**Drug Interactions with HIV Protease Inhibitors**

**John G. Gerber, MD**

The rapid approval by the Food and Drug Administration (FDA) of the HIV protease inhibitors was celebrated by both people with HIV and health care providers alike because of the potent antiviral activity of these drugs. However, because of the lipophilic nature of these molecules, and the large dose that needs to be administered to observe an antiviral effect, interaction with a host of xenobiotic metabolizing enzymes has been observed, which can result in adverse drug interactions with drugs that use those enzymes for metabolism.

Because of the short time period from development to approval, almost all the drug interaction studies with the protease inhibitors are unpublished or have yet to be performed; therefore, it is difficult to make rational decisions about how to use many of those drugs concomitantly with protease inhibitors. Since people with advanced HIV disease use perhaps as many as 8 to 10 drugs for the treatment or prophylaxis of opportunistic infections and for the treatment of HIV itself and the psychiatric problems that arise with a chronic fatal disease, significant drug interactions resulting in toxic effects are unavoidable.

For practicing clinicians it is more important than ever that before adding a protease inhibitor to the therapeutic regimen, the prescriber reviews the drug list of the patient. It is crucial to understand how those drugs are eliminated (renal vs hepatic, and, if hepatic, conjugation vs oxidation), so as to make rational choices about those drugs by altering doses as necessary to reduce the likelihood of toxic effects or loss of efficacy.

**Pharmacokinetic Principles**

To understand drug interactions it is important to review some pharmacokinetic principles of hepatic drug metabolism, and certain aspects about the cytochrome P450 isozymes involved with xenobiotic metabolism. Hepatic clearance of a drug is determined by two independent processes. One is hepatic blood flow and the other is the intrinsic capacity of the liver to metabolize a drug, known as intrinsic clearance. The capacity of the liver to metabolize a drug (intrinsic hepatic clearance) is determined by the avidity of the drug to the metabolizing enzyme and the concentration of the enzyme in the liver. If the liver has a large capacity to metabolize a drug— and thus a very large intrinsic hepatic clearance—the rate-limiting step to its metabolism is the hepatic blood flow (the rate of delivery), and small changes in the metabolizing enzymes will not have an effect on hepatic clearance as will alterations in hepatic blood flow. These drugs are described as having perfusion-limited metabolism. If the liver has a limited capacity to metabolize a drug, hepatic clearance is determined exclusively by hepatic enzymatic activity. Alterations in hepatic enzymatic activity will thus result in profound changes in hepatic clearance. These drugs are described as having perfusion-independent metabolism. Many drugs fall within these two extremes, and both hepatic blood flow and enzymatic activity determine hepatic clearance.

Because most of the drugs used in clinical medicine are administered orally and are thus subject to first-pass metabolism in the bowel and the liver, drugs with high avidity to metabolizing enzymes (i.e., drugs with high intrinsic hepatic clearance) have large first-pass metabolism and thus decreased bioavailability to systemic circulation. Therefore, if the activity of these enzymes is perturbed by administering another drug, the amount of the orally administered drug that reaches the systemic circulation may be greatly altered. Compounds that inhibit the metabolizing enzymes of drugs will have an effect on the kinetics of drugs with either high or low intrinsic clearance although by different mechanisms. Drugs with high intrinsic clearance will have greatly increased bioavailability secondary to inhibition of first-pass metabolism (thus a greater amount of the drug will reach the systemic circulation); while drugs with low intrinsic clearance will have greatly reduced hepatic clearance (elimination) of the drug. The overall effect will be an increase in plasma concentration at steady state and an increase in the area-under-the-time concentration curve (AUC) for those drugs, with consequent toxic effects of the drugs with low therapeutic ratios.

This concept is important to understand because both the potent protease inhibitors ritonavir and indinavir produce significant inhibitory effects on some of the cytochrome P450 isozymes involved in drug metabolism. Cytochrome P450 constitutes a superfamily of hemoproteins involved in monooxygenase reactions of a host of endogenous compounds as well as xenobiotics. The reason for adding an oxygen molecule to a xenobiotic is to make the compound more hydrophilic so that it can be excreted by the kidney or through the biliary system. Although hundreds of cytochrome P450 genes have been characterized, only three gene families—CYP1, CYP2, and CYP3—are thought to be responsible for the hepatic metabolism of xenobiotics. Within these families there are subfamilies as established by a capital letter, which is followed by an arabic numeral referring to the specific enzyme. Of these P450 enzymes, six represent the most important enzymes involved in drug metabolism. As shown in the table these six enzymes are 1A2, 2C9, 2C19, 2D6, 2E1, and 3A3. Of all these enzymes, the 3A is the most abundant and represents 30% of all the P450 proteins found in the liver. Because these are microsomal (membrane-bound) enzymes, they cannot be crystallized, and thus the three dimensional structures have not been definitively established. These enzymes have overlapping substrate specificity, but numerous drugs use primarily a single isof orm for metabolism. Since drug inhibitors and inducers are frequently

Both of the protease inhibitors, ritonavir and indinavir, have significant inhibitory effects on some of the cytochrome P450 isozymes involved in drug metabolism.

Isozyme specific, drugs that use a single isozyme for metabolism would be much more affected than would drugs that use numerous isozymes for metabolism.

Drug metabolism is frequently stereospecific; thus, the components of a racemic mixture of drugs may use different isozymes for metabolism. A good example is warfarin, which is a racemic mixture of both the S- and R-enantiomer; however, only S-warfarin is the substrate for the 2C9 isozyme, and many important drug interactions occur at that isozyme (eg, metronidazole, sulfamethoxazole) because S-warfarin is the more potent anticoagulant.

Both ritonavir and indinavir are extremely lipophilic and use primarily the P4503A isozyme for metabolism. Ritonavir is significantly more lipophilic than is indinavir as demonstrated by the more extensive protein binding of and almost undetectable renal excretion of the former. Both drugs in vitro studies have demonstrated a ca-
Table 1. P450 Isozymes That Have Been Shown to Metabolize Clinically Important Drugs.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Enzyme</th>
<th>Substrates</th>
<th>Inducers</th>
<th>Antimicrobial Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>P4501A2</td>
<td>caffeine, theophylline, acetaminophen, imipramine</td>
<td>cigarette smoke</td>
<td>ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>charcoal food omeprazole</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>P4502C9</td>
<td>phenytoin, S-warfarin, tolbutamide, ibuprofen, naproxen</td>
<td></td>
<td>fluconazole</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>P4502C19</td>
<td>omeprazole, diazepam, demethyl diazepam, proguanil, imipramine, propranolol</td>
<td></td>
<td>sulfamethoxazole metronidazole</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>P4502D6*</td>
<td>codeine, hydrocodone, flecainide, encainide, fluoxetine, imipramine, amitriptyline, haloperidol, metoprolol, desipramine, nortryptiline</td>
<td>genetic polymorphism</td>
<td>quinidine</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>P4502E1</td>
<td>acetaminophen, ethanol</td>
<td></td>
<td>isoniazid, ethanol</td>
</tr>
<tr>
<td>CYP3A</td>
<td>P4503A*</td>
<td>cyclosporine, nifedipine, diltiazem, lidocaine, lovastatin, erythromycin, clarithromycin, quinidine, terfenadine, verapamil, midazolam, triazolam, astemizole, tacol, cisapride, ketoconazole, itraconazole, estrogens, corticosteroids, and others</td>
<td>rifampin phenobarb phenytoin dexamethasone</td>
<td>erythromycin clarithromycin ketoconazole itraconazole fluconazole</td>
</tr>
</tbody>
</table>

Ritonavir inhibits this isozyme. *Indinavir inhibits this isozyme.

Pacify to inhibit P4503A isozyme in a competitive manner; ritonavir also inhibits P4502D6 but with higher affinity toward the P4503A isozyme. There are more published data on ritonavir’s mechanism of inhibition than that of indinavir. Ritonavir competitively inhibits P4503A and P4502D6 by interacting with high affinity at the substrate binding site. In addition, its thiazole side chain interacts with the heme component of the P450 isozyme, thus preventing the attachment of oxygen. This is called a type II binding and it has been well described for the lipophilic imidazole compounds such as ketoconazole. The mechanism of inhibition of P4503A by indinavir has not been published, but present data suggest that there is no type II binding to P450 isozymes and that the drug only interacts competitively at the substrate binding site.

In terms of drug interaction, more data are available for ritonavir than for indinavir, and it is almost impossible to directly compare these two drugs until more complete data are published. However, ritonavir clearly appears to have different activity in the liver than indinavir. In addition to competitively inhibiting the P4503A and 2D6 isozymes, ritonavir induces the P4501A2 and 3A isozymes as demonstrated by the lowered theophylline AUC with ritonavir and the lowered plasma concentration of ritonavir with continued use. In fact, the improved adverse reaction profile of ritonavir with continued use is thought to be due to autoinduction and lowered plasma concentration over time. In addition, ritonavir induces the family of enzymes involved with glucuronidation as demonstrated by the 25% decrease in the zidovudine AUC. Indinavir does not appear to have the capacity to induce hepatic enzymes, and blood concentrations of the drug remain stable over time. The suggestion that ritonavir is a more potent inhibitor of cytochrome P4503A than indinavir stems from data reported by Kempf et al at the Third Conference on Retroviruses and Opportunistic Infections held in Washington, DC, that showed that when indinavir was administered concomitantly with ritonavir in rats, the indinavir AUC increased 800%; in contrast, the ritonavir AUC remained unchanged. Similar data are not available in humans.

A number of drugs are metabolized by the cytochrome P4503A isozymes. A partial list is provided in the table. The P4502D6 isozyme also has a varied substrate specificity. The P4502D6 isozyme is one of the drug metabolizing enzymes that demonstrates genetic polymorphism. Genetic polymorphism refers to the observation that approximately 5% to 10% of Caucasians do not show phenotypic expression of this isozyme and are termed poor metabolizers. Thus, in this subgroup an inhibitor would not be expected to produce any additional effect on the metabolism of drugs that use P4502D6.

It is important to distinguish drug interactions with protease inhibitors that have been performed and reported from potential drug interactions based on the knowledge of the specific cytochrome P450 involved in the drug's metabolism. For the latter, drugs with very low therapeutic indices must not be used with protease inhibitors since the outcome may prove to be fatal. Some of these examples are described below.

Studies of Drug Interactions with Protease Inhibitors

**Clarithromycin.** Ritonavir increases the plasma concentration of clarithromycin by an average of 77%, with a range of 56% to 103%. Although this interaction does not seem to be very significant, the generation of the 14(R)OH clarithromycin was completely inhibited by ritonavir. This hydroxylated metabolite of clarithromycin is
Drugs with very low therapeutic indices must not be used with protease inhibitors because the outcome could be fatal.

Rifaxitin. Ritonavir significantly inhibits the metabolism of rifabutin. Rifabutin is metabolized in the liver by two main pathways. One is a deacetylation step that uses an esterase to form desacetyl rifabutin, and the other pathway involves the P450A isozymes, resulting in a more soluble demethylated metabolite (see Figure 1). Desacetyl rifabutin is as active as rifabutin against MAC, but normally its plasma concentration is only about 10% of that of the parent drug. Ritonavir increases rifabutin AUC by approximately 4-fold, but increases the desacetyl rifabutin AUC by 35-fold. Since the metabolism of desacetyl rifabutin uses the P450A isozyme almost exclusively, these data suggest a profound inhibition of P450A isozyme by ritonavir.

Because rifabutin toxic effects may be secondary to both the parent drug and the metabolite, at present concomitant use of rifabutin and ritonavir is contraindicated. Two-way interaction may well be present, but there are no published data on the effect of rifabutin on ritonavir kinetics.

Indinavir also inhibits the metabolism of rifabutin but to a significantly lesser extent. Indinavir increases rifabutin AUC by a mean of 2.73-fold; however, the increase in the desacetyl rifabutin AUC is only 4.76-fold above baseline. This again suggests significantly less inhibition of the P450A isozymes by indinavir compared with ritonavir. The package insert recommends a 50% reduction in the dose of rifabutin when used concomitantly with indinavir, but this combination still should be used with caution until data on toxic effects are generated. Rifabutin has been shown to have a significant effect on indinavir kinetics by reducing indinavir AUC by 32%.

Fluconazole. Indinavir has been shown to have no significant effect on fluconazole kinetics, which is not surprising since to a large extent fluconazole is renally eliminated, and has been shown to produce nonsignificant changes in ritonavir and indinavir AUC. This finding demonstrates that fluconazole is a fairly weak inhibitor of the P450A isozyme. In contrast, ketoconazole has been shown to increase indinavir AUC by 68%, consistent with the more potent effect of ketoconazole on the P450A isozymes.

Zidovudine, didanosine. Since most of the nucleoside analogue reverse transcriptase inhibitors are prodrugs that require extensive intracellular metabolism to the active triphosphate metabolite, any change in the kinetics of the parent drug may not necessarily translate into changes in clinical efficacy. Indinavir has been shown to have no significant interaction with the nucleoside analogues, but ritonavir has been shown to reduce zidovudine AUC because of its ability to induce glucuronidation. In addition, the combination of ritonavir and didanosine should be used with considerable caution because both drugs increase serum uric acid levels and can increase serum triglyceride concentrations, possibly potentiating didanosine to cause pancreatitis.

Oral contraceptives. Ritonavir and indinavir have opposite effects on the kinetics of ethinyl estradiol. Administration of indinavir has been shown to produce a 24% increase in ethinyl estradiol AUC; in contrast, ritonavir has reportedly resulted in a 40% decrease in ethinyl estradiol AUC. The most likely explanation for these findings may reside in the ability of ritonavir to induce glucuronidation and other cytochrome P450 isozymes involved in ethinyl estradiol metabolism.

Trimethoprim/sulfamethoxazole. Neither ritonavir nor indinavir has had clinically significant effect on the kinetics of these drugs.

Theophylline. Ritonavir has been shown to decrease theophylline AUC by 43% because of its ability to induce the P450A isozyme. Whether this interaction occurs to a lesser extent in smokers is an important issue to be addressed because smoking is also a potent inducer of the P450A isozyme. Indinavir has not demonstrated a significant pharmacokinetic interaction with theophylline, but this finding needs to be specifically verified in non-P450A-induced subjects because P450A is responsible for a fraction of theophylline’s metabolism.

Desipramine. Ritonavir has increased desipramine AUC by 145%. Since desipramine metabolism uses primarily the P450D6 isozyme, these data suggest that the effect of ritonavir on P450D6 is not insignificant. Desipramine is also a high hepatic clearance drug, and the effect of ritonavir on desipramine is likely secondary to inhibition of first-pass metabolism and, therefore, to an increase in bioavailability. There are no interactive pharmacokinetic data on indinavir and desipramine. However, based on in vitro and in vivo studies showing only little inhibition of the P450D6 by indinavir, major interaction seems unlikely.

Potential Drug Interactions with Protease Inhibitors and Drugs with a Low Therapeutic Index

Although the package inserts specify drugs that are contraindicated, it is worth reviewing some of these drugs to clarify the mechanisms by which this interaction may occur.

Terfenadine (Seldane). This non-sedating antihistaminic drug has a very potent effect on rectifying potassium (K+) channels in cardiac tissue, thus resulting in the prolongation of Q-T intervals on electrocardiogram (ECG) with consequent torsade de pointes arrhythmia. Under normal circumstances, terfenadine is completely metabolized by P450A isozymes during its first pass through the liver to the active carboxylate metabolite, which has no cardio toxic effect. Thus, systemic blood concentration of terfenadine cannot be measured. With inhibitors of P450A, terfenadine concentrations can be detected in plasma, with consequent effect on cardiac repolarization. Both ritonavir and indinavir...
In general, drugs that are renally excreted or mainly conjugated by the liver are safe to use with protease inhibitors. Drugs metabolized by P4503A are at highest risk; those that use P4502D6 have less interaction.

**Codetine.** There is evidence suggesting that the analgesic effect of codetine is secondary to the generation of the active O-demethylated metabolite, morphine. Patients who do not express the cytochrome P4502D6 isozyme, or who have inhibited P4502D6, do not obtain significant pain relief from codeine. Hydrocodone is also metabolized to the potent opioid hydromorphone by the cytochrome P4502D6 isozyme. Thus, a drug interaction resulting in the loss of these drugs’ analgesic efficacy may follow concomitant use with ritonavir.

The addition of protease inhibitors to the list of available antiretrovirals is an important advance. However, because of the lipophilic nature of these molecules, they have major effects on the activity of the cytochrome P450 isozymes, resulting in toxic drug interactions. The elucidation of these interactions is at an early stage, and an increasing number of studies will be published in the near future, helping practitioners to understand how to use other drugs with protease inhibitors optimally and safely. In addition, the effect of protease inhibitors on protein binding of other drugs needs to be elucidated because altered protein binding may have major effects on the activity of some drugs. In contrast with indinavir, ritonavir is very highly protein bound. As a general principle, drugs that are renally excreted or that are mainly conjugated by the liver are safe to use concomitantly with protease inhibitors. Drugs that are metabolized by the P4503A isozymes are the most at risk for interaction, with less interaction with drugs that use P4502D6. In high concentrations, ritonavir may have an effect on P4502C9; however, there are no correlates in vivo. Although at first glance drug interaction issues are daunting, with a thorough understanding of how drugs that are used in the treatment of HIV disease are metabolized and what their therapeutic indices are, toxic drug interactions can be prospectively identified and averted.

John G. Gerber is Professor of Medicine and Pharmacology, Divisions of Clinical Pharmacology and Infectious Diseases, at the University of Colorado Health Sciences Center in Denver.

**Suggested Readings**


Kempf D, Marsh K, Denissen J, et al. Coadministration with ritonavir enhances the plasma levels of HIV protease inhibitors by inhibition of cytochrome P450. Presented at Third Conference on Retroviruses and Opportunistic Infections; January 28–February 1, 1996; Washington, DC.
