Update on Rifampin Drug Interactions II

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• Rifampin is a potent inducer of hepatic P450 oxidative enzymes. Clinically important drug interactions have been documented between rifampin and numerous other drugs, such as oral anticoagulants, oral contraceptives, cyclosporine, digitalis, and ketoconazole. New, potentially clinically significant rifampin drug interactions have been reported for haloperidol, several antiarrhythmics, fluconazole, diltiazem, and select benzodiazepines. Further research has been conducted for previously reported drug interactions with rifampin involving such drugs as glucocorticoids, cyclosporine, verapamil, and oral anticoagulants. Proper management of these interactions is essential to avoid therapeutic failures on initiating rifampin therapy and potential toxic reactions after discontinuing rifampin. New rifampin drug interactions will continue to be identified with future investigations.

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Rifampin is a potent inducer of the hepatic cytochrome P450 enzyme system in humans.[1-3] During the 5 years since the last review of this topic in the ARCHIVES, several new drug interactions have been reported, and further information on previously reported interactions has accumulated. A summary of previously reported interactions[4,5] is given in Table 1, and Table 2 summarizes interactions discussed in this review.[6-22]

ANTACIDS

A study was conducted by Gupta et al[6] to discern if antacids affected the serum concentrations of rifampin. Patients with pulmonary tuberculosis were divided into three groups of 15 patients each. Patients received either aluminum hydroxide, a mixture of aluminum hydroxide plus magnesium trisilicate, or no antacid along with their antituberculosis medications (rifampin, 10 to 12 mg/kg; isoniazid, 300 mg; and ethambutol, 20 mg/kg). A statistically greater number of patients receiving aluminum hydroxide had peak serum rifampin concentrations less than 6.5 mg/L, compared with the other groups. It was hypothesized that the subtherapeutic rifampin concentrations were due to delayed gastric emptying attributable to aluminum ions. More studies should be conducted to verify this potential interaction.

HALOPERIDOL

Takeda et al[7] measured serum haloperidol concentrations at steady-state after oral administration as well as the half-life of intravenous (IV) haloperidol in schizophrenic patients with and without tuberculosis. Patients receiving antituberculosis therapy exhibited mean steady-state serum haloperidol concentrations that were lowered by more than half when compared with those of schizophrenic patients taking no antituberculosis medications. Additionally, a shortening of the mean haloperidol half-life was noted for three patients taking haloperidol, isoniazid, and rifampin vs patients without tuberculosis taking haloperidol alone (4.9 vs 10.2 hours, respectively).

NUTRITIONAL STATUS

An examination of the single-dose kinetics of rifampin, isoniazid, or the combination was undertaken by Garg and associates.[23] All patients were slow acetylators and were nonsmokers. With the use of a crossover design, all patients received oral doses of isoniazid (300 mg), rifampin (450 mg), and the combination. Nutritional status had no apparent effect on rifampin kinetics alone or in combination with isoniazid.

These results contrast with those of an earlier pharmacokinetic study in 10 well-nourished volunteers, eight malnourished volunteers, and 10 malnourished patients with tuberculosis (all smokers and occasional drinkers).[24] Statistically significant increases in the mean rifampin apparent oral clearance and decreases in the mean rifampin area under the plasma concentration–time curve (AUC) and in rifampin plasma protein binding were observed for both malnourished groups compared with the well-nourished group.

Most of the studies on malnutrition and drug metabolism have been conducted in developing countries, such as Africa and India.[25] When viewed from the perspective of rifampin therapy in countries where the incidence of malnutrition and tuberculosis is high, significant numbers of patients may be affected.

ANTIARRHYTHMICS

Rice et al[8] studied the effect of rifampin treatment on tocainide pharmacokinetics in eight healthy volunteers.

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Table 1.—Previously Described Rifampin Drug Interactions*

Drug	Comments
Anticoagulants, oral†	Increase anticoagulant dose based on monitoring of prothrombin time
β-Blockers	May need to increase propranolol or metoprolol dose
Chloramphenicol	Monitor serum chloramphenicol concentrations; increase dose if needed
Contraceptives, oral†	Use other forms of birth control; document patient counseling in chart
Cyclosporine†	Monitor serum cyclosporine concentrations; increased dose will likely be needed
Digitoxin†	Monitor serum digitoxin concentrations; monitor for arrhythmia control and signs and symptoms of heart failure; increase dose if needed
Digoxin	Monitor serum digoxin concentrations; monitor for arrhythmia control and signs and symptoms of heart failure; clinically significant interaction most likely in patients with decreased renal function
Glucocorticoids†	Increase glucocorticoid dose twofold to threefold with concomitant rifampin therapy
Ketoconazole†	Avoid this combination if possible; monitor serum ketoconazole concentrations; increase dose if needed; space rifampin and ketoconazole doses by 12 h
Methadone†	Increase methadone dose with concurrent rifampin therapy; control withdrawal symptoms
Phenytoin†	Monitor serum phenytoin concentrations; increase phenytoin dose if needed
Quinidine†	Monitor serum quinidine concentrations; monitor for arrhythmia control; increase dose if needed
Sulfonylureas	Increase sulfonylurea dose based on blood glucose control; monitor blood glucose with discontinuation of rifampin therapy
Theophylline†	Monitor serum theophylline concentrations; increased dose will likely be needed
Verapamil†	Use alternative agent to verapamil if possible, because even very large increase in oral verapamil may not be sufficient; monitor serum verapamil concentrations; monitor patient for clinical response

*See Baciewicz and Self[4] and Baciewicz et al[5] for further information; for each interaction, carefully adjust doses when rifampin is discontinued; enzyme induction effect is gradually reduced over 1 to 2 weeks.
†Major clinical significance is well established.

All subjects received a single oral dose of tocainide hydrochloride, 600 mg at baseline. After a 4-week washout period, each subject ingested 300 mg of oral rifampin every 12 hours for a total of 10 doses. A second dose of tocainide, 600 mg, was then given, with all subjects continuing to take rifampin, 300 mg every 12 hours, for 6 more doses. Rifampin administration led to a significant reduction in the tocainide half-life, from 13.2 to 9.4 hours, and a 34% increase in apparent oral clearance.

Staum[9] reported a case of a 62-year-old white woman hospitalized with cardiac arrhythmias and anxiety who had been taking rifampin, 600 mg daily, for 2 weeks before admission. On day 1 of admission, she was begun on a regimen of oral disopyramide, 100 mg every 8 hours, and continued to receive rifampin. By day 3, the disopyramide serum concentrations were 0.9 mg/L (therapeutic range, 6 to 18 mg/L). On day 5, the dose was tripled and rifampin treatment was discontinued. The disopyramide concentration rose to 8.1 mg/L by day 10. Her dose was then gradually reduced to 250 mg every 8 hours, resulting in a concentration of 7.5 mg/L (day 15). This case is consistent with the earlier study by Aitio et al[10] showing a decrease in the mean disopyramide half-life and AUC by approximately one-half.

Mauro et al[26] observed a 62-year-old white man who was taking rifampin, 600 mg daily, before his admission for ventricular tachycardia that necessitated treatment with lorcainide (200-mg IV bolus, then 100 mg orally every 8 hours). With concurrent rifampin therapy, the patient required 800 to 900 mg of lorcainide daily to maintain therapeutic plasma concentrations and to suppress his arrhythmia.

A recent case report described dramatically lowered plasma concentrations of propafenone with concomitant loss of arrhythmia control associated with rifampin therapy.[11] After rifampin was discontinued, propafenone concentrations returned to values similar to those obtained before rifampin treatment, and arrhythmia control was restored.

ANTI-INFECTIVES

To investigate the use of rifampin and novobiocin as combination therapy against methicillin-resistant *Staphylococcus aureus*, Drusano et al[27] evaluated the interaction potential between these drugs in 10 healthy male volunteers. In this randomized, double-blind, crossover study, novobiocin half-life was shortened from 5.85 to 2.66 hours. Despite this finding, trough serum concentrations of novobiocin alone and in combination with rifampin exceeded the minimum inhibitory concentration for 90% of the methicillin-resistant *S aureus* strains tested. The clinical significance remains to be determined.

The pharmacokinetics of IV ciprofloxacin before and after long-term rifampin treatment were assessed in healthy rabbits by Barriere et al,[28] who observed a rifampin induction effect. Chandler and coworkers[12] studied concomitant rifampin and ciprofloxacin treatment in 12 patients in a nursing home (mean age, 74 years) infected with *S aureus*. No significant differences between ciprofloxacin alone and rifampin plus ciprofloxacin were observed for ciprofloxacin pharmacokinetic factors (including half-life and oral clearance). The combination also resulted in therapeutic serum concentrations of both drugs.

Table 2.—Updated Rifampin Drug Interactions*

Drug	Comments
Antacids[6]	May need to space rifampin and aluminum hydroxide doses apart by several hours; more study needed
Haloperidol[7]	Monitor serum haloperidol concentrations; alter dosing regimen if needed; limited initial study indicates serum concentrations and half-life are reduced by about 50%
Tocainide[8]	Monitor arrhythmia control; increase dose if needed; 1 trial in healthy subjects found nearly 30% decrease in tocainide serum half-life
Disopyramide[9,10]	Monitor arrhythmia control; increase dose if needed; initial study indicates decrease in disopyramide serum half-life of about 50%
Propafenone[11]	Monitor plasma propafenone concentrations; monitor arrhythmia control; increase dose if needed
Ciprofloxacin[12]	No interaction noted in humans to date; more study needed
Dapsone[13,14]	Decrease serum concentrations; studies needed in patients with *Pneumocystis carinii* pneumonia
Fluconazole[15,16]	May need to increase fluconazole dose; monitor signs and symptoms of infection; 1 trial in healthy subjects found 22% decrease in fluconazole serum half-life
Nifedipine[17]	Monitor clinical response; may need to increase dose; contolled study needed
Diltiazem†[18-20]	Conider alternative agent to diltiazem if possible, because even very large increase in oral diltiazem may not be sufficient; may monitor serum diltiazem concentrations (see Table 1 regarding similar interaction with verapamil); monitor clinical response
Diazepam[21,22]	Monitor clinical response; may need to increase diazepam dose; 300% increase in diazepam oral clearance has been reported

*Agents available in the United States; for each interaction, carefully adjust doses when rifampin is discontinued; enzyme induction effect is gradually reduced over 1 to 2 weeks.
†More study needed in patients; probably of major clinical significance.

The influence of concurrent dapsone (100 mg) and rifampin (600 mg) was studied in 30 patients with clinically active leprosy.[13] Despite a reduced serum dapsone concentration, it was concluded that 2 weeks of concomitant dapsone and rifampin therapy will still produce dapsone plasma concentrations much higher than the minimum inhibitory concentration for *Mycobacterium leprae*. Pieters et al[14] studied the influence of once-monthly rifampin on the half-life of dapsone. Three days after rifampin administration, the mean half-life of dapsone was reduced by 63% and the mean trough dapsone concentration was decreased by 23%. When the *M leprae* minimum inhibitory concentration (2.5 to 10 μg/L) was considered, it was concluded that the mean serum dapsone concentration measured 24 hours after intake remained well above this range.

Newer drug regimens are being sought to treat *Pneumocystis carinii* pneumonia in patients infected with human immunodeficiency virus.[29] Dapsone with trimethoprim may be an effective alternative to sulfamethoxazole-trimethoprim in mild to moderate first cases, with a lower incidence of adverse effects.[30] Because of an increased incidence of tuberculosis in patients with the acquired immunodeficiency syndrome, the likelihood of treating patients for both diseases is great.

There have been several reported cases of rifampin interactions with ketoconazole, including treatment failures,[5,31,32] and the Food and Drug Administration has recommended against their concomitant use.[33] The pharmacokinetic interaction between ketoconazole and rifampin was studied by Doble et al[34] in six healthy male subjects. A significant lowering of mean peak plasma ketoconazole concentrations and the ketoconazole AUC was demonstrated with concurrent oral or IV rifampin therapy. It was suggested that no impairment of rifampin absorption would occur when rifampin is administered as soon as 30 minutes after ketoconazole (in contrast to a previous study[5]).

Fluconazole, unlike ketoconazole, is not extensively metabolized by P450 enzymes, being mainly excreted unchanged in the urine (up to 80% of a dose compared with 2%, respectively). In a study conducted by Apseloff et al,[15] 16 healthy male volunteers were administered a single 200-mg oral dose of fluconazole on day 1 (as baseline). This was followed by a 7-day washout period after which eight of the volunteers received rifampin, 600 mg daily, and eight volunteers received placebo for 20 days. Both groups then received a single 200-mg oral dose of fluconazole 2 hours before receiving rifampin or placebo. Rifampin pretreatment resulted in a 22% decrease in the mean fluconazole half-life and a 23% decrease in the mean fluconazole AUC. Coker and colleagues[16] reported on the clinical relapse of cryptococcal meningitis in three patients infected with human immunodeficiency virus, which they attributed to concurrent rifampin-fluconazole administration. It was suggested that physicians exercise vigilance and become alert to the possibility of relapse whenever the combination is used. Blomley et al[35] reported a possible rifampin-itraconazole interaction in a single case.

CYCLOSPORINE

A number of well-documented cases have previously been reviewed concerning a possible drug interaction between rifampin and cyclosporine,[5] and several new cases have appeared.[36-38] Recent studies[39,40] have used in vitro cell culture techniques to characterize rifampin induction of cyclosporine metabolism further. Roberts et al[41] examined the effects of rifampin on cyclosporine pharmacokinetics in six healthy volunteers who received one oral dose (10 mg/kg) and one IV dose (3 mg/kg) of cyclosporine on day 1 (baseline). All subjects then received 600 mg

of rifampin at bedtime for 11 days. One dose of oral and IV cyclosporine was again administered on days 8 and 11. The prerifampin and postrifampin IV cyclosporine clearances were not different, yet cyclosporine bioavailability was reduced by 20%. The AUCs of IV cyclosporine before and after rifampin administration were not significantly different, but the AUC of oral cyclosporine was reduced by about 70% after rifampin. The authors suggested that, contrary to the popular belief that rifampin induces the hepatic metabolism of cyclosporine, rifampin instead decreases the bioavailability of cyclosporine by decreasing cyclosporine absorption and/or inducing intestinal P450 enzyme metabolism. A recent in vitro study of cyclosporine absorption[42] suggested that the gut wall may be a site of first-pass metabolism of cyclosporine in vivo. However, colonic mucosa from six patients was used as the model (and one sample of gastric mucosa), even though cyclosporine is mostly absorbed from the upper gastrointestinal tract.

Al-Sulaiman and coworkers[43] reported that there is an increasing reluctance among clinicians to use the combination of rifampin and cyclosporine. However, the authors suggested that with careful dose and frequency adjustments, it is possible to use this combination without compromising graft function or patient care. In their experience, the cyclosporine dose must be significantly increased and the frequency of cyclosporine administration may need to be increased to three times daily as the rifampin-induced cyclosporine clearance increases.

CALCIUM-CHANNEL BLOCKERS

Evidence is accumulating that nifedipine and diltiazem may be at least partly metabolized by the same rifampin-inducible P450 enzymes, which may translate into clinically relevant drug interactions. A case report of the interaction between oral verapamil and rifampin has been reported,[5] and a study of this interaction[44] revealed that concurrent therapy with rifampin dramatically decreased oral verapamil bioavailability and abolished the electrocardiographic effects of verapamil.

Exacerbation of angina in a 71-year-old male patient described by Tsuchihashi and colleagues[17] was attributed to rifampin administration. One month after initiation of antituberculosis therapy, the patient began experiencing renewed chest pain at rest that was refractory to antianginal medications, including nifedipine. An electrocardiogram demonstrated ST-segment elevation and second-degree atrioventricular block. After rifampin treatment, nifedipine showed a dramatic decrease in plasma concentration. Reintroduction of rifampin therapy was thought again to precipitate anginal attacks, and complete cessation of rifampin treatment was reported to leave the patient angina free for a 1-year duration of follow-up.

Diltiazem is extensively metabolized in the liver to at least five metabolites. Pichard and colleagues[18] conducted an in vitro study of rifampin and diltiazem and concluded that rifampin induced diltiazem metabolism. On the basis of this evidence, it can be reasonably hypothesized that the coadministration of diltiazem and rifampin in vivo may increase diltiazem metabolism. This possibility was evaluated in healthy male volunteers by Drda et al.[19] After enzyme induction with rifampin, diltiazem concentrations at all time points were below the limit of detection in nine subjects. Even if these concentrations were assumed to be at the sensitivity limit, rifampin induction caused large increases in the mean apparent oral clearance of diltiazem and decreases in both mean maximal plasma concentrations and AUC compared with prerifampin diltiazem kinetics. Furthermore, rifampin induction decreased diltiazem pharmacodynamic effects as assessed by a lack of statistically significant increases in the PR interval. The effect of combination diltiazem and rifampin on plasma theophylline concentrations was determined by Adebayo and colleagues[20] in eight nonsmoking male subjects. The data revealed that diltiazem, 240 mg daily for a week, had no effect on theophylline metabolism. Rifampin, 600 mg daily for 8 days, taken alone, induced theophylline metabolism, and the combination of rifampin with diltiazem slightly elevated the mean theophylline half-life (control half-life, 9.6 hours; rifampin alone, 5.5 hours; rifampin plus diltiazem, 6.2 hours). Thus, diltiazem appeared to attenuate rifampin-induced theophylline metabolism due to P450 enzyme inhibition.

BENZODIAZEPINES

The disposition and elimination of diazepam before and after rifampin induction was investigated by Ohnhaus et al.[21] Plasma and urine samples were collected for analyses of diazepam and its metabolites desmethyldiazepam, 3-hydroxydiazepam, and oxazepam. The maximal mean diazepam plasma concentration was decreased only after administration of 1200 mg of rifampin. A 300% increase in mean oral clearance of diazepam after both rifampin treatments was observed, with roughly a 400% preferential increase in the mean partial metabolic clearances to desmethyldiazepam and 3-hydroxydiazepam (as opposed to oxazepam). Similarly, Ochs et al[22] reported an increase in single-dose diazepam clearance and a shortened diazepam half-life after pretreatment with rifampin. Brockmeyer et al[45]reported that the clearance of a single oral dose of nitrazepam, 5 mg, was increased by 83% after administration of rifampin, 600 mg daily, compared with the same dose of nitrazepam alone in healthy volunteers. In this same report, the pharmacokinetics of single-dose temazepam, 10 mg, were not altered by rifampin.

OTHER DRUGS

A case of a possible interaction between rifampin and enalapril was reported by Kandiah et al.[46] With rifampin administration, the AUC of enalapril did not decline, but the AUC of enalaprilat (the active metabolite of enalapril) decreased 9%, while plasma concentrations of enalaprilat remained at therapeutic levels. This single case was not well documented, and controlled study is needed.

Patel and associates[47] administered 40 mg of oral piroxicam to six healthy volunteers. Rifampin had no apparent effect on mean piroxicam plasma concentrations, time to peak plasma concentration, half-life, or piroxicam AUC.

Previous reports have suggested an interaction with rifampin and tolbutamide and chlorpropamide.[4] Self et al[48] described a possible interaction of rifampin and glyburide in a 67-year-old woman. On discontinuation of rifampin after a 9-month course, serum glyburide concentrations were measured. Trough serum glyburide concentrations rose sharply by fivefold to sixfold after rifampin treatment was stopped, yet the patient's blood glucose concentrations did not appreciably change before or after rifampin

treatment. The patient's glyburide dose had been constant for several months.

Despite numerous well-designed studies[5] in healthy nonsmoking male subjects that have shown increased theophylline clearance due to treatment with rifampin, one case report and one study have reported delayed theophylline clearance[49] and increased serum concentrations of theophylline[50] in patients receiving rifampin. It is unknown to what extent variables in these reports, such as severe pulmonary disease,[51] other drugs (including alcohol),[52,53] and isoniazid (including acetylation phenotype),[54,55] as well as such diseases as hepatic cirrhosis,[51,56] contributed to the delayed theophylline elimination. Considering the previous studies *clearly* showing an increased clearance of theophylline when given concomitantly with rifampin, we remain unconvinced that theophylline clearance will decrease with rifampin therapy. Further study of *single-dose* rifampin would be appropriate to validate the results of Halawa.[50]

Additional reports and studies of drug interactions with rifampin have appeared for methadone,[57] chloramphenicol,[58] warfarin,[59,60] oral contraceptives,[61] estrone sulfate,[62] doxycycline,[63,64] phytonadione,[65] vitamin D metabolites,[66] and mephenytoin.[67,68] Studies demonstrating enzyme-inducing effects of rifampin on the β-blockers bisoprolol,[69] pirmenol,[70] and tertatolol[71] have been done. Increased elimination of glucocorticoids due to rifampin continues to be reported, including instances of adrenal crisis.[72-80] A recent study found a statistically significant enzyme induction effect observed after 2 days of rifampin[81]; thus, clinicians should be aware of the possibility of clinically significant hepatic enzyme induction due to less than 1 week of rifampin treatment.

CONCLUSIONS

In conclusion, most drugs that interact with rifampin require a dosage increase when given concomitantly; therefore, discontinuing rifampin treatment will require a dosage reduction of the interacting drug. As opposed to most of the interactions previously reviewed[4,5] that are of major clinical significance, most of the interactions reported during the last 5 years will require more study to establish their clinical significance. Other reports of rifampin interactions should be expected with further investigations.

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