal of Clinical Pharmacology, 1991. **40**: p. 631–3.
61. Ridtitid, W., M. Wongnawa, W. Mahatthanatrakul, N. Raungsri, and M. Sunbhanich, *Ketoconazole increases plasma concentrations of antimalarial mefloquine in healthy human volunteers.* J Clin Pharm Ther, 2005. **30**: p. 285–90.
62. Bassi, P.U., C.O. Onyeji, and O.E. Ukponmwan, *Effects of tetracycline on the pharmacokinetics of halofantrine in healthy volunteers.* British Journal of Clinical Pharmacology, 2004. **58**: p. 52–5.
63. Babalola, C.P., Y.T. Kolade, A.A. Olaniyi, A. Adedapo, and G.K. Scriba, *Effect of fluconazole on the pharmacokinetics of halofantrine in healthy volunteers.* Journal of Clinical Pharmacy and Therapeutics, 2009. **34**: p. 677–82.
64. GlaxoSmithKline (2008) *Product Information: HALFAN(TM), halofantrine hydrochloride tablet.*
65. White, N.J., M. van Vugt, and F. Ezzet, *Clinical pharmacokinetics and pharmacodynamics and pharmacodynamics of artemether-lumefantrine.* Clinical Pharmacokinetics, 1999. **37**: p. 105–25.
66. Ashley, E.A., K. Stepniewska, N. Lindegardh, A. Annerberg, A. Kham, A. Brockman, et al., *How much fat is necessary to optimize lumefantrine oral bioavailability?* Tropical Medicine and International Health, 2007. **12**: p. 195–200.
67. Sim, I.K., T.M. Davis, and K.F. Ilett, *Effects of a high-fat meal on the relative oral bioavailability of piperaquine.* Antimicrob Agents Chemother, 2005. **49**: p. 2407–11.
68. Hai, T.N., S.F. Hietala, N. Van Huong, and M. Ashton, *The influence of food on the pharmacokinetics of piperaquine in healthy Vietnamese volunteers.* Acta Tropica, 2008. **107**: p. 145–9.
69. McElnay, J.C., H.A. Mukhtar, P.F. D'Arcy, D.J. Temple, and P.S. Collier, *The effect of magnesium trisilicate and kaolin on the in vivo absorption of chloroquine.* Journal of Tropical Medicine and Hygiene, 1982. **85**: p. 159–63.
70. Sowunmi, A., *Disposition of oral quinine in African patients suffering from acute uncomplicated falciparum malaria.* East African Medical Journal, 1996. **73**: p. 519–23.
71. Sowunmi, A., *Disposition of quinine in plasma after a single oral and intramuscular dose in healthy adult Africans.* East African Medical Journal, 1996. **73**: p. 111–4.
72. Babalola, C.P., O.O. Bolaji, F.A. Ogunbona, A. Sowunmi, and O. Walker, *Pharmacokinetics of quinine in African patients with acute falciparum malaria.* Pharmacy World and Science, 1998. **20**: p. 118–22.
73. Pukrittayakamee, S., S. Looareesuwan, D. Keeratithakul, T.M. Davis, P. Teja-Isavadharm, B. Nagachinta, et al., *A study of the factors affecting the metabolic clearance of quinine in malaria.* European Journal of Clinical Pharmacology, 1997. **52**: p. 487–93.
74. Simpson, J.A., T. Agbenyega, K.I. Barnes, G. Di Perri, P. Folb, M. Gomes, et al., *Population pharmacokinetics of artesunate and dihydroartemisinin following intra-rectal dosing of artesunate in malaria patients.* PLoS Med, 2006. **3**: p. e444.
75. Kaneko, A., Y. Bergqvist, G. Taleo, T. Kobayakawa, T. Ishizaki, and A. Bjorkman, *Proguanil disposition and toxicity in malaria patients from Vanuatu with high frequencies of CYP2C19 mutations.* Pharmacogenetics, 1999. **9**: p. 317–26.
76. Kaneko, A., Y. Bergqvist, M. Takechi, M. Kalkoa, O. Kaneko, T. Kobayakawa, et al., *Intrinsic efficacy of proguanil against falciparum and vivax malaria independent of the metabolite cycloguanil.* J Infect Dis, 1999. **179**: p. 974–9.
77. Kaneko, A., O. Kaneko, G. Taleo, A. Bjorkman, and T. Kobayakawa, *High frequencies of CYP2C19 mutations and poor metabolism of proguanil in Vanuatu.* Lancet, 1997. **349**: p. 921–2.

78. Bahadur, N., J.B. Leathart, E. Mutch, D. Steimel-Crespi, S.A. Dunn, R. Gilissen, et al., *CYP2C8 polymorphisms in Caucasians and their relationship with paclitaxel 6alpha-hydroxylase activity in human liver microsomes.* Biochemical Pharmacology, 2002. **64**: p. 1579–89.
79. Gasasira, A.F., M.R. Kamya, J. Achan, T. Mebrahtu, J.N. Kalyango, T. Ruel, et al., *High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda.* Clinical Infectious Diseases, 2008. **46**: p. 985–91.
80. Asmar, B.I., S. Maqbool, and A.S. Dajani, *Hematologic abnormalities after oral trimethoprim-sulfamethoxazole therapy in children.* American Journal of Diseases of Children, 1981. **135**: p. 1100–3.
81. Bernstein, L.S., *Adverse reactions to trimethoprim-sulfamethoxazole, with particular reference to long-term therapy.* Canadian Medical Association Journal, 1975. **112**: p. 96–8.
82. Bussmann, H., C.W. Wester, A. Thomas, V. Novitsky, R. Okezie, T. Muzenda, et al., *Response to zidovudine/didanosine-containing combination antiretroviral therapy among HIV-1 subtype C-infected adults in Botswana: two-year outcomes from a randomized clinical trial.* Journal of Acquired Immune Deficiency Syndromes, 2009. **51**: p. 37–46.
83. Moh, R., C. Danel, S. Sorho, D. Sauvageot, A. Anzian, A. Minga, et al., *Haematological changes in adults receiving a zidovudine-containing HAART regimen in combination with cotrimoxazole in Cote d'Ivoire.* Antivir Ther, 2005. **10**: p. 615–24.
84. Levine, A.M., R. Karim, W. Mack, D.J. Gravink, K. Anastos, M. Young, et al., *Neutropenia in human immunodeficiency virus infection: data from the women's interagency HIV study.* Archives of Internal Medicine, 2006. **166**: p. 405–10.
85. Kline, M.W., R.B. Van Dyke, J.C. Lindsey, M. Gwynne, M. Culnane, R.E. McKinney, Jr., et al., *A randomized comparative trial of stavudine (d4T) versus zidovudine (ZDV, AZT) in children with human immunodeficiency virus infection. AIDS Clinical Trials Group 240 Team.* Pediatrics, 1998. **101**: p. 214–20.
86. Van Dyke, R.B., L. Wang, and P.L. Williams, *Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children.* Journal of Infectious Diseases, 2008. **198**: p. 1599–608.
87. Violari, A., M.F. Cotton, D.M. Gibb, A.G. Babiker, J. Steyn, S.A. Madhi, et al., *Early antiretroviral therapy and mortality among HIV-infected infants.* New England Journal of Medicine, 2008. **359**: p. 2233–44.
88. Aurpibul, L., T. Puthanakit, T. Sirisanthana, and V. Sirisanthana, *Haematological changes after switching from stavudine to zidovudine in HIV-infected children receiving highly active antiretroviral therapy.* HIV Med, 2008. **9**: p. 317–21.
89. Anderson, P.L., T.N. Kakuda, S. Kawle, and C.V. Fletcher, *Antiviral dynamics and sex differences of zidovudine and lamivudine triphosphate concentrations in HIV-infected individuals.* AIDS, 2003. **17**: p. 2159–68.
90. Capparelli, E.V., M. Mirochnick, W.M. Dankner, S. Blanchard, L. Mofenson, G.D. McSherry, et al., *Pharmacokinetics and tolerance of zidovudine in preterm infants.* Journal of Pediatrics, 2003. **142**: p. 47–52.
91. Mentre, F., S. Escolano, B. Diquet, J.L. Golmard, and A. Mallet, *Clinical pharmacokinetics of zidovudine: inter and intraindividual variability and relationship to long term efficacy and toxicity.* European Journal of Clinical Pharmacology, 1993. **45**: p. 397–407.
92. Bridges, E.G., A. Faraj, and J.P. Sommadossi, *Inhibition of mammalian DNA polymerase-associated 3' to 5' exonuclease activity by 5'-monophosphates of 3'-azido-3'-deoxythymidine and 3'-amino-3'-deoxythymidine.* Biochemical Pharmacology, 1993. **45**: p. 1571–6.
93. Tornevik, Y., B. Ullman, J. Balzarini, B. Wahren, and S. Eriksson, *Cytotoxicity of 3'-azido-3'-deoxythymidine correlates with 3'-azidothymidine-5'-monophosphate (AZTMP) levels, whereas anti-human immunodeficiency virus (HIV) activity correlates with 3'-azidothymidine-5'-triphosphate (AZTTP) levels in cultured CEM T-lymphoblastoid cells.* Biochemical Pharmacology, 1995. **49**: p. 829–37.

94. Bethell, D., Y. Se, C. Lon, D. Socheat, D. Saunders, P. Teja-Isavadharm, Khemawoot, et al., *Dose-dependent risk of neutropenia after 7-day courses of artesunate monotherapy in Cambodian patients with acute Plasmodium falciparum malaria*. Clinical Infectious Diseases, 2010. **51**: p. 105–14.
95. Hatton, C.S., T.E. Peto, C. Bunch, G. Pasvol, S.J. Russell, C.R. Singer, et al., *Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria.* Lancet, 1986. **1**: p. 411–4.
96. Orrell, C., F. Little, P. Smith, P. Folb, W. Taylor, P. Olliaro, et al., *Pharmacokinetics and tolerability of artesunate and amodiaquine alone and in combination in healthy volunteers.* Eur J Clin Pharmacol, 2008. **64**: p. 683–90.
97. Winstanley, P.A., O. Simooya, J.M. Kofi-Ekue, O. Walker, L.A. Salako, G. Edwards, et al., *The disposition of amodiaquine in Zambians and Nigerians with malaria.* Br J Clin Pharmacol, 1990. **29**: p. 695–701.
98. Martin-Carbonero, L., M. Nunez, J. Gonzalez-Lahoz, and V. Soriano, *Incidence of liver injury after beginning antiretroviral therapy with efavirenz or nevirapine.* HIV Clin Trials, 2003. **4**: p. 115–20.
99. Larrey, D., A. Castot, D. Pessayre, P. Merigot, J.P. Machayekhy, G. Feldmann, et al., *Amodiaquine-induced hepatitis. A report of seven cases.* Ann Intern Med, 1986. **104**: p. 801–3.
100. Raymond, J.M., F. Dumas, C. Baldit, P. Couzigou, C. Beraud, and M. Amouretti, *Fatal acute hepatitis due to amodiaquine.* Journal of Clinical Gastroenterology, 1989. **11**: p. 602–3.
101. Nosten, F., F.O. ter Kuile, C. Luxemburger, C. Woodrow, D.E. Kyle, T. Chongsuphajaisiddhi, et al., *Cardiac effects of antimalarial treatment with halofantrine.* Lancet, 1993. **341**: p. 1054–6.
102. Castot, A., P. Rapoport, and P. Le Coz, *Prolonged QT interval with halofantrine.* Lancet, 1993. **341**: p. 1541.
103. Traebert, M., B. Dumotier, L. Meister, P. Hoffmann, M. Dominguez-Estevez, and W. Suter, *Inhibition of hERG K+ currents by antimalarial drugs in stably transfected HEK293 cells.* European Journal of Pharmacology, 2004. **484**: p. 41–8.
104. Schiemann, R., J.P. Coulaud, and O. Bouchaud, *Seizures after antimalarial medication in previously healthy persons.* Journal of Travel Medicine, 2000. **7**: p. 155–6.
105. Luijckx, G.J., M.C. De Krom, and B.C. Takx-Kohlen, *Does chloroquine cause seizures? Presentation of three new cases and a review of the literature.* Seizure, 1992. **1**: p. 183–5.
106. Thapar, M.M., M. Ashton, N. Lindegardh, Y. Bergqvist, S. Nivelius, I. Johansson, et al., *Time-dependent pharmacokinetics and drug metabolism of atovaquone plus proguanil (Malarone) when taken as chemoprophylaxis.* Eur J Clin Pharmacol, 2002. **58**: p. 19–27.
107. Taylor, W.R. and N.J. White, *Antimalarial drug toxicity: a review.* Drug Saf, 2004. **27**: p. 25–61.
108. Ansdell, V.E., S.G. Wright, and D.B.A. Hutchinson, *Megaloblastic Anemia Associated with Combined Pyrimethamine and Co-Trimoxazole Administration.* Lancet, 1976. **2**: p. 1257–1257.
109. Fleming, A.F., D.A. Warrell, and H. Dickmeiss, *Letter: Co-trimoxazole and the blood.* Lancet, 1974. **2**: p. 284–5.
110. Pukrittayakamee, S., S. Wanwimolruk, K. Stepniewska, A. Jantra, S. Huyakorn, S. Looareesuwan, et al., *Quinine pharmacokinetic-pharmacodynamic relationships in uncomplicated falciparum malaria.* Antimicrobial Agents and Chemotherapy, 2003. **47**: p. 3458–63.

Chapter 17
Antiprotozoal and Anthelmintic Agents

Geoffrey Edwards

Abstract Since combination chemotherapy is becoming normal practice in the management of parasitic disease there have been predictions of a vast array of potential interactions caused by drug classes sharing common routes of elimination. This chapter reviews the key interactions likely to occur or those that have been seen to occur when drugs are administered with food or with other agents in the management of malaria and helminthiases. There is a particular emphasis on those drugs contributing to artemisinin combination therapy (ACT) and the potential for interaction between antiparasitics and antiretroviral drugs. While many of these interactions may be of little clinical significance, changes in pharmacokinetics may occasionally contribute to an enhanced pharmacological response and increased toxicity. No review of this kind can hope to be exhaustive. The aim is to address those interactions where clinical relevance has been demonstrated or where a pathway of drug metabolism or transport may have the potential for competition. Over 30 years of investigation, the pharmacokinetics and metabolic pathways of a variety of antiparasitic drugs have been reported. Notably, there have been numerous investigations of the combinations of artemisinin drugs and a variety of partner agents, but fortunately few drug-drug or food-drug interactions of clinical relevance have been seen. The most important of these interactions involve poorly soluble agents like halofantrine and albendazole. Here food intake may exacerbate the pharmacological response or, in the case of halofantrine, lead to adverse effects.

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17.1 Introduction

Combination chemotherapy is becoming normal practice in the management of parasitic disease. In malaria such a strategy is dictated by a requirement to combine the aim of effective chemotherapy with the wish to minimize the emergence of drug resistance [1–3]. The control of lymphatic filariasis and onchocerciasis involves combinations geared at reducing transmission as a prelude to elimination of diseases posing huge socio-economic problems [4, 5]. There are several arguments favouring the use of drug combinations in the treatment of malaria. Synergy among drugs or the potentiation of their individual effects is the reason for use in the treatment of an individual patient. Resistance of parasites is the main reason why drugs are being combined for individual patients and why combinations are advocated on a population level. Development of resistance as a result of drug pressure depends upon numerous factors [2]. Among them, genetic determinants include mutation frequency and the number of mutations required for expression of resistance. Single point mutations may confer resistance to inhibitors of dihydrofolate reductase in *Plasmodium falciparum.* Combination with other drugs is advantageous when the number of genes required to express resistance is increased; for example, with combinations such as sulfadoxine with pyrimethamine (Fansidar™). The survival and selection of resistant parasites - may additionally depend on the pharmacodynamics of the component drugs. Parasitaemia should ideally be reduced rapidly in order to reduce the opportunity for the development of mutations and the likelihood that parasites will survive under drug pressure. Rapid reduction of the parasite burden in patients with malaria and the relatively short terminal elimination half life of the artemisinin drugs leads to little or no selective pressure, yet parasites may not fully be eliminated and recrudescence may take place. The benefits of the artemisinin drugs are better realized when combined with other drugs. Drugs with longer half lives may cause greater selection pressure, notably when used as monotherapy in areas with relatively high transmission. Advantages of combination therapy need to be viewed alongside the increased probability of drug-drug interactions. During the last 25 years, the clinical pharmacokinetics and metabolism of many antiparasitic agents has been elucidated, particularly the role of drug metabolizing enzymes, notably cytochromes P450, and drug transporter proteins [6–11]. Moreover, the usefulness of this information is now being realized as we begin to learn more about the pharmacodynamics of antiparasitic agents [12]. While these advances have led to predictions of a vast array of potential interactions caused by drug classes sharing common routes of elimination, it is important to focus on those drugs for which there is strong evidence that such interactions have clinical consequences. Equally important is the consequence of dietary change on pharmacokinetics. Patients normally take drugs with meals unless advised to the contrary. Diets may differ substantially between developed and underdeveloped countries where diseases susceptible to antiparasitic agents are most prevalent. Failure to understand the nature of any food effects may lead to a poor clinical outcome and/or unacceptable adverse effects [13, 14]. Finally, many drug-drug interactions can be postulated on

the basis of common pathways of metabolism among combinations of therapeutic agents. While it is outside the scope of this review to deal with all possible effects, they will be highlighted with regard to antiretroviral therapy where the possibility of co-administration is high and an interaction more likely.

17.2 Interactions with Food

Many of the factors which influence oral bioavailability can be altered by food; acutely, where a drug is taken with a meal, and chronically, where regularly consumed food products may impact the disposition of a drug taken repeatedly. The nature of such interactions is complex and, as may be influenced by the quantity of food ingested as well as its composition. Moreover, both pharmacokinetics and drug response may be affected. Food may change the bioavailability of many drugs and influence their dose response relationships, making awareness of the more clinically-relevant examples essential. Food can unintentionally reduce or increase the effect of the drug, resulting in therapeutic failure or increased toxicity. The influence of drug formulation on interactions with food is predictable from knowledge of gastric function, with solutions and suspensions less susceptible to food interactions than solid formulations and enteric coated drugs more susceptible, as retention of the capsule in the stomach delays drug release [13].

17.2.1 Food Interactions with Antiparasitic Drugs

17.2.1.1 Antimalarial Agents

Halofantrine

Halofantrine is one of three classes of arylaminoalcohols identified as in the United States as potential antimalarial agents by the World War II Chemotherapy Programme. It is a blood schizonticide with selective activity against intra-erythrocytic asexual stages of *Plasmodia*. Bioavailability of halofantrine is low with wide intra- and inter-subject variability [15, 16]. The absorption of halofantrine may increase dramatically when taken with food. Both C_{max} and AUC of halofantrine and desbutyl-halofantrine are increased by an order of magnitude after the administration of a 250 mg dose of halofantrine hydrochloride with a fatty meal [16]. Studies in dogs have shown that the clearance of halofantrine is influenced by the composition of plasma lipoproteins and may help to explain the dramatic changes in circulating plasma concentrations in the post-prandial state [17]. The most serious effects of halofantrine relate to QTc prolongation, torsades de pointes or sudden cardiac death [18–23]. These events led to the curtailment of the drug as a front-line antimalarial agent. Although some of them occurred in patients with congenital long QT syndrome, halofantrine-induced

Table 17.1 The five artemisinin combination treatments (ACT's) listed above are those currently recommended by WHO. Details of their manufacturer and brand name are given where appropriate. Those marked N/A are not yet available as co-formulations

ACT	Proprietary brand	Manufacturer	Date of introduction
Artemether-Lumefantrine (AL)	Coartem®, Riamet®	Novartis	2006
Artesunate-Mefloquine (AS + MQ)	N/A	N/A	N/A
Artesunate-SP (AS + SP)	N/A	N/A	N/A
Artesunate-Amodiaquine (AS + AQ)	Coarsucam®	Sanofi-Aventis	2008
Dihydroartemisinin-Piperaquine (DHA + PPQ)	Artekin®	Chong Qing Holley, Sigma-Tau	2008

QT prolongation was noticed in individuals with normal QT intervals. Additionally, adverse effects of halofantrine have been observed in patients receiving standard doses of the drug, indicating this problem may not be restricted to over dosage [19]. It is believed that the basis for QTc prolongation is inhibition by halofantrine of the delayed rectifier potassium (HERG) channel and that such effects are related to the circulating plasma concentrations of halofantrine [23, 24].

Artemisinin, its Derivatives and Partner Drugs

Artemisinin (qinghaosu) was introduced into clinical practice in the 1980's. Subsequently, semi-synthetic derivatives were developed and these have been used in some tropical countries since the early 1990s. Several artemisinin derivatives including artesunate, artemether and arteether, alone or in combination with other antimalarials are currently registered in a number of Western countries and commercially available throughout the world. In recent times, the World Health Organization (WHO) and others have recognized the therapeutic benefits of combining the short-acting artemisinins with longer-acting antimalarials such as lumefantrine, mefloquine and piperaquine [25, 26]. The currently available ACT therapies are included in Table 17.1 and described in detail below. In order for such antimalarial drug combinations to be effective, the parasite biomass must be reduced sufficiently by one of the drug components so that the chances of mutation to the other, more slowly eliminated drug are greatly reduced. This is the rationale behind the combination of artemisinin derivatives with mefloquine and other drugs. The artemisinin derivatives are the most active of the available antimalarial compounds and produce a fractional reduction in parasite biomass of approximately 10^4 per asexual cycle. So, 3 days of treatment, which involves two cycles, usually produces a 10^8-fold reduction in biomass, leaving a maximum of 10^5 parasites for the other antimalarial drug (usually mefloquine or lumefantrine) to clear. This reduces considerably the exposure of the parasite population to mefloquine or lumefantrine, thereby reducing the chance of an escape-resistant mutant arising from the infection [12].

Artemether and Lumefantrine

Artemether-lumefantrine (CoArtem™) represents the first coformulated ACT that was introduced into the market to treat acute uncomplicated *Plasmodium falciparum* malaria. Food, especially dietary fat, may enhance the oral availability of artemether and especially lumefantrine [27, 28]. Administration of artemether and lumefantrine to healthy volunteers at the same time as a high-fat meal increases the bioavailability of both drugs by 2 and 16-fold, respectively when compared with the fasted state. This may be particularly important given the reduced food intake of many patients in the acute phase of malaria. As if to emphasize this point, a double-blind trial of patients with uncomplicated malaria in Thailand demonstrated that the extent and variability of lumefantrine absorption improved alongside clinical recovery as normal food intake was resumed [29]. This prompts a debate as to how much dietary fat is necessary to achieve plasma concentrations of lumefantrine that would affect total parasite clearance in combination with artemether. A population model developed from lumefantrine concentration measurements in a crossover study in healthy volunteers receiving with different volumes of Soya milk or with no milk demonstrated that 36 mL of soya milk (containing 1.2 g of fat) was associated with 90% of the lumefantrine exposure obtained with 500 mL regular milk (16 g fat) [30]. Data on relative lumefantrine exposure in African children receiving artemether-lumefantrine within a randomized trial were assessed against their consumption of different foods [31]. The relative increase in mean lumefantrine absorption was 1.57-fold in patients drinking milk and 2.74-fold in those eating pancakes versus those who fasted; a much smaller difference than that observed between fasting and fed volunteers [26, 27]. Interestingly, a group of children with malaria who did not eat when any of the six artemether-lumefantrine dose regimens in this study were administered were cured. Fat intake in sub-Saharan countries is approximately 15–30 g/day during breast feeding; greater than 10 g/day in the post-weaning phase and upwards of 30–60 g/day in a normal diet, supporting the view that typically fat intake is consonant with optimal efficacy of lumefantrine. A trial of 957 patients in Uganda receiving artemether-lumefantrine in hospital under supervision with a meal containing 23 g fat or unsupervised at home after the first dose with advice to take the drug with a meal or breast milk, showed both groups to have identical and complete cure rates [32, 33]. Lumefantrine plasma concentrations were higher in the supervised group, but the clinical response showed that home food consumption was sufficient to achieve pharmacologically effective concentrations of lumefantrine [33, 34]. Finally, a recent report has established that concomitant food administration can markedly enhance the absorption of lumefantrine in children, an important target group for CoArtem™ [35]. It may be concluded that a very small amount of dietary fat may be necessary to ensure adequate absorption of lumefantrine, and that standard African diets or breast milk are sufficient to fulfil this need. However, it is important that patients maintain normal food or milk intake during drug administration and to resume intake quickly once able to do so. Van Agtmael and colleagues [36, 37] have argued that an oral treatment course with artemether is probably more effective when the tablets are taken

with grapefruit juice. They demonstrated a two-fold increase in the concentrations of artemether and dihydroartemisinin in plasma during treatment. Although grapefruit juice did not reverse auto-induction of artemether metabolism, it could conceivably reduce recrudescence with artemether monotherapy by enhancing effective plasma concentrations. Interestingly, in preclinical studies of experimental infection with *Schistosoma mansoni*, co administration of grapefruit juice with artemether achieved complete protection of the host from damage induced by schistosomal infection again suggesting an effect of the juice on the pharmacokinetics of artemether [38].

Artesunate-Amodiaquine

Artesunate-amodiaquine is one of a group of artemisinin combination treatments currently recommended by the WHO (Table 17.1) and adopted as first-line treatment in many African countries [39, 40]. Relative to the fasting state, the administration of the fixed-dose combination after a high-fat breakfast resulted in a statistically significant increase in circulating concentrations of amodiaquine and desethyl amodiaquine which could affect the safety and tolerability of the two drugs, and a decrease in the blood concentrations of artesunate and dihydroartemisinin that might affect their efficacy [41].

Piperaquine

Piperaquine (PQ) is a *bis*-quinoline antimalarial drug that was first synthesized in the 1950s. It was seen as less toxic than chloroquine, and its efficacy against chloroquine-resistant strains of *Plasmodium falciparum* led to widespread distribution in China and Indochina in the 1970s. With the emergence of piperaquine-resistant parasites, its use declined, but the continuing search for suitable partner drugs prompted a renewed interest in piperaquine [42]. Fixed-dose combinations with dihydroartemisinin are marketed in China and Vietnam. Sim and colleagues [43] investigated the oral bioavailability of piperaquine with food relative to the fasting state and discovered a 1.2 fold increase after a high-fat meal. Side effects (i.e. postural blood pressure changes, electrocardiographic corrected QT interval, serum glucose, and other biochemical and haematological indices) were similar in the fasting and fed states. Confusingly, a later study revealed no significant difference in drug exposure between fed and fasting subjects after administration of piperaquine with dihydroartemisinin with or without a standard Vietnamese meal [44]. Different drug products were used in these studies and it is possible that differences in drug formulation significantly influenced the bioavailability of piperaquine. Additionally, a relatively small change in the fraction of dose absorbed, from, e.g. 10–20%, would result in a doubling of the AUC and a halving of the CL/*F*. It should

also be noted that the ethnicities and gender distribution of the study populations were different.

Mefloquine

Mefloquine is a chiral quinoline-methanol active against asexual forms of the species of *Plasmodium* that infect humans. Mefloquine is poorly water-soluble and the extent of its absorption is increased modestly when taken with food [45]. Because its oral bioavailability is relatively high, this interaction is probably irrelevant to the treatment of malaria, but it may be of importance when using mefloquine for chemoprophylaxis.

Atovaquone

Atovaquone is a hydroxyl-naphthoquinone with broad-spectrum anti-protozoal activity initially selected for development as an antimalarial agent on the basis of potent activity against drug-resistant strains of *Plasmodium falciparum* in vitro. Atovaquone was subsequently found to be active against a number of other microorganisms including *Pneumocystis carinii* and *Toxoplasma gondii.* Studies on the in vitro potentiation of atovaquone by other antimalarial drugs revealed evidence of marked synergistic activity with proguanil stimulated the subsequent clinical evaluation of these two drugs, culminating in the development of a fixed dose combination for the treatment and prevention of malaria. Food increases the bioavailability of atovaquone from tablets by 200–290% and from various suspensions by 26–174% which is chiefly attributable to the fat content of the meal [46]. In patients with HIV, target concentrations for the treatment of *Pneumocystis carinii* pneumonia are more consistently reached when atovaquone is administered with food or a nutrition supplement with a moderate fat content [47, 48]. The findings of some of the major investigations into the effect of food on the pharmacokinetics of antimalarial agents are summarized in Table 17.2.

17.2.1.2 Anthelmintics

Benzimidazoles

Albendazole and mebendazole are benzimidazole carbamates with a broad spectrum of anthelmintic activity. While poor absorption may be advantageous for therapy of helminth infections located in the gut lumen, successful treatment of tissue helminth infections, such as hydatid disease or neurocysticercosis, with albendazole requires a sufficient quantity of active drug to reach the site of infection. All of the

Table 17.2 Key food-drug interactions with antimalarial agents

Antimalarial agent (s)	Interaction	Effect on drug	[a]Reference(s)
Halofantrine (HF)	C_{max} of HF ↑ AUC of HF ↑	Possible ↑ in QT prolongation.	[15–17]
Artemether (ARM)/ lumefantrine (LUM)	**High fat**: F of ARM and LUM ↑ 2–16-fold	Increased systemic exposure that might affect efficacy of LUM or ARM	[27, 28]
	Milk: F of LUM ↑ 1.57-fold		
	Pancakes: F of LUM ↑ 2.74-fold		[30]
	Grapefruit juice: F of LUM ↑ two-fold		[28]
Artesunate (ARTS)/ amodiaquine (AQ)	**High fat**: F of AQ ↑ after high-fat breakfast	Increased systemic exposure that might affect efficacy of AQ	[36, 37]
	High fat: AUC of AQ and desethyl AQ ↑		[41]
	AUC of ARTS and dihydroartemisinin ↓		
Piperaquine (PIP)	**High fat**: F of PIP↑ 20%. Contradicted by later study	Increased systemic exposure that might affect efficacy of PIP.	[43]
Mefloquine (MQ)	**Food**: AUC of MQ↑	No clinical relevance as MQ already has high F.	[45]
Atovaquone (ATQ)	**Fatty meal**: F of ATQ ↑ 200–290% and 26–174% in suspensions	More consistent target concentrations of ATQ achieved in *Pneumocystis carinii*	[46]

Standard abbreviations for bioavailability (F) and area under the curve (AUC) are used. Values in square parentheses refer to circulating concentrations of a particular drug. If no additional information is available concerning the effect or its clinical importance, this is indicated by n/a.

[a] Note that the references given are the key source in each case. The reader is referred to the text of the chapter for more detailed information

benzimidazole derivatives exhibit low and variable bioavailability. The bioavailability of albendazole is increased markedly when taken with food, which enhances its chemosterilant properties against systemic parasitic infections [49–51].

Ivermectin

Ivermectin is a potent antiparasitic drug from the macrocyclic lactone family; the most powerful agents against a broad spectrum of ecto- and endoparasites. It was used exclusively in veterinary medicine due to its high efficacy and wide margin of safety until 1987 when it was introduced into humans use for the treatment of onchocerciasis [52, 53]. Since then, it has been used in combination with ABZ and diethylcarbamazine (DEC) for the treatment and control of onchocerciasis and lymphatic filariasis [5]. While information about the influence of food on the pharmacokinetics of ivermectin is scarce, co-ingestion of alcoholic drinks however is not

Table 17.3 Key food-drug interactions with anthelmintics

Antimalarial agent (s)	Interaction	Effect on drug	[a]Reference (s)
Albendazole (ALB)	**Fatty meal**: AUC of ALB sulfoxide↑	↑ chemosterilant properties vs. systemic parasites	[49–51]
Ivermectin (IVM)	**Beer *Vs* water**: AUC of IVM ↑ **Orange juice**: AUC and C_{max} ↓	n/a	[54, 55]
Praziquantel (PZQ)	**Food *Vs* fed**: AUC and C_{max} of PZQ ↑ 100–200% **Fat**: AUC of PZQ ↑ 180% **Carbohydrate**: AUC PZQ ↑ 271% **High-oil meal**: 134% **Low-oil meal**: 174%	n/a	[56–59]

Standard abbreviations for bioavailability (F) and area under the curve (AUC) are used. Values in square parentheses refer to circulating concentrations of a particular drug. If no additional information is available concerning the effect or its clinical importance, this is indicated by n/a.
[a]Note that the references given are the key source in each case. The reader is referred to the text of the chapter for more detailed information

recommended, because of the association of ivermectin with GABA receptors, and the effect of alcohol in the central nervous system. In healthy volunteers given ivermectin orally (150 μg/kg), plasma concentrations were significantly higher when co-administered with beer (750 mL) than with an equivalent volume of water [54]. When ivermectin was administered to 16 individuals with water or orange juice, the juice was associated with a decreased AUC and maximum serum concentration (C_{max}), possibly because fruit juices and constituents are potent inhibitors of certain drug transporters [55].

Praziquantel

Praziquantel is a pyrazino-isoquinoline whose potent anthelminthic activity against all *Schistosoma* species and the majority of other trematodes and cestodes was seen as a major advance in medical parasitology. Several studies have shown that administration of praziquantel with food increases its bioavailability. An early investigational study using fasting and fed healthy volunteers demonstrated that both C_{max} and AUC were 2–3 times higher in the fed state [56]. A more recent study showed that meals high in fat and carbohydrate increased AUC by 180% and 271% respectively [57]. These data were consistent with a further study involving healthy volunteers where meals with high and low oil contents were associated with mean AUC praziquantel values that were 134% and 174% respectively of those during fasting [58]. After a single oral dose of praziquantel with grapefruit juice, AUC and C_{max} were both increased [59]. The findings of some of the major investigations into the effect of food on the pharmacokinetics of anthelmintics are summarized in Table 17.3.

17.3 Anti-Malarial Drug-Drug Interactions

17.3.1 4-Aminoquinolines

17.3.1.1 Amodiaquine

Amodiaquine has been used in the treatment of malaria for over 40 years having once been considered as a successor to chloroquine in East Africa. The use of amodiaquine in prophylaxis was ended due to unacceptable incidences of agranulocytosis and hepatotoxicity [60–62]. CYP2C8 is primarily responsible for the metabolism of amodiaquine and exclusively catalyses the formation of desethyl-amodiaquine hinting at a potential interaction with co-substrates [63, 64]. Paradoxically, ketoconazole, an inhibitor of CYP3A4, was associated with decreased formation of desethyl-amodiaquine in human liver microsomes [65]. More recently, amodiaquine received a new lease of life as a partner drug with artesunate, where a pharmacokinetic interaction has been observed such that the total AUC for dihydroartemisinin and desethyl-amodiaquine was significantly reduced when compared with the equivalent parameters from the individual drugs [66]. Artesunate is rapidly converted to dihydroartemisinin, suggesting its principal role is as a prodrug for the former. Dihydroartemisinin is largely glucuronidated, principally by UGT1A9 and UGT2B7, suggesting that common CYP isoenzymes are not involved in the metabolism of either drug pointing to some other, as yet poorly understood mechanism for the interaction [67, 68]. Clinically, however, these observations may be of limited importance, as cure rates with this combination are still generally higher than with amodiaquine monotherapy.

17.3.1.2 Chloroquine

Magnesium trisilicate and kaolin caused a modest reduction in the bioavailability of chloroquine. To avoid drug loss, it is suggested that the chloroquine should not be administered with gastrointestinal medications of this type or that they should be separated by at least 4 h to reduce the risk of adsorption to antacids or adsorbents [69, 70]. In vitro and in vivo, chloroquine is an inhibitor of CYP2D6 and possibly a substrate for this polymorphically expressed enzyme, but the relevance of this finding to drug-drug interactions is yet to be established fully [71–73]. A small reduction was observed in C_{max} for the fluoroquinolone ciprofloxacin when it was administered with chloroquine but the clinical significance of this observation is unknown [74]. The rapid reduction in parasitaemia after the administration of chloroquine could be a valuable contribution to combination therapy, but the relatively long half life would induce substantial pressure to favour chloroquine-resistant strains. Moreover, because of the currently widespread resistance to chloroquine, it would appear to be of little value in combination with other agents [65]. One approach to overcome resistance to chloroquine has been to combine it with non-antimalarial agents that reverse chloroquine resistance. Often this would require using super-therapeutic and

potentially dangerous, doses. Chlorpheniramine, a histamine H1 receptor antagonist, can ameliorate chloroquine-induced pruritus. A therapeutic dose of chlorpheniramine increased the oral bioavailability of chloroquine by 70% in Nigerian children with uncomplicated falciparum malaria [75]. The mechanism is unexplained and the sample size was small.

17.3.2 8-Aminoquinolines

17.3.2.1 Primaquine

The hepatic biotransformation of primaquine and metabolites is partly mediated by cytochromes P450 [76] but it is not clear how any interactions might manifest themselves. The principal plasma metabolite is carboxy-primaquine [77, 78]. Clinically, the most significant interactions would be those that facilitate the formation or accumulation of toxic metabolites [65]. In vitro studies have shown that conversion to carboxy-primaquine is inhibited by ketoconazole, a potent CYP3A4 inhibitor. In vitro studies with human liver microsomes did not indicate any effect of quinine, artemether, artesunate, halofantrine or chloroquine [79]. In humans, a small decrease in C_{max} and AUC of carboxyprimaquine were observed after co-administration with quinine [80] but this is probably of little clinical relevance. While quinine may enhance the gastrointestinal side effects of higher dosages of primaquine, it may simultaneously offer some protection against primaquine-induced methaemoglobinaemia [81]. The combination of chloroquine and primaquine may increase methaemoglobin concentrations in healthy individuals [81–83]. However, it is mainly in subjects with NADH-cytochrome 5b reductase deficiency that this combination causes clinically significant methaemoglobinaemia and in such subjects primaquine would be contraindicated [84]. Although co-administration with mefloquine had no effect on the elimination of primaquine, or its main metabolite carboxyprimaquine, in healthy Thai male adults here may be a minor inhibitory effect of mefloquine on the formation of carboxyprimaquine [80]. The combination of primaquine with other haemolytic agents, e.g. some sulphonamides, should be avoided; notably the combination with dapsone, which is also a potent inducer of methaemoglobin, which enhances haemolysis [85].

17.3.3 Antifolates

Combination of inhibitors of folate synthesis takes advantage of their synergism and the observation that different genes contribute to the resistance phenotype, thus reducing the likelihood that resistant strains will be selected. Unfortunately, resistance to these drugs has developed in most endemic areas of the world, but the degree of resistance varies [86].

17.3.3.1 Biguanides

Proguanil and chlorproguanil are biguanides that inhibit dihydrofolate reductase (DHFR) which is an enzyme involved in the folate-thymidylate pathway. Proguanil is a prodrug, since it is rapidly transformed in the liver to the DHFR inhibitor cycloguanil. The metabolism of proguanil is mediated jointly by CYP3A4 and CYP2C19 [87–89]. A genetic polymorphism in CYP2C19 enzyme, with up to 20% poor metabolizers in Asian and African populations, has been demonstrated [90–92]. Poor metabolizers have reduced plasma concentrations of cycloguanil during prophylaxis and this could conceivably contribute to prophylactic failure in this group, but the large inter-subject variability and the role of CYP3A4 means there is no clear association [88, 89, 91]. Chlorproguanil is a chloro derivative of proguanil and intrinsically it is more active. A similar difference in activity exists with regard to its active metabolite, chlorcycloguanil, when compared with cycloguanil [93]. Chlorproguanil has recently received considerable attention, notably due to its combination with dapsone (i.e. LapDap™). It was envisaged that such a combination would in have several advantages over existing antifolate combinations [94]. It is known that pyrimethamine-resistant strains retain sensitivity to other DHFR inhibitors, and the much shorter half-life of chlorproguanil means the selection pressure of chlorproguanil for development of resistance would be reduced. However, the chlorproguanil-dapsone combination has been withdrawn from clinical use due to unacceptable toxicity [95–97]. Surprisingly, there have been few reports of drug-drug interactions and certainly none of any clinical relevance involving the partner drugs with which proguanil or cycloguanil are likely to be administered. The H_2 receptor antagonist cimetidine significantly increased C_{max}, AUC and elimination half-life and reduced total body clearance of proguanil. C_{max} and AUC of cycloguanil were significantly decreased pointing to effects on CYP isoenzymes [98].

17.3.3.2 Sulfonamides and Sulfones

Dapsone (4′, 4′-diaminodiphenylsulfone) is the most widely used sulfone, but has limited antimalarial activity. Against malaria, it has mainly been used as a prophylactic in combination with pyrimethamine (Maloprim™). Dapsone is rapidly absorbed and metabolised, principally to mono-acetyl-dapsone, and to dapsone hydroxylamine with food inducing a five-fold increase in C_{max}. The major metabolite, mono-acetyl-dapsone, is excreted after de-acetylation. The intrinsic antiparasitic activity of this metabolite is comparable to that of the parent compound [99]. Acetylation displays considerable inter-subject variation which has a genetic basis. N-Hydroxylation, a CYP-mediated phase I reaction is age-dependent and is the biochemical basis for the toxicity of dapsone, mainly haemolytic anaemia and methaemoglobinaemia, by formation of the haematotoxic hydroxylamine metabolite [100, 101]. In vitro, CYP3A, CYP2C9 and CYP2E1 have been found to mediate *N*-hydroxylation, but not CYP1A2 and CYP2D6 In vivo, CYP3A4 is involved but not CYP2D6 and CYP2C19. The involvement of CYP3A4 points to the possibility

of drug-drug interactions with inhibitors or inducers of this enzyme [102–104]. Interestingly, administration of cimetidine with dapsone can reduce hydroxylation and ameliorate toxicity [105, 106]. Sulfonamides are inhibitors of DHPS and historically have been used extensively in combination with inhibitors of DHFR in the prevention and treatment of malaria, notably sulfadoxine, sulfalene (sulfametopyrazine) and sulfamethoxazole [86]. Chiefly they appear in fixed-dose combinations; sulfadoxine and sulfalene in combination with pyrimethamine (Fansidar™ and Metakelfin™ respectively) and sulfamethoxazole in combination with trimethoprim as cotrimoxazole. Most sulfonamides are acetylated or undergo glucuronidation. The principal metabolites are inactive. Sulfonamides display a wide variety of pharmacokinetic variablity .Sulfadoxine and sulfalene are eliminated relatively slowly, whereas sulfamethoxazole has a shorter half-life [107]. Few pharmacokinetic interactions of clinical importance involving antimalarial sulfonamides have been reported, due probably to the limited involvement of cytochromes P450 in their metabolism although certain sulfonamides (e.g. sulfaphenazole) may inhibit CYP2C9 [108]. Finally, the initial CYP2C9-mediated activation to a chemically reactive hydroxylamine that is displayed by dapsone is common to antimalarial sulfonamides and is a mediator of chemical reactivity [109].

17.3.4 Atovaquone

The combination of proguanil and atovaquone was originally developed to combat multi-drug-resistant falciparum malaria [110]. In vitro, proguanil has a specific synergistic effect with atovaquone, which is dependent, not on its active metabolite cycloguanil, but proguanil itself [111]. Therefore, the combination is effective in cycloguanil resistance and genetic polymorphism for CYP2C19 or its inhibition by other drugs is unlikely to affect efficacy [112].

In healthy Caucasians, the pharmacokinetics of proguanil, cycloguanil and atovaquone are unaffected by combination. In patients with *P. falciparum* malaria, the pharmacokinetics of proguanil with atovaquone was comparable to with healthy volunteers treated solely with proguanil. In a population pharmacokinetic study, there appeared to be a difference in the oral clearance of proguanil between poor and extensive metabolizers and a small but clinically unimportant difference between racially different groups when compared with monotherapy. There is no effect of co-administration with proguanil on the pharmacokinetics of atovaquone [112, 113].

17.3.5 Artemisinin and Derivatives

Artemisinin drugs rapidly reduce the parasite burden. Because of the short half-life of most artemisinin derivatives, recrudescence occurs after monotherapy. In combination with other drugs, the rapidly acting artemisinin may help to minimize

selection pressure [2, 3, 114]. While the pharmacokinetics of the combination of artemether and lumefantrine (CoArtem™) are identical to the pharmacokinetics of the individual agents, there is a minor retardation in the rate of absorption. However, there is no reduction in AUC. A time-dependent decline in artemether and corresponding increase in concentrations of dihydroartemisinin was observed [115]. When combined with artemether, the C_{max} of pyrimethamine was increased significantly and the volume of distribution was reduced slightly. The reason for these changes is not known [116]. Chlorproguanil-dapsone -artesunate was in development for the treatment of uncomplicated *Plasmodium falciparum* malaria. Artesunate did not significantly affect the pharmacokinetics of chlorproguanil or dapsone. In the case of chlorproguanil and mono-acetyl-dapsone, small to moderate increases in exposure with artesunate dosing were observed. There was a greater than proportional increase in artesunate and DHA exposure with increasing artesunate dose. These effects were not considered to be clinically relevant. However, it should be noted that the chlorproguanil-dapsone-artesunate programme has now been stopped following unacceptable haematological toxicity in patients with glucose-6-phosphate dehydrogenase deficiency during a phase III trial [95–97]. After repeated doses, plasma concentrations of artemisinin decline steadily, with a 6- to 7-fold reduction of the AUC after 6 days of daily administration [117, 118]. It is likely that artemisinin induces its own metabolism but the exact mechanism has not yet been elucidated. It is also not known if the production of metabolites is increased. This time-dependent decline of artemisinin also occurs after rectal administration, which suggests that the site of induction is hepatic [119]. This effect has also been observed with artemether and also dihydroartemisinin after oral administration of artesunate [120] and probably contributes to the high rate of recrudescence. The time-dependent pharmacokinetics of artemisinin suggests that artemisinin is a selective inducer of drug metabolism. This view is supported by artemisinin increasing the activity of CYP2C19 but not CYP3A4. However, the time-dependent decline of the AUC for artemisinin is not associated with the CYP2C19 phenotype. It is thought that at least one other enzyme, most likely CYP2B6, catalyzes the auto-induction of artemisinin [121, 122]. A study in healthy volunteersevaluated the combination of oral artesunate (100 mg),administered before and during a 5-day course of artemisinin (500 mg). Curiously the apparent oral clearance of dihydroartemisinin was 3-fold lower in the presence of artemisinin, suggesting a competitive interaction and the possibility that combination therapy with artesunate and artemisinin might be useful [123]. Administration of artemether-lumefantrine with ketoconazole, a potent inhibitor of CYP3A4 increased the area under the plasma concentration-time curve for both artemether (2.4-fold) and lumefantrine (1.7-fold) [124].

17.3.6 Cinchona Alkaloids

Quinine is transformed into 3-hydroxyquinine principally by CYP3A4 [125]. Co-administration with rifampicin and cigarette smoking each increase the metabolic

clearance of quinine [126, 127]. That smoking increases quinine clearance points to a role for CYP1A in its elimination [126]. Fortunately, among other antimalarials, there are few potent inducers or inhibitors of CYP3A4 and clinically relevant interactions revolving around enzyme induction and inhibition are unlikely. However, there is a wide range of possible interactions with other drugs, notably those used in the treatment of HIV (see below) and interactions involving drug transport proteins. The diastereoisomer of quinine, quinidine, used as an antimalarial in North America, is the more potent inhibitor of CYP2D6 in vivo [128]. Theoretically, drug-drug interactions would be expected to be more problematic, but in the context of antimalarial therapy relatively few have been observed. In preclinical studies it has been shown that the clearance of quinine clearance increased by a number of drugs that induce cytochromes P450, such as phenobarbitone [129]. The clearance of quinine is inhibited by cimetidine, an inhibitor of cytochromes P450 [130]. Quinine is known to inhibit the metabolism of phenobarbitone and carbamazepine metabolism [131] and to reduce the clearance of flecainide [132] although not excessively [133]. Quinine and quinidine may increase the plasma concentrations of digoxin although the magnitude of the effect is less for quinine than for quinidine [134, 135]. The clearance of quinidine is unaltered in smokers [136]. Elimination of quinidine is markedly increased by phenobarbitone, phenytoin, and rifampicin, but reduced by inhibitors of cytochrome P450 isoenzymes, such as cimetidine, amiodarone, verapamil and erythromycin [137, 138]. Pharmacokinetic interactions between phenobarbitone and quinine have not been noted in patients with cerebral malaria where both drugs are commonly co-administered without evidence of toxicity [139, 140]. Quinine and quinidine have potent effects on repolarization in cardiac conduction tissue and interactions with digoxin and other antiarrthymic agents may be clinically important. The dose of digoxin may need to be reduced and plasma concentrations of quinine, quinidine and digoxin monitored in patients receiving both agents.

17.3.7 Mefloquine

Mefloquine has a very long terminal elimination half –life [6]. This may increase selection pressure and it is probably the principal reason why resistance developed soon after its introduction in Thailand. Mefloquine was at one time combined with sulfadoxine-pyrimethamine in a fixed combination, but the high degree of resistance against sulfadoxine-pyrimethamine meant there was no protective effect for mefloquine [141, 142]. A combination of mefloquine and the artemisinin derivatives is effective against multi-drug resistant parasites. Moreover, it is argued that use of the combination will also delay the development of mefloquine resistance where monotherapy has not been used. Mefloquine is metabolised by CYP3A4 to carboxymefloquine [143]. While co-administration of mefloquine has no effect on the pharmacokinetics of primaquine or carboxy-primaquine in healthy Thai males [80], there is some evidence that a combination of mefloquine, primaquine and sulfadoxine-pyrimethamine may reduce the half life of mefloquine compared with a combination

of mefloquine and sulfadoxine-pyrimethamine, but this is of little clinical significance [144]. Mefloquine co-administration to patients with uncomplicated falciparum malaria increased the AUC of artemisinin by one third to one half and reduced the apparent volume of distribution and clearance without affecting half-life. Since the metabolic fate of artemisinin is largely unknown, there is no obvious explanation for this observation [145]. Mefloquine did not affect the pharmacokinetics of dihydroartemisinin in healthy Thai males and patients with malaria and dihydroartemisinin did not affect the pharmacokinetics of mefloquine in the same group [146, 147]. In a large study in Thai children with falciparum malaria; the AUC of mefloquine on day 0 was also lower than the AUC on day 2 when artesunate was given for 3 days. The authors suggested that the recovery from malaria was the main cause of the increased bioavailability [148]. Food intake, as suggested in a previous study, was not a significant factor. However, in a study comparing adult Thai patients and healthy volunteers, malaria slowed the rate of absorption somewhat without effect on AUC [149]. Finally, in another study there was no difference between single dose and 2 divided dose regimens [150]. Such conflicting data do not provide convincing evidence for an interaction between artesunate and mefloquine. A limited study in patients with uncomplicated malaria revealed the AUC of mefloquine to be slightly reduced when given 24 h after artemether [151]. In a further volunteer study, the same group reported that there was no interaction between artemether and quinine, mefloquine or primaquine [152]. Co-artemether (40 mg artemether + 480 mg lumefantrine) given in six doses over 60 h following a 1,000 mg dose of mefloquine elicited a significant decrease (30–40%) in plasma lumefantrine concentrations compared with lumefantrine alone. However, the authors considered that clinical effects were unlikely to be influenced by the interaction [153]. It is concluded that there is no clinically relevant interaction between mefloquine and dihydroartemisinin.

Reciprocal interactions with mefloquine are unimportant as the antimalarial efficacy of the artemisinin component is governed by the combined activity of artemether and dihydroartemisinin. However, it may be prudent to delay the administration of mefloquine until initial recovery has been achieved by one of the artemisinin drugs [65]. In patients with acute malaria, despite mefloquine prophylaxis, treatment with halofantrine was is associated with significant QT_c prolongation and the risk of sudden death. This observation points to an effect of mefloquine on ventricular re-polarization [21]. While there are no data relating to the cardiotoxicity of other quinoline antimalarial drugs including quinine in the context of prophylactic failure of mefloquine, two studies have looked at patients with falciparum malaria who received combination treatment with quinine and mefloquine. In the first of these, plasma concentrations of mefloquine increased markedly when quinine therapy was curtailed [154] while, in the other, no significant cardiovascular effects were noticed [155]. Treatment with quinolines is probably best avoided if a patient has been taking mefloquine. Furthermore, where quinine or quinidine is the only available agents for treating severe malaria, electrocardiographic monitoring is advised.

The risk of convulsions may also be greater [156]. As mentioned previously, artemisinin-mefloquine combinations clear parasitaemia rapidly, reduce the risk

of recrudescence and are mutually protective against the development of parasite resistance. They have been used as first-line treatment for falciparum malaria in the tropics, but no significant cardiotoxic or other interaction has been observed. This could be due in part to the relatively short half-lives of the artemisinin derivatives and the slow absorption of mefloquine [157]. It was once thought mefloquine might interact with other cardioactive drugs such as anti-arrhythmic agents, adrenergic and calcium channel blockers, antihistamines, tricyclic antidepressants and major tranquillisers, but this now seems unlikely [157, 158]. The findings of some of the major investigations into drug-drug interactions among antimalarials and co-administered drugs are summarized in Table 17.4.

17.4 Anthelmintic Drug-Drug Interactions

17.4.1 Albendazole

Albendazole is converted in vivo into albendazole sulfoxide, the systemically active form of the drug and albendazole sulfone, which is inactive, in sequential sulfoxidation. CYP450 and flavin monoxygenases have been implicated in the reaction. CYP450 is the main determinant of sulfonation [159, 160]. Plasma concentrations of albendazole sulphoxide are increased in the presence of cimetidine and after ingestion of grapefruit juice [161] Albendazole has a chiral centre and it appears that that the formation of albendazole (−) sulfoxide is dependent upon on P450 isoenzymes, whereas the formation of albendazole (+) sulfoxide is dependent upon on flavin monoxygenases. Subsequent oxidation to albendazole sulfone is wholly dependent on P450 enzymes [160, 162]. Albendazole, although a substrate of CYP3A4, is neither a substrate nor an inhibitor of P-glycoprotein or Breast Cancer Resistant protein, BCRP/ABCG2. Accordingly, interactions between albendazole and P-gp substrates or inhibitors are unlikely to be clinically important [163, 164].

17.4.2 Ivermectin

Ivermectin and other macrocyclic lactones are highly lipophilic molecules and therefore widely distributed in the body [165, 166]. The antiparasitic activities of ivermectin and other macrocyclic lactones are related to the presence of effective concentrations for a suitable length of time in the systemic circulation and in target tissues [167, 168]. Information regarding the metabolism of ivermectin in humans is scanty [169]. It is extensively metabolised by human cytochromes P450. The predominant isoform responsible is CYP3A4 converting the drug to at least 10 metabolites, most of them hydroxylated and demethylated derivatives [170]. A number of radioactive metabolites were reported after oral administration of ^{14}C- ivermectin to

Table 17.4 Key drug-drug interactions with antimalarial agents

Antimalarial agent(s)	Interaction	Effect on drug/ importance	[a]Key reference(s)
4-aminoquinolines	**In vitro**: AQ metabolism ↓ by ketoconazole.	v	[65]
Amodiaquine (AQ)			
Chloroquine (CQ)	F of CQ ↓ by antacids	n/a	[69, 70]
8-aminoquinolines	– C_{max} and AUC of carboxy PQ ↓ by quinine	– No clinical relevance	[81–85]
Primaquine (PQ)	– PQ + CQ or PQ + DAP ↑ methaemoglobin	– Avoid PQ/DAP combination	
Antifolates	**PG and cycloguanil**: AUC and C_{max} of ↑ by cimetidine.	n/a	[98]
Biguanides			
Proguanil (PG)			
Chlorproguanil (CG)			
Sulfa drugs			
Dapsone (DAP)	**DAP**: Hydroxylation ↓ by cimetidine	– Amelioration of DAP toxicity	[105, 106]
Sulfonamides	**Sulfaphenazole**: Inhibition of CYP2C9	– Potential CYP based drug-drug interactions	[109]
Artemisinin and derivatives	**ARM/ART**: Time dependent ↓ in [ARM] and ↑ in [DHA] repeat dosage of ARM	n/a	[115]
Artemether/ lumefantrine (ARM/LUM)	Time dependent ↓ in [ART] on repeat dosage.		[117–119]
Artemisinin (ART)	**Pyrimethamine**: C_{max} ↑ and Vd ↓ with ARM	– Not clinically relevant	[116]
Artesunate (ARTS)			
Dihydroartemisinin (DHA)	**ART**: Cl_{oral} of DHA ↓75% by ART	– Not clinically relevant	[123]
	AUC of ARM ↑ (140%) and AUC of LUM ↑ (70%) by ketoconazole	– Increased activity of ARM and LUM	[124]
Mefloquine (MQ)	**PQ/sulfadoxine/ MQ**: $t_{½}$ of MQ ↓	No clinical significance	[144]
	ARM/MQ; $t_{½}$ of ART unchanged; Vd of ART ↓ AUC of ART ↑	n/a	[145]
	ARTS/MQ: AUC and F of MQ ↑ from day 0 to day 2 when ARTS given for 3 days.	Recovery from malaria leads to ↑ AUC and F.	[148]
	ARM/MQ: AUC of MQ ↓ slightly after ARM.	n/a	[151]
	Co-ARM (6 doses)/**MQ**: AUC of LUM↓.30–40%.	n/a	[153]
	QN: [MQ] ↓ after QN stopped	n/a	[154]

Standard abbreviations for bioavailability (F) and area under the curve (AUC) are used. Values in square parentheses refer to circulating concentrations of a particular drug. If no additional information is available concerning the effect or its clinical importance, this is indicated by n/a.

[a]Note that the references given are the key source in each case. The reader is referred to the text of the chapter for more detailed information

Table 17.5 Key drug-drug interactions with anthelmintics

Anthelmintic agent	Interaction	Effect on drug/importance	[a]Key reference (s)
Albendazole (ABZ)	[ABZ-sulfoxide] ↑ by cimetidine and grapefruit juice	↑ and prolonged activity of ABZ-sulfoxide	[161]
Ivermectin (IVM)	IVM is a substrate for/inhibitor of p-glycoprotein and substrate for CYP3A4	Potential ↑ in incidence of CNS related adverse events	[172]
Praziquantel (PZQ)	**Cimetidine**: PZQ AUC ↑ 100%. (similar effect with diphenhydramine and 17α-ethinylestradiol)	Enhanced effectiveness in cysticercosis	[179, 180]
	Carbamazepine: F of PZQ ↓	n/a	[181]
	Phenytoin: F of PZQ ↓	n/a	
	Chloroquine: F of PZQ ↓	n/a	[182]
	Ketoconazole: [PZQ] ↑ 100%. **Rifampicin**: [PZQ] ↓	Some dose adjustment may be needed	[178, 183]

Standard abbreviations for bioavailability (F) and area under the curve (AUC) are used. Values in square parentheses refer to circulating concentrations of a particular drug. If no additional information is available concerning the effect or its clinical importance, this is indicated by n/a

[a] Note that the references given are the key source in each case. The reader is referred to the text of the chapter for more detailed information

healthy volunteers [171]. Ivermectin is both a substrate and inhibitor of P-gp [172], and has been demonstrated to inhibit P-gp, ABCC1, ABCC2, and ABCC3 activities after stimulation by their respective activators [173, 174], and preclinical studies have indicated that it is a potential inducer of several cytochrome P450 subfamilies including CYP1A, CYP2B and CYP3A [175]. It is apparent that all of this information points to numerous possibilities for drug-drug interactions, orchestrated largely through transporter proteins.

17.4.3 Praziquantel

The commercial preparation of praziquantel is a racemate composed of levo R (−) and dextro S (+) isomers of which only the (−) enantiomer has antischistosomal activity, both in vivo and in vitro [176]. The isomers do, however, have similar toxicity. Orally administered praziquantel is rapidly absorbed, measurable amounts appearing in the blood as early as 15 min after dosing with peak levels occurring after 1–2 h. The maximum plasma concentrations after standard dose of 40 mg/kg shows wide inter individual variations in the range of 200–2,000 ng/mL. praziquantel undergoes pronounced liver first pass metabolism, with rapid disappearance from the circulation, the plasma half-life ranging between 1 and 3 h. Elimination occurs through urine and faeces and is more than 80% complete after 24 h [177]. The main metabolites are represented by mono-, di-, and tri-hydroxylated compounds

that are produced in the liver by microsomal cytochrome P450, particularly by the isoforms 2B1 and 3A, which are experimentally inducible by phenobarbitone [177, 178]. The most abundant metabolite is the 4-hydroxycyclohexyl-carbonyl analogue, which represents 60% of the metabolites. The bioavailability of praziquantel is increased by simultaneous administration of substances that inhibit cytochrome P450 activities e.g. cimetidine causes a 100% increase [179, 180]. For this reason, cimetidine has been used in combination with praziquantel, especially in the treatment of neurocysticercosis, where high concentrations are required. Diphenhydramine and 17α-ethinylestradiol each have the same effect. Epileptic drugs, especially carbamazepine and phenytoin, as well as corticosteroids reduce its bioavailability [181]. Chloroquine similarly decreases its bioavailability to a significant extent [182]. Ketoconazole, a CYP3A inhibitor, has been observed to double the plasma concentration of praziquantel in humans, while rifampicin, an inducer of drug metabolism, has been reported dramatically to reduce its concentration, and dose adjustment upon co-administration has been recommended [178, 183].

To date, praziquantel has not conclusively been characterised in relation to its effects on drug transporters. In a study involving permeability through Caco-2 cells, praziquantel did not show potential for interacting with cellular efflux pumps at a concentration range of 10–100 μg/mL despite being highly permeable [184]. A related study concluded that praziquantel, among other anthelmintics, was an inhibitor of P-gp without being its substrate based on transport along Caco-2 monolayers [185]. The findings of some of the major investigations into drug-drug interactions among anthelmintics and co-administered drugs are summarized in Table 17.5.

17.5 Antiretroviral and Antiparasitic Drug-Drug Interactions

Given the co-existence of HIV and a variety of parasitic infections in the tropics, it is appropriate separately to review potential pharmacokinetic interactions. Generally, such interactions involve protease inhibitors and non-nucleotide reverse transcriptase inhibitors The former are among the most potent inhibitors of cytochromes P450 and their role in pharmacokinetic interactions is exacerbated by some protease inhibitors being auto-inducers. Protease inhibitors may also inhibit or be substrates of the multi-drug efflux transporter P-glycoprotein. Such properties are advantageous in boosting plasma protease inhibitor concentrations by ritonavir, or the reduction of hepatic clearance by inhibition of CYP3A4 in gut or liver. The non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz may inducer CYP3A4, while delavirdine is an inhibitor of the same enzymes and also enhances the bioavailability of the protease inhibitors .However, such properties may contribute to the high risk of drug-drug interactions, some of which may be serious, as a result of inhibition or induction of drug metabolism. However, it is relevant to note that few clinical data exist to support interactions between antiretroviral and antimalarial drugs and risk assessment is based primarily on prior knowledge of the pharmacokinetics of these drugs or in vitro screens [186].

17.5.1 Antifolates

Since proguanil is a prodrug activated partly by CYP2C19 and CYP3A4 [87–89] there is concern that inhibition of metabolism by ritonavir or ritonavir-containing boosted protease inhibitor regimens will reduce its pharmacological effect. However, synergy with atovaquone is related to proguanil, not cycloguanil [111]. When the two drugs are co-administered, CYP2C19 inhibition may offset decreased cycloguanil formation and potentially enhance this synergistic effect.

17.5.2 Artemisinin and Its Derivatives

Since artemether is metabolized via CYP3A4 to dihydroartemisinin [124] inhibition of CYP3A4 could conceivably reduce dihydroartemisinin but increase artemether and potentially increase the relatively short half-life of artemether. The effects of protease inhibitors and non-nucleoside reverse transcriptase inhibitors are uncertain. Lumefantrine and halofantrine are extensively metabolized by CYP3A4 [124] and inhibition of halofantrine metabolism could potentially prolong the QT interval; given the narrow therapeutic index of halofantrine, any combination with protease inhibitors is contraindicated and nevirapine and efavrirenz should be used with caution. Lumefantrine does not seem to prolong the QT interval and is much safer than halofantrine, which is now discontinued. Nevertheless, interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors are likely, and the manufacturer advises that co-administration of CYP3A4 inhibitors such as protease inhibitors are contraindicated. Given the increasing use of lumefantrine-artemether for malaria, caution should be exercised when using protease inhibitors and non-nucleoside reverse transcriptase inhibitors [186].

17.5.3 Atovaquone

Atovaquone decreases the oral clearance of zidovudine, leading to a 35 ± 23% increase in its plasma AUC. The clinical significance of this is not known, and presently no dose modification is recommended [187]. Atovaquone lowers indinavir exposure, reducing trough plasma concentrations by one quarter [186]. A healthy volunteer study noted an AUC decrease of 5% for indinavir but an increase in atovaquone AUC of 13% and C_{max} of 16% when the drugs were co-administered. These small changes do not demand any dose adjustment for atovaquone when given with indinavir [188]. The clinical significance of reduced concentrations of indinavir is uncertain as these were healthy volunteer studies carried out without boosting with ritonavir which is no longer advised. Moreover, clinical studies have shown higher plasma indinavir in Thai patients with much lower body weight and, given the toxicity

of indinavir at higher doses, dosage adjustments are not indicated for ritonavir-boosted indinavir when given with atovaquone or Malarone™. Co-administration with lopinavir may decrease plasma concentrations of atovaquone, resulting in the need to increase the dosage of the latter [186].

17.5.4 Cinchona Alkaloids

As quinine is extensively metabolized by CYP3A4 [125], exposure could be increased by ritonavir or ritonavir-boosted protease inhibitor regimens. Induction of CYP 3A4 by nevirapine and efavirenz could conceivably reduce plasma concentrations of quinine. Quinine is both a substrate and inhibitor of P-gp in vitro and thus has the potential to be involved in a number of drug-drug interactions with other agents that may be co-substrates of this transporter, notably protease inhibitors [185].

17.5.5 Mefloquine

No interaction between ritonavir and mefloquine was noted after a single dose, but the plasma AUC for ritonavir was reduced by 31% and the C_{max} by 36% after multiple dosing [189]. The pharmacokinetics of mefloquine was not significantly influenced by ritonavir.

17.6 Conclusions

Combination chemotherapy is at the heart of any treatment protocol for infectious disease. In the treatment of malaria, the drugs being used most frequently are the artemisinin derivatives. Introduced in South-East Asia they are potent antimalarials and generally well tolerated. However, artemisinin drugs have a very short half-life and thus a multiple dose regimen of 7 days is required to achieve an acceptable cure rate. When artemisinins are used as monotherapy, recrudescence of malaria is common. .Combining an artemisinin drug with a partner drug that has a longer half-life improves the efficacy of the artemisinin. It also reduces treatment duration with the artemisinin and the likelihood of development of resistance to the partner drug. Artemisinin-based combination therapy has already been shown to improve treatment efficacy and contain drug resistance in South-East Asia. Fortunately, few clinically important drug-drug interactions with partner drugs have been observed, although some of the partner drugs themselves may be predisposed to initiate such interactions. More importantly, the tendency for the treatment of other infections that might be expected to co-exist such as filariasis, HIV disease and tuberculosis to involve multiple drug treatment points to increased risk of interactions. Urgent investigation of these is merited.

References

1. White NJ. Assessment of the pharmacodynamic properties of antimalarial drugs *in vivo*. Antimicrob. Agents Chemother 1997; 41:1413–1422
2. White N. Antimalarial drug resistance and combination chemotherapy. Philos Trans R Soc Lond B Biol Sci 1999; 354:739–749.
3. Eastman RT, Fidock DA. Artemisinin-based combination therapies: a vital tool in efforts to eliminate malaria. Nat Rev Microbiol 2009; 7:864–874.
4. Ottesen EA, Ismail MM, Horton J. The role of albendazole in programmes to eliminate lymphatic filariasis. Parasitol Today 1999; 15:382–386.
5. Molyneux DH, Bradley M, Hoerauf A, Kyelem D, Taylor MJ Mass drug treatment for lymphatic filariasis and onchocerciasis. Trends Parasitol 2003; 19:516–522.
6. White NJ. Clinical Pharmacokinetics of Antimalarial Drugs. Clin Pharmacokinet 1985; 10:187–215.
7. Edwards G, Breckenridge AM. Clinical pharmacokinetics of anthelmintic drugs. Clin Pharmacokinet 1988; 15:67–93.
8. Edwards G, Winstanley PA, Ward SA Clinical pharmacokinetics in the treatment of tropical diseases. Some applications and limitations. Clin Pharmacokinet 1994; 27:150–165.
9. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine: clinical implications. Clin. Pharmacokinet 1996; 30:263–299.
10. Winstanley P. The contribution of clinical pharmacology to antimalarial drug discovery and development. Br J Clin Pharmacol 2003; 55:464–468.
11. Kerb R, Fux R, Mörike K, Kremsner PG, Gil JP, Gleiter CH. Pharmacogenetics of antimalarial drugs: effect on metabolism and transport. Lancet Infect Dis 2009; 9:760–774.
12. Edwards G, Krishna S Pharmacokinetic and pharmacodynamic issues in the treatment of parasitic disease. Eur J Clin Microbiol Infect Dis 2004; 22:233–242.
13. Winstanley PA, Orme ML. The effects of food on drug bioavailability. Br J Clin Pharmacol 1989; 28:621–628.
14. Schmidt LE, Dalhof K. Food-Drug Interactions. Drugs 2002; 62:1481–1502.
15. Broom C. Human pharmacokinetics of halofantrine hydrochloride. Parasitol Today 1989; (Suppl):15–20.
16. Milton KA, Edwards G, Ward SA, Orme ML'E, Breckenridge AM. Pharmacokinetics of halofantrine in man: effect of food and dose size. Br J Clin Pharmacol 1989; 28:71–77.
17. Brocks DR, Ramaswamy M, MacInnes AI, Wasan KM. The stereoselective distribution of halofantrine enantiomers within human, dog and rat plasma lipoproteins. Pharm Res 2000; 17:427–431.
18. Castot A, Rapoport P, Le Coz, P. Prolonged QT interval with halofantrine. Lancet 1993; 341:1541.
19. Karbwang J, Na Bangchang K, Bunnag D, Harinasuta KT. Cardiac effect of halofantrine. Lancet 1993; 342:501.
20. Monlun E, Le Metayer P, Szwandt S, et al. J. Cardiac complications of halofantrine: a prospective study of 20 patients. Trans R. Soc Trop Med Hyg 1995; 89:430–433.
21. Nosten F, ter Kuile FO, Luxemburger C, et al. Cardiac effects of antimalarial treatment with halofantrine. Lancet 1993; 341:1054–1056.
22. Monlun E, Pillet O, Cochard JF, Favarel Garrigues JC, Le Bras M. Prolonged QT interval with halofantrine. Lancet 1993; 341:1541–1542.
23. Toivonen L, Viitasalo M, Siikamaki H, Raatikka M, Pohjola-Sintonen S. Provocation of ventricular tachycardia by antimalarial drug halofantrine in congenital long QT syndrome. Clin Cardiol 1994; 17:403–404.
24. Tie H, Walker BD, Singleton CB, et al. Inhibition of HERG potassium channels by the antimalarial agent halofantrine. Br J Pharmacol 2000; 130:1967–1975.
25. Ilett KF, Batty KT. Artemisinin and its derivatives. In: Yu, VL, Edwards G, McKinnon PS, Peloquin C, Morse GD. Antimicrobial Therapy and Vaccines. Volume II: Antimicrobial Agents 2006; 981–1002. ESun Technologies, LLC, Pittsburgh PA, USA www.antimicrobe.org.

26. Djimdé A, Lefèvre G. Understanding the pharmacokinetics of Coartem. Malar J 2009; 12: Suppl 1:S4.
27. White NJ, van Vugt M, Ezzet F Clinical pharmacokinetics and pharmacodynamics and pharmacodynamics of artemether-lumefantrine. Clin Pharmacokinet 1999; 37:105–125.
28. Ezzet F, van Vugt M, Nosten F, Looareesuwan S, White NJ. Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. Antimicrob Agents Chemother 2000; 44:697–704.
29. Ezzet F, Mull R, Karbwang J Population pharmacokinetics and therapeutic response of CGP 56697 (artemether + benflumetol) in malaria patients. Br J Clin Pharmacol 1998; 46:553–561.
30. Ashley EA, Stepniewska K, Lindegårdh N, et al. How much fat is necessary to optimize lumefantrine oral bioavailability? Trop Med Int Health 2007; 12:195–200.
31. Borrmann S, Sallas WM, Marrast A-C, Lefèvre G, Kern SE. Exposure to lumefantrine in infants and children receiving artemether-lumefantrine for uncomplicated malaria: impact of African diet components. American Society of Tropical Medicine and Hygiene Annual Meeting, 7–11 December 2008, New Orleans, USA.
32. Premji ZG, Abdulla S, Ogutu B, et al. The content of African diets is adequate to achieve optimal efficacy with fixed-dose artemether-lumefantrine: a review of the evidence. Malar J 2008; 7:244.13.
33. Piola P, Fogg C, Bajunirwe F, et al. Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated Plasmodium falciparum malaria in Mbarara, Uganda: a randomized trial. Lancet 2005; 365:1467–1473.
34. Checchi F, Piola P, Fogg P, et al. Supervised versus unsupervised antimalarial treatment with six-dose artemether-lumefantrine: pharmacokinetics and dosage-related findings from a clinical trial in Uganda. Malar J 2006; 5:59.
35. Borrmann S, Sallas WM, Machevo S, et al. The effect of food consumption on lumefantrine bioavailability in African children receiving artemether-lumefantrine crushed or dispersible tablets (Coartem) for acute uncomplicated Plasmodium falciparum malaria. Trop Med Int Health 2010; 15:434–441.
36. Van Agtmael MA, Gupta V, Van Der Graaf CA, van Boxtel CJ. The effect of grapefruit juice on the time-dependent decline of artemether plasma levels in healthy subjects. Clin Pharmacol Ther 1999; 66:408–414.
37. Van Agtmael MA, Gupta V, van der Wosten TH, Rutten JP, van Boxtel CJ. Grapefruit juice increases the bioavailability of artemether. Eur J Clin Pharmacol 1999; 55:405–410.
38. El-Lakkany NM, Seif el-Din SH, Badawy AA, Ebeid FA. Effect of artemether alone and in combination with grapefruit juice on hepatic drug-metabolising enzymes and biochemical aspects in experimental Schistosoma mansoni. Int J Parasitol 2004; 34:1405–1412.
39. Zwang J, Olliaro P, Barennes H, et al. Efficacy of artesunate-amodiaquine for treating uncomplicated falciparum malaria in sub-Saharan Africa: a multi-centre analysis. Malar J 2009; 23:203.
40. Fitoussi S, Thang C, Lesauvage E, et al. Bioavailability of a co-formulated combination of amodiaquine and artesunate under fed and fasted conditions. A randomised, open-label crossover study. Arzneim Forsch 2009; 59:370–376.
41. Stepniewska K, Taylor W, Sirima SB, et al. Population pharmacokinetics of artesunate and amodiaquine in African Children. Malar J 2009; 8:200.
42. Davis TM, Hung TY, Sim IK, Karunajeewa HA, Ilett KF. Piperaquine: a resurgent antimalarial drug. Drugs 2005; 65:75–87.
43. Sim IK, Davis TM, Ilett KF. Effects of a high-fat meal on the relative oral bioavailability of piperaquine. Antimicrob Agents Chemother 2005; 49:2407–2411.
44. Hai TN, Hietala SF, Van Huong N, Ashton M The influence of food on the pharmacokinetics of piperaquine in healthy Vietnamese volunteers. Acta Trop 2008; 107:145–149.
45. Crevoisier C, Handschin J, Barre J, Roumenov D, Kleinbloesem C. Food increases the bioavailability of mefloquine. Eur J Clin Pharmacol 1997; 53:135–139.

46. Rolan PE, Mercer AJ, Weatherley BC, et al. Examination of some factors responsible for a food-induced increase in absorption of atovaquone. Br J Clin Pharmacol 1994; 37:13–20.
47. Dixon R, Pozniak AL, Watt HM, Rolan P, Posner J. Single-dose and steady-state pharmacokinetics of a novel microfluidized suspension of atovaquone in human immunodeficiency virus-seropositive patients. Antimicrob Agents Chemother 1996; 40:556–560.
48. Falloon J, Sargent S, Piscitelli SC, Bechtel C, LaFon SW, Sadler B, et al. Atovaquone suspension in HIV-infected volunteers: pharmacokinetics, pharmacodynamics and TMP-SMX interaction study. Pharmacotherapy 1999; 19:1050–1056.
49. Lange H, Eggers R, Bircher J. Increased systemic availability of albendazole when taken with a fatty meal. Eur. J Clin. Pharmacol 1988; 34:315–317.
50. Awadzi K, Hero M, Opoku NO, Buttner DW, Coventry PA, Prime MA, et al. The chemotherapy of onchocerciasis XVII. A clinical evaluation of albendazole in patients with onchocerciasis; effects of food and pretreatment with ivermectin on drug response and pharmacokinetics. Trop Med Parasitol 1994; 45:203–208.
51. Nagy J, Schipper HG, Koopmans RP, Butter JJ, Van Boxtel CJ, Kager PA. Effect of grapefruit juice or cimetidine co-administration on albendazole bioavailability. Am J Trop Med Hyg 2002; 66:260–263
52. Lindley, D. Merck's new drug free to WHO for river blindness programme. Nature 1987; 329:752.
53. Steel, JW.Pharmacokinetics and metabolism of avermectins in livestock. Vet Parasitol 1993; 48:45–57
54. Shu EN, Onwujekwe EO, Okonkwo PO. Do alcoholic beverages enhance availability of ivermectin? Eur J Clin Pharmacol 2000; 56:437–438.
55. Vanapalli SR, Chen Y, Ellingrod VL, et al. Orange juice decreases the oral bioavailability of ivermectin in healthy volunteers. Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics. Washington (USA), 2–5 April, 2003.
56. Homeida M, Leahy W, Copeland S, Ali MM, Harron DW. Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. Ann Trop Med Parasitol 1994; 5:551–559.
57. Castro N, Medina R, Sotelo J, Jung H. Bioavailability of praziquantel increases with concomitant administration of food. Antimicrob. Agents Chemother 2000; 44:2903–2904.
58. Mandour ME, el Turabi H, Homeida MM, et al. Pharmacokinetics of praziquantel in healthy volunteers and patients with schistosomiasis. Trans R. Soc Trop Med Hyg 1990; 84:389–393.
59. Castro N, Jung H, Medina R, Gonzalez-Esquivel D, Lopez M, Sotelo J. Interaction between grapefruit juice and praziquantel in humans. Antimicrob Agents Chemother 2002; 46:1614–1616.
60. Hatton CS, Peto TE, Bunch C, et al. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. Lancet 1986; 1:411–414.
61. Larrey D, Castot A, Pessayre D, et al. Amodiaquine-induced agranulocytosis. A report of seven cases. Ann Intern Med 1986; 104:801–803.
62. Neftel KA, Woodtly W, Schmid M. Amodiaquine induced agranulocytosis and liver damage. Br Med J 1986; 292:721–723.
63. Li XQ, Bjorkman A, Andersson TB, Ridderstrom M, Masimirembwa CM. Amodiaquine clearance and its metabolism to N-desethylamodiaquine is mediated by CYP2C8: a new high affinity and turnover enzyme-specific probe substrate. J Pharmacol Exp Ther 2002; 300:399–407.
64. Gil JP. Amodiaquine pharmacogenetics. Pharmacogenomics 2008; 9:1385–1390.
65. Giao PT, deVries PJ. Pharmacokinetic interactions of antimalarial agents. Clin Pharmacokinet 2001; 40:348–373.
66. Orrell C, Little F, Smith P, et al. Pharmacokinetics and tolerability of artesunate and amodiaquine alone and in combination in healthy volunteers. Eur J Clin Pharmacol 2008; 64:683–690.

67. Maggs JL, Madden S, Bishop LP, O'Neill PM, Park BK. The rat biliary metabolites of dihydroartemisinin, an antimalarial endoperoxide. Biochem Pharmacol 1997; 25:1200–1204.
68. Ilett KF, Ethell BT, Maggs JL, et al. Glucuronidation of dihydroartemisinin in vivo and by human liver microsomes and expressed UDP-glucuronosyltransferases. Drug Metab Dispos 2002; 30:1005–1012.
69. McElnay JC, Sidahmed AM, D'Arcy PF.Examination of the chloroquine-kaolin drug absorption interaction using the buccal partitioning model. J Clin. Hosp Pharm 1982; 7:269–273.
70. McElnay JC, Mukhtar HA, D'Arcy PF, Temple DJ, Collier PS. The effect of magnesium trisilicate and kaolin on the in vivo absorption of chloroquine. J Trop Med Hyg 1982; 85:159–163.
71. Lancaster DL, Adio RA, Tai KK, et al. Inhibition of metoprolol metabolism by chloroquine and other antimalarial drugs. J Pharm Pharmacol 1990; 42:267–271.
72. Masimirwembra, C, Hasler, JA, Johansson, I. Inhibitory effects of antiparasitic drugs on cytochrome P450 2D6. Eur J Clin Pharmacol 1995; 48:35–38.
73. Simooya OO, Sijumbil G, Lennard MS, Tucker GT. Halofantrine and chloroquine inhibit CYP2D6 activity in healthy Zambians. Br J Clin Pharmacol 1998; 45:315–317.
74. Ilo CE, Ilondu NA, Okwoli N, et al. Effect of chloroquine on the bioavailability of ciprofloxacin in humans. Am J Ther 2006; 13:432–435.
75. Okonkwo CA, Coker HA, Agomo PU, et al. Effect of chlorpheniramine on the pharmacokinetics of and response to chloroquine of Nigerian children with falciparum malaria. Trans R Soc Trop Med Hyg 1999; 93:306–311.
76. Constantino L, Paixão P, Moreira R, Portela MJ, Do Rosario VE, Iley J. Metabolism of primaquine by liver homogenate fractions. Evidence for monoamine oxidase and cytochrome P450 involvement in the oxidative deamination of primaquine to carboxyprimaquine. Exp Toxicol Pathol 1999; 51:299–303.
77. Baker JK, McChesney JD, Hufford CD, Clark AM. High-performance liquid chromatographic analysis of the metabolism of primaquine and the identification of a new mammalian metabolite. J Chromatogr 1982; 230:69–77
78. Mihaly GW, Ward SA, Edwards G, Orme ML, Breckenridge AM. Pharmacokinetics of primaquine in man: identification of the carboxylic acid derivative as a major plasma metabolite. Br J Clin Pharmacol 1984; 17:441–446.
79. Na Bangchang K, Karbwang J, Back DJ. Primaquine metabolism by human liver microsomes: effect of other antimalarial drugs. Biochem Pharmacol 1992; 44:587–590.
80. Edwards G, McGrath CS, Ward SA, et al. Interactions among primaquine, malaria infection and other antimalarials in Thai subjects. Br J Clin Pharmacol 1993; 35:193–198.
81. Clayman CB, Arnold J, Hockwald RS, Yount Jr EH, Edgecomb JH, Alving AS. Toxicity of primaquine in Caucasians. J Am Med Assoc 1952; 149:1563–1568.
82. Greaves J, Evans DA, Fletcher KA. Urinary primaquine excretion and red cell methaemoglobin levels in man following a primaquine: chloroquine regimen. Br J. Clin Pharmacol 1980; 10:293–295.
83. Fletcher KA, Evans DA, Gilles HM, Greaves J, Bunnag D, Harinasuta T. Studies on the pharmacokinetics of primaquine. Bull WHO 1981; 59:407–412.
84. Cohen RJ, Sachs JR, Wicker DJ, Conrad ME. Methemoglobinemia provoked by malarial chemoprophylaxis in Vietnam. N Engl J Med 1968; 279:1127–1131.
85. Eppes RB, McNamara JV, DeGowin RL, Carson PE, Powell RD. Chloroquine-resistant Plasmodium falciparum: protective and hemolytic effects of 4, 4'-diaminodiphenylsulfone (DDS) administered daily together with weekly chloroquine and primaquine. Mil Med 1967; 132:163–175.
86. Nzila A. The past, present and future of antifolates in the treatment of Plasmodium falciparum infection. J Antimicrob Chemother 2006; 57:1043–1054.
87. Birkett DJ, Rees D, Andersson T, et al. In vitro proguanil activation to cycloguanil by human liver microsomes is mediated by CYP3A isoforms as well as by S-mephenytoin hydroxylase. Br J Clin Pharmacol 1994; 37:413–420.

88. Skjelbo E, Mutabingwa TK, Bygbjerg I, et al. Chloroguanide metabolism in relation to the efficacy in malaria prophylaxis and the S-mephenytoin oxidation in Tanzanians. Clin Pharmacol Ther 1996; 59:304–311.
89. Rasmussen BB, Nielsen TL, Brosen K. Fluvoxamine inhibits the CYP2C19-catalysed metabolism of proguanil in vitro. Eur J Clin Pharmacol 1998; 54:735–740.
90. Helsby NA, Edwards G, Breckenridge AM, et al. The multiple dose pharmacokinetics of proguanil. Br J Clin Pharmacol 1993; 35:653–656.
91. Kaneko A, Bergqvist Y, Taleo G, et al. Proguanil disposition and toxicity in malaria patients from Vanuatu with high frequencies of CYP2C19 mutations. Pharmacogenetics 1999; 9:317–326.
92. Watkins WM, Mberu EK, Nevill CG, et al. Variability in the metabolism of proguanil to the active metabolite cycloguanil in healthy Kenyan adults. Trans R Soc Trop Med Hyg 1990; 84:492–495.
93. Veenendaal JR, Edstein MD, Rieckmann KH. Pharmacokinetics of chlorproguanil in man after a single oral dose of Lapudrine. Chemotherapy 1988; 34:275–283.
94. Amukoye E, Winstanley PA, WatkinsWM, et al. Chlorproguanil dapsone: effective treatment for uncomplicated falciparum malaria. Antimicrob Agents Chemother 1997; 41:2261–2264.
95. Tiono A, Dicko A, Ndububa D et al. Chlorproguanil-dapsone-artesunate vs. chlorproguanil-dapsone: a randomised, double-blind phase III trial for the treatment of acute uncomplicated Plasmodium falciparum malaria. Am J Trop Med Hyg 2008; 79 (Suppl): 172.
96. Premji Z, Umeh R, Owusu-Agyei S, et al. Chlorproguanil-dapsone-artesunate vs. artemether-lumefantrine: a randomised, double-blind phase III trial for the treatment of acute, uncomplicated Plasmodium falciparum malaria in African children and adolescents. Am J Trop Med Hyg 2008; 79 (Suppl): 225.
97. Miller AK, Bandyopadhyay N, Wootton DG, Duparc S, Kirby PL, Winstanley PA, et al Pharmacokinetics of chlorproguanil, dapsone, artesunate and their major metabolites in patients during treatment of acute uncomplicated Plasmodium falciparum malaria. Eur J Clin Pharmacol 2009; 65:977–987.
98. Kolawole JA, Mustapha A, Abdul-Aguye I, Ochekpe N, Taylor RB. Effects of cimetidine on the pharmacokinetics of proguanil in healthy subjects and in peptic ulcer patients. J. Pharm Biomed Anal 1999; 20:737–743.
99. Edstein MD, Veenendaal JR, Rieckmann KH. Multiple-dose kinetics in healthy volunteers and in vitro antimalarial activity of proguanil plus dapsone. Chemotherapy 1990; 36:169–176.
100. Bluhm RE, Adedoyin A, McCarver DG, et al. Development of dapsone toxicity in patients with inflammatory dermatoses: activity of acetylation and hydroxylation of dapsone as risk factors. Clin Pharmacol Ther 1999; 65:598–605.
101. Irshaid Y, Adedoyin A, Lotze M, et al. Monoacetyldapsone inhibition of dapsone N-hydroxylation by human and rat liver microsomes. Drug Metab Dispos 1994; 22:161–164.
102. Gill HJ, Tingle MD, Park BK. N-Hydroxylation of dapsone by multiple enzymes of cytochrome P450: implications for inhibition of haemotoxicity. Br J Clin Pharmacol 1995; 40:531–538
103. May DG, Porter J, Wilkinson GR, et al. Frequency distribution of dapsone N-hydroxylase, a putative probe for P4503A4 activity, in a white population. Clin Pharmacol Ther 1994; 55:492–500.
104. Mitra AK, Thummel KE, Kalhorn TF, et al. Metabolism of dapsone to its hydroxylamine by CYP2E1 in vitro and in vivo. Clin Pharmacol Ther 1995; 58:556–566.
105. Coleman MD, Scott AK, Breckenridge AM, et al. The use of cimetidine as a selective inhibitor of dapsone N-hydroxylation in man. Br J Clin Pharmacol 1990; 30:761–767.
106. Tingle MD, Coleman MD, Park BK. The effect of preincubation with cimetidine on the N-hydroxylation of dapsone by human liver microsomes. Br J Clin Pharmacol 1991; 32:120–123.

107. Watkins WM. Winstanley PA. Folate Antagonists. In: Yu, VL, Edwards G, McKinnon PS, Peloquin C, Morse GD. Antimicrobial Therapy and Vaccines. Volume II: Antimicrobial Agents 2006; 1049–1069. ESun Technologies, LLC, Pittsburgh PA, USA www.antimicrobe.org.
108. Miners JO, Birkett DJ. Cytochrome P4502C9: an enzyme of major importance in human drug metabolism. Br J Clin Pharmacol 1998; 45:525–538.
109. Knowles S, Shapiro LE, Shear NH. Reactive metabolites and adverse drug reactions; clinical considerations. Clin Rev Allergy Immunol 2003; 24:229–238.
110. Radloff PD, Philipps J, Nkeyi M, et al. Atovaquone and proguanil for Plasmodium falciparum malaria. Lancet 1996; 347(9014):1511–1514.
111. Srivastava IK, Vaidya AB. A mechanism for the synergistic antimalarial action of atovaquone and proguanil. Antimicrob Agents Chemother 1999; 43:1334–1339.
112. Gillotin C, Mamet JP, Veronese L. Lack of a pharmacokinetic interaction between atovaquone and proguanil. Eur J Clin Pharmacol 1999; 55:311–315.
113. Hussein Z, Eaves CJ, Hutchinson DB, et al. Population pharmacokinetics of proguanil in patientswith acute P. falciparum malaria after combined therapy with atovaquone. Br J Clin Pharmacol 1996; 42:589–597.
114. German PI, Aweeka FT. Clinical pharmacology of artemisinin-based combination therapies. Clin Pharmacokinet 2008; 47:91–102.
115. van Agtmael MA, Cheng-Qi S, Qing JX, et al. Multiple dose pharmacokinetics of artemether in Chinese patients with uncomplicated falciparum malaria. Int J Antimicrob Agents 1999; 12:151–158.
116. Tan-ariya P, Na-Bangchang K, Ubalee R, et al. Pharmacokinetic interactions of artemether and pyrimethamine in healthy male Thais. Southeast Asian J Trop Med Public Health 1998; 29:18–23.
117. Hassan AM, Ashton M, Kihamia CM, et al. Multiple dose pharmacokinetics of oral artemisinin and comparison of its efficacy with that of oral artesunate in falciparum malaria patients. Trans R Soc Trop Med Hyg 1996; 90:61–65.
118. Ashton M, Hai TN, Sy ND, et al. Artemisinin pharmacokinetics is time-dependent during repeated oral administration in healthy male adults. Drug Metab Dispos 1998; 26:25–27.
119. Ashton M, Nguyen DS, Nguyen VH, et al. Artemisinin kinetics and dynamics during oral and rectal treatment of uncomplicated malaria. Clin Pharmacol Ther 1998; 63:482–493.
120. Khanh NX, de Vries PJ, Ha LD, et al. Declining concentrations of dihydroartemisinin in plasma during 5-day oral treatment with artesunate for falciparum malaria. Antimicrob Agents Chemother 1999; 43:690–692.
121. Svensson US, Ashton M. Identification of the human cytochrome P450 enzymes involved in the in vitro metabolism of artemisinin. Br J Clin Pharmacol 1999; 48:528–535.
122. Svensson US, Ashton M, Trinh NH, et al. Artemisinin induces omeprazole metabolism in human beings. Clin Pharmacol Ther 1998; 64:160–167.
123. Zhang SQ, Hai TN, Ilett KF, Huong DX, Davis TM, Ashton M. Multiple dose study of interactions between artesunate and artemisinin in human volunteers. Br J Clin Pharmacol 2001; 52:377–385.
124. Lefèvre G, Carpenter P, Souppart C, Schmidli H, McClean M, Stypinski D. Pharmacokinetics and electrocardiographic pharmacodynamics of artemether-lumefantrine (Riamet®) with concomitant administration of ketoconazole in healthy subjects. Br J Clin Pharmacol 2002; 54:485–492.
125. Zhao XJ, Yokoyama H, Chiba K, et al. Identification of human cytochrome P450 isoforms involved in the 3-hydroxylation of quinine by human liver microsomes and nine recombinant human cytochromes P450. J Pharmacol Exp Ther 1996; 279:1327–1334.
126. Wanwimolruk S, Wong SM, Zhang H, et al. Metabolism of quinine in man: identification of a major metabolite, and effects of smoking and rifampicin pretreatment. J Pharm Pharmacol 1995; 47:957–963.
127. Wanwimolruk S, Wong SM, Coville PF, Viriyayudhakorn S, Thitiarchakul S. Cigarette smoking enhances the elimination of quinine. Br J Clin Pharmacol 1993; 36:610–614.

128. Muralidharan G, Hawes EM, McKay G, Midha KK. Quinine is a more potent inhibitor than quinidine in rat of the oxidative metabolic routes of methoxyphenamine which involve debrisoquine 4-hydroxylase. Xenobiotica 1991; 21:1441–1450.
129. Krishna S. Quinine and quinidine. In: Yu, VL, Edwards G, McKinnon PS, Peloquin C, Morse GD. Antimicrobial Therapy and Vaccines. Volume II: Antimicrobial Agents 2006; 1167–1194. ESun Technologies, LLC, Pittsburgh PA, USA. www.antimicrobe.org.
130. Wanwimolruk S, Sunbhanich M, Pongmarutai M, Patamasucon P. Effects of cimetidine and ranitidine on the pharmacokinetics of quinine. Br J Clin Pharmacol 1986; 22:346–350.
131. Amabeoku GJ, Chikuni O, Akino C, Mutetwa S. Pharmacokinetic interaction of single doses of quinine and carbamazepine, phenobarbitone and phenytoin in healthy volunteers. E Afr Med J 1993; 70:90–93.
132. Suphakawanich W, Thithapandha A. Inhibition of hepatic drug metabolism by quinine. Asia Pacific J Pharmacol 1987; 2:241–247.
133. Munafo A, Reymond-Michel G, Biollaz J. Altered flecainide disposition in healthy volunteers taking quinine. Eur J Clin Pharmacol 1990; 38:269–273.
134. Hager WD, Fenster P, Mayersohn M, Perrier D, Graves P, Marcus FI, et al. Digoxin-quinidine interaction. Pharmacokinetic evaluation. N Engl J Med 1979; 300:1238–1241.
135. Wandell M, Powell JR, Hager WD, Fenster PE, Graves PE, Conrad KA, et al. Effect of quinine on digoxin kinetics. Clin Pharmacol Ther 1980; 28:425–430.
136. Edwards DJ, Axelson JE, Visco JP, van Every S, Slaughter RL, Lalka D. Lack of effect of smoking on the metabolism and pharmacokinetics of quinidine in patients. Br J Clin Pharmacol 1987; 23:351–354.
137. Gonzalez FJ, Idle JR. Pharmacogenetic phenotyping and genotyping. Clin. Pharmacokinet 1994; 26:59–70.
138. Spinler SA, Cheng JW, Kindwall KE, Charland SL. Possible inhibition of hepatic metabolism of quinidine by erythromycin. Clin Pharmacol Ther 1995; 57:89–94.
139. White NJ, Looareesuwan S, Phillips RE, Chanthavanich P, Warrell DA. Single dose phenobarbitone prevents convulsions in cerebral malaria. Lancet 1988; ii: 64–66.
140. Winstanley PA, Newton CR, Pasvol G, et al. Prophylactic phenobarbitone in young children with severe falciparum malaria: pharmacokinetics and clinical effects. Br J Clin Pharmacol 1992; 33:149–54.
141. White NJ. Antimalarial pharmacokinetics and treatment regimens. Br J Clin Pharmacol 1992; 34:1–10.
142. Nosten F, van Vugt M, Price R, et al. Effects of artesunate mefloquine combination on incidence of Plasmodium falciparum malaria and mefloquine resistance in western Thailand: a prospective study. Lancet 2000; 356(9226):297–302.
143. Na Bangchang K, Karbwang J, Back DJ. Mefloquine metabolism by human liver microsomes. Effect of other antimalarial drugs. Biochem Pharmacol 1992; 43:1957–1961.
144. Karbwang J, Back DJ, Bunnag D, et al. Pharmacokinetics of mefloquine in combination with sulfadoxine-pyrimethamine and primaquine in male Thai patients with falciparum malaria. Bull World Health Org 1990; 68:633–638.
145. Hassan AlinM, AshtonM, Kihamia CM, et al. Clinical efficacy and pharmacokinetics of artemisinin monotherapy and in combination with mefloquine in patients with falciparum malaria Br J Clin Pharmacol 1996; 41:587–592.
146. Na Bangchang K, Tippawangkosol P, Thanavibul A, et al. Pharmacokinetic and pharmacodynamic interactions of mefloquine and dihydroartemisinin. Int J. Clin Pharmacol Res 1999; 19:9–17.165.
147. Na Bangchang K, Tippawangkosol P, Ubalee R, et al. Comparative clinical trial of four regimens of dihydroartemisinin mefloquine in multidrug-resistant falciparum malaria. Trop Med Int Health 1999; 4:602–610.
148. Price R, Simpson JA, Teja-Isavatharm P, et al. Pharmacokinetics of mefloquine combined with artesunate in children with acute falciparum malaria. Antimicrob Agents Chemother 1999; 43:341–346.

149. Boudreau EF, Fleckenstein L, Pang LW, et al. Mefloquine kinetics in cured and recrudescent patients with acute falciparum malaria and in healthy volunteers. Clin Pharmacol Ther 1990; 48:399–409.
150. Na Bangchang K, Molunto P, Banmairuroi V, et al. Pharmacokinetics of mefloquine when given as a single and two divided-dose regimens. Int J Clin Pharmacol Res 1995; 15:215–220.
151. Na-Bangchang K, Karbwang J, Molunto P, Banmairuroi V, Thanavibul A. Pharmacokinetics of mefloquine, when given alone and in combination with artemether, in patients with uncomplicated falciparum malaria. Fundamental Clin Pharmacol 1995; 9:576–582.
152. Na-Bangchang K, Karbwang J, Ubalee R, Thanavibul A, Saenglertsilapachai S. Absence of significant pharmacokinetic and pharmacodynamic interactions between artemether and quinoline antimalarials. Eur J Drug Metab Pharmacokinet 2000; 25:171–178.
153. Lefèvre G, Bindschedler M, Ezzet F, Schaeffer N, Meyer I, Thomsen MS. Pharmacokinetic interaction trial between co-artemether and mefloquine. Eur J Pharm Sci 2000; 10:141–151.
154. Chanthavanich P, Looareesuwan S, White NJ, et al. Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. Am J Trop Med Hyg 1985; 34:1028–1036.
155. Supanaranond W, Suputtamongkol Y, Davis TM, et al. Lack of a significant adverse cardiovascular effect of combined quinine and mefloquine therapy for uncomplicated malaria. Trans R Soc Trop Med Hyg 1997; 91:694–696.
156. Palmer KJ, Holliday SM, Brogden RN. Mefloquine. A review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1993; 45:430–475.
157. White AC, Gard DA, Sessoms SL. Cutaneous vasculitis associated with mefloquine. Ann Intern Med 1995; 123:894.
158. Davis TME. Mefloquine. In: Yu, VL, Edwards G, McKinnon PS, Peloquin C, Morse GD. Antimicrobial Therapy and Vaccines. Volume II: Antimicrobial Agents 2006; 1091–1104. ESun Technologies, LLC, Pittsburgh PA, USA. www.antimicrobe.org.
159. Rawden, HC, Kokwaro, GO, Ward, SA, Edwards, G. Relative contribution of cytochromes P-450 and flavin-containing monoxygenases to the metabolism of albendazole by human liver microsomes. Br J Clin Pharmacol 2000; 49:313–322.
160. Souhaili-El Amri H, Mothe O, Totis M, et al Albendazole sulfonation by rat liver cytochrome P-450c. J. Pharmacol Exp Ther 1988; 246:758–764.
161. Nagy J Schipper HG, Koopmans RP, Butter JJ Van Boxtel CJ, Kager PA. Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability. Am J Trop Med Hyg 2002; 66:260–263.
162. el Amri HS, Fargetton X, Delatour P, Batt AM. Sulphoxidation of albendazole by the FAD-containing and cytochrome P-450 dependent mono-oxygenases from pig liver microsomes. Xenobiotica 1987; 17:1159–1168.
163. Merino G, Alvarez AI, Prieto JG, Kim RB. The anthelmintic agent albendazole does not interact with p-glycoprotein. Drug Metab Dispos 2002; 30:365–369.
164. Merino G, Jonker JW, Wagenaar E, et al. Transport of anthelmintic benzimidazole drugs by breast cancer resistance protein (BCRP/ABCG2). Drug Metab Dispos 2005; 33:614–618.
165. Krishna, DR Klotz, U. Determination of ivermectin in human plasma by high-performance liquid chromatography. Arzneim Forsch 1993; 43:609–611.
166. Scott, EW, McKellar, QA. The distribution and some pharmacokinetic parameters of ivermectin in pigs. Vet Res Commun 1992; 16:139–146.
167. Lanusse C, Lifschitz A, Virkel G et al. Comparative plasma disposition kinetics of ivermectin, moxidectin and doramectin in cattle. J Vet Pharmacol Ther 1997; 20:91–99.
168. McKellar QA, Benchaoui HA. Avermectins and milbemycins. J Vet Pharmacol Ther 1996; 19:331–351.
169. Gonzalez Canga, A, Sahagun Prieto AM, Diez Liebana MJ, Fernandez Martinez N, Sierra Vega M, Garcia Vieitez, JJ. The pharmacokinetics and interactions of ivermectin in humans--a mini-review. AAPS J 2008; 10:42–46.
170. Zeng Z, Andrew NW, Arison BH, Luffer-Atlas D, Wang RW. Identification of cytochrome P4503A4 as the major enzyme responsible for the metabolism of ivermectin by human liver microsomes. Xenobiotica 1998; 28:313–321.

171. Fink DW, Porras AG. Pharmacokinetics of ivermectin in animals and humans. In W.C. Campbell (ed.), Ivermectin and abamectin: Springer, New York, 1989; 113–130.
172. Edwards G Ivermectin: does P-glycoprotein play a role in neurotoxicity? Filaria J 2003; 2 Suppl 1: S8.
173. Lespine A, Dupuy J, Orlowski S et al Interaction of ivermectin with multidrug resistance proteins (MRP1, 2 and 3). Chem Biol Interact 2006; 159:169–179.
174. Pouliot JF, L'Heureux F, Liu Z, Prichard RK, Georges E. Reversal of P-glycoprotein-associated multidrug resistance by ivermectin. Biochem Pharmacol 1997; 53:17–25.
175. Skalova L, Szotakova B, Machala M, et al. Effect of ivermectin on activities of cytochrome P450 isoenzymes in mouflon (Ovis musimon) and fallow deer (Dama dama). Chem Biol Interact 2001; 137:155–167.
176. Wu MH, Wei CC, Xu, ZY et al. (1991) Comparison of the therapeutic efficacy and side effects of a single dose of levo-praziquantel with mixed isomer praziquantel in 278 cases of schistosomiasis japonica. Am J Trop Med Hyg 1991; 45:345–349.
177. Giorgi M, Salvatori AP, Soldani G et al. Pharmacokinetics and microsomal oxidation of praziquantel and its effects on the P450 system in three-month-old lambs infested by Fasciola hepatica. J Vet Pharmacol Ther 2001; 24:251–259.
178. Ridtitid W, Wongnawa M, Mahatthanatrakul W, Punyo J, Sunbhanich M. Rifampin markedly decreases plasma concentrations of praziquantel in healthy volunteers. Clin Pharmacol Ther 2002; 72:505–513.
179. Jung H, Medina R, Castro N, Corona, T Sotelo J. Pharmacokinetic study of praziquantel administered alone and in combination with cimetidine in a single-day therapeutic regimen. Antimicrob Agents Chemother 1997; 41:1256–1259.
180. Metwally A, Bennett JL, Botros, S, Ebeid F. Effect of cimetidine, bicarbonate and glucose on the bioavailability of different formulations of praziquantel. Arzneim Forsch 1995; 45:516–518.
181. Masimirembwa CM, Hasler JA. Characterisation of praziquantel metabolism by rat liver microsomes using cytochrome P450 inhibitors. Biochem Pharmacol 1994; 48:1779–1783.
182. Masimirembwa CM, Naik YS, Hasler JA. The effect of chloroquine on the pharmacokinetics and metabolism of praziquantel in rats and in humans. Biopharm Drug Dispos 1994; 15:33–43.
183. Ridtitid W, Ratsamemonthon K, Mahatthanatrakul W, Wongnawa M. Pharmacokinetic interaction between ketoconazole and praziquantel in healthy volunteers. J Clin Pharm Ther 2007; 32:585–593.
184. Gonzalez-Esquivel D, Rivera J, Castro N, Yepez-Mulia L, Jung Cook H. In vitro characterization of some biopharmaceutical properties of praziquantel. Int J Pharm 2005; 295:93–99.
185. Hayeshi R, Masimirembwa C, Mukanganyama S, Ungell AL. The potential inhibitory effect of antiparasitic drugs and natural products on P-glycoprotein mediated efflux. Eur J Pharm Sci 2006; 29:70–81.
186. Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs AIDS 2005; 19:995–1005.
187. Lee BL, Tauber MG, Sadler B, Goldstein D, Chambers HF. Atovaquone inhibits the glucuronidation and increases the plasma concentrations of zidovudine. Clin Pharmacol Ther 1996; 59:14–21.
188. Emmanuel A, Gillotin C, Farinotti R. Atovaquone suspension and indinavir have minimal pharmacokinetic interaction. In: XII International Conference on AIDS, Geneva, 1998. Abstract No. 12384.
189. Khaliq Y, Gallicano K, Tisdale C, Carignan G, Cooper C, McCarthy A. Pharmacokinetic interaction between mefloquine and ritonavir in healthy volunteers. Br J Clin Pharmacol 2001; 51:591–600.

Chapter 18
Drug Interaction Considerations Throughout Drug Development

Kellie Schoolar Reynolds

Abstract The objectives of a drug interaction program are to determine whether there are interactions with an NME (new molecular entity) that necessitate a dose adjustment of the NME or other drugs that it might be used with, or whether an interaction requires a contraindication or special precautions. The program should begin early in drug development so the clinical implications of interactions can be assessed adequately in clinical studies. It is important that all studies are conducted using rigorous scientific procedures. The clinical significance of interactions should be assessed based on exposure-response knowledge of the affected drug. Drug labels need to include complete information about the potential for drug interactions, including instructions for dose adjustments and special monitoring or precautions.

18.1 Introduction

Drug development scientists have been interested in the impact of drug interactions on the safety and efficacy of drugs for many years. A number of regulatory actions highlight the importance of the issue. The withdrawals of terfenadine, astemizole and cisapride occurred, in part, because of safety concerns related to drug interactions. Mibefradil is a CYP3A inhibitor that was withdrawn from the market because of drug interactions that led to markedly increased concentrations of CYP3A substrates. In 2002, an FDA Advisory Committee recommended against approval of pleconaril for the treatment of the common cold, in part because of the potential for drug interactions [1]. Pleconaril is a CYP3A inducer and its administration may

The views presented in this chapter do not necessarily reflect those of the FDA

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decrease plasma concentrations of CYP3A substrates, including some contraceptive steroids [2]. We can reflect on these and other examples when we consider the appropriate timing of drug interaction evaluations, methods for evaluation of drug interaction potential and their significance, and effective methods to communicate the risk of drug interactions.

The FDA published the *Draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, and Implications for Dosing and Labeling* in September 2006 [3]. The 2006 draft guidance combines and updates information from the April 1997 guidance on in vitro drug metabolism and drug interaction studies [4] and the November 1999 guidance on in vivo drug metabolism and drug interaction studies [5]. The 2006 draft guidance describes in vitro techniques for evaluating the potential for metabolism-based drug interactions, in vitro techniques for evaluating the potential for P-glycoprotein (P-gp)-based drug interactions, the correlation of in vitro and in vivo findings, the timing of the in vitro and in vivo studies, recommendations on in vivo study design, study population, choice of interacting drug, dose selection, statistical considerations, and labeling that may result from in vitro and in vivo studies.

Since the publication of the draft guidance in 2006, there have been many advances in the understanding of drug interaction mechanisms and the techniques to predict and evaluate drug interactions. For example, knowledge increased regarding drug transporters other than P-gp, culminating in the International Transporter Consortium report [6] on membrane transporters in drug development. Development and refinement of physiologically-based pharmacokinetic (PBPK) modeling and simulation tools led to additional methods for evaluating drug interactions, including complex interactions that involve multiple enzymes or enzymes plus transporters [7, 8].

This chapter does not provide details on most of the scientific issues related to drug interactions because other chapters address the scientific issues. Instead, this chapter focuses on the broad drug development considerations that surround the evaluation of drug interactions. The issues discussed in this chapter apply to most drug classes; however, the discussion of clinical implications and the actual examples apply to drugs that are administered to patients with infectious diseases.

The specific objectives of a drug interaction program are to determine whether there are any interactions with an NME (new molecular entity) that necessitate a dose adjustment, a warning, or a contraindication. Although the potential for drug interactions should be considered for all NMEs, in vivo drug interaction studies are not necessary for all NMEs. One should consider the potential for drug interactions within the context of a drug's pharmacokinetic properties, intended clinical use, and known safety and efficacy.

This chapter provides an overview of considerations when evaluating the potential for an NME to interact with other drugs. The topics covered include

Timing of drug interaction evaluations during drug development
In vitro drug metabolism studies
In vitro drug transporter studies
When in vivo drug interaction studies are necessary
In vivo study design issues

In vivo drug interaction cocktail studies
Interpretation of in vivo study results
Labeling issues
Considerations for interactions with pharmacokinetically enhanced protease inhibitors
Other considerations

18.2 Timing of Drug Interaction Evaluations During Drug Development

The effect of an NME on the pharmacokinetics of other drugs and the effects of other drugs on the pharmacokinetics of an NME should be determined early in drug development so the clinical implications can be assessed adequately in clinical studies. Because suboptimal concentrations of anti-infective and antiviral drugs can lead to treatment failure and drug resistance, it is helpful to have some knowledge of the potential for drug interactions before these drugs are administered to patients. If drug interaction information is not available when studies in patients begin, it is important to restrict the use of concomitant medications. The restriction of concomitant medications may be acceptable in studies of the treatment of some infections of short duration, such as otitis media or uncomplicated influenza. However, some infections, such as HIV and tuberculosis, require long-term combination therapy. As a general rule, the evaluation of the potential for drug interactions should be adequate to allow the safe conduct of each phase of development. Thus, if a proposed treatment for HIV can be administered as monotherapy to a group of HIV-infected patients for 10 days, drug interaction information is not needed prior to the conduct of a 10-day monotherapy study. However, investigators need drug interaction information prior to administering a drug as part of combination therapy to HIV infected patients.

18.3 Considerations for In Vitro Drug Metabolism Studies

In vitro drug metabolism studies can play a powerful role in the assessment of drug interactions, acting as a screening tool. Goals of in vitro drug metabolism studies are to identify the major metabolic pathways that affect the NME and its metabolites, including the specific enzymes involved; and to determine the effects of the NME on drug metabolizing enzymes. When these goals are met it is possible to prioritize the conduct of in vivo drug interaction studies. For example, if in vitro drug metabolism studies indicate that an NME is not metabolized by CYP3A, it is not necessary to determine the effect of in vivo CYP3A inhibitors or inducers on the NME. Likewise, if in vitro drug metabolism studies indicate an NME is not a CYP3A inhibitor or inducer, it is not necessary to determine the in vivo effect of the drug on CYP3A substrates. A PhRMA position paper acknowledges the importance of in vitro studies that provide the negative findings described above [9]. The in vitro

studies may provide the only information regarding the lack of an interaction with a specific enzyme. As such, it is essential that data in support of these negative findings be obtained using methods supported by the most up-to-date scientific data, and the methodology should be well documented for submission to regulatory authorities [9]. Important considerations for all in vitro drug metabolism studies are the model system, probe drugs (substrates, inhibitors), drug concentrations, tissue handling, and study conditions [3, 9].

A full in vitro drug metabolism program can provide a large amount of information regarding the potential for drug interactions with an NME. Studies conducted to determine what enzymes metabolize a drug include general experiments that identify the types of metabolites formed, followed by more specific experiments that identify enzymes that metabolize the drug. If the available data indicate that CYP enzymes contribute to a drug's clearance, studies to identify drug metabolizing CYP enzymes in vitro are important. Relevant CYP enzymes for evaluation are CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A [3, 10, 11]. If in vivo ADME studies indicate glucuronidation is an important metabolic pathway for a drug, in vitro studies can determine which UGT isoforms are responsible for metabolism [10].

An NME may inhibit or induce CYP-mediated drug metabolism, even if the drug is not metabolized by the enzyme. Most drug interaction programs include an in vitro evaluation of the potential to inhibit and induce CYP enzymes. The studies should use human materials or recombinant human materials to provide reliable information about the potential for interactions in humans [10, 11].

18.4 Considerations for In Vitro Drug Transporter Studies

Numerous transporters play a role in permeability across the gastrointestinal tract, penetration of the blood–brain barrier, and transport into the liver and kidney cells. Interactions can occur at any of the sites [12]. Thus, information about interactions with drug transporters can aid in the prediction and identification of drug interactions. The contribution of drug transporters to absorption and disposition of drugs and to drug interactions was first appreciated for P-gp. As explained in the 2010 report from the International Transporter Consortium, many other drug transporters are involved in drug interactions [6]. In order to gain a full appreciation for the potential drug interactions with an NME, it is important to conduct in vitro studies to determine whether it is a substrate for P-gp or breast cancer resistance protein (BCRP). If hepatic or biliary secretion is a major elimination pathway for the drug, it is important to conduct in vitro studies to determine whether it is a substrate for organic anion transporting polypeptide 1B1 or 1B3 (OATP1B1, OATP1B3). If the drug undergoes active renal secretion, it is important to conduct in vitro studies to determine whether it is a substrate for organic cation transporter 2 (OCT2) or organic anion transporter 1 or 3 (OAT1, OAT3) [6, 10, 13]. Most NMEs have the potential to be administered with a wide range of other drugs, so it is important to

conduct in vitro studies to determine whether an NME is an inhibitor of relevant transporters (P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3) [6, 10].

18.5 When In Vivo Drug Interaction Studies Are Necessary

18.5.1 The Effect of Other Drugs on the NME

In vitro drug metabolism, in vitro drug transport, and in vivo pharmacokinetic information help determine whether formal in vivo drug interaction studies are needed. The first consideration is the contribution of renal and metabolic pathways to in vivo clearance. If metabolism does not contribute to clearance, there is usually no need to conduct metabolism based drug interaction studies. As indicated in Fig. 18.1, if a particular enzyme contributes significantly to elimination, in vivo studies with inhibitors and inducers of that enzyme are recommended. An efficient approach is to first evaluate the effects of a potent inhibitor and a potent inducer; examples are ketoconazole and rifampin, respectively, if the NME is a CYP3A substrate. If the potent inhibitor and inducer do not have a significant effect on the drug, no further studies are needed for that enzyme. Figure 18.1 indicates factors to consider if the potent inducer or inhibitor has a significant effect on the drug [3, 11, 14].

If in vitro study results indicate the NME is a substrate for P-gp or BCRP, the potential contribution of the transporter-mediated pathway should be considered in order to determine whether an in vivo interaction study is needed. For example, an

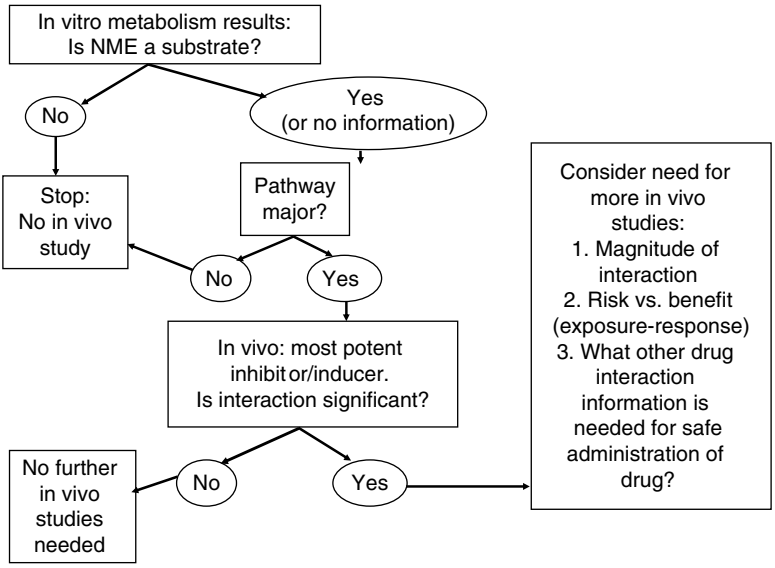

Fig. 18.1 Decision tree for NME as a substrate for CYP enzymes

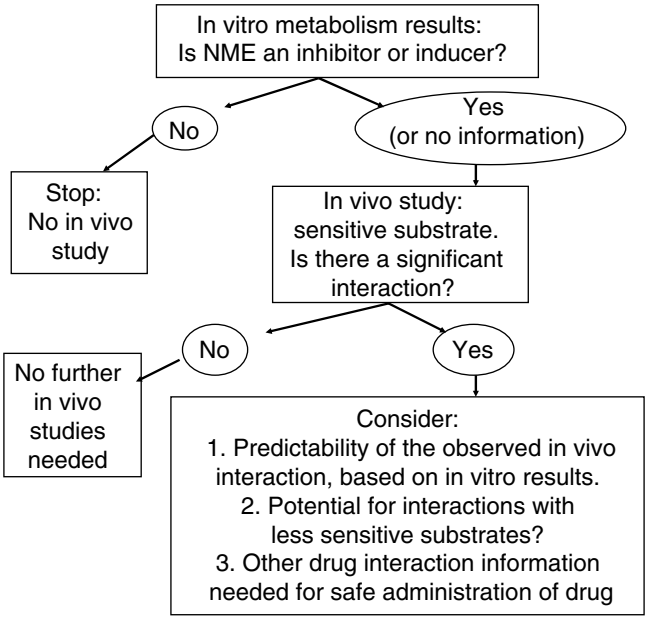

Fig. 18.2 Decision tree for NME that is an inhibitor or inducer of CYP enzymes

NME that has poor solubility, low permeability, and undergoes minimal metabolism may be significantly affected by an inhibitor, so an in vivo interaction study with an inhibitor is important. If an in vitro study is considered important for the NME as a potential substrate for OATP1B1, OATP1B3, OCT2, OAT1, or OAT3 and the in vitro study indicates the NME is a substrate for a transporter, an in vivo interaction study with an inhibitor of the transporter can provide important information [6].

18.5.2 NME as a Potential CYP Inhibitor

As indicated in Fig. 18.2, if in vitro evidence does not rule out the possibility that a drug is a metabolic inhibitor, in vivo interaction studies should be conducted. Significant enzyme inhibition is expected when the concentration of the inhibitor present at the active site is similar to or greater than Ki (dissociation constant of the enzyme-inhibitor complex; defines the affinity of the inhibitor for the enzyme). In theory, the magnitude of the interaction (percent increase in AUC) can be expressed quantitatively as the following equation-

$$R = 1 + [I]/\,Ki,$$

where R is the percent increase in AUC and [I] is the concentration of the inhibitor (NME) present at the active site of the enzyme [9]. The ratio of [I]/Ki is often used

Table 18.1 Factors that affect [I] and Ki

Factors that affect [I]	Factors that affect Ki
1. Uncertainty regarding the concentration that best represents the concentration at the enzyme binding site (unbound plasma concentration, total plasma concentration, hepatic cytosol concentration)	1. Substrate specificity (mainly a problem with CYP3A, degree of inhibition of one substrate may not predict degree of inhibition of another substrate for the same enzyme)
2. Uncertainty regarding the impact of first pass exposure (hepatic and intestinal)	2. Binding to components of the in vitro incubation system
	3. Substrate and inhibitor depletion during the in vitro experiment

to predict the likelihood of an in vivo interaction. However, there are a number of limitations to the use of [I]/Ki as a predictor of in vivo inhibition. The limitations are due to factors that affect interpretation of [I] and Ki, as outlined in Table 18.1 [9].

The second two factors that affect Ki emphasize the importance of good in vitro study design and conduct. Both lists reiterate the fact that the [I]/Ki ratio is not exact enough to predict the degree of inhibition in vivo.

With the listed limitations in mind, [I]/Ki can be used as a screening tool to determine whether an in vivo interaction study is needed. When calculating [I]/Ki, [I] represents the mean steady-state C_{max} value for total drug (bound plus unbound) following administration of the highest proposed clinical dose. The 2006 draft drug interaction guidance recommends that an in vivo interaction study be conducted if the ratio is ≥0.1 [3].

If in vitro studies indicate the NME may inhibit an enzyme, an informative approach is to conduct an in vivo interaction study with a sensitive substrate for the enzyme, such as midazolam or buspirone for CYP3A [3]. It is acceptable to use any sensitive substrate for the enzyme being evaluated, if the potential increase in concentrations due to inhibition will not lead to safety concerns. If there is no interaction with a sensitive substrate, no further inhibition studies are needed for that enzyme. However, if coadministration of the NME results in an increase in plasma concentrations of a sensitive substrate, further studies with less sensitive substrates may be informative.

To prioritize in vivo drug interaction studies, it is reasonable to consider the potential for in vivo inhibition in rank order across the different CYP enzymes. For example, consider an NME with the following in vivo and in vitro characteristics:

$$\text{In vivo } C_{max} = 0.2\ \mu\text{M}\left(\text{use as } [\text{I}]\right)$$

$$\text{CYP3A} - \text{Ki} = 0.33\ \mu\text{M};\ [\text{I}]/\text{Ki} = 0.6$$

$$\text{CYP2D6} - \text{Ki} = 1.0\ \mu\text{M};\ [\text{I}]/\text{Ki} = 0.2$$

$$\text{CYP2C9} - \text{Ki} = 2.0\ \mu\text{M};\ [\text{I}]/\text{Ki} = 0.1$$

It is acceptable to conduct the in vivo studies in ascending order of [I]/Ki. If the NME interacts with a sensitive CYP3A substrate and increases its AUC, a study with a CYP2D6 substrate is needed. If there is no interaction with the CYP2D6 substrate, there is no need to conduct an in vivo inhibition study with a CYP2C9 substrate. The above scenario is altered if metabolites also inhibit CYP enzymes. In such a case, the rank order needs to consider the effects of the NME and metabolites on other drugs.

Because of the limitations related to [I] and Ki (Table 18.1), the [I]/Ki approach is considered very conservative. As a conservative approach, it is a good screening method. If $[I]/Ki < 0.1$, the likelihood of a significant in vivo interaction is low. However, if $[I]/Ki \geq 0.1$, physiologically based pharmacokinetic (PBPK) modeling can provide more information about the need for an in vivo drug interaction study. The PBPK approach may provide a more reliable estimate of the likelihood of in vivo inhibition because the approach considers multiple drug-related and physiological factors. The PBPK approach requires more information than the [I]/Ki approach, including concentration vs time profiles for the parent drug and any metabolites that inhibit the enzyme under evaluation. The inhibition Ki for the metabolites is also needed [8].

18.5.3 NME as Potential CYP Inducer

Enzyme induction can lead to lack of efficacy, which is an important safety issue for patients taking anti-infective and anti-viral agents. There are several different approaches for interpreting in vitro enzyme induction data and determining whether an in vivo study is needed. The in vitro studies are conducted with human hepatocytes (fresh or cryopreservered) and the typical endpoints are changes in enzyme activity or mRNA of the target gene [9, 15]. The 2006 draft guidance states that induction of enzyme activity to at least 40% of the positive control induction level indicates a positive inductive response [3, 9]. A newer approach is to use an increase in mRNA greater than a predefined threshold level (such as four-fold). The new approach may lead to less false negative results (conclude no induction, but there is induction) than the previous 40% threshold for enzyme activity [15]. If there are no in vitro data, or if in vitro data indicate an NME may be an enzyme inducer, in vivo interaction studies should be conducted. It is important that the potential for induction of CYP1A2, CYP2B6, and CYP3A be evaluated. CYP2C8, 2C9 and 2C19 are co-induced with CYP3A, so a negative result for CYP3A indicates studies with CYP2C are not needed [10].

18.5.4 NME as a Potential Transporter Inhibitor

The in vitro IC_{50} value of the NME for the transporter under consideration helps determine whether an in vivo study is needed. The IC_{50} value indicates inhibition

potency (lower value indicates greater potency). Orally administered drugs that inhibit the efflux inhibitors P-gp or BCRP in vitro may inhibit efflux from the intestine or from tissue. $[I]_1$ (NME mean steady state Cmax at highest administered dose) and $[I]_2$ (theoretical maximal gastrointestinal NME concentration; highest clinical dose in mg in a volume of 250 mL) are used to determine the need for an in vivo study. If $[I]_1/IC_{50} \geq 0.1$ or $[I]_2/IC_{50} \geq 10$, the NME should be evaluated to determine whether the drug is an inhibitor in vivo [6, 16].

The determination of the need for in vivo studies of the NME as a potential inhibitor of OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 considers the unbound steady-state C_{max} of the NME at the highest dose and the in vitro IC_{50} of the NME for the transporter. If unbound $C_{max}/IC_{50} \geq 0.1$, an in vivo interaction study with a sensitive substrate for the transporter is important. There is an additional consideration for OATP1B1 and OATP1B3 because the clinically relevant substrates for the OATPs are HMG-CoA reductase inhibitors (statins). If the NME is predicted to increase the AUC or Cmax of a relevant statin (such as rosuvastatin or pravastatin) by 100%, an in vivo interaction study with a sensitive substrate is relevant [6].

18.6 In Vivo Study Design Issues

18.6.1 General Design Issues

In vivo drug interaction studies are designed to compare substrate concentrations with and without the interacting drug. The appropriate study design varies, depending on the specific objective of the study and the characteristics of the drugs [3, 14]. The inhibiting/inducing drug and the substrates should be dosed so that the exposure is relevant to their clinical use. A randomized crossover design is often preferred, because the interaction can be evaluated in each individual subject and the design controls for sequence effect. However, a parallel design is acceptable for drugs with long elimination half-lives, to decrease the chance of carryover from one treatment to the next. A one-sequence crossover study is acceptable when both drugs are administered chronically. The choice of single or multiple dose administration for each drug is based on the clinical use of the drug and the ability to extrapolate to the clinically relevant situation.

18.6.2 Selection of Study Population

Drug interaction studies are often conducted in healthy volunteers because there are less confounding factors that may alter pharmacokinetics. In some cases, safety concerns may preclude the use of healthy volunteers. If the study enrolls healthy volunteers, it is important to consider whether there are factors that may impede

Table 18.2 Selection of study population

Study objective	Population
Answer scientific question: "Does NME inhibit CYP3A in vivo?"	Healthy volunteers provide the least complicated evaluation.
Determine whether a dose adjustment is needed when the NME is administered with another drug, but a dose adjustment will not be incorporated into the study.	Either population is acceptable, but healthy volunteers may be easier to study.
Determine the appropriate dose adjustment for the NME or other drug when the two are coadministered	It is most appropriate to conduct the study in patients. If prior knowledge indicates that the pharmacokinetics of both drugs are similar in healthy volunteers and patients, then either population may be used. Also, if the study may result in subtherapeutic concentrations of the HIV drug for a prolonged period of time, it is best to conduct the study in healthy volunteers.

extrapolation to the relevant patient population. For some antibiotics, the relevant patient population is quite similar to healthy volunteers; thus, extrapolation across the population is not an issue. The situation may be more complex for HIV drugs. There are cases where pharmacokinetic parameters are similar for HIV-infected patients and healthy volunteers; however, differences have been documented for some drugs, including saquinavir [17] and atazanavir [18]. The differences may be due to decreased absorption in HIV patients, differences in metabolism, or the presence of concomitant medications. There is some evidence that CYP3A activity is more variable in patients infected with HIV [19], which is important because of the contribution of CYP3A to protease inhibitor and non-nucleoside reverse transcriptase inhibitor metabolism. In the face of differences between healthy volunteers and the relevant patient population, one should consider the objective of the study when selecting the study population (Table 18.2).

When drug interaction studies are conducted in healthy volunteers and there is a question regarding the applicability to the relevant population, sparse sampling in clinical efficacy trials that include patients taking the two drugs can be useful [3, 20].

18.6.3 Choice of Interacting Drugs

It is appropriate to conduct interaction studies with probe inhibitors and substrates, to demonstrate the in vivo magnitude of interactions with a specific enzyme. If a study with a probe inhibitor or substrate indicates the drug may significantly affect other drugs (inhibition or induction) or may be affected by other drugs, the next step is to consider several factors-

- Important drugs in the target population that may interact
- Narrow therapeutic index drugs that may be affected

- Relevant potent enzyme inhibitors or inducers that may affect the NME
- Commonly used drugs that may interact

The above criteria can help guide the conduct of further interaction studies. In each case, it is important to consider the worst-case scenario (maximum magnitude of interaction) and use knowledge of exposure-response relationships (safety and efficacy) to determine the need for specific interactions. In some cases, it may be appropriate to not study a combination, but recommend the drugs not be coadministered, if the combination is likely to result in excessive or subtherapeutic concentrators and a dose adjustment is not possible.

18.6.4 Analytes Measured in Drug Interaction Studies

The objective of a drug interaction study and the characteristics of the metabolites dictate whether it is necessary to measure parent drug, metabolite(s), or both. When the substrate drug has an active or toxic metabolite, the metabolite usually should be measured. In cases where the metabolites are not active, measuring some metabolites may help explain the mechanism of an interaction.

The HIV nucleoside reverse transcriptase inhibitors (NRTIs) present a unique drug interaction issue. A majority of the NRTIs do not undergo extensive metabolism in the plasma. However, all of the NRTIs undergo anabolic phosphorylation by intracellular kinases to form the active triphosphates that competitively inhibit viral reverse transcriptase [21]. Most HIV treatment regimens include one or two NRTIs, in addition to drugs from other classes. In some cases the combination of two NRTIs may interfere with the intracellular phosphorylation of at least one of the compounds, even though no interaction is observed in the plasma. Knowledge of the enzymes that catalyze phosphorylation for two NRTIs help determine whether an interaction is likely. For example, the same enzyme catalyzes phosphorylation of zidovudine and stavudine, and coadministration of the two NRTIs leads to reduced formation of stavudine triphosphate [21]. Knowledge of phosphorylation pathways, in addition to in vitro combination studies, helps determine whether two NRTIs may interact with one another. If an interaction is possible, a drug interaction study that evaluates intracellular triphosphate concentrations should be conducted prior to administering the two drugs together in clinical trials. These interaction studies are more difficult than interaction studies that evaluate the parent drug in plasma. The studies that evaluate intracellular triphosphate concentrations are affected by cellular kinase activity, exposure to the enzyme, and difficult analytic techniques.

18.7 In Vivo Drug Interaction Cocktail Studies

Cocktail studies involve the administration of two or more probe substrates for different enzymes (cocktail) to characterize changes in pharmacokinetics when the study drug is administered [22–25]. If adequate data indicate that the probe

substrates are sensitive and do not interact with one another across a wide range of concentrations, the study design is acceptable, and the sample size provides adequate power, the results of a cocktail study can serve as stand-alone evidence that an interaction will not occur. Thus, the cocktail studies are useful if in vitro studies are not conducted or if in vitro results are not definitive. If a cocktail study indicates that an interaction is likely, it is typically necessary to conduct additional in vivo studies with substrates of the affected enzyme [3, 10, 11].

18.8 Interpretation of In Vivo Study Results

The 2006 draft drug interaction guidance includes an extensive discussion of the interpretation of in vivo drug interaction study results [3]. Most studies evaluate pharmacokinetic endpoints, such as the exposure measures AUC and C_{max}. For many anti-infective and antiviral drugs trough concentration (C_{min}) is an important exposure measure.

The results of drug interaction studies should be reported as 90% confidence intervals around the geometric mean ratio of the pharmacokinetic measure of the substrate with and without the interacting drug [26]. Confidence intervals are informative because they provide an estimate of the distribution of the change in exposure to the substrate drug [3]. After the 90% confidence interval of the effect is determined, the clinical significance must be determined. Knowledge regarding no-effect boundaries for the substrate drug aid interpretation of interaction study results. No effect boundaries define the interval within which a change in systemic exposure measure is considered not clinically meaningful [3]. No-effect boundaries can be based on dose or concentration-response relationships for the substrate drug. For example, consider an NME that was evaluated at doses ranging from 50 to 400 mg once daily, all doses were safe and well tolerated, but 200 mg once daily was selected because it was on the plateau of the dose–response curve. In this case, an interacting drug that doubles the systemic exposure to the NME is not a concern, because concentrations associated with double the dose (assuming dose proportional pharmacokinetics) were safe.

18.9 Labeling Issues

The 2006 draft guidance on drug interactions indicates that all relevant information on the metabolic pathways and pharmacokinetic interactions should be included in the PHARMACOKINETICS subsection of the CLINICAL PHARMACOLOGY section of the label [3]. The clinical consequences of metabolism and drug interactions should be included in DRUG INTERACTIONS, WARNINGS and PRECAUTIONS, CONTRAINDICATIONS, or DOSAGE and ADMINISTRATION

sections, as appropriate. The information should be of sufficient detail to allow health care providers to provide adequate instructions to patients.

In certain cases, information can be extrapolated from one drug interaction study to another set of drugs, with an explanation that similar results are expected. For example, if a drug is a strong inhibitor of CYP3A, it does not need to be tested with all CYP3A substrates to warn about an interaction with sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic range. For example, the Viracept label indicates that nelfinavir is a CYP3A inhibitor that increases simvastatin plasma concentrations by approximately 500% [27]. Because the mechanism of the interaction is stated, the reader can assume that coadministration of nelfinavir with lovastatin would result in an interaction of a similar magnitude, because lovastatin is a CYP3A substrate with similar presystemic metabolism as simvastatin [28].

The DRUG INTERACTION section can include a brief summary of potential mechanisms of drug interactions. It can also list mechanisms that have been excluded. It is important to list mechanisms that have not been studied. This section includes a description of clinically significant interactions and practical instructions for preventing or managing them. The interactions may be observed in drug interaction studies or predicted based on known mechanisms. Recommendations for dose adjustments of coadministered drugs are included in this section. Interactions mentioned in DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS can be discussed in more detail in this section. This section does not include details of drug interactions studies, but instead includes a cross-reference to the information in the CLINICAL PHARMACOLOGY section.

The drug interaction portion of the PHARMACOKINETICS subsection includes a summary of drug interactions studies conducted with the drug. The information may be included as text or in a table or figure, depending on the number of studies and level of detail needed for clarity. It is important to include information that helps prevent misinterpretation of the study results. Relevant study information includes parallel or crossover design, number of subjects, population studied (patients or healthy volunteers), and dose and duration for each drug. The results should be presented as the change in relevant pharmacokinetic exposure measures (AUC, C_{max}, C_{min}, T_{max}). The relevance of different exposure measure varies for different drugs and drug classes. It is important to indicate the variability of the interaction. Results should be presented as mean change and the 90% confidence interval around the mean change. For example, a 48% percent increase in AUC can be expressed as ↑48% (90%CI: ↑24%, ↑76%).

The PHARMACOKINETIC subsection should cross-reference other sections of the label that provide clinical instructions, dose adjustments, warning or precautions, or contraindications based on the drug interaction studies.

It is acceptable to include statements in the DRUG INTERACTION, PRECAUTIONS and WARNINGS, and CONTRAINDICATIONS sections of the label for interactions that are expected due to known mechanisms of interactions, even if the specific drug interaction information is not available. Some examples are shown in Table 18.3.

Table 18.3 Examples: drug interaction information in labels, not based on a drug interaction study

Drug label	Label section and example of information	Basis for inclusion of information in label
All protease inhibitors [17, 18, 27, 29–34]	CONTRAINDICATIONS – Pimozide	The protease inhibitors inhibit CYP3A. Pimozide metabolism is highly dependent on CYP3A, and elevated pimozide concentrations could lead to serious and life-threatening events.
All protease inhibitors [17, 18, 27, 29–34]	CONTRAINDICATIONS or WARNINGS and PRECAUTIONS – Recommend against coadministration with St. John's wort, because protease inhibitor concentrations may decrease and lead to loss of virological response.	St. John's wort induces CYP3A. Induction of CYP3A affects all protease inhibitors. Data are available for indinavir and St. John's wort.
Kaletra® (lopinavir/ritonavir) [31]	PRECAUTIONS – Coadministration of Kaletra and itraconazole may lead to increased itraconazole concentrations. High doses of itraconazole are not recommended in combination with Kaletra.	Coadministration of Kaletra and ketoconazole leads to increased ketoconazole concentrations. CYP3A mediated interactions are often similar for ketoconazole and itraconazole.

18.10 Considerations for Interactions with Pharmacokinetically Enhanced Protease Inhibitors

The addition of a low dose of ritonavir to a protease inhibitor regimen can increase concentrations and decrease elimination rate of the protease inhibitor. This practice is known as pharmacokinetic enhancement or ritonavir-boosting. If a protease inhibitor (or other drug) is always administered with ritonavir, drug interaction studies need to include ritonavir.

18.10.1 Extrapolation Across Pharmacokinetically Enhanced Regimens

It is well accepted that much of the effect of ritonavir on other protease inhibitors is due to ritonavir's potent inhibition of CYP3A [35]. Some investigators assume that ritonavir will dominate the drug interaction potential of ritonavir-boosted regimens, so the effect will be similar across all regimens that include ritonavir

100 mg twice daily (or across all regimens that include ritonavir 100 mg once daily, or ritonavir 200 mg once daily). However, this assumption has not been validated by data. In addition, the available scientific literature indicates that interactions may not be similar across all regimens that include the same ritonavir dosing regimen. Interactions with ritonavir are complicated because ritonavir inhibits enzymes other than CYP3A and it induces several enzymes, including CYP3A. Ritonavir induces CYP3A due to its activation of the pregnane X receptor (PXR) [36]. In addition to CYP3A, PXR regulates expression of CYP2B, CYP2C, and numerous transporters [37, 38]. The effect of ritonavir on other drugs is a complex interplay of inhibition plus induction of numerous enzymes and transporters. It is difficult to predict the net effect of ritonavir-boosted regimens without an in vivo study because the effect on enzymes and transporter is not consistent across the other protease inhibitors. Thus, it is not possible to conclude that drug interactions will be consistent across ritonavir-boosted regimens that include the same ritonavir dose.

18.11 Other Considerations

18.11.1 Interactions via Mechanisms Other Than Drug Metabolism

Although most discussions of drug interactions focus on drug metabolism and drug transporters, it is important to remember that there are other mechanisms of drug interactions. Ruling out the potential for drug metabolism or drug transporter related interactions does not mean there will not be significant interactions with the drug. Pharmacokinetic drug interactions may involve alterations in absorption, transport, distribution, metabolism, or excretion of a drug- or a combination of these factors. When developing an NME, it is important to consider all mechanisms of drug interactions.

18.11.2 Interactions with Dietary Supplements and Dietary Components

Drugs can interact with dietary supplements (St. John's wort, garlic, echinacea), citrus fruit juices (grapefruit juice, Seville orange juice), alcohol, and other food components (cruciferous vegetables, charbroiled meat) in the same way they interact with other drugs [39, 40]. These interactions can lead to therapeutic failure or adverse events. It is important to recognize the potential for such interactions, understand the science behind the interactions, and make appropriate recommendations in product labels.

18.11.3 Role of Genetic Polymorphisms

There is genetic variability in the activity of a number of drug metabolizing enzymes, including CYP2D6, CYP2C9, and CYP2C19 [41]. Due to the variability, patients may be categorized as poor metabolizers, extensive metabolizers, or ultrarapid extensive metabolizers for the various enzymes. The magnitude of a metabolism based drug interaction varies, depending on the individual's baseline enzyme activity. For example, inhibition of CYP2D6 will not have much effect on a CYP2D6 poor metabolizer. Thus, it is important to know the metabolic phenotype of individuals included in a drug interaction study.

18.12 Summary

Scientists in regulatory agencies, drug industry, and academia are interested in the impact of drug interactions on the safety and efficacy of drugs. The specific objectives of a drug interaction program are to determine whether there are any interactions with an NME (new molecular entity) that necessitate a dose adjustment of the NME or other drugs that it might be used with, or whether an interaction requires a contraindication or special precautions.

The effect of an NME on the pharmacokinetics of other drugs and the effects of other drugs on the pharmacokinetics of an NME should be determined early in drug development so the clinical implications can be assessed adequately in clinical studies. The drug interaction program can include in vitro and in vivo evaluations. Throughout the evaluation of drug interactions, it is important that all studies are conducted using scientifically accepted procedures. The clinical significance of any observed interactions should be assessed based on exposure-response knowledge of the affected drug. Finally, the drug labels need to include complete information about the potential for drug interactions, including instructions for dose adjustments and special monitoring or precautions.

References

1. Senior K. FDA panel rejects common cold treatment. Lancet Infect Dis 2002;2:264.
2. Hayden FG, Herrington DT, Coats TL, Kim K, Cooper EC, Villano SA, Liu S, Hudson S, Pevear DC, Collett M, McKinlay M. Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of double-blind, randomized, placebo-controlled trials. Clin Infect Dis 2003;33:1523–1532.
3. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Drug interaction studies- study design, data analysis, and implications for dosing and labeling (September 2006). Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry.

4. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Drug metabolism/drug interaction studies in the drug development process: studies in vitro (April 1997). Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry.
5. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: In vivo drug metabolism/drug interaction studies—study design, data analysis, and recommendations for dosing and labeling (November 1999). U.S. Department of Health and Human Services, Food and Drug Administration.
6. Giacomini KM, Huang SM, Tweedie DJ, et al. Membrane transporters in drug transport. Nat Rev Drug Discov 2010;9:215–236.
7. Rostami-Hodjegan A, Tucker GT. Simulation and prediction of in vivo drug metabolism in human populations from in vitro data. Nat Rev Drug Discov 2007;6:140–148.
8. Zhao P, Zhang L, Grillo JA, et al. Applications of physiologically-based pharmacokinetic (PBPK) modeling and simulation during regulatory review. Clin Pharmacol Ther 2011;89: 259–267.
9. Bjornsson TD, Callaghan JT, Einolf HJ, et al. The conduct of in vitro and in vivo drug-drug interaction studies: A Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. Drug Metab Disp 2003;31:815–832.
10. Zhang L, Reynolds KS, Zhao P, Huang SM. Drug interaction evaluation: an integrated part of risk assessment of therapeutics. Tox Appl Pharmacol 2010;243:134–145.
11. Huang SM, Strong JM, Zhang L, et al. New era in drug interaction evaluations: US Food and Drug Administration update on CYP enzymes, transporters, and the guidance process. J Clin Pharmacol 2008;48:662–670.
12. Ayrton A, Morgan P. Role of transport proteins in drug absorption, distribution and excretion. Xenobiotica 2001;31:469–497.
13. Huang SM, Woodcock J. Transporters in drug development: advancing on the Critical Path. Nat Rev Drug Discov 2010;9:175–176.
14. Huang SM, Temple R, Throckmorton DC, Lesko LJ. Drug interaction studies: study design, data analysis, and implications for dosing and labeling. Clin Pharmacol Ther 2007;81:298–304.
15. Fahmi OA, Kish M, Boldt S, Obach RS. Cytochrome P450 3A4 messenger RNA is a more reliable marker than CYP3A4 activity for detecting PXR-activated induction of drug-metabolizing enzymes. Drug Metab Dispos 2010;38:1605–1611.
16. Zhang L, Zhang Y, Strong JM, Reynolds KS, Huang SM. A regulatory viewpoint on transporter-based drug interactions. Xenobiotica 2008;38:709–724.
17. Saquinavir (Invirase), product information, Genentech USA, Inc., South San Francisco, CA, 2010.
18. Atazanavir (Reyataz) product information. Bristol Myers Squibb, Princeton, NJ, 2010.
19. Slain D, Pakyz A, Israel DS, Monroe S, Polk R. Variability in activity of hepatic CYP3A4 in patients infected with HIV. Pharmacotherapy 2000;20:898–907.
20. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry population pharmacokinetics (February 1999). U.S. Department of Health and Human Services, Food and Drug Administration.
21. Stein DS and Moore KHP. Phosphorylation of nucleoside analog antiretrovirals: a review for clinicians. Pharmacotherapy 2110;21:11–34.
22. Frye RF, Matzke GR, Adedoyin A, Porter JA, Branch RA. Validation of the five-drug "Pittsburgh cocktail" approach for assessment of selective regulation of drug-metabolizing enzymes. Clin Pharmacol Ther 1997;62:365–376.
23. Christensen M, Andersson K, Dalen P, Mirghani RA, Muirhead GJ, Nordmark A, Tybring G, Wahlberg A, Yasar U, Bertilsson L. The Karolinska cocktail for phenotyping of five human cytochrome P450 enzymes. Clin Pharmacol Ther 2003;73:517–528.
24. Chainuvati S, Nafziger AN, Leeder JS, Gaedigk A, Kearns GL, Sellers E, Zhang Y, Kashuba ADM, Rowland E, Bertino JS. Combined phenotypic assessment of cytochrome P450 1A2,

2C9, 2C19, 2D6, and 3A, N-acetyltransferase-2, and xanthine oxidase activities with the "Cooperstown 5 + 1 cocktail". Clin Pharmacol Ther 2003;74:437–447.
25. Blakey GE, Lockton JA, Perrett J, Norwood P, Russell M, Aherne A, Plume J. Pharmacokinetic and pharmacodynamic assessment of a four-probe metabolic cocktail for CYPs 1A2, 3A4, 2 C9, 2D6, and 2E1. Br J Clin Pharmacol 2004;57:162–169.
26. Schuirman DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the bioequivalence of average bioavailability. J Pharmacokinet Biopharm 1987;15: 657–680.
27. Nelfinavir (Viracept) product information, Agouron Pharmaceuticals, La Jolla, CA, 2010.
28. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. Clin Pharmacokinet 2002;41:343–370.
29. Ritonavir (Norvir), product information, Abbott Laboratories, North Chicago IL, 2010.
30. Indinavir (Crixivan) product information. Merck & Co, Inc, Whitehouse Station, NJ, 2010.
31. Lopinavir/ritonavir (Kaletra) product information. Abbott Laboratories, North Chicago, IL, 2010.
32. Fosamprenavir (Lexiva) product information. GlaxoSmithKline, Research Triangle Park, NC, 2010.
33. Tipranavir (Aptivus) product information. Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, 2010.
34. Darunavir (Prezista) product information. Tibotec, Raritan, NJ, 2010.
35. Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. J Antimicrob Chemother 2004;53:4–9.
36. Luo G, Cunningham M, Kim S, et al. CYP3A4 induction by drugs: correlation between pregnane X receptor reporter gene assay and CYP3A4 expression in human hepatocytes. Drug Metab Disp 2002;30:795–804.
37. Wang H, LeCluyse EL. Role of orphan nuclear receptors in the regulation of drug-metabolizing enzymes. Clin Pharmacokinet 2003;42:1331–1357.
38. Handschin C, Meyer UA. Induction of drug metabolism: the role of nuclear receptors. Pharmacol Rev 2003;55:649–673.
39. Huang SM, Hall SD, Watkins P, et al. Drug interactions with herbal products and grapefruit juice: a conference report. Clin Pharmacol Ther 2004;75:1–12.
40. Harris RZ, Jang GR, Tsunoda S. Dietary effects on drug metabolism and transport. Clin Pharmacokinet 2003;42:1071–1088.
41. Rogers JF, Nafziger AN, Bertino JS. Pharmacogenetics affects dosing, efficacy, and toxicity of cytochrome P450-metabolized drugs. Am J Med 2002;113:746–750.

Chapter 19
Probe Cocktail Studies

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Abstract The conduct of drug interaction studies was revolutionized by the ability to evaluate more than one potential drug-drug interaction (DDI) within a single study. Cocktail studies provide a means to screen for DDIs through multiple metabolic pathways within a single study. Usually conducted in healthy volunteers, these studies use concurrent administration of probe substrates and assessment of biomarkers to simultaneously assess drug metabolizing enzyme (DME) activities before (baseline) and during drug treatment. Evaluation of DME can be for effect of a drug on constitutive DME or to evaluate the effect of an inhibitor or inducer on the pharmacokinetics and pharmacodynamics of the DME pathway of the drug in question. Studies should be designed with the use of safe, validated probes and published, validated cocktails. Advantages of using cocktail studies in drug development include reduced subject variability, increased efficiency, and lower costs. Potential limitations can be addressed by proper study design. Because cocktail studies assess the potential extent of DDIs, inferences for drug dosing and use may be drawn.

Abbreviations

AUC	Area under the concentration time curve
CI	Confidence intervals
C_{max}	Maximum concentration
CYP	Cytochrome P450
DDI	Drug-drug interaction

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DME	Drug metabolizing enzymes
EM	Extensive metabolizer
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
NAT2	N-acetyltransferase 2
PhRMA	Pharmaceutical Research and Manufacturers of America
PM	Poor metabolizer
UM	Ultra-rapid metabolizer

19.1 Purpose and Use of Cocktail Studies

The conduct of drug interaction studies has been revolutionized by the ability to evaluate more than one potential drug-drug interaction (DDI) within a single study. DDI studies were formerly conducted as a group of studies to evaluate the potential of interactions through common or suspected metabolic pathways that were expected to be of clinical significance [1]. Earlier DDI studies primarily used specific, approved drugs with narrow therapeutic indices (e.g., digoxin, phenytoin, theophylline, warfarin) that were likely to be co-administered and for which there could be important clinical consequences. However, these types of studies had significant limitations and were applicable only to the specific drugs studied.

Cocktail studies provide a means to screen for DDIs through multiple metabolic pathways within a single study. A cocktail study is comprised of concurrent administration of probe substrates and assessment of biomarkers to simultaneously assess DME activities before (baseline) and during drug treatment. Evaluation of DME can be for the effect of a drug on constitutive DME (i.e., is the drug under study an inhibitor, inducer or activator?) or to evaluate the effect of an inhibitor, inducer or activator on the pharmacokinetics of the DME pathway for the drug in question. By observing whether changes in activity occur with co-administration of the treatment drug, the mechanistic basis of, and the qualitative potential for, drug interactions can be evaluated.

The most frequent use for cocktail studies is to determine the constitutive activity of defined DMEs and then reevaluate the DME activities after inhibition, activation and/or induction by an investigational drug. Most often, these studies are conducted to evaluate the potential for both inhibition and induction. Cocktail studies are particularly important when there are shared metabolic pathways and the clinically relevant pharmacokinetic DDIs through these pathways are uncertain [2]. At least theoretically, cocktail studies can be used to assess DDIs involving transporter pathways. However, validated probes and biomarkers have not yet been identified for common transporters [3]. This chapter will therefore focus on cocktail studies for assessment of drug metabolizing enzymes (DMEs), but the same principles apply to evaluation of transporter-related DDIs [3] or interactions that result from both DMEs and transporters.

A probe is a substance, typically a drug, that is a selective substrate for a specific DME or a substrate metabolized to a specific metabolite by a specific DME pathway. A biomarker is the metric used to evaluate the DME activity (or phenotype) of the

given probe through the specific enzyme pathway. A variety of pharmacokinetic parameters may be used as biomarkers. These include total area-under-the-concentration time curve ($AUC_{0-\infty}$) and systemic or partial clearance of the probe or a metabolite, or metabolic ratios of a metabolite to the parent compound [4]. Biomarkers may be measured in variety of biologic samples, but are most often measured in serum, plasma or urine.

Cocktail studies are usually conducted in healthy volunteers. It is important to remember that factors in addition to the co-administered drugs can influence DME and such factors are more likely to be present in patients than in healthy volunteers. Examples of these factors include active disease states such as cancer [5], renal, hepatic and cardiac failure [6–8], cytokine levels [9], human immunodeficiency virus infection [10], environmental exposures such as tobacco smoke [11], alcohol consumption [12], fruit juice consumption [13–15], other dietary exposures [16], age (particularly for children less than 1 year of age) [17], and pregnancy [18]. In addition, medical interventions such as hemodialysis can alter DME activity [19]. Therefore, studies conducted in healthy volunteers reflect phenotypes and DDI potential within similar, healthy populations and may not reflect either basal DME activity or the enzyme activity changes that occur in patient populations with acute or chronic health conditions. DDI studies conducted in healthy subjects can potentially describe the worst case scenario since inflammatory disease often results in a reduction in DME activity and thus reduces the potential for inhibitory DDIs [20]. Thus, the extent of an identified DDI may be reduced in a patient or may change over time as the disease is treated or progresses. When studies are conducted in patients, the investigator should not compromise on biomarker sampling; this has been a limitation for application of cocktail studies in the clinical setting.

In drug development, cocktail studies have numerous advantages. First, the effect of interindividual variability in DME over time is minimized by conducting one study in the same subjects rather than five or more studies in different subjects. Second, intraindividual variability is decreased by using subjects as their own controls (and thus controlling for genetic factors) [21, 22]. Third, research costs are reduced by assessing multiple enzyme systems in one study rather than during multiple studies of one enzyme system [2, 23]. Finally, combining the above factors leads to increased efficiency and a compressed timeline for drug development.

There are also potential limitations but these can be addressed by proper study design. DDIs are possible among the probes. If interactions occur, they could result in findings of greater or lesser DME activity changes than those actually related to the actions of the treatment drug. For this reason, it is essential that the combination of probes has been validated as a cocktail. This validation is separate from the work required to validate individual probes and biomarkers, and it should not be assumed that individually validated probes and biomarkers can be combined to make a validated cocktail. Other challenges are a lack of safe probes and limited availability of some probes that are part of validated cocktails. Special requirements may be needed for sample collection and handling, and these special requirements may not be described or readily accessible in the literature, but rather personally known to investigators or laboratories. Lastly, sensitive and specific assays may be lacking for

validated biomarkers. Recent advances in assay methodologies allow for multiple biomarkers to be assayed simultaneously using small specimen quantities [24, 25] and this is increasing the feasibility of conducting cocktail studies. Small quantities of blood can be collected and thereby reduce subject risk while lowering study costs. In order to obtain accurate results, it is essential that individual probes, biomarkers, and each cocktail combination be adequately validated prior to use [2], and that the exact validated cocktail methodology be followed during study conduct [26].

A cocktail study may not completely eliminate requirements for additional DDI studies, but the approach of using cocktail studies prior to more specific definitive studies has been endorsed at a consensus conference that included the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) [27]. Investigators can anticipate that if a significant change in basal DME activity is identified during a cocktail study, the regulatory agency with oversight may require additional specific DDI studies for the investigational drug and other frequently co-administered drugs that are expected to result in clinically significant DDIs. The rationale for requiring specific DDI studies is open to debate since DDIs cannot be quantitatively predicted or used to provide specific dosage adjustments for individual patients [28]. Initial cocktail studies should use the most selective probe substrates that are part of a validated cocktail. If subsequent studies are conducted, other clinically relevant validated probes can be used.

19.2 *In Vitro* Studies and the Conduct of Cocktail Studies

In vitro studies are the first step in prediction of DDIs. The FDA recommends that appropriate *in vitro* screening be done to evaluate whether therapeutic concentrations of an investigational drug are metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A isozymes [29]. Of these, all but CYP2C8 are considered major metabolic pathways [29, 30]. While other CYP enzymes (e.g., CYP2A6, CYP2B6 and CYP2E1) are less frequently involved in clinically important DDIs, they should be considered for study when appropriate. For example, if an investigational new drug is likely to be co-administered with a drug primarily metabolized by CYP2B6, *in vitro* screening for a DDI should be conducted.

The Pharmaceutical Research and Manufacturers of America (PhRMA) published recommendations for conduct of *in vitro* DDI studies [31] that are based on FDA guidance and a joint conference of regulatory and scientific agencies [27]. The recommended study types commonly use pooled human liver microsomes or cDNA-expressed human CYPs and may underestimate or overestimate effects that will occur *in vivo*. Multiple factors influence the accuracy of predicted DDIs from *in vitro* studies. These include probe selection, determination of intrinsic clearance, choice of substrate and inhibitor concentration ranges, effect of organic solvents on enzyme activity, buffering of the system, and whether transcellular transporters are important *in vivo* [32]. Underestimation can occur when hepatic drug concentrations are substantially higher than plasma concentrations after oral drug administration [33]. Because the free fraction of drug is generally responsible for *in vivo* DDIs, DDIs may

be overestimated when *in vivo* plasma or hepatic protein binding is high. In addition, the contribution of an enzyme to the overall metabolic clearance *in vivo* may be either underestimated or overestimated if the metabolic pathway is partially saturated at *in vivo* concentrations such as those found during first pass metabolism [34].

In vitro screening can be used to investigate whether inhibition, activation or induction affects elimination through the DME systems. If screening assays find that an enzyme pathway does not metabolize an investigational drug, then clinical studies to evaluate CYP450 inhibitors or inducers are unlikely to be required by regulatory agencies. The FDA goes so far as to say that if no inhibition or induction is found *in vitro*, then no *in vivo* interaction studies are needed [29]. However, *in vitro* studies may not predict DDI in a number of circumstances. These situations include when induction or activation occur or predominate *in vivo*, measurable plasma concentrations are incorrectly extrapolated to hypothetical concentrations at the site of metabolic activity, the relative contribution of CYP pathways is not accurately known, mechanism-based inactivation takes place, an improper enzyme inhibition model is chosen, interactions occur with transporters rather than DMEs, or CYP inhibitors also affect P-glycoprotein or other transporters [35, 36].

There are numerous examples of *in vitro* screenings that were not predictive of *in vivo* DDIs [35]. Given the possible problems of bias and error with *in vitro* testing, and that not all factors affecting *in vitro-in vivo* correlations may be known, confirmation of presence or lack of *in vivo* DDIs may be desirable even when *in vitro* screening is negative. Also, although some methods are available, *in vitro* screening may be unable to adequately assess the potential for DDIs that occur through enzyme induction [31].

A full discussion of the proper design and application of *in vitro* studies is beyond the scope of this chapter but is discussed at length elsewhere [27, 31, 37, 38]. The PhRMA recommendations give specific study design guidelines to assist investigators in the conduct of *in vitro* studies [31].

19.3 Cocktail Study Methodology

19.3.1 Probes and Biomarkers

Probes, biomarkers and specific cocktail combinations must each be validated. Choosing validated probes and biomarkers is essential for the acquisition of accurate and useful data. Specific recommendations for validation criteria have been published [3, 4, 39, 40]. Probes should be substrates that are specific for the elimination pathway of an individual CYP enzyme in *in vitro* studies [29]. If more than one metabolic pathway is involved in the metabolism of the probe, the second pathway should constitute <10% of the total clearance [39]. Although not required for validation, probes should be safe and commercially available worldwide [4]. Consistent use of validated probes allows for comparison between studies and in different populations.

Biomarkers are the metrics used to assess the metabolism of the probe drug. Biomarkers must be reproducible (i.e., have a low coefficient of variation for

Table 19.1 Validated *in vivo* probe CYP substrates

CYP enzyme	Validated probe substrates
CYP1A2	Caffeine [51–53], theophylline [53]
CYP2B6	Bupropion [54, 55]
CYP2C8	Rosiglitazone [56, 57]
CYP2C9	*(S)*-warfarin[58], tolbutamide [59]
CYP2C19	*(S)*-mephenytoin [60, 61], omeprazole [62–64], lansoprazole [65], [^{13}C]pantoprazole [66, 67]
CYP2D6	Debrisoquine* [40], dextromethorphan [40, 68], desipramine [69]
CYP2E1	Chlorzoxazone [70, 71]
CYP3A	Midazolam (IV ± oral) [45, 46, 72], alfentanil [73–75], felodipine [76], triazolam [77, 78]

*debrisoquine is not available in North America or Asia

repeated tests). The biomarker should reflect known genetic polymorphisms and should not be dependent upon other factors unrelated to enzyme activity (e.g., urinary pH, urinary flow, renal function) [41–43]. During *in vivo* studies, biomarkers need to measure change from baseline to induction as well as from baseline to inhibition. They should also be able to assess activation. Sampling of the biomarker over time must be appropriate to quantitate both induction or inhibition and this means that sampling strategies will usually differ by study phase.

Biomarkers that are direct metrics are preferred; e.g., total area under the plasma or serum concentration time curve (AUC), total body clearance, and total AUC metabolic ratios [4, 26]. When AUC is used, the complete AUC (i.e., $AUC_{0-\infty}$) and not partial AUC, should be determined. Thus, appropriate sampling duration is required in order to characterize at least 80–85% of the AUC with plasma versus time concentrations (<15–20% extrapolation) [44]. If metabolites are used as part of the biomarker, correlation of metabolite formation with the activity and content of the enzyme in subcellular fractions should have been shown [40, 45, 46]. Indirect metrics such as urinary or plasma metabolic ratios (metabolite:drug) or recovery ratios (drug + metabolite) have frequently been used but are not recommended and generally have not been validated [41, 47]. Simpler ratios and single point measurements are usually not satisfactory parameters and can lead to errors in interpretation [41, 48–50]. This is particularly true when divergent primary metabolic pathways are mediated by different enzymes and lead to the formation of the same secondary metabolite [27]. Limited sampling strategies are published for many biomarkers but may introduce excessive variability and lack adequate accuracy when applied within the setting of cocktail studies [48, 50]. As listed above, there are many issues and limitations in published biomarkers. Thus, the investigator should be cognizant that just because a probe or biomarker has been used alone or as part of a cocktail does not make it validated or appropriate for use.

As of this writing, the following probes (noted with the enzymes that they measure) and biomarkers have been validated. Many have been used in validated cocktails and the findings published. As such, the following probes and biomarkers are appropriate for use in DDI studies. This is not an exhaustive list of validated probes or biomarkers. Table 19.1 lists validated single probes by enzyme pathway. Table 19.2 lists validated cocktails that include at least four probes for CYP pathways of major importance.

Table 19.2 Validated multi-drug cocktails with at least four validated probe substrates for CYP enzymes of major importance and their preferred biomarkers

		Cooperstown cocktail 5+1	Sanofi-Aventis	Inje cocktail
Reference		Chainuvati et al. [79]	Turpault et al. [80]	Ryu et al. [24]
CYP1A2	Probe	Caffeine 2 mg/kg	Caffeine 100 mg	Caffeine 93 mg
	Biomarker	Plasma paraxanthine:caffeine $AUC_{0-12\,h}$	Plasma paraxanthine:caffeine $AUC_{0-24\,h}$	Plasma paraxanthine:caffeine $AUC_{0-12\,h}$
CYP2C9	Probe	Oral warfarin 10 mg	Warfarin 10 mg	Losartan 50 mg
	Biomarker	Plasma (*S*)-warfarin $AUC_{0-\infty}$	Plasma (*S*)-warfarin $AUC_{0-\infty}$	Losartan is not a valid probe, therefore no biomarker is recommended
CYP2C19	Probe	Oral omeprazole 40 mg	Omeprazole 20 mg	Omeprazole 20 mg
	Biomarker	5OH-omeprazole:omeprazole $AUC_{0-10\,h}$	Plasma omeprazole $AUC_{0-\infty}$	Plasma omeprazole:5OH-omeprazole $AUC_{0-12\,h}$
CYP2D6	Probe	Oral dextromethorphan 30 mg	Metoprolol 100 mg	Dextromethorphan 30 mg
	Biomarker	Plasma dextromethorphan:dextrophan $AUC_{0-\infty}$ ratio or apparent dextromethorphan CL	Metoprolol is not a valid probe, therefore no biomarker is recommended	Plasma dextromethorphan:dextrophan $AUC_{0-\infty}$ ratio
CYP3A	Probe	IV midazolam 0.025 mg/kg	Oral midazolam 0.03 mg/kg	Oral midazolam 2 mg
	Biomarker	Plasma midazolam $AUC_{0-\infty}$ Plasma 1′OH midazolam:midazolam $AUC_{0-\infty}$	Plasma midazolam $AUC_{0-\infty}$ Plasma 1′OH midazolam:midazolam $AUC_{0-\infty}$	Plasma midazolam $AUC_{0-\infty}$ Plasma 1′OH midazolam:midazolam $AUC_{0-\infty}$

19.3.1.1 CYP1A2

Caffeine is a validated probe with caffeine systemic clearance or the plasma paraxanthine to caffeine ratio $AUC_{0-\infty}$ as the biomarker [51, 52]. Although urinary metabolite ratios are frequently used as the biomarker [68], these are not optimal for the reasons examined elsewhere in the chapter. Chlorzoxazone inhibits *in vivo* caffeine metabolism [81] and therefore these two probes should not be used together. Theophylline is also a validated CYP1A2 probe [53].

19.3.1.2 CYP2B6

The probe bupropion has been validated and the *(S, S)*-hydroxybupropion:*(S)*-bupropion $AUC_{0-\infty}$ ratio is the validated biomarker [54, 55]. CYP2B6 is considered an enzyme of emerging importance but currently no CYP2B6 probe is part of a validated cocktail.

19.3.1.3 CYP2C8

Rosiglitazone is a selective substrate and valid probe for CYP2C8 [56, 57] but is not currently part of a validated cocktail. Also, CYP2C8 is considered an enzyme of emerging importance and may not be necessary to evaluate in all settings.

19.3.1.4 CYP2C9

(S)-warfarin is a validated CYP2C9 probe with plasma *(S)*-warfarin $AUC_{0-\infty}$ as the biomarker [58]. Low dose (125 mg) tolbutamide is also a validated CYP2C9 probe with oral tolbutamide plasma clearance [62] as the biomarker [59]. Unfortunately, tolbutamide use in a cocktail has only been validated with caffeine and dextromethorphan [82] and this limits its usefulness in studies that also wish to evaluate CYP2C19 and CYP3A isozymes. Losartan is used as a CYP2C9 probe in some cocktails but does not adequately distinguish between common CYP2C9 genotypes [83–85] and may also interact with other commonly used probe drugs (i.e., caffeine, omeprazole or debrisoquine) [86]. While *(S)*-flurbiprofen has been validated as a cocktail component, it does not correlate with other validated CYP2C9 probes (i.e., *(S)*-warfarin, tolbutamide) and exhibits greater variability in inhibition [58]. For these reasons, Kumar et al. have suggested *(S)*-warfarin $AUC_{0-\infty}$ as the preferred CYP2C9 biomarker [58].

19.3.1.5 CYP2C19

Omeprazole is the most commonly used, validated CYP2C19 probe [62–64] with the 5-hydroxyomeprazole:omeprazole $AUC_{0-10\,h}$ as the preferred biomarker [24, 52].

Many studies use a single 2- or 3-h metabolic ratio as the biomarker but this is suboptimal as the omeprazole C_{max} can vary markedly [62, 87]. Lansoprazole is also a validated probe [65] but is not included in a validated cocktail. *(S)*-mephenytoin has been proposed as a CYP2C19 probe [60, 61] but there are issues with the stability and duration of urine collection [88] as well as safety concerns [68]. In addition, mephenytoin is generally not commercially available. For these reasons, mephenytoin is not recommended. [^{13}C] pantoprazole shows promise as a CYP2C19 probe although it has not been validated as a cocktail component [66, 67].

19.3.1.6 CYP2D6

Oral dextromethorphan is the preferred CYP2D6 probe [40], with use of plasma dextromethorphan:dextrophan AUC ratio$_{0-\infty}$ or plasma dextromethorphan oral clearance as biomarkers [41]. While the 12-h urinary dextromethorphan to dextrophan ratio has been validated, it should be viewed as inferior to plasma measurements because of issues related to urine specimen collection and handling, including pH considerations [40]. Debrisoquine is a validated CYP2D6 probe, and if used, the 12-h urinary debrisoquine:4-hydroxydebrisoquine metabolic ratio is the validated biomarker [40, 68]. However, debrisoquine is of limited usefulness because it is not available in North America or Asia. Desipramine is a validated probe [69] but has safety issues and is not part of a validated cocktail. Metoprolol is used in some validated cocktails and has metabolic properties that make it a desirable probe. However, metoprolol cannot be considered a validated CYP2D6 probe because it does not correlate with the metabolic ratios of other validated probes (i.e., debrisoquine, dextromethorphan) in non-Caucasian populations [40]. There are few situations where one would be interested in DDI data that are only applicable to Caucasian populations. A recent review of CYP2D6 probes has been published by Frank et al. [40].

19.3.1.7 CYP3A Isozymes

Midazolam is the validated, gold-standard CYP3A isozyme probe [29, 45, 46], although some researchers believe that more than one probe is needed when assessing CYP3A activity [89]. Validated CYP3A isozymes biomarkers include midazolam AUC$_{0-\infty}$ and plasma 1-hydroxymidazolam:midazolam AUC$_{0-\infty}$ ratio [45]. Single point ratios of 1-hydroxymidazolam:midazolam have been used but these are demonstrated to be invalid biomarkers [48, 90]. Although simvastatin is listed as a recommended CYP3A isozyme probe in the most recent FDA guidance [29], simvastatin does not correlate with CYP3A activity during inhibition or induction and therefore should not be used as a CYP3A probe [91]. Both oral and intravenous alfentanil are validated CYP3A isozyme probes with plasma alfentanil AUC$_{0-\infty}$ as the biomarker [73, 74]. However, alfentanil is not part of a validated cocktail. Because quinine has not been validated, is a P-glycoprotein substrate, and inhibits CYP2D6, it should

not be used in cocktail studies [86, 92]. Triazolam is a validated CYP3A probe but is not part of a validated cocktail [77, 78]. Felodipine is proposed as a CYP3A probe [76] but correlation with other CYP3A probes has not been done [93]. At one time, dapsone was used as a CYP3A probe but subsequent research showed it to be suboptimal. Dapsone is metabolized by CYP3A isozymes, CYP2C9 and CYP2E1 [94, 95], lacks correlation with other CYP3A isozyme probes, and fails to accurately assess CYP3A inhibition or induction [4, 36, 96–98]. The erythromycin breath test is not specific for CYP3A isozymes (and is also a P-glycoprotein substrate) and should not be used [99]. Some authors have suggested other drugs (e.g., buspirone [93, 100] and sildenafil [29, 93]) as CYP3A probes. While these may be appropriate for *in vitro* assessment of CYP3A activity [101, 102], data that support use as *in vivo* probes are currently lacking.

Finding a selective CYP3A5 substrate has been challenging. Because CYP3A5 and CYP3A4 are structurally similar, the specificities of substrates and inhibition are also very similar [103] as are the determinants of constitutive expression [104]. No validated, specific CYP3A5 probe is currently available. Also, CYP3A5 is considered an enzyme of emerging importance rather than a major enzyme [105].

19.3.1.8 CYP2E1

Chlorzoxazone is the preferred probe for CYP2E1 and has been validated at the 250 mg dose [70, 71]. The corresponding biomarker is the plasma 6-hydroxychlorzoxazone: chlorzoxazone $AUC_{0-\infty}$ ratio [106, 107] or apparent chlorzoxazone clearance [70]. Chlorzoxazone inhibits CYP3A isozymes and an interaction has been demonstrated when chlorzoxazone 250 mg is dosed with oral midazolam [4, 108]. Therefore these two probes should not be co-administered during a cocktail study and CYP3A isozymes cannot be assessed while evaluating CYP2E1 with chlorzoxazone. As CYP2E1 is consider an enzyme of limited importance, exclusion of this enzyme from cocktail studies is unlikely to be a problem.

19.3.1.9 Miscellaneous

One validated CYP probe can be used to measure the activity of a phase II enzyme, N-acetyltransferase (NAT2). The presence of NAT2 genotype variants have been evaluated with caffeine [109, 110] or dapsone [111], although the two probes were not highly correlated in an acutely ill population [112]. Usually NAT2 activity is evaluated during a cocktail study when urinary caffeine metabolite ratios are collected because caffeine has been administered to evaluate a CYP enzyme rather than primarily to determine acetylator status. Little is known about how changes in NAT2 activity relate to changes in the measured biomarkers. For this reason, assessment of the biomarkers is primarily used to evaluate NAT2 phenotype, not the potential for DDIs via NAT2.

19.3.2 Validated Cocktails

Once validated probes and biomarkers have been identified, it is important to assure that the cocktail combination of probes has also been validated. First one should evaluate whether the probes used in the cocktail study have been validated as a cocktail. Second, one should be sure that a validation of the combination of probes in the cocktail has been published. There must be clear evidence that there are no clinical or metabolic interactions among the probe drugs when used concurrently [26].

There are a number of reasons that published cocktails may not be appropriate for use. Use of validated probes and biomarkers without appropriate evidence of a lack of interaction between the probes is insufficient. Use of validated cocktails, but choosing biomarkers that are invalid or have yet to be validated can also lead to erroneous results.

Unfortunately, many unvalidated cocktails are in use and cocktail studies are frequently published that use unvalidated or invalid probes, biomarkers and/or cocktails. For example, a cocktail may include one or more component probes that are invalid or have been shown not to be valid, e.g., the 6β-hydroxycortisol:cortisol molar ratio [113–115] and the 4-h (single point) 1-hydroxymidazolam:midazolam ratio for measuring CYP3A isozymes activity [48]. Another possibility is that the component probe has been validated, but the chosen biomarker has not [4]. For example, while midazolam is a validated probe for CYP3A isozyme activity, there are numerous midazolam biomarkers that are used but not validated. Midazolam clearance and $AUC_{0-\infty}$ are validated biomarkers [39, 45, 46]; neither single point midazolam concentrations [90, 116] nor the 1-hydroxymidazolam:midazolam single point ratio accurately measures CYP3A isozyme activity [48]. In other words, midazolam is a validated probe, midazolam clearance and $AUC_{0-\infty}$ are validated biomarkers, but single point concentrations or single point metabolic ratios are not validated biomarkers and should not be used. Substitution of validated biomarkers can be done if the individual probe and its use as part of a cocktail are validated.

Another problem is that the cocktail components may have been individually validated but the concurrent administration of the probes has not [117, 118]. Finally, some *in vitro* probes and cocktails are suggested for *in vivo* use without supporting *in vivo* data [119]. Thus, it is essential that the investigator be sure that the probe drugs, biomarkers, and cocktail combination have each been validated in order to assure accurate study results.

19.4 Application of Cocktail Study Methodology

During a study, all DME polymorphisms that may be relevant (based on preclinical data) should be evaluated. When there is evidence that 30% or more of an investigational drug is cleared through CYP-mediated metabolism, the cocktail study should be designed to include at least the CYP enzymes of major metabolic importance

(i.e., CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) [31]. Other CYP enzymes that are considered to be of emerging importance (i.e., CYP2C8, CYP2B6, and CYP3A5) should be included if *in vitro* assays suggest they play a role in metabolism of the investigational drug of interest [31]. CYP1A1, CYP1B1, CYP2A6, CYP2E1 and CYP4A11 are considered to be of low importance and typically do not need to be investigated in cocktail studies.

Some validated cocktails lack the ability to evaluate an important and relevant DME pathway. For example, the validated Cooperstown cocktail did not include a CYP2C9 probe [120] although CYP2C9 is responsible for metabolism of approximately 20% of marketed drugs [121]. This problem was overcome by addition of a CYP2C9 probe (warfarin) and validation of a new combination, the Cooperstown 5 + 1 cocktail [79]. The Cooperstown 5 + 1 cocktail evaluates all of the major DME pathways although CYP3A isozymes assessment is limited to hepatic activity. Although it has been used, oral midazolam to assess intestinal plus hepatic CYP3A activity has not been validated as part of this cocktail. The 6-drug Pittsburgh cocktail is able to assess CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 [21, 97]. However, the CYP2C19 (mephenytoin) is not valid, CYP2E1 is a DME of low importance, and this cocktail does not contain a valid probe drug for CYP3A. Since CYP3A is responsible for approximately 50% of drug metabolism via CYP enzymes [36], this severely limits the utility of the Pittsburgh cocktail. Although it is a 6-drug cocktail, it only contains validated probes for three CYPs of major importance. While addition of midazolam to this cocktail would probe CYP3A isozymes, doing so without a complete validation of the cocktail would be scientifically unsound.

Published, validated cocktails that contain at least four validated probes for the five major CYPs are shown in Table 19.2. These include the Cooperstown 5 + 1 drug cocktail [79], the Sanofi-Aventis cocktail [80], and the Inje cocktail [24]. The reader should be aware that there are published investigations that use these probe cocktails but fail to evaluate validated biomarkers. It is also important to note that most investigators cannot acquire the entire set of probe drugs needed for the Pittsburgh cocktail. Currently there are no cocktails that combine validated CYP probes with a validated P-glycoprotein probe and in fact, no validated P-glycoprotein probes exist [3].

19.5 Subject Selection

A decision should be made during study design as to whether inclusion criteria will specify extensive metabolizers (EMs) identified by *a priori* genotyping or previous phenotyping, or will allow other metabolizer genotypes. One option is to genotype subjects and use genotype during the screening period to determine eligibility. Another is to use genotype to stratify during the analysis phase. When genotyping is done prior to the study, the additional costs of post hoc pharmacogenetic analyses may be avoided. Knowledge of subject phenotype may be required to appropriately interpret findings [122–124].

Using pharmacogenomic inclusion/exclusion criteria can increase statistical power by reducing the variability introduced by inclusion of a range of polymorphisms. By reducing intersubject variability, the sample size is reduced. Using subjects with EM genotypes to evaluate DDI potential is most common because such individuals have a greater quantity of enzyme and therefore are at greater risk for a DDI [125]. Individuals with PM genotypes have little or no enzyme production and therefore are unlikely to experience metabolic DDIs, and studies in PMs may result in underestimation of DDIs if results are not stratified by phenotype [125, 126]. Exclusion of poor metabolizers (PMs) may also increase trial safety by removing the risks associated with excessive drug exposure and limiting or avoiding the need for intensive monitoring during study drug administration. For these reasons, exclusion of subjects who are PMs makes a study more efficient. Likewise, inclusion of ultra rapid metabolizer phenotypes (UMs) may result in overestimation of DDIs and can result in markedly different findings than if only EMs are studied [127].

Alternatively, cocktail studies can be specifically designed to evaluate DDI by enzyme genetic polymorphism. Some researchers include EMs and IMs (if phenotyping or genotyping has been done prior to study start). If a drug is metabolized by a polymorphic enzyme then enrollment of adequate numbers of subjects who are PMs and EMs can allow comparison of pharmacokinetic parameters and thereby indicate the extent of the DDI that is expected with strong enzyme inhibition. In such a situation, additional interaction studies with such inhibitors would be unnecessary [29]. Enrollment of EM genotypes is encouraged when studying polymorphic DMEs. Although the focus of their statement is on pharmacogenomics studies, the Industry Pharmacogenomics Working Group (http://i-pwg.org) has endorsed the use of homogeneous populations when possible [124].

When genotype is not used to determine study eligibility, it is essential that the methods and quality of evaluating both genotype and phenotype be included in the protocol because lack of accurate phenotyping or incorrect genotype can result in spurious findings [124]. When multiple genotypes and phenotypes are included, the results should be presented by phenotype subgroup. Subgroup data presentation provides the maximal information for understanding DDI potential.

A cocktail protocol must also control environmental factors that may result in inhibition or induction of DMEs. Food-drug interactions [13, 14], cigarette smoking [11], or alcohol consumption [12] should be avoided when possible, or at a minimum, assessed and recorded [16].

19.6 Drug Dosage and DME Evaluations

The investigational drug dose and duration should be sufficient to estimate maximum induction or inhibition at clinically relevant dosages. Therefore, the investigational drug should be dosed at the highest dose likely to be employed in clinical use. The drug(s) used to inhibit or induce the enzyme pathways should also be dosed at the

highest clinical dose and its shortest dosing interval [29]. Dosing the investigational, inhibitory and induction drugs in this manner will maximize the chance of identifying an interaction.

Exposure measures (e.g., total AUC, maximum concentration [C_{max}], time to C_{max}) and pharmacokinetic parameters (e.g., clearance, volume of distribution) should be measured in every study. Additional measures such as pharmacodynamic parameters should be considered when appropriate. When the objective of the study is to quantify the effects on different enzymes, the complete AUC or pharmacokinetic parameter for the biomarker (not metabolic ratios) is the preferred metric [26, 41]. Simpler ratios such as metabolite to parent drug ratios in urine may have more confounding factors and the magnitude of an effect may be difficult to translate into inhibition potency, induction potency, and treatment recommendations. If a study assesses single parent to metabolite ratios (rather than a complete AUC), further *in vivo* evaluation may be required to provide quantitative data on changes in exposure.

19.7 Sampling, Assays and Sample Analyses

If *in vitro* data indicate CYP inhibition, induction, or activation there should be appropriate adjustment of the specimen sampling strategy. The frequency of sampling must allow accurate determination of the relevant measures and parameters for the parent drug and the active metabolites. Baseline sampling should be performed on the same schedule as during the cocktail validation study. Further modifications to the sampling scheme can be based on baseline DME activity and genotype, the expectation of inhibition or induction, and the substrate specificity for the enzyme system.

There may be important issues related to handling specimens prior to assay. Appropriate and consistent storage of blood and urine samples during collection is essential. When metabolic ratios are dependent upon renal clearance and a drug is lipid soluble, then diurnal variation in urinary pH has the potential to affect intraindividual variability in urinary ratios (for the parent drug) and plasma ratios (for the metabolite) [42]. As such, control of the duration of specimen collections should be standardized [27]. One must also know that the timing of the specimen collection is adequate to identify changes related to either inhibition or induction.

Stability of the probe in urine or plasma is required (i.e., the biomarker should not change over time, either prior to assay or during specimen storage). Urinary pH can influence detectable metabolic ratios and lead to a marked increase in variability [42]; in some circumstances it is necessary to stabilize the urine during collection [41, 43]. For example, urine samples for dextromethorphan and its metabolites should be deconjugated with β-glucuronidase before measurement in order to include unconjugated dextromethorphan and the 3-hydroxy methorphinan metabolite. Failure to deconjugate the urine may lead to incorrect measurement of metabolites [40].

Analytical interference should not be caused by the probe, investigational drug, or metabolites. The assay must be sensitive enough to allow determination of drugs

and metabolites in the collected samples. In general LC-MS-MS is recommended as an analytical instrument due to its precision, specificity and ability to quantitate very low concentrations of substances in body fluids. Deuterated drug is encouraged as the internal standard. Documentation of a lack of analytical interference between the cocktail drugs, their metabolites, and any internal standards is also important [128].

19.8 Statistical Considerations

Consideration of the desired study power, inter- and intraindividual variability in enzyme activity, and definition of a clinically important mean group difference in the measured biomarkers are all important aspects of study design. Each will influence the sample size calculations. Having an adequate number of subjects is essential and lack of attention to sample size may result in an under powered study [125]. Information on intraindividual variability for many CYP biomarkers can be found in the review by Zhou et al. [2] as well as the original research publications.

Sample size should be calculated for both the CYP enzyme of greatest interest based on *in vitro* findings and the biomarker with the greatest intraindividual variability. Calculating sample size from each of these and then using the larger sample size will provide adequate power for all of the CYPs under study. Routine use of the FDA recommended minimal sample size of 12 [129] can lead to a study with inadequate power.

Correct statistical evaluation begins with log transformation of the data. The rationale for this is that most pharmacokinetic metrics are not normally distributed but are right skewed [26, 29]. Log transformation tends to normalize or "correct" the distribution of the data. When data are normally distributed, measures of variance (e.g., confidence intervals, standard deviations, interquartile ranges) are symmetrical. In many studies, the sample size is too small to adequately evaluate for data distribution and hence, log transformation is recommended regardless of the apparent distribution of the raw data [129].

Regulatory agencies agree that DDI studies should be analyzed using bioequivalence criteria rather than statistical testing (i.e., significance testing) [27]. Results for the biomarker metric (e.g., total AUC or C_{max}) should be reported as the 90% confidence intervals (CI) around the geometric mean ratio of the biomarker measurements before and after treatment. The ratio is constructed from either the enzyme activity during investigational drug administration (treatment) to basal enzyme activity (baseline), or the enzyme activity during investigational drug plus inhibitor/inducer (treatment) to enzyme activity during investigational drug treatment alone (baseline). Confidence intervals provide an estimate of the distribution of the observed systemic exposure of treatment versus the control state and convey a probability of the magnitude of the interaction [29].

As a general rule, to meet bioequivalence criteria the 90% CI should be within the conventional limits of 0.8–1.25 for AUC and 0.7–1.43 for C_{max} [29]. However, it is recommended that these limits be flexible and dependent upon the pharmacodynamics

of the investigational drug or other clinical or safety considerations [27]. If the investigator plans to report 90% CI but specify limits other than the conventional limits noted above, these should be stated prior to study conduct. If a study is intended for submission to a regulatory agency, that agency should agree to any change in the confidence interval limits before the protocol design is finalized. Significance testing (e.g., parametric tests such as Student's *t*-test or nonparametric tests such as the Wilcoxon Sign Rank test) rather than bioequivalence testing is not appropriate because small, consistent systemic exposure differences can be statistically significant ($p < 0.05$) but not clinically relevant [26, 27, 29]. Unfortunately, not all cocktail validation studies have been analyzed with the appropriate statistical methodology.

Data presentation should include both interindividual variability and intraindividual variability (by metabolizer phenotype if appropriate). Reporting mean data with standard deviations is inadequate. For interactions in which an increase in variability is of concern (e.g., narrow therapeutic index drugs), the focus of the statistical analysis should be on measures of variability [29] rather than measures of central tendency such as the mean or median. This is because the measures of variability assist in prediction of the range of the DDIs anticipated to occur in the clinical setting. The mean change in enzyme activity is less useful from a clinical perspective.

19.9 Application of Cocktail Studies and Conclusions

Cocktail studies can assess the potential for DDIs and therefore assist the pharmaceutical industry with go/no-go decisions. They also allow assessment of the need for additional, specific DDI studies. Because cocktail studies assess the potential extent of DDIs, qualitative recommendations for drug dosing and use may be made. Evaluation of variability in the extent of DDIs can result in useful clinical information. For example, the presence of large inter-individual variability in clearance may translate into large inter-individual differences in the extent of DDIs. The importance and implications of enzyme polymorphism for different genotypes and the implications for product labeling can also be evaluated.

Both the FDA [26] and the EMA [29] endorse the use of cocktail studies to evaluate for DDIs when such studies are conducted in an adequate number of subjects and use validated biomarkers and cocktails [26, 29]. The FDA recommends that metabolic DDIs be explored for investigational compounds, including those that are not significantly eliminated by metabolism [29]. The FDA then works with the sponsor to determine whether further DDI studies are needed after studies with *in vitro* probes and early *in vivo* studies have been completed [29]. Specific suggestions about preferred probe substrates and study designs are provided in FDA guidance [29] although not all of the probe substrate recommendations are supported by review of the literature or validation studies.

The EMA recommends that cocktail studies use safe, validated probes and provides specific criteria that should be present in the probe drugs [26]. In addition, this

agency specifies that validated cocktails should be used and prefers cocktails that are supported by published validation data.

There is little published guidance available in English from Japan's Ministry of Health, Labor and Welfare (MHLW). What is available is consistent with recommendations provided by the FDA and EMA [27].

In order to predict DDIs in the clinical setting and make clinical adjustments to dosing, it is necessary to have information on substrate specificity, the extent of inhibition or induction, inter-individual variability of the CYP enzyme, and whether inhibition/induction is affected by the disease state in which the drug is used. This information is often difficult to acquire from clinical studies. For this reason, conducting cocktail studies in patient populations may provide valuable data. There is a need for investigation of variability of inhibition within metabolizer phenotypes for mild-moderate inhibition and narrow therapeutic index drugs as well as investigation of variability of inhibition within enzymes such as CYP3A4 where there are no polymorphisms but up to sevenfold interindividual variability in enzyme activity [36, 45, 130–132].

We hope that the future development of cocktails will include validation of cocktails that contain safe and validated probe drugs that are readily available worldwide and validated biomarkers that can be collected efficiently and assayed easily and concurrently.

References

1. In vivo drug metabolism/drug interaction studies--study design, data analysis, and recommendations for dosing and labeling. In: (CDER) CfDEaR, (CBER) CfBEaR, eds. Guidance for Industry. Rockville, MD: Food and Drug Administration, 1999.
2. Zhou H, Tong Z, McLeod JF. "Cocktail" approaches and strategies in drug development: valuable tool or flawed science? J Clin Pharmacol 2004;44:120–34.
3. Ma JD, Tsunoda SM, Bertino JS, Jr., Trivedi M, Beale KK, Nafziger AN. Evaluation of in vivo p-glycoprotein phenotyping probes: a need for validation. Clin Pharmacokinet 2010;49: 223–37.
4. Fuhr U, Jetter A, Kirchheiner J. Appropriate phenotyping procedures for drug metabolizing enzymes and transporters in humans and their simultaneous use in the "cocktail" approach. Clin Pharmacol Ther 2007;81:270–83.
5. Baker SD, van Schaik RH, Rivory LP, et al. Factors affecting cytochrome P-450 3A activity in cancer patients. Clin Cancer Res 2004;10:8341–50.
6. Frye RF, Zgheib NK, Matzke GR, et al. Liver disease selectively modulates cytochrome P450--mediated metabolism. Clin Pharmacol Ther 2006;80:235–45.
7. Frye RF, Schneider VM, Frye CS, Feldman AM. Plasma levels of TNF-alpha and IL-6 are inversely related to cytochrome P450-dependent drug metabolism in patients with congestive heart failure. J Card Fail 2002;8:315–9.
8. McConn DJ, 2nd, Lin YS, Mathisen TL, et al. Reduced duodenal cytochrome P450 3A protein expression and catalytic activity in patients with cirrhosis. Clin Pharmacol Ther 2009;85:387–93.
9. Lee CM, Pohl J, Morgan ET. Dual mechanisms of CYP3A protein regulation by proinflammatory cytokine stimulation in primary hepatocyte cultures. Drug Metab Dispos 2009;37: 865–72.

10. Jones AE, Brown KC, Werner RE, et al. Variability in drug metabolizing enzyme activity in HIV-infected patients. Eur J Clin Pharmacol 2010. Epub 01/20/2010.
11. Hukkanen J, Vaisanen T, Lassila A, et al. Regulation of CYP3A5 by glucocorticoids and cigarette smoke in human lung-derived cells. J Pharmacol Exp Ther 2003;304:745–52.
12. He P, Court MH, Greenblatt DJ, Von Moltke LL. Genotype-phenotype associations of cytochrome P450 3A4 and 3A5 polymorphism with midazolam clearance in vivo. Clin Pharmacol Ther 2005;77:373–87.
13. Saari TI, Laine K, Neuvonen M, Neuvonen PJ, Olkkola KT. Effect of voriconazole and fluconazole on the pharmacokinetics of intravenous fentanyl. Eur J Clin Pharmacol 2008; 64:25–30.
14. Culm-Merdek KE, von Moltke LL, Gan L, et al. Effect of extended exposure to grapefruit juice on cytochrome P450 3A activity in humans: comparison with ritonavir. Clin Pharmacol Ther 2006;79:243–54.
15. Ngo N, Yan Z, Graf TN, et al. Identification of a cranberry juice product that inhibits enteric CYP3A-mediated first-pass metabolism in humans. Drug Metab Dispos 2009;37:514–22.
16. Zhou SF. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. Curr Drug Metab 2008;9:310–22.
17. Blake MJ, Gaedigk A, Pearce RE, et al. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. Clin Pharmacol Ther 2007;81:510–6.
18. Tracy TS, Venkataramanan R, Glover DD, Caritis SN. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol 2005;192:633–9.
19. Nolin TD, Appiah K, Kendrick SA, Le P, McMonagle E, Himmelfarb J. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. J Am Soc Nephrol 2006;17:2363–7.
20. Morgan ET, Goralski KB, Piquette-Miller M, et al. Regulation of drug-metabolizing enzymes and transporters in infection, inflammation, and cancer. Drug Metab Dispos 2008;36:205–16.
21. Zgheib NK, Frye RF, Tracy TS, Romkes M, Branch RA. Validation of incorporating flurbiprofen into the Pittsburgh cocktail. Clin Pharmacol Ther 2006;80:257–63.
22. Ozdemir V, Kalowa W, Tang BK, et al. Evaluation of the genetic component of variability in CYP3A4 activity: a repeated drug administration method. Pharmacogenetics 2000;10:373–88.
23. Schellens JH, van der Wart JH, Brugman M, Breimer DD. Influence of enzyme induction and inhibition on the oxidation of nifedipine, sparteine, mephenytoin and antipyrine in humans as assessed by a "cocktail" study design. J Pharmacol Exp Ther 1989;249:638–45.
24. Ryu JY, Song IS, Sunwoo YE, et al. Development of the "Inje cocktail" for high-throughput evaluation of five human cytochrome P450 isoforms in vivo. Clin Pharmacol Ther 2007;82: 531–40.
25. Rezk NL, Brown KC, Kashuba AD. A simple and sensitive bioanalytical assay for simultaneous determination of omeprazole and its three major metabolites in human blood plasma using RP-HPLC after a simple liquid-liquid extraction procedure. J Chromatogr B Analyt Technol Biomed Life Sci 2006;844:314–21.
26. CHMP Efficacy Working Party Therapeutic Subgroup on Pharmacokinetics. London: European Medicines Agency, 2009.
27. Tucker GT, Houston JB, Huang SM. Optimizing drug development: strategies to assess drug metabolism/transporter interaction potential--toward a consensus. Pharm Res 2001;18:1071–80.
28. Bertino Jr JS, Nafziger AN. Labeling of drug interactions. Is change needed? Clin Pharmacol Ther 2007;81(Suppl):S90.
29. Drug interaction studies-study design, data analysis, and implications for dosing and labeling. In: Research CfDEa, Research CfBEa, eds. Guidance for industry. Rockville, MD: U.S. Food and Drug Administration, 2006.
30. Ingelman-Sundberg M. Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms. Naunyn Schmiedebergs Arch Pharmacol 2004;369:89–104.
31. Bjornsson T, Callaghan J, Einolf H, Fischer V, Gan L, Grimm S, et al. The conduct of in vitro and in vivo drug-drug interaction studies: a PhRMA perspective. J Clin Pharmacol 2003; 43:443–69.

32. Venkatakrishnan K, von Moltke LL, Obach RS, Greenblatt DJ. Drug metabolism and drug interactions: application and clinical value of in vitro models. Curr Drug Metab 2003;4:423–59.
33. Krosser S, Neugebauer R, Dolgos H, Fluck M, Rost KL, Kovar A. Investigation of sarizotan's impact on the pharmacokinetics of probe drugs for major cytochrome P450 isoenzymes: a combined cocktail trial. Eur J Clin Pharmacol 2006;62:277–84.
34. Rostami-Hodjegan A, Tucker G. 'In silico' simulations to assess the 'in vivo' consequences of 'in vitro' metabolic drug–drug interactions. Drug Discover Today: Technologies 2004;1:441–8.
35. Davit B, Reynolds K, Yuan R, et al. FDA evaluations using in vitro metabolism to predict and interpret in vivo metabolic drug-drug interactions: impact on labeling. J Clin Pharmacol 1999;39:899–910.
36. Weaver RJ. Assessment of drug-drug interactions: concepts and approaches. Xenobiotica 2001;31:499–538.
37. .Lu C, Hatsis P, Berg C, Lee FW, Balani SK. Prediction of pharmacokinetic drug-drug interactions using human hepatocyte suspension in plasma and cytochrome P450 phenotypic data. II. In vitro-in vivo correlation with ketoconazole. Drug Metab Dispos 2008;36:1255–60.
38. Lu C, Miwa GT, Prakash SR, Gan LS, Balani SK. A novel model for the prediction of drug-drug interactions in humans based on in vitro cytochrome p450 phenotypic data. Drug Metab Dispos 2007;35:79–85.
39. Watkins P. Noninvasive tests of CYP3A enzymes. Pharmacogenetics 1994;4:171–84.
40. Frank D, Jaehde U, Fuhr U. Evaluation of probe drugs and pharmacokinetic metrics for CYP2D6 phenotyping. Eur J Clin Pharmacol 2007;63:321–33.
41. Borges S, Li L, Hamman MA, Jones DR, Hall SD, Gorski JC. Dextromethorphan to dextrorphan urinary metabolic ratio does not reflect dextromethorphan oral clearance. Drug Metab Dispos 2005;33:1052–5.
42. Ozdemir M, Crewe KH, Tucker GT, Rostami-Hodjegan A. Assessment of in vivo CYP2D6 activity: differential sensitivity of commonly used probes to urine pH. J Clin Pharmacol 2004;44:1398–404.
43. Labbe L, Sirois C, Pilote S, et al. Effect of gender, sex hormones, time variables and physiological urinary pH on apparent CYP2D6 activity as assessed by metabolic ratios of marker substrates. Pharmacogenetics 2000;10:425–38.
44. Bioavailability and bioequivalence requirements; Abbreviated applications; Final Rule. In: Food and Drug Administration H, ed: U.S. Department of Health and Human Services, 2002:77668–75.
45. Thummel KE, Shen DD, Podoll TD, et al. Use of midazolam as a human cytochrome P450 3A probe: II. Characterization of inter- and intraindividual hepatic CYP3A variability after liver transplantation. J Pharmacol Exp Ther 1994;271:557–66.
46. Thummel KE, Shen DD, Podoll TD, et al. Use of midazolam as a human cytochrome P450 3A probe: I. In vitro-in vivo correlations in liver transplant patients. J Pharmacol Exp Ther 1994;271:549–56.
47. Streetman DS, Kashuba AD, Bertino JS, Jr., Kulawy R, Rocci ML, Jr., Nafziger AN. Use of midazolam urinary metabolic ratios for cytochrome P450 3A (CYP3A) phenotyping. Pharmacogenetics 2001;11:349–55.
48. Lee LS, Bertino JS, Jr., Nafziger AN. Limited Sampling Models for Oral Midazolam: Midazolam Plasma Concentrations, Not the Ratio of 1-Hydroxymidazolam to Midazolam Plasma Concentrations, Accurately Predicts AUC as a Biomarker of CYP3A Activity. J Clin Pharmacol 2006;46:229–34.
49. Ma JD, Nafziger AN, Kashuba AD, et al. Limited sampling strategy of S-warfarin concentrations, but not warfarin S/R ratios, accurately predicts S-warfarin AUC during baseline and inhibition in CYP2C9 extensive metabolizers. J Clin Pharmacol 2004;44:570–6.
50. Rogers JF, Nafziger AN, Kashuba AD, et al. Single plasma concentrations of 1′-hydroxymidazolam or the ratio of 1′-hydroxymidazolam:midazolam do not predict midazolam clearance in healthy subjects. J Clin Pharmacol 2002;42:1079–82.
51. Fuhr U, Rost KL. Simple and reliable CYP1A2 phenotyping by the paraxanthine/caffeine ratio in plasma and in saliva. Pharmacogenetics 1994;4:109–16.

52. Johnson BM, Song IH, Adkison KK, et al. Evaluation of the drug interaction potential of aplaviroc, a novel human immunodeficiency virus entry inhibitor, using a modified Cooperstown 5+1 cocktail. J Clin Pharmacol 2006;46:577–87.
53. Sarkar MA, Jackson BJ. Theophylline N-demethylations as probes for P4501A1 and P4501A2. Drug Metab Dispos 1994;22:827–34.
54. Faucette SR, Hawke RL, Lecluyse EL, et al. Validation of bupropion hydroxylation as a selective marker of human cytochrome P450 2B6 catalytic activity. Drug Metab Dispos 2000; 28:1222–30.
55. Kharasch ED, Mitchell D, Coles R. Stereoselective bupropion hydroxylation as an in vivo phenotypic probe for cytochrome P4502B6 (CYP2B6) activity. J Clin Pharmacol 2008;48:464–74.
56. Totah RA, Rettie AE. Cytochrome P450 2C8: substrates, inhibitors, pharmacogenetics, and clinical relevance. Clin Pharmacol Ther 2005;77:341–52.
57. Niemi M, Backman JT, Neuvonen PJ. Effects of trimethoprim and rifampin on the pharmacokinetics of the cytochrome P450 2C8 substrate rosiglitazone. Clin Pharmacol Ther 2004;76:239–49.
58. Kumar V, Wahlstrom JL, Rock DA, Warren CJ, Gorman LA, Tracy TS. CYP2C9 inhibition: impact of probe selection and pharmacogenetics on in vitro inhibition profiles. Drug Metab Dispos 2006;34:1966–75.
59. Jetter A, Kinzig-Schippers M, Skott A, et al. Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. Eur J Clin Pharmacol 2004;60:165–71.
60. Kupfer A, Preisig R. Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. Eur J Clin Pharmacol 1984;26:753–9.
61. Xie HG, Stein CM, Kim RB, Wilkinson GR, Flockhart DA, Wood AJ. Allelic, genotypic and phenotypic distributions of S-mephenytoin 4′-hydroxylase (CYP2C19) in healthy Caucasian populations of European descent throughout the world. Pharmacogenetics 1999;9:539–49.
62. Chang M, Tybring G, Dahl ML, et al. Interphenotype differences in disposition and effect on gastrin levels of omeprazole--suitability of omeprazole as a probe for CYP2C19. Br J Clin Pharmacol 1995;39:511–8.
63. Lasker JM, Wester MR, Aramsombatdee E, Raucy JL. Characterization of CYP2C19 and CYP2C9 from human liver: respective roles in microsomal tolbutamide, S-mephenytoin, and omeprazole hydroxylations. Arch Biochem Biophys 1998;353:16–28.
64. Karam WG, Goldstein JA, Lasker JM, Ghanayem BI. Human CYP2C19 is a major omeprazole 5-hydroxylase, as demonstrated with recombinant cytochrome P450 enzymes. Drug Metab Dispos 1996;24:1081–7.
65. Miura M, Tada H, Yasui-Furukori N, et al. Pharmacokinetic differences between the enantiomers of lansoprazole and its metabolite, 5-hydroxylansoprazole, in relation to CYP2C19 genotypes. Eur J Clin Pharmacol 2004;60:623–8.
66. Thacker DL, Modak AS, Lemler SM, Flockhart DA, Desta Z. Cytochrome P450 (CYP) 2C19 specific breath test using (+)-[13C]-pantoprazole as a phenotype probe. Clin Pharmacol Ther 2010;87(Suppl 1):S51.
67. Desta Z, Modak A, Nguyen PD, et al. Rapid identification of the hepatic cytochrome P450 2C19 activity using a novel and noninvasive [13C]pantoprazole breath test. J Pharmacol Exp Ther 2009;329:297–305.
68. Streetman D, Bertino J, Jr., Nafziger A. Phenotyping of drug-metabolizing enzymes in adults: a review of in-vivo cytochrome P450 phenotyping probes. Pharmacogenetics 2000;10: 187–216.
69. Spina E, Avenoso A, Campo GM, Scordo MG, Caputi AP, Perucca E. Effect of ketoconazole on the pharmacokinetics of imipramine and desipramine in healthy subjects. Br J Clin Pharmacol 1997;43:315–8.
70. Frye RF, Adedoyin A, Mauro K, Matzke GR, Branch RA. Use of chlorzoxazone as an in vivo probe of cytochrome P450 2E1: choice of dose and phenotypic trait measure. J Clin Pharmacol 1998;38:82–9.
71. Mishin VM, Rosman AS, Basu P, Kessova I, Oneta CM, Lieber CS. Chlorzoxazone pharmacokinetics as a marker of hepatic cytochrome P4502E1 in humans. Am J Gastroenterol 1998;93:2154–61.

72. Tsunoda S, Velez R, von Moltke L, Greenblatt D. Differentiation of intestinal and hepatic cytochrome P450 3A activity with use of midazolam as an in vivo proble: effect of ketoconazole. Clin Pharmacol Ther 1999;66:461–71.
73. Chaobal HN, Kharasch ED. Single-point sampling for assessment of constitutive, induced, and inhibited cytochrome P450 3A activity with alfentanil or midazolam. Clin Pharmacol Ther 2005;78:529–39.
74. Kharasch ED, Walker A, Hoffer C, Sheffels P. Intravenous and oral alfentanil as in vivo probes for hepatic and first-pass cytochrome P450 3A activity: noninvasive assessment by use of pupillary miosis. Clin Pharmacol Ther 2004;76:452–66.
75. Kharasch ED, Hoffer C, Walker A, Sheffels P. Disposition and miotic effects of oral alfentanil: a potential noninvasive probe for first-pass cytochrome P4503A activity. Clin Pharmacol Ther 2003;73:199–208.
76. Jalava KM, Olkkola KT, Neuvonen PJ. Itraconazole greatly increases plasma concentrations and effects of felodipine. Clin Pharmacol Ther 1997;61:410–5.
77. von Moltke LL, Greenblatt DJ, Harmatz JS, et al. Triazolam biotransformation by human liver microsomes in vitro: effects of metabolic inhibitors and clinical confirmation of a predicted interaction with ketoconazole. J Pharmacol Exp Ther 1996;276:370–9.
78. Perloff MD, von Moltke LL, Court MH, Kotegawa T, Shader RI, Greenblatt DJ. Midazolam and triazolam biotransformation in mouse and human liver microsomes: relative contribution of CYP3A and CYP2C isoforms. J Pharmacol Exp Ther 2000;292:618–28.
79. Chainuvati S, Nafziger AN, Leeder JS, et al. Combined phenotypic assessment of cytochrome p450 1A2, 2C9, 2C19, 2D6, and 3A, N-acetyltransferase-2, and xanthine oxidase activities with the "Cooperstown 5+1 cocktail". Clin Pharmacol Ther 2003;74:437–47.
80. Turpault S, Brian W, Van Horn R, et al. Pharmacokinetic assessment of a five-probe cocktail for CYPs 1A2, 2C9, 2C19, 2D6 and 3A. Br J Clin Pharmacol 2009;68:928–35.
81. Berthou F, Goasduff T, Lucas D, Dreano Y, Le Bot MH, Menez JF. Interaction between two probes used for phenotyping cytochromes P4501A2 (caffeine) and P4502E1 (chlorzoxazone) in humans. Pharmacogenetics 1995;5:72–9.
82. Bruce MA, Hall SD, Haehner-Daniels BD, Gorski JC. In vivo effect of clarithromycin on multiple cytochrome P450s. Drug Metab Dispos 2001;29:1023–8.
83. Yasar U, Forslund-Bergengren C, Tybring G, et al. Pharmacokinetics of losartan and its metabolite E-3174 in relation to the CYP2C9 genotype. Clin Pharmacol Ther 2002;71:89–98.
84. Allabi AC, Gala JL, Horsmans Y, et al. Functional impact of CYP2C95, CYP2C96, CYP2C98, and CYP2C911 in vivo among black Africans. Clin Pharmacol Ther 2004;76:113–8.
85. Babaoglu MO, Yasar U, Sandberg M, et al. CYP2C9 genetic variants and losartan oxidation in a Turkish population. Eur J Clin Pharmacol 2004;60:337–42.
86. Christensen M, Andersson K, Dalen P, et al. The Karolinska cocktail for phenotyping of five human cytochrome P450 enzymes. Clin Pharmacol Ther 2003;73:517–28.
87. Hassan-Alin M, Andersson T, Niazi M, Rohss K. A pharmacokinetic study comparing single and repeated oral doses of 20 mg and 40 mg omeprazole and its two optical isomers, S-omeprazole (esomeprazole) and R-omeprazole, in healthy subjects. Eur J Clin Pharmacol 2005;60:779–84.
88. Tybring G, Bottiger Y, Widen J, Bertilsson L. Enantioselective hydroxylation of omeprazole catalyzed by CYP2C19 in Swedish white subjects. Clin Pharmacol Ther 1997;62:129–37.
89. Masica AL, Mayo G, Wilkinson GR. In vivo comparisons of constitutive cytochrome P450 3A activity assessed by alprazolam, triazolam, and midazolam. Clin Pharmacol Ther 2004;76:341–9.
90. Kim JS, Nafziger AN, Tsunoda SM, et al. Limited sampling strategy to predict AUC of the CYP3A phenotyping probe midazolam in adults: application to various assay techniques. J Clin Pharmacol 2002;42:376–82.
91. Chung E, Nafziger AN, Kazierad DJ, Bertino JS, Jr. Comparison of midazolam and simvastatin as cytochrome P450 3A probes. Clin Pharmacol Ther 2006;79:350–61.
92. Mirghani RA, Ericsson O, Tybring G, Gustafsson LL, Bertilsson L. Quinine 3-hydroxylation as a biomarker reaction for the activity of CYP3A4 in man. Eur J Clin Pharmacol 2003; 59:23–8.

93. Foti RS, Rock DA, Wienkers LC, Wahlstrom JL. Selection of alternative CYP3A4 probe substrates for clinical drug interaction studies using in vitro data and in vivo simulation. Drug Metab Dispos 2010;38:981–7.
94. Mitra AK, Thummel KE, Kalhorn TF, Kharasch ED, Unadkat JD, Slattery JT. Metabolism of dapsone to its hydroxylamine by CYP2E1 in vitro and in vivo. Clin Pharmacol Ther 1995;58:556–66.
95. Gill HJ, Tingle MD, Park BK. N-Hydroxylation of dapsone by multiple enzymes of cytochrome P450: implications for inhibition of haemotoxicity. Br J Clin Pharmacol 1995;40:531–8.
96. Gass RJ, Gal J, Fogle PW, Detmar-Hanna D, Gerber JG. Neither dapsone hydroxylation nor cortisol 6beta-hydroxylation detects the inhibition of CYP3A4 by HIV-1 protease inhibitors. Eur J Clin Pharmacol 1998;54:741–7.
97. Frye RF, Matzke GR, Adedoyin A, Porter JA, Branch RA. Validation of the five-drug "Pittsburgh cocktail" approach for assessment of selective regulation of drug-metabolizing enzymes. Clin Pharmacol Ther 1997;62:365–76.
98. Sharma A, Pilote S, Belanger PM, Arsenault M, Hamelin BA. A convenient five-drug cocktail for the assessment of major drug metabolizing enzymes: a pilot study. Br J Clin Pharmacol 2004;58:288–97.
99. Kinirons MT, O'Shea D, Kim RB, et al. Failure of erythromycin breath test to correlate with midazolam clearance as a probe of cytochrome P4503A. Clin Pharmacol Ther 1999;66:224–31.
100. Ragueneau-Majlessi I, Boulenc X, Rauch C, Hachad H, Levy RH. Quantitative correlations among CYP3A sensitive substrates and inhibitors: literature analysis. Curr Drug Metab 2007;8:810–4.
101. Zhu M, Zhao W, Jimenez H, et al. Cytochrome P450 3A-mediated metabolism of buspirone in human liver microsomes. Drug Metab Dispos 2005;33:500–7.
102. Ku HY, Ahn HJ, Seo KA, et al. The contributions of cytochromes P450 3A4 and 3A5 to the metabolism of the phosphodiesterase type 5 inhibitors sildenafil, udenafil, and vardenafil. Drug Metab Dispos 2008;36:986–90.
103. Xie HG, Wood AJ, Kim RB, Stein CM, Wilkinson GR. Genetic variability in CYP3A5 and its possible consequences. Pharmacogenomics 2004;5:243–72.
104. Lin YS, Dowling AL, Quigley SD, et al. Co-regulation of CYP3A4 and CYP3A5 and contribution to hepatic and intestinal midazolam metabolism. Mol Pharmacol 2002;62:162–72.
105. Daly AK. Significance of the minor cytochrome P450 3A isoforms. Clin Pharmacokinet 2006;45:13–31.
106. Lucas D, Ferrara R, Gonzalez E, et al. Chlorzoxazone, a selective probe for phenotyping CYP2E1 in humans. Pharmacogenetics 1999;9:377–88.
107. Girre C, Lucas D, Hispard E, Menez C, Dally S, Menez JF. Assessment of cytochrome P4502E1 induction in alcoholic patients by chlorzoxazone pharmacokinetics. Biochem Pharmacol 1994;47:1503–8.
108. Palmer JL, Scott RJ, Gibson A, Dickins M, Pleasance S. An interaction between the cytochrome P450 probe substrates chlorzoxazone (CYP2E1) and midazolam (CYP3A). Br J Clin Pharmacol 2001;52:555–61.
109. Jetter A, Kinzig M, Rodamer M, Tomalik-Scharte D, Sorgel F, Fuhr U. Phenotyping of N-acetyltransferase type 2 and xanthine oxidase with caffeine: when should urine samples be collected? Eur J Clin Pharmacol 2009;65:411–7.
110. Kalow W, Tang BK. The use of caffeine for enzyme assays: a critical appraisal. Clin Pharmacol Ther 1993;53:503–14.
111. Rothman N, Hayes RB, Bi W, et al. Correlation between N-acetyltransferase activity and NAT2 genotype in Chinese males. Pharmacogenetics 1993;3:250–5.
112. O'Neil WM, Drobitch RK, MacArthur RD, et al. Acetylator phenotype and genotype in patients infected with HIV: discordance between methods for phenotype determination and genotype. Pharmacogenetics 2000;10:171–82.
113. Galteau MM, Shamsa F. Urinary 6beta-hydroxycortisol: a validated test for evaluating drug induction or drug inhibition mediated through CYP3A in humans and in animals. Eur J Clin Pharmacol 2003;59:713–33.

114. Luo X, Li XM, Hu ZY, Cheng ZN. Evaluation of CYP3A activity in humans using three different parameters based on endogenous cortisol metabolism. Acta Pharmacol Sin 2009;30:1323–9.
115. Chen YC, Gotzkowsky SK, Nafziger AN, et al. Poor correlation between 6beta–hydroxycortisol:cortisol molar ratios and midazolam clearance as measure of hepatic CYP3A activity. Br J Clin Pharmacol 2006;62:187–95.
116. Penzak SR, Busse KH, Robertson SM, Formentini E, Alfaro RM, Davey RT, Jr. Limitations of using a single postdose midazolam concentration to predict CYP3A-mediated drug interactions. J Clin Pharmacol 2008;48:671–80.
117. Wang Z, Gorski JC, Hamman MA, Huang SM, Lesko LJ, Hall SD. The effects of St John's wort (Hypericum perforatum) on human cytochrome P450 activity. Clin Pharmacol Ther 2001;70:317–26.
118. Tomalik-Scharte D, Jetter A, Kinzig-Schippers M, et al. Effect of propiverine on cytochrome P450 enzymes: a cocktail interaction study in healthy volunteers. Drug Metab Dispos 2005;33:1859–66.
119. Videau O, Delaforge M, Levi M, et al. Biochemical and analytical development of the CIME cocktail for drug fate assessment in humans. Rapid Commun Mass Spectrom 2010;24:2407–19.
120. Streetman DS, Bleakley JF, Kim JS, et al. Combined phenotypic assessment of CYP1A2, CYP2C19, CYP2D6, CYP3A, N-acetyltransferase-2, and xanthine oxidase with the "Cooperstown cocktail". Clin Pharmacol Ther 2000;68:375–83.
121. Rendic S. Summary of information on human CYP enzymes: human P450 metabolism data. Drug Metab Rev 2002;34:83–448.
122. Furman KD, Grimm DR, Mueller T, et al. Impact of CYP2D6 intermediate metabolizer alleles on single-dose desipramine pharmacokinetics. Pharmacogenetics 2004;14:279–84.
123. Kim MJ, Bertino JS, Jr., Gaedigk A, Zhang Y, Sellers EM, Nafziger AN. Effect of sex and menstrual cycle phase on cytochrome P450 2C19 activity with omeprazole used as a biomarker. Clin Pharmacol Ther 2002;72:192–9.
124. Bromley CM, Close S, Cohen N, et al. Designing pharmacogenetic projects in industry: practical design perspectives from the Industry Pharmacogenomics Working Group. Pharmacogenomics J 2009;9:14–22.
125. Williams JA, Johnson K, Paulauskis J, Cook J. So many studies, too few subjects: establishing functional relevance of genetic polymorphisms on pharmacokinetics. J Clin Pharmacol 2006;46:258–64.
126. Eap CB, Lessard E, Baumann P, et al. Role of CYP2D6 in the stereoselective disposition of venlafaxine in humans. Pharmacogenetics 2003;13:39–47.
127. Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J 2007;7:257–65.
128. Scott RJ, Palmer J, Lewis IA, Pleasance S. Determination of a 'GW cocktail' of cytochrome P450 probe substrates and their metabolites in plasma and urine using automated solid phase extraction and fast gradient liquid chromatography tandem mass spectrometry. Rapid Commun Mass Spectrom 1999;13:2305–19.
129. Statistical approaches to establishing bioequivalence. Guidance for Industry. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, 2001:1–48.
130. Lin YS, Lockwood GF, Graham MA, et al. In-vivo phenotyping for CYP3A by a single-point determination of midazolam plasma concentration. Pharmacogenetics 2001;11:781–91.
131. Watkins PB, Wrighton SA, Maurel P, et al. Identification of an inducible form of cytochrome P-450 in human liver. Proc Natl Acad Sci U S A 1985;82:6310–4.
132. Kronbach T, Fischer V, Meyer UA. Cyclosporine metabolism in human liver: identification of a cytochrome P-450III gene family as the major cyclosporine-metabolizing enzyme explains interactions of cyclosporine with other drugs. Clin Pharmacol Ther 1988;43:630–5.

Chapter 20
Design and Data Analysis in Drug Interaction Studies

David E. Nix and Keith Gallicano

Abstract This chapter covers basic concepts pertaining to designing drug-drug interaction studies and interpreting results. Planning a drug-drug interaction study should encompass a statement of the rationale for doing the study. The basic design involves a 2 period randomized cross-over study with two treatment sequences; however, more complex and alternative study designs are discussed. Considerations include dose and duration of precipitant drug, washout period between treatments, and whether the potential interaction that results will affect the pharmacokinetic assessment plan. Existing information available for the test agents should be reviewed to formulate expected outcomes. The expected outcomes should be considered to ensure that the proper pharmacokinetic and sometimes pharmacodynamic information is collected for all treatments. All drug-drug interaction studies should be planned to incorporate bioequivalence testing and to present mean ratio of Treatment/Reference and corresponding 90% confidence intervals. The "no-effect" bounds, typically 80.00–125.0%, should be stated in the plan and based on consideration of the therapeutic index and pharmacokinetic variability of the object drug.

20.1 Study Rationale

Drug interaction studies should be considered for drugs that are likely to be administered concomitantly to large numbers of patients. The drugs may be indicated for the same disease process and their use in combination is considered therapeutically rational. Alternatively, the drugs may have different indications, but the two disease

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processes occur frequently in the same population. Drugs involved in interactions are divided into precipitant drugs (drugs that cause a change in the pharmacokinetics and/or pharmacodynamics of another drug) and the object drug (drug affected by the precipitant drug). A drug can act as a precipitant drug and an object drug at the same time when two drugs effect each other during concomitant administration.

To study large numbers of potential interactions routinely for all drugs is not feasible or desirable. Consequently, screening methods are required to identify drugs that are likely to interact. A chemist who is knowledgeable about drug interactions affecting gastrointestinal absorption may be able to identify potential interactions involving chelation, physical binding, or other incompatibility. Metabolism of object drugs may be studied using in vitro cytochrome P450 (CYP) enzyme preparations to identify enzymes involved in the metabolism [1, 2]. Databases are available of drugs that inhibit or induce various CYP subtypes. Once metabolism is determined to be a major elimination pathway and the responsible enzyme subtypes are known, these databases can be used to identify potentially interacting drugs [3]. Preliminary interaction studies of substrates with metabolic inhibitors and inducers can be performed using the same in vitro enzyme preparations as those used to determine metabolic pathways of substrates [2, 4]. Similar methods have been adapted to investigate drug interactions involving intestinal metabolism and drug transport [5–7].

Interactions involving protein binding displacement are not usually clinically significant. However, protein binding interactions should be examined for drugs that: (1) exhibit high binding to plasma proteins (>95%); (2) have a narrow therapeutic index; (3) occupy most of the available plasma protein-binding sites at clinically relevant concentrations; and (4) have a small volume of distribution (<10 L/70 kg) and are restrictively cleared by the major organ of elimination (e.g., low hepatic clearance), or are nonrestrictively cleared (e.g., high renal clearance) and are administered parenterally [8, 9]. Preliminary protein binding studies can be carried out in vitro, recognizing that metabolites may contribute to protein displacement interactions. Interactions involving renal clearance changes may be expected for drugs that rely heavily on renal excretion for their elimination. For these drugs, the presence of significant tubular secretion or reabsorption suggests possible interactions. Pharmacodynamic interactions should be suspected for drugs that have similar pharmacologic or toxicologic effects.

20.2 Study Design – General Issues

Current regulatory guidances provide some insight into designs for in vivo drug interaction studies [10, 11]. These guidances recommend three designs: (1) randomized crossover, (2) one-sequence crossover, or (3) parallel. A position paper by Pharmaceutical Research and Manufacturers of America (PhRMA) Drug Metabolism and Clinical Pharmacology Technical Working Groups has defined a minimal best practice for in vitro and in vivo pharmacokinetic drug-drug interaction studies targeted to drug development, with the goal of harmonizing approaches by regulatory agencies and industry sponsors [12].

Drug interaction studies involve the measurement of pharmacokinetics or a specific pharmacodynamic effect in the presence and absence of a precipitant drug. Such studies typically employ a within-subject design in which individuals receive both treatments in either fixed or random order. A fixed-order design denotes a longitudinal or one-sequence crossover study in which the treatments are administered sequentially over two or more time periods and all participants are grouped into a single sequence. Longitudinal studies are often conducted in patients who are receiving long-term therapy of the object drug or taking drugs with long elimination half-lives (>72 h). A two-period, longitudinal study involves the administration of the object drug alone followed by measurement of the pharmacokinetics or effect parameter(s) over time in period 1. A washout period may or may not be necessary. Then, the object and suspected precipitant drugs are concomitantly administered simultaneously or at different times in period 2. Measurements of the pharmacokinetics or effect parameters are repeated following administration of the combination treatment. In the longitudinal design, potential period effects are merged with the treatment effects. If a 30% change in the clearance of the object drug is observed, the change may have been caused by the precipitant drug or to some other intercurrent event. Perhaps the food intake differed between the two periods (treatment phases), or a portion of the subjects acquired a mild viral infection between the two periods. If females are included as subjects, the number of subjects in the luteal phase of the menstrual cycle may differ between the two periods.

The study must be designed will full knowledge of the pharmacokinetics of both drugs. If the study involves single doses of the object drug, then adequate washout of the first dose must be allowed before starting the second treatment phase. For the control treatment, measuring serum concentrations or effect for at least 4–5 half-lives is important. If reduced clearance and increased half-life are expected with the interaction, the sampling time may need to be extended following concomitant treatment. If the study involves multiple-dose administration of the object drug, then the serum concentrations should reach steady-state during both periods, particularly if the object drug has time-dependent pharmacokinetics, before assessing the pharmacokinetic or effect parameter(s).

The major advantage of a two-period, longitudinal design is that the potential for carryover effect from prior administration of the precipitant drug is avoided. A switch-back design in which the object drug is replicated at least once after the precipitant drug is discontinued is useful to determine the effects of starting and stopping a metabolic inhibitor or inducer on the baseline characteristics of the object drug. Such a design was used to establish the rebound to baseline pharmacokinetic parameters of steady-state zidovudine at 14 day after rifampin was discontinued in period 2 [13].

20.2.1 Cross-Over Designs

A cross-over study evaluates treatments administered in two or more planned sequences with subjects randomly allocated to the different sequences. The design is characterized by T, P, S in which T is the number of treatments, P is the number

of periods and S is the number of sequences. All of these numbers must be ≥2 [14]. Designs that have a single (fixed) sequence are sometimes referred to as "crossover-like", but should be considered as a longitudinal study rather than a crossover study because single sequences cannot be randomized.

There are two main types of crossover designs: nonreplicated and replicated. Nonreplicated designs have the same number of treatments as periods, and the number of sequences increases as the factorial of T (i.e., when $T=3$, $S=6$). Replicate designs have more periods than treatments, such that at least one treatment is replicated within a subject. Optimum designs are those that are balanced with equal numbers in each sequence, and balanced for carryover effects and variance for the given number of treatments. A design that has each treatment followed by a different treatment the same number of times is balanced for carryover. In a variance-balanced design each treatment appears the same number of times in each period. The presence of a carryover effect is important to assess in drug interaction studies, and enough subjects in each sequence are needed to allow testing of this effect.

The simplest nonreplicated crossover design is the 2, 2, 2 design. This design is the most frequently used crossover design in drug interaction studies. Suppose treatment A involves giving the object drug alone and treatment B involves giving the object drug with the precipitant drug. Subjects would receive the two treatments in one of two sequences, AB or BA, in which treatment A or B would be given during the first period and then switched to the other treatment during the second period. Carryover effects may be introduced for subjects receiving treatment B (sequence BA) in the first period if drug exposures of the object drug are increased by the precipitant drug. An adequate washout period must be planned between the two periods to prevent differential carryover in the two sequences. This may sometimes be difficult if the duration of an "adequate" washout period is not known a priori. Carryover and sequence effects, however, are confounded in the 2, 2, 2 design, and studies in which the two treatments are replicated must be conducted for optimal evaluation of carryover effects.

When nonreplicated studies involve more than two periods, the number of sequences should be carefully planned rather than testing all possible sequences. Usually a subset of sequences is chosen that defines a variance-balanced design. In a three-period, crossover pharmacokinetic study with treatments A, B and C, the six possible sequences ABC, ACB, BAC, BCA, CAB, and CBA must be included to maintain a carryover-balanced design. If carryover is a concern when the object and precipitant drugs are given together in treatments B and C, then a large sample size may be required to ensure an adequate number of subjects per sequence to test the carryover effect. A three-period crossover design in which two drugs are given alone and together during the three phases is often used to investigate bi-directional drug interactions. A four-period, crossover study would have 4! or 24 possible sequences. However, only four sequences, ABCD, BDAC, CADB, and DCBA, are necessary for a variance- and crossover-balanced study.

There is considerable interest in replicate crossover designs for bioequivalence studies in which the test and reference treatments are administered each on two separate occasions. This allows for assessment of intraindividual variability in systemic exposure and estimation of carryover effects. The analysis of replicate

designs considers that some individuals may differ from the mean response and allows for the determination of "individual bioequivalence". Optimal designs for carryover estimation of the two treatments are AA, BB, AB and BA for two-period designs, ABB and BAA for three-period designs, and AABB, BBAA, ABBA and BAAB for four-period designs [14–17]. Switchback designs, either ABA and BAB, or ABAB and BABA, are preferred to estimate the intra-individual variability [14]. Similar designs may be employed for drug interaction studies because they increase the confidence that a drug interaction detected is a true interaction and not an expression of intra-subject variability.

Replicate measurements may also be obtained in more traditional study designs. As an example, the object drug may be administered as a multiple-dose regimen and measurements can be made during more than 1 day or dosing interval before changeover to the next treatment. This was done in a randomized crossover study to investigate the interaction between cimetidine and theophylline [18]. Theophylline was administered at a subject specific dose (concentration controlled) for 23 day. Subjects received treatment 1 (cimetidine or placebo) on days 5–11, washout on days 12–16, and treatment 2 (cimetidine or placebo) on d 17–23. Cimetidine and placebo treatments were assigned by a randomized crossover allocation. The pharmacokinetics of theophylline was assessed on the first, fourth and seventh days of each treatment period. In the analysis, the data from the fourth and seventh days were treated as replicate measurements of the effect at steady state. Because theophylline exhibits large intersubject variability in clearance, doses were adjusted in a run-in phase to provide similar mean steady-state concentrations before evaluating the interaction. This example also shows how concentration control can be incorporated into the design of a drug interaction study.

20.2.2 Parallel Designs

A parallel design may be used for evaluating drug interactions. However, such designs are less desirable, usually because the drug variability is greater between individuals than within individuals. A simple parallel design study consists of two groups of subjects/patients, one group that is receiving the object drug and one that is receiving the object drug concomitantly with the suspected precipitant drug. Most studies of this type are performed in patient populations that are receiving the drug or drugs therapeutically. There may be problems with comparability of the two patient groups in terms of pharmacokinetics of the object drug regardless of the precipitant drug. The two groups may or may not be randomly selected. If random assignment is not used, additional issues of bias must be considered. When studies of this type are necessary, the use of population modeling is recommended for evaluating the presence or absence of the interaction. An example of using population modeling to evaluate a drug interaction involved imipramine and alprazolam [19]. The parallel design may be advantageous for drugs with long elimination half-lives in studies where a long washout period is impractical for a crossover or longitudinal design.

A placebo-controlled, parallel-group study can be conducted when possible inherent group differences in a parallel design or time-dependent effects in a single-sequence longitudinal design are a concern. Subjects in each group receive treatment on more than one occasion and treatment effects are adjusted for baseline values in the first period (placebo) of each treatment group. Alternatively, the mean treatment differences are estimated within each group and then these differences are compared between treatment groups. A placebo-controlled, parallel-group design was used to show no clinically significant effect of indinavir on the pharmacokinetics of voriconazole [20] and to demonstrate that ritonavir inhibited the metabolism of rifabutin [21].

20.2.3 Mechanistic Aspects

Drug interactions may be very complex. The mechanism of potential interaction is important to hypothesize from in vitro studies, previous clinical and preclinical studies, and experience with other related drugs. Such knowledge is essential to planning a good drug interaction study. Most studies are designed to evaluate the effect of a precipitant drug on an object drug. The precipitant drug may cause some physical or physiologic effect that alters the pharmacokinetics or pharmacodynamics of the object drug. Several questions need to be posed about the precipitant drug in relation to developing the study methods. What are the doses and administration schedules that are relevant to clinical practice? Is the interaction concentration dependent within the range of clinically achievable concentrations? Does the interaction take time to develop (e.g., P450 induction)? What is the primary goal of the study (e.g., to find the maximum potential interaction)? In some circumstances, one may be interested in whether the pharmacokinetics and/or pharmacodynamics of both drugs are affected by concomitant administration.

Multiple dosing of the precipitant drug is often desirable. The object drug may be administered as a single dose or in a multiple-dose regimen designed to achieve steady state. A single dose may be appropriate when inhibition of elimination is suspected and safety concerns are substantial. In such cases, unpredictable accumulation would be avoided. One exception occurs when an object drug undergoes extensive first-pass metabolism and the precipitant drug inhibits this metabolism. Much greater systemic bioavailability may result even with single-dose administration.

Concerns about multiple-dose studies are exemplified by a study of voriconazole effects on cyclosporine pharmacokinetics. This study included renal transplant patients receiving treatment with cyclosporine that was continued throughout the study. Subjects received voriconazole or placebo for 7.5 days (period 1), underwent a washout period of at least 4 days, then received the alternate treatment (voriconazole or placebo) for 7.5 days. Although 14 subjects were entered, only 7 completed the study and all 7 were withdrawn during the voriconazole treatment. Voriconazole resulting in a mean 1.7-fold increase in cyclosporine exposure [22]. Although a multiple-dose regimen of the object drug may simulate clinical use and provide

greater applicability, safety would favor a single-dose study in healthy subjects first. The addition of procedures to limit exposure to high concentrations during the interaction phase for a follow-up multiple-dose study needs to be considered. For example, the study could employ a dose reduction during the combination treatment. More extensive knowledge of the potential study outcomes, frequent and careful clinical monitoring, and perhaps real-time drug concentration monitoring may be necessary when the object drug is administered in a multiple-dose regimen.

20.2.4 Study Population

Drug interaction studies are most commonly performed in healthy volunteers. Healthy subjects are easier to recruit, the investigators can better control concomitant medications and activities, and study participation may be safer compared to patients with target illnesses. There is no compelling reason why performing a pharmacokinetic interaction study in healthy volunteers is less desirable than performing the study in a target population likely to receive both drugs, unless disease in the target population influences the magnitude of interaction or safety considerations prevent the use of healthy volunteers. The elderly are often cited as a group more susceptible to drug interactions. This is true because elderly patients receive more drugs and interactions only occur when two or more drugs are given concurrently [23]. In addition, geriatric patients may eliminate drugs more slowly and therefore achieve higher concentrations than young counterparts. Administering a dose regimen to healthy volunteers that provides serum concentrations and systemic exposure (area under the serum concentration-time curve, AUC) similar to those expected in elderly patients may control the latter factor. The same is true for patients with organ failure who have reduced drug clearance. However, dose adjustments used for these patients in clinical practice should also be considered.

Interaction studies that involve pharmacodynamic assessments may or may not be best performed in the target population, depending on the nature of the pharmacodynamic effect. Suppose an object drug reduces wheezing and acute bronchospasm, and increases forced expiratory volume in 1 s (FEV-1) in patients with asthma. Administration of a precipitant drug in combination with the object drug leads to worsening of symptoms and lowering the FEV-1 in asthma patients. However, these effects are not seen in patients without asthma. Such an interaction would need to be studied in the target population.

One report of an interaction between a laxative polymer and digoxin found a pharmacokinetic interaction consistent with a 30% decrease in digoxin absorption. The concluding statement was “there was no consequence of this interaction on heart rate and atrial ventricular conduction”. The study was conducted in healthy volunteers and digoxin administration was not associated with changes in atrial ventricular conduction with or without the laxative administration. Although a small decrease in heart rate was noted following digoxin dosing, the laxative did not alter the observed change [24]. This study demonstrates the importance of using

relevant pharmacodynamic parameters and the importance of the study population. The pharmacodynamic parameter should be a validated surrogate marker and be sensitive to changes in response. Had the study been conducted in patients with atrial fibrillation, changes may have been more apparent. Discussions on specific issues relating to pharmacodynamic drug interactions are beyond the scope of this chapter because the endpoint parameters depend on the pharmacology of the specific drug class and the characteristics of the parameter itself.

20.3 Pharmacokinetic Interaction Studies

20.3.1 Interactions Affecting Drug Absorption

Drug interactions may involve absorption or other aspects of drug delivery. This chapter does not address pharmaceutical or physicochemical interactions that occur in vitro or ex vivo such as incompatibility in intravenous admixtures or interactions that occur within intravenous administration tubes. Drug interactions commonly occur with drugs that are administered orally. Most of these interactions involve the effect of a precipitant drug on gastric pH or physical interactions between the two drugs. If an acidic environment in the stomach is required for optimal dissolution, reduced absorption in the presence of drugs that increase gastric pH may occur. The interaction between acid suppressants (e.g., cimetidine or omeprazole) and ketoconazole or itraconazole are classic examples of this type of interaction [25, 26]. Interaction studies should be performed for drugs that have greatly reduced solubility at neutral pH compared to pH < 3. One must be careful to provide sufficient doses of the acid suppressant to increase gastric pH to >6 during the absorption period [27]. Continuous monitoring of gastric pH is recommended to ensure that the target pH is attained.

Many drugs bind or complex with other drugs, thereby preventing gastrointestinal absorption. Examples of this type of interaction include tetracycline and calcium carbonate, ciprofloxacin and aluminum antacids or iron products, and norfloxacin and sucralfate [28–30]. These interactions occur when both drugs are present in the stomach and upper gastrointestinal tract at the same time. Maximum interaction usually occurs when the precipitant drug is administered slightly before or at the same time as the object drug [29]. Although not well studied, differences in gastric pH, gastric emptying time, and transintestinal secretion of drug may influence the extent of these interactions.

20.3.2 Interactions Affecting Drug Distribution

Drug distribution may be affected by drug interactions. However, many studies conclude differences in volume of distribution that represent artifact rather than true

differences. Changes in volume of distribution should be examined using intravenous dosing whenever possible. When oral administration is used, apparent changes in volume of distribution may represent changes in bioavailability. Comparisons should be made using steady-state volume of distribution (V_{ss}) only. Frequently V_{area} (also designated as V_z) is used for comparisons. However, this parameter is greatly affected by changes in the terminal elimination rate constant for pharmacokinetic models more complex than models involving monoexponential decay.

Steady-state volume of distribution may also be affected by experimental problems. Suppose a drug is well described using a three-compartment model when administered alone. The same drug is given after 10 days of rifampin treatment and the clearance is greatly enhanced. Drug concentrations are substantially lower following rifampin treatment, and the profile is best described using a two-compartment model. Presumably, the third exponential phase would remain present but the concentrations may be undetectable with the assay used. V_{ss} is equal to mean residence time (AUMC/AUC) multiplied by systemic clearance (Cl) for an iv bolus dose, where AUMC is the area under the first moment of the plasma concentration-time curve. Although AUC would be decreased and Cl increased as a result of the interaction, these parameters would be affected minimally by missing the third exponential phase. However, the third exponential phase contributes a large portion of the total AUMC for the control treatment. Excluding this phase following rifampin treatment will cause an apparent decrease in the V_{ss}. Thus, problems fitting the control and interaction phases to the same model with equal reliability could result in apparent changes in V_{ss} when no true change occurred. Similar problems would occur with noncompartmental analysis, but the problem would not be as apparent.

Examples of drug interactions affecting distribution include the interaction between ceftriaxone and drugs that increase free fatty acid concentrations (e.g., heparin). Free fatty acids displace ceftriaxone from protein binding [31]. This interaction is generally not clinically significant because the increased free fraction (microbiologically active drug) results in no change in average steady-state unbound concentrations in plasma even though renal clearance is increased. In general, for orally administered drugs that are highly protein bound, protein displacement interactions may be clinically relevant when the object drug has a narrow therapeutic range, a small volume of distribution (<10 L/70 kg) and long elimination half-life [8, 9].

Another potentially significant situation involves parenterally administered drugs that exhibit a high extraction ratio. Here nearly all of the drug that passes through the organ is removed or metabolized including both bound and unbound drug. Displacement from protein binding will have no effect on the total clearance of the drug. However, the increased free fraction of drug may result in greater pharmacodynamic activity while the precipitant drug is present. For the interaction to be significant, the object drug must have a narrow therapeutic index so that the increase in free drug concentration will have toxicologic significance. Overall, protein binding displacement interactions are rarely clinically significant.

20.3.3 Interactions Affecting Renal Excretion

Changes in renal excretion of drugs can be subdivided into filtration, secretion, and reabsorption. Glomerular filtration of drugs is limited by protein binding and only unbound drug is filtered. Drug interactions involving displacement of an object drug from serum protein will result in transiently higher unbound serum concentrations and lead to increased renal clearance for object drugs that have a low renal extraction ratio. The clinical significance of protein binding displacement is limited by the compensatory increase in renal clearance. Lower total serum concentrations from increased clearance may compensate for the increased free fraction.

Tubular secretion involves active transport of drugs from the serum to the tubular lumen. Separate transport systems are present for acids and bases, but these transport systems have a very low degree of specificity. Precipitant drugs may inhibit tubular secretion resulting in reduced renal clearance. Drugs that are extensively eliminated in the urine and have significant tubular secretion (renal clearance of free drug greater than 150% of glomerular filtration or high renal extraction ratio) are good candidates for studying this interaction mechanism. The normal glomerular filtration rate is about 120 mL/min and the renal blood flow is approximately 1,100 mL/min for a 70 kg adult. A drug can have a renal clearance approaching renal blood flow rate, as is observed with para-aminohippuric acid, owing to its extensive tubular secretion. The partitioning of a drug into red blood cells and the ability to diffuse out of red blood cells may also influence tubular secretion.

Probenecid is an example of a drug that inhibits tubular secretion by competing for the transport system. Probenecid may be administered with certain beta-lactam drugs to prolong their elimination rate. The beta-lactam agents most affected by this interaction have a high ratio of renal clearance to glomerular filtration rate and rely on the kidney as their major clearance organ. Before penicillin-resistance was prevalent, a combination of probenecid and high-dose amoxicillin was used to provide single-dose treatment for uncomplicated gonorrhea [32].

To assess drug interactions involving renal excretion, collection of both urine and plasma (or serum) is required. A measure of the glomerular filtration rate before or during the study is helpful to explore the mechanism of interaction. Glomerular filtration rate (GFR) can be determined by radiolabeled ^{99m}Tc-diethylenetriamine pentaacetic acid clearance, ^{125}I-iothalamate clearance, inulin clearance, or creatinine clearance (with concurrent cimetidine treatment) [33–35]. Measurement of creatinine clearance also serves as a rough measure of GFR. However, overestimation of GFR is expected owing to a small component of tubular secretion. Although unusual, the tubular secretion of creatinine may be large. As cimetidine inhibits the tubular secretion of creatinine, concurrent treatment during urine collection can improve the estimate of GFR [35]. Estimates of GFR from serum creatinine have been improved by use of a new prediction equation; however, the equation is based on a typical CLcr/GFR ratio [36].

Competitive inhibition of tubular secretion is typically concentration dependent and is influenced by the concentration of the precipitant and object drugs.

Concentration-dependent renal clearance of the object drug is established by collecting urine in intervals less than or equal to one half-life duration. Blood samples collected at the beginning and end of each urine collection interval are a minimum requirement, but more blood samples taken during the collection interval will provide a better estimate of plasma AUC. The renal clearance is calculated for each interval and would be expected to increase as drug concentrations (plasma AUC) decline. A precipitant drug may have only minor effect on the renal clearance when concentrations of the object drug are high, because saturation may already be present. However, the precipitant drug should prevent the increase in renal clearance seen at low concentrations of the object drug. The precipitant drug must be present in sufficient concentrations throughout the observation period to observe inhibition. Thus, continuous infusion or frequent dosing of the precipitant drug may be required unless the half-life of the precipitant drug is long. An interaction study also may be planned using dosing regimens likely to be used in clinical practice. However, information about the mechanism of interaction may be lost. An assumption usually made in pharmacokinetics is that clearance of the object drug is stable during each assessment period. If there are large differences in peak and trough drug concentrations of the precipitant drug over the period in which the pharmacokinetics of the object drug is assessed, this assumption may be violated because the degree of inhibition depends on inhibitor concentration. Information about the mechanism of interaction may also be lost if urine is collected in only one interval to obtain the average renal clearance.

Tubular reabsorption is usually a passive process whereby drug present in the tubular lumen (high concentration) diffuses back into the capillary lumen and returns to circulation. The drug must be un-ionized to diffuse across the tubular membrane. Interactions occur from altered pH in the tubular lumen or from physical interaction between the precipitant and object drug within the tubular lumen. An independent measure of tubular secretion, filtration and reabsorption is not possible in the clinical setting. Instead, only the overall renal clearance is measured and the intrinsic clearance is compared to GFR to classify the elimination as net tubular reabsorption, filtration, or net tubular secretion.

20.3.4 Interactions Affecting Drug Metabolism

CYP enzymes metabolize many anti-infective drugs whose pharmacokinetics are affected by drugs that inhibit or induce these enzymes. Several anti-infective agents act as inhibitors (ritonavir, ciprofloxacin, etc.) or inducers (rifampin, rifabutin, etc.) of CYP enzymes. Goals for a metabolism interaction study are important to set. The goal may be to determine if a clinically significant interaction is likely between two drugs or to determine more broadly if a drug serves as a precipitant drug involving a particular enzyme system. The precipitant drug should be administered in a clinically relevant, multiple-dose regimen for sufficient duration to achieve steady-state pharmacokinetic conditions. Longer durations of treatment may be required for

time-dependent interactions. For example, maximum induction with rifampin takes 10–13 days [37]. When no prior knowledge is available, multiple dosing for at least 1 week is usually sufficient. A longitudinal design in which the object drug is studied alone then following treatment with the precipitant drug is preferred in the absence of prior knowledge about the interaction offset time. If the offset time is of interest, the object drug may be studied again at various times after the precipitant drug is stopped.

More than 50% of drugs that undergo metabolism are metabolized primarily by CYP3A enzymes. These enzymes are induced by rifampin, rifabutin, phenytoin, carbamazepine, and barbiturates, and are present in the gastrointestinal tract, liver and other organs. CYP3A4 enzymes are responsible for first-pass metabolism of many drugs, and their inhibition may lead to pronounced increases in systemic bioavailability of orally administered object drugs. Precipitant drugs may induce or inhibit CYP3A4. Candidate object drugs are those that rely on metabolism by CYP3A4 enzymes for a substantial portion of their clearance. Midazolam is an excellent marker of CYP3A4 activity because its elimination depends almost entirely on hydroxylation by CYP3A subfamily of enzymes to form 1-hydroxy midazolam [38, 39]. Drugs that affect CYP3A activity in the gastrointestinal tract or liver may affect the apparent clearance of oral midazolam. *N*-demethylation of erythromycin is also catabolized by CYP3A and this metabolism occurs mostly in the liver. The intravenous administration of [^{14}C-*N*-methyl]-erythromycin and measurement of $^{14}CO_2$ in breath provides a convenient marker of CYP3A4 activity in the liver (not gastrointestinal tract) [40–42] even though potential limitations of the test have been identified [43]. Cortisol is metabolized to 6β-hydroxycortisol by CYP3A4 isozymes. The measurement of urinary 6β-hydroxycortisol/cortisol ratio remains fairly stable without circadian differences. Agents that affect CYP3A4 enzyme activity usually cause changes in the 6β-hydroxycortisol/cortisol ratio [41, 42]. These markers are useful tools to identify induction or inhibition of CYP3A4, although changes in clearance may not correlate quantitatively among the different markers.

Other common metabolic enzyme pathways involve CYP1A2 and the polymorphic CYP2D6 and CYP2C19 isozymes. Probe drugs are caffeine and theophylline for CYP1A2 [44, 45], debrisoquin and dextromethorphan for CYP2D6 [46], and omeprazole and mephenytoin for CYP2C19 activity [47]. For caffeine and theophylline, changes in systemic clearance are usually evaluated. The measurement of paraxanthine/caffeine ratio in saliva at 6 h after caffeine intake also correlates with CYP1A2 activity [48]. CYP2D6 activity can be assessed by measuring changes in the dextromethorphan/dextrophan ratio in urine [46]. CYP2C19 activity can be evaluated from the urinary *S*-mephenytoin/*R*-mephenytoin ratio after administration of racemic mephenytoin [49]. Genotypic tests that determine the presence of single nucleotide polymorphisms (SNP's) known to affect drug clearance are becoming more widely available.

Markers of CYP isozyme activity are useful to evaluate whether a potential precipitant drug effects metabolism. There is also need to evaluate whether a drug serves as an object drug resulting in toxicity, loss of therapeutic activity, or reduced effectiveness. Agents that are known to inhibit CYP1A2 (cimetidine, enoxacin),

CYP3A4 (itraconazole, ketoconazole), CYP2D6 (quinidine, cimetidine) and CYP2C19 (omeprazole, fluconazole) are well known [50–54]. However, not all of these drugs have specific effects on only one isozyme. Rifampin, rifabutin, carbamazepine and phenytoin are inducers of CYP3A4 and other enzymes [50, 51]. Lists of enzyme inhibitors and enzyme substrates can be found in recent publications [50, 52, 53].

If feasible, active or toxic metabolites in plasma and urine should be measured because the magnitude and direction of metabolite pharmacokinetic changes are often unpredictable. Multiple metabolic enzymes and pathways can confound predictions. The AUC of metabolite may be altered even if the metabolite is not the directly affected pathway. Alterations in metabolite pharmacokinetics do not always translate to measurable effects on AUC of parent drug. Detectable changes in AUC of the parent drug may not be apparent if a minor metabolic pathway is affected or if compensatory changes in hepatic and renal clearance occur. Thus, there is a danger in concluding "no interaction" from data involving only the parent drug. Metabolic parameters such as the metabolic AUC ratio and the urinary recovery ratio of metabolite to parent drug can give useful information on mechanisms of interaction, particularly if the metabolite is eliminated exclusively by renal excretion.

20.3.4.1 Impact of Pharmacogenomics

Metabolic interactions are sometimes complicated by the existence of polymorphic enzyme expression. A recent trend in metabolic interaction studies is to characterize subjects by genotype and or phenotype into extensive, intermediate, or poor metabolizers. In several of the studies reviewed, subjects were recruited without considering genotype or phenotype, leading to a very low number of subjects in less common metabolic groups [55–62]. Although more difficult and perhaps more expensive, the design would be improved by recruiting subjects based on genotype or phenotype with a target minimum number of subjects in each category. Larger clinical trial units should consider developing a subject database that includes genotype results for enzymes such as CYP3A5, CYP2C19, CYP2C9, and CYP2D6. Subject recruitment could be planned using a predictor panel concept similar to that used in microbiology to examine susceptibility against a panel of bacteria with categorized resistance mechanisms [63].

The impact of metabolic polymorphisms may vary substantially as demonstrated in the following examples. The effect of ritonavir on voriconazole exposure was studied in 20 subjects, which included 8 homozygous extensive metabolizers (EM's), 8 heterozygous EM's, and 4 poor metabolizers (PM's) based on CYP2C19 genotype. Total exposure ($AUC_{0-\infty}$) was increased 54% in homozygous EM's, 94% in heterozygous EM's, and 907% in PM's. Voriconazole CL/F varied about eightfold during the placebo phase and part of this variation was due to metabolizer status. Adding ritonavir resulted in about 70-fold variation from the highest CL/F in a homozygous EM subject at baseline to the lowest CL/F in a PM subject receiving ritonavir [55]. CYP3A4 is not polymorphic in expression; however, a small

portion of the population expresses CYP3A5, which metabolizes essentially the same substrates as CYP3A4. Consequently, subjects expressing CYP3A5 tend to be EM's. Drugs that inhibit CYP3A4 may not have the same magnitude of effect on CYP3A5, which is typically less susceptible to inhibition [56]. Using grapefruit juice as an enzyme inhibitor of both CYP3A4 and CYP3A5, the urinary 6β-hydroxycortisol/cortisol ratio varied depending on CYP3A5 genotype. Likewise, genotype of MDR1 (P-glycoprotein) was associated with urinary 6β-hydroxycortisol/cortisol ratio in a pattern that suggested that both polymorphisms affect this cortisol endpoint [57].

Findings have been mixed with CYP2C19. Moclobemide resulted in a significant increase in omeprazole AUC, an effect that was limited to EM's [58]. However, in the case of tacrolimus with administration of either lansoprazole or rabeprazole, an interaction was noted only in CYP2C19 PM's who also had the CYP3A5*3/*3 genotype. Essentially CYP3A become more important in these subjects and CYP3A4 and CYP3A5 exhibit a similar substrate profile [59]. Clarithromycin inhibited CYP2C19 mediated metabolism of omeprazole in EM's, IM's and PM's to a similar extent. However, clinical implications become apparent after considering that coadministration of the two drugs in PM's resulted in 30-fold higher exposure (AUC) compared to the AUC in the EM group receiving omeprazole alone [60]. Oral contraceptives were shown to enhance carisoprodol AUC by 60% overall; however, there was no difference with respect to CYP2C19 genotype (EM's versus IM's) [61].

Some interactions are extremely complex as noted with the mixed inhibitor inducer HIV protease inhibitor combination, tipranavir/ritonavir. The combination produced weak induction of CYP1A1, moderate induction of CYP2C19, potent induction of P-glycoprotein, and potent inhibition of CYP2D6 and CYP3A after multiple dosing [62].

Given the potential differences in the effects of metabolic interactions based on genotype, either measuring genotype or perhaps planning studies with genotype entry criteria should be considered.

20.3.5 Interactions Affecting Other Elimination Pathways

Some drugs are eliminated by fecal excretion and are excreted in bile or by transintestinal secretion. Enterohepatic recycling occurs when drugs are eliminated in bile as conjugates. Deconjugation occurs in the small intestine, thereby allowing for reabsorption of the parent drug. A precipitant drug that interferes with deconjugation will prevent enterohepatic recycling (reabsorption) and increase the apparent clearance. Potential examples of this interaction type involves antibacterial drugs and oral contraceptives [64]. Precipitant drugs that physically trap or bind another drug within the gastrointestinal lumen may also enhance the clearance of the object drug. Examples of this interaction include iron salts or aluminum hydroxide with doxycycline [65, 66].

20.4 Pharmacostatistical Techniques

Advances have been made in the past decade to facilitate detection and evaluation of drug interactions. The intent of this section is to focus on the recommended approaches for presenting and analyzing pharmacostatistical drug interaction data. In discussions below, the terms "test" and "reference" treatments refer to the administration of the object and precipitant drugs in combination (test) and administration of the object drug alone (reference).

20.4.1 Statistical Analysis Approach

There are many approaches, both parametric and nonparametric, to analyzing comparative data from drug interaction studies. The recommended strategy by regulatory agencies in the United States [10] and Europe [67, 68], editors of clinical pharmacology journals [69, 70], and others [71, 72] is to adapt the confidence interval approach used in average bioequivalence studies [14, 73]. The purpose of a bioequivalence or comparative bioavailability study is to demonstrate that the shape and magnitude of blood or plasma concentration-time profiles produced by the drug formulations under study are sufficiently alike that therapeutic equivalence can be assumed. In drug interaction studies the aim is usually to show that an interaction is not clinically meaningful by the similarity of concentration-time profiles or other pharmacokinetic characteristics. In traditional analysis, the null hypothesis stipulates that parameters for the object drug are equivalent for the test and reference treatment. When a significant difference is found, the null hypothesis would be rejected and a difference would be concluded. A small, clinically unimportant difference may be statistically significant at the 5% level of significance ($\alpha = 0.05$).

The lack of significance does not necessarily imply "no interaction". In such cases, the statistical power, or probability of detecting a specified difference, must be considered. The specified difference should be a change that would be considered clinically important given the available pharmacodynamic and toxicologic information. A large, clinically important difference between treatments may not be statistically significant if sample size is small and within- and/or between-individual pharmacokinetic variability is large. Therefore, classical statistical approaches that attempt to confirm an interaction by rejecting the null hypothesis of "no difference" are inappropriate because the consumer risk is not controlled.

An alternative approach is required that adequately defines the risk to the consumer. Because a drug-drug interaction consists of different drug treatments, one should test the null hypothesis of "nonequivalence" by demonstrating "equivalence" or "lack of pharmacokinetic interaction", as first proposed by Steinijans et al. [74]. In this manner the risk to the patient of a clinically relevant interaction can be defined within established limits. Generic drugs are approved on the basis of bioequivalence compared to a reference product. Risk to consumers is considered

low for most drugs when substituting a generic drug that is considered bioequivalent. The same principal applies when a potential interacting drug is studied and despite concomitant administration, the exposure to the object drug remains bioequivalent to the object drug given alone.

Two important assessment criteria must be defined before invoking the equivalence approach: (1) the range of clinically acceptable variation in pharmacokinetic response of the affected drug, and (2) the risk to the consumer of incorrectly concluding a "lack of pharmacokinetic interaction". The range of clinically acceptable variation defines the equivalence range (clinical no-effect boundary). The range can be determined from population (group) average dose and/or concentration-response relationships, pharmacokinetic and pharmacodynamic models, and other available information for the object drug [10]. The consumer risk is the type I or α error in statistics and is usually set at 5%.

The equivalence method is based on the two one-sided *t*-test procedure of rejecting the interval hypotheses that the test/reference ratio is less than the lower equivalence limit and greater than the upper equivalence limit. At the 5% level of consumer risk, this procedure is operationally identical to the method of declaring equivalence (or lack of interaction) if the shortest 90% confidence interval for the ratio is entirely within the prespecified equivalence range. More generally, the $100\times(1-2\alpha)$% confidence limits around the ratio (test/reference) of the means or medians of the test and reference treatments constrain the consumer risk to $100\times(\alpha)$% as well as indicate the precision of a negative outcome. In bioequivalence studies the accepted equivalence range is ±20%, which corresponds to a lower limit of 80% and an upper limit of 120% for original data or 125% for logarithmic transformed data. A range of ±20% seems reasonable to assess product quality, but for drug interactions these limits may be wider or narrower depending on the patient population, the therapeutic index and pharmacokinetic variability of the object drug. For example, a range of clinically acceptable variation of 30% for changes in zidovudine AUC was suggested [75] whereas a range variation of 50% for changes in indinavir AUC was proposed [76]. No dose adjustment is required if the confidence interval falls within the no-effect boundary, and the boundary does not have to be symmetrical around the mean difference on the original or logarithmic scales [10, 77]. Equivalence limits of the form $(\theta, 1/\theta)$ have been proposed for data on both the original and logarithmic scales, where θ is the lower limit for the test/reference ratio [78]. The upper limit would be the reciprocal (e.g., limits of 0.8 and 1.25).

Statistical inferences are made on either absolute (test-reference) or relative (test/reference) differences in the arithmetic means, geometric means (from logarithmic transformed data), harmonic means (from reciprocal transformed data), or medians of pharmacokinetic variables. Parametric analysis of variance (ANOVA) models appropriate for the study design are used to test differences in means and nonparametric methods such as the Wilcoxon rank sum test or Wilcoxon signed rank test are used to test differences in medians. If the study design is unbalanced from an unequal number of subjects in each sequence (crossover) or from missing data then assessments are based on least-squares means. Because clinicians prefer to think in

terms of relative rather than absolute changes, pharmacokinetic differences are usually expressed as a ratio. Confidence limits around these mean differences (mean ratios) for within-subject comparisons in crossover studies and between-group comparisons in parallel studies are constructed from the residual mean-square error (MSE) term in ANOVA. The ANOVA provides exact confidence limits for relative differences of geometric means if the distribution of variables is truly log-normal. Only approximate limits for relative differences of arithmetic means are possible, because ANOVA ignores variability in the reference mean unless Fieller's theorem is applied [79]. Nonparametric approximate 90% confidence limits can be calculated for two-period, two-sequence crossover studies [80]. One should be cautious in concluding "no interaction" when approximate confidence limits generated from parametric or non-parametric techniques are within but near the equivalence limits. Also, inferences on mean data may not reflect how certain individuals in the study population respond to the interaction. A particular strata of individuals may show an apparent interaction even though the overall mean data indicate no pharmacokinetic interaction.

20.4.2 Logarithmic Transformation of Pharmacokinetic Variables

All pharmacokinetic variables, except those such as t_{max} that depend on discreet sampling times, are logarithmically transformed before ANOVA [14, 74, 81]. Harmonic means have been proposed for inferences on half-life [82]. Transformation converts a multiplicative model to an additive model, which is the basis of ANOVA [ln(test/reference) = ln(test) − ln(reference)]. Decisions on t_{max} are best handled by nonparametric analysis. Most pharmacokinetic data have positively skewed distributions created by the truncation of these quantities at zero and have variances that depend on the mean. Transformation reduces the skewness and brings the distribution of data closer to normal. However, the main reason for transforming the data is to stabilize or make equal the within-subject (crossover study) or between-group (parallel study) variance and not to normalize the between-subject parameters [81]. Another advantage of transformation is that it is the best way to handle ratios for relative or proportional differences, and calculation of the associated confidence limits is straightforward, as discussed above.

For most studies the outcome will not change regardless of whether the original or log scale is used. There are two instances where conclusions can be opposite in a within-subject design [81]. If certain subjects with larger than average responses show larger than expected absolute differences, variability is increased on the original scale, whereas larger than expected absolute differences for smaller than average responses are expanded on the log scale. If this occurs, for example when fast and slow metabolizers are studied together, then the within-subject variability and the relative mean changes can be different on the two scales.

20.4.3 Crossover Design and Analysis of Variance

The ANOVA for a crossover design includes the effects of sequence, subject within sequence, treatment, period, and, except for the 2, 2, 2 design, carryover. All effects except the sequence effect are tested by the MSE term. The sequence effect is tested against the subject-within-sequence error term. Any subgroup comparison of fixed effects (e.g., males and females) is tested with the subject mean-square error term.

The sequence effect measures the difference between the groups of subjects defined by their sequence. In statistical parlance, this effect is known as the treatment-by-period interaction, which is a measure of the differential effect of the treatment (test-reference) in each of the periods. In the 2, 2, 2 design the sequence effect is caused by three confounded sources: (1) a difference between subjects in the two sequences (i.e., group effects), (2) an unequal carryover of one treatment into the next period compared to the other treatment, or (3) a treatment-by-period interaction. In a 2, 2, 2 study, the presence of a sequence effect requires that the data be analyzed for each period separately; for example, when unequal carryover effects are present then data from only period 1 should be used.

The period effect measures the difference between study periods or alternatively the differential effect of the treatment in each of the sequences. In a 2,2,2 study, the period effect is completely confounded with treatment-by-sequence interaction. Any difference in treatment comparison (treatment-reference) between the two sequence groups cannot be distinguished from period effects. If there are carryover effects or if more than two periods are included, then the period effect and treatment-by-sequence interaction are not interchangeable. The period effect can be caused by equal carryover in each sequence from period to period, bias in analytical data if samples in each period were analyzed in different batches, differences in the study environment or procedures, and changes with time in stage of disease.

The presence of a treatment effect implies that differences between periods are in opposite directions for the two sequence groups (i.e., in a 2, 2, 2 study, if P2 – P1 in S1 is negative then P2 – P1 in S2 may be positive). Treatment effect is completely confounded with period-by-sequence effect in a 2, 2, 2 study provided there is no differential carryover present. The estimate of treatment differences will not be biased if a period effect is present.

The MSE term is a measure of the intrasubject variability, and is usually converted to a coefficient of variation (CV_W) to estimate the consistency of the magnitude of interaction among the subjects [83]. The CV_W is estimated as $100\% \times (e^{MSE} - 1)^{½}$ for logarithmic transformed data, and as $100\% \times (MSE)^{½}/Y$ for original data, where Y is either the least-squares mean of the reference treatment or the combined mean of the two least-squares treatment means being compared.

The goal of any within-subjects design is too minimize the CV_W. The interaction is considered highly variable for a particular pharmacokinetic parameter if the CV_W is >30%. The CV_W is a very informative parameter but is rarely reported in the literature. Values for a number of drugs orally administered in crossover bioequivalence studies have been tabulated by Steinijans et al. [84]. The CV_W is important to

know because the width of the confidence interval around the difference of treatment means, the calculation of post-hoc power to detect these differences, and an estimation of sample sizes for planning future interaction studies are directly related to this value.

There are a number of sources of variation in CV_W: the true intrasubject pharmacokinetic variation exhibited by a single person, analytical variability (measurement errors), within-batch variation in manufacture of the drug formulation, nonadherence to the medications, and the random subject-by-treatment interaction. This latter source is caused by random variability of treatments within subjects or within identifiable subgroups of the population studied. Each individual may behave differently to the test treatment or subjects in subgroups may show similar variation within subgroups but different responses to the test treatment among subgroups. An example could be smokers responding differently from nonsmokers to one of the treatments. On the log scale, the random subject-by-treatment interaction is minimized if all subjects show the same relative change in the same direction.

20.4.4 Sample Size and Post-Hoc Power Calculations

The sample size of the study needs to be planned with consideration of the purpose of the study. If the purpose of the study is to evaluate a potential drug interaction that is suspected based on preliminary data, the sample size can be somewhat conservative. However, if the goal is to demonstrate the lack of interaction for an individual drug when a member of the same drug class exhibits the interaction (class labeling) then the sample size should be larger. Estimations of sample size for a within-subject drug interaction study require a knowledge of CV_w for the interaction. These values may be greater than those reported for drugs in bioequivalence studies [84] because not all subjects will respond to the precipitant drug to the same degree. Tables of sample sizes for 2, 2, 2 crossover designs to attain a power of 80% or 90% at the 5% nominal level for a given CV_w and expected relative difference in treatment medians or means are published for the multiplicative (logarithmic) model with equivalence ranges of 0.7–1.43 [85], 0.8–1.25 [78, 86], and 0.9–1.11 [85]. Similar tables are published for the additive (original) model [87] and for parallel designs [78, 88]. The minor influence of the between-subject coefficient of variability on sample size estimates for the 2, 2, 2 crossover design is demonstrated in [78].

Post-hoc power calculations are useful for negative studies to estimate differences that can be detected with a certain power (usually 80% at the 5% significance level) or to estimate the power of the study to detect a specified difference (usually 20% difference from reference at the 5% significance level). These calculations require an estimation of the standard error of the difference in mean or medians. General equations for point hypothesis testing for original and logarithmic data using a central *t*-distribution are provided in references [79, 89]. General equations for interval hypothesis testing using a noncentral *t*-distribution for crossover and parallel designs are given in references [78, 79].

20.5 Pharmacokinetic Metrics and Characteristics

The major assumption in bioequivalence is that the Cl of the drug under investigation is constant over the course of the study and that AUC is a pure characteristic of extent of bioavailability (F). In drug interactions both clearance and bioavailability can change after oral administration. Therefore, changes in AUC can result from alterations in either parameter. Schall et al. [90]. have proposed the terminal elimination half-life ($t_{½,z}$) and the ratio of AUC/$t_{½,z}$ as characteristics for Cl and F, respectively, in drug-drug interaction studies. Assuming a constant volume of distribution, an increase in Cl will decrease $t_{½,z}$ and an increase in the ratio of AUC/$t_{½,z}$ suggests an increase in F. In single-dose bioequivalence studies, both AUC from time of dosing to the time of last measurable sample (t_z) (AUC_{0-tz}) and AUC_{0-tz} extrapolated to infinity ($AUC_{0-\infty}$) are used as metrics to characterize F because $t_{½,z}$ is assumed to be unaffected by changes in only F. However, if $t_{½,z}$ changes from drug interactions then only $AUC_{0-\infty}$ should be used to characterize drug exposure because changes in AUC_{0-tz} and $AUC_{0-\infty}$ may not be proportional.

Because AUC is a composite characteristic of Cl and F, and peak drug levels (C_{max}) reflect both rate and extent of absorption, these metrics can be used to indicate drug exposure [91]. AUC is the ideal metric for total systemic drug exposure and C_{max} is a measure of peak systemic exposure. The term drug exposure conveys more clinical relevance than the term "rate and extent of drug absorption" because drug safety and effectiveness are concerns in drug interaction studies.

20.6 Presentation and Interpretation of Drug Interaction Data

There are generally three ways to present comparative pharmacokinetic data for changes in the test treatment relative to the reference treatment: (1) a test/reference ratio expressed as a percentage, (2) an x-fold change, where x is the test/reference ratio, or (3) a percentage change [(test/reference ratio − 1) × 100%]. For example, an AUC ratio of 200% indicates a 2-fold increase and a 100% increase in AUC. Often x-fold changes are confused with percentage change, and the reader needs to be aware of which method of calculation was used.

Current thinking favors expressing the results in terms of a test/reference geometric mean ratio and the corresponding 90% confidence limits for AUC and C_{max} parameters. A search for formal clinical drug interaction studies of anti-infective medications over the period of 2001–2003 (assessed 1/6/04 via medline) found 23 published studies. Only five (22%) of these studies provided 90% confidence limits and used bioequivalence testing. Review of the period of 2008–2009 (assessed 7/14/10 via medline) revealed 59 published studies formally evaluating a drug-drug interaction involving pharmacokinetics. Two studies employed alternative study designs and used population analysis. Of the remaining 57 studies, 43 (75%) used the equivalence approach with geometric mean ratios and 90% confidence intervals reported. Although, this review shows improvement over the 7 year interval, continued

effort is needed because 25% of relevant studies still use outdated analysis methods. The use of 95% confidence limits should not be confused with 90% confidence limits. The former bounds will be wider and may lead to different conclusions in equivalence testing. Reporting the 95% confidence limits is another way of reporting a test of significance at the 5% level of significance. For example, AUC of bosentan increased 2.1-fold (95% confidence interval 1.5–2.7) after concomitant administration with ketoconazole [92]. The 95% confidence interval would be examined to determine if it includes the value 1.0, and if not, as in this case, a statistically significant interaction at the 5% level of significance ($p<0.05$) would be concluded.

20.6.1 No-Effect Boundary

The "no-effect boundary" or acceptable range needs to be established a priori. If a drug interaction is concluded, the clinical significance of the interaction and recommendations on how to manage the interaction need to be formulated. The FDA guidance for metabolic interaction studies allows three approaches for developing a no-effect boundary. The first approach is to describe the range of the selected exposure parameters over a range of doses that are normally used. The sponsor should include information on dose and or concentration-response studies or PK/PD models to support the recommendation. If the exposure parameters remain within this range in the presence of a potential precipitant drug, the sponsor could conclude that "no interaction is expected". The second approach requires a replicate study design and addresses the question of switchability. This approach involves assessment of individual bioequivalence rather than average bioequivalence. Studies employing this second approach for a drug interaction study have not been published. The third approach defaults to bioequivalence criteria where the 90% confidence interval for geometric mean exposure parameter ratio (test/reference) falls within 80–125% [10]. This latter approach is most commonly used.

The use of bioequivalence criteria should eliminate a substantial portion of studies that statistically conclude a drug interaction when only small clinically insignificant differences occur. As an example, digoxin steady-state AUC was 25.5 ng·h/ml after digoxin alone and 23.9 ng·h/ml after digoxin plus zaleplon (a hypnotic agent). From a test of significance (ANOVA, $p=0.018$) a drug interaction would have been concluded. The geometric mean ratio (test/reference) was 93% with a 90% confidence interval of 89–98%, and this would more appropriately lead to a "no-effect" conclusion [93]. Potential problems with the bioequivalence approach include too small of a sample size and high variability. If the sample size is too small, confidence intervals tend to be wide, and this could result in a 90% confidence interval that falls outside of the "no-effect boundary" despite a mean ratio near 100%. Too large of a sample size with the bioequivalence approach does not cause adverse consequences other than excessive study costs and ethical issues of imparting risk to numbers of subjects greater than needed. For tests of significance, too small of a sample size will lead to low power and inability to detect an important drug

interaction, and too large of a study population may cause detection of small, clinically insignificant changes.

Not only does the no-effect boundary need to be established a priori, use of unconventional ranges needs to be justified. In a study evaluating the effect of montelukast on digoxin, several problems are apparent. The authors used a no-effect boundary of 70–143% without appropriate justification. Digoxin exhibits a narrow therapeutic index and relatively low variability in exposure parameters in a healthy population. The mean digoxin $AUC_{0-\infty}$ was 43.2 ng·h/ml for digoxin alone and 39.2 ng·h/ml for digoxin plus montelukast. Although the 90% confidence interval for $AUC_{0-\infty}$ was 70–118%, the authors concluded that montelukast has no effect on the pharmacokinetics of digoxin [94]. The use of this expanded no-effect boundary for a drug with a narrow therapeutic index is concerning. Moreover, the 90% confidence interval is too wide to fit within the range of 80–125%. The study involved a small sample size ($n = 10$) and did not address power.

In another study, which evaluated the effects of proton pump inhibitors on theophylline, the no-effect boundary was expanded to 70–143% for steady-state C_{max}, but not for steady-state AUC [95]. There is no pharmacokinetic basis to suspect a change in rate of absorption of theophylline from acid suppression, and the reason for the expanded boundary was not addressed. Because the observed 90% confidence limit for steady-state C_{max} fell within the range of 80–125%, conclusions remain appropriate. In some cases involving drugs (e.g., ethionamide) with moderate to high variability in exposure parameters, it may be difficult to obtain 90% confidence intervals that fall within the usual no-effect boundaries, requiring the use of large sample sizes or expanded boundaries [96].

An example of a study that used an expanded no-effect boundary and provided justification involved interactions between didanosine, and indinavir, ketoconazole and ciprofloxacin [97]. A no-effect boundary of 75–133% was used. The authors cited a study where the AUC of indinavir was increased 29% with clarithromycin administration and the interaction was concluded to be not clinically significant. For ciprofloxacin, the authors cited the package insert and a publication and considered that a 48% increase in ciprofloxacin AUC in elderly subjects did not result in a recommendation for reducing the dose. For ketoconazole, the authors cited a study that reported a 59% increase in ketoconazole AUC when administered with food compared to fasting and considered that the labeling did not contain a recommendation for administering ketoconazole with food [97]. In another study, in which ketoconazole significantly increased the exposure of desloratadine, the interaction was concluded to be not clinically relevant as no changes in ECG parameters were observed [98]. Although such observation does not totally rule out clinical significance in special populations, the value of concomitant pharmacodynamic assessment is apparent.

20.6.2 Studies to Confirm Clinical Strategy

Another potential area of misinterpretation is when the doses and/or dosing intervals of the drug under investigation are different in the test and reference arms of the study.

This may occur if the purpose is to obtain equivalent drug exposures over a specified time period in the absence and presence of an interacting drug. The magnitude of pharmacokinetic effect can appear smaller or larger if the control dose is larger or smaller. For example, 800 mg of indinavir every 8 h was estimated to give about the same AUC over 24 h as 400 mg indinavir every 12 h in the presence of 400 mg ritonavir every 12 h (99). From single-dose indinavir data, the magnitude of the interaction was actually about a fivefold increase in AUC if 400 mg of indinavir was used as the reference [99]. Depending on the purpose of the study, the analysis should be based on dose-normalized or dose-independent parameters (e.g., clearance or AUC/dose) for drugs that display linear pharmacokinetics, and the reporting should reflect the actual differences in these parameters to avoid misinterpretation.

20.7 Summary

Many issues remain to be resolved concerning optimal design of drug interaction studies. Traditional issues such as defining the research hypothesis (question of interest); determining the appropriate study population (healthy volunteers or patients); determining the study design (crossover, longitudinal or parallel; washout requirements, etc.); deciding between single-dose or steady-state; and deciding which pharmacokinetic and/or pharmacodynamic endpoints to evaluate, should depend on knowledge of the drugs involved, preliminary data on the potential interaction, and general knowledge of pharmacokinetics and drug interactions. Defining whether a drug interaction exists is now considered an equivalence problem where endpoints are compared between the object drug given with and without the precipitant drug. The acceptable clinical no-effect boundary associated with equivalence must be somewhat flexible depending on the therapeutic index of the object drug and variability of the endpoints. The use of replicate designs improves the ability to examine carryover, reduces the required sample size, and allows determination of intrasubject variability in the interaction. However, studies involving replicate treatments are more expensive and the analysis is more complex. Although replicate designs are being used for bioequivalence studies and are widely discussed, such designs are not uniformly accepted as a promising new standard in drug interaction studies.

References

1. Ekins S. Past, present, and future applications of precision-cut liver slices for in vitro xenobiotic metabolism. Drug Metabol Rev 1996;28:591–623.
2. Decker CJ, Laitinen LM, Bridson GW, Raybuck SA, Tung RD, Chaturvedi PR. Metabolism of amprenavir in liver microsomes: role of CYP3A4 inhibition for drug interactions. J Pharm Sci 1998;87:803–807.
3. Bonnabry P, Sievering J, Leemann T, Dayer P. Quantitative drug interactions prediction system (Q-DIPS): a computer-based prediction and management support system for drug metabolism interactions. Eur J Clin Pharmacol 1999;55:341–347.

4. Rodrigues AD, Wong SL. Application of human liver microsomes in metabolism-based drug-drug interactions: in vitro-in vivo correlations and the Abbott Laboratories experience. Adv Pharmacol 1997;43:65–101.
5. Koudriakova T, Iatsimirskaia E, Utkin I, et al. Metabolism of the human immunodeficiency virus protease inhibitors indinavir and ritonavir by human intestinal microsomes and expressed cytochrome P4503A4/3A5: mechanism-based inactivation of cytochrome P4503A by ritonavir. Drug Metab Dispos 1998;26:552–561.
6. Hochman JH, Yamazaki M, Ohe T, Lin JH. Evaluation of drug interactions with P-glycoprotein in drug discovery: in vitro assessment of the potential for drug-drug interactions with P-glycoprotein. Curr Drug Metab 2002;3:257–273.
7. Benet LZ, Cummins CL, Wu CY. Transporter-enzyme interactions: implications for predicting drug-drug interactions from in vitro data. Curr Drug Metab 2003;4:393–398.
8. Rolan PE. Plasma protein binding displacement interactions--why are they still regarded as clinically important? Br J Clin Pharmacol 1994;37:125–128.
9. Sansom LN, Evans AM. What is the true clinical significance of plasma protein binding displacement interactions? Drug Safety 1995;12:227–233.
10. Draft Guidance for Industry. In vivo drug metabolism/drug interaction studies - study design, data analysis, and recommendations for dosing and labeling. September 2006. U.S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research.
11. Therapeutic Products Programme Guidance Document. Drug-drug interactions: studies in vitro and in vivo. September 21, 2000. Therapeutic Products Directorate, Health Canada.
12. Bjornsson TD, Callaghan JT, Einolf HJ, et al. The conduct of in vitro and in vivo drug-drug interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. Drug Metab Dispos 2003;31:815–832.
13. Gallicano KD, Sahai J, Shukla VK, et al. Induction of zidovudine glucuronidation and amination pathways by rifampicin in HIV-infected patients. Br J Clin Pharmacol 1999;48:168–179.
14. Ormsby E. Statistical methods in bioequivalence. In: Jackson AJ (ed). Generics and Bioequivalence, Boca Raton, FL: CRC Press, 1994, pp. 1–27.
15. Fleiss JL. A critique of recent research on the two-treatment crossover design. Controlled Clin Trials 1989;10:237–243.
16. Vuorinen J. A practical approach for the assessment of bioequivalence under selected higher-order cross-over design. Statist Med 1997;16:2229–2243.
17. Chow SC, Liu JP. On assessment of bioequivalence under a higher-order crossover design. J Biopharm Stat 1992;2:239–256.
18. Nix DE, Di Cicco RA, Miller AK, et al. The effect of low-dose cimetidine (200 mg twice daily) on the pharmacokinetics of theophylline. J. Clin Pharmacol 1999;39:855–865.
19. Grasela TH Jr., Antal EJ, Ereshefsky L, Wells BG, Evans RL, Smith RB. An evaluation of population pharmacokinetics in therapeutic trials. Part II. Detection of a drug–drug interaction. Clin Pharmacol Ther 1987; 42:433–441.
20. Purkins L, Wood N, Kleinermans D, Love ER. No clinically significant pharmacokinetic interactions between voriconazole and indinavir in healthy volunteers. Br J Clin Pharmacol 2003;56:62–68.
21. Cato A, Cavanaugh J, Shi H, Hsu A, Leonard J, Granneman R. The effect of multiple doses of ritonavir on the pharmacokinetics of rifabutin. Clin Pharmacol Ther 1998;63:414–421.
22. Romero AJ, Pogamp PL, Nilsson LG, Wood N. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. Clin Pharmacol Ther 2002;71:226–234.
23. Cadieux RJ. Drug interactions in the elderly. How multiple drug use increases risk exponentially. Postgrad Med 1989;86:179–186.
24. Ragueneau I, Poirier JM, Radembino N, Sao AB, Funck-Brentano C, Jaillon P. Pharmacokinetic and pharmacodynamic drug interactions between digoxin and macrogol 4000, a laxative polymer, in healthy volunteers. Br J Clin Pharmacol 1999;48:453–456.
25. Piscitelli SC, Goss TF, Wilton JH, D'Andrea DT, Goldstein H, Schentag JJ. Effects of ranitidine and sucralfate on ketoconazole bioavailability. Antimicrob Agents Chemother 1991;35: 1765–1771.

26. Blum RA, D'Andrea DT, Florentino BM, et al. Increased gastric pH and the bioavailability of fluconazole and ketoconazole. Ann Intern Med 1991;114:755–757.
27. Lebsack ME, Nix D, Ryerson B, et al. Effect of gastric acidity on enoxacin absorption. Clin Pharmacol Ther 1992;52:252–256.
28. Lehto P, Kivisto KT, Neuvonen PJ. The effect of ferrous sulphate on the absorption of norfloxacin, ciprofloxacin and ofloxacin. Br J Clin Pharmacol 1994;37:82–85.
29. Nix DE, Watson WA, Lener ME, et al. Effects of aluminum and magnesium antacids and ranitidine on the absorption of ciprofloxacin. Clin Pharmacol Ther 1989;46:700–705.
30. Parpia SH, Nix DE, Hejmanowski LG, Goldstein HR, Wilton JH, Schentag JJ. Sucralfate reduces the gastrointestinal absorption of norfloxacin. Antimicrob Agents Chemother 1989;33:99–102.
31. Jungbluth GL, Pasko MT, Beam TR, Jusko WJ. Ceftriaxone disposition in open-heart surgery patients. Antimicrob Agents Chemother 1989;33:850–856.
32. Megran DW, Lefebvre K, Willetts V, Bowie WR. Single-dose oral cefixime versus amoxicillin plus probenecid for the treatment of uncomplicated gonorrhea in men. Antimicrob Agents Chemother 1990;34:355–357.
33. Gaspari F, Perico N, Remuzzi G. Measurement of glomerular filtration rate. Kidney Internat 1997;63 (suppl.):S151–154.
34. Brochner-Mortensen J. Current status on assessment and measurement of glomerular filtration rate. Clin Physiol 1985;5:1–17.
35. Hellerstein S, Berenbom M, Alon US, Warady BA. Creatinine clearance following cimetidine for estimation of glomerular filtration rate. Pediatr Nephrol 1998;12:49–54.
36. Levey AS, Bosch JP, Breyer-Lewis J, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–470.
37. Baciewicz AM, Self TH. Rifampin drug interactions. Arch Intern Med 1984;144:1667–1671.
38. Wandel C, Bocker R, Bohrer H, Browne A, Rugheimer E, Martin E. Midazolam is metabolized by at least three different cytochrome P450 enzymes. Br J Anaest 1994;73:658–661.
39. Thummel KE, Shen DD, Podoll TD, et al. Use of midazolam as a human cytochrome P450 3A probe: II. Characterization of inter- and intraindividual hepatic CYP3A variability after liver transplantation. J Pharmacol Exper Ther 1994;271:557–566.
40. Lown KS, Thummel KE, Benedict PE, et al. The erythromycin breath test predicts the clearance of midazolam. Clin Pharmacol Ther 1995;57:16–24.
41. Watkins PB, Turgeon DK, Saenger P, et al. Comparison of urinary 6-beta-cortisol and the erythromycin breath test as measures of hepatic P450IIIA (CYP3A) activity. Clin Pharmacol Ther 1992;52:265–273.
42. Hunt, CM, Watkins, PB, Saenger P, et al. Heterogeneity of CYP3A isoforms metabolizing erythromycin and cortisol. Clin Pharmacol Ther 1992;51:18–23.
43. Chiou WL, Jeong HY, Wu TC, Ma C. Use of the erthromycin breath test for in vivo assessments of cytochrome P4503A activity. Clin Pharmacol Ther 2001;70:305–310.
44. Sarkar MA, Jackson BJ. Theophylline N-demethylations as probes for P4501A1 and P4501A2. Drug Metab Dispos 1994;22:827–834.
45. Ziebell J, Shaw-Stiffel T. Update on the use of metabolic probes to quantify liver function: caffeine versus lidocaine. Digest Dis 1995;13:239–250.
46. Anthony LB, Boeve TJ, Hande KR. Cytochrome P-450IID6 phenotyping in cancer patients: debrisoquin and dextromethorphan as probes. Cancer Chemother Pharmacol 1995;36: 125–128.
47. Flockhart DA. Drug interactions and the cytochrome P450 system. The role of cytochrome P450 2C19. Clin Pharmacokin 1995;29(Suppl. 1):45–52.
48. Fuhr U, Rost KL, Engelhardt R, et al. Evaluation of caffeine as a test drug for CYP1A2, NAT2 and CYP2E1 phenotyping in man by in vivo versus in vitro correlations. Pharmacogenetics 1996;6:159–176.
49. Brockmoller J, Rost KL, Gross D, Schenkel A, Roots I. Phenotyping of CYP2C19 with enantiospecific HPLC-quantification of R- and S-mephenytoin and comparison with the intron4/exon5 G-->A-splice site mutation. Pharmacogenetics 1995;5:80–88.

50. Tanaka E. Clinically important pharmacokinetic drug-drug interactions: role of cytochrome P450 enzymes. J Clin Pharm Ther 1998;23:403–416.
51. Lomaestro BM, Piatek MA. Update on drug interactions with azole antifungal agents. Ann Pharmacother 1998;32:915–928.
52. Caraco Y. Genetic determinants of drug responsiveness and drug interactions. Ther Drug Monitor 1998;20:517–524.
53. Shannon M. Drug-drug interactions and the cytochrome P450 system: an update. Pediatr Emerg Care 1997;13:350–353.
54. Guengerich FP. Role of cytochrome P450 enzymes in drug-drug interactions. Adv Pharmacol 1997;43:7–35.
55. Mikus G, Schöwel V, Drzewinska M, et al. Potent cytochrome P4502C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. Clin Pharmacol Ther 2006;80:126–135.
56. Isoherranen N, Ludington SR, Givens RC, et al. The influence of CYP3A5 expression on the extent of hepatic CYP3A inhibition is substrate-dependent: An in vitro-in vivo evaluation. Drug Metabol Disposit 2008;36:146–154.
57. Li D, Abudula A, Abulahake M, Zhu AP, Lou YQ, Zhang GL. Influence of CYP3A5 and MDR1 genetic polymorphisms on urinary 6β-hydroxycortisol/cortisol ratio after grapefruit juice intake in health Chinese. J Clin Pharmacol 2010;50:775–784.
58. Cho JY,Yu KS, Jang IJ, Yang BH, Shin SG, Yim DS. Omeprazole is inhibited by a single dose of moclobemide in homozygotic EM genotype for CYP2C19. Br J Clin Pharmacol 2001;53:393–397.
59. Miura M, Inoue K, Kagaya H, Satoh S, Tada H, Sagae Y, Habuchi T, and Suzuki T. Influence of rabeprazole and lansoprazole in the pharmacokinetics of tacrolimus in relation to CYP2C19, CYP3A5 and MDR1 polymorphisms in renal transplant recipients. Biopharm Drug Disposit 2007;28:167–175.
60. Furuta T, Ohashi K, Kobayashi K, et al. Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. Clin Pharmacol Ther 1999;66:265–274.
61. Bramness JG, Skurtveit S, Gulliksen M, Breilid H, Steen VM, Morland J. The CYP2C19 genotype and the use of oral contraceptives influence the pharmacokinetics of carisoprodol in healthy human subjects. Eur J Clin Pharmacol 2005;61:499–506.
62. Dumond JB, Vourvahis M, Rezk NL, et al. A phenotype-genotype approach to predicting CYP450 and P-glycoprotein drug interactions with the mixed inhibitor/inducer tipranavir/ritonavir. Clin Pharmcol Ther 2010;87:735–742.
63. Bradford PA, Sanders CC. Use of a predictor panel to evaluate susceptibility test methods proposed for piperacillin-tazobactam. Antimicrob Agents Chemother 1993;37:2578–2585.
64. Zachariasen RD. Loss of oral contraceptive efficacy by concurrent antibiotic administration. Women Health 1994;22:17–26.
65. Nguyen VX, Nix DE, Gillikin S, Schentag JJ. Effect of oral antacid administration on the pharmacokinetics of intravenous doxycycline. Antimicrob Agents Chemother 1989;33:434–436.
66. Neuvonen PJ, Penttila O. Effect of oral ferrous sulphate on the half-life of doxycycline in man. Eur J Clin Pharmacol 1974;7:361–363.
67. Note for Guidance on the investigation of drug interactions. December 1997. Committee for Proprietary Medicinal Products (CPMP), The European Agency for the Evaluation of Medicinal Products Human Medicines Evaluation Unit.
68. Müller HJ, Gundert-Remy U. The regulatory view on drug-drug interactions. Int J Clin Pharmacol Ther 1994;32: 269–273.
69. Hitzenberger G, Steinijans VW. To reject or not to reject recent experience with bioequivalence papers. Int J Clin Pharmacol Ther 1994;32: 161–164.
70. Waller PC, Jackson PR, Tucker GT, Ramsay LE. Clinical pharmacology with confidence. Br J Clin Pharmacol 1994;37:309,310.
71. Fuhr U, Weiss M, Kroemer HK, et al. Systematic screening for pharmacokinetic interactions during drug development. Int J Clin Pharmacol Ther 1996;34:139–151.

72. Kuhlmann J. Drug interaction studies during drug development: which, when, how? Int J Clin Pharmacol Ther 1994;32:305–311.
73. Pidgen AW. Statistical aspects of bioequivalence - a review. Xenobiotica 1992;22:881–893.
74. Steinijans VW, Hartmanns M, Huber R, Radtke HW. Lack of pharmacokinetic interaction as an equivalence problem. Int J Clin Pharmacol Ther Toxicol 1991;29:323–328.
75. Gallicano KD, Sahai J, Swick L, Seguin I, Pakuts A, Cameron DW. Effect of rifabutin on the pharmacokinetics of zidovudine in patients infected with human immunodeficiency virus. Clin Infect Dis 1995;21:1008–1011.
76. De Wit S, Debier M, De Smet M, et al. Effect of fluconazole on indinavir pharmacokinetics in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 1998; 42:223–227.
77. Huang S-M, Lesko LJ, Williams RL. Assessment of the quality and quantity of drug-drug interaction studies in recent NDA submissions: study design and data analysis issues. J Clin Pharmacol 1999;39:1006–1014.
78. Hauschke D, Kieser M, Diletti E, Burke M. Sample size determination for proving equivalence based on the ratio of two means for normally distributed data. Statist Med 1999;18:93–105.
79. Chow S-C, Liu J-P(eds). Design and analysis of bioavailability and bioequivalence studies, second edition, revised and expanded. New York, NY: Marcel Dekker, 2000.
80. Wijnand H.P. Some nonparametric confidence intervals are non-informative, notably in bioequivalence studies. Clin Research Reg Affairs 1996;13:65–75.
81. Midha KK, Ormsby ED, Hubbard JW, et al. Logarithmic transformation in bioequivalence: application with two formulations of perphenazine. J Pharm Sci 1993;82:138–144.
82. Roe DJ, Karol MD. Averaging pharmacokinetic parameter estimates from experimental studies: statistical theory and application. J Pharmaceut Sci 1997;86:621–624.
83. Hauschke D, Steinijans VW, Diletti E, et al. Presentation of the intrasubject coefficient of variation for sample size planning in bioequivalence studies. Int J Clin Pharmacol Ther 1994;32:376–378.
84. Steinijans VW, Sauter R, Hauschke D, et al. Reference tables for the intrasubject coefficient of variation in bioequivalence studies. Int J Clin Pharmacol Ther 1995;33:427–430.
85. Diletti E, Hauschke D, Steinijans VW. Sample size determination: extended tables for the multiplicative model and bioequivalence ranges of 0.9 to 1.11 and 0.7 to 1.43. Int J Clin Pharmacol Ther Tox 1992;8:287–290.
86. Hauschke D, Steinijans VW, Diletti E, Burke M. Sample size determination for bioequivalence assessment using a multiplicative model. J Pharmacokin Biopharm 1992;20:557–561.
87. Lui, J-P, Chow S-C. Sample size determination for the two one-sided tests procedure in bioequivalence. J Pharmacokin Biopharm 1992;20:101–104.
88. Chow SC, Wang H. On sample size calculation in bioequivalence studies. J Pharmacokin Pharmacodyn 2001;28:155–169.
89. Gallicano K, Sahai J, Zaror-Behrens G, Pakuts A. Effect of antacids in didanosine tablet on bioavailability of isoniazid. Antimicrob Agents Chemother 1994;38:894–897.
90. Schall R, Hundt HKL, Luus HG. Pharmacokinetic characteristics for extent of absorption and clearance in drug/drug interaction studies. Int J Clin Pharmacol Ther 1994;32:633–637.
91. Tozer TN, Bois FY, Hauck WW, Chen M-L, Williams RL. Absorption rate vs. exposure: which is more useful for bioequivalence testing? Pharm Res 1996;13:453–456.
92. van Giersbergen PL, Halabi A, Dingemanse J. Single and multiple dose pharmacokinetics of bosentan and its interaction with ketoconazole. Br J Clin Pharmacol 2002;53:589–595.
93. Sanchez Garca P, Paty I, Leister CA, et al. Effect of zaleplon on digoxin pharmacokinetics and pharmacodynamics. Am J Health-Syst Pharm 2000;57:2267–2270.
94. Depr M, Van Hecken A, Verbesselt R, et al. Effect of multiple doses of montelukast, a CysLT1 receptor antagonist, on digoxin pharmacokinetics in healthy volunteers. J Clin Pharmacol 1999;39:941–944.
95. Dilger K, Zheng Z, Klotz U. Lack of drug interaction between omeprazole, lansoprazole, pantoprazole and theophylline. Br J Clin Pharmacol 1999;48:438–444.

96. Auclair B, Nix DE, Adam RD, James GT, Peloquin CA. Pharmacokinetics of ethionamide administered under fasting conditions or with orange juice, food, or antacids. Antimicrob Agents Chemother 2001;45:810–814.
97. Damle BD, Mammaneni V, Kaul S, Knupp C. Lack of effect of simultaneously administered didanosine encapsulated enteric bead formulation (Videx EC) on oral absorption of indinavir, ketoconazole, or ciprofloxacin. Antimicrob Agents Chemother 2002;46:385–391.
98. Banfield C, Herron J, Keung A, Padhi D, Affrime M. Desloratadine has no clinically relevant electrocardiographic or pharmacodynamic interactions with ketoconazole. Clin Pharmacokinetics 2002;41(Suppl. 1):37–44.
99. Hsu A, Granneman GR, Cao G, et al. Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. Antimicrob Agents Chemother 1998;42:2784–2791.

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