Drug Interactions with HIV Protease Inhibitors

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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time period from development to approval, almost all the drug interaction studies with the protease inhibitors are unpublished or have yet to be performed; therefore, it is difficult to make rational decisions about how to use many of those drugs concomitantly with protease inhibitors.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 as profound 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 (ie, 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 isoform for metabolism. Since drug inhibitors and inducers are frequently isozyme specific, drugs that use a single isozyme for metabolism would be much more affected than would drugs that use numerous isozymes for metabolism.

Both of the protease inhibitors, ritonavir and indinavir, have significant inhibitory effects on some of the cytochrome P450 isozymes involved in drug 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 in vitro studies have demonstrated a ca-

Table 1. P450 Isozymes That Have Been Shown to Metabolize Clinically Important Drugs.

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

*Ritonavir inhibits this isozyme. †Indinavir inhibits this isozyme.

pacity 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

generated by the P4503A isozyme, suggesting nearly complete shutdown of this pathway by ritonavir. Because 14(R)OH clarithromycin is also active, and since some of the gram-negative activity of clarithromycin is secondary to the synergistic interaction of the 14(R)OH metabolite with clarithromycin, the optimal benefits of using clarithromycin in treating *Haemophilus sp.* infection may be lost when ritonavir is administered concurrently. The unchanged form of clarithromycin is the active drug against *Mycobacterium avium* complex (MAC).

Indinavir also increases the plasma concentration of clarithromycin by 53%; however, the 14(R)OH clarithromycin AUC decreases only by 50%. These data again suggest a much more potent effect with ritonavir on the P4503A isozymes. Clarithromycin increases plasma concentration of both ritonavir and indinavir by only minor increments.

Drugs with very low therapeutic indices must not be used with protease inhibitors because the outcome could be fatal.

Rifabutin. 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 P4503A 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 P4503A isozyme almost exclusively, these data suggest a profound inhibition of P4503A 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 P4503A 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%.

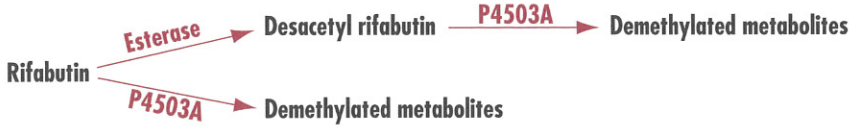

Figure 1. Rifabutin is metabolized in the liver by two main pathways—via an esterase, resulting in the formation of desacetyl rifabutin, and via the P4503A isozymes, resulting in a more soluble demethylated metabolite.

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 P4503A isozyme. In contrast, ketoconazole has been shown to increase indinavir AUC by 68%, consistent with the more potent effect of ketoconazole on the P4503A 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 P4501A2 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 P4501A2 isozyme. Indinavir has not demonstrated a significant pharmacokinetic interaction with theophylline, but this finding needs to be specifically verified in non-P4501A2–induced subjects because P4503A is responsible for a fraction of theophylline's metabolism.

Desipramine. Ritonavir has increased desipramine AUC by 145%. Since desipramine metabolism uses primarily the P4502D6 isozyme, these data suggest that the effect of ritonavir on P4502D6 is not insignificant. Desipramine is also a high hepatic clearance drug, and the effect of ritonavir on desipramine is most 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 data showing very little inhibition of the P4502D6 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 P4503A isozymes during its first pass through the liver to the active carboxylate metabolite, which has no cardiotoxic effect. Thus, systemic blood concentration of terfenadine cannot be measured. With inhibitors of P4503A, terfenadine concentrations can be detected in plasma, with consequent effect on cardiac repolarization. Both ritonavir and indinavir

inhibit P4503A activity and thus would increase terfenadine bioavailability. However, because the outcome of this drug interaction is potentially fatal, it would be unethical to confirm this by performing such studies in humans. Thus, terfenadine should never be given to patients on either ritonavir or indinavir.

Other proarrhythmic drugs. The mechanism of toxicity of astemizole (Hismanal) is similar to that of terfenadine and thus the same restrictions apply to this drug. Loratadine (Claritin) does not seem to have an effect on rectifying K^+ channels in vitro or in vivo so this drug can probably be used safely. There are a host of other drugs that interact with rectifying K^+ channels in the cardiac tissue and that are metabolized by the P4503A or P4502D6 isozymes and whose use is thus contraindicated or restricted. Cisapride (Propulsid) and many of the antiarrhythmic drugs are contraindicated with concomitant use of ritonavir or indinavir. Tricyclic antidepressants should be used with considerable caution, and concentrations of these drugs should be measured, if possible, when used along with ritonavir. Diphenhydramine hydrochloride (Benadryl) also affects K^+ channels and its metabolism may be affected by protease inhibitors.

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.

Midazolam (Versed). Many of the benzodiazepine sedative/hypnotic drugs use P4503A for metabolism and thus their use is contraindicated in patients taking ritonavir or indinavir. Midazolam metabolism has been studied best, and this drug is metabolized exclusively by P4503A isozymes. Because the hepatic clearance of this drug is approximately 400 mL/min, both liver blood flow and hepatic enzymatic activity contribute to its overall clearance; thus, prolonged sedation is to be expected when this drug is administered intravenously in patients taking protease inhibitors. Triazolam (Halcion) is also a potent substrate for P4503A isozymes, and thus interaction similar to that observed with midazolam is to be expected. Lorazepam (Ativan), temazepam (Restoril), and oxazepam (Serax) are metabolized either solely or primarily by conjugation, and thus pharmacokinetic interaction is not to be expected with concomitant use of these drugs with protease inhibitors.

Calcium channel blockers. Essentially all of the calcium channel blockers are metabolized by the P4503A isozymes, and many of these drugs have high hepatic clearance and thus undergo extensive first-pass metabolism. Both ritonavir and indinavir can be expected to increase the systemic bioavailability of these drugs and decrease their hepatic clearance. Because the therapeutic effect of calcium channel blockers can be measured by monitoring blood pressure, pulse rate, and ECGs, these parameters must be followed closely if protease inhibitors are given to patients on calcium channel blockers. It is suspected that these drugs may be very difficult to use concomitantly with potent protease inhibitors.

Lovastatin. Because this HMG-CoA reductase inhibitor and its active metabolites use P4503A isozymes for further metabolism, use of lovastatin with protease inhibitors may result in a potentially fatal drug interaction. It is important to bear this in mind because severe toxicologic drug interactions have been observed with the concomitant use of imidazole antifungal drugs and lovastatin (ie, severe rhabdomyolysis and one death). Although much less is known about the metabolism of other HMG-CoA reductase inhibitors, all these drugs should be used with caution. The structure of simvastatin is very similar to that of lovastatin and thus its metabolic pathway is probably similar to that of lovastatin.

Codeine. There is evidence suggesting that the analgesic effect of codeine 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.

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Suggested Readings

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