REVIEW ARTICLE

Drug Safety 1999 Feb; 20 (2): 147-169
0114-5916/99/0002-0147/$11.50/0

Drug Interactions of HIV Protease Inhibitors

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Contents

Abstract

All the currently available protease inhibitors are metabolised by the cytochrome P450 (CYP) enzyme system. All are inhibitors of CYP3A4, ranging from weak inhibition for saquinavir to very potent inhibition for ritonavir. Thus, they are predicted to have numerous drug interactions, although few such interactions have actually been documented either in pharmacokinetic studies or in clinical

reports. This article reviews the published literature with an emphasis on the magnitude of interactions and on practical recommendations for management.

Many of the drugs commonly taken by patients with HIV have a strong potential to interact with the protease inhibitors. In particular, the non-nucleoside reverse transcriptase inhibitors are also metabolised by CYP and have been shown to interact with protease inhibitors. Delaviridine is an inhibitor of CYP3A4, but nevirapine and efavirenz are inducers of CYP3A4. The protease inhibitors also interact with each other, and these interactions are being explored for their potential therapeutic benefits. Other commonly used drugs are also known to affect protease inhibitor metabolism, including inhibitors such as clarithromycin and the azole antifungals and inducers such as the rifamycins. Drugs that are known to be significantly affected by the protease inhibitors include ethinylestradiol and terfenadine; many other drugs have lesser or potential interactions.

Although little specific data is available on the drug interactions of protease inhibitors, this lack of data should not be interpreted as a lack of interaction. Retrospective chart reviews have demonstrated that potentially severe drug interactions are frequently overlooked. Much more clinical data is needed, but pharmacists and physicians must always be vigilant for drug interactions, both those that are already documented and those that are predictable from pharmacokinetic profiles, in patients receiving protease inhibitors.

The protease inhibitors are one of the newest classes of antiretroviral drugs used for the management of patients infected with HIV. Patients infected with HIV often take many other medications for the sequelae of the disease, such as opportunistic infections, dementia, wasting, haematological and endocrine disorders and nephropathy, which present predominantly in the later stages of the illness. Combinations of antiretrovirals are being used to augment and prolong the virological and immunological benefits of these drugs and also to delay the emergence of resistance. Before initiating new treatment regimens in patients infected with HIV, clinicians need to consider issues such as drug-drug interactions.

The currently available protease inhibitors are all metabolised in the liver by the cytochrome P450 (CYP) enzyme system, especially the CYP3A4 isoenzyme.[1] Differences in drug interaction profiles between the 4 protease inhibitors depend on their varying affinities for the various CYP enzymes.[2] The CYP system is also the major hepatic enzyme complex involved in the metabolism of many other drugs. Its various isoenzymes can be either induced or inhibited by a number of agents, and the protease inhibitors, particularly ritonavir, are among the more potent inhibitors of CYP3A4.[3,4]

Drug interactions can be divided into two main categories: pharmacokinetic and pharmacodynamic. In a pharmacokinetic interaction, changes in the absorption, distribution, metabolism or excretion of a drug occur, whereas in a pharmacodynamic interaction, synergy, additivity or antagonism may affect the efficacy or toxicity of the drug.

Although many drug interactions are listed in the product labelling of the protease inhibitors, few studies have been conducted that evaluate the actual magnitude of those interactions, and even fewer recommendations have made regarding how to address these interactions. Several recent articles have reviewed the characteristics of the protease inhibitors,[1,2,5-11] and there are also 2 good general overviews of drug interactions in patients with HIV[12,13] and a recent review of the drug interactions of ritonavir.[14]

This article reviews the current published literature, most of which is still in the form of letters and abstracts, regarding specific drug interactions of the protease inhibitors with the aim of assisting

Table I. Overview of approved protease inhibitors[7,11,14]

Drug	Bioavailability (%)	Effect of food on absorption	$t_{½}$ (h)	Approved dosage	Specific major adverse effects	Inhibition of CYP
Saquinavir-HGC	4	↑↑	1-2	600mg q8h		0/+
Saquinavir-SGC	331% relative to saquinavir-HGC	↑↑	1-2	1200mg q8h		0/+
Ritonavir	66-75	0/↑	3-5	600mg q12h	GI; paraesthesia; taste distortion	+++
Indinavir	60-65	↓	1.8	800mg q8h	Renal stones; ↑ bilirubin	++
Nelfinavir	>78	↑↑	3.5-5	750mg q8h	Diarrhoea	+/++

CYP = cytochrome P450 enzyme system; **GI** = gastrointestinal effects (e.g. nausea, vomiting or diarrhoea); **HGC** = hard-gelatin capsules; **q8h** = every 8 hours (3 times daily); **q12h** = every 12 hours (twice daily); **SGC** = soft-gelatin capsules; **$t_{½}$** = elimination half-life; **0** = no change or no inhibition; ↑ = increased; ↑↑ = markedly increased; ↓ = decreased; + = weak inhibition; ++ = moderate inhibition; +++ = potent inhibition.

clinicians when initiating new drug therapies. An emphasis is placed on estimating the magnitude of known drug interactions and making recommendations for appropriate management.

1. Brief Overview of Available Agents

Four protease inhibitors are currently approved by the US Food and Drug Administration. They are ritonavir, indinavir, nelfinavir and saquinavir, which is available as hard-gelatin capsules (saquinavir-HGC) or soft-gelatin capsules (saquinavir-SGC). Several significant differences distinguish these 5 products (table I). Specific features which deserve special attention are discussed in the following sections.

1.1 Pharmacokinetics

As mentioned in the introduction, each of the protease inhibitors is metabolised extensively by the CYP enzyme system.[1] High first-pass metabolism is a major problem with saquinavir, contributing to its poor bioavailability and limiting its potency against HIV.[1] However, the newer, soft-gelatin capsule formulation of saquinavir has substantially improved bioavailability compared with the older, hard-gelatin formulation.[15] Both formulations are still in clinical use.

1.2 Adverse Effects

Several metabolic abnormalities have been documented in patients receiving combination therapy that includes protease inhibitors.[7,11] These include hyperlipidaemia and hyperglycaemia, manifesting as overt diabetes mellitus in some patients. Redistribution of body fat, often observed as truncal obesity or cervical fat pads resembling the 'buffalo hump' of hypercortisolism, has also been described and is often referred to as 'protease paunch' or 'crix belly'. In addition, an increased incidence of bleeding has been observed in patients with haemophilia. These effects have been seen with each of the protease inhibitors, but their cause is still not entirely clear.

Gastrointestinal adverse effects have also been noted with each of the protease inhibitors, although this problem is probably greatest with ritonavir.[7,11] Diarrhoea is particularly common with nelfinavir, but is usually manageable with antidiarrhoeal agents such as loperamide.[16] In addition, abnormalities in liver function tests have occasionally occurred with each of these agents.[11] Indinavir in particular has been associated with an asymptomatic increase in indirect bilirubin.[7]

Adverse effects that are specific to individual agents are listed in table I. However, one adverse effect deserves special mention because of the potential role of drug interactions in increasing its incidence. The risk of nephrolithiasis with indinavir may be related to plasma concentrations of the protease inhibitor. Dieleman et al.[17] reported that 14 of 15 patients with urological symptoms while on indinavir had plasma concentrations that were higher than those at matching time points in

14 control patients (indinavir recipients without urological symptoms). Thus, drug interactions that result in increased indinavir concentrations may increase the risk of nephrolithiasis. The risk of renal stones may also be decreased by maintaining a fluid intake of at least 1.4 L of water/day,[18] which may represent a substantial difficulty for the patient.

1.3 Potential for Drug Interactions

Eagling et al.[3] studied the inhibitory potential of saquinavir, ritonavir and indinavir against CYP1A2, CYP2C9, CYP2E1 and CYP3A4 in human liver microsomes *in vitro*. Probe substrates used were phenacetin (CYP1A2), tolbutamide (CYP2C9), chlorzoxazone (CYP2E1) and testosterone (CYP3A4). Ritonavir was found to be the most potent inhibitor of CYP3A4-mediated testosterone 6β-hydroxylation and CYP2C9-mediated tolbutamide hydroxylation, with concentrations achieving 50% inhibition (IC_{50}) of 0.034 ± 0.013 μmol/L and 4.2 ± 1.3 μmol/L, respectively. The inhibitory activity of ritonavir against CYP3A4 was similar to that of ketoconazole observed in other studies. The effects of ritonavir on CYP1A2 and CYP2E1 were negligible. Indinavir was an order of magnitude less potent in inhibiting CYP3A4 (IC_{50} 0.43 ± 0.14 μmol/L) and did not produce significant inhibition of CYP1A2-, CYP2C9- or CYP2E1-catalysed reactions. Saquinavir was the least potent inhibitor of CYP3A4 (IC_{50} 2.14 ± 0.48 μmol/L) and produced intermediate inhibition of CYP2C9 (IC_{50} 53.9 ± 9.9 μmol/L). Like the other 2 protease inhibitors, it did not significantly inhibit CYP1A2 or CYP2E1. Thus, saquinavir appears to be a substantially less potent inhibitor of CYP3A4 than either ritonavir or indinavir.

Similar results were obtained in studies by Iribarne et al.[19] and von Moltke et al.[4] The latter study also included nelfinavir, which appeared to have an inhibitory potential less than ritonavir but greater than indinavir against CYP2C9, and less than either ritonavir or indinavir but greater than saquinavir against CYP3A. Nelfinavir did not have significant inhibitory activity against the other isoenzymes studied.

Because many AIDS patients may also require treatment for tuberculosis at some point in their disease, one particular drug interaction that has received attention is that between rifampicin (rifampin) and the protease inhibitors. The US Centers for Disease Control and Prevention (CDC) have recently revised recommendations for the treatment of tuberculosis in patients receiving concurrent protease inhibitors.[20] The preferred regimen in these patients would substitute rifabutin for rifampicin in the standard 6-month tuberculosis therapy, with the clarification that rifabutin should not be given with saquinavir-HGC, ritonavir or delaviridine. Dosage adjustments of rifabutin and/or the protease inhibitor may need to be made and are discussed in detail below. For patients in whom rifamycin is contraindicated, a 9-month streptomycin-base regimen may be used with any of the antiretroviral agents. In patients not yet receiving antiretroviral therapy, the conventional rifampicin-based regimen is still considered first-line, but concurrent use of rifampicin with any of the protease inhibitors is contraindicated. Prior recommendations to temporally discontinue protease inhibitor therapy while treating tuberculosis with rifampicin are now discouraged. The recently approved antimycobacterial, rifapentine, is thought to have an intermediate induction potential relative to that of other rifamycins

1.4 Dosage Regimens

Close attention must be paid to the timing of protease inhibitor administration with regard to meals. With the exception of indinavir, the protease inhibitors should be taken with food to enhance absorption and/or improve tolerability.[15,16,21,22] Indinavir should be taken on an empty stomach or with a light meal, that is low in fat.[18]

Another method of improving the tolerability of ritonavir is to use an escalating dosage schedule.[22] Several methods have been suggested, but one easy-to-remember scheme is to give 300mg twice daily for the first 3 days, followed by 400mg twice

daily for 4 days, 500mg twice daily for 5 days, and continuing with the full 600mg twice daily.

Subtherapeutic concentrations of protease inhibitors have been associated with clinical failures and the emergence of resistance.[2,7,23] In particular, low indinavir trough concentrations appear to result in submaximal suppression of HIV. For example, Acosta et al.[24] reported on the kinetics of indinavir in 13 protease inhibitor–naïve patients receiving indinavir 800mg 3 times daily, 7 of whom had undetectable viral loads (<500 copies/ml).[24] Compared with 6 patients who still had detectable

Table II. Drug interactions with saquinavir

Concomitant drug	Interaction	Comments	Reference(s)
Clarithromycin	↑ AUC of clarithromycin by 45%; ↓ AUC of active metabolite by 24%; ↑ AUC of saquinavir-SGC by 177%	No dosage adjustment needed for either drug	15, 30
Cotrimoxazole (trimethoprim-sulfamethoxazole)	↑ Saquinavir-HGC AUC by 12%	No dosage adjustment needed for either drug	31
Cyclosporin	3-fold ↑ in cyclosporin trough concentration; 3- to 4-fold ↑ in AUC of saquinavir-HGC	Monitor cyclosporin concentration and for toxicity of either drug	32
Delaviridine	520% ↑ in C_{ss} of saquinavir-HGC	No dosage adjustment needed for either drug; may be a favourable combination; monitor hepatic enzymes	33
Efavirenz	60% ↓ in concentration of saquinavir-SGC	Avoid use of efavirenz with saquinavir-SGC as the sole protease inhibitor	34
Indinavir	5- to 8-fold ↑ in saquinavir-HGC concentration	Favourable kinetics, but antagonism has been observed *in vitro*	35
Ketoconazole	↑ AUC of saquinavir-SGC by 130%	No dosage adjustment needed for either drug	15
Midazolam	Prolonged sedation reported	Contraindicated with saquinavir-SGC; if combination needed, closely monitor sedation and respiration; may require reversal with flumazenil	36
Nelfinavir	≥5-fold ↑ in AUC of saquinavir-SGC and -HGC; little change in nelfinavir AUC	May be favourable combination; lower dosages of saquinavir-SGC (800mg 3 times daily) being evaluated	37-39
Nevirapine	↓ AUC of saquinavir-HGC by 27%	No dosage adjustment recommended for either drug; however, combination may not be favourable	40
Ranitidine	↑ AUC of saquinavir-SGC by 67%	No dosage adjustment needed for either drug	15
Rifabutin	↓ AUC of saquinavir-HGC by 45%	Consider alternative antimycobacterial (e.g. clarithromycin)	41
Rifampicin (rifampin)	↓ AUC of saquinavir-SGC by 84%	Avoid combination; see text for alternatives	15, 21
Ritonavir	≥10-fold ↑ AUC of saquinavir-HGC	Combination used clinically; may use lower dosages (e.g. 400mg twice daily for both ritonavir and saquinavir-HGC)	42, 43
Terfenadine	↑ AUC of terfenadine by 368%; ↑ AUC of active metabolite by 120%	Combination contraindicated	15, 30
Warfarin	↑ INR reported	Increase monitoring; warfarin dosage reduction may be needed	44
Astemizole, ergots, cisapride, triazolam	Potential for ↑ concentrations of object drugs	Combinations contraindicated; may result in serious adverse effects	15, 21
Phenobarbital (phenobarbitone), phenytoin, carbamazepine	Potential for ↓ concentrations of saquinavir	May result in decreased efficacy or increased resistance to saquinavir; consider increasing dosage of saquinavir	15, 21

AUC = area under the plasma concentration-time curve; **C_{ss}** = steady-state concentration; **HGC** = hard-gelatin capsules; **INR** = international normalised ratio; **SGC** = soft-gelatin capsules; ↑ = increased; ↓ = decreased.

virus, these 7 had higher median indinavir trough concentrations (0.14 *vs* 0.02 μg/ml, p = 0.05); the area under the plasma concentration-time curve (AUC) was also lower in the group with detectable virus. The authors concluded that a minimum threshold exposure to indinavir may be necessary for optimal suppression of HIV.

Burger et al.[25] obtained similar results and suggested that indinavir concentrations should remain above 0.075 μg/ml (the IC_{95} for HIV) for at least 90% of the administration interval. Harris et al.[26] also concluded that indinavir trough concentrations were a better predictor of virological effect than peak concentrations.

Thus, drug interactions may be of particular consequence for indinavir if they result in diminished trough concentrations. Subtherapeutic concentrations of other protease inhibitors may be similarly dangerous, and these relationships are being further evaluated.[27-29]

2. Saquinavir

Table II summarises drug interactions with saquinavir.

2.1 Reverse Transcriptase Inhibitors

Delaviridine, a relatively new non-nucleoside reverse transcriptase inhibitor (NNRTI), has been observed to inhibit CYP3A and CYP2C9, and thus would be expected to have an effect on the metabolism of the protease inhibitors.[45] Cox et al.[33] studied the pharmacokinetic interaction between delaviridine 400mg 3 times daily and saquinavir-HGC 600mg 3 times daily. The steady-state concentration of saquinavir in combination with delaviridine was 291 ± 189 μg/L compared with 56 ± 26 μg/L with saquinavir alone, a >5-fold increase. The authors reported that saquinavir had no clinically relevant effect on delaviridine kinetics.

At the moment, there are limited safety and no efficacy data available for the use of this combination, but delaviridine may prove useful in augmenting the efficacy of saquinavir. Reversible increases in hepatic enzymes were noted in this study, so hepatic enzymes should be monitored frequently if this combination is prescribed.

In contrast to delaviridine, nevirapine, the other marketed NNRTI, is an inducer of CYP3A.[46] Sahai et al.[40] evaluated the combination of saquinavir-HGC 600mg 3 times daily with nevirapine 200mg twice daily in 21 HIV-positive patients. The AUC of saquinavir was decreased by 27%, and the peak plasma concentration (C_{max}) was decreased by 29%. Saquinavir had no significant effect on the kinetics of nevirapine. Although the difference in saquinavir concentrations was statistically significant, the authors suggested that it was not clinically significant and recommended no dosage adjustment for either drug. However, this combination should probably be avoided until more clinical data become available.

The newly approved NNRTI efavirenz is both an inducer and an inhibitor of CYP3A4. Investigators using this agent were recently warned of a potential interaction with saquinavir.[34] Healthy volunteers receiving efavirenz 600mg once daily with saquinavir-SGC 1200mg 3 times daily demonstrated a 60% decrease in saquinavir concentrations compared with those receiving saquinavir-SGC alone. Efavirenz concentrations were also decreased by about 10%, but this was not suggested to be clinically significant. The manufacturer of efavirenz currently recommends against using this drug in combinations containing saquinavir as the sole protease inhibitor.

Significant interactions between the protease inhibitors and the nucleoside reverse transcriptase inhibitors are not expected because of their different routes of elimination. No changes in saquinavir concentrations were noted when saquinavir-HGC was given with either zidovudine 200mg 3 times daily or zalcitabine 0.75mg 3 times daily.[21]

2.2 Other Antimicrobials

Clarithromycin 500mg twice daily for 7 days given with saquinavir-SGC 1200mg 3 times daily for 7 days resulted in a 45% increase in the AUC of clarithromycin and a 39% increase in its C_{max}.[15,30] There was also a 24% decrease in the

AUC and a 34% decrease in the C_{max} of the 14-hydroxy metabolite of clarithromycin, which provides most of the activity against *Haemophilus influenzae*. In addition, the AUC of saquinavir was increased by 177%, with a 187% increase in C_{max}. The clinical significance of this interaction is unknown, and no dose adjustment is recommended.

Inducers of CYP3A4 are likely to decrease the serum concentrations of saquinavir. When saquinavir-HGC 600mg 3 times daily was given concurrently with rifabutin 300mg once daily, the AUC_{0-8h} of saquinavir decreased from 1179 μg/L · h before rifabutin to 644 μg/L · h after 2 weeks of concurrent therapy, a 45% decrease.[41] The C_{max} of saquinavir also decreased by 38%, from 377 to 233 μg/L. Similarly, when given with a more potent enzyme inducer, rifampicin 600mg once daily, the AUC of saquinavir-SGC decreased by 84% and the C_{max} decreased by 79%.[15] Considering the already low concentrations of saquinavir achieved with current formulations, use of either saquinavir product with rifampicin or rifabutin should be avoided.

2.3 Other Drugs

Terfenadine 60mg twice daily for 11 days given with saquinavir-SGC 1200mg 3 times daily for 4 days resulted in a 368% increase in the AUC of terfenadine along with a 253% increase in C_{max}.[15,30] There was also a 120% increase in the AUC of the active acid metabolite of terfenadine and a 93% increase in its C_{max}. Therefore, the combination of terfenadine and either saquinavir formulation should be avoided because of the possibility of terfenadine-associated arrhythmias. Similar increases are anticipated with astemizole, again resulting in potential arrhythmias. Fexofenadine, which is the active acid metabolite of terfenadine, lacks the parent compound's potential to cause arrhythmias, and therefore may be a safer alternative. Loratidine may also be a better choice as a nonsedating antihistamine.

Prolonged sedation with midazolam, requiring reversal with flumazenil, was noted in a case report of a patient who was receiving saquinavir-HGC.[36] After midazolam 5mg this patient did not awaken spontaneously and required flumazenil 300μg. The patient was still not free of sedative effects until more than 5 hours after receiving the midazolam. In contrast, before initiation of saquinavir, the patient recovered spontaneously and was free of sedative effects at 2 hours after receiving midazolam. It was proposed that the prolonged sedation was the result of an interaction between saquinavir and midazolam, since both agents are metabolised by CYP3A4. The combination of midazolam and saquinavir-SGC is contraindicated.[15]

Similarly, hypoprothrombinaemia was reported in a patient started on saquinavir-HGC while receiving long-term warfarin therapy.[44] The patient's international normalised ratio (INR) increased from a baseline of 1.96 to 2.28 in the 5 months preceding saquinavir to 4.24 at 8 weeks after initiation of the protease inhibitor. Increased monitoring is required when a protease inhibitor is started in a patient being anticoagulated with warfarin, and a reduction of warfarin dosage may be required.

Several other interactions are described in the saquinavir-SGC package insert and are included in table II. Although formal pharmacokinetic studies have not been done with the following drugs, the manufacturer states that their use with saquinavir-SGC is contraindicated: astemizole, cisapride, ergot derivatives, midazolam and triazolam.[15] The product labelling also warns of potential induction of the metabolism of saquinavir by phenobarbital (phenobarbitone) phenytoin, carbamazepine and corticosteroids such as dexamethasone.[15,21]

3. Ritonavir

Ritonavir is mainly metabolised by CYP3A4, with smaller contributions by the CYP2D6 and CYP2C9/10 isoforms.[7] As discussed in section 1.3, it is a more potent inhibitor of CYP3A4 than any of the other protease inhibitors.[3,4,19] In addition to inhibiting CYP3A4, CYP2D6 and CYP2C9/10, ritonavir has been noted to induce CYP1A2 and hepatic glucuronidation.[7] As a result, the manufacturer has warned[22] that several

drugs are contraindicated for use with ritonavir because of the strong possibility that ritonavir will significantly alter the metabolism of these agents (table III). However, of these agents, specific pharmacokinetic studies have only been performed with rifabutin and alprazolam. The package insert also lists many other less severe drug interactions that are likely to occur with ritonavir (table III).

Table III. Potential effects of ritonavir on the pharmacokinetics of other drugs[22]

Contraindicated
Alprazolam, amiodarone, astemizole, bepridil, amfebutamone (bupropion), cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergotamine, estazolam, flecainide, flurazepam, midazolam, pethidine (meperidine), pimozide, piroxicam, propafenone, propoxyphene, quinidine, rifabutin, terfenadine, triazolam, zolpidem
Increased AUC
Alfentanil, amitriptyline, amlodipine, bromocriptine, carbamazepine, chlorpromazine, clarithromycin, clomipramine, clonazepam, cyclosporin, desipramine, dexamethasone, dexfenfluramine, diltiazem, disopyramide, dronabinol, erythromycin, ethosuximide, etoposide, felodipine, fentanyl, fluoxetine, fluvastatin, haloperidol, hydrocodeine, imipramine, indinavir, isradipine, itraconazole, ketoconazole, lidocaine (lignocaine), loratidine, lovastatin, maprotiline, methadone, methamphetamine, metoprolol, mexilitene, miconazole, nefazodone, nicardipine, nifedipine, nimodipine, nislodipine, nortriptyline, ondansetron, oxycodone, paclitaxel, paroxetine, penbutolol, perphenazine, pindolol, pravastatin, prednisone, quinine, risperidone, saquinavir, sertraline, simvastatin, tacrolimus, tamoxifen, thioridazine, timolol, tramadol, trazodone, trimipramine, venlafaxine, verapamil, vinblastine, vincristine, *R*-warfarin
Variable or unknown effect
Albendazole, betaxolol, chloroquine, cyclophosphamide, daunorubicin, diclofenac, digoxin, doxazosin, doxepin, doxorubicin, ergonovine, ethionamide, flurbiprofen, fluvoxamine, gemfibrozil, glimepiride, glipizide, glibenclamide (glyburide), ibuprofen, ifosfamide, indomethacin, lansoprazole, levamethadyl, losartan potassium, methylphenidate, methysergide, metronidazole, nabumetone, nevirapine, omeprazole, pentoxifylline, phenobarbital (phenobarbitone), phenytoin, prazosin, primaquine, prochlorperazine, proguanil, promethazine, propranolol, pyrimethamine, rifampicin (rifampin), sulindac, terazosin, tocainide, tolbutamide, *S*-warfarin
Decreased AUC
Atovaquone, clofibrate, codeine, diphenoxylate, ethinylestradiol, hydromorphone, ketoprofen, ketorolac, lamotrigine, loperamide, lorazepam, metoclopramide, morphine, naproxen, oxazepam, propofol, temazepam, theophylline, valproic acid (sodium valproate)
AUC = area under the plasma concentration-time curve.

Interactions that have actually been documented are presented in table IV.

3.1 Reverse Transcriptase Inhibitors

The combination of ritonavir and delaviridine has been evaluated in two small studies of HIV-positive patients. Fourteen patients receiving ritonavir 600mg twice daily and nucleoside reverse transcriptase inhibitors had delaviridine 400mg 3 times daily added.[49] The 12-hour AUC of ritonavir increased from 68 ± 26 to 111 ± 60 mg/L • h, a 63% increase. The C_{max} increased by 65%, from 10.7 ± 4.8 to 17.7 ± 10.0 mg/L. The authors concluded that lower dosages of ritonavir may be sufficient in patients receiving delaviridine, especially in patients having difficulty tolerating the protease inhibitor.

A second study evaluated the impact of ritonavir on delaviridine kinetics.[50] Patients receiving delaviridine 400mg 3 times daily with ritonavir 600mg twice daily were noted to have kinetic parameters similar to those in historical controls who received delaviridine monotherapy.

An interaction between ritonavir and efavirenz has also been reported recently.[53] 20 healthy volunteers received efavirenz 200mg daily and ritonavir at a rapidly escalating dosage up to 500mg twice daily. Each regimen was administered first as monotherapy and then in combination. With the combination, the AUC of efavirenz increased by 21%, with a similar 17% increase for ritonavir. The authors concluded that if patients experience intolerance to ritonavir while also receiving efavirenz, the ritonavir dosage could be reduced to 500mg twice daily from the normal dosage of 600mg twice daily.

3.2 Other Antimicrobials

Rifabutin 150mg once daily was given for 14 days, followed by addition of either placebo or an escalating dosage of ritonavir up to 500mg twice daily, to 24 healthy men and women.[63] In the 5 volunteers who received both active drugs and were evaluable, this combination resulted in a 4-fold increase in AUC and a 2.5-fold increase in

Table IV. Drug interactions with ritonavir

Concomitant drug	Interaction	Comments	Reference
Alprazolam	↓ AUC of alprazolam by 12%	Questionable clinical significance but combination contraindicated by manufacturer	47
Clarithromycin	↑ AUC of clarithromycin by 77%; ↓ AUC of active metabolite by 100%; ↑ AUC of ritonavir by 12%	Dosage adjustment needed for clarithromycin once creatinine clearance <60 ml/min (<3.6 L/h)	48
Delaviridine	↑ AUC of ritonavir by 63%; no change in delaviridine concentrations	May be favourable combination, but few clinical data	49, 50
Desipramine	↑ AUC of desipramine by 145%; ↓ AUC of active metabolite by 15%	Consider decreasing desipramine dosage empirically or based on serum concentration monitoring	51
Didanosine	↓ AUC of didanosine by 13%	No dosage adjustment needed for either drug	52
Efavirenz	↑ AUC of ritonavir by 17%; ↑ AUC of efavirenz by 21%	No dosage adjustment needed for efavirenz; consider decreasing ritonavir dosage to 500mg twice daily	53
Ergotamine	Patient presented with symptoms in both arms; pain, paraesthesias, pallor, and coldness	Combination contraindicated	54
Ethinylestradiol	↓ AUC of ethinylestradiol by 41%	Increase dosage of ethinylestradiol or use alternative contraceptive measures	55
Fluconazole	↑ AUC of ritonavir by 12%	No dosage adjustment needed for either drug	56
Fluoxetine	↑ AUC of ritonavir by 19%	No dosage adjustment needed for either drug	57
Indinavir	↑ AUC of indinavir by ≤475%; little change in ritonavir concentrations	Combination may be favourable but potential for cross-resistance	58
Ketoconazole	↑ AUC of ketonazole by 329%; little change in ritonavir concentrations	Consider ↓ ketoconazole dosage; monitor liver function tests	59
Levothyroxine	Increased TSH level	Increase levothyroxine dosage based on thyroid function testing	60
Methadone	↓ AUC of methadone by 36%; no change in ritonavir concentrations	Questionable clinical significance; may need to increase methadone dosage	61
Metronidazole	Disulfiram reaction	Avoid combination	22
Nelfinavir	↑ AUC of nelfinavir by 152%; ↑ AUC of ritonavir by 9%	May be favourable combination, but few clinical data	16, 62
Rifabutin	↑ AUC of rifabutin by 300%; 35-fold ↑ in AUC of active metabolite	High prevalence of rifabutin adverse effects; combination contraindicated – use alternative antimycobacterial	63, 64
Rifampicin (rifampin)	↓ AUC of ritonavir by 35%	Avoid combination; see text for alternatives	22
Saquinavir	≥10-fold ↑ AUC of saquinavir-HGC	Combination used clinically; may use lower dosages (e.g. 400mg twice daily for both ritonavir and saquinavir-HGC)	42, 43
Sulfamethoxazole	↓ AUC of sulfamethoxazole by 20%	No dosage adjustment needed	65
Theophylline	↓ AUC of theophylline by 43%	Increase theophylline dosage based on serum concentrations	66
Trimethoprim	↑ AUC of trimethoprim by 20%	No dosage adjustment needed	65
Warfarin	↑ Warfarin requirement reported in 1 patient after ritonavir started	↑ Monitoring; warfarin dosage increase may be needed	67
Zidovudine	↓ AUC of zidovudine by 26%; no change in ritonavir concentrations	No dosage adjustment needed	68

AUC = area under the plasma concentration-time curve; **HGC** = hard-gelatin capsules; **TSH** = thyroid-stimulating hormone; ↑ = increased; ↓ = decreased.

C_{max} of rifabutin. There was also a 35-fold increase in AUC and a 16-fold increase in C_{max} of the active 25-*O*-desacetyl-rifabutin metabolite. 5 of the 7 volunteers who did not complete the rifabutin/ritonavir portion of the trial withdrew due to the development of leucopenia. However, drug concentrations obtained before these patients withdrew were not significantly different at that time from those in the patients who eventually completed the protocol. Rifabutin is a less potent inducer of CYP than is rifampicin, but the effect of rifabutin on ritonavir kinetics has not been formally evaluated. Because of the increased likelihood of rifabutin toxicity, especially uveitis, arthralgia and leucopenia,[64] the combination of rifabutin and ritonavir is contraindicated by the manufacturer.[22] An alternative to rifabutin for antimycobacterial therapy, such as clarithromycin, is recommended during ritonavir therapy; use of lower dosages of rifabutin is also being investigated.

However, like ritonavir, clarithromycin is also an inhibitor of CYP3A4. Clarithromycin 500mg twice daily for 4 days together with ritonavir 200mg 3 times daily resulted in a 12% increase in the AUC_{0-24h} of ritonavir (from 85.2 ± 30.4 to 95.8 ± 38.3 mg/L · h) and a 15% increase in C_{max} (from 5.80 ± 1.76 to 6.69 ± 2.88 mg/L).[48] A greater effect on the kinetics of clarithromycin was seen, with a 77% increase in AUC_{0-24h} (from 49.0 ± 14.1 to 86.9 ± 20.4 mg/L · h) and a 31% increase in C_{max} (from 3.93 ± 1.17 to 5.13 ± 1.08 mg/L). 99% decreases in AUC (from 15.7 ± 4.5 to 0.04 ± 0.11 mg/L · h) and C_{max} (from 0.90 ± 0.25 to 0.01 ± 0.02 mg/L) of 14-hydroxy-clarithromycin were also noted. The clinical impact of this interaction has not yet been determined, but a reduction in clarithromycin dosage by 50% is recommended when the patient's creatinine clearance is between 30 and 60 ml/min (1.8 and 3.6 L/h) and by 75% when the patient's creatinine clearance is <30 ml/min (<1.8 L/h).[22]

The azole antifungal fluconazole has also been shown to inhibit the metabolism of ritonavir.[56] Eight healthy individuals received ritonavir 200mg 4 times daily in conjunction with fluconazole 200mg once daily (after a 400mg loading dose). The AUC_{0-24h} of ritonavir increased from 151 ± 36 mg/L · h during ritonavir monotherapy to 169 ± 41 mg/L · h with fluconazole, a 12% increase. The C_{max} of ritonavir also increased from 8.95 ± 2.41 to 10.25 ± 2.69 mg/L, a 15% increase ($p < 0.02$ for both comparisons). Fluconazole parameters were not evaluated. The authors concluded that the interaction between ritonavir and fluconazole was not clinically significant and recommended no dosage adjustments for either drug.

Ketoconazole has also been evaluated with concurrent ritonavir.[59] After 3 days of ritonavir alone, 12 healthy volunteers received ritonavir 500mg twice daily along with ketoconazole 200mg once daily for 7 days. The pharmacokinetic parameters of ketoconazole were significantly altered by ritonavir, with a 51% increase the C_{max} from 4.65 ± 2.24 to 7.04 ± 2.96 mg/L and a 329% increase in the 24-hour AUC from 28.8 ± 15.1 to 94.7 ± 43.4 mg/L · h ($p < 0.001$ for both comparisons). However, ritonavir concentrations were not significantly altered by ketoconazole. A dosage reduction appears to be appropriate for ketoconazole when given with ritonavir, particularly in the light of the fact that both drugs may cause elevations of hepatic enzymes.

3.3 Other Drugs

Frye et al.[47] studied the pharmacokinetic and pharmacodynamic effects of an escalating dosage of ritonavir, up to 500mg twice daily, on a single 1mg dose of alprazolam in healthy volunteers. The AUC of alprazolam was decreased by 12% ($p = 0.15$), with a 16% decrease in C_{max} ($p = 0.009$) and a decrease in half-life from 13.5 to 11.9 hours ($p = 0.07$). This was surprising, considering the ability of ritonavir to inhibit CYP3A4; however, ritonavir is known to induce other CYP isoenzymes which may be involved to a lesser degree in the metabolism of alprazolam. No clinically significant difference was seen when comparing functional impairment and peak sedation, but duration of sedation was prolonged in the group receiving the combination, again a surprising result considering the phar-

macokinetic changes noted. The authors concluded that contraindication of ritonavir and alprazolam coadministration is unwarranted, and that dosage adjustments are not necessary for either drug. Patients should still be monitored for prolonged sedation. Further studies may be warranted to resolve the apparent contradictions of this trial.

Desipramine 100mg given as a single dose following an escalating dosage of ritonavir up to 500mg twice daily in 14 healthy male and female volunteers resulted in a 145% increase in AUC and a 22% increase in C_{max} of desipramine.[51] A 15% decrease in AUC and a 67% decrease in C_{max} of the active 2-hydroxy-desipramine metabolite was also observed. All of the volunteers had the CYP2D6 extensive metaboliser phenotype. Because of the large changes in desipramine serum concentrations, dosage reduction and serum concentration monitoring of desipramine may be required. Other antidepressants, including other tricyclic antidepressants and selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors, such as fluoxetine,[57] may also be expected to interact with ritonavir, so increased monitoring will be necessary with any of these agents.

Ethinylestradiol 50μg given as a single dose following an escalating dosage of ritonavir up to 500mg twice daily in 23 healthy female volunteers resulted in a 41% decrease in AUC from 1670 ± 377 to 993 ± 292 ng/L · h and a 32% decrease in C_{max} of the estrogen from 104 ± 24 to 71 ± ng/L ($p < 0.001$ for both comparisons).[55] Changes in the pharmacokinetics of ethinylestradiol were thought to be due to induction of CYP hydroxylation and/or hepatic glucuronidation. Alternative methods of contraception may be necessary for patients who are receiving ritonavir.

Theophylline may also be affected by coadministration with ritonavir via induction of CYP1A2. Theophylline 3 mg/kg 3 times daily was given with an escalating dosage of ritonavir up to 500mg twice daily in 27 participants.[66] After 10 days of coadministration, there was a 43% decrease in AUC, a 32% decrease in C_{max} and a 57% decrease in trough concentration (C_{min}) of theophylline. Serum concentration monitoring and dosage adjustment of theophylline may be necessary when patients are also taking ritonavir.

Caballero-Granado et al.[54] reported the case of an HIV-positive man who had been taking ergotamine tartrate 1 to 2 mg/day for 5 years to manage chronic migraine headaches. At 10 days after initiation of ritonavir 600mg twice daily, the patient presented with symptoms in both arms, characterised by pain, paraesthesias, pallor alternating with areas of cyanosis, and coldness. Pulses were absent, and Doppler testing revealed a lack of radial and ulnar arterial flow. With prostaglandin treatment and discontinuation of the ergotamine and ritonavir, the symptoms eventually resolved. The patient was not rechallenged.

The combination of ergots and ritonavir is contraindicated by the manufacturer.[22] Common symptoms of ergotism include gastrointestinal upset, headache, dizziness, confusion, somnolence, and cramping/tingling of the extremities. Alternative means of managing migraines have not been suggested, but several analgesics from different classes [e.g. pethidine (meperidine), piroxicam and propoxyphene] are also suspected to interact with ritonavir.[22] The triptans (e.g. sumatriptan, zolmitriptan and naratriptan) are also metabolised by CYP and therefore caution should be taken during concomitant use with the protease inhibitors. Paracetamol (acetaminophen) and aspirin (acetylsalicylic acid) may be safer alternatives for pain relief.

Tseng and Fletcher[60] reported a case of a patient with hypothyroidism who had been stabilised for 1 year on levothyroxine. At 1 month after initiating ritonavir 600mg twice daily, the patient's level of thyroid stimulating hormone (TSH) increased dramatically to 18.47 mU/L from a baseline value of 2.31 mU/L 10 months earlier. This necessitated an increase in levothyroxine dosage from 0.125 to 0.25 mg/day. Even at this dosage, the patient's TSH remained slightly increased at 7.35 mU/L. Later abnormalities in liver function tests resulted in the discontinuation of ritonavir and subsequent reduction in the levothyroxine dosage

Table V. Drug interactions with indinavir

Concomitant drug	Interaction	Comments	Reference
Atovaquone	↓ AUC of indinavir by 5%; ↑ AUC of atovaquone by 13%	No dosage adjustment needed for either drug	69
Cimetidine	No change in indinavir AUC	No dosage adjustment needed for either drug	18
Clarithromycin	↑ AUC of indinavir by 29%; ↑ AUC of clarithromycin by 53%	No dosage adjustment needed for either drug	18
Efavirenz	↓ AUC of indinavir by 35%	Increase indinavir dosage to 1000mg 3 times daily	70
Ethinylestradiol	↑ AUC of ethinylestradiol by 24%	No dosage adjustment needed for either drug	18
Delaviridine	↑ Indinavir AUC and trough, no change in peak	Consider decreasing indinavir dosage to 600mg 3 times daily	71
Fluconazole	↓ AUC of indinavir by 24%; no change in fluconazole concentrations	No dosage adjustment needed for either drug	72
GM-CSF	↑ AUC of indinavir by 9%	No dosage adjustment needed	73
Grapefruit juice	↓ AUC of indinavir by 26%	Avoid combination	18
Interleukin-2	↑ Indinavir AUC by 87%	No dosage adjustment needed at this time, but further evalution is warranted	74
Isoniazid	↑ AUC of isoniazid by 13%	No dosage adjustment needed for either drug	18
Ketoconazole	↑ AUC of indinavir by 68%	Decrease indinavir dosage to 600mg 3 times daily	18
Lamivudine	↓ AUC of lamivudine by 6%	No dosage adjustment needed for either drug	18
Nelfinavir	↑ AUC of nelfinavir by 83%; ↑ AUC of indinavir by 51%	Combination may be favourable; concomitant use being studied using twice daily regimens	16, 62, 75
Nevirapine	↓ AUC of indinavir by 28%	? Increase indinavir dosage to 1000mg 3 times daily	76
Norethindrone	↑ AUC of norethindrone by 26%	No dosage adjustment needed for either drug	18
Quinidine	↑ AUC of indinavir by 10%	No dosage adjustment needed for either drug	18
Rifabutin	↑ AUC of rifabutin by 204%; ↓ AUC of indinavir by 32%	Uveitis has been associated with this combination; decrease rifabutin dosage by 50%; ? increase indinavir dosage to 1200mg 3 times daily	18, 20
Rifampicin (rifampin)	↓ AUC of indinavir by 89%	Avoid combination; see text for alternatives	18
Ritonavir	↑ AUC of indinavir by ≤480%; little change in ritonavir concentrations	Combination may be favourable but potential for cross-resistance	58
Saquinavir	5- to 8-fold ↑ in saquinavir-HGC concentrations	Favourable kinetics, but antagonism has been observed *in vitro*	35
Stavudine	↑ AUC of stavudine by 25%	No dosage adjustment needed for either drug	18
Sulfamethoxazole	No changes in either AUC	No dosage adjustment needed for either drug	18
Trimethoprim	↑ AUC of trimethoprim by 19%	No dosage adjustment needed for either drug	18
Warfarin	↓ Warfarin requirement reported in 1 patient after indinavir stopped	↑ Monitoring; warfarin dosage increase may be needed	67
Zidovudine	↑ AUC of indinavir by 0-13%; ↑ AUC of zidovudine by 17-36%	No dosage adjustment needed for either drug	18
Antacids, H_2-antagonists, omeprazole, lansoprazole	May ↓ indinavir absorption	Separate doses by at least 1 hour	18
Didanosine	Didanosine buffers may ↓ indinavir absorption	Separate doses by at least 1 hour	18
Terfenadine, astemizole, cisapride, triazolam, midazolam	Potential for ↑ concentrations of object drugs	Combinations contraindicated; may result in serious adverse effects	18

AUC = area under the plasma concentration-time curve; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **HGC** = hard-gelatin capsules; ↑ = increased; ↓ = decreased.

back to 0.125 mg/day. The patient's TSH was maintained at 5.87 mU/L on this dosage, even after reinstitution of protease inhibitor therapy with indinavir. The increase in this patient's levothyroxine requirement was probably due to increased glucuronidation caused by ritonavir; thus, indinavir is less likely to cause this interaction.

One pharmacodynamic interaction of note is that both the liquid and capsule formulations of ritonavir contain alcohol (ethanol), and thus may precipitate a disulfiram-like reaction in patients taking metronidazole, ketoconazole or other drugs with this potential.[22]

4. Indinavir

Drug interactions with indinavir are summarised in table V.

4.1 Reverse Transcriptase Inhibitors

The NNRTI nevirapine was evaluated in combination with indinavir.[76] 18 HIV-positive patients received indinavir 800mg 3 times daily in combination with an escalating dosage of nevirapine up to 200mg twice daily. Coadministration resulted in a 28% reduction in the AUC of indinavir and an 11% decrease in C_{max}, both of which were statistically significant ($p < 0.05$). As for the combination of nevirapine with the other protease inhibitors, this change in pharmacokinetic parameters may not be clinically significant. However, an increase in the indinavir dosage to 1200mg 3 times daily may be considered if this combination is used.

Efavirenz has been evaluated at a dosage of 200mg once daily in combination with indinavir 800 or 1000mg 3 times daily.[70] The 8-hour AUC for indinavir was reduced by about 35% by combination with efavirenz. The authors suggested that increasing the indinavir dosage to 1000mg 3 times daily compensated for the induction of indinavir metabolism, because the AUC for indinavir 1000mg 3 times daily with efavirenz was similar to that for indinavir 800mg 3 times daily as monotherapy. The effect of indinavir on the pharmacokinetics of efavirenz was not reported.

In addition, single 400 and 600mg doses of indinavir have been studied in combination with delaviridine 400mg 3 times daily in 14 healthy men.[71] Although the differences in delaviridine pharmacokinetic parameters were statistically significant, the magnitude of those differences was less than 5% and probably not of clinical importance. In contrast, compared with an 800mg dose of indinavir before initiation of delaviridine, the pharmacokinetic parameters of indinavir during delaviridine administration were significantly greater than expected based on the dose reduction to 400 or 600mg. For example, the AUC after a 600mg dose of indinavir with delaviridine was 44% greater than after an 800mg dose of indinavir alone. Indinavir concentrations at 8 hours after administration were also 2- to 5-fold greater when comparing the 400 and 600mg doses with the 800mg dose. Changes in C_{max}, however, were dose-proportional, and thus should not result in an increase in adverse effects such as nephrolithiasis, which may be related to peak concentrations. The authors suggested that it may be possible to reduce both the dose and administration frequency of indinavir when used in conjunction with delaviridine.

4.2 Other Antimicrobials

Indinavir 800mg 3 times daily and rifabutin 300mg once daily for 10 days resulted in a 32 ± 19% decrease in AUC of indinavir and a 204 ± 142% increase in AUC of rifabutin.[18] As discussed in section 1.4, a reduced indinavir AUC could have serious consequences in terms of decreased efficacy and increased risk of viral resistance. Alternatively, the increased rifabutin concentrations may be associated with increased toxicity, such as uveitis. Consequently, the manufacturer recommends a 50% dosage reduction for rifabutin when it is given with indinavir. An increase in the indinavir dosage to 1200mg 3 times daily may also be considered.[20]

The coadministration of indinavir 800mg 3 times daily and rifampicin 600mg once daily for 1 week resulted in a 89 ± 9% decrease in the AUC of

Table VI. Drug interactions with nelfinavir

Concomitant drug	Interaction	Comments	Reference
Delaviridine	↑ AUC of nelfinavir by 92%; ↓ AUC of delaviridine by 42%	No dosage adjustment recommended for either drug; monitor patients for neutropenia; avoid combination if possible	77
Didanosine	No change in nelfinavir AUC	No dosage adjustment needed for either drug	16
Efavirenz	↑ AUC of nelfinavir by 17%; no change in efavirenz AUC	No dosage adjustment needed for either drug	78
Ethinylestradiol	↓ AUC of ethinylestradiol by 47%	↑ Ethinylestradiol dosage or use alternative contraceptive measures	16, 62
Indinavir	↑ AUC of nelfinavir by 83%; ↑ AUC of indinavir by 51%	Combination may be favourable; concomitant use being studied using twice daily administration of each	16, 62, 75
Ketoconazole	↑ AUC of nelfinavir by 35%	No dosage adjustment needed for either drug	16
Lamivudine	↑ AUC of lamivudine by 10%	No dosage adjustment needed for either drug	16
Nevirapine	Contradictory studies but probably no change in concentrations of either drug	No dosage adjustment needed for either drug	79-81
Norethindrone	↓ AUC of norethindrone by 18%	Consider alternative method of contraception	16
Rifabutin	↓ AUC of nelfinavir by 32%; ↑ AUC of rifabutin by 207%	↓ Rifabutin dosage by 50%; ? ↑ nelfinavir dosage to 1000mg 3 times daily	16, 20
Rifampicin (rifampin)	↓ AUC of nelfinavir by 82%; little change in rifampicin concentrations	Combination contraindicated; see text for alternatives	16, 62
Ritonavir	↑ AUC of nelfinavir by 152%; ↑ AUC of ritonavir by 9%	May be favourable combination, but few clinical data	16, 62
Saquinavir	≥5-fold ↑ in AUC of saquinavir-SGC and -HGC; little change in nelfinavir AUC	May be favourable combination; lower dosages of saquinavir-SGC (800mg 3 times daily) being evaluated	37-39
Stavudine	No change in nelfinavir AUC	No dosage adjustment needed for either drug	16
Terfenadine	↑ Terfenadine plasma concentration	↑ Risk of arrhythmias; combination contraindicated	16, 62
Zidovudine	↓ AUC of zidovudine by 35%; no change in nelfinavir concentrations	No dosage adjustment needed	16
Phenobarbital (phenobarbitone), phenytoin, carbamazepine	Potential for ↓ concentrations of nelfinavir	May result in ↓ efficacy or ↑ resistance to saquinavir; consider increasing dosage of saquinavir	16

AUC = area under the plasma concentration-time curve; **HGC** = hard-gelatin capsules; **SGC** = soft-gelatin capsules; ↑ = increased; ↓ = decreased.

indinavir.[18] Coadministration of indinavir and rifampicin is not recommended by the manufacturer; alternatives for management of the HIV patient with tuberculosis have been outlined in section 1.3.

Administration of ketoconazole 400mg with indinavir 400mg resulted in a 68 ± 48% increase in the AUC of indinavir.[18] Because of this increase in the plasma concentration of indinavir, reduction of indinavir dosage to 600mg 3 times daily should be considered when it is coadministered with ketoconazole to minimise the risk of toxicity such as nephrolithiasis and hepatic dysfunction. Concomitant administration of indinavir with itraconazole has not been studied but the same interaction is likely to occur.

Fluconazole is a less potent inhibitor of CYP3A4 and thus may be a better tolerated alternative. When indinavir 1000mg 3 times daily was given with fluconazole 400mg once daily to 13 patients with HIV infection, the 8-hour AUC for indinavir decreased from 39.1 to 29.8 μmol/L · h ($p = 0.08$), a 24% decrease.[72] The C_{max} of indinavir also decreased from 17.2 to 15 μmol/L, a nonsignificant difference. The pharmacokinetic parameters of fluconazole were not affected by indinavir. The decrease in the AUC of indinavir was not

thought to be clinically significant and was also not statistically significant, as reflected by a p value > 0.05. As an inhibitor of CYP3A4, fluconazole would be expected to increase indinavir concentrations, so the results seen in this trial were unexpected. No dosage adjustment was recommended for either drug.

4.3 Other Drugs

Stimulation of the immune system with cytokines such as interleukin-2 (IL-2) is a growing area of interest for the management of HIV infection. Infusions of IL-2 are known to elevate blood levels of several endogenous cytokines, such as IL-6 and tumour necrosis factor-α, which have been shown experimentally to inhibit CYP3A4.[74] Thus, IL-2 may be expected to alter the elimination of protease inhibitors. Consequently, the pharmacokinetics of indinavir were evaluated in 17 patients after 5 days of continuous infusion with IL-2 3 to 12 MIU/day.[74] All patients had previously been maintained on antiretroviral regimens including indinavir 800mg 3 times daily. In the 9 patients who had prospective pharmacokinetic sampling, the 8-hour indinavir AUC increased by 87% from 15.8 to 29.5 mg/L · h ($p < 0.05$). The C_{max} and C_{min} also increased, but this change was not statistically significant. These patients also had a 20-fold increase in IL-6 levels after the 5-day infusion. The changes in indinavir concentrations were supported by the purely observational study, in which 8 patients had an increase in trough concentrations from 264 ± 493 to 670 ± 677 μg/L ($p < 0.05$). Much more extensive research is needed to evaluate the clinical impact of this and other anticipated interactions with IL-2 and other cytokines.

Although formal pharmacokinetic studies are lacking, coadministration of indinavir with astemizole, terfenadine, midazolam and cisapride is contraindicated.[18] As with the other protease inhibitors, alternative agents should be selected. Other interactions that have been documented by the manufacturer are described in table V.

5. Nelfinavir

Drug interactions with nelfinavir are summarised in table VI.

5.1 Reverse Transcriptase Inhibitors

The kinetics of nelfinavir have been evaluated in combination with several NNRTIs. Merry et al.[79] studied the combination of nelfinavir 750mg 3 times daily and nevirapine 200mg once daily for 1 week, followed by twice daily, in 7 HIV-positive patients. Nevirapine was started on day 3 of nelfinavir therapy, with nelfinavir concentrations measured on the day before nevirapine was added and again on the eighth day of the full dosage of nevirapine. The authors noted that the mean nelfinavir $AUC_{0\text{-}8h}$ decreased from 23.4 to 11.6 mg/L · h, a 50% decrease. The C_{max} of nelfinavir also decreased from 4.4 to 2.5 μg/L, a 43% decrease. Nevirapine concentrations were similar to those reported during nevirapine monotherapy. The authors concluded that an increase in the nelfinavir dosage may be necessary. However, an editorial in the same journal pointed out a possible flaw in the methodology of this study.[81] In particular, it appears that nelfinavir may induce its own metabolism, with peak concentrations being found on day 2 and then falling by up to 50% by day 6 of therapy. Since prenevirapine nelfinavir concentrations were measured on day 2 in the Merry et al.[79] study, the subsequent 50% decrease in AUC may have been due to autoinduction alone.

Supporting this possibility, Skowron et al.[80] found no significant differences in the AUC, C_{max} or C_{min} of any of the 3 antiretrovirals when nelfinavir 750mg 3 times daily was given to 25 patients in combination with stavudine 30 to 40mg twice daily and nevirapine 200mg once daily for 14 days, followed by 200mg twice daily. In this study, the nevirapine was added on day 8 of the nelfinavir/stavudine combination. Therefore, nelfinavir concentrations on day 7 should have been at steady state. Furthermore, by the end of week 9, 16 of 19 patients had viral loads <400 copies/ml; this level of suppression was maintained in 8 of 9

patients at week 21. The combination of nelfinavir and nevirapine merits further evaluation, but it appears that dosage adjustments may not be necessary for either drug.

Nelfinavir has also been evaluated in combination with delaviridine.[77] A group of 24 healthy volunteers received nelfinavir 750mg 3 times daily with delaviridine 400mg 3 times daily. This combination resulted in an increase in the $AUC_{0\text{-}8h}$ of nelfinavir from 26 ± 11 to 50 ± 11 mg/L · h, with a doubling of the elimination half-life from 3.1 ± 0.6 to 6.3 ± 1.2 hours ($p < 0.001$ for both comparisons). The $AUC_{0\text{-}8h}$ of delaviridine decreased from 210 ± 112 to 122 ± 24 μmol/L · h ($p < 0.1$). 4 participants were forced to leave the study because of neutropenia, which resolved upon discontinuation of both drugs. Consequently, this combination may best be avoided until more data become available. However, if the combination of nelfinavir and delaviridine is used, patients should be closely monitored for neutropenia.

Fiske et al.[78] studied the pharmacokinetics of nelfinavir in combination with efavirenz in healthy men. Participants received nelfinavir 750mg 3 times daily in combination with efavirenz 600mg once daily. The 8-hour AUC of nelfinavir was increased from 25.8 ± 10 to 30.3 ± 10.3 mg/L · h, a 17% increase, and C_{max} increased from 4.30 ± 1.43 to 5.16 ± 1.63 mg/L ($p < 0.05$ for both). As a result, the AUC of AG-1042, a metabolite of nelfinavir with activity similar to that of the parent compound, decreased from 7.83 ± 3.64 to 5.19 ± 2.74 mg/L · h ($p < 0.05$). Efavirenz kinetics were not significantly affected by coadministration with nelfinavir (24-hour AUC 248 ± 78 μmol/L · h for monotherapy *vs* 229 ± 101 μmol/L · h for the combination). The authors concluded that no dosage adjustment is necessary for the combination of nelfinavir and efavirenz.

5.2 Other Antimicrobials

Kerr et al.[62] evaluated the interactions between nelfinavir and representative antimicrobials in a small trial involving 12 healthy volunteers. When ketoconazole 400mg once daily was given with nelfinavir 500mg 3 times daily, the AUC of nelfinavir was increased by 35% and the C_{max} was increased by 25%. The manufacturer recommends no dosage adjustments when this combination is used.[16] Conversely, the coadministration of rifampicin 600mg once daily for 7 days and nelfinavir 750mg 3 times daily for 5 to 6 days resulted in an 82% decrease in the AUC of nelfinavir and a 76% decrease in C_{max}. Rifampicin kinetics were not significantly altered. As for the other protease inhibitors, combination with rifampicin should be avoided.

The coadministration of rifabutin 300mg once daily for 8 days with nelfinavir 750mg 3 times daily for 7 to 8 days resulted in a 32% decrease in the AUC of nelfinavir and a 25% reduction in C_{max}.[16] The AUC of rifabutin was increased by 207%, with a 146% increase in C_{max}. The manufacturer recommends a decrease in the rifabutin dosage by 50% when given with nelfinavir. No dosage adjustment is specified, but some experts recommend increasing the dosage to 1000mg 3 times daily.[20]

5.3 Other Drugs

In addition to the antimicrobials discussed in section 5.2, Kerr et al.[62] also evaluated the interactions between nelfinavir and several other drugs. The coadministration of a single dose of terfenadine 60mg with nelfinavir 750mg 3 times daily for 7 days resulted in an increase in the C_{max} of terfenadine from <5 μg/L to 5 to 15 μg/L. Terfenadine is contraindicated with nelfinavir.[16]

Ethinylestradiol 35μg daily for 15 days with nelfinavir 750mg 3 times daily for 7 days resulted in a 47% decrease in AUC and a 28% decrease in C_{max} of ethinylestradiol. This reduction in estrogen concentration may be due to induction of estrogen glucuronidation by nelfinavir. Concomitant use of norethindrone 0.4mg daily for 15 days and nelfinavir 750mg 3 times daily for 7 days in 12 healthy women resulted in an 18% reduction in the AUC of norethindrone, with no change in C_{max}.[16] The clinical significance of these changes is un-

known, but alternative methods of contraception should be considered in women taking nelfinavir.

Because of a strong potential for serious interactions, nelfinavir is also contraindicated with astemizole, midazolam, triazolam and cisapride. Interaction with anticonvulsants that have enzyme-inducing capabilities, such as phenobarbital, phenytoin and carbamazepine, is also likely and may require an increase in the daily dosage of nelfinavir.[16] Table VI lists other interactions that have been documented for nelfinavir.

6. Dual Therapy with Protease Inhibitors

Due to the possibility of favourable pharmacokinetic interactions, combinations of protease inhibitors, one of which may augment the concentrations of the other, are being investigated as a therapeutic alternative in the management of HIV. In particular, combinations with saquinavir are being investigated because of the generally poor bioavailability of this protease inhibitor. The combination of ritonavir and saquinavir is now widely used and has been suggested as an alternative component of a multidrug antiretroviral regimen.[82,83]

6.1 Combinations Including Saquinavir

Several researchers have demonstrated that saquinavir concentrations are dramatically increased when saquinavir-HGC is coadministered with ritonavir. Hsu et al.[42] studied several single-dose and multiple-dose combinations of saquinavir-HGC and ritonavir in healthy volunteers and found that saquinavir plasma concentrations were significantly increased when coadministered with ritonavir, with 50- to 132-fold increases in the AUC of saquinavir and ≥23-fold increases in C_{max}. This dramatic change probably reflects a decrease in the first-pass metabolism of saquinavir as well as decreased systemic clearance. The kinetics of ritonavir were not significantly affected by the coadministration of saquinavir, a result confirmed in another study of HIV-positive patients.[43]

The manufacturers have noted that the combination of ritonavir and saquinavir-SGC, each given at a dosage of 400mg twice daily, resulted in a 121% increase in the AUC of saquinavir and a 64% increase in its C_{max}.[15] Ritonavir concentrations were unchanged. The impact on the hard-gelatin formulation, also at 400mg twice daily, was much more significant, with a 1587% increase in AUC and a 1277% increase in C_{max}.[15] Thus, the combination of ritonavir and saquinavir, particularly the hard-gelatin formulation, appears to have a favourable pharmacokinetic interaction, and several clinical studies have demonstrated the therapeutic benefits of this regimen.

McCrea et al.[35] studied the kinetics of indinavir 800mg 3 times daily with saquinavir-HGC 600mg or saquinavir-SGC 800mg or 1200mg given as single doses. Indinavir increased the mean AUC and C_{max} of saquinavir by 5- to 8-fold. Despite the pharmacokinetic benefits seen with this combination, one *in vitro* study noted antagonism between saquinavir and indinavir at higher inhibitory concentrations.[84] This combination should probably be avoided until further clinical data become available.

Kravcik et al.[37] studied the interaction between single doses of nelfinavir 750mg or saquinavir-SGC 1200mg given after 4 days of administration of the other agent (saquinavir-SGC 1200mg 3 times daily or nelfinavir 750mg 3 times daily). Nelfinavir increased saquinavir exposure 5-fold (saquinavir AUC 2.9 mg/L · h alone *vs* 14.6 mg/L · h in combination). Saquinavir-SGC had minimal effects on the pharmacokinetics of nelfinavir (nelfinavir AUC 31.0 mg/L · h alone *vs* 36.3 mg/L · h in combination). The authors plan further evaluation of nelfinavir in combination with a lower dosage of saquinavir-SGC (800mg 3 times daily).

Similar 5-fold increases in the AUC and C_{max} of saquinavir were seen with the hard-gel formulation when nelfinavir 750mg 3 times daily was added to saquinavir-HGC 600mg 3 times daily.[38] Even greater changes were seen in a study reported by Gallicano et al.[39] using the same dosages of saquinavir-HGC and nelfinavir. Preliminary data from four HIV-positive patients indicated a nearly 13-fold increase in the AUC of saquinavir and a 10-fold increase in C_{max}. The magnitude of this

interaction appears to have some degree of variability. No recommendations are available at this time regarding combined use of these 2 drugs, but several clinical trials are ongoing.

6.2 Combinations Including Ritonavir

The effect of ritonavir on indinavir kinetics was evaluated in 39 healthy participants by Hsu et al.[58] Several dosage regimens were compared in an attempt to find one which allowed twice-daily administration of indinavir. Across all of the regimens, ritonavir increased the AUC of indinavir by up to 475% and C_{max} by up to 110% compared with conventional thrice daily indinavir. Indinavir had no significant effect on ritonavir parameters. The authors concluded that a combination of indinavir 400mg twice daily with ritonavir 400mg twice daily would result in indinavir exposures similar to that achieved with indinavir 800mg 3 times daily alone. They also suggested that the combination resulted in less interindividual variability in indinavir concentrations and fewer food restrictions. A follow-up study also reported that, when given together, indinavir and ritonavir may be taken with or without food.[85] This combination deserves further investigation, especially to address concerns regarding cross-resistance between the 2 agents.

Ritonavir 500mg 3 times daily for 3 doses and nelfinavir 750mg as a single dose resulted in a 152% increase in the AUC of nelfinavir and a 44% increase in C_{max}.[16] However, nelfinavir 750mg 3 times daily for 5 doses had little effect on the pharmacokinetics of a single dose of ritonavir.

6.3 Combinations Including Indinavir

Administration of indinavir 800mg 3 times daily for 7 days with nelfinavir 750mg given as a single dose to 6 healthy individuals resulted in an 83% increase in the AUC of nelfinavir and a 31% increase in C_{max}.[16,62] Conversely, when indinavir was given as a single dose and nelfinavir was given 3 times daily for 7 days, there was a 51% increase in the AUC of indinavir with no significant change in C_{max}.

Havlir et al.[86] reported that the combination of indinavir 1000mg twice daily and nelfinavir 750mg twice daily resulted in AUC, C_{max} and C_{min} values for both drugs which were very similar to those achieved with the individual drugs given alone in their usual dosages administered every 8 hours. The C_{min} of nelfinavir was slightly decreased with the combination, from 1.5 to 0.7 mg/L. The combination was also effective in reducing HIV RNA to <500 copies/ml in 7 of 10 patients from a baseline of ≥30 000 copies/ml. The authors conducted a further evaluation using a 1000mg twice daily dosage of nelfinavir.[75] Ten of 13 patients maintained an undectable viral load at this dosage after a median of 44 weeks of therapy. Compared with conventional nelfinavir monotherapy (750mg 3 times daily), nelfinavir 1000mg twice daily given with indinavir resulted in nearly identical AUC values; peaks were slightly higher and troughs were slightly lower with this regimen. Further dosage optimisation studies are ongoing.

6.4 Investigational Protease Inhibitors

The current protease inhibitors have also been shown to increase concentrations of some of the investigational protease inhibitors. A single 800mg dose of indinavir increased the C_{max} and 8-hour AUC of amprenavir (141W94, VX-478) by 31 and 64%, respectively.[87] Ritonavir also inhibited amprenavir metabolism, increasing the AUC by 8-fold in rats.[88] Other amprenavir interactions have recently been reported.[89] Exposure to several drugs is increased in the presence of amprenavir; examples include zidovudine (31% increase in AUC) and ketoconazole (44% increase in AUC). Conversely, amprenavir exposure was also altered by coadministration with other antimicrobials. The AUC of amprenavir increased when given with ketoconazole (32%) and clarithromycin (18%). Decreases in the AUC of amprenavir were seen with efavirenz (36%), rifampicin (81%) and rifabutin (14%). The authors recommended avoiding the combination of amprenavir and rifampicin, while the other interactions could be compensated for by dosage adjustments as necessary.

Table VII. Summary of interactions between drugs commonly used in treatment of HIV infection

Object drug	Saquinavir	Ritonavir	Indinavir	Nelfinavir
Zidovudine	NDA	↓O, NDA	NDA	NDA
Didanosine	SD	↓O, NDA	SD	SD
Zalcitabine	NDA	NDA	NDA	NDA
Stavudine	NDA	NDA	NDA	NDA
Lamivudine	NDA	NDA	NDA	NDA
Nevirapine	↓PI, !	NDA	↓PI, ?IDPI	?NDA
Delaviridine	↑PI, ✓	↑PI, ✓	↑PI, ?DDPI	↑PI, ↓O, ?!
Efavirenz	↓PI, !	↑PI, ?DDPI	↓PI, IDPI	NDA
Saquinavir		↑O, ✓	↑O, ✓	↑O, ✓
Ritonavir	↑PI, ✓		↑PI, ✓	↑PI, ✓
Indinavir	↑PI, ✓	↑O, ✓		↑PI, ↑O, ✓
Nelfinavir	↑PI, ✓	↑O, ✓	↑PI, ↑O, ✓	
Trimethoprim	NDA	↑O, NDA	NDA	NDA
Sulfamethoxazole	NDA	↓O, NDA	NDA	NDA
Fluconazole	NDA	↑PI, NDA	↓PI, NDA	NDA
Ketoconazole/itraconazole	↑PI, ✓	↑O, ?DDO	↑PI, DDPI	↑PI, NDA
Clarithromycin	↑PI, ↑O, NDA	↑PI, ↑O, NDA[a]	↑PI, ↑O, NDA	NDA
Azithromycin	NDA	NDA	NDA	NDA
Rifabutin	↓PI, !	↑O, !	↓PI, ↑O, DDO, ?IDPI	↓PI, ↑O, DDO, ?IDPI
Rifampicin (rifampin)	↓PI, !	↓PI, !	↓PI, !	↓PI, !

a Decrease dosage of clarithromycin when creatinine clearance <60 ml/min (<3.6 L/h).

DDO = decrease dosage of object drug; **DDPI** = decrease dosage of protease inhibitor; **IDPI** = increase dosage of protease inhibitor; **NDA** = no dosage adjustment needed; **SD** = separate doses to maximise absorption of protease inhibitor; **!** = potentially unfavourable combination; ✓ = potentially favourable combination; ↓**O** = decreases concentrations of object drug; ↑**O** = increases concentrations of object drug; ↓**PI** = decreases concentrations of protease inhibitor; ↑**PI** = increases concentrations of protease inhibitor; **?** = possibly.

Another study evaluated the combination of amprenavir 1200mg twice daily with clarithromycin 500mg twice daily for 7 doses in 14 healthy men.[90] This combination resulted in an 18% increase in the AUC of amprenavir with a 15% increase in C_{max}. Clarithromycin concentrations were not significantly altered, but the AUC and C_{max} of the active 14-hydroxy metabolite were decreased by 35% and 32%, respectively. The authors concluded that these changes were not clinically significant.

Ritonavir significantly increased exposure to the highly potent protease inhibitor ABT-378, which is rapidly cleared from the blood when given alone.[91] During coadministration in rats, the AUC of ABT-378 was increased by 13-fold, with a nearly 7-fold increase in C_{max}. Plasma concentrations remained above 1 mg/L for 9 to 12 hours, compared with a rapid decline after ABT-378 alone. These and other protease inhibitor combinations are being further investigated.

7. Conclusions

It is important to realise that the frequent lack of specific data regarding drug interactions with protease inhibitors does not imply a lack of interaction. Physicians and pharmacists should take the time to review a patient's concomitant medications, considering the route of elimination for each drug. Clinicians must remind patients to openly disclose any and all medications they are receiving, including over-the-counter medications.

Van Cleef et al.[92] conducted a retrospective review of the charts of 114 patients who were receiving either indinavir, ritonavir or saquinavir. They looked for potential drug interactions with protease inhibitor in these patients, including contraindicated drugs, drugs requiring a dosage adjustment and drugs that were likely to interact but had not

been formally studied. Overall, 31% of indinavir recipients, 77% of ritonavir recipients and 42% of saquinavir recipients were found to have one or more potential interactions. The median number of interactions per patient was 0.5 for indinavir, 3 for ritonavir and 1 for saquinavir. The most common interacting drug was rifabutin. The probability of finding an interaction increased as the CD4+ cell count decreased. This report further demonstrates the need for alert prospective monitoring of patients who are receiving protease inhibitors.

A similar chart review was conducted for 165 patients receiving protease inhibitors in HIV speciality clinics at 2 university medical centres.[93] A total of 111 drug interactions were found in 82 patients, with 52% of these interactions classified as potentially serious to life-threatening. Interactions with clarithromycin, rifabutin and tricyclic antidepressants were most common. Especially troubling is that, of 26 patients who had a life-threatening interaction at the time that the protease inhibitor was first prescribed, only 14 had an appropriate change in therapy at that time, with 3 more changes by the time of follow-up. The clinical outcomes of these interactions were not described.

A summary of interactions between the protease inhibitors and other medications commonly used in patients with HIV is provided in table VII. Few pharmacokinetic interactions have been documented, and the studies that are currently available are often rather limited. These studies were often conducted in healthy volunteers and may not reflect the complex pharmacokinetic and pharmacodynamic milieu that may exist in AIDS patients. Also, previous studies have examined the interaction between 2 drugs only. Patients with HIV are almost always receiving multiple medications, which add further layers of complexity when trying to predict and adjust for potential interactions. Much more data – both in the form of further pharmacokinetic trials and case reports of actual clinical experience – are needed to help clinicians make sound judgments regarding drug therapy in this patient population.

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