

TABLE 12. CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS INVOLVING THE RIFAMYCINS*

Drug Class	Drugs Whose Concentrations Are Substantially Decreased by Rifamycins (References)	Comments	
Antiinfectives	HIV-1 protease inhibitors (saquinavir, indinavir, nelfinavir, amprenavir, ritonavir, lopinavir/ritonavir) (1, 20–25)	Can be used with ribabutin. Ritonavir, 400–600 mg twice-daily, probably can be used with rifampin. The combination of saquinavir and ritonavir can also be used with rifampin.	
	Nonnucleoside reverse transcriptase inhibitors Delavirdine (26, 27) Nevirapine (28) Efavirenz (29)	Delavirdine should not be used with any rifamycin. Doses of nevirapine (28) and efavirenz (29) need to be increased if given with rifampin, no dose increase needed if given with rifabutin (5)	
	Macrolide antibiotics (clarithromycin, erythromycin) (30–32)	Azithromycin has no significant interaction with rifamycins	
	Doxycycline (33)	May require use of a drug other than doxycycline	
	Azole antifungal agents (ketoconazole, itraconazole, voriconazole) (34–38)	Itraconazole ketoconazole, and voriconazole concentrations may be subtherapeutic with any of the rifamycins. Fluconazole can be used with rifamycins, but the dose of fluconazole may have to be increased	
	Atovaquone (39)	Consider alternate form of <i>Pneumocystis carinii</i> treatment or prophylaxis	
	Chloramphenicol (40)	Consider an alternative antibiotic	
	Mefloquine (41)	Consider alternate form of malaria prophylaxis	
	Hormone therapy	Ethinylestradiol, norethindrone (42–44)	Women of reproductive potential on oral contraceptives should be advised to add a barrier method of contraception when taking a rifamycin
		Tamoxifen (45)	May require alternate therapy or use of a norrifamycin-containing regimen
Levothyroxine (46, 47)		Monitoring of serum TSH recommended; may require increased dose of levothyroxine	
Narcotics	Methadone (48, 49)	Rifampin and rifapentine use may require methadone dose increase; rifabutin infrequently causes methadone withdrawal	
Anticoagulants	Warfarin (50)	Monitor prothrombin time; may require two- to threefold dose increase	
Immunosuppressive agents	Cyclosporine, tacrolimus (51–53)	Rifabutin may allow concomitant use of cyclosporine and a rifamycin; monitoring of cyclosporine serum concentrations may assist with dosing	
	Corticosteroids (54–57)	Monitor clinically; may require two- to threefold increase in corticosteroid dose (58)	
Anticonvulsants	Phenytoin (59), lamotrigine (60)	Therapeutic drug monitoring recommended; may require anticonvulsant dose increase	
Cardiovascular agents	Verapamil (61), nifedipine (62, 63), diltiazem (a similar interaction is also predicted for felodipine and nisoldipine)	Clinical monitoring recommended; may require change to an alternate cardiovascular agent	
	Propranolol (64), metoprolol (65)	Clinical monitoring recommended; may require dose increase or change to an alternate cardiovascular drug	
	Enalapril (66), losartan (67)	Monitor clinically; may require a dose increase or use of an alternate cardiovascular drug	
	Digoxin (among patients with renal insufficiency) (68), digitoxin (69)	Therapeutic drug monitoring recommended; may require digoxin or digitoxin dose increase	
	Quinidine (70, 71)	Therapeutic drug monitoring recommended; may require quinidine dose increase	
	Mexilitine (72), tocainide (73), propafenone (15)	Clinical monitoring recommended; may require change to an alternate cardiovascular drug	
Bronchodilators	Theophylline (74)	Therapeutic drug monitoring recommended; may require theophylline dose increase	
Sulfonylurea hypoglycemics	Tolbutamide, chlorpropamide, glyburide, glimepiride, repaglinide (75–79)	Monitor blood glucose; may require dose increase or change to an alternate hypoglycemic drug	
Hypolipidemics	Simvastatin (80), fluvastatin (81)	Monitor hypolipidemic effect; may require use of an alternate hypolipidemic drug	
Psychotropic drugs	Nortriptyline (82)	Therapeutic drug monitoring recommended; may require dose increase or change to alternate psychotropic drug	
	Haloperidol (83), quetiapine (84)	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug	
	Benzodiazepines (e.g., diazepam [85], triazolam [86]), zolpidem (87), buspirone (88)	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug	

* For reference citations, refer to Section 7.2.

Some of these drug–drug interactions can be managed with close clinical or laboratory monitoring and dose increases of the medication(s) affected by the rifamycins (Table 12). In other cases, the magnitude of the decrease in concentrations of a concomitant medication may be such that serum concentrations

cannot be restored by a dose increase. If the dose of a medication is increased to compensate for the effect of a rifamycin, it is critical to remember that the dose of this drug will probably need to be decreased within the 2 weeks after the rifamycin is discontinued and its inductive effect resolves.

In some situations, rifabutin can sometimes be used in place of rifampin, if there is an unacceptable drug-drug interaction between rifampin and another drug, such as cyclosporine (51) and most of the HIV-1 protease inhibitors (89). All the rifamycins may cause unacceptable decreases in the serum concentrations of certain drugs, such as delavirdine (26, 27, 90), ketoconazole and itraconazole (34, 91).

7.2.2. Drug interactions due to isoniazid. Isoniazid is a relatively potent inhibitor of several cytochrome P450 isozymes (CYP2C9, CYP2C19, and CYP2E1) (92), but has minimal effect on CYP3A (20). As an inhibitor, isoniazid can increase concentrations of some drugs to the point of toxicity. The clearest examples of toxicity due to the inhibitory activity of isoniazid are the anticonvulsants, phenytoin (93, 94) and carbamazepine (95, 96). Isoniazid also increases concentrations of benzodiazepines metabolized by oxidation, such as diazepam (85) and triazolam (97), but not those metabolized by conjugation, such as oxazepam (97). It is worth noting that rifampin has the opposite effect on the serum concentrations of many of these drugs. The available data demonstrate that the inductive effect of rifampin outweighs the inhibitory effect of isoniazid, so that the overall effect of combined therapy with rifampin and isoniazid is a decrease in the concentrations of drugs such as phenytoin (59) and diazepam (85).

Isoniazid may increase toxicity of other drugs—acetaminophen (98), valproate (99), serotonergic antidepressants (100), disulfiram (101), warfarin (102), and theophylline (103)—but these potential interactions have not been well studied.

7.2.3. Drug interactions due to fluoroquinolones. Ciprofloxacin (104) inhibits the metabolism of theophylline and can cause clinical theophylline toxicity (105). However, levofloxacin (106), gatifloxacin (107), and moxifloxacin (108) do not affect theophylline metabolism.

References

(Includes references cited in Table 12.)

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