Rifampin and Rifabutin Drug Interactions
An Update

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Rifampin is a potent inducer of cytochrome P-450 oxidative enzymes. A few examples of well-documented clinically significant interactions include interactions with warfarin, oral contraceptives, cyclosporine, glucocorticoids, ketoconazole or itraconazole, theophylline, quinidine sulfate, digoxin or digoxin, verapamil hydrochloride, human immunodeficiency virus–related protease inhibitors, zidovudine, delavirdine mesylate, nifedipine, and midazolam. Recent reports have demonstrated clinically relevant interactions with numerous other drugs, such as buspirone hydrochloride, zolpidem tartrate, simvastatin, propafenone hydrochloride, tacrolimus, ondansetron hydrochloride, and opiates. Rifabutin reduces serum concentrations of antiretroviral agents, but less so than rifampin. To avoid a reduced therapeutic response, therapeutic failure, or toxic reactions when rifampin is added to or discontinued from medication regimens, clinicians need to be cognizant of these interactions. Enhanced knowledge of known interactions will continue to develop, including research on the induction of specific cytochrome P-450 isoenzymes and on the importance of the P-glycoprotein transport system. New rifampin and rifabutin interactions will be discovered with further investigations.

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Rifampin is a potent inducer of the hepatic and intestinal cytochrome P-450 (CYP) enzyme system and the P-glycoprotein (P-gp) transport system, which results in numerous clinically significant drug interactions.1-4 Schuetz et al5 found that rifampin intracellular concentrations and, therefore, the extent by which rifampin was able to induce CYP3A was strongly correlated with P-gp levels.

P-glycoprotein is a transmembrane protein that is a member of the adenosine triphosphate–binding cassette family, a group of molecules that control concentrations of endogenous and exogenous substances across cell membranes by functioning as cellular efflux pumps.6 The gene that encodes this protein is the multidrug resistance gene (MDR1). MDR1 expression manifested as P-gp is widely distributed throughout the body, and is found at many sites that are key to drug bioavailability and distribution, such as the intestinal lumen, the liver, the kidney, and the blood-brain barrier.6 Interpatient and intrapatient variability in the expression of the gene product of MDR1, P-gp, has a significant effect on the bioavailability and site distribution of many drugs. Hoffmeyer et al7 discovered that patients with specific polymorphisms of MDR1 had significantly different levels of P-gp activity in the duodenum. Moreover, the ability of rifampin to induce P-gp and thereby lower digoxin levels (described later) was greatly governed by these polymorphisms of the MDR1 gene. This may partially explain the wide interpatient variability in CYP3A induction by rifampin. The subject of P-gp as a mechanism for drug interactions has been recently reviewed.6

As the number of new agents marketed increases, the potential for clinically significant drug interactions heightens. Since the last review of this topic in the ARCHIVES,4 several new interactions involving rifampin have been reported. In addition, because of the importance of rifabutin in treating tuberculosis in patients with the acquired immunodeficiency syndrome (AIDS),8 interactions with this agent are included.

A summary of previously reviewed rifampin interactions1-4 that are well documented and of major clinical significance

Author affiliations are listed at the end of this article.
is given in Table 1, while rifampin interactions that may be clinically relevant but less well documented are listed in Table 2.

**PSYCHOTROPIC AGENTS**

**Sertraline Hydrochloride**

Sertraline is a commonly used selective serotonin reuptake inhibitor that is thought to undergo extensive first-pass metabolism by the CYP3A4 isoenzyme. Markowitz and DeVane described a 34-year-old man receiving rifampin, 600 mg/d, as part of treatment for a staphylococcal skin infection, concurrently with sertraline, 200 mg/d. After 7 days of rifampin therapy, the patient reported feeling anxious and excessively worried. Subsequent blood samples revealed that sertraline concentrations increased 3-fold (from 18 to 55 ng/mL) 1 week after discontinuation of rifampin, and the active metabolite of sertraline was increased greater than 2-fold. The treatment of the patient was later changed to another agent after symptoms were still present 1 week after discontinuing rifampin. These researchers suggest the potential for therapeutic failure or withdrawal symptoms if inducers of CYP3A4 are used during sertraline therapy.

**Nortriptyline Hydrochloride**

Two prior case reports have documented a decrease in nortriptyline levels when used concomitantly with rifampin. Although nortriptyline is predominantly metabolized by CYP2D6, Venkatakrishnan et al found that CYP3A4 contributes to the hydroxylation of nortriptyline. Cytochrome P-450 3A4 is characterized as having a low affinity and a low capacity for nortriptyline metabolism. However, the authors suggest that the
concentration by CYP3A4 increases as nortriptyline concentrations increase because of impaired CYP2D6 function (eg, poor metabolizers [PMs] or patients treated with CYP2D6 inhibitors) or concomitant administration with an inducer of the CYP3A4 isoenzyme.

**Buspirone Hydrochloride**

Buspirone, a common anxiolytic agent, undergoes extensive first-pass metabolism via the CYP3A4 isoenzyme. Lamberg et al conducted a randomized, placebo-controlled, crossover study of the effects of rifampin on buspirone pharmacokinetics. Ten healthy volunteers received rifampin, 600 mg/d, for 5 days and buspirone, 30 mg, on day 6. During the rifampin phase, the area under the concentration-time curve (AUC) of buspirone decreased by 89.6%. The maximum concentration (Cmax) and half-life decreased by 83.7% and 52.8%, respectively. No subjects in the rifampin arm had measurable buspirone concentrations at 6, 8, or 10 hours after taking the therapeutic agent. These results indicate an increase in presystemic and systemic clearance of buspirone.

The same group of investigators studied the effects of rifampin on the active piperazine metabolite of buspirone. Using samples from their previous study, plasma concentrations of the piperazine metabolite were not significantly affected by rifampin. Based on the results of these studies, concomitant administration of buspirone with rifampin should be avoided because of the potential for therapeutic failure.

**Clozapine**

Joos et al described a 33-year-old schizophrenic patient who was stable while receiving clozapine, 400 mg/d, for 2 years. After 3½ weeks of treatment with rifampin, 600 mg/d, as part of treatment for pulmonary tuberculosis, the patient began experiencing increased restlessness and paranoid thoughts. Subsequent clozapine serum concentrations were dramatically reduced by 600%. On discontinuation of rifampin, clozapine serum concentrations increased to the therapeutic level within 3 days.

**Zolpidem Tartrate**

Zolpidem, a short-acting hypnotic agent, is predominantly metabolized by CYP3A4. In a randomized, balanced, placebo-controlled, crossover study by Villikka et al, 8 volunteers were used to examine the possible interaction between rifampin and zolpidem. Rifampin, 600 mg/d, was administered for 5 days, with zolpidem, 20 mg, given on day 6. Rifampin reduced the AUC and the Cmax of zolpidem by 73% and 58%, respectively, and the half-life was decreased from 2.5 to 1.6 hours. The pharmacodynamic effects (drowsiness) of zolpidem were also reduced and shortened during the rifampin phase. These findings suggest that this interaction is likely to be clinically relevant.

**Midazolam**

Reports of the induction of midazolam metabolism by rifampin have already been reviewed, and the results of a new study are consistent with the previous findings. When midazolam, 15 mg, was administered orally on days 1 and 4 after a 5-day course of rifampin, 600 mg/d, the AUC of midazolam was decreased by 97.7% and 86.8%, respectively, and the Cmax was decreased by 94.6% and 79.8%, respectively. Concentrations of the active metabolite were also reduced by 20% to 40% of the control during the rifampin phase. The researchers also concluded that if switching from inhibition (in this study, with itraconazole) to induction of CYP3A4 enzymes, a 400-fold change in the pharmacokinetics of oral midazolam may be observed. Using midazolam as a substrate during rifampin induction, Gorski et al found that intestinal CYP3A4 may be preferentially altered by rifampin.

**CARDIOVASCULAR DRUGS**

**Simvastatin**

Simvastatin, a widely used agent for hypercholesterolemia, and its active metabolite, simvastatin acid, are metabolized to inactive metabolites by CYP3A4. Kyrklund et al enrolled 10 healthy patients in a randomized, placebo-controlled, crossover study to examine the effects of rifampin on the pharmacokinetics of simvastatin. After a 5-day course of rifampin, 600 mg/d, simvastatin, 40 mg, was given on day 6. Rifampin reduced the AUC of simvastatin and simvastatin acid by 87% and 93%, respectively. The Cmax of both agents was decreased by 90% by rifampin. Based on the results of this study, it is likely that concomitant use of rifampin with simvastatin may significantly reduce the cholesterol-lowering effect of simvastatin. The researchers postulate that rifampin may interact with lovastatin and atorvastatin calcium because of their CYP3A4 activity, but further investigation is warranted. According to the manufacturer of fluvastatin sodium, rifampin reduces the AUC and Cmax of the agent by 51% and 59%, respectively.

**Digoxin**

There have been previous reports of a digoxin-rifampin interaction that involved patients with renal failure or a moderate decline in renal function. In patients with normal renal function, digoxin is eliminated from the body almost entirely as unchanged drug. Nonrenal clearance mechanisms of this interaction have not been clearly defined.

Greiner et al examined the role of intestinal P-gp in the interaction of digoxin and rifampin in 8 healthy men given a 2-week course of rifampin, 600 mg/d, and then digoxin, 1 mg, either orally or intravenously (IV). After rifampin administration, the AUC and Cmax of oral digoxin decreased by 43% and 58%, respectively. The oral bioavailability of digoxin decreased by 30.1% during rifampin therapy. Rifampin also increased intestinal P-gp levels 3.5-fold. These results suggest that P-gp regulates digoxin disposition, which can lead to altered drug concentrations. Patients should be closely monitored for arrhythmia control and signs and symptoms of heart failure during concurrent rifampin administration.

**Propafenone Hydrochloride**

While one previous case report suggested a clinically important interaction between rifampin and propafenone, 2 recent controlled tri-
reverse transcriptase inhibitor. Demonstrate that rifampin is the most inductions potencies. In vitro data cin derivatives have different CYP3A... 3 commercially available rifamycins... administration. Dilger et al studied the consequences of rifampin treatment on propafenone disposition in CYP2D6 extensive metabolizer (EM) and PM phenotypes. Twelve volunteers (6 EMs and 6 PMs) ingested rifampin, 600 mg/d, for 9 days, followed by a single IV infusion of unlabeled propafenone, 140 mg, and a single dose of labeled oral propafenone, 300 mg. There were no significant differences in the pharmacokinetics of IV propafenone before and after rifampin administration; however, the bioavailability of oral propafenone decreased by 67% and 41% in the EM and PM groups, respectively. The propafenone metabolism mediated by CYP2D6 was not enhanced; however, clearance via CYP3A4/1A2 and glucuronidation and sulfation were greatly increased by rifampin. These results indicate a 67% and 71% reduction in active propafenone concentrations in the EM and PM groups, respectively. Such reductions in propafenone concentrations may cause a loss of arrhythmia control.

The same group of researchers found similar data when evaluating the effects of rifampin on the pharmacokinetics and pharmacodynamics of propafenone in elderly persons. Bioavailability decreased by 87% and 52% in the EMs and PMs, respectively, during rifampin induction. They also found that during enzyme induction, maximum QRS prolongation decreased significantly after oral propafenone therapy. Induction of gut wall metabolism may play a major role because gastrointestinal extraction of propafenone increased almost 4-fold during rifampin administration.

**ANTIRETROVIRAL AGENTS**

The 3 commercially available rifamycin derivatives have different CYP3A induction potencies. In vitro data demonstrate that rifampin is the most potent, followed by rifampentine and rifabutin. Initial clinical evidence indicated that rifabutin has less propensity than rifampin to cause an important induction of drug metabolism, and these reports have been reviewed. Consequently, the drug interactions between rifabutin and protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors, drugs with narrow therapeutic ranges, are easier to manage than those with rifampin. The PIs and the nonnucleoside reverse transcriptase inhibitors not only are CYP3A substrates but are also inhibitors and inducers of this same isoform, with the net result being either an increase or a decrease of the rifabutin levels, frequently necessitating rifabutin and PI dosage adjustment. The extent and effect of the inhibition of rifabutin metabolism by amphenavir were demonstrated in a recent study by Polk et al. When combined with amphenavir in healthy volunteers, rifabutin given at the standard dose of 300 mg/d was associated with poor tolerability and resulted in leukopenia in 7 of 11 subjects. This abnormally high rate of adverse reactions could have been caused by the nearly 3-fold increase in rifabutin's AUC. For this reason, the rifabutin dose must be decreased and/or the dosing interval increased when coadministered with a PI. Spradling et al found that even after adjusting the rifabutin and antiretroviral agent doses, rifabutin levels were suboptimal among many patients taking more than one PI or PIs combined with efavirenz. However, Narita et al found that after rifabutin and PI doses were adjusted, rifabutin levels were only marginally lower in patients receiving either indinavir or nelfinavir mesylate based on highly active antiretroviral therapy (HAART), a reduction that was not clinically significant. Among the nonnucleoside reverse transcriptase inhibitors, a drug interaction between a nucleoside and rifamycin has only been reported with zidovudine. Rifabutin and rifampin decreased the zidovudine AUC by 32% and 47%, respectively. A dramatic reduction (25%-96%) in the AUC of PIs and nonnucleoside reverse transcriptase inhibitors occurs when rifampin is coadministered because of CYP3A/P-gp induction (Table 3). The most recent Centers for Disease Control and Prevention guidelines state that rifampin should only be administered in individuals undergoing HAART in 3 situations: (1) if the patient is taking efavirenz, (2) if the patient is taking ritonavir, or (3) if the patient is taking ritonavir plus saquinavir mesylate. However, more recent evidence suggests that these guidelines may require modification. While the ritonavir-saquinavir combination dosed at 400 mg each twice daily given with rifampin resulted in adequate levels of saquinavir, newer methods of dosing this combination (ritonavir, 100 mg/d, and saquinavir, 1600 mg/d; or ritonavir, 100 mg, and saquinavir, 1000 mg, both twice daily) are being used, which may result in a different magnitude of interaction with rifampin. Indeed, De Gast et al found that rifampin administered with 100 mg of ritonavir and 800 mg of indinavir, twice daily, resulted in a greatly reduced indinavir AUC. In addition, the most recent Centers for Disease Control and Prevention guidelines state that no dosage adjustment is necessary when efavirenz is given with rifampin. However, efavirenz levels were significantly lower when given with rifampin at the usual efavirenz dose of 600 mg, but were increased to the normal range when the efavirenz dose was increased to 800 mg, a strategy that proved successful in treating patients coinfected with the human immunodeficiency virus (HIV) and tuberculosis.

**Table 3. Percentage by Which Rifampin and Rifabutin Lower the AUC of PIs and NNRTIs**

<table>
<thead>
<tr>
<th>PI/Mono</th>
<th>Indinavir</th>
<th>Nelfinavir</th>
<th>Saquinavir</th>
<th>Amprenavir</th>
<th>Ritonavir</th>
<th>Ritonavir and Lopinavir</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>Delavirdine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>89</td>
<td>82</td>
<td>84</td>
<td>82</td>
<td>35</td>
<td>75</td>
<td>25</td>
<td>37</td>
<td>96</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>32</td>
<td>32</td>
<td>40</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>80</td>
</tr>
</tbody>
</table>

*Data adapted from previously published guidelines. AUC indicates area under the concentration-time curve; PI, protease inhibitor; and NNRTI, nonnucleoside reverse transcriptase inhibitor.*
ANTIBIOTICS COMMONLY USED AS TREATMENT OR PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS IN PATIENTS WITH HIV OR AIDS

Dapsone

In 7 HIV-positive patients receiving 100 mg of dapsone twice weekly for Pneumocystis carinii pneumonia prophylaxis, rifampin increased dapsone clearance by 69% to 122% (depending on which pharmacokinetic models were used), a magnitude that would most likely be clinically significant.39 The investigators believed that the increased clearance of dapsone was largely because of a significant first-pass effect. Moreover, they observed that monoacetyldapsone was undetectable in plasma.

Azithromycin

Two different dosing regimens of azithromycin and rifabutin were evaluated in HIV-positive and HIV-negative volunteers.35 Fifty study subjects received either 1200 mg of azithromycin plus 600 mg of rifabutin daily or 600 mg of azithromycin plus 300 mg of rifabutin daily. While no significant drug interactions were found between the 2 drugs, the rate of neutropenia was quite high at 66%, found between the 2 drugs, the rate of neutropenia was quite high at 66%, consistently and the extent of drug interactions is difficult to predict based on pharmacokinetic studies only examining 2 drugs.

Fluconazole and/or Clarithromycin

Researchers38 found, in 10 HIV-infected patients, that when rifabutin, 300 mg/d, was administered with either clarithromycin, 500 mg/d, or fluconazole, 200 mg/d, the rifabutin AUC was increased by 76%. When clarithromycin and fluconazole were administered simultaneously with rifabutin at the previously mentioned doses, the metabolic inhibitory effect was additive, with a 152% increase in the rifabutin AUC. These authors caution that in real clinical situations, many drugs are given concomitantly and the extent of drug interactions is difficult to predict based on pharmacokinetic studies only examining 2 drugs.

Itraconazole

Itraconazole and rifampin are commonly used together in HIV-infected patients, and literature reviewing an interaction between these 2 agents has been reviewed. A new study has emerged to further substantiate evidence of an interaction. Jarutenasiriruk and Sririwitiyajan39 studied 6 healthy patients and 3 patients with AIDS to evaluate the effect of rifampin on the pharmacokinetics of itraconazole. All subjects received rifampin, 600 mg, for 2 weeks followed by a single 200-mg dose of oral itraconazole. On concomitant administration, itraconazole serum concentrations were undetectable in all but one healthy volunteer, whose levels were quite low. Based on these data, the concurrent use of rifampin and itraconazole should be avoided because of the risk of therapeutic failure.

IMMUNOSUPPRESSANTS

Two case reports suggestive of clinically relevant interactions of rifampin with tacrolimus (a substrate for CYP3A4 and P-gp) have been previously summarized.4 Hebert et al40 evaluated the pharmacokinetics of tacrolimus in 6 healthy volunteers. Subjects were treated with either a single oral dose (0.1 mg/kg) or an IV dose (0.025 mg/kg) of tacrolimus, before and after 18 days of rifampin, 600 mg/d. With coadministration of rifampin, the clearance of tacrolimus increased nearly 50%. Oral bioavailability also decreased 30% during concomitant rifampin therapy. Chenhsu et al41 described a 61-year-old kidney transplant recipient in whom tacrolimus therapy was maintained. Rifampin was prescribed as part of tuberculosis therapy, and subsequent tacrolimus serum concentrations decreased from 5 to 8 to 1.5 ng/mL. A 10-fold increase in the tacrolimus dose was needed to maintain pre-rifampin serum concentrations. These results are consistent with previous reports and warrant the need for careful monitoring of tacrolimus trough concentrations when rifampin is added to either IV or oral tacrolimus therapy.

Although the highly significant rifampin-cyclosporine interaction has been previously reviewed,2 the effects of rifampin on cyclosporine disposition continue to be evaluated.42 Kim et al43 found that doses of cyclosporine had to be increased 2.5- to 3-fold to maintain satisfactory blood concentrations.

ANTIEMETIC AGENTS

Ondansetron Hydrochloride

A randomized crossover study44 in 10 healthy volunteers suggested that rifampin may cause a clinically significant interaction with ondansetron, a potent antiemetic agent. Ondansetron, 8 mg IV and orally, was administered before and after rifampin, 600 mg/d, for 5 days. The AUC of oral and IV ondansetron was reduced by 65% and 48%, respectively, after rifampin administration. Rifampin de-
increased the Cmax of oral ondansetron by 50% and increased IV ondansetron clearance by 83%. Based on these results, concomitant use of rifampin with ondansetron may result in a reduced antiemetic effect.

**Dolasetron Mesylate**

Dimmitt et al45 studied the pharmacokinetic disposition of dolasetron, 200 mg, and its active metabolite, hydrodolasetron, in 18 healthy men before and after the administration of rifampin, 600 mg/d, for 1 week. Dolasetron plasma concentrations were below the detectable limit throughout all phases of the study, but during concurrent rifampin treatment, the clearance of hydrodolasetron increased by 39%. Although the researchers suggested that no dosage adjustment is necessary during concomitant rifampin administration, studies in patients are needed to verify that no dosage increases will be required.

**OPIATES**

Fromm et al46 discussed a loss of the analgesic effect of morphine sulfate in 10 healthy volunteers because of the coadministration of rifampin. Morphine, 10 mg orally, was administered before and near the end of 13 days of treatment with rifampin, 600 mg/d. Rifampin therapy resulted in a significant reduction in the AUC (28%) and the Cmax (41%) of morphine. Using the cold pressor test to determine pain sensation, the administration of rifampin resulted in no analgesic effect of morphine. Because a major drug interaction was observed between morphine and rifampin, the assessment of pain should be performed more frequently during rifampin therapy to determine a loss of the analgesic effect. The need for increased morphine doses should be anticipated.

Caraco et al47 evaluated the effects of rifampin on codeine phosphate metabolism mediated by CYP3A4. Kivisto et al48 conducted 2 randomized, placebo-controlled, crossover studies to evaluate the effects of rifampin on the pharmacokinetics of tamoxifen and toremifene in 10 and 9 healthy volunteers, respectively. Volunteers took either 600 mg of rifampin or placebo orally once a day for 5 days; on the sixth day, 80 mg of tamoxifen or 120 mg of toremifene was administered. Rifampin significantly decreased the plasma concentrations of tamoxifen and toremifene with the AUC reduced by 86% and 87%, respectively. The Cmax and half-life of both agents were also decreased by 55% and 44%, respectively, with rifampin treatment. The pharmacokinetic variables of the active metabolites for each agent changed significantly vs placebo during rifampin therapy. Although the clinical significance of these interactions has yet to be determined, the dosage of tamoxifen and toremifene may need significant adjustment during concomitant use of rifampin.

The highly important rifampin–oral contraceptive interaction (induction of estrogen and progesterone metabolism) has already been reviewed, and a new study50 evaluating rifampin and rifabutin effects on oral contraception has been conducted. Although the effects of rifampin were significantly greater than those of rifabutin, an alternate form of birth control should be used, along with patient counseling and documentation with either agent.

Nolan et al51 described a 50-year-old man with a history of hypothyroidism who was stable while taking levothyroxine sodium, 0.025 mg/d. Rifampin, 600 mg/d, was added as part of therapy for persistent infection with methicillin sodium–resistant *Staphylococcus aureus*. After 2 weeks of rifampin therapy, the patient's thyrotropin level increased by 202% (9.44 mmol/L) from the most recent pretreatment thyrotropin value (4.67 mmol/L). Thyrotropin levels returned to baseline 9 days after discontinuation of rifampin therapy. The researchers suggested that this interaction may be due to enhanced hepatic clearance of the levothyroxine.

Rifampin decreases the plasma concentrations and effects of repaglinide,21 an oral hypoglycemic agent extensively metabolized by CYP3A4. Repaglinide, 0.5 mg, was administered to 9 healthy volunteers before and after a 5-day course of rifampin, 600 mg/d. Concomitant treatment with rifampin significantly decreased the mean AUC of repaglinide by 57% and the Cmax by 41%. Subsequently, blood glucose concentrations were increased significantly during rifampin administration. These researchers suggested that blood glucose concentrations should be closely monitored and that the repaglinide dosage should be adjusted appropriately during CYP3A4 induction. This same group of investigators studied the effect of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide in 10 healthy subjects. Consistent with initial case reports previously reviewed,3,4 these investigators found that rifampin, 600 mg/d orally for 5
Table 4. Updated Rifampin Drug Interactions*

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin receptor (5-HT₃) antagonists</td>
<td>Monitor clinical response; increase dose if needed; use another agent if needed</td>
</tr>
<tr>
<td>Buspirone hydrochloride</td>
<td>Monitor clinical response; increased dose will likely be needed or use another agent if possible</td>
</tr>
<tr>
<td>3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors</td>
<td>Monitor lipid panel; increased dose will likely be needed for simvastatin; further research needed for other agents in this class</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Monitor for decreased clinical response; increase dose if needed or use another agent if possible</td>
</tr>
<tr>
<td>Opiates (morphine or codeine)</td>
<td>Monitor pain control and clinical response; increased dose may be needed in extensive metabolizers; use another agent if possible; may be associated with ethnic variability</td>
</tr>
<tr>
<td>Propafenone hydrochloride</td>
<td>Monitor clinical response; increased dose may be needed or use another agent if possible</td>
</tr>
<tr>
<td>Tamoxifen citrate or toremifene citrate</td>
<td>Monitor clinical response; increased dose may be needed or use another agent if possible</td>
</tr>
<tr>
<td>Zolpidem tartrate</td>
<td>Monitor clinical response; increased dose may be needed or use another agent if possible</td>
</tr>
</tbody>
</table>

*Carefully adjust dosage when rifampin is initiated and discontinued. The enzyme induction effect is gradually reduced during a 1- to 2-week period or longer when rifampin therapy is discontinued. Based on the small number of reports, further studies are needed for most of these agents.

**Table 4.** Updated Rifampin Drug Interactions

CONCLUSIONS

Rifampin has numerous well-documented clinically significant drug interactions associated with its use. Since the initial discovery of several important rifampin interactions more than 25 years ago, new interactions continue to be found. Updated information on rifampin interactions is summarized in Table 4. As rifabutin use continues to increase in patients with HIV or AIDS, drug interactions with this agent are increasingly being reported. Although rifabutin interactions are generally less dramatic than rifampin interactions, many are clinically relevant. Table 3 offers a comparison of rifabutin and rifampin interactions. Whenever clinicians prescribe therapy with either rifampin or rifabutin, it is prudent to screen for drug interactions. As these agents continue to be used, discovery of new interactions should be anticipated.

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