Implications of Cytochrome P450 Interactions When Prescribing Medication for Hypertension

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Many of the estimated 50 million Americans with high blood pressure receive medications for hypertension and for other conditions, placing them at risk for adverse drug interactions. The risk for hypertension and for adverse drug reactions is highest in the elderly, who have the greatest need for pharmacologic therapy. The most important class of drug interactions involves the cytochrome P450 microsomal enzyme system, which handles a variety of xenobiotic substances. A potential for interactions with these enzymes exists with calcium channel blockers, β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers but not with diuretic antihypertensives, which are renally eliminated and more vulnerable to drug interactions that occur in the kidney. This article reviews the cytochrome P450 enzyme system, identifies drugs and foods that have been implicated in metabolic interactions with antihypertensive agents, and suggests measures for reducing the risk of adverse events when drugs are coadministered.

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An estimated 50 million Americans have hypertension. Although the benefits of antihypertensive therapy are well established, it is clear that treatment with more than 1 drug may be necessary to achieve satisfactory blood pressure control. Moreover, many patients with hypertension require medication therapy for other diseases or conditions. The intersection of the high prevalence of hypertension, combination antihypertensive therapy, and drug-treated comorbid conditions results in the possibility of many drug interactions. The elderly are particularly vulnerable. Not only does this population take the most medications, but it also undergoes age-related changes in body and organ mass and in cardiac, hepatic, and renal function. Findings from one review indicate that adverse drug reactions account for 10% to 17% of the medical reasons for acute hospital admission of elderly patients. The importance of adverse drug reactions as a cause of morbidity and mortality in the United States has been emphasized by several recent studies that have made clear that more than 100,000 deaths result from adverse drug reactions each year in US hospitals, representing the fourth to sixth leading cause of death. The adverse effects of drugs and drug interactions are of great importance to patients. Being prescribed the wrong drug or drugs that interact is among the primary concerns of patients as they enter a physician’s office.

INTERACTIONS RESULTING IN REMOVAL OF DRUGS FROM THE MARKET

The novel calcium channel blocker mibefradil dihydrochloride (Posicor; Hoffmann-LaRoche Inc, Nutley, NJ) was withdrawn from the market because of potentially dangerous interactions when it was coprescribed with any of more than 25 drugs, some of them resulting in rhabdomyolysis, renal failure, and death. Terfenadine (Seldane; Marion Merrell Dow Inc, Kansas City, Mo) and astemizole (Hismanal; Janssen Pharmaceutica, Titusville, NJ), widely prescribed antihistamines, were also withdrawn. These agents serve as substrates for cytochrome P450 3A, whose inhibition by ketoconazole or several macrolide antibiotics may result in
prolongation of the electrocardiographic QT interval and lethal cardiotoxicity.\textsuperscript{9,10} The combination of cisapride, the oral gastrointestinal tract prokinetic agent used for the treatment of gastroesophageal reflux disease, with several drugs that elevate its plasma concentrations has resulted in serious and sometimes fatal ventricular arrhythmias, including torsade de pointes. Therefore, concomitant use of cisapride with the antibiotics clarithromycin, erythromycin, and troleandomycin; the antidepresant nefazodone hydrochloride; the antifungals fluconazole, ketoconazole, and itraconazole; and the protease inhibitors indinavir sulfate and ritonavir is contraindicated.\textsuperscript{11} There is a longer list of other drugs that must be prescribed with great caution to patients receiving cisapride. Numerous warnings to physicians and health care providers about potentially lethal drug interactions with cisapride did not improve appropriate prescribing of the drug. It became clear that more than 30\% of the prescriptions were inappropriate,\textsuperscript{12} and sale of the drug in the United States was restricted by the manufacturer and the Food and Drug Administration in July 2000.\textsuperscript{13} The recent series of drug withdrawals owing to drug interactions seems to emphasize the importance of educating physicians, nurses, pharmacists, and their patients about drug interactions, but it also makes abundantly clear that we do not have effective means of doing so at present. The interaction compiled by the Institute of Medicine titled \textit{To Err Is Human}\textsuperscript{14} made clear that preventable drug interactions contribute significantly to the burden of iatrogenic disease and that the danger of this situation worsening is considerable as the number of medicines available to an aging population increases.

**ADVERSE DRUG INTERACTIONS DUE TO ANTIHYPERTENSIVE DRUGS**

Drug interactions with many antihypertensive agents that are metabolized by the cytochrome P450 system have been reported. For example, cimetidine hydrochloride can decrease metabolism and increase steady-state plasma concentrations of several concomitantly administered drugs, including calcium channel blockers.\textsuperscript{15} Azole antifungal agents such as ketoconazole and fluconazole can also affect the metabolism of calcium channel blockers and some angiotensin II receptor blockers.\textsuperscript{16} Even grapefruit juice can increase drug bioavailability via the cytochrome P450 system.\textsuperscript{17} This article reviews the mechanisms of the microsomal enzyme system that contribute to normal metabolism and drug interactions, identifies a variety of drugs implicated in interactions with antihypertensive agents, and suggests measures for reducing the risk of adverse events when other drugs are coadministered with antihypertensive agents.

For pharmacokinetic reasons, most orally administered drugs are lipid soluble and nonpolar rather than hydrophilic and polar. Once absorbed, lipophilic drugs undergo a 2-stage biotransformation in the liver. In phase I, they are converted to active or inactive metabolites. However, because excretion ultimately depends on aqueous solubility in urine or feces, many drugs and their active metabolites undergo a second biotransformation (phase II) to render them polar and hydrophilic. Highly hydrophilic drugs (eg, atenolol and nadolol), on the other hand, generally escape hepatic metabolism and are excreted largely unchanged in urine. Many orally administered drugs are actually prodrugs, exerting all or most of their pharmacologic effect only on conversion to active metabolites (eg, quinapril hydrochloride to quinaprilat and losartan potassium to a carboxylic acid metabolite).

Most important phase I reactions are catalyzed by the cytochrome P450 microsomal enzymes, a set of heme-containing proteins localized primarily in hepatocytes but also in the intestines.\textsuperscript{18,19} Collectively, these enzymes catalyze oxidative and reductive reactions on a variety of substrates (ie, the drugs or other xenobiotic substances that are acted on). Some drugs are substrates for only 1 enzyme, whereas others are substrates for more than 1. Certain drugs act on enzymes that metabolize other substrates in a way that has lasting effects; these are the agents most likely to be involved in clinically important drug interactions.

The nomenclature for cytochrome P450 enzymes is based on how homologous their amino acid sequences are.\textsuperscript{19,20} A hierarchy of cytochrome P450 classification (designated with the prefix CYP) proceeds from the family (designated by Arabic numerals) to the subfamily (designated by capital letters) to individual isoforms (designated by Arabic numerals), eg, CYP3A4. Although hundreds of cytochromes P450 have been identified, only 6 isoforms catalyze the oxidative metabolism of most drugs in common use: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.\textsuperscript{21} The **Figure** depicts the proportion of drugs metabolized by the major cytochrome P450 isoforms. Extensive metabolism by CYP3A4 in the intestinal mucosa and the liver contributes to the low oral bioavailability of many drugs.\textsuperscript{19}

Two major mechanisms are responsible for cytochrome P450-mediated drug interactions: induction and potent inhibition. Induction refers to increased synthesis or decreased degradation of cytochrome P450 enzymes, actions that expedite conversion to inactive metabolites. Thus, induction results in decreased plasma levels of the substrate and a decrease in its pharmacodynamic effect. Examples of inducers are rifampin and phenobarbital, which decrease the bioavailability of propranolol hydrochloro-
ride, metoprolol succinate, and calcium channel blockers. Table 1 lists drugs that induce or inhibit cytochrome P450 enzymes for antihypertensive agents. Smoking delivers chemicals that induce CYP1A2, but it has little effect on the hepatic metabolism of antihypertensive agents.

Inhibition refers to either enzyme inactivation or mutual competition of substrates for a catalytic site. Both responses have the net effect of decreasing the rate of drug metabolism and thereby prolonging the half-life of the affected drug or active metabolite and amplifying its pharmacodynamic (or toxic) effect. Examples of inhibitors are fluconazole and erythromycin. Examples of substrates whose bioavailability is potently increased by inhibitors are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins," except pravastatin sodium, fluvalastatin sodium, and cerivastatin sodium). Antidepressants such as fluoxetine hydrochloride and paroxetine are active inhibitors of the metabolism of CYP2D6 substrates, whereas antifungals, macrolide antibiotics, and grapefruit juice potently inhibit CYP3A-mediated metabolism.

The ability to metabolize a drug along a specific pathway of the cytochrome P450 enzyme system can be modulated by genetic polymorphisms, causing some individuals to be poor (slow) metabolizers and others to be extensive (rapid) metabolizers. Genotyping studies24 have identified polymorphisms in the gene coding for CYP2D6, which mediates the metabolism of many commonly used drugs. Both poor and extensive metabolizers of debrisoquin sulfate (a phenotyping probe for CYP2D6) may be susceptible to interactions between tricyclic antidepressants, selective serotonin reuptake inhibitors, neuroleptics, or antiarrhythmic drugs and other CYP2D6 substrates, including lipophilic β-renergic blocking agents. No polymorphic variations have been detected in the genes for CYP3A3/4, although there seem to be interindividual differences in activity.25

Among possible metabolic drug interactions, inhibition of enzyme activity seems more relevant than induction because the former often occurs immediately, whereas the latter usually takes time to bring about its effect. Clinically important drug interactions commonly occur when a drug potently inhibits another drug-metabolizing enzyme. In this regard, several of different kinds of enzyme inhibition that can impair drug metabolism have been described:

- Competitive inhibition: This is the most common kind of inhibition, but it is unlikely to be the most clinically relevant. It occurs as a result of competition for the active site of an enzyme by the inhibitor and the substrate.
- Formation of metabolite intermediate complexes: The metabolite forms a catalytically inactive complex with the enzyme, thereby reducing the enzyme activity. A number of important interactions that use this mechanism have been described, most notably between diltiazem hydrochloride and simvastatin.26,27
- Mechanism-based inhibition: A substrate is transformed by the enzyme, and the compound formed inactivates the enzyme. This mechanism, originally described by Ortiz de Montellano and colleagues28,29 and referred to as suicide inhibition, is characterized by a time-dependent loss of enzyme activity and irreversible modification of the enzyme.

### Table 1. Some Drugs That Interact Metabolically With Antihypertensive Drugs

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>CYP3A4†</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
</tr>
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<tbody>
<tr>
<td><strong>Substrates</strong></td>
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<tr>
<td>Propranolol hydrochloride</td>
<td>Diltiazem hydrochloride</td>
<td>Losartan potassium</td>
<td>Propranolol hydrochloride</td>
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<tr>
<td>Metoprolol succinate</td>
<td>Verapamil hydrochloride</td>
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<tr>
<td>Timolol maleate</td>
<td>Nifedipine (and other calcium channel blockers)</td>
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<tr>
<td>Carvedilol</td>
<td>Losartan potassium</td>
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<tr>
<td>Ciclosporine</td>
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<tr>
<td><strong>Inducers/Enhancers</strong></td>
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<tr>
<td>None</td>
<td>Rifampin</td>
<td>Rifampin</td>
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<td></td>
<td>Alcohol</td>
<td>Phenobarbital</td>
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<td>Phenytoin sodium</td>
<td>Carbamazepine</td>
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<tr>
<td><strong>Inhibitors</strong></td>
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<tr>
<td>Quinidine sulfate</td>
<td>Ketoconazole</td>
<td>Flunonazole</td>
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<tr>
<td>Fluoxetine hydrochloride</td>
<td>Itraconazole</td>
<td>Cimetidine</td>
<td>Flunonazole</td>
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<tr>
<td>Norfluoxetine hydrochloride</td>
<td>Grapefruit juice</td>
<td>Amiodarone</td>
<td>Hydrochloride</td>
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<td>Paroxetine hydrochloride</td>
<td>Cimetidine</td>
<td>Ketoconazole</td>
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<td>Amiodarone hydrochloride</td>
<td>Hydrochloride</td>
<td>Flucloxacil</td>
<td>Ticapidine</td>
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<td>Cimetidine hydrochloride</td>
<td>Clarithromycin</td>
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<td>Hydrochloride</td>
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<td>Clonazepam hydrochloride</td>
<td>Erythromycin</td>
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<td>Haloperidol</td>
<td>Verapamil hydrochloride</td>
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<tr>
<td>Various antivirals</td>
<td>Nefazodone hydrochloride</td>
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<tr>
<td>Mibefradil dihydrochloride</td>
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</tbody>
</table>

* Adapted with permission from Harvey and Preskorn22 and Michalets.23†CYP3A3 and CYP3A4 are virtually identical in amino acid sequencing and catalytic activity and are considered to be one and the same in this article.

**DRUG INTERACTIONS BY ANTIHYPERTENSIVE CLASS**

### β-Adrenergic Blocking Agents

The pharmacokinetics of β-adrenergic blocking agents such as propranolol is strongly affected by cytochrome P450 inducers and inhibitors. For example, rifampin causes a 2- to 3-fold increase in propranolol clearance, which lowers plasma propranolol concentrations to subtherapeutic levels.31 Quinidine sulfate, on the other hand, inhibits hepatic metabolism of propranolol by CYP2D6,
thereby raising its plasma concentrations. Many other examples of clinically relevant metabolic drug interactions involving β-adrenergic blocking agents exist. The inhibition of CYP2D6 by cimetidine may lead to additional reductions in heart rate and intraocular pressure when cimetidine is administered with timolol maleate ophthalmic solution.32 Similarly, because quinidine inhibits CYP2D6, an excessive β-blockade may occur after administration of timolol eye drops in patients treated with quinidine.33 Diphenhydramine hydrochloride inhibits the metabolism of metoprolol by CYP2D6 in extensive metabolizers, thereby prolonging the negative chronotropic and inotropic effects of the drug.34 Also, 8-day treatment with hydroxychloroquine sulfate, a drug used in the treatment of chronic inflammatory diseases, significantly increased the bioavailability and the maximal plasma concentrations of metoprolol.37

Several other potential cytochrome P450–associated drug interactions involving β-adrenergic blocking agents remain to be elucidated. Although water-soluble β-adrenergic blocking agents, such as sotalol hydrochloride, nadolol, and atenolol, are essentially not metabolized in the liver, and thereby are less prone to metabolic drug interactions, many lipophilic β-adrenergic blocking agents are metabolized by CYP2D6. Clinicians should anticipate toxic interactions of β-adrenergic blocking agents when coadministered with drugs that inhibit CYP2D6.

Calcium Channel Blockers

Calcium channel blockers serve as substrates for and inhibitors of CYP3A4.40-42 Mibefradil has a broad range of effects on several isoforms, including prolongation or amplification of the pharmacodynamic effects of CYP2D6 and CYP3A substrates. Because there was a lack of information about inhibition of the drug transporter P-glycoprotein by mibefradil,43 potential toxic metabolic drug interactions with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and nonnitrating antihistamines were not predicted by in vitro studies of interaction of the drug with cytochrome P450 3A.44 When life-threatening interactions with these drugs were reported, mibefradil was withdrawn from the market in the United States.

Some drugs may reduce the clinical effects of calcium channel blockers. For example, treatment with rifampin (600 mg daily for 12 days) nearly abolished the effects of orally administered verapamil (120 mg twice daily) on atrioventricular nodal conduction. Although the enantiomers of verapamil are metabolized by CYP3A4, CYP3A5, CYP2C8, and, to a minor extent, CYP2E1,45 the interaction of rifampin with verapamil was attributed to the induction of CYP3A4 in the gastrointestinal tract by rifampin because no significant interaction occurred when verapamil was administered intravenously.46-48 Similar to this interaction with verapamil, rifampin-induced gut wall metabolism reduced the bioavailability of nifedipine because of increased gut wall metabolism.49

The core coat formulation of nisoldipine allows its absorption across the entire gastrointestinal tract. The significant first-pass metabolism (only 5.5% bioavailability) of this formulation makes it vulnerable to concomitant use of drugs that induce or inhibit CYP3A4 that is well documented to be present and inducible by rifampin in the intestine.50 Other drugs may add to the effects of calcium channel blockers, and the possibility exists that symptomatic hypotension occurs when CYP3A4 inhibitors are given with some dihydropyridine calcium antagonists.51 In this regard, human intestinal perfusion studies52 have demonstrated that the inhibition of CYP3A4 or of P-glycoprotein by ketoconazole increases the transport of verapamil into the circulation. Moreover, ketoconazole potently inhibited the metabolism of nisoldipine,53 and itraconazole significantly increased plasma concentrations and effects of oral felodipine use.54 Thus, the concomitant use of azole antifungals with dihydropyridine calcium antagonists should be avoided. Also, other interactions, such as the allosteric inhibitory effect of quinidine on the metabolism of nifedipine by CYP3A,55 may increase the effects of calcium channel blockers.

Daily doses of cimetidine (800-1200 mg), but not ranitidine hydrochloride (300 mg), significantly increased the mean±SD total area under the plasma nifedipine concentration time curve from 381±197 to 687±234 ng/h per milliliter. Corresponding to this increase in the bioavailability of nifedipine caused by cimetidine, more marked and longer changes in heart rate were observed in the standing position.55,56 These findings indicate that doses of nifedipine should be reduced by 50% when this drug is coadministered with cimetidine. Also, these results
suggest that pharmacodynamic responses to most β-adrenergic blocking agents or dihydropyridine calcium channel blockers should be monitored closely when coadministered with cimetidine. However, inhibition by cimetidine is generally relatively weak, and studies that demonstrate statistically significant pharmacokinetic changes do not prove that clinically significant pharmacodynamic consequences inevitably ensue.

A recent study focused on the in vitro inhibition of human cytochrome P450 enzymes caused by 13 clinically used dihydropyridines. The data obtained led the researchers to suggest that important in vivo drug interactions should occur only between nicardipine hydrochloride and other drugs metabolized by CYP2C9 or CYP3A. It was shown, however, that nifedipine, verapamil, and diltiazem decrease the clearance of theophylline (usually by ≥25%). In total, most calcium channel blockers studied inhibit the metabolism of cyclosporine. In particular, and possibly because of the metabolite intermediate complex that forms between diltiazem and CYP4503A4, diltiazem in doses as low as 10 mg increased the bioavailability of cyclosporine and should therefore result in the need for a lower dose to maintain efficacy or avoid toxic effects. Because cyclosporine is an expensive drug, the coprescription of diltiazem and cyclosporine is a way of reducing the high costs of cyclosporine. Similarly, the verapamil-induced change in cyclosporine pharmacokinetics allows the dose of cyclosporine to be reduced by one-third to one-half.

Verapamil significantly increased mean peak serum concentration and bioavailability of simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase. This interaction probably resulted from the inhibition of CYP3A4 or P-glycoprotein by verapamil. Although the clinical significance of this finding is not clear, it indicates that this combination of drugs should be avoided or the dose of simvastatin reduced. One meta-analysis suggested that calcium channel blockers do not increase the risk of myopathy when used concomitantly with simvastatin. This suggests that not all patients who experience a pharmacokinetic change will encounter a clinically relevant toxic response.

Diltiazem inhibits the metabolism of triazolam, probably by inhibiting the activity of CYP3A. When patients using diltiazem were anesthetized with large doses of midazolam hydrochloride and alfentanil hydrochloride, a significant delay in tracheal extubation was attributed to reduced metabolism of these anesthetics secondary to inhibition of CYP3A by diltiazem. Similarly, either diltiazem or mibefradil considerably increased plasma levels of methylprednisolone and enhanced suppression of morning plasma cortisol levels. This finding suggests that care should be taken when methylprednisolone is coadministered with diltiazem for a long period.

Although mibefradil and isradipine inhibit CYP3A4 in vitro, only mibefradil, in usual clinical doses, markedly increased the peak plasma concentrations (1.8-fold), the total area under the plasma triazolam concentration time curve (9-fold), and the pharmacodynamic effects of triazolam. Moreover, the results of another study showed that 5 doses of verapamil, 80 mg, or diltiazem, 60 mg, given over 2 days considerably increased plasma buspirone hydrochloride concentrations reached after 10 mg of this anxiolytic was given to healthy volunteers. Although 3-fold and 6-fold increases in the area under the buspirone plasma concentration time curve were observed with verapamil and diltiazem, respectively, only minor adverse effects were reported for both drug interactions.

An important interaction occurs between grapefruit juice and dihydropyridine calcium channel blockers. For example, grapefruit juice selectively down-regulates CYP3A4 in the small intestine wall and reduces first-pass metabolism, thereby increasing peak serum concentration and bioavailability of felodipine. A more marked interaction occurs with felodipine, nitrendipine, and nisoldipine, whereas less pronounced increases were found in the plasma concentrations of nifedipine, nimodipine, and verapamil. When a single dose of felodipine (5 mg), extended release, was administered with 250 mL of grapefruit juice to healthy elderly people, significantly lower systolic and diastolic blood pressures were observed. The same did not occur after 6 days of treatment with the same dose of felodipine.

**Angiotensin-Converting Enzyme Inhibitors**

Most angiotensin-converting enzyme inhibitors (eg, benazepril hydrochloride, cilazapril, enalapril, fosinopril sodium, perindopril erbumine, quinapril, ramipril, andtrandolapril) are prodrugs metabolized in the liver; captorplil and lisinopril are not. Some animal studies provide information suggesting that prodrugs seem to undergo CYP3A4-dependent biotransformation. However, the angiotensin-converting enzyme inhibitors are not involved in significant cytochrome P450-mediated interactions with other drugs.

**Angiotensin II Receptor Blockers**

Losartan and irbesartan seem to be primarily metabolized by CYP2C9. Incubation with human liver microsomes in vitro show that losartan is extensively transformed by CYP2C9 and CYP3A4 (a minor effect) to an active carboxylic acid metabolite, E-3174, that accounts for most of its angiotensin II receptor antagonism activity. Its biotransformation is inhibited by sulfaphenazole and ketoconazole, which act on CYP2C9 and CYP3A4, respectively. Indeed, reports of cytochrome P450-mediated drug interactions with the prudrug members of this class in humans are minimal. Although erythromycin has no effect on the pharmacokinetics of losartan, rifampin decreases the half-life of losartan and its metabolite by 50% in healthy volunteers, an interaction that is probably clinically significant. Moreover, fluconazole, a potent CYP2C9 inhibitor, was administered daily for 20 days to 16 male subjects who received daily doses of losartan. It significantly raised plasma concentrations of losartan and inhibited formation of the active metabolite E-3174. In contrast, fluconazole had no effect on the steady-state pharmacokinetics of eprosartan mesylate given daily to 16 other male subjects.
Irbesartan is metabolized mainly along the CYP2C9 pathway. However, unlike losartan, irbesartan does not require biotransformation to an active metabolite, and its own metabolism is essentially unaffected by other drugs. A recent in vitro study investigating the potential effects of 5 different angiotensin II receptor blockers on cytochrome P450 enzymes showed that losartan and irbesartan were the most potent inhibitors of CYP2C9, with only a small affinity for CYP2A1 and CYP3A4. Val-
sartan, eprosartan, and candesartan are not metabolized by the cyto-
chome P450 system and, therefore, have low potential for drug interac-
tions via these enzymes.

In a randomized crossover study in 12 healthy male volunteers, single doses of cimetidine increased the maximum plasma level of coadmin-
istered valsartan by approximately 50%. However, this pharmacokinetic perturbation was due not to a cyto-
chome P450–mediated interaction but rather to inhibition of acid secre-
tion by the H2-receptor blocker, which increased the rate of valsartan absorp-
tion. It is unlikely to have any important clinical effect because valsartan is cleared mainly by biliary excretion as unchanged drug and does not ac-
cumulate in plasma.

There is a 49% increase in digoxin peak plasma concentration and a 20% increase in trough digoxin concentration when coadminis-
tered with telmisartan. The mechanism is unknown; however, it is not thought to be related to the cytochrome P450 system.

Other cytochrome P450 interactions involving angiotensin II blockers remain to be elucidated. The data available now suggest that clinically relevant interactions are more probable with losartan and ir-
besartan. However, further studies are needed to clarify this issue.

Other Antihypertensive Agents

Hydrochlorothiazide and chemi-
cally related diuretics are not metabo-
lized. Furosemide is biotransformed to a glucuronide, and spironola-
tone is biotransformed to sulfur-
containing metabolites, but neither has a significant effect on the cyto-
chome P450 system.

Although drugs that block α1-
receptors, such as prazosin hydro-
chloride and doxazosin mesylate, and clonidine hydrochloride, which blocks α2-receptors, are metabo-
lized by the liver, they do not seem to interact with other drugs via cyto-
chome P450 pathways.

MINIMIZING THE OCCURRENCE OF DRUG INTERACTIONS

Overall Precautions

Most drug interactions are pre-
ventable by forethought, although some patient variables, such as use of over-the-counter drugs and consumption of alcoholic beverages, are difficult to control. In-
quiry about the use of over-the-
counter products and drugs pre-
scribed by other physicians should be routine at every visit (Table 2). Caution is particularly appropriate when prescribing newly intro-
duced drugs because not all inter-
actions can be identified in the limited number of patients enrolled in clinical trials, and in vitro screening protocols are not perfect. It is important to consider any hepatic or renal dysfunction and to recognize high-risk conditions.

Patients should be advised not to drink grapefruit juice con-
comitantly with calcium channel blockers and other drugs that may raise blood levels significantly by inhibition of CYP3A4–mediated first-pass metabolism. In addition, caution should be taken when patients use St John’s wort con-
comitantly with other medica-
tions, especially those metabolized by CYP3A4.

The physician should be aware that cimetidine may increase blood levels of calcium channel blockers and lipophilic β-adrenergic block-
ing agents.

Adjustments in the Elderly

Because individuals older than 65 years take the greatest number of drugs on average, their risk of drug interactions rises. In addition, it is not uncommon for elderly individu-
als to make errors at home because of poor vision or forgetfulness, tak-

ing the wrong medication, or tak-
ing an additional dose.

Drug dosages often have to be decreased because of age-related losses in weight and decreases in renal and hepatic function. Also, the rate at which drugs are oxidized by cytochrome P450 enzymes may be significantly decreased. Although intrinsic metabolic activity per unit of liver volume probably does not de-
cline with age, blood flow will. Con-
sequently, there is an increase in the bioavailability for high-extraction drugs, but low-extraction drugs may be less affected.

For the foregoing reasons, phy-
sicians should try to prescribe medications for elderly patients that allow a reasonable margin of error. With respect to cytochrome P450–mediated drug interactions, a logical guideline in writing a prescription might be whether the particular agent is an inducer, inhibitor, or substrate for concomitantly administered com-
pounds.

COMMENT

Awareness of drug interactions in-
volving the cytochrome P450 en-
zyme system has increased in the past decade. The specific isoforms in-
volved in drug metabolism have been identified, and genetic polymor-
phisms in some of these isoforms seem to explain interindividual dif-
fences in drug metabolism. Al-
though this growth in the knowl-
edge base permits physicians to predict certain interactions more sys-
tematically, much remains to be

| Table 2. Quick List of Guidelines to Be Remembered When Prescribing Drugs |
|--------------------------|--------------------------|
| **AVOID Medication Errors** | **** |
| Obtain a list of current medications and their doses then check for the following: | **|
| Allergies | **|
| Vitamins and herbal products | **|
| Old medicines discontinued within the past month | **|
| Interactions using a pocket reference or software program | **|
| Dependence on any current or discontinued therapy | **|
| Mendelian patterns; ask about family medication sensitivity and preferences | **|
learned as new compounds enter the armamentarium and older ones are scrutinized more closely. Thanks to advances in computer modeling and in vitro analysis, the metabolic profiles of investigational agents will be better characterized before they enter clinical trials so that the experience with mibefradil is less likely to be repeated. It is reasonable to infer that drugs that are deemed relatively safe today because their metabolism is not catalyzed by cytochrome P450 enzymes will also be less likely to have adverse interactions with new drugs that enter clinical practice in the future. Nevertheless, the importance of postmarket surveillance should never be overlooked.

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