

Update: Clinically Significant Cytochrome P-450 Drug Interactions

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Recent technologies have resulted in an explosion of information concerning the cytochrome P-450 isoenzymes and increased awareness of life-threatening interactions with such commonly prescribed drugs as cisapride and some antihistamines. Knowledge of the substrates, inhibitors, and inducers of these enzymes assists in predicting clinically significant drug interactions. In addition to inhibition and induction, microsomal drug metabolism is affected by genetic polymorphisms, age, nutrition, hepatic disease, and endogenous chemicals. Of the more than 30 human isoenzymes identified to date, the major ones responsible for drug metabolism include **CYP3A4, CYP2D6, CYP1A2, and the CYP2C** subfamily. (Pharmacotherapy 1998;18(1):84-112)

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Summary

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Nomenclature

The cytochrome P (CYP)-450 isoenzymes are a group of heme-containing enzymes embedded primarily in the lipid bilayer of the endoplasmic reticulum of hepatocytes (Figure 1).¹ These metabolic enzymes are also present in high concentrations in enterocytes of the small intestine, with smaller quantities in extrahepatic tissues (kidneys, lungs, brain). They are involved in oxidative metabolism (phase I) of a number of different drug classes as well as endogenous substances such as steroid hormones, fatty acids, and prostaglandins.²⁻⁴ The nomenclature first suggested by Nebert et al in 1987 and widely used today employs a three-tier classification consisting of the family (> 36% homology in amino acid sequence), subfamily (77% homology), and individual gene (e.g., CYP3A4).³⁻⁵

Knowledge of the substrates, inhibitors, and inducers of CYP-450 isoenzymes assists in predicting clinically significant drug interactions. It is also important to recognize that genetic polymorphism in the functional expression of some CYP-450 isoenzymes, such as CYP2D6, contributes to marked interpatient variability in drug metabolism, leading to poor metabolizers (PMs) and extensive metabolizers (EMs).^{2, 3, 6} In addition to genetic influences, microsomal drug metabolism is affected by age, nutrition, stress, hepatic disease, hormones, and other endogenous chemicals.¹ Although more than 30 human CYP-450 isoenzymes have been identified to date, the major ones responsible for drug metabolism are CYP3A4, CYP2D6, CYP1A2, and the CYP2C subfamily.

Substrates, Inhibition, and Induction

Some drugs may be metabolized by more than

one isoenzyme. For example, the pharmacologically active enantiomer S-warfarin is metabolized by the CYP2C9 enzyme, whereas R-warfarin is metabolized by the CYP3A4 and CYP1A2 systems.^{7, 8} Therefore, when one enzyme system is inhibited or induced by an interacting drug, a clinically significant interaction may or may not occur. Another example is tricyclic antidepressants, which are metabolized by CYP2D6, CYP1A2, and CYP3A4. Inhibition or genetic absence of one isoenzyme can lead to compensation through the secondary isoenzyme pathway. Similar to warfarin, oxidative metabolism can be preserved, and a clinically significant interaction may or may not occur.⁹

In addition, a drug may inhibit or induce the activity of a specific isoenzyme even though it is not a substrate at that particular site. For example, quinidine is metabolized by the CYP3A4 enzyme, but it is a potent inhibitor of CYP2D6.^{2, 10}

Inhibition

Inhibition most often occurs as a result of competitive binding at the enzyme's binding site. Competitive inhibition depends on the affinity of the substrate for the enzyme being inhibited, the concentration of substrate required for inhibition, and the half-life of the inhibitor drug. The onset and offset of enzyme inhibition are dependent on the half-life and time to steady state of the inhibitor drug. For example, chloramphenicol (CYP2C9), acute ethanol ingestion, and cimetidine (CYP1A2) inhibit drug metabolism within 24 hours of a single dose, but amiodarone (CYP2C9) inhibitory interactions may not surface for months because of its long half-life.¹¹

The time to maximum drug interaction (onset

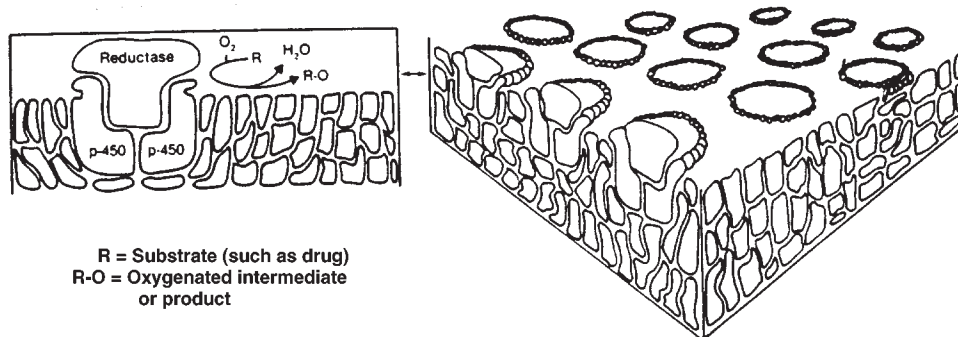


Figure 1. Cytochrome P-450 enzyme system. Reprinted by permission from *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*, third edition, edited by WE Evans, JJ Schentag, and WJ Jusko, published by Applied Therapeutics, Inc., Vancouver, WA, © 1992.

and termination) is also dependent on the time required for the inhibited drug to reach a new steady state.^{6, 12} For example, with the cimetidine-theophylline interaction, maximum increases in theophylline concentrations are not seen for approximately 2 days, since this time is required for theophylline to reach a new steady state.¹³ Another example is phenytoin. With its concentration-dependent half-life, steady-state changes in phenytoin serum concentration can take days to occur. Of interest, if the half-life of the inhibitor drug is shorter than that of the inhibited drug, less time is required to revert to a lower steady-state concentration after the inhibitor is stopped than is required to increase to a new steady-state concentration when the inhibitor is started. This is because the half-life of the affected drug is shorter after discontinuation of the inhibitor.²⁻⁴

A second and less common mechanism of inhibition is noncompetitive, which can occur as a result of inhibitor inactivation of the enzyme with normal substrate binding. The duration of this type of inhibition may be longer if new enzymes are synthesized after the inhibitor drug is discontinued.¹

Another contributing factor to the significance of enzyme inhibition is the hepatic extraction ratio of the affected drug. In general, systemic clearance of low-extraction-ratio drugs is expected to be affected to a greater extent than that of high-extraction-ratio drugs. However, with high-extraction-ratio drugs with significant first pass metabolism, it is well known that significant changes in oral absorption can occur in the presence of inhibitory drugs.¹

Induction

Enzyme induction, first recognized in the 1940s, occurs when hepatic blood flow is increased or the synthesis of more CYP-450 enzymes is stimulated. In animal models, phenobarbital increases liver weight in a dose-dependent manner. In humans, liver biopsies in patients taking anticonvulsants resulted in up to 52% larger absolute liver size.¹⁴ Like inhibitors, inducers tend to be lipophilic, and the time course of the interaction is dependent on the half-life of the inducer. For example, rifampin's short half-life results in enzyme induction (CYP3A4, CYP2C) apparent within 24 hours, whereas phenobarbital's longer half-life of 3–5 days requires approximately 1 week for induction (CYP3A4, CYP1A2, CYP2C) to become apparent.

Both of these agents interact with warfarin metabolism. Whereas rifampin's effects occur within 4 days, phenobarbital's effects take 14–22 days to occur.^{15, 16}

A complicating factor is that the time course of induction is also dependent on the time required for enzyme degradation and new enzyme production. In other words, the rate-limiting factor may be the half-life of CYP450 enzyme turnover, which ranges from 1–6 days.¹⁷ Since rifampin is eliminated more rapidly than the excess cytochrome enzymes, the rate-limiting factor in the duration of the interaction would be enzyme turnover. With phenobarbital, accumulation and elimination would be the rate-limiting factor in the onset and offset of induction.¹⁷

Enzyme induction is also influenced by age and liver disease. The ability to induce drug metabolism may decrease with age, as evidenced by reports that drug metabolism in elderly subjects (> 60 yrs) is not influenced by polycyclic aromatic hydrocarbons (PAH) in cigarette smoke, as it is in younger subjects.^{1, 18} Also, patients with cirrhosis or hepatitis may be less susceptible to enzyme induction.¹

CYP3A4 Isoenzyme

The CYP3A4 isoenzyme is responsible for the metabolism of the widest range of drugs and endogenous compounds in humans. It accounts for 60% of cytochrome enzymes in the liver and 70% of those in enterocytes found in the gut wall responsible for first-pass metabolism.^{2, 3, 17} No evidence to date suggests the 3A4 isoenzyme exhibits genetic polymorphism.¹⁹ Common substrates, inhibitors, and inducers of CYP3A4 are listed in Table 1.^{2, 3, 9, 10, 16, 17, 19-117}

In recent years there has been an explosion of discussion about the 3A4 system because of life-threatening arrhythmic side effects that can occur as a result of enzyme inhibition and accumulation of the non-sedating antihistamines terfenadine and astemizole²⁰⁻²⁵ and cisapride.²⁶⁻³⁰

Significant Inhibitory Interactions: Antihistamines

Terfenadine has been removed from the market because of its serious cardiovascular drug interactions. Its active carboxy metabolite, fexofenadine, is available and devoid of the fatal drug interactions.³¹ Astemizole undergoes extensive first-pass metabolism to active metabolites, and, like terfenadine, the parent compound is the cardiotoxic entity.³² In many cases, drug interactions with terfenadine have

Table 1. Cytochrome 3A4 Isoenzyme: Substrates, Inducers, and Inhibitors^{2, 3, 9, 10, 16, 17, 19-117}

Substrates			
Alfentanil	Diazepam (minor)	Ketoconazole	Quinine
Alprazolam	Diltiazem	Lansoprazole (minor)	Rifampin
Amitriptyline (minor)	Disopyramide	Lidocaine	Ritonavir
Amlodipine	Donepezil	Losartan	Saquinavir
Astemizole	Doxorubicin	Lovastatin	Sertraline
Atorvastatin	Dronabinol	Mibefradil	Tacrolimus
Busulfan	Erythromycin	Miconazole	Tamoxifen
Cannabinoids	Estrogens, oral	Midazolam	Temazepam
Carbamazepine	contraceptives	Navelbine	Terfenadine
Cisapride	Ethosuximide	Nefazodone	Testosterone
Clindamycin	Etoposide	Nelfinavir	Triazolam
Clomipramine	Felodipine	Nicardipine	Verapamil
Clonazepam	Fentanyl	Nifedipine	Vinblastine
Cocaine	Fexofenadine	Nimodipine	Vincristine
Cyclobenzaprine	Ifosfamide	Nisoldipine	R-warfarin
(demethylation)	Imipramine	Ondansetron	Zileuton
Cyclophosphamide	Indinavir	Paclitaxel	
Cyclosporine	Isradipine	Pravastatin	
Dapsone		Prednisone	
Dexamethasone		Quinidine	
Dextromethorphan			
Inhibitors		Inducers	
Amiodarone	Metronidazole	Carbamazepine	
Cannabinoids	Mibefradil	Dexamethasone	
Clarithromycin	Miconazole	Ethosuximide	
Erythromycin	Nefazodone	Phenobarbital	
Fluconazole	Nelfinavir	Phenytoin	
Fluoxetine	Norfloxacin	Primidone	
Fluvoxamine	Quinine	Rifabutin	
Grapefruit juice	Ritonavir	Rifampin	
Indinavir	Saquinavir	Troglitazone	
Itraconazole	Sertraline		
Ketoconazole	Troleandomycin		
Omeprazole (slight)	Zafirlukast		

been extrapolated to astemizole.³¹ Terfenadine, available since 1985, was first reported in 1990 to cause QT prolongation and torsades de pointes when given together with ketoconazole.²³ A prospective study of six healthy volunteers given the combination noted increased parent terfenadine concentrations and QT prolongation (mean 82-msec increase).²²

In vitro, the ability of itraconazole, an antifungal similar to ketoconazole, to inhibit the 3A4 system is 10 times less potent than that of ketoconazole, but inhibitory differences in vivo are less impressive.³³ Fluconazole also inhibits 3A4 in vitro, but did not increase parent terfenadine concentrations or cause arrhythmias at dosages of 200 mg/day.³² However, dosages above 200 mg/day caused QT prolongation in subsets of patients.³⁴

The antifungal agents itraconazole, ketoconazole, fluconazole, and intravenous miconazole should not be coadministered with astemizole due to the

serious nature of potential drug interactions, although single doses of fluconazole for candidiasis are not likely to present a problem. The new antifungal terbinafine does not appear to inhibit the 3A4 system and is an alternative for the treatment of onychomycosis.¹¹⁸

Erythromycin alone can cause QT prolongation,¹¹⁹ and when combined with terfenadine does so as well (mean 10-msec increase) but to a lesser degree than when given with antifungal agents.²⁰ This effect was also reported with clarithromycin³¹ but not with azithromycin or dirithromycin, which may be alternatives for patients receiving astemizole.³⁵⁻³⁷

In vitro evidence exists for inhibition of the 3A4 isoenzyme by the antidepressant drugs fluvoxamine, fluoxetine, nefazodone, and sertraline. In addition, plasma concentrations of drugs metabolized by 3A4 such as carbamazepine and some benzodiazepines increased when given concomitantly with these four agents.^{9, 19, 39, 40} To

date, there are no *in vitro* data or case reports involving paroxetine in the inhibition of 3A4.¹⁹

Data on significant drug interactions with these antidepressants and antihistamines is less clear than with antifungals and macrolides. Fluoxetine caused arrhythmias in patients concomitantly receiving terfenadine.^{41, 42} Another concern with fluoxetine is the long half-life of the parent compound (4–6 days) and its active metabolite norfluoxetine (4–16 days). The consequences of an interaction may be minimized by delaying administration of astemizole for 2–4 weeks after discontinuing fluoxetine.⁴³ Prescribing information for both fluvoxamine and nefazodone lists concomitant administration with astemizole as a contraindication,^{44–46} and sertraline information warns against concomitant administration with astemizole.⁴⁷ Thus, fluoxetine, fluvoxamine, nefazodone, and sertraline should be administered cautiously, if at all, to patients taking astemizole (Table 2).^{2, 3, 7–11, 14–118} In patients receiving astemizole, alternatives for the treatment of depression are paroxetine¹⁹ and venlafaxine.⁴⁸ The tricyclic antidepressants should also be prescribed cautiously since they can cause arrhythmias.⁹

Fresh or frozen grapefruit juice inhibits CYP3A4 enzymes found in enterocytes. The inhibitory substance was once thought to be naringenin, a human metabolite of naringin.^{49–51} However, the primary substance responsible for inhibition was identified *in vitro* to be a furanocoumarin compound widely found in nature, 6,7-dihydroxybergamottin. This inhibitory substance is less potent than ketoconazole but considerably more active than cimetidine. Lack of 6,7-dihydroxybergamottin in orange juice probably accounts for the absence of cytochrome inhibitory effects.^{52–54} Inhibition of terfenadine metabolism with quantifiable levels of the terfenadine parent compound, an increase in area under the curve (AUC) of 55%, and a mean QT prolongation of 14 msec were reported in patients ingesting grapefruit juice 240 ml concomitantly with terfenadine 60 mg twice/day.^{55, 56} Other studies reported similar pharmacokinetic changes but associated with no electrocardiographic changes.⁵⁷

Recently the calcium channel blocker, mibefradil, has been shown to inhibit both CYP3A4 and CYP2D6 and cause syncope in some patients taking β -blockers. Because mibefradil could theoretically increase plasma concentrations of astemizole, its concurrent use should be avoided.³⁸

Another cytochrome 3A4 inhibitor is quinine. At dosages greater than 430 mg/day, quinine is

contraindicated with astemizole since the combination may result in QT prolongation.⁵⁸ It is prudent to limit the use of quinine and tonic water in patients receiving astemizole.

In vitro, the protease inhibitors saquinavir, zidovudine, zalcitabine, and didanosine inhibit cytochrome 3A4.⁵⁹ To date, neither pharmacokinetic studies nor *in vivo* drug-drug interaction studies have been conducted for these agents with antihistamines. Prescribing information for zidovudine⁶⁰ lists concomitant administration with astemizole as a contraindication, and prescribing information for saquinavir,⁶¹ zalcitabine,⁶² and didanosine⁶³ issue precautions regarding concomitant astemizole administration because of the potential for life-threatening cardiotoxic interactions.

Other recommendations to minimize the risk of cardiotoxic drug interactions include avoiding astemizole dosages greater than 10 mg/day, prescribing alternative agents (Table 2), prescribing astemizole cautiously in patients with cardiac conditions that predispose them to QT prolongation, administering the drug cautiously in patients taking other agents that can prolong the QT interval (e.g., type Ia or III antiarrhythmics; some psychotropics such as haloperidol, droperidol, tricyclic antidepressants), and administering astemizole cautiously in patients with hepatic disease.

Significant Inhibitory Interactions: Cisapride

The fact that cisapride can cause tachycardia, palpitations, and extrasystoles was first observed in a review of records of over 13,000 patients receiving the agent.²⁸ Postulations about the cause of tachycardia include activation of serotonin-4 receptors on the myocardium⁶³ and prolonged atrioventricular conduction due to its structural similarity to procainamide.³⁰ The first report of an arrhythmic drug interaction with cisapride was with erythromycin (for 2 days only) with dosages of cisapride that were rapidly escalated to 40 mg every 6 hours. The patient developed a QT interval of 550 msec from a normal baseline with progression to polymorphic nonsustained ventricular tachycardia. The QT interval returned to normal after the cisapride dosage was decreased to 5 mg every 6 hours.²⁹

Janssen Pharmaceutica continues to receive numerous reports of torsades de pointes, prolonged QT intervals, and deaths.²⁷ Over 50% of these patients were concomitantly receiving ketoconazole, itraconazole, or fluconazole, and erythromycin,

Table 2. 3A4 Clinically Significant Drug Interactions^{2-3, 7-11, 14-118}

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Antiarrhythmics			
Disopyramide	Carbamazepine (ind)	May need initial dosage increase; monitor SC&E.	Gabapentin Lamotrigine Topiramate Valproate
Lidocaine (less likely)	Phenobarbital (ind)		
Quinidine	Phenytoin (ind)		
Disopyramide	Indinavir (inh)	Decrease initial dosage 50%; monitor SC&E.	
Lidocaine	Nelfinavir (inh)		
	Ritonavir (inh)		
	Saquinavir (inh)		
Disopyramide	Rifampin (ind)	Need initial dosage increase; monitor SC&E.	Azithromycin Dirithromycin
Quinidine	Clarithromycin (inh)	Reports of increased quinidine levels; monitor QT interval.	
	Erythromycin (inh) Troleandomycin (inh)		
Lidocaine	Cimetidine (inh)	Reports of toxicity not consistent; up to 30% increase in serum conc; monitor SC&E.	Famotidine Nizatidine Ranitidine
Quinidine	Cimetidine (inh)	Conflicting data; up to 50% increase in serum conc reported; monitor SC&E.	Famotidine Nizatidine Ranitidine Gabapentin Lamotrigine Topiramate Valproate
	Phenobarbital (ind) Phenytoin (ind) Rifampin (ind)	Monitor concentrations more carefully.	
	Metronidazole	3-fold increase in trough conc; monitor SC&E.	
	Amiodarone (inh)	Decrease dosage 30–50% on initiation; monitor QT interval.	
	Ketoconazole (inh) Itraconazole (inh) Fluconazole (inh) Miconazole i.v. (inh)	30-fold increase in serum conc after 7 days, monitor QRS.	
Anticoagulants			
R-warfarin	Cisapride (inh) Amiodarone (inh)	One report of increased INR. Delayed interaction; decrease dosage 25% on initiation.	Metoclopramide
	Fluconazole (inh) Itraconazole (inh) Ketoconazole (inh)	May cause 2-3-fold increase in INR; monitor INR more carefully on starting or stopping; may also be 1A2 mediated.	
	Erythromycin (inh) ?Clarithromycin (inh) Omeprazole (inh)	Seen within 7 days; monitor INR daily. Effects appear after a few days; dose related; monitor INR more carefully.	Azithromycin Dirithromycin Lansoprazole
Anticonvulsants			
Carbamazepine	Erythromycin (inh) Clarithromycin (inh) Fluoxetine (inh) Fluvoxamine (inh) Sertraline (inh)	Decrease dosage by 25%; seen within 24 hrs. Anecdotal reports of increased conc with blurred vision, tremor in some patients; monitor SC&E.	Azithromycin Dirithromycin
	Isoniazid (inh)	Can cause toxicity; more pronounced in slow acetylators.	
Carbamazepine	Indinavir (inh)	Decrease initial dosage 50%; monitor serum conc.	
Ethosuximide	Nelfinavir (inh)		
	Ritonavir (inh)		
	Saquinavir (inh)		

Table 2. 3A4 Clinically Significant Drug Interactions^{2, 3, 7-11, 14-118} (continued)

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Carbamazepine Ethosuximide	Rifampin (inh)	Monitor serum conc; may need initial dosage increase.	
Antifungal agents Itraconazole Ketoconazole	Rifampin (inh) Carbamazepine (inh) Phenobarbital (inh) Phenytoin (inh)	Consider dosage increase; poor clinical response reported; fluconazole less affected. Poor clinical response noted.	Fluconazole Fluconazole Gabapentin Lamotrigine Topiramate Valproate
Antidepressants Nefazodone Sertraline Trazodone Desipramine	Indinavir (inh) Nelfinavir (inh) Ritonavir (inh) Saquinavir (inh)	Decrease initial dosage 50%; monitor for SE.	
Antiemetics Dronabinol Ondansetron	Indinavir (inh) Nelfinavir (inh) Ritonavir (inh) Saquinavir (inh)	Decrease initial dosage 50%; monitor for SE.	
Antifungal agents Itraconazole Ketoconazole	Phenobarbital (inh) Phenytoin (inh) Rifampin (inh)	Therapeutic failures reported; fluconazole not as affected.	Fluconazole
Antihistamines and cisapride Astemizole Cisapride	Clarithromycin (inh) Erythromycin (inh) Troleandomycin (inh) Fluconazole (inh) Itraconazole (inh) Ketoconazole (inh) Miconazole i.v. (inh) Fluoxetine (inh) Fluvoxamine (inh) Nefazodone (inh) Sertraline (inh) Grapefruit juice (inh) Quinine, tonic water (inh) Indinavir (inh) Nelfinavir (inh) Ritonavir (inh) Saquinavir (inh) Mibefradil (inh) Zafirlukast (inh) Zileuton (inh)	Avoid these combinations. Avoid use. Avoid combinations. Avoid > 200 ml/day. Avoid > 430 mg/day. Avoid combinations.	Cetirizine ^a Clemastine ^a Loratadine ^a Metoclopramide ^a Azithromycin Dirithromycin Terbinafine for onychomycosis Paroxetine Venlafaxine Orange juice, other juices Other antiretrovirals Other CCBs Other asthma regimens
Loratadine	Indinavir (inh) Ritonavir (inh) Saquinavir (inh)	Decrease initial loratadine dosage 50%; therapeutic monitoring; no cardiac side effects reported.	
Cisapride	Metronidazole (inh)	Avoid combination.	Metoclopramide, other antibiotics

Table 2. 3A4 Clinically Significant Drug Interactions^{2, 3, 7-11, 14-118} (continued)

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Benzodiazepines			
Alprazolam	Fluoxetine (inh)	Decrease initial alprazolam dosage 50% and triazolam dosage 75%; monitor for oversedation.	Temazepam
Midazolam	Fluvoxamine (inh)		
Triazolam	Nefazodone (inh) ?Grapefruit juice		
	Indinavir (inh) Nelfinavir (inh) Ritonavir (inh) Saquinavir (inh)	Delayed interaction; adjust dosage; monitor for SE.	Temazepam Other antiretrovirals
Midazolam	Rifampin (ind)	Hypnotic effects substantially diminished; monitor and give higher initial dosages of benzodiazepine.	
Triazolam			
?Other benzodiazepines			
Midazolam	Erythromycin (inh)	Decrease initial triazolam dosage 50%; monitor for oversedation.	Azithromycin Dirithromycin
Triazolam			
Triazolam	Itraconazole (inh)	27-fold increase in conc with sedation, decreased psychomotor abilities.	
Others	Ketoconazole (inh) Fluconazole (inh)		
Midazolam	Cimetidine (inh)	Some CNS effects documented.	Famotidine Nizatidine Ranitidine
Triazolam			
Calcium channel blockers			
Amlodipine	Grapefruit juice (inh) (200 ml/day)	Decrease initial CCB dosage 50%; monitor for dizziness, headache, peripheral edema, hypotension.	Orange juice, other juices
Felodipine			
Isradipine			
Mibefradil			
Nicardipine	Erythromycin (inh)	Decrease initial CCB dosage 50%; monitor for SE.	Azithromycin Dirithromycin
Nifedipine			
Nimodipine	Itraconazole (inh)	Decrease initial CCB dosage 50%; monitor for SE.	?Fluconazole
Nisoldipine	Ketoconazole (inh)		
Verapamil			
	Indinavir (inh) Nelfinavir (inh) Ritonavir (inh) Saquinavir (inh)		Other antiretrovirals
	Rifampin (ind) Rifabutin (ind)	May need initial dosage increase; monitor clinical effects; best documented with diltiazem, verapamil, nifedipine.	
Nifedipine	Phenobarbital (ind)	Theoretical; best documented with nifedipine and phenobarbital.	
Others			
Nifedipine	Cimetidine (inh)	Conflicting results; some reports of decreased BP, HR.	Famotidine Nizatidine Ranitidine
Verapamil			
Chemotherapeutic agents			
Busulfan	Itraconazole (inh)	Report of increased serum conc in BMT pts.	Fluconazole
Doxorubicin	Cyclosporine (inh) Paclitaxel (inh)	Elevated concentrations; more nausea and vomiting.	
Etoposide	Phenobarbital (ind) Phenytoin (ind) Cyclosporine (inh)	170% increase in clearance. 2-fold increase in half-life.	

Table 2. 3A4 Clinically Significant Drug Interactions^{2, 3, 7-11, 14-118} (continued)

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Etoposide Paclitaxel Tamoxifen Vinblastine Vincristine	Indinavir (inh) Nelfinavir (inh) Ritonavir (inh) Saquinavir (inh)	Decrease initial chemotherapy dosage 50%.	
Tamoxifen	Erythromycin (inh) Cyclosporine (inh) Nifedipine (inh) Diltiazem (inh)		
Vinblastine	Doxorubicin (inh) Etoposide (inh) Ketoconazole (inh) Erythromycin (inh)		
Vincristine	Nifedipine (inh)		
Estrogens, corticosteroids Oral contraceptives	Benzodiazepines (ind)	Induce or compete with contraceptives; use alternative contraception for short courses; for long courses use higher dosages or medroxyprogesterone acetate.	Medroxyprogesterone acetate
Oral contraceptives Corticosteroids	Rifampin (ind) Rifabutin (ind) Carbamazepine (ind) Ethosuximide (ind) Phenobarbital (ind) Phenytoin (ind) Primidone (ind)	Use alternative contraception or increase dosage to 50 µg estradiol. 40% reduction in serum levels; monitor for breakthrough bleeding; alternative contraception (e.g., medroxyprogesterone) desirable.	Gabapentin Lamotrigine Topiramate Valproate
Oral contraceptives	Troglitazone (ind)	Reduces concentrations by 30%; use alternative contraception.	
Methylprednisolone Prednisolone ?Other corticosteroids	Ketoconazole (inh)	AUC increased; significance unknown.	
HMG-CoA reductase inhibitors Lovastatin Atorvastatin Fluvastatin Pravastatin Simvastatin	Erythromycin (inh) Clarithromycin (inh) Troleandomycin (inh) Itraconazole (inh) Cyclosporine (inh)	Monitor for myopathy; most common with lovastatin. Monitor for myopathy.	Azithromycin Dirithromycin
	Indinavir (inh) Nelfinavir (inh) Ritonavir (inh) Saquinavir (inh)	Decrease initial dosage 50%; therapeutic monitoring.	Other antiretrovirals
Immunosuppressants Cyclosporine Tacrolimus	Indinavir (inh) Nelfinavir (inh) Ritonavir (inh) Saquinavir (inh) Norfloxacin (inh) Rifampin (ind) Amiodarone (inh)	Decrease initial dosage 50%; therapeutic monitoring. Seen in pediatric transplant patients. May need initial dosage increase; monitor SC&E. Decreases clearance by 50%; monitor SC&E.	Other antiretrovirals Ciprofloxacin

Table 2. 3A4 Clinically Significant Drug Interactions^{2, 3, 7-11, 14-118} (continued)

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Cyclosporine Tacrolimus	Erythromycin (inh)	Avoid combination or reduce dosage by 50%; can see within 2 d; monitor trough conc 2-3 x/wk.	Azithromycin, Dirithromycin
	Clarithromycin (inh)		
	Troleandomycin (inh)		
	Roxithromycin (inh)		
	Fluconazole (inh)	Consider 50% dosage reduction when starting azole; monitor trough conc more carefully.	Ketoconazole 100-200 mg often given to improve F
	Itraconazole (inh)		
	Ketoconazole (inh)		
	Mibefradil (inh)	Monitor trough conc more carefully.	Diltiazem often given to improve F
	Nicardipine (inh)		
	Nifedipine (inh)		
	Diltiazem (inh)		
	Verapamil (inh)		
	Methylprednisolone (inh)	Competitive metabolism; monitor trough conc.	
	Carbamazepine (ind)		Gabapentin Lamotrigine Topiramate Valproate
Phenobarbital (ind)			
Phenytoin (ind)			
Oral contraceptives (inh)	Not well documented; may need dosage decrease; monitor trough conc.		
Macrolides			
Clarithromycin	Indinavir (inh)	AUC increases by 77% with ritonavir and 53% with indinavir; decrease clarithromycin dosage by 50% for Cl _{cr} 30-60 ml/min and 75% for Cl _{cr} < 30 ml/min.	
	Nelfinavir (inh)		
	Ritonavir (inh)		
	Saquinavir (inh)		
	Rifampin (ind)	Will decrease serum conc by 120% with rifampin and 50% with rifabutin; clinical significance unknown.	
	Rifabutin (ind)		
Erythromycin	Ritonavir (inh)	Decrease initial dosage 50% (based on in vitro data).	
Miscellaneous			
Rifabutin	Clarithromycin (inh)	Increase serum conc; increased risk of icterus and uveitis; monitor for ocular SE.	Alternative MAC prophylaxis
	Fluconazole (inh)	Increases AUC by 80%; increased risk of icterus and uveitis; monitor for ocular SE.	
	Indinavir (inh)	204% increase in AUC; decrease initial rifabutin dosage by half.	
	Nelfinavir (inh)		
	Ritonavir (inh)	4-fold increase in AUC; increased risk of SE; combination contraindicated.	
Cyclobenzaprine	Fluoxetine (inh)	Observe for QT prolongation.	
Narcotic analgesics			
Alfentanil	Erythromycin (inh)	Monitor for oversedation; marked increase in AUC of opiate.	Azithromycin
Alfentanil Fentanyl	Indinavir (inh)	Decrease initial dosage 50%; monitor for oversedation.	
	Nelfinavir (inh)		
	Ritonavir (inh)		
	Saquinavir (inh)		
	Rifampin (ind)	Increase initial dosage; monitor for withdrawal.	
Fentanyl	Cimetidine (inh)	Reports of doubling in terminal half-life; monitor for SE.	Famotidine Nizatidine Ranitidine

Table 2. 3A4 Clinically Significant Drug Interactions^{2-3, 7-11, 14-118} (continued)

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives		
Protease inhibitors					
Indinavir	Rifabutin (ind)	40% decrease in saquinavir AUC with rifabutin and 80% decrease with rifampin; rifampin decreases ritonavir AUC 35%; may need dosage increase; see specific MMWR guidelines.	Nucleoside or nonnucleoside combinations		
Nelfinavir	Rifampin (ind)				
Ritonavir	Carbamazepine (ind) Phenobarbital (ind) Phenytoin (ind) Tobacco (ind)	Use cautiously.	Nucleoside or nonnucleoside combinations Gabapentin Lamotrigine Topiramate Valproate		
Saquinavir					
Indinavir				Increases AUC 30%.	Azithromycin Dirithromycin
				Erythromycin (inh) Troleandomycin (inh)	
Indinavir	Ketoconazole (inh) Fluconazole (inh)	Ketoconazole increases AUC by 150%; with ketoconazole, decrease initial indinavir dosage to 600 mg q8h; decrease saquinavir dosage if ketoconazole dosage is > 200 mg/day.			
Saquinavir					
Ritonavir	Smoking (ind)	18% decrease in AUC; no specific recommendations at present.			
Saquinavir	Ritonavir (inh) Other protease inhibitors?	Increases conc by 18-fold to improve saquinavir absorption.			

SC&E = serum concentration and effects; INR = international normalized ratio; SE = side effects; CCB = calcium channel blockers; BP = blood pressure; HR = heart rate; BMT = bone marrow transplantation; F = bioavailability; Cl_{cr} = creatinine clearance; MAC = *Mycobacterium avium intracellulare* complex; AUC = area under the concentration-time curve.

^aAlternative antihistamines and prokinetic agents in all interactions listed.

clarithromycin, or metronidazole. Risk factors for arrhythmia were identified as history of coronary disease and arrhythmia, renal insufficiency, electrolyte imbalance, and long-term use of agents associated with arrhythmia or prolonged QT intervals such as amiodarone and phenothiazines.²⁷

Three reports in our institution in 1995–1996 involved fluconazole or erythromycin interactions with cisapride. Two patients were receiving both fluconazole 100 and 400 mg/day and cisapride 20 mg every 6 hours, had no known cardiac disease, developed ventricular fibrillation, and had resolution with no further arrhythmias after cisapride was discontinued. One of these patients initially had recurrence of sustained ventricular tachycardia after lidocaine was discontinued and before cisapride was discontinued. The third patient had a history of cardiac disease and was receiving erythromycin 500 mg intravenously every 6 hours plus oral cisapride 10 mg every 12 hours. His QT interval increased from 352 msec

at baseline to 440 msec, and he died from ventricular fibrillation-cardiac arrest. The drug interaction was postulated as a potential culprit.

Similar to antihistamines, only in vitro data about enzyme inhibition, and no actual patient-specific data, are the bases for contraindications and warnings against concomitant cisapride with other drugs such as fluvoxamine, mibefradil, nefazodone, sertraline, ritonavir, saquinavir, and indinavir.^{38, 44–46, 60–62} It would also seem prudent to avoid administering fluoxetine, quinine, and grapefruit juice with cisapride because of the fatal consequences of potential interactions, and because similar interactions were documented with terfenadine. As is the case with astemizole, steps to minimize the cisapride drug interactions include avoiding cisapride dosages greater than 20 mg every 6 hours and exercising caution in patients with hepatic disease or other risk factors for QT prolongation.

Hypoprothrombinemic effects of warfarin were reported when given in combination with

cisapride. The patient's international normalization ratio (INR) at baseline was 2.2–2.5 and increased to 10.7, first noted 3 weeks after the patient began cisapride 10 mg 4 times/day. Competitive binding or inhibition by cisapride was postulated.⁶⁹ The clinical significance of this interaction remains to be established.

Significant Inhibitory Interactions: R-Warfarin

Fluconazole, itraconazole, and ketoconazole reportedly increase the anticoagulant effects of warfarin. Two-fold (fluconazole) and 3-fold (ketoconazole) increases in prothrombin time have been reported. Even low dosages of fluconazole 100 mg/day for 7 days were implicated to reduce the clearance of both isomers of warfarin.^{7, 8, 33}

Numerous reports describe enhancement of the hypoprothrombinemic effects of warfarin when given in combination with erythromycin. Prothrombin times increased up to 2-fold after 7 days of therapy, but there are few reports of bleeding complications. The clinical relevance of this interaction probably depends on many patient factors including age, rate of warfarin clearance, concurrent drug therapy, and ability to shunt to noninhibited pathways.³³ The interaction has not been observed with azithromycin, but like erythromycin, caution is advised with concurrent clarithromycin therapy.^{33, 36}

Omeprazole has a benzimidazole moiety similar to the imidazole ring of cimetidine and has been studied for inhibitory drug interactions. It inhibits the metabolism of R-warfarin, and this interaction is likely to be 3A4 mediated. The effects appear after omeprazole has been taken for a few days, seem to be dose related, and do not abate immediately on discontinuing the drug. Careful INR monitoring is recommended in patients receiving this combination. Lansoprazole does not alter the clearance of warfarin and may be an alternative treatment.^{65–68}

Significant Inhibitory Interactions: Benzodiazepines and Narcotic Analgesics

Alfentanil, alprazolam, midazolam, temazepam, and triazolam are among the currently known substrates of cytochrome 3A4.^{9, 19, 39, 40, 72} The benzodiazepines have fairly well documented interactions. Pharmacokinetic studies with alprazolam showed increased serum concentrations and prolonged half-life when given with the inhibitors fluoxetine and fluvoxamine.¹⁹ Fluoxetine increased plasma concentrations of

diazepam and alprazolam, but enhancement of psychomotor effects was not seen.⁴³

Another antidepressant, nefazodone, increased alprazolam plasma concentrations 2-fold and potentiated alprazolam-induced psychomotor impairment and sedation.^{71–74} Nefazodone also increased triazolam plasma concentrations and half-life by 1.7- and 3-fold, respectively.^{71–73} Initial dosage reductions of alprazolam by 50% and triazolam by 75% should be made when adding nefazodone to existing therapy with these agents.^{71–74}

Grapefruit juice 200 ml increased peak plasma concentrations of orally administered midazolam by 56% and AUC by 52%. The clinical importance of this increase is unknown.⁴⁹

Temazepam, although metabolized by the 3A4 system, does not result in significant pharmacokinetic or pharmacodynamic interactions as assessed by psychomotor performance with inhibitors such as erythromycin and itraconazole.^{76, 77} Lack of interaction potential with temazepam compared with midazolam, alprazolam, and triazolam may be due to different metabolic pathways and lack of significant first-pass metabolism of temazepam. Erythromycin reduced clearance of triazolam by 52% and decreased midazolam clearance enough to cause unconsciousness. If it is not possible to avoid these combinations, the benzodiazepine dosage should be decreased by 50% and the patient monitored carefully for respiratory depression and other signs of toxicity.³⁶ Inhibitors of 3A4 should therefore be administered with caution to patients taking alprazolam or triazolam and to those undergoing surgical procedures requiring midazolam as a component of anesthesia.

For the opioids, the only well-documented 3A4-mediated interaction is with alfentanil and erythromycin.^{70, 79} Reports include prolonged respiratory depression associated with alfentanil in patients who were receiving erythromycin before surgery.⁷⁰ Administration of cimetidine with fentanyl doubles the latter's elimination half-life, thus potentially enhancing its pharmacologic effects and duration of action.⁷⁰

Significant Induction Interactions: Benzodiazepines and Narcotic Analgesics

Rifampin can significantly impair the efficacy of some benzodiazepines. A 96% reduction in the AUC of midazolam was accompanied by nonexistent hypnotic effects when administered with rifampin to 10 healthy volunteers in a

double-blind crossover study.⁷⁸ Similar results were reported with triazolam and rifampin, with markedly reduced effects of triazolam based on psychomotor tests.⁷⁹

Like benzodiazepines, it is well known that rifampin increases the rate of metabolism of many opioids and may induce withdrawal symptoms.^{16, 70, 77}

Significant Inhibitory Interactions: Cardiovascular Drugs

Most calcium channel-blocking agents are dependent on the 3A4 isoenzyme system for metabolism. Other cardiovascular drugs metabolized by 3A4 are the hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors.^{1, 17}

Grapefruit juice 200–250 ml given before drug administration increased the AUC of felodipine by 185%, with an average increase of 240%. Similar results occurred with nifedipine, nimodipine, and verapamil but not with diltiazem.^{50, 55} Furthermore, this pharmacokinetic interaction was clinically significant, with lower diastolic blood pressure, higher heart rate, and more frequent vasodilation-related side effects with felodipine, nisoldipine (5-fold increase in AUC), and nifedipine.^{55, 80, 81} This information supports cautioning patients about concomitant ingestion of grapefruit juice and calcium antagonists.

A patient taking oral felodipine 10 mg/day was given oral erythromycin 250 mg twice/day and developed flushing, ankle and leg edema, and tachycardia. When erythromycin was discontinued, felodipine levels were reduced from 6 to less than 2 nmol/L and symptoms resolved.⁸² On average, it appears that erythromycin increases felodipine concentrations by 3-fold.⁵⁵ Other studies have demonstrated similar increases in felodipine concentrations when given with erythromycin.⁸³ Other reports documented substantial peripheral edema and/or elevated calcium antagonist serum concentrations during concurrent administration of itraconazole with felodipine, isradipine, or nifedipine.^{84–86} An 8-fold increase in felodipine's AUC was seen when the agent was given with itraconazole 200 mg/day, and was associated with statistically significant changes in systolic and diastolic blood pressures and heart rate.⁸⁶

If concurrent therapy of potent 3A4 inhibitors with calcium antagonists is required, the patient should be monitored for signs of toxicity and the dosage of calcium channel blocker decreased, if necessary.

As mentioned, HMG-CoA reductase inhibitors are metabolized by the 3A4 system and have dose-related toxic effects on skeletal muscle that may range from diffuse myalgia and myopathy to severe rhabdomyolysis. These effects are reported most frequently with lovastatin but have also been reported rarely with the other statins.^{87, 88} The risk of rhabdomyolysis appears to be greatest when HMG-CoA reductase inhibitors are combined with 3A4 inhibitor drugs or agents that compete with 3A4 metabolism.^{89–94} This interaction has been well described with cyclosporine, and less often with gemfibrozil and niacin.⁸⁹

In a double-blind, crossover trial, itraconazole increased lovastatin peak concentrations by 20-fold in 12 healthy volunteers. Side effects were not reported in any subjects except one who experienced a 10-fold increase in creatine kinase.⁹⁰ Reports of severe rhabdomyolysis occurring after the addition of itraconazole to lovastatin and niacin therapy underscore the potential harm of these interactions. Myopathy also occurred after itraconazole was added to cyclosporine and simvastatin therapy in a transplant recipient.⁹¹ Numerous authors described the development of rhabdomyolysis when lovastatin was combined with erythromycin. Myopathy is quickly reversible when the statin is discontinued.^{92–94}

Concomitant administration of ritonavir and lovastatin increased the AUC of lovastatin by 3-fold. Little information is available about protease inhibitors, but careful dosing with statins is prudent.^{58, 60–62} Giving statins with 3A4 inhibitors should be avoided or dosages of statins reduced to avoid the potential for rhabdomyolysis. Patients should be instructed to monitor for signs of myopathy such as muscular pain, tenderness, or weakness, and plasma creatine kinase should be measured if symptoms develop.

Significant Induction Interactions: Calcium Channel Blockers

In one study, enzyme induction with rifampin resulted in up to a 32-fold increase in verapamil clearance and a 25-fold decrease in verapamil bioavailability after oral administration.⁹⁵ The effect of oral verapamil on atrioventricular conduction was nearly abolished with rifampin administration, and the authors concluded that prehepatic metabolism of verapamil was induced by rifampin. Rifampin is expected to have a similar reaction with other calcium channel blockers.

Significant Interactions: Quinidine

Quinidine is known to be a cytochrome 2D6 inhibitor but is metabolized by the 3A4 system. Cytochrome 3A4 interactions that are well documented include those with cimetidine,^{2, 13} phenytoin, phenobarbital,^{2, 120} and rifampin.^{2, 114} Of interest, metronidazole is a 3A4 inhibitor due to its interaction with cisapride,²⁷ and a potential interaction of quinidine with either metronidazole or ciprofloxacin was reported. A 3-fold difference in quinidine trough concentrations was noted, but with no changes in the patient's QT interval.¹⁰ An interaction with metronidazole seems more likely since it is a known 3A4 inhibitor. Quinidine concentrations should be monitored and patients assessed for signs of toxicity in these instances.

Significant Inhibitory and Induction Reactions: Chemotherapeutic Agents

Little is known about pharmacokinetic interactions with chemotherapeutic agents, but it is likely that important interactions have not been identified. The 3A4 enzyme was important in the metabolism of several agents, including epipodophylotoxins, tamoxifen, ifosfamide, paclitaxel, and vinca alkaloids. Although beyond the scope of this review, it is interesting to note that 3A4 catalyzes the activation of the prodrug ifosfamide, raising the possibility that it could be activated in tumor tissues containing this enzyme. Cytochrome 3A4 substrates may also modulate multidrug resistance to cancer chemotherapy.⁹⁷

Cyclosporine increased the AUC of doxorubicin by 55% and decreased doxorubicin clearance by 50%. The addition of cyclosporine also increased doxorubicin-induced nausea and vomiting. Similar myelosuppression was observed when comparing doxorubicin alone with doxorubicin (60% of the control dose) plus cyclosporine.⁹⁸ Similar pharmacokinetic results were obtained and a higher frequency of drug-related toxicity was observed in patients receiving cyclosporine.⁹⁹ Simultaneous administration of doxorubicin and paclitaxel also resulted in significantly elevated concentrations of doxorubicin, suggesting that paclitaxel may inhibit its metabolism.¹⁰⁰

Ifosfamide is an alkylating agent that requires biotransformation to produce its pharmacologically active cytotoxic compound. This activation by the 3A4 system also results in the formation of a therapeutically inactive but neurotoxic metabolite by *N*-dechloroethylation. Few studies have been done, but 3A4 inducers such as

rifampin, carbamazepine, phenobarbital, and phenytoin are postulated to enhance efficacy and toxicity through 3A4 activation. In immunohistochemical studies, some patients with pulmonary carcinoma showed expression of the 3A4 enzyme, and studies are continuing to assess if this presence leads to local activation and a better response to ifosfamide.

In contrast, inhibitors and other substrates of 3A4, such as ketoconazole, itraconazole, diltiazem, verapamil, and cyclosporine, could possibly interfere with activation and efficacy of ifosfamide. The clinical significance of inhibition is unknown at present.⁹⁷

In vitro, vinblastine metabolism is inhibited by other anticancer drugs, including doxorubicin and etoposide, together with more familiar inhibitors, ketoconazole and erythromycin. Although not studied clinically, these interactions may alter the antitumor activity and/or toxicity of vinblastine.¹⁰¹ Concomitant treatment with vincristine, another vinca compound, and nifedipine resulted in a 4-fold increase in vincristine's elimination half-life. Clinical studies are necessary to validate the pharmacokinetic data, but greater cytotoxicity could be anticipated.¹⁰²

Busulfan is another chemotherapeutic agent that may be metabolized through the 3A4 system. A study in 13 bone marrow transplant recipients found an average 20% reduction in busulfan clearance in patients receiving itraconazole compared with those receiving either fluconazole or placebo. Itraconazole is known to be a more potent inhibitor of 3A4 than fluconazole.³⁴ The nature of this interaction has yet to be elucidated, but inhibition of oxidative metabolism may be a factor.¹⁰³

Etoposide is significantly affected when administered concurrently with inducers such as phenobarbital and phenytoin, with a mean 170% increase in clearance reported with these drugs. On the other hand, concurrent administration with cyclosporine resulted in an 80% increase in AUC and a 2-fold increase in etoposide half-life.⁹⁷ In vitro, tamoxifen metabolism is inhibited by erythromycin, cyclosporine, nifedipine, and diltiazem. No clinical data are available, but interactions are likely to occur and should be investigated.¹⁰⁴

Few clinical data exist to make sound conclusions regarding interactions with chemotherapeutic agents. However, significant interactions with cytochrome 3A4 inhibitors or inducers are likely to become more apparent in the near future.

Table 3. Cytochrome 2D6 Isoenzyme: Substrates, Inducers, and Inhibitors^{2, 3, 9, 16, 19, 33, 43, 48, 58, 60, 70, 96, 114, 120-125}

Substrates		Inducers	
Amitriptyline (hydroxylation)	Donepezil	Meperidine	Propafenone
Bisoprolol	Doxepin	Methadone	Propranolol
Chlorpromazine	Flecainide	Methamphetamine	Risperidone
Clomipramine	Fenfluramine	Metoprolol	Thioridazine
Clozapine	Fluphenazine	Mexiletine	Timolol
Codeine	Fluoxetine	Morphine	Tramadol
Cyclobenzaprine (hydroxylation)	Haloperidol	Nortriptyline (hydroxylation)	Trazodone
Desipramine	Hydrocodone	Oxycodone	Venlafaxine
Dexfenfluramine	Imipramine (hydroxylation)	Paroxetine	
Dextromethorphan	Maprotiline	Perphenazine	
Inhibitors		Inducers	
Amiodarone	Paroxetine		Carbamazepine
Cimetidine	Propafenone		Phenobarbital
Clomipramine	Quinidine		Phenytoin
Desipramine	Ritonavir		Rifampin
Fluoxetine	Sertraline		Ritonavir
Fluphenazine	Thioridazine		
Haloperidol			
Mibefradil			

Significant Inhibitory Interactions: Protease Inhibitors

As previously described, protease inhibitors saquinavir, ritonavir, indinavir, and nelfinavir are substrates and inhibitors of the cytochrome 3A4 system. Ritonavir is also a significant inhibitor of the 2D6 isoenzyme system (Table 3).^{2, 3, 9, 16, 19, 33, 43, 48, 58, 60, 70, 114, 120-124}

These agents are likely to be given in combination with nucleosides and several other drugs (e.g., antimicrobials, antivirals) used to treat infections in patients with the acquired immunodeficiency syndrome. When comparing these agents, ritonavir appears to be a more potent inhibitor, and patients receiving it will require additional monitoring to avoid significant interactions. Indinavir appears to be less potent and is a reversible inhibitor of 3A4.¹²⁵ Therefore, it may be rational to give ritonavir in the early stage of human immunodeficiency virus (HIV) disease before a patient begins receiving numerous drugs that may interact and require complex dosage alterations.

Due to the poor absorption of saquinavir, it has been studied in combination with ritonavir to increase its plasma concentrations. Ritonavir has increased saquinavir concentrations by 18-fold.¹²⁵ This concept of combination therapy with other protease inhibitors warrants further study.

Occupational exposure to HIV may now result in a 4-week course of indinavir or other protease inhibitor.¹⁰⁵ Little clinical information and few case reports are available regarding drug

interactions with these agents, but the potential for interactions has been addressed based on pharmacokinetic *in vitro* data.¹⁰⁸ The majority of these data are with ritonavir, but prescribers should be aware that concomitant administration of drugs metabolized by the 3A4 system with other protease inhibitors may also result in interactions.

Concomitant administration of the 3A4 inhibitor ketoconazole with indinavir should include a dosage reduction of indinavir to 600 mg every 8 hours.⁶² Ketoconazole increases the AUC of saquinavir by 150%, but the consistency and extent of this interaction varies widely among patients.¹²⁵ Generally, when given in combination with saquinavir, dosage adjustment is not required unless ketoconazole dosages greater than 200 mg/day are given.⁶¹

Fluconazole's effect on protease inhibitor concentrations is unknown, but it may not produce as large an increase in their concentrations as the addition of ketoconazole because it is not thought to be as potent of an inhibitor.¹²⁵ Similarly, concomitant administration of fluconazole 200 mg/day and ritonavir 200 mg 4 times/day resulted in insignificant changes in the half-life of ritonavir. Dosage adjustments are not necessary.⁶⁰

Protease inhibitors increase rifabutin concentrations by inhibiting 3A4 metabolism. Ritonavir and nelfinavir increase the rifabutin AUC by 4-fold and 207%, respectively.⁶³⁻⁶⁵ These increases are associated with an increased risk of side effects including uveitis, making the

Table 4. 2D6 Clinically Significant Drug Interactions^{2, 3, 9, 16, 19, 33, 38, 43, 48, 58, 60, 70, 96, 114, 120-130}

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Analgesics Codeine	All 2D6 inhibitors, especially quinidine	Avoid; monitor for diminished analgesic effects; higher risk in PMs and EMs taking inhibitors; reduced morphine conc by 95%.	Other analgesics
Fentanyl Hydrocodone Meperidine Methadone Oxycodone Propoxyphene	Ritonavir (inh)	Marked increase in AUC; use alternative analgesics; monitor for toxicity; especially significant for fentanyl, meperidine, propoxyphene.	
Hydrocodone Oxycodone Meperidine Methadone	Rifampin (ind)	Increase dosage; well-documented reports of withdrawal.	
	Carbamazepine (ind) Phenobarbital (ind) Phenytoin (ind) Primadone (ind)	Increase dosage; monitor for withdrawal (well documented).	Other anticonvulsants
Meperidine	Cimetidine (inh)	22% decrease in clearance with respiratory depression, sedation; not seen with morphine.	Famotidine Nizatidine Ranitidine
Tramadol	Ritonavir (inh)	May need initial dosage decrease (based on in vitro data).	
Antiarrhythmics Flecainide Mexiletine Propafenone	Fluoxetine (inh) Paroxetine (inh) Sertraline (inh) (less effect) Amiodarone (inh)	Avoid combination due to narrow therapeutic index of antiarrhythmics. Reduce dosage 30-50% when starting amiodarone.	?Fluvoxamine Venlafaxine
	Quinidine (inh)	EMs at greatest risk; consider dosage decrease by 50%; monitor ECG.	
Mexiletine	Ritonavir (inh)	May need initial dosage decrease (based on in vitro data).	
Mexiletine Propafenone	Rifampin (ind)	May need initial dosage increase; monitor clinical effects.	
	Phenobarbital (ind) Phenytoin (ind)	Monitor for diminished effects.	
Propafenone	Cimetidine (inh)	Reports of up to 50-75% increase in serum conc with QRS prolongation; monitor ECG.	
Antidepressants Amitriptyline Desipramine Doxepin Imipramine Nortriptyline Trazodone	Fluoxetine (inh) Paroxetine (inh) Sertraline (inh)	Give lower dosages in combination; monitor for SE; wait 2-4 wks after fluoxetine discontinued.	Fluvoxamine Venlafaxine
	Cimetidine (inh)	Monitor psychomotor performance; orthostatic hypotension, urinary retention other symptoms reported.	Famotidine Nizatidine Ranitidine
	Mibefradil (inh)	May require substantial dosage adjustment.	
	Carbamazepine (ind) Phenobarbital (ind) Phenytoin (ind) Primadone (ind) Chronic ETOH ingestion (ind) Acute ETOH ingestion (inh)	Inhibits metabolism; increases serum conc.	Gabapentin Lamotrigine Topiramate Valproate

Table 4. 2D6 Clinically Significant Drug Interactions^{2, 3, 9, 16, 19, 33, 38, 43, 48, 58, 60, 70, 96, 114, 120-130} (continued)

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Amitriptyline Clomipramine Desipramine Imipramine Maprotiline Nortriptyline	Ritonavir (inh)	May need initial dosage decrease (based on in vitro data).	
Desipramine Imipramine Others?	Quinidine (inh)	Monitor for signs of TCA toxicity (arrhythmias, confusion, sedation); higher risk in EMs.	Other combinations desirable
Fluoxetine Paroxetine Venlafaxine	Ritonavir (inh)	May need initial dosage decrease (based on in vitro data).	
Fluoxetine	Clarithromycin (inh)	One case of delirium reported.	Azithromycin Dirithromycin
Trazodone	Paroxetine (inh) ?Other SSRIs	Reports of serotonergic syndrome.	
Antipsychotics Chlorpromazine Haloperidol Perphenazine Thioridazine	Ritonavir (inh) Fluoxetine (inh) Paroxetine (inh) Sertraline (inh)	May need initial dosage decrease (based on in vitro data). Increases serum conc after 7-10 days; confirmed with fluoxetine and haloperidol; monitor for side effects.	
β -Blockers Bisoprolol Labetalol Metoprolol Pindolol Propranolol Timolol	Ritonavir (inh) Rifampin (ind) Fluoxetine (inh) Paroxetine (inh) Sertraline (inh) (less effects) Mibefradil (inh)	May need initial dosage decrease (based on in vitro data). May need initial dosage increase; monitor clinical effect. Monitor for clinical effects; inhibits metabolism.	Other β -blockers not metabolized (e.g., atenolol, nadolol) Other β -blockers Fluvoxamine Venlafaxine
Propranolol	Smoking, PAH (ind) Quinidine (inh)	Lower plasma conc in smokers; monitor for effect. Higher risk in EMs.	Other β -blockers
Miscellaneous Cyclobenzaprine Dexfenfluramine Fenfluramine	Fluoxetine (inh) Fluoxetine (inh) Fluvoxamine (inh) Paroxetine (inh) Sertraline (inh)	Observe for QT prolongation. Avoid combination; theoretical; increased risk of serotonergic syndrome; increased risk in PMs.	

PMS = poor metabolizers; EMs = extensive metabolizers; AUC = area under the concentration-time curve; SE = side effects; PAH = polycyclic aromatic hydrocarbons; TCA = tricyclic antidepressant.

combination contraindicated.¹²⁵ Concomitant administration of indinavir with rifabutin led to a 204% increase in rifabutin AUC. Therefore, an adjustment to one-half the standard rifabutin dosage is recommended for patients receiving this combination.^{62, 125} Of note, a similar interaction was observed between rifabutin and fluconazole, making monitoring for ocular side

effects and uveitis essential.¹²⁵

Benzodiazepines and opiates have demonstrated reduced clearance when given in combination with ritonavir and indinavir. If used in combination with protease inhibitors, dosages should be reduced or alternative agents should be considered.¹²⁵

Other drugs studied concomitantly with

ritonavir and noted to have a significant (> 3-fold) increase in their AUC include benzodiazepines, calcium channel blockers, antidepressants, antiarrhythmics, corticosteroids, anticoagulants, and opiates.¹²⁵ Ritonavir increased the AUC of many 2D6-metabolized drugs by 1.5- to 3-fold (Table 4),^{2, 3, 9, 16, 19, 33, 43, 48, 58, 60, 70, 114, 120-130} together with changes in some 1A2-metabolized drugs (Table 5).^{2, 3, 9, 16, 18, 36, 37, 39, 40, 45, 96, 114, 117, 120, 131-139} Large dosage adjustments (50% reduction) may be required with these drugs.

Ritonavir caused a 77% increase in the AUC of clarithromycin. Prescribing information for ritonavir recommends no dosage adjustment in patients with normal renal function, a 50% reduction in clarithromycin dosage in patients with creatinine clearance (Cl_{cr}) of 30-60 ml/minute, and a 75% reduction for Cl_{cr} below 30 ml/minute. Another specific example of an AUC increase associated with ritonavir is desipramine (145% increase in AUC). Desipramine dosages should be decreased when the drug is given concurrently with ritonavir.⁶⁰

Protease inhibitors should be prescribed cautiously in combination with drugs primarily metabolized by the 3A4 system and those metabolized by the 2D6 system (ritonavir only). Concurrent administration should be accompanied by careful clinical monitoring for side effects and dosage adjustments in some patients.

Significant Induction Interactions: Protease Inhibitors

One major interaction of concern with these drugs is rifampin's and rifabutin's induction of metabolism. Rifampin 300-600 mg/day decreased saquinavir concentrations by 80%, making saquinavir dosage adjustments necessary. Rifampin decreased the maximum concentration and AUC of ritonavir by 25% and 35%, respectively.¹²⁵ Rifabutin is a less potent inducer than rifampin, but decreased saquinavir plasma concentrations by 40%.^{61, 125} The clinical significance of these decreases in protease inhibitor concentrations is unknown, but given the fact that resistance is associated with suboptimal plasma levels of these drugs, consequences could be serious.¹²⁵

Guidelines for concomitant administration of rifampin with protease inhibitors were published recently by the Centers for Disease Control and Prevention in the *Morbidity and Mortality Weekly Report*.⁵⁹ If protease inhibitor therapy cannot be

Table 5. Cytochrome 1A2 Isoenzyme: Substrates, Inducers, and Inhibitors^{2, 3, 9, 16, 18, 36, 37, 39, 40, 45, 96, 114, 117, 120, 131-139}

Substrates	Inhibitors
Amitriptyline (demethylation)	Cimetidine
Caffeine	Ciprofloxacin
Clomipramine (demethylation)	Clarithromycin
Clozapine	Enoxacin
Cyclobenzaprine	Erythromycin
(demethylation)	Fluvoxamine (potent)
Desipramine (demethylation)	Grapefruit juice
Diazepam	Isoniazid
Haloperidol	Ketoconazole
Imipramine (demethylation)	Levofloxacin
Tacrine	Norfloxacin
Theophylline	Omeprazole?
R-warfarin	Paroxetine
Zileuton	
Inducers	
Phenobarbital	
Phenytoin	
Rifampin	
Ritonavir	
Smoking/PAH	

PAH = polycyclic aromatic hydrocarbons.

discontinued during rifampin therapy, two options are available. The first is to administer a four-drug tuberculosis regimen that includes rifampin for a minimum of 2 months or until bacteriologic response (usually 3 mo) is achieved. Rifampin can be discontinued and a modified regimen continued for 16 additional months after that time. This option cannot be attempted in isoniazid-resistant patients. Option 2 is to continue protease inhibitor therapy with indinavir 800 mg every 8 hours, or switch to indinavir if the patient is taking another protease inhibitor, and administer a four-drug, 9-month regimen that contains rifabutin 150 mg/day (one-half usual dosage) instead of rifampin. This is based on the fact that rifabutin has less inducing effect than rifampin and has comparable antituberculosis activity in vitro.⁵⁹

Other agents that are known inducers of 3A4, including phenobarbital, phenytoin, carbamazepine, and dexamethasone, should be given cautiously with these drugs; alternatives are recommended, if possible.¹²⁵ Tobacco, another known inducer, is associated with an 18% decrease in the AUC of ritonavir.⁶⁰ Specific dosage adjustments in smokers have not been developed.

Significant Interactions: Cyclosporine

Numerous drug interactions with cyclosporine have surfaced in recent years that are associated

with its metabolism and presystemic metabolism by the 3A4 enzyme in the liver and intestine, respectively. It is postulated that gastrointestinal tract metabolism may in part explain its erratic absorption.¹⁰⁷⁻¹⁰⁹ In fact, 3A4 inhibition has been given intentionally to improve cyclosporine's bioavailability and decrease its dosage requirements. Ketoconazole 200–400 mg/day can decrease dosage requirements by 60–80%. Serum concentrations begin to increase within 2 days, but 2–4 weeks may be required for stabilization.^{110, 111}

Diltiazem in variable dosages decreased cyclosporine dosage requirements by as much as 30%.¹¹² In some studies, grapefruit juice increased the drug's AUC by 19–60% when given within 90 minutes before or after cyclosporine.^{52, 56} However, other authors showed no change in cyclosporine AUC or trough concentrations with concomitant administration of grapefruit juice 1.5 L/day.⁵⁵ Therefore, the effect with grapefruit juice is highly variable, and the clinical significance is unknown.

A study in pediatric renal transplant recipients showed that lower dosages of cyclosporine are required in patients also receiving norfloxacin. This has not been seen with ciprofloxacin.¹¹³

Other drugs that alter cyclosporine concentrations secondary to cytochrome 3A4 inhibition include verapamil, nifedipine,¹⁰⁷⁻¹⁰⁹ fluconazole, itraconazole, ketoconazole, erythromycin, clarithromycin,^{33, 108, 109} tacrolimus,^{108, 109} and mibefradil.³⁸ Cyclosporine concentrations are decreased secondary to enzyme induction with rifampin,^{16, 33, 108, 109, 114} phenytoin, carbamazepine, and phenobarbital.^{108, 109, 120} Cyclosporine trough levels, signs of toxicity, and adequate immunosuppressive response should be monitored when these drugs are begun or discontinued in combination with cyclosporine.

Significant Induction Interactions: Estrogens and Corticosteroids

Reports of breakthrough bleeding and unintended pregnancies due to drug interactions are increasing, perhaps due to the fact that estrogen and progestin concentrations of oral contraceptives are decreased. Clinically significant drug interactions with oral contraceptives secondary to 3A4 enzyme induction include carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and rifampin,^{114, 115, 117, 120} They have not been reported with gabapentin, lamotrigine, topiramate, and valproate. With these interactions,

a higher-dose oral contraceptive (50 µg ethinyl estradiol), medroxyprogesterone, or nonhormonal alternative method of contraception is desirable.

Similarly, corticosteroid clearance is increased with the same concomitant agents. Patients receiving corticosteroids for chronic diseases should be monitored for exacerbation of symptoms in these situations.¹²⁰

Other potential interactions are with benzodiazepines, which also may compete with or induce microsomal hepatic enzymes. They may reduce the effectiveness of oral contraceptives, whereas oral contraceptives can enhance the effect of benzodiazepines by competing with their clearance. During short courses of benzodiazepines, an alternative method of contraception is desirable. Oral contraceptives themselves reduce prednisolone clearance up to 50%, increase serum phenytoin concentrations, decrease metoprolol clearance, and reduce theophylline clearance up to 33%.¹¹⁷ How clinically significant these interactions are remains to be determined.

Significant Inhibitory Interactions: Corticosteroids

Little information is available regarding inhibition of estrogen or corticosteroid metabolism. Ketoconazole increases the AUC of both prednisolone and methylprednisolone in humans through inhibition of metabolism. Further studies are required to clarify the clinical significance of this alteration.³³

2D6 Isoenzyme

The 2D6 isoenzyme is the most intensely studied CYP450 enzyme since a genetic polymorphism in its drug metabolism was identified over 15 years ago. Administration of dextromethorphan followed by measurement of *O*-demethylated metabolite excretion in urine is an accurate and noninvasive way of phenotyping individuals as either EMs or PMs for 2D6 activity. The PMs lack this enzyme as a result of an autosomal recessively transmitted defect in its expression. Of note, approximately 5–10% of whites are PMs compared with 1–3% of African-Americans and Asians.^{2, 3}

For drugs that are highly dependent on clearance to an inactive metabolite by 2D6, PMs may have a larger response and be at greater risk of toxicity than EMs. For example, there is an association between PMs and tricyclic antidepressant-induced cardiotoxicity and with neuroleptic-induced side effects.¹⁹ Furthermore,

inhibition can reduce the metabolic rate in an EM to a value comparable with that of a PM.^{2, 5, 9, 40} When drugs are converted to an active metabolite by 2D6 (e.g., conversion of codeine to morphine), the drug may be ineffective in PMs. Induction cannot convert PMs to EMs, because only inactive or relatively inactive forms of the enzyme can be induced. To date, specific inducers of 2D6 have yet to be clearly identified,^{21, 9} but significant interactions between 2D6-metabolized drugs with the well-known inducers rifampin¹¹⁴ and anticonvulsants¹²⁰ have been described for years.

Large numbers of drugs affecting the cardiovascular and central nervous systems have been identified as substrates for 2D6 (Table 3).^{2, 9, 39, 40, 43, 70, 96, 121, 122, 124}

Significant Inhibitory Interactions: Antidepressants and Antipsychotics

In vivo, the selective serotonin reuptake inhibitor (SSRI) antidepressants fluoxetine and paroxetine are equipotent inhibitors of 2D6. Sertraline has less pronounced inhibition, and fluvoxamine is almost devoid of inhibitory effects.^{9, 122, 132} Coadministration with tricyclic antidepressants (TCAs) has been a focus of interest since these drugs are coadministered in some cases for resistant patients. Administration of desipramine with fluoxetine 20 mg/day and paroxetine 20 mg/day produced up to 4- and 3-fold increases, respectively, in peak serum concentrations. Similar results were shown with nortriptyline and imipramine.⁹ This inhibition is reversed within 1 week of discontinuing paroxetine, 1–2 weeks with sertraline, and up to 5 weeks with fluoxetine because of the prolonged half-lives of the parent compound and its metabolite.^{9, 19}

On average, the percentage increase in TCA plasma concentrations over baseline has ranged from 58–150% with sertraline 50 mg/day and 110–375% with fluoxetine 20 mg/day.¹⁹ Clinical sequelae resulting from the coadministration of SSRIs and TCAs have been reported only rarely, but full dosages of both agents could clearly lead to plasma concentrations in the toxic range. A summary of 25 cases involving combinations of fluoxetine and various TCAs showed that the magnitude of increased TCA concentrations is variable, does not correlate with the occurrence of adverse effects, and is not predictable.¹²⁴ Lower dosages with these combinations along with careful monitoring for side effects seem

warranted (Table 4).^{2, 3, 9, 16, 19, 33, 38, 43, 48, 58, 60, 70, 114, 120–130} Paroxetine was reported to interact with trazodone, with serotonergic syndrome occurring with 24 hours of administration of paroxetine 20 mg.¹⁹

We encountered a potential drug interaction in our institution that may have been mediated partly by fluoxetine inhibition of the 2D6 system. A 59-year-old woman was admitted for Achilles tendon repair. Her baseline QT interval on admission was prolonged (497 msec). Her drugs before admission included cyclobenzaprine, fluoxetine, diclofenac, amlodipine, and triamterene-hydrochlorothiazide. She had no known history of cardiac disorders except for hypertension. During outpatient surgery she had sudden onset of torsades de pointes that deteriorated into ventricular fibrillation. Preoperatively, she received droperidol, which is known to potentiate QT prolongation and should be given cautiously to patients with baseline QT prolongation.¹²⁶ The woman converted to normal sinus rhythm with magnesium sulfate and defibrillation. All drugs were discontinued, and her QT interval returned to below baseline levels by postoperative day 1. The question remained about the etiology of her baseline QT prolongation; we postulated inhibition of cyclobenzaprine metabolism by fluoxetine.

Cyclobenzaprine is hepatically metabolized, has a structure similar to TCAs (2D6, 3A4, 1A2 metabolized),⁹⁶ and caused conduction abnormalities in cases of overdose. In addition, its average half-life is 24 hours, which corresponds to the gradual decrease in the patient's QT interval.¹²⁷ Fluoxetine is a known inhibitor of 2D6, 3A4, and 2C, and reportedly increases serum concentrations of TCAs due to these effects.^{9, 19, 122–124} Although not documented, the potential exists for inhibition of cyclobenzaprine metabolism by fluoxetine.

Interactions secondary to enzyme inhibition by SSRIs and that are documented by pharmacokinetic studies and case reports occurred with flecainide, propafenone, haloperidol, and other antipsychotics. Due to the narrow therapeutic index and high-risk patients who receive type Ic antiarrhythmics, SSRIs should be avoided in patients taking these drugs.¹⁹ Vigilant pharmacodynamic monitoring should accompany therapy with SSRIs in patients treated with other drugs metabolized by the 2D6 enzyme.

Although clarithromycin has not been identified as a 2D6 substrate or inhibitor, a report of delirium in a 53-year-old man who was receiving long-term fluoxetine 80 mg/day and

clarithromycin indicates this potential. The patient's delirium quickly cleared after he stopped the drugs, and did not recur with erythromycin alone or when he restarted fluoxetine 80 mg/day. The authors concluded that the delirium was consistent with fluoxetine intoxication, which could have resulted from inhibition of metabolism by clarithromycin.¹²⁸

Other potential interactions with TCAs include mibefradil and quinidine. Quinidine is the most potent 2D6 inhibitor identified to date.³⁹ It inhibited TCA metabolism and resulted in 85% reduction in desipramine clearance and a 35% decrease in imipramine clearance.¹²⁹ Mibefradil is a CYP2D6 inhibitor and can increase plasma levels of TCAs, necessitating substantial dosage reductions.³⁸ Patients receiving these combinations should be monitored for signs of TCA toxicity.

Significant Induction Interactions: Narcotic Analgesics

Several opioids including meperidine, methadone, and morphine are metabolized by the 2D6 enzyme. Several well-documented interactions result from enzyme induction and loss of opioid activity.⁷⁰ Rifampin 600–900 mg/day precipitated withdrawal symptoms when given to 21 patients with tuberculosis receiving methadone maintenance.¹³⁰ Similar effects were reported with rifampin 450 mg/day.^{16, 70} Consideration should be given to opioid dosage increases when rifampin is begun, and patients should be monitored closely for symptoms of withdrawal. Similar enzyme-inducing effects and signs of narcotic withdrawal with up to 50% reduction in methadone concentrations were documented with methadone and phenytoin, phenobarbital, and carbamazepine. Pharmacokinetic studies also indicated that reductions in the clearance of meperidine could be expected with these enzyme-inducing agents.^{70, 120}

Pharmacodynamic monitoring would appear to be the most appropriate management strategy when narcotics are given concurrently with enzyme-inducing agents.^{2, 3, 9, 16, 19, 33, 43, 48, 58, 60, 70, 114, 120–130}

Significant Inhibitory Interactions: Narcotic Analgesics

Coadministration of cimetidine 1200 mg/day with meperidine decreased meperidine clearance by up to 22%.⁷⁰

Special care should be taken when administering codeine with 2D6 inhibitors or when no clinical

effect is achievable. Codeine is a prodrug and 10% of the dose is *O*-demethylated to the active metabolite, morphine. This demethylation is impaired in PMs and reduced in EMs during treatment with inhibitor drugs.³ The combination should probably be avoided since diminution of codeine's effect is highly probable.

1A2 Isoenzyme

The 1A2 isoenzyme is of clinical interest because of the large number of drug interactions associated with theophylline dealkylation and because of its inducibility by PAH in cigarette smoke and charcoal-broiled foods. No genetic polymorphism has been defined but possibly exists because of observations of a trimodal pattern of caffeine metabolism. The 1A2 enzyme is also responsible for metabolism of the *R*-isomer of warfarin as well as with several benzodiazepines. As noted in Table 5,^{2, 3, 9, 16, 18, 36, 37, 39, 40, 45, 96, 114, 117, 120, 131–139} drugs known to be inhibitors of 1A2 include fluvoxamine (very potent),^{2, 19, 39, 132} cimetidine,^{13, 131} macrolides,^{36, 37, 131} and several of the quinolones.^{131, 134–136}

Significant Inhibitory Interactions: Theophylline

Cimetidine is an enzyme inhibitor and causes a pharmacokinetic interaction with theophylline (theophylline clearance is decreased approximately 30%). Pharmacodynamic data are lacking, however. An initial dosage reduction should be considered in patients with a baseline theophylline level above 12 µg/ml due to theophylline's narrow therapeutic index.^{13, 131}

Fluvoxamine is a potent inhibitor of 1A2, unlike the other SSRIs. It increased theophylline concentrations 2- to 3-fold, along with significant increases in haloperidol and clozapine concentrations.^{19, 132} The majority of patients had increased plasma theophylline concentrations accompanied by clinical symptoms.¹³²

Interactions with macrolides are fairly well documented. In most studies, erythromycin and clarithromycin decreased theophylline clearance 20–25% after 7 days of concomitant administration. Most clinicians recommend theophylline dosage reduction and careful monitoring if the baseline theophylline level is above 12 µg/ml. Other macrolides such as azithromycin and dirithromycin are routinely suggested as alternatives.^{36, 37, 131} In one patient, however, addition of azithromycin to a maintenance theophylline regimen resulted in an increase in serum concentration from the usual 12.7–15.5

µg/ml to 20 µg/ml, and discontinuation of azithromycin resulted in a 80% decrease in the concentration. This was confirmed with two rechallenges.¹³² Thus, clinicians should be aware of the potential for an interaction with azithromycin.

Several quinolones commonly decrease theophylline clearance. Enoxacin has the greatest potential, with a 50–65% reduction in clearance, followed by ciprofloxacin with a 25–30% decrease and norfloxacin with a 10–15% decrease.^{75, 131, 134–136} These interactions resulted in symptoms of theophylline toxicity including seizures. Up to 50% dosage reduction is recommended for patients with a baseline theophylline level above 12 µg/ml when beginning these combinations.^{129, 130, 132–134} Clinically significant interactions with ofloxacin, levofloxacin, lomefloxacin, and sparfloxacin are unusual, making them alternative quinolones.

Isoniazid also decreases theophylline clearance after at least 6 days of concomitant administration. This appears to be most pronounced in slow acetylators, with up to a 2-fold increase in theophylline concentrations.^{16, 131}

Oral contraceptives decrease theophylline clearance by 30%, necessitating more careful monitoring when starting or discontinuing concomitant therapy with theophylline. The proposed mechanism is inhibition of metabolism.¹¹⁷ Grapefruit juice has no effect on theophylline metabolism, although it may have some 1A2 inhibitory effects.¹³¹

Significant Induction Interactions: Theophylline

The PAH in cigarette smoke induce 1A2 enzymes responsible for theophylline metabolism. It was estimated that smokers may require up to twice the dosage relative to that of nonsmokers, and a dosage reduction by one-fourth to one-third during abstinence. Some reports indicate that enzyme induction is present for up to several months after smoking cessation.^{18, 131}

Other well-established induction interactions with theophylline including rifampin and the anticonvulsant drugs carbamazepine, phenobarbital, and phenytoin^{114, 120, 131} are summarized in Table 6.^{2, 3, 9, 16, 18, 36, 37, 39, 40, 45, 114, 117, 120, 131–139}

Significant Inhibitory Interactions: R-Warfarin

As discussed, the R-isomer of warfarin is the less pharmacologically active form, but significant drug interactions have resulted from inhibition of its metabolism. The R-isomer is partially metabolized by the 3A4 system, and

several of these drug interactions have been discussed.

A series of case reports described the interaction between warfarin and quinolones that can occur as early as day 2 or as late as day 16 after beginning quinolone therapy. Hemorrhagic complications attributed to this interaction have been reported as well. Ciprofloxacin, norfloxacin, ofloxacin (least likely), nalidixic acid, and enoxacin were implicated in these reports. According to pharmacokinetic studies, the interaction is probably secondary to inhibition of the R-stereoisomer of warfarin, which is partly metabolized by the 1A2 isoenzyme.^{33, 135, 136} However, several prospective, placebo-controlled trials showed no clinically significant effect.^{138, 139} Since warfarin is metabolized by enzymes from three different families, most individuals may be able to shunt its metabolism to a noninhibited pathway. Although this interaction may be rare and unpredictable, careful monitoring of the INR is warranted during concomitant therapy (Table 6).^{2, 3, 9, 16, 18, 36, 37, 39, 40, 45, 114, 117, 120, 131–139} Alternative quinolones with little to no inhibitory properties include levofloxacin, lomefloxacin, and sparfloxacin.

The manufacturer of fluvoxamine has received 11 reports of interactions with warfarin. The drug increases the measured warfarin concentrations by 65%; all patients in case reports had elevated prothrombin times and some had bleeding complications.¹³² The safety of combining warfarin with other SSRIs was studied in patients previously maintained with warfarin. Fluoxetine appears to have no effect, and both paroxetine and sertraline caused an increase in prothrombin time, with reports of minor bleeding with paroxetine.^{19, 43} Close INR monitoring is warranted during therapy with any SSRI.

Warfarin metabolism is known to be inhibited by cimetidine, but data on pharmacodynamic and clinical effects are lacking. It seems prudent to monitor the INR carefully during combination therapy or to consider an alternative histamine₂ (H₂) antagonist.¹³ The enzyme-inhibitory effects of cimetidine are attributed to its imidazole ring.

Significant Inhibitory Interactions: Antidepressants, Antipsychotics, and Benzodiazepines

Fluvoxamine increases plasma concentrations with clinical symptoms of toxicity (e.g., confusion, tremor, extrapyramidal syndrome) in patients receiving amitriptyline (2-fold increase), clomipramine (8-fold), clozapine (3.2- to 11.8-

Table 6. 1A2 Clinically Significant Drug Interactions^{2, 3, 9, 16, 18, 36, 37, 39, 40, 45, 114, 117, 120, 131-139}

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives	
Theophylline	Rifampin (ind)	Can occur within 2-4 days; may need initial dosage increase; monitor serum conc.		
	Erythromycin (inh) Clarithromycin (inh) Troleandomycin (inh)	Usually not seen for 7 days but reported as early as 2 days; more careful monitoring if baseline level ≥ 12 $\mu\text{g/ml}$.	Azithromycin Dirithromycin	
	Ritonavir (ind)	Decrease in theophylline AUC by 43%; increased theophylline dosage may be required; monitor serum conc.		
	Enoxacin (inh) Ciprofloxacin (inh) Norfloxacin (inh)	Seen in 2-6 days; consider decreasing dosage 30-50% if baseline level ≥ 12 $\mu\text{g/ml}$; check level 2 days into therapy.	Levofloxacin Lomefloxacin Ofloxacin Sparfloxacin	
	Fluvoxamine (inh)	Confirmed by reports; monitor SC&E.	Fluoxetine Paroxetine Sertraline Venlafaxine	
	Cimetidine (inh)	Can occur within 24 hrs; reduce initial dosage 40% if baseline level ≥ 12 $\mu\text{g/ml}$.	Famotidine Nizatidine Ranitidine	
	Isoniazid (inh)	Up to 2-fold increase in serum conc; more pronounced in slow acetylators; monitor serum conc.		
	Oral contraceptives (inh)	Decreased clearance 30%; more significant if > 35 μg estrogen.		
	Zileuton (inh)	Reported to reduce clearance; monitor more carefully.		
	Smoking, PAH (ind)	Increase initial dosage by 50%; monitor serum conc; effects may persist for 3 mo after smoking cessation.		
	Carbamazepine (ind) Phenobarbital (ind) Phenytoin (ind)	Monitor serum conc more carefully; can see within 5 days with phenytoin.	Gabapentin Lamotrigine Topiramate Valproate	
	Anticoagulant R-warfarin	Ciprofloxacin (inh) Enoxacin (inh) Nalidixic acid (inh) Norfloxacin (inh) Cimetidine (inh)	Occurs in 2-16 days; unpredictable but can be clinically significant; monitor INR more carefully.	Levofloxacin Lomefloxacin Ofloxacin Sparfloxacin
		Fluvoxamine (inh) (most potent) Fluoxetine (inh) Paroxetine (inh) Sertraline (inh) Zileuton (inh)	Dose dependent with at least 400-800 mg/day cimetidine; monitor INR more carefully. Many case reports of increased INR with bleeding. Increased INRs reported; monitor more carefully.	Famotidine Nizatidine Ranitidine
Antidepressants and antipsychotics Amitriptyline Clomipramine Desipramine Imipramine		Fluvoxamine (inh)	Cases of increased serum conc with clinical symptoms of confusion, tremor.	

Table 6. 1A2 Clinically Significant Drug Interactions^{2, 3, 9, 16, 18, 36, 37, 39, 40, 45, 114, 117, 120, 131-139} (continued)

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Chlordiazepoxide Diazepam Others?	Smoking, PAH (ind)	Less drowsiness in smokers; may require higher dosages.	
Clozapine Haloperidol	Fluvoxamine (inh)	Avoid combination; resulted in markedly increased serum conc with symptoms of EPS.	Fluoxetine Paroxetine Sertraline
Miscellaneous Tacrine	Smoking, PAH (ind)	Mean plasma conc 1/3 less in smokers; may require higher dosages.	
	Cimetidine (inh)	Decreases clearance 30%; monitor for anticholinergic side effects.	Famotidine Nizatidine Ranitidine
	Enoxacin (inh) Ciprofloxacin (inh) Norfloxacin (inh)	Theoretical.	Lomefloxacin Ofloxacin Sparfloxacin

AUC = area under the concentration-time curve; SC&E = serum concentration and effects; INR = international normalized ratio; PAH = polycyclic aromatic hydrocarbons; EPS = extrapyramidal syndrome.

fold), desipramine (1-fold), and imipramine (1.3- to 5.7-fold).¹³² Patients receiving these combinations should be monitored for side effects and toxicity.

Significant Induction Interactions: Benzodiazepines

Similar to theophylline, the inducing effects of smoking are associated with less drowsiness in patients taking chlordiazepoxide and diazepam. This was studied in a comprehensive in-hospital drug surveillance program comparing 2274 nonsmokers, light smokers, and heavy smokers receiving these benzodiazepines. Smokers may require larger dosages of benzodiazepines to achieve a sedative or anxiolytic effect.¹⁸

2C Isoenzyme

The 2C subfamily consists of isoenzymes 2C9, 2C10, 2C19, and others. Cytochrome 2C19 exhibits genetic polymorphism, with 20% of Asians and African-Americans and 3-5% of Caucasians reported as PMs.^{2, 19} Drugs metabolized by the 2C subfamily include phenytoin (2C9), S-warfarin (2C9), and omeprazole. Diazepam, clomipramine, amitriptyline, and imipramine are demethylated by 2C enzymes. Known inhibitors of 2C enzymes include amiodarone (2C9) and omeprazole (2C19). Fluvoxamine, fluoxetine, and sertraline may inhibit these enzymes on the basis of increases in plasma concentrations of drugs believed to be

metabolized by this subfamily.^{19, 130} In addition, as noted in Table 7,^{2, 13, 65-68, 120, 132, 140-143} chloramphenicol,^{33, 120} cimetidine,^{13, 120} and isoniazid^{16, 120} are probable inhibitors on the basis of significant interactions with phenytoin.

Significant Inhibitory Interactions: Phenytoin

Case reports of 26 patients with steady-state phenytoin concentrations described a 67-309% increase in serum concentrations with the addition of the inhibitor fluoxetine within 5-13 days. Symptoms of toxicity occurred.¹⁹ Fluvoxamine, although a better recognized 3A4 and 1A2

Table 7. Cytochrome 2C Isoenzyme: Substrates, Inducers, and Inhibitors^{2, 13, 16, 33, 65-68, 120, 132, 140-143}

Substrates	Inhibitors
Amitriptyline	Amiodarone (2C9)
Clomipramine	Chloramphenicol (2C9)
Diazepam	Cimetidine (2C9)
(demethylation 2C9)	Fluconazole
Imipramine	Fluoxetine
Losartan (2C9)	Fluvastatin
Omeprazole	Fluvoxamine (2C9, potent)
Phenytoin (2C9)	Isoniazid
S-warfarin (2C9)	Ketoconazole (weak)
Tolbutamide	Omeprazole (2C9, 2C19)
Topiramate (2C19)	Sertraline
	Topiramate (2C19)
Inducers	Zafirlukast (2C9)
Carbamazepine	
Phenobarbital	
Phenytoin	
Rifampin	

Table 8. 2C Clinically Significant Drug Interactions^{2, 11, 13, 15, 16, 19, 33, 65-68, 120, 132, 140-143}

Substrate	Inhibitor, Inducer, Competing Substrate	Management	Alternatives
Anticonvulsants Phenytoin	Rifampin (ind)	Monitor serum conc more carefully when starting and stopping therapy.	
	Isoniazid (inh)	Monitor serum conc more carefully; more pronounced in slow acetylators; monitor for ataxia, nystagmus, drowsiness.	
	Cimetidine (inh) ?Ranitidine (inh)	Dose dependent; mild phenytoin intoxication in some cases; monitor SC&E; adjust dosages as necessary.	Famotidine Nizatidine
	Omeprazole (inh)	Up to 30% increase in half-life; monitor serum conc carefully or give alternative.	Lansoprazole
	Fluconazole (inh)	Predictable increase in serum conc after 14 days; monitor levels carefully.	
	Chloramphenicol (inh)	Up to 2-fold increase in serum conc.	Other antimicrobials
	Amiodarone (inh)	2-3-fold increase in serum conc within 3-4 weeks; reduce dosage based on serum conc.	
	Topiramate (inh)	25% increase in serum conc in some pts; monitor serum conc.	
	Fluoxetine (inh) Fluvoxamine (inh)	Reports of serious toxicity with nausea, vomiting, vertigo; avoid if possible.	
Anticoagulants S-Warfarin (more pharmacologically active isomer)	Rifampin (ind)	Seen within 2-4 days; monitor INR daily when starting and stopping therapy	
	Carbamazepine (ind) Phenobarbital (ind) Phenytoin (ind)		Gabapentin Lamotrigine Topiramate Valproate
	Chloramphenicol (inh)	Monitor INR more carefully when starting and stopping therapy.	Other antimicrobials
	Metronidazole (inh)	Bleeding episodes reported; monitor INR more carefully.	Other antimicrobials
	Amiodarone (inh)	Delayed interaction 1 wk-2 mo; decrease dosage 25% when starting therapy.	
	Zafirlukast (inh)	Mean PT increase 35%; monitor PT more carefully.	
Benzodiazepines Diazepam	Fluoxetine (inh) Fluvoxamine (inh)		
	Diazepam	Omeprazole (inh)	In vivo increases in serum conc; monitor for SE.
Miscellaneous Topiramate	Carbamazepine (ind) Phenobarbital (ind) Phenytoin (ind) Valproate (ind)	Reductions in serum conc observed.	

SC&E = serum concentration and effects; INR = international normalized ratio; PT = prothrombin time; SE = side effects.

inhibitor, may also have some 2C enzyme-inhibitory effects. The manufacturer has received reports of drug interactions with phenytoin that included nausea, vomiting, and vertigo.¹³² Due to phenytoin's narrow therapeutic window and nonlinear pharmacokinetics, these combinations should be avoided or phenytoin dosages reduced (Table 8).^{2, 11, 13, 15, 16, 19, 33, 65-68, 120, 132, 140-143}

Cases of mild phenytoin intoxication were reported when taken concomitantly with cimetidine. Other H₂ antagonists are without these effects and would be more desirable choices.^{13, 120} A study in eight healthy volunteers showed impaired elimination of phenytoin after omeprazole 40 mg/day for 8 days. Phenytoin's elimination half-life was increased by an average of 27%.⁶⁵ Patients taking these combinations should be monitored closely, or lansoprazole may be given as an alternative in patients receiving phenytoin.^{66, 143}

An increase in phenytoin concentration seems to be predictable when fluconazole is added. Nystagmus and ataxia occurred in two patients with excessive phenytoin concentrations after initiation of fluconazole 200–400 mg/day.¹⁴⁰ Studies in healthy volunteers showed up to 75% increase in AUC and 128% increase in trough phenytoin concentrations after 14 days of fluconazole.^{33, 120}

Isoniazid is another inhibitor that increases phenytoin concentrations. This interaction seems to be most pronounced in slow acetylators.¹⁶ A new antiepileptic agent, topiramate, also increases phenytoin serum concentrations up to 25% in some patients. Patients should be monitored carefully when receiving this combination antiepileptic regimen.¹⁴¹

Significant Induction Interactions: Phenytoin

Administration of rifampin with phenytoin and other anticonvulsants can cause therapeutic failure due to enzyme induction. Serum concentrations should be monitored regularly when beginning or discontinuing rifampin with these regimens.^{16, 114}

Significant Inhibitory Interactions: S-Warfarin

The S-isomer of warfarin is metabolized by the 2C9 isoenzyme. A significant interaction that appears to be 2C9 mediated is with amiodarone and warfarin. Amiodarone decreases the total body clearance of both R- and S-warfarin. Any alterations in clearance of the R-isomer could be due to amiodarone inhibition of 3A4. The

interaction can be seen from 1 week to 2 months after starting amiodarone and may persist 1–3 weeks after discontinuation. Most clinicians recommend reducing the warfarin dosage by 25% when beginning amiodarone therapy.^{11, 142}

Significant Induction Interactions: S-Warfarin

Patients previously stabilized with warfarin can suffer failed anticoagulation with the addition of rifampin, or overanticoagulation when rifampin is discontinued.^{16, 114} Similar problems exist with coadministration of carbamazepine, phenobarbital, and phenytoin.¹²⁰

Significant Inhibitory Interactions: Benzodiazepines

In vivo, omeprazole inhibits the metabolism of diazepam and increases the elimination half-life of diazepam by an average of 130%. It is not entirely clear, but the interaction may be 2C9 mediated. Patients receiving this combination over the long term should be monitored for side effects, or alternative agents should be considered.⁶⁵

Summary

Our knowledge of and ability to predict drug interactions have improved with growing understanding of substrates, inhibitors, and inducers of CYP-450 isoenzymes. This review underscores the need for definitive in vivo drug interaction studies and continued patient reporting by clinicians, since in vitro data are not always consistent with in vivo experience and since many variables (age, hepatic function, multiple metabolic pathways) influence patient outcomes. The information in this review should help health care providers in making decisions to manage CYP-450 drug interactions. Clinicians should be cognizant of potential interactions and become familiar with the substrates, inhibitors, and inducers of the common enzymatic pathways responsible for drug metabolism.

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