Drug Interactions with Antibacterial Agents

John R. Horn, PharmD, and Philip D. Hansten, PharmD
Seattle, Washington

Antibacterial drugs, such as quinolones, macrolides, rifampin, isoniazid, and trimethoprim-sulfamethoxazole, can interact with other drugs in a wide variety of clinically significant ways. They are frequently administered with other prescription and nonprescription medications. Antibacterial agents may interact by causing a change in the pharmacokinetics or pharmacodynamics of a second drug. In other cases, the antimicrobial may be affected by the action of another drug. Interactions involving antimicrobials often result from alterations in the absorption of the antimicrobial from the gastrointestinal tract or changes in the hepatic metabolism or renal elimination of the drugs concurrently administered. While certain classes of antibacterial drugs are known to interact with many other drugs, the interaction potential of most classes of antimicrobials is not uniform among members of the class. This diversity in interaction potential provides the clinician with an opportunity to avoid potential interactions by means of appropriate drug selection. An understanding of the common, clinically significant drug interactions involving antibacterial agents will enable the physician to avoid unnecessary adverse drug reactions.

Key words. Antibacterial agents; drug interactions; antibiotics. (*J Fam Pract 1995; 41:81-90*)

Many antibacterial agents have properties that predispose them to interactions with other drugs. Antibacterial agents can cause the drug interaction (acting as the "precipitant drug") or can themselves be affected (acting as the "object drug"). Some of these interactions, such as the inhibition of tetracycline absorption by antacids, are well known, whereas others are more obscure and often overlooked. Drug interactions can be either pharmacokinetic or pharmacodynamic in nature. *Pharmacokinetic* interactions are most commonly described and occur when pharmacokinetic factors (eg, clearance, volume of distribution, half-life) of the object drug are altered. A *pharmacodynamic* drug interaction occurs when the concentration–effect relationship of the object drug is changed. Some interactions, such as that occurring between quinolones and theophylline, may involve both pharmacokinetic and pharmacodynamic changes. The clinical importance of a drug interaction to a given patient depends not only on the inherent danger of the drug combination, but also on the presence of predisposing factors: dose and duration of therapy with the drugs, sequence of administration, timing of doses, route of administration, monitoring planned for the patient, other drugs the patient is receiving, presence or absence of predisposing diseases, pharmacogenetics, and the reason for using the drug(s). Thus, the same interacting drug combination can produce a serious adverse outcome in one patient and no adverse effect in another. This review highlights antimicrobial interactions that have the potential to produce adverse outcomes. Drugs included in the discussion are quinolones, macrolides, rifampin, isoniazid, metronidazole, penicillin, tetracycline, cephalosporins, chloramphenicol, and trimethoprim-sulfamethoxazole.

Quinolone Interactions

Quinolone antimicrobials interact with various other drugs in clinically important ways (Table 1). These interactions usually involve either an inhibition of quinolone absorption or quinolone-induced inhibition of the metabolism of another drug. As with most drug classes, quinolone antimicrobials have similar therapeutic properties but differ in their potential for interaction with other

Submitted, revised, January 30, 1995.

From the Department of Pharmacy, School of Pharmacy, University of Washington, Seattle. Requests for reprints should be addressed to John R. Horn, PharmD, Department of Pharmacy, School of Pharmacy, Mail Stop SC-69, University of Washington, Seattle, WA 98195.

ISSN 0094-3509

Table 1. Quinolone Drug Interactions of Potential Clinical Importance

Interacting Drug	Comments
Antacids	Reduced absorption of all available quinolones. Effect may be large, so it is best to avoid antacids in patients receiving these drugs. If combination is given, separate doses by at least 2 hours, and give quinolone first.
Caffeine	Ciprofloxacin and enoxacin inhibit caffeine metabolism, thus increasing caffeine plasma concentrations. Norfloxacin probably has less effect; neither ofloxacin nor lomefloxacin appears to affect caffeine metabolism.
Cyclosporine	Data are conflicting although case reports suggest that ciprofloxacin and norfloxacin can increase cyclosporine plasma concentrations and/or increase the risk of nephrotoxicity. Pharmacokinetic studies suggest no interaction. Ofloxacin does not appear to affect cyclosporine pharmacokinetics.
Didanosine	Buffers in didanosine can markedly reduce the gastrointestinal absorption of ciprofloxacin; other quinolones are probably similarly affected.
Iron	Reduced absorption of ciprofloxacin and probably other quinolones. Effect may be almost as large as with antacids. Multivitamins with zinc produce only a small reduction in ciprofloxacin absorption.
Sucralfate	Marked reduction in absorption of norfloxacin, ciprofloxacin, and probably other quinolones. Avoid combination if possible.
Theophylline	Enoxacin: Large reduction in theophylline clearance; theophylline toxicity likely. Ciprofloxacin: Moderate reduction in theophylline clearance; theophylline toxicity may occur in susceptible patients. Norfloxacin: Usually small reduction in theophylline clearance, but some cases of severe theophylline toxicity reported. Lomefloxacin and ofloxacin: Little or no effect on theophylline clearance.
Warfarin	Several cases of enhanced hypoprothrombinemic response reported with ciprofloxacin, norfloxacin, and ofloxacin but more data are needed.

drugs. The most pronounced of these differences can be seen in their inhibition of the metabolism of other drugs.

Inhibition of Quinolone Absorption

Trivalent and divalent cations, including calcium, magnesium, aluminum, zinc, and iron, have been shown to reduce the absorption of quinolone antimicrobials, possibly by chelation of the cation and the quinolone molecule.[1–10] This may result in a dramatic reduction in the bioavailability of the quinolone and a fall in serum concentration of 40% to over 90%. Ciprofloxacin,[1] enoxacin,[2] lomefloxacin,[3] norfloxacin,[4] and ofloxacin[5] are affected by divalent and trivalent cations found in antacids. Sucralfate, which contains aluminum, has been shown to dramatically inhibit the absorption of several quinolones, including ciprofloxacin and norfloxacin.[6,7] Iron salts and zinc can reduce ciprofloxacin bioavailability, although the magnitude is usually less than that observed with antacid administration. Typical reduction in quinolone bioavailability due to iron or zinc is approximately 20% to 65%.[8] Didanosine (DDI) tablets contain magnesium and aluminum buffers that have been shown to reduce by 98% the area under the plasma concentration–time curve of concurrently administered ciprofloxacin.[9] Even the calcium in milk and yogurt can reduce the bioavailability of ciprofloxacin by about 30%.[10]

The onset of absorption interactions with the quinolones is rapid, with a decrease in antimicrobial concentration occurring within 1 or 2 days. There are few studies comparing the potential for various quinolones to interact with cations; however, the quinolones that have been tested exhibit a similar degree of interaction.

Inhibition of absorption can be avoided by administering the quinolone at least 2 hours before or 6 hours after the antacid or other cation.[1] Doses of an antacid or other precipitant drug administered closer in time to administration of the quinolone may produce a greater reduction in the quinolone serum concentration.

Quinolone-Induced Inhibition of Drug Metabolism

Some quinolone antimicrobials are capable of inhibiting the metabolism of other drugs, including theophylline, caffeine, and warfarin.

INTERACTION WITH THEOPHYLLINE. The inhibitory effect of quinolones on theophylline metabolism has been well described.[11–13] Theophylline and caffeine are metabolized by cytochrome P4501A2 (CYP1A2) in the liver. Some quinolones have been shown to inhibit the activity of this enzyme, and thereby reduce the clearance of theophylline and caffeine.[14,15] Coadministration of theophylline and any of several quinolones can lead to an increase in theophylline serum concentrations and toxic reactions, including tachycardia, nausea, and seizures. It usually takes 2 to 3 days after the addition of a quinolone to observe its maximum effect on plasma theophylline concentrations.

Quinolones exhibit large differences in their ability to inhibit the metabolism of theophylline. For example, enoxacin is the most potent inhibitor, with up to a 65% reduction in theophylline clearance reported.[16] There-

fore, enoxacin should not be administered to patients receiving theophylline because of the high likelihood that doing so would increase theophylline concentrations to toxic levels. Ciprofloxacin inhibits theophylline clearance by about 30%,[11,16] whereas norfloxacin, ofloxacin, and lomefloxacin usually produce a minimal effect.[13,17] If either ciprofloxacin or enoxacin is given, the patient should be monitored for signs and symptoms of theophylline toxicity.

Patients with upper normal theophylline concentrations before the initiation of a quinolone are the most likely to develop adverse reactions. Elderly patients and patients with preexisting seizure disorders may be at increased risk of developing an adverse reaction (ie, seizure).[18]

INTERACTION WITH WARFARIN. The mechanism by which quinolone antimicrobials affect warfarin is not known. It is suspected that quinolones inhibit the metabolism of warfarin, leading to accumulation of the anticoagulant and enhanced hypoprothrombinemic effects. Several cases of increased anticoagulant response have been reported with ciprofloxacin,[19] norfloxacin,[20] and ofloxacin.[21] Other investigators have not found a significant effect of quinolones on warfarin or prothrombin times.[22,23] Thus, it appears that an interaction of significant magnitude occurs in only a few patients and any interaction between warfarin and the quinolones is uncommon. If an interaction occurs, it would likely take 5 to 10 days to see the maximum effect of the quinolone on the prothrombin time or international normalized ratios (INRs). Until more data are available, patients who are stabilized on warfarin should be monitored for changes in their anticoagulation status when a quinolone is prescribed. With any interaction involving warfarin, INRs should be monitored after 3 days and repeated as necessary until a stable prothrombin time is established.

Macrolide Interactions

The currently available macrolide antimicrobials include erythromycin, troleandomycin, azithromycin, and clarithromycin. The primary mechanism by which they interact with other drugs is inhibition of hepatic microsomal metabolism, but the magnitude of this effect varies among the macrolides (Tables 2 and 3). A number of drugs, including theophylline, carbamazepine, methylprednisolone, and warfarin, have been reported to be inhibited by erythromycin and troleandomycin[24] (Table 3). In most cases, the mechanism of the listed interactions involves macrolide-induced inhibition of metabolism. An exception is the increase in digoxin bioavailability caused by erythromycin's suppression of gut bacteria (*Eubacterium lentum*).[25] This interaction occurs in only about 10% of patients receiving the combination and usually is of limited significance.

Table 2. Inhibition of Hepatic Drug Metabolism by Macrolide Antibiotics

Macrolide	Comments
Azithromycin	Early evidence suggests that azithromycin does not inhibit hepatic drug metabolism. It does not appear to interact with carbamazepine, theophylline, or terfenadine.
Clarithromycin	Appears to act as an inhibitor of hepatic metabolism, but relative potency compared with erythromycin not clear; it appears to inhibit the metabolism of theophylline, carbamazepine, and terfenadine.
Erythromycin	Inhibits the metabolism of various drugs; is known to inhibit cytochrome CYP3A4, but may affect other isozymes of cytochrome P450 as well.
Troleandomycin	Inhibits hepatic drug metabolism; examples include carbamazepine, corticosteroids, and theophylline.

The mechanism by which the inhibition of metabolism occurs is somewhat complex. Erythromycin and troleandomycin actually induce some cytochrome P450 drug-metabolizing enzymes in the liver. The induced enzymes then metabolize the macrolide to a nitrosoalkane metabolite, which forms a complex with the enzyme. This complex prevents the enzyme from metabolizing other drugs any further.[26] The enzyme CYP3A4 appears to be most susceptible to inhibition by the macrolide antimicrobials.

Because interactions with macrolides feature this unique dual mechanism, the maximum effect is usually not apparent for several days. This probably explains why studies using 1 or 2 days of erythromycin therapy have failed to report any effect on theophylline metabolism.[27] The maximum effect of the macrolide on theophylline serum concentrations may not be observed for 5 to 7 days.[24] There is some evidence, however, that the effect of macrolides on object drugs other than theophylline may occur sooner.[24]

It is clear that troleandomycin produces some of the largest effects on the clearance of other drugs. For example, troleandomycin has been reported to reduce the clearance of theophylline by up to 50%,[28] whereas erythromycin tends to have a more modest effect (20% to 40% reduction) on theophylline.[29,30] Clarithromycin has also been reported to decrease the clearance of theophylline, and it has been recommended that plasma concentrations of theophylline be monitored in patients receiving theophylline and clarithromycin concomitantly.[31] Concentra-

Table 3. Macrolide Drug Interactions of Potential Clinical Importance

Interacting Drug	Comments
Astemizole	See terfenadine, below.
Benzodiazepines	Erythromycin can considerably increase the serum concentrations of oral midazolam and triazolam (both of these benzodiazepines are metabolized by CYP3A4).
Bromocriptine	Preliminary study suggests that erythromycin markedly increases serum concentrations of bromocriptine.
Carbamazepine	Marked increase in plasma carbamazepine concentration with toxicity noted in several cases; confirmed in healthy subjects. Probably due to inhibition of carbamazepine metabolism.
Cyclosporine	Marked increases in plasma cyclosporine following erythromycin in several cases and in healthy subjects; probably due to inhibition of cyclosporine metabolism.
Digoxin	Increased serum digoxin following erythromycin in selected patients (only 10% of population appears to be at risk); mechanism appears to be erythromycin-induced reduction in the bacterial degradation of digoxin in the intestine.
Felodipine	Isolated case reports suggest that erythromycin increases felodipine adverse effects (felodipine is metabolized by CYP3A4).
Lovastatin	Isolated cases of myopathy (muscle pain, weakness) with the combination of lovastatin and erythromycin but causal relationship not established.
Terfenadine	Terfenadine undergoes extensive first-pass metabolism, so almost no parent drug reaches the systemic circulation. Erythromycin and probably clarithromycin inhibit this metabolism, and the increased terfenadine serum concentrations can result in cardiac arrhythmias (eg, torsades de pointes). Early evidence suggests that astemizole can produce the same result if combined with erythromycin. Erythromycin also inhibits the metabolism of loratadine; however, loratadine does not appear to be cardiotoxic.
Theophylline	Increased serum theophylline, usually beginning only after several days of erythromycin; effect is modest in many cases, but severe toxicity has occurred. Clarithromycin and troleandomycin also inhibit theophylline metabolism.
Warfarin	Markedly enhanced hypoprothrombinemic response to warfarin following erythromycin noted in several cases; probably due to inhibition of warfarin metabolism. The interaction was less marked in controlled studies in healthy subjects.

tions of the commonly administered antihistamine terfenadine (Seldane) have been reported to more than double with clarithromycin and with erythromycin.[32] Clarithromycin administration has also been associated with increased plasma concentrations of carbamazepine.[31] Unlike the other macrolides, azithromycin does not appear to cause any changes in the metabolism of other drugs[32] (Table 2).

Drug interactions with macrolides can be avoided by choosing alternative, noninteracting antimicrobials or selecting a macrolide with minimal interaction potential, eg, azithromycin. If microbial sensitivities mandate the use of an interacting macrolide, the physician should keep in mind that the onset of the interaction may be delayed by several days in some cases.

Rifampin Interactions

Because of the increasing use of rifampin, especially in patients with the human immunodeficiency virus (HIV) infection who are often taking several drugs, it is imperative that clinicians understand the interaction potential of rifampin.

Rifampin is a potent inducer of hepatic metabolic enzymes, including CYP3A4 and CYP1A2. This broad range of induction results in the susceptibility of a large number of drugs to rifampin-induced metabolic enhancement (Table 4). Enzyme induction can occur within 2 to 4 days after initiation of rifampin therapy,[33] causing an increase in the object drug's metabolism and a reduction in its serum concentration, which may lead to loss of efficacy. The discontinuation of rifampin will result in a return to pre-rifampin metabolic activity. Therefore, if a drug's dosage was increased to correct for the induction effects of rifampin, the patient may be at risk of developing excessive drug concentrations if dosages are not readjusted to pre-rifampin levels after cessation of rifampin therapy.

A number of the interactions listed in Table 4 have important clinical outcomes. The administration of rifampin with verapamil or diltiazem, oral contraceptives, corticosteroids, cyclosporine, dapsone, warfarin, or theophylline may result in a loss of object-drug efficacy. Patients should be carefully monitored for reduced response, and an increase in object drug dosage should be provided as needed.

Isoniazid Interactions

Like rifampin, isoniazid is primarily used to treat tuberculosis. However, isoniazid inhibits rather than induces

Table 4. Rifampin Drug Interactions of Potential Clinical Importance

Interacting Drug	Comments
Antiarrhythmic agents	Rifampin appears to substantially enhance the metabolism of several antiarrhythmic drugs such as disopyramide, mexiletine, propafenone, quinidine, and tocainide. An adjustment in antiarrhythmic dosage may be needed if rifampin therapy is initiated, discontinued, or changed.
Antifungal agents	Rifampin can reduce plasma concentrations of "azole" antifungal agents such as fluconazole (Diflucan), itraconazole (Sporanox), and ketoconazole (Nizoral), although the degree to which this would reduce the antifungal effect has not been established.
Beta-adrenergic blockers	Rifampin appears to increase the hepatic metabolism of beta-blockers such as propranolol, metoprolol, and bisoprolol.
Calcium channel blockers	Rifampin appears to stimulate the hepatic metabolism of verapamil, diltiazem, and nifedipine; other calcium channel blockers may be similarly affected.
Contraceptives, oral	Rifampin may enhance the metabolism of contraceptive hormones, thus increasing the risk of menstrual irregularities and unintended pregnancy.
Corticosteroids	Rifampin may enhance the metabolism of corticosteroids, increasing their dosage requirements.
Cyclic antidepressants	Isolated case reports suggest that rifampin enhances the metabolism of cyclic antidepressants.
Cyclosporine	Numerous reports have described reduced cyclosporine serum concentrations due to rifampin. If rifampin must be used, a substantial increase in cyclosporine dosage may be needed.
Dapsone	Rifampin appears to substantially enhance the hepatic metabolism of dapsone in HIV-infected patients; the magnitude of the effect appears sufficient to reduce dapsone efficacy, but additional study is needed.
Digitalis glycosides	Rifampin may enhance the hepatic metabolism of digitoxin, substantially reducing its plasma concentrations. Rifampin may also reduce digoxin plasma concentrations, but the magnitude of the effect appears less since renal elimination is more important for digoxin than digitoxin.
Methadone	Rifampin stimulates the metabolism of methadone and may result in withdrawal symptoms.
Phenytoin	Rifampin may enhance the hepatic metabolism of phenytoin, reducing its plasma concentrations.
Sulfonylurea hypoglycemics	Rifampin appears to enhance the hepatic metabolism of tolbutamide and glyburide. There is little information on other oral hypoglycemics, but they may also interact with rifampin.
Theophylline	Rifampin appears to stimulate the metabolism of theophylline and may increase theophylline dosage requirements.
Warfarin	Rifampin substantially reduced warfarin's hypoprothrombinemic response; adjustment of warfarin dosage is likely to be needed if rifampin therapy is initiated, discontinued, or changed.

hepatic metabolism (Table 5). For example, isoniazid administration can cause the serum concentrations of carbamazepine to increase twofold to threefold.[34,35] Isoniazid begins to exert its inhibitory effects shortly after therapy is initiated, and carbamazepine toxicity has been reported after only a few days of concomitant isoniazid therapy. Phenytoin, another antiseizure drug, also shows increased concentrations after the administration of isoniazid, especially in patients who are "slow" acetylators of isoniazid. Therefore, phenytoin intoxication is more frequent in patients receiving both isoniazid and phenytoin than in those receiving phenytoin alone.[36]

Patients with higher carbamazepine or phenytoin concentrations before isoniazid administration are likely at greatest risk of developing an adverse reaction from this combination. Careful monitoring for evidence of toxicity of the object drug will help avoid an adverse outcome.

Metronidazole Interactions

Metronidazole's chemical structure contains an imidazole ring, which is found in many other drugs known to inhibit hepatic drug metabolism: for example, cimetidine, ketoconazole, miconazole, and omeprazole. Thus, it is not surprising that metronidazole has been reported to act as an inhibitor of drug metabolism.

Perhaps the most important interaction with metronidazole involves warfarin. Metronidazole inhibits the metabolism of warfarin, resulting in accumulation of warfarin and an enhanced anticoagulant effect.[37] Therefore, this combination should be avoided if possible. However, if it is necessary to administer metronidazole to a patient stabilized on warfarin therapy, careful monitoring of the prothrombin time and observation for excessive anticoagulation are required. The maximum effect on warfarin response is usually observed within 5 to 7 days of metro-

Table 5. Isoniazid Drug Interactions of Potential Clinical Importance

Interacting Drug	Comments
Acetaminophen	Hepatotoxicity has been attributed to the combined use of acetaminophen and isoniazid, but a causal relationship has not been established.
Antacids	Aluminum hydroxide gel may inhibit the gastrointestinal absorption of isoniazid. Magaldrate has been known to produce a weaker inhibition of isoniazid absorption, but little is known about the effect of other antacids.
Carbamazepine	Isoniazid can substantially increase serum concentrations of carbamazepine especially with isoniazid doses of 200 mg/day or more.
Disulfiram	Some patients on isoniazid and disulfiram have developed changes in affect and behavior, although a causal relationship has not been conclusively established.
Phenytoin	Isoniazid predictably increases serum concentrations of phenytoin; toxicity may occur, especially in patients who are slow isoniazid acetylators.
Theophylline	Isoniazid has been reported to produce modest reductions in theophylline clearance, and isolated cases of theophylline toxicity have been reported.

nidazole administration, but the maximum change may not be seen for 2 weeks. Patients stabilized on warfarin have developed bleeding episodes after receiving metronidazole for 1 to 2 weeks; however, prothrombin times may change in as few as 2 to 3 days. Although some effect may occur, patients receiving single doses of metronidazole are less likely to develop significant enzyme inhibition.

Penicillin Interactions

Although penicillin and its modern derivatives are still widely used antimicrobials, few interactions have been reported with this group of agents. Both penicillins and methotrexate are eliminated by renal tubular secretion, and large doses of penicillins can inhibit the renal clearance of methotrexate, which can cause an accumulation of methotrexate and toxicity even when low doses are used.[38] A reduction of the methotrexate dose may be required when a patient is receiving concomitant penicillin therapy.

Most penicillin derivatives are extensively eliminated by renal tubular secretion, a process that is inhibited by probenecid. This effect can be used advantageously in the treatment of certain infections, such as gonorrhea. Penicillin toxicity could occur if probenecid is administered with large doses of penicillin.

Nafcillin has been reported to inhibit the efficacy of warfarin. Several patients have shown loss of hypoprothrombinemic response during concomitant warfarin and nafcillin therapy,[39] although the mechanism for this interaction is unknown. A similar interaction has been reported following dicloxacillin administration, but information regarding other penicillinase-resistant penicillins is lacking. Until more data are available, patients stabilized on warfarin should be monitored for reduction in warfarin effect during treatment with nafcillin. If warfarin doses are increased during nafcillin therapy, the warfarin dose should probably be reduced when the course of antimicrobials is finished.

Ampicillin and amoxicillin have been associated with menstrual irregularity and, by association, with unplanned pregnancy in women taking oral contraceptives.[40] It has been suggested that the mechanism responsible for this effect is an interruption in the enterohepatic circulation of estrogens due to reduction in colonic bacteria. This interaction appears to occur in a limited number of patients. Women with a low bioavailability of ethinyl estradiol or intestinal flora that are particularly sensitive to ampicillin or amoxicillin may be particularly at risk. Patients taking oral contraceptives should be counseled regarding the risk of contraceptive failure and offered additional methods of birth control during cycles in which ampicillin or amoxicillin is administered.[41]

Tetracycline Interactions

As noted with ampicillin, tetracycline has also been associated with spotting, breakthrough bleeding, and unplanned pregnancy in patients taking oral contraceptives.[40] Patients using oral contraceptives should be counseled regarding the risk of contraceptive failure and offered additional methods of birth control during cycles in which tetracycline is administered.[41] Narrow spectrum, nonenzyme-inducing antibiotics would be least likely to reduce oral contraceptive efficacy.

Inhibition of Tetracycline Absorption

Tetracyclines are well known to be susceptible to chelation in the gut by divalent and trivalent cations, including aluminum, magnesium, calcium, and iron.[42] Even a glass of milk can reduce the bioavailability of tetracycline by 50% and significantly inhibit its efficacy. Other drugs containing cations, such as sucralfate, also may inhibit the absorption of tetracyclines. Doxycycline may be less susceptible to the effects of food on its absorption, compared

with other tetracyclines.[43] Bismuth subsalicylate has also been reported to reduce tetracycline bioavailability.[44] These interactions can be avoided by administering the tetracycline 2 hours before the antacid- or cation-containing product, thus allowing complete antimicrobial absorption before the antacid is ingested.

Enhanced Hepatic Metabolism of Tetracyclines

Most tetracyclines are only minimally metabolized in the liver and, thus, are unlikely to be affected by hepatic enzyme inducers or inhibitors. Doxycycline, however, is metabolized in the liver, and its plasma concentrations can be substantially reduced by concurrent therapy with such agents as carbamazepine, phenobarbital, phenytoin, and rifampin.[45–47] Little is known regarding the effect of these changes on the antibacterial response to doxycycline, but the magnitude of the changes suggests that they may be clinically important. It has been proposed that rifampin-induced stimulation of doxycycline metabolism might be responsible for treatment failures in some patients with brucellosis.[48]

Cephalosporin Interactions

Cephalosporins are widely used anti-infective agents that appear to be involved in relatively few clinically important drug interactions.

Inhibition of Cephalosporin Absorption

Cephalosporins do not appear to be particularly susceptible to alteration in absorption caused by drug interactions. However, the gastrointestinal absorption of two cephalosporins, cefpodoxime proxetil and cefuroxime axetil, seem to be pH-dependent. Therefore, antacids and H_2-receptor antagonists can substantially reduce the absorption of these two cephalosporins.[49–51] One would expect omeprazole, a profound suppressor of gastric acid production, to produce a similar reduction in bioavailability of these cephalosporins, but there are no data on this interaction. Oral iron dramatically reduces the gastrointestinal absorption of cefdinir,[52] but little is known about the effect of iron on the absorption of cephalosporins currently available in the United States.

When antacids bind with other drugs in the gastrointestinal tract, one can usually minimize the interaction by giving the object drug at least 2 hours before or 6 hours after the antacid. Waiting up to 6 hours after antacid administration may be necessary to ensure that the antacid has passed beyond the antimicrobial absorptive sites (small intestine). However, since the effect of antacids on the bioavailability of cefpodoxime proxetil and cefuroxime axetil appears to be caused by increased gastric pH rather than binding, it may not be necessary to wait the full 6 hours after the antacid. Clinical studies are needed to establish the timing required to prevent this interaction. Avoiding the effect of H_2-receptor antagonists on these cephalosporins can probably be accomplished by administering the cephalosporin when the effect on gastric pH is minimal. For patients receiving an H_2-receptor antagonist administered as a single bedtime dose, gastric pH is highest throughout the night and immediately preceding meals.[53] Cefpodoxime proxetil and cefuroxime axetil doses should not be administered during these times. Theoretically, the effect of larger doses of H_2-receptor antagonists or omeprazole would be more difficult to avoid, since their effect on gastric pH may be more persistent.

Inhibition of Cephalosporin Renal Elimination

Most cephalosporins are extensively eliminated by renal tubular secretion, a process that is inhibited by probenecid. Given the relative lack of dose-dependent toxicity of cephalosporins, however, it is unlikely that this interaction would produce adverse effects.

Cephalosporin-Induced Disulfiram-like Reactions

Cephalosporins that contain an *N*-methylthiotetrazole (NMTT) side chain (eg, cefamandole, cefoperazone, cefotetan, and moxalactam) have been associated with disulfiram-like reactions following alcohol ingestion. Symptoms typically include flushing, nausea, headache, and tachycardia. Since cefmetazole also has the NMTT side chain, it would be expected to produce this effect as well.[54] Cephalosporins with the NMTT side chain have also been associated with hypoprothrombinemia and bleeding, a point that should be considered in patients receiving anticoagulants.[54,55]

Chloramphenicol Interactions

Chloramphenicol As an Inhibitor of Drug Metabolism

Chloramphenicol inhibits the hepatic microsomal metabolism of some other drugs. For example, substantial increases in phenytoin plasma concentrations have been reported in patients receiving concurrent chloramphenicol.[56] Chloramphenicol also appears to inhibit the metab-

Table 6. Trimethoprim-Sulfamethoxazole Drug Interactions of Potential Clinical Importance

Interacting Drug	Comments
Amantadine	Isolated case reports suggest that this combination may result in adverse central nervous system effects (eg, confusion). Both amantadine and trimethoprim are secreted by the renal tubules and may compete for renal elimination.
Dapsone	Increased serum concentrations of both dapsone and trimethoprim have been reported due to competition for renal elimination.
Methotrexate	Isolated cases of megaloblastic anemia have been reported, purportedly due to synergistic folic acid deficiency.
Phenytoin	Increased serum phenytoin has been observed in subjects, but incidence of phenytoin toxicity has not been established.
Procainamide	Trimethoprim substantially reduced renal clearance of both procainamide and its active metabolite (*N*-acetylprocainimide) in controlled studies; incidence of toxicity not established.
Sulfonylurea hypoglycemics	Enhanced hypoglycemic effect of sulfonylureas has been reported. Rarely, trimethoprim-sulfamethoxazole *alone* has been associated with hypoglycemia.
Warfarin	Well documented with substantial inhibition of warfarin metabolism in controlled studies; several cases of bleeding reported.

olism of dicoumarol,[57] chlorpropamide,[58] and tolbutamide.[57] Chloramphenicol probably also inhibits the metabolism of other drugs, but its relatively infrequent use limits our information about these interactions.

When possible, chloramphenicol should be avoided in patients receiving the aforementioned drugs. If it is necessary to use chloramphenicol with these drugs, the patient should be monitored for altered object-drug effect after chloramphenicol is initiated and after it is discontinued. The time course of the interactions varies depending on the pharmacokinetics of the object drug.

Trimethoprim-Sulfamethoxazole Interactions

Both components of the combination product trimethoprim-sulfamethoxazole (TMP/SMX) may interact with other drugs (Table 6). Trimethoprim is a weak base that may compete with other weak bases for active renal tubular secretion. There is also some evidence that trimethoprim can inhibit the hepatic metabolism of other drugs. Sulfonamides may inhibit hepatic drug metabolism and displace other drugs from plasma protein binding, although the latter effect alone is usually insufficient to produce clinically important drug interactions.

TMP/SMX Renal Interactions

Trimethoprim appears to compete with procainamide for active renal tubular secretion, thus substantially increasing plasma concentrations of procainamide and its active metabolite *N*-acetylprocainamide (NAPA).[59] The magnitude of the effect is sufficient to increase the risk of procainamide toxicity, and patients should be monitored for altered procainamide concentrations if trimethoprim is initiated, discontinued, or changed in dosage. Limited clinical evidence suggests that trimethoprim-sulfamethoxazole can increase the risk of adverse mental effects in patients receiving amantadine;[60] this effect is also probably due to the trimethoprim component.

Methotrexate toxicity has been reported in several patients following administration of TMP/SMX.[61,62] Since methotrexate undergoes renal tubular secretion, and this process is affected by weak acids, such as aspirin and nonsteroidal anti-inflammatory drugs, it has been assumed that the sulfamethoxazole component is responsible for the interaction. Nonetheless, an effect of trimethoprim has not been ruled out. In any case, it is generally best to avoid TMP/SMX in patients receiving methotrexate. If the combination is used, careful attention to early detection of methotrexate toxicity is essential.

TMP/SMX As an Inhibitor of Drug Metabolism

Because both trimethoprim and sulfonamides are capable of inhibiting hepatic drug metabolism, it is not always clear which component is responsible for a given interaction. TMP/SMX has been shown to substantially increase phenytoin plasma concentrations; in this case, the trimethoprim rather than the sulfamethoxazole appears to be responsible.[63] TMP/SMX has also been reported to increase the hypoglycemic effect of sulfonylureas; in this case, sulfamethoxazole is the most likely cause.[64] Complicating the evaluation of the latter interaction is that TMP/SMX alone has been associated with hypoglycemia, although rarely.[65] TMP/SMX should probably be avoided in patients who are being treated with the anticoagulant warfarin because of the risk of hypoprothombinemia and bleeding.[66]

Summary

Antibacterial agents interact with other drugs by a variety of mechanisms, such as inhibition of gastrointestinal ab-

sorption, alteration in gastrointestinal bacterial flora, hepatic enzyme induction, hepatic enzyme inhibition, and alteration in renal elimination. Some of these interactions can cause clinically important adverse effects or inhibition of drug effects in predisposed individuals. It is important to identify potentially important drug interactions, assess the risk in specific patients, and then take appropriate measures in those found to be at risk. For more information on the interactions described in this review, consult standard textbooks of drug interactions.[67]

References

1. 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; 46:700–5.
2. Grasela TH Jr, Schentag JJ, Sedman AJ, et al. Inhibition of enoxacin absorption by antacids or ranitidine. Antimicrob Agents Chemother 1989; 33:615–7.
3. Foster TS, Blouin R. The effect of antacid timing on lomefloxacin bioavailability. Pharmacotherapy 1991; 11:101.
4. Nix DE, Wilton JH, Ronald B, Distlerath L, Williams VC, Norman A. Inhibition of norfloxacin absorption by antacids. Antimicrob Agents Chemother 1990; 34:432–5.
5. Flor S, Guay DRP, Opsahl JA, Tack K, Matzke GR. Effects of magnesium-aluminum hydroxide and calcium carbonate antacids on bioavailability of ofloxacin. Antimicrob Agents Chemother 1990; 34:2436–8.
6. Brouwers JRBJ, Van Der Kam HJ, Sijtsma J, Proost JH. Important reduction of ciprofloxacin absorption by sucralfate and magnesium citrate solution. Drug Invest 1990; 2:197–9.
7. Parpia SH, Nix DE, Heymanowski LG, Goldstein HR, Wilton JH, Schentag JJ. Sucralfate reduces the gastrointestinal absorption of norfloxacin. Antimicrob Agents Chemother 1989; 33:99–102.
8. Polk RE, Healy DP, Sahai J, Drwal L, Racht E. Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother 1989; 33:1841–4.
9. Sahai J, Gallicano K, Oliveras L, Khaliq S, Hawley-Foss N, Garber G. Cations in the didanosine tablet reduce ciprofloxacin bioavailability. Clin Pharmacol Ther 1993; 53:292–7.
10. Neuvonen PJ, Kivisto KT, Lehto P. Interference of dairy products with the absorption of ciprofloxacin. Clin Pharmacol Ther 1991; 50:498–502.
11. Schwartz J, Jauregui L, Lettieri J, Bachmann K. Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. Antimicrob Agents Chemother 1988; 32:75–7.
12. Rogge MC, Solomon WR, Sedman AJ, Welling PG, Toothaker RD, Wagner JG. The theophylline-enoxacin interaction: I. Effect of enoxacin dose size on theophylline disposition. Clin Pharmacol Ther 1988; 44:579–87.
13. Sano M, Kawakatsu K, Ohkita C, et al. Effects of enoxacin, ofloxacin and norfloxacin on theophylline disposition in humans. Eur J Clin Pharmacol 1988; 35:161–5.
14. Harder S, Staib AH, Beer C, Papenburg A, Stille W, Shah PM. 4-quinolones inhibit biotransformation of caffeine. Eur J Clin Pharmacol 1988; 35:651–6.
15. Fuhr U, Strobl G, Manaut F, et al. Quinolone antibacterial agents: relationship between structure and in vitro inhibition of the human cytochrome P450 isoform CYP1A2. Mol Pharmacol 1993; 43: 191–9.
16. Wijnands WJA, Vree TB, Van Herwaarden CLA. The influence of quinolone derivatives on theophylline clearance. Br J Clin Pharmacol 1986; 22:677–83.
17. Robson RA, Begg EJ, Atkinson HC, Saunders DA, Frampton CM. Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline. Br J Clin Pharmacol 1990; 29: 491–3.
18. Grasela TH Jr, Dreis MW. An evaluation of the quinolone-theophylline interaction using the Food and Drug Administration spontaneous reporting system. Arch Intern Med 1992; 152:617–21.
19. Kamada AK. Possible interaction between ciprofloxacin and warfarin. DICP 1990; 24:27–8.
20. Linville T, Matanin D. Norfloxacin and warfarin [letter]. Ann Intern Med 1989; 110:751–2.
21. Baciewicz AM, Ashar BH, Locke TW. Interaction of ofloxacin and warfarin. Ann Intern Med 1993; 119:1223.
22. Bianco TM, Bussey HI, Farnett LE, Linn WD, Rousch MK, Wong YWJ. Potential warfarin-ciprofloxacin interaction in patients receiving long-term anticoagulation. Pharmacotherapy 1992; 12:435–9.
23. Rocci ML, Vlasses PH, Distlerath LM, et al. Norfloxacin does not alter warfarin's disposition or anticoagulant effect. J Clin Pharmacol 1990; 30:728–32.
24. Ludden TM. Pharmacokinetic interactions of the macrolide antibiotics. Clin Pharmacokinet 1985; 10:63–79.
25. Lindenbaum J, Rund DG, Butler VP, Tse-Eng D, Saha JR. Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. N Engl J Med 1981; 305:789–94.
26. Delaforge M, Jaouen M, Mansuy D. Dual effects of macrolide antibiotics on rat liver cytochrome P-450. Induction and formation of metabolite-complexes: a structure-activity relationship. Biochem Pharmacol 1983; 32:2309–18.
27. Pfeifer HJ, Greenblatt DJ, Friedman P. Effects of three antibiotics on theophylline kinetics. Clin Pharmacol Ther 1979; 26:36–40.
28. Weinberger M, Hudgel D, Spector S, Chidsey C. Inhibition of theophylline clearance by troleandomycin. J Allergy Clin Immunol 1977; 59:228–31.
29. LaForce CF, Miller MF, Chai H. Effect of erythromycin on theophylline clearance in asthmatic children. J Pediatr 1981; 99:153–6.
30. May DC, Jarboe CH, Ellenburg DT, Roe EJ, Karibo J. The effects of erythromycin on theophylline elimination in normal males. J Clin Pharmacol 1982; 22:125–30.
31. Periti P, Mazzei T, Mini E, Novelli A. Pharmacokinetic drug interactions of macrolides. Clin Pharmacokinet 1992; 23:106–31.
32. Honig P, Wortham D, Zamani K, Conner D, Cantilena L. Effect of erythromycin, clarithromycin and azithromycin on the pharmacokinetics of terfenadine [abstract]. Clin Pharmacol Ther 1993; 53: 161.
33. Borcherding SM, Bastian TL, Self TM, Abou-Shala N, LeDuc BW, La Londe RL. Two- and four-day rifampin chemoprophylaxis regimens induce oxidative metabolism. Antimicrob Agents Chemother 1992; 36:1553–8.
34. Valsalan VC, Cooper GL. Carbamazepine intoxication caused with isoniazid. BMJ 1982; 285:261–2.
35. Wright JM, Stokes EF, Sweeney VP. Isoniazid-induced carbamazepine toxicity and vice versa. N Engl J Med 1982; 307:1325–7.
36. Miller RR, Porter J, Greenblat DJ. Clinical importance of the interaction of phenytoin and isoniazid: a report from the Boston Collaborative Drug Surveillance Program. Chest 1979; 75:356–8.
37. O'Reilly RA. The stereoselective interaction of warfarin and metronidazole in man. N Engl J Med. 1976; 295:354–7.
38. Mayall B, Poggi G, Parkin JD. Neutropenia due to low-dose methotrexate therapy for psoriasis and rheumatoid arthritis may be fatal. Med J Aust 1991; 155:480–4.
39. Davis RL, Berman W Jr, Wernly JA, Kelly HW. Warfarin-nafcillin interaction. J Pediatr 1991; 118:300–3.
40. Sparrow MJ. Pill method failures. N Z Med J 1987; 100:102–5.
41. Miller DM, Helms SE, Brodell RT. A practical approach to antibiotic treatment in women taking oral contraceptives. J Am Acad Dermatol 1994; 30:1008–11.
42. Neuvonen PJ. Interactions with the absorption of tetracyclines. Drugs 1976; 11:45–54.
43. Welling PG, Koch PA, Lau CC, Craig WA. Bioavailability of tetra-

cycline and doxycycline in fasted and nonfasted subjects. Antimicrob Agents Chemother 1977; 11:462–9.
44. Albert KS, Welch RD, De Sante KA, DiSanto AR. Decreased tetracycline bioavailability caused by a bismuth subsalicylate antidiarrheal mixture. J Pharm Sci 1979; 68:586–8.
45. Neuvonen PJ, Penttila O, Lehtovaara R, Aho K. Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. Eur J Clin Pharmacol 1975; 9:147–54.
46. Penttila O, Neuvonen PJ, Aho K, Lehtovarra R. Interaction between doxycycline and some antiepileptic drugs. BMJ 1974; 2:470–2.
47. Neuvonen PJ, Penttila O. Interaction between doxycycline and barbiturates. BMJ 1974; 1:535–6.
48. Ariza J, Gudiol F, Pallares R, et al. Treatment of human brucellosis with doxycycline plus rifampin or doxycycline plus streptomycin: a randomized, double-blind study. Ann Intern Med 1992; 117:25–30.
49. Saathoff N, Lode H, Neider K, Depperman KM, Borner K, Koeppe P. Pharmacokinetics of cefpodoxime proxetil and interactions with an antacid and an H_2 receptor antagonist. Antimicrob Agents Chemother 1992; 36:796–800.
50. 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; 46:647–85.
51. Sommers DEK, 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 Pharmacol 1984; 18:535–9.
52. Ueno K, Tanaka K, Tsujimura K, et al. Impairment of cefdinir absorption by iron ion. Clin Pharmacol Ther 1993; 54:473–5.
53. Pounder RE. Degrees of acid suppression and ulcer healing: dosage considerations. Aliment Pharmacol Ther 1991; 5(suppl 1):5–13.
54. Schentag JJ. Cefmetazole sodium: pharmacology, pharmacokinetics, and clinical trials. Pharmacotherapy 1991; 11:2–19.
55. Angaran DM, Dias VC, Arom KV. The comparative influence of prophylactic antibiotics on the prothrombin response to warfarin in the postoperative prosthetic cardiac valve patient: cefamandole, cefazolin, vancomycin. Ann Surg 1987; 206:155–61.
56. Harper JM, Yost RL, Stewart RB, Ciezkowski J. Phenytoin-chloramphenicol interaction: a retrospective study. Drug Intell Clin Pharm 1979; 13:425–9.
57. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. Lancet 1969; 2:1397–9.
58. Petitpierre B, Perrin L, Rudhardt M, Herrera A, Fabre J. Behaviour of chlorpropamide in renal insufficiency and under the effect of associated drug therapy. Int J Clin Pharmacol Ther Toxicol 1972; 6:120–4.
59. Kosoglou T, Rocci ML Jr, Vlasses PH. Trimethoprim alters the disposition of procainamide and *N*-acetylprocainamide. Clin Pharmacol Ther 1988; 44:467–77.
60. Speeg KV, Leighton JA, Maldonado AL. Case report: toxic delirium in a patient taking amantadine and trimethoprim-sulfamethoxazole. Am J Med Sci 1989; 298:410–2.
61. Groenendal H, Rampen FHJ. Methotrexate and trimethoprim-sulphamethoxazole—a potentially hazardous combination. Clin Exp Dermatol 1990; 15:358–60.
62. Thomas MH, Gutterman LA. Methotrexate toxicity in a patient receiving trimethoprim-sulfamethoxazole. J Rheumatol 1986; 13: 440–1.
63. Hansen JM, Kampmann JP, Siersbaek-Nielsen K, et al. The effect of different sulfonamides on phenytoin metabolism in man. Acta Med Scand 1979; 624(suppl):106–10.
64. Johnson JF, Dobmeier ME. Symptomatic hypoglycemia secondary to a glipizide-trimethoprim/sulfamethoxazole drug interaction. DICP 1990; 24:250–1.
65. Johnson JA, Kappel JE, Sharif MN. Hypoglycemia secondary to trimethoprim/sulfamethoxazole administration in a renal transplant patient. Ann Pharmacother 1993; 27:304–6.
66. O'Reilly RA. Stereoselective interactions of trimethoprim-sulfamethoxazole with the separated enantiomorphs of racemic warfarin in man. N Engl J Med 1980; 302:33–5.
67. Hansten PD, Horn JR. Drug interactions & updates quarterly. Vancouver, Wash: Applied Therapeutics, Inc, 1994.