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Clinically Significant Cytochrome P450 Drug Interactions

During its short clinical use in this country, mibefradil (Posicor®, Roche Laboratories) inadvertently became a powerful teaching tool to illustrate the importance of Cytochrome P450 drug-drug interactions. One recent case illustrates a frightening incident that occurred as a result of a mibefradil-verapamil drug-drug interaction in an elderly patient.

In mid-June, 1998, an 88-year-old 64-kg patient arrived at an area emergency room with complaints of abdominal pain. Prior to the incident, his family had reported increasing recent confusion and arranged a visit from a home health nurse. Otherwise, he was in good health except for mild hypertension. In the emergency room, his heart rate was 41; the EKG showed sinus arrest with a slow idioventricular escape rhythm, and blood pressure was only 59/30. A transcutaneous pacer was placed, he was treated with oxygen, IV bicarbonate, and a dopamine infusion; he was intubated and flown by helicopter to a regional medical center. At this facility, blood lactate was 6.0. A temporary ventricular pacer was inserted, and adequate perfusion was re-established. In a short time he became hypertensive, and a nitroglycerin drip was started. Cardiac enzymes were normal. Overnight he resumed sinus rhythm, the acidosis resolved and he was extubated without problems. He was discharged home on the third hospital day.

In retrospect, this life-threatening incident probably occurred as a result of a cytochrome P450-mediated drug interaction between mibefradil and verapamil. The patient's admission medications included metoprolol extended-release 50 mg po QD and verapamil-extended-release, which had been started only that morning. Mibefradil had been discontinued two days previously by his family physician, who had been alarmed by the June 8 withdrawal of the product by the manufacturer. Unfortunately, the manufacturer had not yet sent out the second Dear Doctor letter with the caution that no alternative calcium channel blockers should be started until mibefradil is completely eliminated from the body.

Four similar case reports of patients on beta-blockers who went into cardiogenic shock when their blood pressure medication was changed from mibefradil to other calcium channel blockers was published in the July 8, 1998 issue of *JAMA*. (ME Mullins et al, Life-threatening interaction of mibefradil and

beta-blockers with dihydropyridine calcium channel blockers. *JAMA* 1998;280:157-158). One of the case patients died. Because mibefradil has a half-life of 17-25 hours, it requires a prolonged washout period. On June 8, Roche withdrew mibefradil, which had a history of multiple serious drug-drug interactions, from the U.S. market. Only on June 12 was a Dear Doctor letter sent to caution physicians that if other calcium-channel blockers were substituted for mibefradil, a seven- to fourteen-day washout period should precede administration of the new medication. Mibefradil inhibits CYP3A4 and has effects on the metabolism of at least 26 other medications.

In this journal issue, we present a discussion of clinically relevant cytochrome P450 drug interactions, their significance, and how to recognize patients at risk. The article also offers a perspective on the mibefradil case, and what clinical practitioners can learn from it. We encourage all pharmacists to increase their awareness of P450 interactions in order to ensure the safe use of medications affected by this phenomenon.

Background

The liver is the major site of drug biotransformation. Oxidative Phase I enzymatic reactions like hydroxylation terminate the biological activity of drugs in one or more steps. Phase II conjugation reactions such as glucuronidation sequentially complete the process of transforming metabolites into more water-soluble compounds that can be more easily eliminated by the kidneys.¹ The cytochrome P450 enzymes located in the membranes of the smooth endoplasmic reticulum are responsible for Phase I drug metabolism. These cytochrome P450 enzymes (CYP) occur in the microsomal

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fraction of homogenized liver tissue when it is fractionated by centrifugation, and often are referred to as microsomal enzymes. Metabolism of drugs and other foreign compounds (xenobiotics) also occurs to some extent in all body tissues, but mostly in liver, lung, intestinal tract, kidney, and skin.

Information about the CYP superfamily has increased exponentially in recent years, and it has been subclassified into families and subfamilies, based on the overlap of shared amino acid sequences. Families are designated by an Arabic numeral, subfamilies by a capital letter, and each individual isozyme (or its gene) by a numeral, so that each isozyme is represented in the format CYPnXm, like CYP2D6.² Drug metabolism is carried out primarily by families 1, 2, and 3. Other P450s catalyze steroid hormone biosynthesis in the mitochondria of liver, kidney, adrenal glands, placenta and gonads.³

Updated compilations of drugs metabolized by the microsomal P450 enzymes list clinically useful medications that are substrates for CYP.⁴ Individual isozymes have overlapping specificities, so that a particular drug substrate may be metabolized by more than one isozyme.³

Types of Drug Interactions

The liver has been recognized for many decades as the major site of drug metabolism. By the 1960's, the drug-metabolizing enzymes in the liver were characterized as heme proteins, now known as the cytochrome P450 microsomal enzymes. Adverse drug reactions are possible if compounds that act as inducers or inhibitors of these enzymes disrupt enzyme function. Enzyme induction can result in accelerated enzyme synthesis, faster drug metabolism and subtherapeutic drug concentrations. Enzyme inhibition can lead to accumulation of a drug, and if the drug has a narrow therapeutic window, serious toxicity may develop in a short time. Fortunately, because many drugs can be metabolized by more than one enzyme, inhibition of one pathway often brings an alternative pathway into play.⁵

Induction

Enzyme induction usually represents an absolute increase in enzyme synthesis, but phenobarbital, a well-known enzyme inducer, increases blood flow to the liver, and its use results in increases of up to 50% in liver size.⁴ Currently there are less than a dozen clinically important P450 inducers that are drugs. These include phenobarbital, other anticonvulsants and rifampin. One of the more serious recent examples is the induction of CYP3A4 by rifampin in HIV patients using protease inhibitors. Addition of rifampin decreases the AUC (area under the curve) of saquinavir by 80%, and of ritonavir by 35%.

The onset and duration of the interaction depend both on the kinetics of the drug and of the half-life of the CYP enzyme, which ranges from 1-6 days.⁴ Phenobarbital-induced changes

may be delayed for 14-22 days because of the long interval before peak phenobarbital plasma levels are reached, and the effects may linger after phenobarbital is discontinued. In contrast, the onset of rifampin-induced increases in enzyme activity is only four days, and the induced enzymes persist after the drug has been eliminated.

Important non-pharmacologic inducers include the polycyclic aromatic hydrocarbons in cigarette smoke, which cause the induction of CYP1A2 and result in higher dosing requirements of drugs like theophylline in smokers.⁴ Chronic alcohol use induces CYP2E1, but its effects on metabolism of CYP2E1 substrates like acetaminophen are less predictable.

Inhibition

Some potential drug-drug interactions can be predicted by identification of the isozyme that metabolizes the drugs in question, often because the inhibitor is a specific, often competitive inhibitor of the substrate. A good example is the inhibition of the metabolism of tricyclic antidepressants like desipramine by fluoxetine.⁶ The substrate, desipramine, is metabolized by CYP2D6, and its metabolism is strongly inhibited by binding of fluoxetine to the same isozyme. Fluoxetine at a dose of 20 mg daily can produce a four-to-five-fold increase in the plasma concentration of desipramine, so that a decrease in desipramine dose is necessary to avoid unpleasant or toxic side effects. The duration of the interaction depends on the half-life of the inhibitor.⁴ A drug can be both a substrate and an inhibitor for a particular isozyme.

A drug that is not a substrate can also inhibit the activity of a non-substrate isozyme.⁵ Quinidine is metabolized by CYP3A3/4, but powerfully inhibits CYP2D6. The corollary that follows is that identification of the isozyme(s) responsible for the metabolism of a drug is insufficient information to predict all potential drug interactions with confidence. Some of the additional information can be supplied by *in vitro* screening of new drugs by human microsomal liver enzymes as a routine part of investigational drug development. Such model systems so far have inconsistent predictive value, and in some cases, clinical interactions have been more significant than the prediction of the model studies.^{7,8} Many package inserts of drugs recently approved by the FDA have included a listing of the CYP isozymes that metabolize a drug *in vitro*; the information is often printed in both the "clinical pharmacology" and "precautions" sections.

Sometimes, detailed knowledge of metabolic pathways can predict the clinical significance of an interaction. For example, the potential drug interactions of tertiary tricyclic antidepressants like imipramine by inhibitors of CYP2D6 are limited, because oxidative metabolism can still go on through secondary pathways catalyzed by CYP1A2, CYP2C19, and CYP3A3/4.⁵ While it is helpful to know the extent of the theoretical possibilities, only clinical experience is able to prove which

interactions are clinically significant. Meanwhile, both the prescriber and the dispenser of new medications are faced with creative evaluation of risks versus benefits.

Patient Factors

Genetic differences in humans affect the function of several of the P450 enzymes. Genetic polymorphism in isozyme function has been most intensively studied in CYP2D6. For example, 5-10% of Caucasians and Mexican-Americans, but only 1-2% of Asians lack the CYP2D6 isozyme, and are characterized as poor metabolizers.⁵ Poor metabolizers (PMs) may be identified by administration of a probe drug like dextromethorphan that is metabolized by CYP2D6. Urine from the subjects is collected and analyzed for dextromethorphan and dextrorphan, its principal metabolite.⁵ The ratio of dextromethorphan to dextrorphan is ≈ 0.3 in PMs and <0.3 for extensive metabolizers (EMs) of 2D6. Similarly, CYP2C9 is absent in about 1% of Caucasians, and CYP2C19 is absent in 15-30% of Asians, while CYP2E1 is hyperactively expressed in about 1% of Caucasians. CYP1A2 and CYP3A do not show genetic variability, but CYP3A3/4 varies widely in enzyme activity among different individuals. Factors that affect human CYP activity are listed in Table 1.⁹

There is no decline in CYP quantity or activity with age, as such.¹⁰ There are age-related decreases in drug clearance that can be explained by declining liver size and blood flow and by measurable decreases in renal function. In addition, there is more variability in drug disposition among elderly patients than among younger individuals, possibly because drug-metabolizing enzyme induction and inhibition may be altered with increasing age. There is growing emphasis on the concept of frailty or debility itself as an indicator of function and as a risk factor for unexpected outcomes like adverse drug events. Frailty, defined as dependence on others for activities of daily living, is a more reliable predictor than age alone of how difficult it can be for an elderly person to re-establish homeostasis after a physical or pharmacologic insult. Not all somatic factors predisposing to CYP450-mediated interactions have been discovered, because only selected patients on serotonergic drug combinations develop clinical problems.

CYP1A2

Cytochrome P450 1A2 metabolizes chemicals and environmental toxins.² Unfortunately, an oxidative reaction sometimes can produce an intermediate that is more toxic than the parent compound. For example, CYP1A2 can activate benzpyrene, a carcinogen present in cigarette smoke, by 7,8-epoxidation. Drug substrates include caffeine, propranolol and theophylline.⁴ CYP1A2 induction by the polycyclic aromatic hydrocarbons (PAH) in cigarette smoke decreases theophylline levels in smokers, so that smokers often require higher theophylline doses than non-smokers. Conversely, smoking cessation can increase theophylline levels. Drugs that inhibit CYP1A2 include cimetidine, fluvoxamine, erythromycin, clarithromycin, enoxacin, ciprofloxacin, isoniazid, especially in slow acetylators, and oral contraceptives. Clinically significant increases in theophylline levels often occur after the addition of one of these well-known inhibitors. Norfloxacin is intermediate. Fluoroquinolones that do not inhibit CYP1A2 include ofloxacin, levofloxacin, lomefloxacin, and sparfloxacin. The fluvoxamine-imipramine interaction can be clinically significant. Table 2 lists clinically important substrates, inhibitors, and inducers of the six most common drug-metabolizing CYP isozymes.

CYP2C9, CYP2C19

CYP2C9 exhibits genetic polymorphism.⁴ About 3-5% of Caucasians and 20% of Asians and African-Americans are poor metabolizers, and PMs taking imipramine, amitriptyline, clomipramine or diazepam may develop higher serum levels than extensive metabolizers. Induction of CYP2C enzymes by rifampin can cause therapeutic failure of phenytoin and S-warfarin. In contrast, phenytoin levels may increase markedly in the presence of inhibitors such as fluoxetine, fluvoxamine, cimetidine, fluconazole, isoniazid, or omeprazole, but not lansoprazole. Because phenytoin has non-linear kinetics, inhibition at the point of enzyme saturation can produce startling increases in plasma levels. One serious interaction is the inhibition of S-warfarin metabolism by amiodarone. Because amiodarone has a slow onset and a prolonged elimination half-life, clinical onset of the interaction may be delayed by one

Table 1. Factors that Influence the Activity of CYP450 in Humans⁹

Factor	Major Drug-Metabolizing Isozymes Affected
Nutrition	1A2 2E1 3A3
Smoking	1A2
Alcohol	2E1
Drugs	1A2 2C 2D6 3A3
Somatic*	1A2 2E1 3A3
Genetic polymorphism	2C9 2C19 2D6 2E1

* Somatic factors include liver function and size, intestinal metabolism, etc

week to two months, and prothrombin times will remain elevated for one to three weeks after treatment is discontinued. Problems may be avoided by decreasing the warfarin dose by 25% when amiodarone is added.

CYP2D6

More than 80 drugs in clinical use are metabolized by CYP2D6.³ Promotional materials from manufacturers of newer antidepressants have emphasized comparative inhibition of CYP2D6 by different drugs in classes such as selective serotonin reuptake inhibitors (SSRIs) after the observation that fluoxetine increases serum levels of tricyclic antidepressants and increases tricyclic adverse effects. All antidepressants except fluvoxamine, nefazodone, citalopram, and bupropion either inhibit CYP2D6 or are metabolized by CYP2D6.¹² Molecular modeling has been more successful in predicting substrates that are metabolized by CYP2D6.¹³ Substrates that fit successfully at the enzymatic site have a basic nitrogen atom that can interact in the same plane with a carboxyl group at the enzymatic site. Some potent inhibitors of CYP2D6, quinidine and haloperidol, for example, bind tightly to this isozyme, but themselves are metabolized by other P450 enzymes.

There is a polymorphic distribution of CYP2D6 in populations, and studies of isoenzyme activity have been facilitated because patient phenotyping can be easily done by studying patient disposition of dextromethorphan. In addition to PMs and EMs of CYP2D6 substrates, there are also ultra-rapid metabolizers, who may need higher than normal doses of drugs like tricyclics.¹⁴ Some authors have recommended routine CYP2D6 phenotyping of patients for whom antidepressants are prescribed in the hope of improving clinical response in the 30% of patients who are initial non-responders. The doses to which patients respond can vary 50-fold, so that phenotyping could guide dosage choice and prevent misapprehensions that could label an ultra-rapid metabolizer as non-compliant. Until phenotyping becomes widely available, careful therapeutic monitoring and follow-up should determine individualized dosage.

If the therapeutic effect of a pro-drug occurs only after conversion to an active metabolite, as in the case of codeine when it is metabolized to morphine by CYP2D6, the drug may be completely ineffective in PMs.

Induction of CYP2D6 by rifampin has precipitated withdrawal symptoms in patients taking methadone, morphine, and meperidine, as have anticonvulsants in patients on methadone.⁴

Inhibition of CYP2D6 by fluoxetine or paroxetine with full doses of imipramine, desipramine or nortriptyline can increase the cardiac toxicity of the tricyclics.⁵ Cardiac arrhythmias, heart block and even sudden death are possible. The situation seldom occurs because clinical combination of tricyclics and

SSRIs typically occurs when one is being tapered when the other is initiated, and low tricyclic doses with SSRIs are usually tolerated without problems.

Fluoxetine or paroxetine also can inhibit metabolism of trazodone and nefazodone to precipitate serotonin syndrome.^{4,15} Serotonin syndrome occurs from an excess of serotonin produced by combinations of serotonin-active agents, and in a very few cases, may result in life-threatening symptoms.^{15,16} It is characterized by changes in mental status (agitation, confusion, mania), autonomic dysfunction (diaphoresis, diarrhea, fever, shivering), and neuromuscular abnormalities (hyperreflexia, incoordination, myoclonus, and tremor). Drug combinations known to have precipitated the problem include meperidine plus MAOIs (monoamine oxidase inhibitors), tricyclic antidepressants (TCAs) plus MAOIs, venlafaxine plus SSRIs, SSRIs plus trazodone or nefazodone, clomipramine plus fluvoxamine, and fluoxetine or paroxetine plus dextromethorphan.¹⁶ Symptoms usually respond to drug discontinuation and the use of post-synaptic serotonin receptor-blockers like cyproheptadine. When a switch from one serotonergic agent to another is anticipated, a washout period of five half-lives of the first agent is a useful strategy to prevent symptom development.

SSRIs may also inhibit the metabolism of Group 1_c antiarrhythmics like flecainide and propafenone to increase the proarrhythmic potential of these drugs.⁴ SSRIs can inhibit the biotransformation of haloperidol and other antipsychotic medications; in some cases, an increased incidence of dystonias has been observed.

Overall, the enzyme-binding potential of CYP2D6 inhibitors, from strongest to weakest, is quinidine = paroxetine > fluoxetine, norfluoxetine >> sertraline, desmethylsertraline > fluvoxamine, nefazodone, venlafaxine, erythromycin and ketoconazole.^{4,8}

CYP3A4

More than 150 drugs, including most calcium channel blockers, benzodiazepines, cyclosporine, and tacrolimus are metabolized by CYP3A4.⁴ In contrast to CYP2D6, CYP3A4 does not exhibit genetic polymorphism, but there are large interindividual variations in isozyme levels.^{3,4} This variance complicates predictions of drug interactions. In addition, as much as 70% of CYP3A4 can occur in the gut to metabolize substrates before they reach the liver, decreasing their bioavailability. Consequently, CYP3A4 is a major agent of first-pass metabolism.

The protease inhibitors used in the treatment of human immunodeficiency virus (HIV) infection, indinavir, nelfinavir, zidovudine, and saquinavir, must attain therapeutic levels in order to prevent relapse. Rifampin, rifabutin, and rifapentine, drugs commonly used in HIV patients, can induce CYP3A4

and produce subtherapeutic protease inhibitor levels.¹⁷ Rifamycins also inhibit verapamil.⁴

Some of the most serious CYP-mediated drug interactions have been caused by accumulation of substrates metabolized by CYP3A4 such as astemizole, terfenadine [now replaced by the manufacturer with its active metabolite fexofenadine (Allegra®)], and cisapride.⁴ A number of potent inhibitors ranging from macrolides and imidazole antibiotics to grapefruit juice have caused elevated substrate plasma levels that have precipitated prolonged QT intervals, torsades de pointes and even death. The manufacturer of cisapride continues to receive reports of serious adverse reactions, and has outlined risk factors for cisapride accumulation. Over 50% of patients with problems were concurrently taking ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin or metronidazole. Pre-existing patient risk factors included coronary disease, arrhythmias, renal impairment, electrolyte abnormalities and other drugs that can cause QT prolongation. Although terfenadine is no longer available, interactions between several of these same inhibitors plus terfenadine can also occur with astemizole, a non-sedating antihistamine with a long half-life.

A chance observation led to the surprising discovery in 1994 that concomitant administration of grapefruit juice could increase plasma felodipine levels five-fold.¹⁸ Drug elimination half-life did not change. As it turned out, the grapefruit juice caused down-regulation of CYP3A4 production in the small intestine and resulted in increased absorption of the felodipine. Normally, pre-systemic metabolism of felodipine in the intestine and in the liver limits its absolute bioavailability to about 15%, even though it is well-absorbed. Other dihydropyridines that interact significantly with grapefruit juice include nifedipine, nimodipine, nisoldipine, and nitrendipine, but not amlodipine. Verapamil interacts, but diltiazem does not. Grapefruit juice also significantly increases the absorption of cyclosporine, saquinavir, terfenadine, midazolam and triazolam. It does not interact with quinidine, prednisone, theophylline, propafenone or ethinylestradiol. Other drugs that may interact include lovastatin, simvastatin, and cisapride.

Repeated administration of grapefruit juice causes a cumulative effect, and the half-life of the effect is about 12 hours.¹⁸ For single doses, the increase in absorption (measured by area under the curve, AUC, and maximum plasma concentrations, C_{max}) varied among individuals from no change to a six-fold increase, but the increases were consistent in the same individual over time.

The risk of myopathies and rhabdomyolysis with lovastatin and simvastatin administration is elevated when inhibitors such as cyclosporine, grapefruit juice, erythromycin, clarithromycin, itraconazole, verapamil, and gemfibrozil are

added to therapy.⁴ Simvastatin levels can be increased by nefazodone. Cyclosporine dosage may have to be adjusted with concomitant administration of ketoconazole, itraconazole, fluconazole, grapefruit juice, erythromycin, clarithromycin, diltiazem, verapamil, and nifedipine. Nifedipine, isradipine and nitrendipine do not affect cyclosporine levels, but cyclosporine can increase nifedipine levels. Indinavir dosage should be reduced when ketoconazole is added.

CYP2E1

Very few drugs, with the exception of acetaminophen, chlorzoxazone, and several inhalation anesthetics, are metabolized by CYP2E1.¹⁹ It is involved in the disposition of a number of chemicals and other foreign compounds. The most important of these substrates is ethanol, which is metabolized by CYP2E1 as well as alcohol dehydrogenase. Chronic ethanol consumption can also induce CYP2E1. The result is that hepatically metabolized foreign substances are removed from the body more quickly. Unfortunately, when 2E1 action produces metabolites that are hepatotoxic, faster production can cause more liver damage. This is the case for acetaminophen, carbon tetrachloride, chloroform, isoniazid, halothane, and ethanol itself. In part because acutely administered ethanol can have inhibitory effects, the circumstances in which ethanol can predispose to increased acetaminophen toxicity are not well understood.^{19,20}

Whitcomb has pointed out that recent fasting is more consistently associated with acetaminophen toxicity than recent alcohol use.²⁰ The patients he studied had consumed between four and ten grams of acetaminophen in 24 hours, for therapeutic reasons, and had developed elevated liver function tests. The proposed mechanism for increased acetaminophen toxicity is a shift among several metabolic routes for the disposition of acetaminophen that is induced by fasting. Normally, 50-60% of acetaminophen is conjugated to glucuronide and sulfate metabolites, a process that is dependent on liver carbohydrate stores. Fasting leads to depleted carbohydrate reserves and more of the acetaminophen is metabolized by microsomal CYP2E1 to N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive hepatotoxin. NAPQI is ordinarily detoxified by glutathione, whose precursors also are reduced by fasting. When glutathione is exhausted, NAPQI binds to hepatocellular proteins to produce cell injury and death. The independent contribution of alcohol to acetaminophen toxicity is further complicated by selection bias, because many chronic alcoholics are in poor nutritional status.

The corollary for patient counseling is that acetaminophen should not be the analgesic of choice when oral intake has been poor for over 24 hours. For children who were not eating because of viral illness, chronic parental administration of acetaminophen in normal therapeutic doses has in some cases resulted in serious hepatotoxicity.²¹

Table 2.
Cytochrome P450 Enzymes Involved in Drug Metabolism: Substrates, Inducers, and Inhibitors

Isozyme	Substrates	Inhibitors	Inducers
CYP1A2	Clozapine Cyclobenzaprine Fluvoxamine Imipramine Mexiletine Propranolol Theophylline	Cimetidine Ciprofloxacin Clarithromycin Enoxacin Erythromycin Fluvoxamine Ofloxacin Ticlopidine	Polycyclic Aromatic Hydrocarbons (Cigarette Smoke) TCDD (dioxin)
CYP2C9	Diclofenac Flurbiprofen Ibuprofen Losartan (not candesartan or telmisartan) Naproxen Phenytoin Piroxicam Sulfamethoxazole Tolbutamide Warfarin	Amiodarone Fluconazole Fluoxetine Isoniazid Paroxetine Ticlopidine Zafirlukast	Phenobarbital Rifampin
CYP2C19	Amitriptyline Clomipramine Cyclophosphamide Diazepam Imipramine Lansoprazole Nelfinavir Omeprazole Phenytoin	Cimetidine Fluoxetine Fluvoxamine Ketoconazole Lansoprazole Omeprazole Paroxetine Ticlopidine	Carbamazepine Norethindrone
CYP2D6	Amitriptyline Clomipramine Codeine Desipramine Dextromethorphan Imipramine Metoprolol Nortriptyline Oxycodone Paroxetine Propranolol Risperidone Thioridazine Timolol	Amiodarone Fluoxetine Haloperidol Indinavir Paroxetine Quinidine Ritonavir Sertraline	Rifampin
CYP2E1	Acetaminophen Chlorzoxazone Ethanol Enflurane Halothane Isoflurane	Disulfiram	Chronic Ethanol Isoniazid
CYP3A	Alprazolam Astemizole Buspirone Calcium Channel Blockers Carbamazepine Cisapride Cyclosporine Protease Inhibitors Lovastatin Midazolam Simvastatin Tacrolimus Triazolam	Amiodarone Cimetidine Clarithromycin Erythromycin Grapefruit Juice Itraconazole Ketoconazole	Carbamazepine Glucocorticoids Phenytoin Rifampin Ritonavir

Table 3. New Drugs Metabolized by CYP450

Drug/Substrate	Indication	CYP Affected
Celecoxib (Celebrex®)	COX-2 inhibitor for arthritis	Metabolized by 2C9; inhibits 2D6
Cilostazol (Pletal®)	Phosphodiesterase III inhibitor, inhibits platelet aggregation, for intermittent claudication	3A4, (2C19)
Citalopram (Celexa®)	SSRI for depression	3A4, 2C19
Efavirenz (Sustiva®)	Non-nucleoside reverse transcriptase inhibitor for HIV	3A4, 2C9, 2C19
Leflunomide (Arava®)	Immune modulator for rheumatoid arthritis	2C9
Montelukast (Singulair®)	Leukotriene receptor antagonist for asthma	3A4, 2C9
Rifapentine (Priftin®)	Antibiotic for tuberculosis	Induces 3A4, 2C8/9 (metabolized by esterase)
Tolcapone (Tasmar®)	COMT inhibitor for Parkinson's disease	Major route: glucuronidation, (COMT) Metabolites: 3A4, 2A6

New Drugs

Table 3 lists the drugs recently approved by the FDA that are substrates, inducers or inhibitors of CYP450 enzymes.

Citalopram

Inhibitors of CYP3A4 like grapefruit juice, azole antifungals, cisapride, erythromycin and clarithromycin, if given with citalopram, could possibly produce symptoms of serotonin syndrome. Omeprazole or other inhibitors of CYP2C19 could precipitate the same problem. Citalopram may be an inhibitor of CYP2D6.

Montelukast

Montelukast does not have significant interactions with digoxin, prednisone, oral contraceptives, theophylline or warfarin, although phenobarbital decreases the AUC of montelukast after administration of single doses. Zafirlukast, a leukotriene receptor antagonist marketed earlier, inhibits both CYP 2C9 and CYP 3A4, and may significantly retard warfarin clearance. Concomitant administration of erythromycin or theophylline may decrease zafirlukast plasma concentrations.

Rifapentine

Rifapentine is a CYP3A4 inducer intermediate in potency between rifampin and rifabutin. It decreases the AUC of indinavir by 70%, and is expected to cause subtherapeutic levels of other protease inhibitors.

Although manufacturers have include other possible P450 interactions in the prescribing information, theoretical considerations are not clearly demarcated from practical concerns.

Risk Factors for Clinically Significant P450 Interactions

Prevention of P450 drug interactions requires a three-tiered initiative to address the three sources of possible problems: drugs that increase risk, patients at increased risk, and healthcare work patterns that are not fail-safe. Table 4 outlines characteristics of some of these risk factors that are encountered in everyday care settings.

Some risk factors can be addressed by regulatory action, such as the manufacturer's recall of mibefradil after it became evident that drug interactions had life-threatening effects in patient populations excluded from premarketing trials. Table 5 is a short list of substrates that have caused many of the serious adverse reactions due to P450 interactions.

Most preventive opportunities occur at the point of care. When medications are ordered and when medication orders are filled, patient information including renal function, liver function, and recent laboratory values, should be scanned. Appropriate medication information should be available electronically or manually. If substitute caregivers generate care directives, the orders should be recorded in the patient record in a format that can easily be reviewed in a timely manner by the attending physician. Drug interaction software should be included in order entry programs and patient medication profiles.

Types of Problem Substrates	Problem Patients	Problem Situations
Narrow Therapeutic Window	Aged >80	Drug Knowledge Deficit
High Affinity for a Single 450 Isozyme	Impaired Renal Function	Patient Knowledge Deficit
Non-linear Kinetics	Frailty	Failure to Check Liver, Kidney Function
Long Half-Life	Sedation/Confusion	Orders by On-Call Caregiver
No Routine Plasma Monitoring	Multi-organ Failure	Order Fill by Substitute RPh
Adequate Therapeutic Levels Imperative	Decreased Ability to Communicate	No computerized drug interaction check
New Meds in Populations Excluded from IND Testing	No Close Family Supervision	

Table 5. Substrates Causing Clinical Problems due to P450 Interactions

<u>Problem Substrates</u>
Calcium Channel Blockers
Cisapride
Cyclosporine
Flecainide
Haloperidol
Lovastatin
Phenytoin
Propafenone
Protease Inhibitors (Indinavir, Nelfinavir, Saquinavir, Ritonavir)
Simvastatin
Theophylline
Tricyclic Antidepressants
Triazolam/alprazolam
Warfarin

Conclusion

The wealth of experimental evidence on the superfamily of cytochrome P450 microsomal enzymes has begun to affect patient care. Clinical applications of cytochrome P450 technology now provide a more rational basis for understanding some well-known drug interactions and for predicting others. Although *in vitro* P450 studies with human liver microsomes are becoming routine for investigational drugs in development, their predictive value is limited, partly because of patient diversity. It is difficult to assess the practical implications of *in vitro* information from a package insert that may specify which isozymes metabolize the new drug as substrate, but may omit potential inhibition or induction reactions of the drug with isozymes for which it is not a substrate. Manufacturers have done preclinical evaluation of some potentially significant drug interactions, based on *in vitro* results and by analogy with related drugs, in volunteers more often than in patients taking the investigational medications. When available, this information may have predictive value. The case of mibefradil illustrates how important it may be to have multiple-dose studies in real patients for some classes of medications. For mibefradil, patients at risk appeared to self-select by disease condition or constellation, and to develop life-threatening complications with calcium channel blockers that could not have been predicted from information available at the time.

Michalets has compiled a very useful table of clinically important CYP450 drug interactions.⁴ Table 6, which follows, contains an updated adaptation of this table, arranged in alphabetical substrate order. Note that drugs or foods that act as inhibitors or inducers can be found by looking up the substrate that they affect. For example, grapefruit juice can be found in CYP3A4 interactions affecting calcium channel blockers or cisapride. Clinical importance, of course, is defined by the practice setting, and because Table 6 is selective, not all-inclusive, it does not try to address all imaginable interaction problems. Practitioners may find it useful to modify sections affecting the types of patients seen in their practice area.

Cytochrome P450 interactions occur only in a minority of known high-risk situations, and the characteristics of subpopulations at actual risk have not yet been identified. Genetic polymorphism can already explain the origin of some interactions, and the clinical availability of patient phenotyping for CYP enzymes may improve dosing guidelines. One potential application of CYP2D6 phenotyping is the development of patient-specific dosing guidelines for antidepressants in the hope that the percentage of initial responders will increase. Meanwhile, therapeutic monitoring of medications will continue to depend on clinical observations of therapeutic effects and tolerability. ■

Table 6. Clinically significant drug interactions mediated by cytochrome P450 enzymes.⁴

Substrate	Competing substrate	Inhibitor/inducer	Management involved	Enzyme	Alternatives
alprazolam	fluoxetine fluvoxamine	inhibitor	Decrease initial doses 50-75%; Monitor for somnolence, dizziness, ataxia; Reduce alprazolam dose	3A4	lorazepam oxazepam temazepam
	?grapefruit juice	inhibitor	theoretical	3A4	
	indinavir nelfinavir ritonavir saquinavir	inhibitor	delayed interaction Decrease dosage	3A4	lorazepam oxazepam temazepam; other antiretrovirals
	nefazodone	inhibitor	psychomotor impairment; Decrease dose	3A4	
amitriptyline	carbamazepine (phenobarbital) (phenytoin) chronic ETOH	inducer		2D6	gabapentin lamotrigine topiramate valproate
	fluoxetine paroxetine sertraline	inhibitor	Give lower dosages in combination; Monitor for side effects; Wait 2-4 weeks after fluoxetine d/c	2D6	fluvoxamine venlafaxine
	fluvoxamine	inhibitor	increased plasma levels: symptoms of confusion, tremor	1A2	
	ritonavir	inhibitor	May need initial dosage decrease	2D6	
amlodipine	itraconazole ketoconazole	inhibitor	Decrease CCB dose 50%; monitor for hypotension, flushing, edema	3A4	
astemizole	clarithromycin erythromycin troleandomycin	inhibitor	Avoid these combos	3A4	cetirizine, clemastine, loratadine, metoclopramide, azithromycin, dirithromycin
	fluconazole itraconazole ketoconazole miconazole IV	inhibitor	Avoid use	3A4	
	fluoxetine fluvoxamine nefazodone sertraline	inhibitor	Avoid combination	3A4	paroxetine venlafaxine
	grapefruit juice quinine tonic water	inhibitor	Avoid >200 ml/day Avoid >430mg/day	3A4	orange juice, other juices
	indinavir nelfinavir ritonavir saquinavir	inhibitor	Avoid combinations	3A4	other antiretrovirals
	zafirlukast zileuton	inhibitor	may increase concentration	3A4	other asthma regimens
carbamazepine	clarithromycin erythromycin	inhibitor	Decrease carbamazepine dose by 25%; seen within 24 hours	3A4	azithromycin dirithromycin
	indinavir nelfinavir ritonavir saquinavir	inhibitor	Decrease initial dosage 50%; Monitor plasma levels	3A4	
	rifampin	inducer	Monitor plasma levels May need initial dosage increase	3A4	
	verapamil	inhibitor	Monitor plasma levels and decrease dose as necessary	3A4	nifedipine
celecoxib	ACE inhibitors	inhibitor	theoretical	2D6	
	fluconazole	inhibitor	2-fold increase in plasma celecoxib levels	2C9	

Substrate	Competing substrate	Inhibitor/inducer	Management involved	Enzyme	Alternatives
cilostazol	grapefruit juice	inhibitor	Avoid grapefruit juice	3A4	orange juice, other juices
	clarithromycin erythromycin	inhibitor	increases cilostazol plasma level; Decrease cilostazol dose to 50 mg per day	3A4	
	diltiazem	inhibitor	increases cilostazol plasma level; Decrease cilostazol dose to 50 mg per day	3A4	
	fluoxetine fluvoxamine sertraline	inhibitor	increases cilostazol plasma level; Decrease cilostazol dose to 50 mg per day	3A4	
	itraconazole ketoconazole	inhibitor	increases cilostazol plasma level; Decrease cilostazol dose to 50 mg per day	3A4	
	nefazodone	inhibitor		3A4	
	omeprazole	inhibitor	increases cilostazol plasma level; Decrease cilostazol dose to 50 mg per day	3A4	
cisapride	clarithromycin erythromycin troleandomycin	inhibitor	Avoid these combos	3A4	metoclopramide; azithromycin dirithromycin
	fluconazole itraconazole ketoconazole miconazole IV	inhibitor	Avoid use	3A4	
	fluoxetine fluvoxamine nefazodone sertraline	inhibitor	Avoid combination	3A4	paroxetine venlafaxine
	grapefruit juice quinine tonic water	inhibitor	Avoid >200ml/day Avoid >430mg/day	3A4	orange juice, other juices
	indinavir nelfinavir ritonavir saquinavir	inhibitor	Avoid combinations	3A4	other antiretrovirals
	metronidazole	inhibitor	Avoid combination	3A4	metoclopramide; other antibiotics
	zafirlukast zileuton	inhibitor	may increase concentration	3A4	other asthma regimens
citalopram	MAO inhibitors	inhibitor	Use two-week washout to prevent serotonin syndrome	3A4, 2C19	
	tricyclic antidepressants	inhibitor	theoretical	3A4, 2C19	
clarithromycin	indinavir nelfinavir ritonavir saquinavir	inhibitor	Decrease clarithromycin dosage by 50% for CrCl=30-60 ml/min and 75% for CrCl<30 ml/min	3A4	
	rifampin rifabutin	inducer	clinical significance unknown	3A4	
clozapine	fluvoxamine	inhibitor	Avoid combination; increased EPS	1A2	fluoxetine paroxetine sertraline
cyclosporine	amiodarone	inhibitor	decreases clearance by 50%; Monitor levels and effects	3A4	
	carbamazepine phenobarbital phenytoin	inducer	Monitor cyclosporine levels	3A4	gabapentin lamotrigine topiramate valproate

Substrate	Competing substrate	Inhibitor/inducer	Management involved	Enzyme	Alternatives
	clarithromycin erythromycin troleandomycin	inhibitor	Avoid combo or reduce dosage 50%; can see within 2 days; Monitor trough 2-3x/week	3A4	azithromycin dirithromycin
	diltiazem mibefradil* nicardipine nifedipine verapamil	inhibitor	Monitor trough levels	3A4	amlodipine isradipine nitrendipine
	fluconazole itraconazole ketoconazole	inhibitor	Consider 50% dosage reduction when starting azole; Monitor trough	3A4	
	grapefruit juice	inhibitor	Avoid	3A4	orange juice, other juices
	indinavir nelfinavir ritonavir saquinavir	inhibitor	Decrease initial dosage 50%	3A4	other antiretrovirals
	norfloxacin	inhibitor	case study	3A4	ciprofloxacin
	oral contraceptives	inhibitor	not well documented; Monitor trough	3A4	
	rifampin	inducer	May need initial dosage increase; Monitor levels	3A4	
desipramine	cimetidine	inhibitor	increased anticholinergic side effects	2D6	famotidine nizatidine ranitidine
	fluoxetine paroxetine sertraline	inhibitor	Give lower dosages in combination; Monitor for side effects; Wait 4-5 weeks after fluoxetine d/c	2D6	(fluvoxamine) venlafaxine
	quinidine	inhibitor	Monitor for signs of TCA toxicity	2D6	
	ritonavir	inhibitor	May need initial TCA dosage decrease	2D6	
disopyramide	clarithromycin erythromycin	inhibitor	disopyramide toxicity; prolonged QT interval, torsades de pointes	3A4	azithromycin dirithromycin
	ritonavir	inhibitor	Decrease initial dosage of disopyramide	3A4	
doxepin	cimetidine	inhibitor	increased anticholinergic side effects	2D6	famotidine nizatidine ranitidine
efavirenz	astemizole	inhibitor	Avoid combination	3A4, 2B6	
	cisapride	inhibitor	Avoid combination	3A4, 2B6	
	clarithromycin	inhibitor		3A4, 2B6	
	ergot derivatives	inhibitor	Avoid combination	3A4, 2B6	
	ethinyl estradiol	inhibitor	ethinyl estradiol plasma levels increased	3A4, 2B6	
	indinavir ritonavir saquinavir	inhibitor	saquinavir plasma levels decreased	3A4, 2B6	Saquinavir should not be used alone; indinavir dose increase to 1000 mg every 8 hours
	midazolam triazolam	inhibitor	Do not administer with efavirenz	3A4, 2B6	
	rifabutin	inhibitor	rifabutin level decreased	3A4, 2B6	
	rifampin	inhibitor	rifampin level decreased	3A4, 2B6	
	warfarin	inhibitor	warfarin effects can be decreased or increased		3A4, 2B6
erythromycin	ritonavir	inhibitor	nausea, vomiting; Decrease initial erythromycin dosage 50%	3A4	
felodipine	erythromycin	inhibitor	nausea, vomiting, flushing, edema; Reduce initial CCB dose 50%	3A4	azithromycin dirithromycin
	grapefruit juice	inhibitor	nausea, vomiting, flushing, edema; Reduce initial CCB dose 50%	3A4	orange juice

Substrate	Competing substrate	Inhibitor/inducer	Management involved	Enzyme	Alternatives
	itraconazole ketoconazole	inhibitor	Reduce felodipine dose as required	3A4	(fluconazole)
	ritonavir	inhibitor	Nausea, vomiting, flushing, edema; Reduce initial CCB dose 50%	3A4	
flecainide	amiodarone	inhibitor	Reduce flecainide dosage 30-50% when starting amiodarone	2D6	
fluoxetine	clarithromycin	inhibitor	one case of delirium reported	2D6	azithromycin dirithromycin
	ritonavir	inhibitor	May need initial dosage decrease	2D6	
haloperidol	fluoxetine	inhibitor	increases plasma level after 7-10 days; Monitor for side effects	2D6	
	fluvoxamine	inhibitor	Avoid combination; increased EPS	1A2	paroxetine sertraline
	ritonavir	inhibitor	May need initial dosage decrease	2D6	
imipramine	cimetidine	inhibitor	increased anticholinergic effects; Decrease imipramine dose 50%	2D6	famotidine nizatidine ranitidine
	fluoxetine paroxetine sertraline	inhibitor	Give lower dosages in combination; Monitor for side effects; Wait 4-5 weeks after fluoxetine d/c	2D6	bupropion venlafaxine
	fluvoxamine	inhibitor	increased plasma level: symptoms of confusion, tremor	1A2	
	quinidine	inhibitor	Monitor for signs of TCA toxicity	2D6	other combinations desirable
	ritonavir	inhibitor	May need initial dosage decrease	2D6	
indinavir	efavirenz	inducer	Increase indinavir dose from 800 to 1000 mg Q 8H	3A4	
	ketoconazole	inhibitor	increases AUC	3A4	fluconazole
	rifabutin rifampin rifapentine	inducer	May need dosage increase; see specific MMWR guidelines	3A4	nucleoside or non- nucleoside combos
	ritonavir	inhibitor	Reduce isradipine dose as required	3A4	
isradipine	grapefruit juice	inhibitor	Decrease initial CCB dose 50%	3A4	orange juice
	itraconazole ketoconazole	inhibitor	Decrease initial CCB dose 50%	3A4	(fluconazole)
	rifampin rifabutin rifapentine	inducer	Increase initial CCB dose	3A4	
	ritonavir	inhibitor	Reduce isradipine dose as required	3A4	
itraconazole	carbamazepine phenobarbital phenytoin	inducer	Avoid combination; therapeutic failures reported	3A4	fluconazole; gabapentin lamotrigine topiramate valproate
	rifampin	inducer	Increase itraconazole dose if response suboptimal; fluconazole less affected	3A4	fluconazole
ketoconazole	phenytoin	inducer	poor clinical response noted	3A4	fluconazole; gabapentin lamotrigine topiramate valproate
	rifampin	inducer	Consider dosage increase; fluconazole less affected	3A4	fluconazole
lovastatin	cyclosporine	inhibitor	Monitor cyclosporine levels; watch for myopathy	3A4	atorvastatin cerivastatin fluvastatin pravastatin
	erythromycin	inhibitor	Avoid combination; myopathy, onset 10-14 days or longer	3A4	azithromycin dirithromycin

Substrate	Competing substrate	Inhibitor/inducer	Management involved	Enzyme	Alternatives
	grapefruit juice	inhibitor	Avoid; increased lovastatin plasma levels	3A4	orange juice
	itraconazole ketoconazole	inhibitor	Not recommended	3A4	fluconazole, with caution
mexiletine	amiodarone	inhibitor	Reduce dosages 30-50% when starting amiodarone; torsades de pointes observed	2D6	
	quinidine	inhibitor	EMs may have higher plasma levels; Monitor ECG; combo may have increased antiarrhythmic effects	2D6	
	rifampin	inducer	Avoid unless mexiletine levels available	2D6	
	ritonavir	inhibitor	May need initial mexiletine dosage decrease	2D6	
midazolam	fluvoxamine	inhibitor	Decrease initial doses 50-75%;	3A4	temazepam
	(grapefruit juice)	inhibitor	Monitor for oversedation	3A4	
nelfinavir	rifabutin rifampin	inducer	May need dosage increase; see specific MMWR guidelines	3A4	nucleoside or non-nucleoside combos
nicardipine	grapefruit juice	inhibitor	Decrease initial CCB dose 50%	3A4	orange juice
	itraconazole (ketoconazole)	inhibitor	Decrease initial CCB dose 50%	3A4	
	rifampin rifabutin rifapentine	inducer	Monitor hypertension; may decrease nicardipine efficacy	3A4	
nifedipine	grapefruit juice	inhibitor	Decrease initial CCB dose 50%	3A4	orange juice
	itraconazole (ketoconazole)	inhibitor	Decrease initial CCB dose 50%	3A4	
	rifampin rifabutin rifapentine	inducer	Monitor clinical effects; may decrease nifedipine efficacy	3A4	
nimodipine	grapefruit juice	inhibitor	Decrease initial CCB dose 50%	3A4	orange juice
	rifampin rifabutin rifapentine	inducer	theoretical	3A4	
nortriptyline	fluoxetine paroxetine sertraline	inhibitor	Give lower dosages in combination. Monitor for side effects. Wait 2-4 weeks after fluoxetine d/c	2D6	fluvoxamine venlafaxine
	quinidine	inhibitor	theoretical	2D6	
oral contraceptives	carbamazepine phenobarbital phenytoin primidone	inducer	Monitor for breakthrough bleeding; alternative contraceptive	3A4	gabapentin lamotrigine topiramate valproate
	rifampin rifabutin	inducer	Use alternative contraceptive or increase dosage to 50 mcg estradiol	3A4	
paroxetine	dextromethorphan	inhibitor	rarely, serotonin syndrome; Limit dextromethorphan dose	2D6	
phenytoin	amiodarone	inhibitor	2-3 fold increase in phenytoin plasma level within 3-4 weeks	2C	
	cimetidine ?ranitidine	inhibitor	dose dependent; Monitor plasma level	2C	famotidine nizatidine
	fluconazole	inhibitor	increase in serum plasma level after 14 days	2C	
	fluoxetine	inhibitor	reports of serious toxicity; Avoid if possible	2C9	(sertraline) (paroxetine)
	fluvoxamine	inhibitor	Monitor phenytoin levels	2C9	
	isoniazid	inhibitor	Monitor levels/side effects	2C	

Substrate	Competing substrate	Inhibitor/inducer	Management involved	Enzyme	Alternatives
	rifampin	inducer	Monitor plasma levels	2C	
propafenone	quinidine	inhibitor	Monitor ECG; EMs may develop propafenone toxicity	2D6	
	rifampin	inducer	Monitor propafenone levels	2D6	
propranolol	quinidine	inhibitor	higher risk in extensive metabolizers	2D6	atenolol nadolol timolol
	rifampin	inducer	Monitor blood pressure; may need initial dosage increase	2D6	other β -blockers
quinidine	amiodarone	inhibitor	Decrease dosage 30-50% on initiation; Monitor QT interval	3A4	
	phenobarbital phenytoin	inducer	May need initial dosage increase; Monitor levels/effect	3A4	gabapentin lamotrigine topiramate valproate
	erythromycin	inhibitor	increases serum level; Monitor QT interval	3A4	azithromycin dirithromycin
	itraconazole ketoconazole	inhibitor	30-fold increase in serum level after 7 days; Monitor QRS	3A4	
	rifampin	inducer	Need initial dosage increase; Monitor levels/effect	3A4	
rifabutin	clarithromycin	inhibitor	increases rifabutin serum level; increased risk of icterus and uveitis	3A4	
	fluconazole	inhibitor	increases serum level; increased risk of icterus and uveitis	3A4	
	indinavir nelfinavir saquinavir ritonavir	inhibitor	Decrease initial rifabutin dosage in half	3A4	alternative MAC prophylaxis
rifampin	indinavir nelfinavir ritonavir saquinavir	inhibitor	Not recommended	3A4	nucleoside or non-nucleoside combinations
ritonavir	carbamazepine phenobarbital phenytoin	inducer	may decrease ritonavir plasma levels; theoretical	3A4	nucleoside or non-nucleoside combos; gabapentin lamotrigine topiramate valproate
	rifabutin rifampin rifapentine	inducer	May need dosage increase; see specific MMWR guidelines	3A4	nucleoside or non-nucleoside combos
saquinavir	carbamazepine phenobarbital phenytoin	inducer	theoretical	3A4	nucleoside or non-nucleoside combos; gabapentin lamotrigine topiramate valproate
	ketoconazole	inhibitor	increased saquinavir AUC when ketoconazole doses >200 mg QD	3A4	
	rifabutin rifampin rifapentine	inducer	May need dosage increase; see specific MMWR guidelines	3A4	nucleoside or non-nucleoside combos
	indinavir ritonavir	inhibitor	increased saquinavir adverse effects if >400 mg QD saquinavir or ritonavir	3A4	
simvastatin	clarithromycin erythromycin	inhibitor	Monitor for myopathy	3A4	azithromycin dirithromycin
	cyclosporine	inhibitor	Initial dose of simvastatin 5 mg; monitor for myopathy	3A4	fluvastatin

Substrate	Competing substrate	Inhibitor/inducer	Management involved	Enzyme	Alternatives
	itraconazole	inhibitor	Monitor for myopathy	3A4	
	nefazodone	inhibitor	case report - rhabdomyolysis	3A4	
tacrolimus	clarithromycin erythromycin	inhibitor	Monitor trough 2-3 times/week; can see within 2 days	3A4	azithromycin dirithromycin
	(diltiazem) nicardipine nifedipine (verapamil)	inhibitor	Monitor tacrolimus trough levels	3A4	amlodipine isradipine nitrendipine
	grapefruit juice	inhibitor	Avoid	3A4	other juices
	itraconazole ketoconazole	inhibitor	Consider 50% dosage reduction when starting azole; Monitor trough	3A4	fluconazole not over 200 mg po QD
	nefazodone	inhibitor	case report – toxic tacrolimus levels		
	rifampin rifabutin rifapentine	inducer	May need initial dosage increase to prevent therapeutic failure; Monitor levels and effects	3A4	
theophylline	phenobarbital phenytoin	inducer	Monitor theophylline levels; increased plasma levels within 5 days with phenytoin	1A2	
	cimetidine	inhibitor	can occur within 24 hours; Reduce initial dosage 40% if baseline level >12	1A2	famotidine nizatidine ranitidine
	ciprofloxacin enoxacin	inhibitor	seen in 2-6 days; Consider decreasing dosage 30-50% if baseline >12; Check level 2 days into therapy	1A2	levofloxacin lomefloxacin norfloxacin ofloxacin sparfloxacin
	(clarithromycin) erythromycin troleandomycin	inhibitor	More careful monitoring if initial level >12; usually not seen for 7 days	1A2	azithromycin dirithromycin
	fluvoxamine	inhibitor	Monitor plasma levels and effects	1A2	fluoxetine paroxetine sertraline venlafaxine
	isoniazid	inhibitor	Monitor levels; usually not clinically significant	1A2	
	oral contraceptives	inhibitor	decreased clearance; significant if >35 mcg estrogen	1A2	
	rifampin	inducer	May need initial dosage increase; Monitor levels; can occur in 2-4 days	1A2	
	smoking	inducer	Increase initial dosage by 50%; Monitor levels; effects may persist for 3 months after smoking cessation	1A2	
	zileuton	inhibitor	Monitor more closely; theophylline plasma levels may double	1A2	
trazodone	fluoxetine paroxetine	inhibitor	Give lower dosages in combination; possible serotonin syndrome; Wait 4-5 weeks after fluoxetine d/c	2D6	fluvoxamine venlafaxine
triazolam	fluvoxamine nefazodone	inhibitor	Decrease initial doses 50-75%; Monitor for oversedation	3A4	lorazepam oxazepam temazepam
	fluconazole itraconazole ketoconazole	inhibitor	Avoid combinations	3A4	lorazepam oxazepam temazepam; terbinafine
verapamil	grapefruit juice	inhibitor	Decrease initial CCB dosage 50%; Monitor for side effects if >200 ml/day	3A4	orange juice, other juices
	phenobarbital phenytoin	inducer	Monitor effectiveness and increase verapamil dose as needed	3A4	
	rifampin	inducer	May need initial dosage increase	3A4	

Substrate	Competing substrate	Inhibitor/inducer	Management involved	Enzyme	Alternatives
Warfarin (R-isomer)	rifabutin				
	amiodarone	inhibitor	delayed interaction; Decrease dosage 25% on initiation	3A4	
	azithromycin clarithromycin erythromycin	inhibitor	can increase INR if over one gram per day in elderly patients	3A4	
	cimetidine ranitidine	inhibitor	may increase INR; Monitor	3A4	
	ciprofloxacin (enoxacin) (ofloxacin) norfloxacin	inhibitor	unpredictable INR increase; occurs in 2-16days; elderly may be at higher risk	1A2	levofloxacin lomefloxacin sparfloxacin trovafloxacin
	cisapride	inhibitor	one report of increased INR	3A4	metoclopramide
	fluconazole itraconazole ketoconazole	inhibitor	can cause 2-3 fold increase in INR	3A4	
	fluoxetine fluvoxamine paroxetine	inhibitor	increased INR	1A2, 2C9	
Warfarin (S-isomer) (most active)	zileuton	inhibitor	increased INR	1A2	
	amiodarone	inhibitor	delayed interaction 1 week-2 months	2C9	
	carbamazepine phenobarbital phenytoin	inducer	Monitor INR to prevent therapeutic failure	2C9	gabapentin lamotrigine topiramate valproate
	metronidazole rifampin	inhibitor inducer	bleeding episode reported seen within 2-4 days; Monitor INR	2C9 2C9	other antimicrobials
	zafirlukast	inhibitor	mean PT increase 35%	2C9	montelukast

Table adapted from Michalets in *Pharmacotherapy* and used with permission⁴

Abbreviations in Table 6.

AUC Area under the curve, **CCB** Calcium channel blocker(s), **Conc** Concentration, **CNS** Central nervous system, **CrCl** creatinine clearance, **d/c** Discontinuation, **ECG** electrocardiogram, **EMs** extensive metabolizers, **EPS** extrapyramidal symptoms, **N&V** nausea and vomiting, *product no longer on the US market

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