

DRUG INTERACTIONS WITH TUBERCULOSIS THERAPY

A potential drug interaction refers to the possibility that one drug may alter the pharmacological effects of another drug given concomitantly. The net result may be enhanced or diminished effects of one or both drugs, or the appearance of a new effect that is not seen with either drug alone.^{1,2}



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The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, where relatively small changes in drug level can have significant adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if undertreated. Not all drug interactions are clinically significant. Some patients experience severe reactions while taking interacting drugs, while other patients appear to be unaffected.^{1,3}

Interactions may be either pharmacokinetic or pharmacodynamic.

PHARMACOKINETIC DRUG-DRUG INTERACTIONS

Pharmacokinetic interactions are divided into those that affect:

- drug absorption
- drug binding
- drug metabolism
- excretion
- transport systems.^{1,2}

The result of pharmacokinetic drug-drug interactions may be an increase or decrease in the concentration of the drug at the site of action.^{1,2} The mechanism most relevant to tuberculosis drug interactions is drug metabolism, which is explained in more detail below.

Drug metabolism interactions

Drugs are metabolised by two types of reactions: phase I reactions that involve oxidation, reduction or hydrolysis in which drugs are turned into more polar compounds, and phase II reactions that involve coupling drugs with some other substance (e.g. glucuronic acid) to make (usually) inactive compounds. These reactions make drugs more easily excretable. Drug metabolism interactions can increase or decrease the amount of drug available by inhibition or induction of metabolism.^{1,2}

Enzyme induction

Enzyme induction frequently affects phase I oxidation, which requires the presence of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and the haem-containing protein cytochrome P450. Enzyme inducers increase the activity of the microsomal enzymes (cytochrome P450 isoenzymes), increasing the rate of metabolism and excretion. As a result, larger doses of drugs metabolised by these enzymes are needed.^{1,2}

Enzyme induction interactions are delayed in both starting and stopping, taking from days to up to 3 weeks to develop fully, and may persist for a similar length of time after the inducing drug is stopped. It is possible to accommodate the interaction by simply raising the dosage of the drug affected, but this requires good moni-

Table I. Important drug interactions with rifampicin

	Rifampicin interaction	Management
ANTIHYPERTENSIVES		
Diuretics Thiazides Spironolactone Furosemide	No interactions found	Safe option
Calcium channel blockers Nifedipine Amlodipine Verapamil	Rifampicin markedly reduces the levels of calcium channel blockers by increasing the metabolism of these drugs in the gastrointestinal wall ²	Monitor response closely and increase dose of calcium channel blocker if needed ²
β-Blockers Propranolol Carvedilol	Rifampicin reduces levels of β-blockers by enzyme induction. (↓AUC of carvedilol by about 70%) ³	β-blockers that undergo extensive liver metabolism (e.g. propranolol) would be expected to be affected by the enzyme-inducing effects of rifampicin Those β-blockers mainly lost unchanged in the urine (e.g. atenolol) would not be expected to be affected ^{2,3} Monitor patient response (blood pressure, signs/symptoms of hepatic dysfunction) and adjust β-blocker dosage as needed ³ Monitor for continuing blood pressure control after the addition or withdrawal of rifampicin, adjusting the ACE inhibitor dose if needed to regain control ³
ACE inhibitors Captopril Enalapril Lisinopril	Two isolated reports of interaction with enalapril, with minor clinical relevance ²	Monitor for continuing blood pressure control after the addition or withdrawal of rifampicin, adjusting the ACE inhibitor dose if needed to regain control ³
ANALGESICS		
Paracetamol	Increased clearance of paracetamol in 2 patients	Clinical importance awaits further study ²
NSAIDs Diclofenac Ibuprofen Aspirin	Small study showed decreased levels of diclofenac ² No interaction found with aspirin, ibuprofen	May need ↑ dosage of diclofenac, more study needed ² Ibuprofen and aspirin are safer options
Tramadol	No interactions found	
Opioids Morphine Codeine	Rifampicin reduces opioid levels ^{2,3}	Monitor for adequate pain control Doses of opioids may need to be increased and re-evaluated when rifampicin is discontinued ³
ANTIFUNGALS		
Itraconazole Ketoconazole	Serum concentrations markedly reduced	This can reduce or abolish the antifungal effects, depending on the infection being treated Serum rifampicin levels can also be reduced by the concurrent use of ketoconazole, and the drugs should be administered 12 hours apart to minimise this interaction
CONTRACEPTIVES		
Oral contraceptives (OC) Ethinylestradiol Levonorgestrel Norgestrel	Rifampicin reduces effectiveness by enzyme induction and by intestinal flora alteration, which in turn, alters the enterohepatic circulation of the drug ³	Very unreliable contraceptive choice when given with rifampicin Breakthrough bleeding and spotting commonly occur and conception and pregnancy may not be prevented ² Should NOT be administered concomitantly Safer alternative — injectable form Interaction may be overcome by shortening the interval between injections to 8 weeks for medroxyprogesterone acetate and to 6 weeks for norethisterone enanthate ⁴
Progestogen-only injectable contraceptives Medroxyprogesterone acetate Norethisterone enanthate	Rifampicin reduces effectiveness by enzyme induction ³	

Table I. Important drug interactions with rifampicin (continued)

	Rifampicin interaction	Management
ARV AGENTS		
Didanosine (ddl)	No interactions found	
Efavirenz (EFV)	Rifampicin reduces EFV levels by enzyme induction ³	Rifampicin can be used with EFV without dosage modification ⁵
Lamivudine	No interactions found	
Lopinavir-ritonavir (Kaletra)	Rifampicin reduces ritonavir levels by enzyme induction ³ ↑ ALT/AST ²	Monitoring of liver function advised Adults: add ritonavir 300 mg every 12 hours to usual Kaletra dose, while patient is on rifampicin and for 1 month after completion of TB therapy ⁶ Children: swap from Kaletra to ritonavir only Alternative: If over 3 years old and over 10 kg, switch to efavirenz If under 3 years old or under 10 kg, switch to ritonavir if appropriate
Nevirapine (NVP)	Rifampicin reduces NVP levels by enzyme induction ³	
Stavudine	No interactions found	
Zidovudine	Rifampicin increases the clearance of AZT ^{2,3,7}	Dosage alterations may NOT be necessary with concurrent use, but be alert for any evidence of a reduced response to AZT ^{2,3,7}
ANTI-EPILEPTICS		
Carbamazepine	One case report of increased level and toxicity of carbamazepine when isoniazid and rifampicin are given together, probably by inhibition of carbamazepine metabolism ^{2,3}	Monitor the patient for signs of carbamazepine toxicity, including ataxia, nystagmus, diplopia, headache, vomiting, apnoea, seizures and coma ³
Phenytoin	Rifampicin markedly reduces phenytoin serum levels by enzyme induction ² When rifampicin is used in combination with isoniazid the phenytoin clearance is not increased as much as when rifampicin is given alone with phenytoin ³	Monitor phenytoin levels and increase the dosage appropriately if rifampicin is started ALONE Decrease the dosage if rifampicin is stopped If rifampicin and isoniazid are given CONCOMITANTLY, the outcome may depend on the isoniazid acetylator status of the patient Fast acetylators will probably also need an increased phenytoin dosage Slow acetylators may need a smaller phenytoin dosage if toxicity is to be avoided All patients should be monitored very closely as the outcome is unpredictable ²
Valproic acid	Rifampicin may decrease valproate levels by increasing clearance ³	Monitor valproate levels and the patient for seizure control. An adjustment in the dosage may be necessary ³

AUC = area under the curve.

toring and there are risks when the inducing drug is stopped without remembering to reduce the dosage of the previously affected drug. Examples of enzyme-inducing drugs are barbiturates, carbamazepine, nevirapine, phenytoin, rifampicin and tobacco smoke.^{1,2}

Enzyme inhibition

Enzyme inhibitors inhibit the microsomal enzymes (cytochrome P450 isoenzymes), decreasing the rate of metabolism and excretion of other drugs that are metabolised by these same enzymes. These drugs begin to accumulate in the body and toxicity may develop within 2 - 3 days. The clinical

significance of the enzyme inhibition interactions depends on the extent to which serum levels rise. Examples of enzyme-inhibiting drugs are allopurinol, chloramphenicol, cimetidine, ciprofloxacin, erythromycin, fluconazole, fluoxetine, isoniazid, ketoconazole, metronidazole, protease inhibitors and verapamil.^{1,2}

Table II. Isoniazid (INH) drug interactions

	INH interaction	Management
Antacids	Absorption of INH is reduced by concurrent use of aluminium hydroxide ^{2,4}	Give INH at least 1 hour before the antacid. Although didanosine tablets contain antacids in the formulation it has been shown that it is too little to affect the bioavailability of INH if given concurrently
Carbamazepine	Serum levels of carbamazepine are markedly and rapidly increased ^{2,4}	Toxicity of carbamazepine can occur if dosage is not reduced appropriately. Concurrent use should not be undertaken unless the effects can be closely monitored and suitable downward dosage adjustments made
Oral contraceptives	One or two cases of failure have been reported ²	The risk of failure appears to be low
Paracetamol	Potential toxicity of paracetamol ²	Normal daily analgesic dosages of 4 g may not be safe. It is prudent to warn patients to limit their use of paracetamol because it seems that some individuals risk possible paracetamol-induced liver toxicity, even with normal doses. More study is needed to clarify the situation ²
Phenytoin	↑ levels of phenytoin with INH alone ²	Slow metabolisers of INH may develop phenytoin toxicity if the dosage of phenytoin is not reduced appropriately. If both rifampicin and INH are given, serum phenytoin levels may fall in patients who are fast acetylators of INH, but may occasionally rise in slow acetylators
Theophylline	Plasma level of theophylline may be increased ⁴	Monitor levels

The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, where relatively small changes in drug level can have significant adverse consequences.

Drug metabolism interactions can increase or decrease the amount of drug available by inhibition or induction of metabolism.^{1,2}

Examples of enzyme-inducing drugs are barbiturates, carbamazepine, nevirapine, phenytoin, rifampicin and tobacco smoke.^{1,2}

Cytochrome P450 isoenzymes and predicting drug interactions

Cytochrome P450 is a large family of related isoenzymes of which about 30 have been identified. The most frequently involved in drug interactions are CYP3A4 and CYP2D6. There are many drugs that are metabolised by these cytochrome P450 isoenzymes. Drugs may be metabolised by more than one cytochrome isoenzyme.^{1,2}

It is of value to know which particular isoenzyme is responsible for the metabolism of a specific drug as this makes it possible to predict with which other drugs it may possibly interact. For example, cyclosporin is metabolised by CYP3A4 and we know that rifampicin is a potent inducer of this enzyme. The result, predictably, is that rifampicin reduces the effects of cyclosporin. Knowing which liver isoenzymes are concerned with metabolism of a drug is a good starting point in predicting drug interactions, but it is not definitive.^{1,2}

PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action, without alterations in the concentrations of either drug. Sometimes one drug competes directly with another for particular receptors, but often the reaction is more indirect and involves the interference with physiological mechanisms, making pharmacodynamic interactions more difficult to classify than pharmacokinetic interactions. There are 4 basic subdivisions:

- additive or synergistic interactions and combined toxicity
- antagonistic or opposing interactions
- interactions due to changes in drug transport mechanisms
- interactions due to disturbances in fluid and electrolyte balance.^{1,2}

Interactions with tuberculosis drugs

First-line agents for the treatment of tuberculosis include rifampicin, isoniazid, ethambutol, pyrazinamide and streptomycin.^{3,4} This article focuses on the pharmacokinetic drug interactions with these first-line agents.

It is impossible to remember all clinically important drug interactions, but when one considers the drugs used for the treatment of tuberculosis, the important interactions are almost exclusively caused by rifampicin. Rifampicin is a potent liver enzyme inducer that increases the activity of the microsomal enzymes so that the pace of metabolism and excretion of other drugs metabolised by the same enzyme system is increased.³

Table I lists the important drug interactions with rifampicin and Table II the interactions involving isoniazid, an enzyme inhibitor.

Ethambutol and pyrazinamide have few significant drug interactions. Ethambutol together with pyrazinamide and thiazide diuretics has the potential to elevate serum urate levels. Pyrazinamide may interact with allopurinol and probenecid as pyrazinamide inhibits the urate clearance. Dosage adjustments of these agents may be necessary.^{2,4}

When using streptomycin one should be aware of the potential for increased risk of oto- or nephrotoxicity with other ototoxic or nephrotoxic drugs. Streptomycin (and other aminoglycosides) possess neuromuscular blocking activity. Appropriate measures should be taken to accommodate the increased neuromuscular blockade and the prolonged and potentially fatal respiratory depression that can occur with anaesthetics and conventional neuromuscular blocking drugs of any kind.^{2,4}

Quinolone antibacterials (second-line tuberculosis agent) should generally be avoided in patients with epilepsy as quinolone antibacterials very occasionally cause convulsions.^{2,4}

Other interactions to be aware of with quinolones are:

- reduced clearance of theophylline, leading to increased serum levels
- increased anticoagulant effect of warfarin (prothombin time should be monitored)
- concurrent use of sucralfate, antacids containing aluminium, calcium or magnesium, or oral iron, zinc or magnesium supplements may reduce absorption of the quinolones
- although the mechanism is not fully understood, the serum levels of ciprofloxacin are markedly reduced if given at the same time as didanosine, probably because of the interaction with the antacid buffers in the didanosine formulation.^{2,4}

CONCLUSION

Drug-drug interactions are only one of the many factors that can alter a patient's response to therapy, but when unexpected effects are seen, a drug interaction should be suspected. Taking careful drug histories is important, because patients may be taking over-the-counter drugs or herbal preparations. Care must be exercised when major changes are made in a drug regimen and drugs that are not necessary must be discontinued. When an interaction is discovered, it is possible that the interacting drugs may be used effectively with adjustment of dosage or other therapeutic modifications.¹

MEDICINES INFORMATION CENTRE

The MIC is a unit situated within the Division of Pharmacology, Department of Medicine, at the University of Cape Town's Faculty of Health Sciences. The Centre was established in 1980 and forms part of a World Health Organization collaborating centre.

The MIC is dedicated to providing unbiased, up-to-date and well-researched drug information, in consultation with a multidisciplinary health care team, to all health care professionals in South Africa. To ensure this,

we have access to the latest updated information databases as well as to clinical consultants from the University of Cape Town's Faculty of Health Sciences, Groote Schuur and Red Cross War Memorial Children's Hospitals and other national and international experts.

Need help? Call the Medicines Information Centre, tel (021) 406-6829 or 086 110 0531, for any information relating to medicines, including drug interactions.

ACKNOWLEDGEMENT

The authors would like to thank Maria Nunez, a pharmacy student at the University of Granada, Spain, for her help with the article.

References available on request.

IN A NUTSHELL

There are many facets to drug-drug interactions.

Although there are numerous potential drug interactions not all are clinically relevant.

Interactions may either be pharmacokinetic or pharmacodynamic.

Pharmacokinetic drug-drug interactions may occur at any point during absorption, distribution, metabolism or excretion.

Pharmacodynamic interactions may be caused by a large variety of mechanisms making them difficult to study and classify.

Rifampicin, a first-line agent for the treatment of tuberculosis, is a potent liver enzyme inducer.

Most of the drug-drug interactions that occur in patients on TB drug therapy will be due to the enzyme-inducing effect of rifampicin.

Isoniazid is an enzyme inhibitor.

When unexpected effects are seen in patients taking many drugs, suspect a drug interaction.