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Clinically Significant Interactions with Drugs Used in the Treatment of Tuberculosis

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Abstract

Clinically significant interactions occurring during antituberculous chemotherapy principally involve rifampicin (rifampin), isoniazid and the fluoroquinolones. Such interactions between the antituberculous drugs and coadministered agents are definitely much more important than among antituberculous drugs themselves. These can be associated with consequences even amounting to therapeutic failure or toxicity. Most of the interactions are pharmacokinetic rather than pharmacodynamic in nature. The cytochrome P450 isoform enzymes are responsible for many interactions (especially those involving rifampicin and isoniazid) during drug biotransformation (metabolism) in the liver and/or intestine. Generally, rifampicin is an enzyme inducer and isoniazid acts as an inhibitor. The agents interacting significantly with rifampicin include anticoagulants, anticonvulsants, anti-infectives, cardiovascular therapeutics, contraceptives, glucocorticoids, immunosuppressants, psychotropics, sulphonylureas and theophyllines. Isoniazid interacts principally with anticonvulsants, theophylline, benzodiapines, paracetamol (acetaminophen) and some food. Fluoroquinolones can have absorption disturbance due to a variety of agents, especially the metal cations. Other important interactions of fluoroquinolones result from their enzyme inhibiting potential or pharmacodynamic mechanisms. Geriatric and immunocompromised patients are particularly at risk of drug interactions during treatment of their tuberculosis. Among the latter, patients who are HIV infected constitute the most important group. This is largely because of the advent of new antiretroviral agents such as the HIV protease inhibitors and the non-nucleoside reverse transcriptase inhibitors in the armamenterium of therapy. Compounding the complexity of drug interactions, underlying medical diseases *per se* may also contribute to or aggravate the scenario. It is imperative for clinicians to be on the alert when treating tuberculosis in patients with difficult co-morbidity requiring polypharmacy. With advancement of knowledge and expertise, it is hoped that therapeutic drug monitoring as a new paradigm of care can enable better management of these drug interactions.

Today, tuberculosis is still a serious global problem.[1] Whilst HIV-attributed tuberculosis is found in both developing and industrialised countries,[1] geriatric tuberculosis appears to be a more important problem in the latter.[2,3] Standardisation of treatment for tuberculosis, as part of the national tuberculosis programme has been recommended by authorities like the World Health Organization (WHO).[4] Furthermore, the clinical importance of drug interactions during antituberculous chemotherapy is being increasingly appreciated.[5]

1. General Considerations in Drug Interactions

1.1 Mechanisms of Drug Interactions and Patients at Risk

Drug interactions are usually considered clinically significant when precipitation of toxicity or a change of therapeutic activity is likely to ensue on their coadministration.[5] Pharmocokinetic interactions refer to those pertinent to derangement in the movement or disposition of the drugs. These in-

clude absorption, distribution, and clearance of drugs, largely by hepatic biotransformation, renal elimination and other ancillary routes.[6] Disease states can also enhance the drug interactions. Examples include diabetes mellitus, chronic renal failure and HIV infection.[6] However, changes in drug binding by proteins do not usually produce clinically significant effects.[7] Biotransformation in the liver is modulated by age and intrinsic liver disease, the former might be related both to hepatic blood flow and liver mass. Malnutrition might have a putative negative effect on drug oxidation. Alcohol and cigarette smoke are potent hepatic enzyme inducers.[8,9] Pharmacodynamic interactions refer to those resulting from the enhanced competition or inhibition of binding of receptors at the target site of drug action, or some change in the pathophysiological mechanisms with either consequential additive/synergistic or antagonistic effects. Disease states can also contribute to such a scenario. An example is isoniazid-induced encephalopathy in patients receiving dialysis as illustrated in several case reports.[10]

During antituberculous chemotherapy, both the aforementioned types of interactions can be encountered, though pharmacokinetic interactions are more common, especially between rifampicin (rifampin) and other drugs used concomitantly.[11-13] The patient populations with tuberculosis particularly at risk for clinically significant pharmacological interactions include the HIV-infected patients,[6,14] elderly patients[15] and recipients of organ transplants.[16] The first group will be discussed in detail in section 4. Elderly patients are at risk largely because of likelihood of polypharmacy, intrinsic effects of age *per se*, as well as the effects of possible nutritional compromise and chronic renal and liver impairment on the drug pharmacokinetics. Organ transplant recipients are at risk through possible nutritional compromise and because of similar reasons, with the exception of old age. Organ transplant recipients are particularly at risk when drug interactions diminish the efficacy of the immunosuppression regimen leading to graft dysfunction or rejection.[16]

1.2 The Cytochrome P450 Enzyme System

Cytochrome P450 (CYP450) represents a group of heme-containing enzymes largely located on the membrane of the endoplasmic reticulum of the hepatocytes and enterocytes. This superfamily of more than 30 related enzymes are responsible for oxidative metabolism of many drugs, as well as endogenous substances such as prostaglandins, fatty acids and steroids.[17] The superfamily can be divided into families and then subfamilies. In humans, enzymes of the CYP1, CPY2 and CYP3 families are responsible for the vast majority of drug metabolism.[18] Table I depicts some representative substrates, inhibitors and inducers of the CYP450 isoform enzymes.[17-23] As one can see, rifampicin and isoniazid, the two main antituberculous drugs, together with ciprofloxacin, the new antimycobacterial agent are conspicuously present, as inducer or inhibitor among others including a number of anticonvulsants, cardiovascular drugs, psychotropic agents and antiretroviral compounds. Drug interactions might be theoretically somewhat predictable based on the knowledge of which compounds induce and inhibit specific CYP450 enzymes.[20-22,24] Induction and inhibition of enzymes are dose- and time-dependent phenomena that are generally reversible once the incriminated agent has been successfully identified and withdrawn.[6,20-22] Induction interactions require long term drug administration and occur more slowly than do inhibition interactions because an increase in the synthesis of enzymes is required. However, due to genetic polymorphism in the population, the impact of an inducer on the enzyme activity of a poor versus extensive metaboliser can be quite different.[20] It is noted that induction effect with rifampicin can occur anytime between <5 to 14 days.[12,21,22] Similarly, some time is required after withdrawal of the inducer for the induced-enzyme system to return to its baseline activity.[6] For inhibition effects, their disappearance is in general rapid upon cessation of the inhibitor.[6,20,21] Furthermore, induction or inhibition not only changes the serum concentrations of the parent drugs but also can alter those of the drug metabolites, some

Table I. Representative substrates, inducers and inhibitors of cytochrome P450 (CYP) enzymes

Enzyme	Substrate	Inducer	Inhibitor
CYP1A2	Caffeine	Cigarette smoke	Cimetidine
	Clozapine	Phenobarbital (phenobarbitone)	Ciprofloxacin
	Phenacetin	Phenytoin	Enoxacin
	R-warfarin	Rifampicin (rifampin)	Erythromycin
	Tacrine		Fluvoxamine
	Theophylline		Isoniazid (?)
			Ritonavir
CYP2C9/10	Phenytoin	Phenobarbital	Fluconazole
	S-warfarin	Phenytoin	Isoniazid
	Tolbutamide	Rifampicin	
CYP2C19	Citalopram	Phenobarbital	Cimetidine
	Diazepam	Phenytoin	Diazepam
	Imipramine	Rifampicin	Fluoxetine
	Lansoprazole		Isoniazid
	Pantoprazole		Omeprazole
	Omeprazole		Sertraline
	S-mephenytoin		
CYP2D6	Amiodarone		Amiodarone
	Amitriptyline		Cimetidine
	Clomipramine		Fluoxetine
	Clozapine		Fluphenazine
	Codeine		Haloperidol
	Desipramine		Paroxetine
	Dextromethorphan		Propoxyphene
	Encainide		Quinidine
	Flecainide		Ritonavir
	Fluoxetine		Sertraline
	Fluvoxamine		Venlafaxine
	Haloperidol		
	Imipramine		
	Metoprolol		
	Mexiletine		
	Nortriptyline		
	Paroxetine		
	Perphenazine		
	Propafenone		
	Propranolol		
	Risperidone		
	Thioridazine		
	Timolol		
CYP2E1	Chlorzoxazone	Ethanol	
	Halothane	Isoniazid	
	Methoxyflurane	Phenobarbital	
	Paracetamol (acetaminophen)		
CYP3A3/4	Alprazolam	Carbamazepine	Cimetidine
	Astemizole	Phenobarbital	Clarithromycin
	Carbamazepine	Phenytoin	Diltiazem
	Cisapride	Rifampicin	Erythromycin
	Cyclosporin		Fluconazole

Table I. Cont'd

Enzyme	Substrate	Inducer	Inhibitor
	Dapsone		Fluoxetine
	Diltiazem		Indinavir
	Erythromycin		Itraconazole
	Felodipine		Ketoconazole
	Lidocaine (lignocaine)		Ritonavir
	Midazolam		Sertraline
	Nifedipine		
	Quinidine		
	Tacrolimus		
	Tamoxifen		
	Terfenadine		
	Testosterone		
	Triazolam		
	Valproic acid (sodium valproate)		
	Verapamil		

of which can be therapeutically active and/or toxic.[20] Therefore, the overall pharmacological results of induction or inhibition may be complex and knowledge of changes in parent drug levels may not be sufficient to enable prediction of consequences of drug interactions.[6,22] Unlike oxidative metabolism in the CYP450 system, glucuronidation and sulphation are generally not affected by enzyme inducers to the same extent.[18]

1.3 The P-Glycoprotein System

P-glycoprotein, a 170 kDa phosphorylated and glycosylated plasma membrane protein belonging to the ATP-binding cassette superfamily of transport proteins was first described in the 1970s.[25] These proteins located largely in the liver and intestine, are encoded by the MDR (multidrug resistance) genes and serve to regulate the transport of drugs.[26,27] The substrates include many of the same drugs that are metabolised by the CYP450 enzymes especially those of the CYP3A family.[23,28] Examples are HIV protease inhibitors, lovastatin, erythromycin, rifampicin, various anticancer drugs (such as doxorubicin, vinblastine, paclitaxel and etoposide), immunosuppressive drugs (such as cyclosporin and tacrolimus) and steroids. Inhibitors of the P-glycoprotein transport system include HIV protease inhibitors, tamoxifen, ketoconazole, midazolam, verapamil and cyclosporin.[28] P-glycoprotein possibly has a role in modulating expression of CYP3A. It has been found that the extent to which rifampicin could induce CYP3A was so affected.[29] This is likely to complicate the prediction of interactions among drugs that are substrates for both P-glycoprotein and the CYP3A systems. Rifampcin has also been shown to increase the P-glycoprotein-mediated excretion of talinolol predominantly in the gut wall, possibly through induction of the transport system.[30] Concomitant rifampicin therapy may also affect digoxin disposition in humans by induction of P-glycoprotein. Experimental data have shown significantly greater reduction of the area under the curve (AUC) of oral digoxin compared with that of intravenous digoxin, together with increased intestinal P-glycoprotein content by 2- to 3-fold, on coadministration of rifampicin and the cardiac glycoside.[31]

2. Interactions Among Antituberculous Drugs

Drug interactions during antituberculous chemotherapy theoretically should be categorised into those occurring among antituberculous drugs and those between antituberculous drugs and other drugs/dietary constituents. The former are generally of little

clinical importance. Thus, they will only be briefly discussed.

The disturbance in pharmacokinetics on coadministration of rifampicin and isoniazid is far from being consistent[32] and is clearly of no significance. Although para-aminosalicylic acid was found to delay the time to reach peak concentration following drug administration (T_{max}), and reduce the peak plasma concentration after single-dose administration (C_{max}) and AUC of rifampicin,[33] this is likely to be of little significance because the two agents are hardly ever used together. During the concomitant administration of pyrazinamide and rifampicin, the AUC of rifampicin was decreased while its clearance was increased.[34] One report also indicated that pyrazinamide and ethionamide could increase serum concentration of isoniazid.[35] The significance of these two aforementioned reports remain unclear, particularly in light of the strong experience of successful application of standard short-course antituberculous chemotherapy regimens embracing the use of isoniazid, rifampicin, pyrazinamide and ethambutol.[4]

Although the WHO encourages the use of fixed dose combinations of rifampicin, isoniazid together with pyrazinamide (or pyrazinamide plus ethambutol) for the treatment of tuberculosis,[4] primarily to enhance adherence and reduce drug resistance, there is still a concern for reduced rifampicin absorption from these combination formulations when manufactured under suboptimal conditions.[36] In fact, the WHO only advises the use of formulations with demonstrated rifampicin bioavailability.[37] To assist with this process, the WHO is engaged in establishing a quality assurance laboratory network to provide national tuberculosis programmes with a mechanism for ensuring procurement of high-quality combination medications.[38] Thus, this potential pharmaceutical interaction among antituberculous drugs merits some attention because of its possible adverse impact on treatment outcomes.[39]

Rifampicin and isoniazid when coadministered might lead to synergistic hepatotoxicity.[40] In a meta-analysis,[40] the mean incidences of drug-related toxic hepatitis were found to be 1.6% (isoniazid), 1.1% (rifampicin) and 2.6% (isoniazid + rifampicin). The underlying mechanism is not totally clear but might apparently be related to the induction of the hydrolase pathway and accumulation of hydrazine and possibly its acetylated derivatives, particularly in those with the slow acetylator phenotype.[41] The presence of underlying liver disease and old age will further increase the risk of hepatotoxicity.[42]

3. Clinically Significant Interactions Between Antituberculous Drugs and Other Drugs/Dietary Constituents

These interactions are often of great clinical relevance. Only those pertinent to isoniazid, rifampicin and the fluoroquinolones will be discussed in detail since these constitute the majority of the clinically significant interactions. Clarithromycin has not been shown to have convincing clinical activity against *Mycobacterium tuberculosis*. Suffice to note that it can act as an enzyme inhibitor leading to dose-related rifabutin toxicity when coadministered with this rifamycin in the management of disseminated *Mycobacterium avium-intracellulare* disease.[43,44] Rifabutin is a less potent hepatic enzyme inducer compared with rifampicin, and thus is less likely to be involved in drug interactions.[45]

3.1 Interactions of Isoniazid

Many of the clinically significant interactions between isoniazid and other agents (pharmaceutical or dietary) are pharmacokinetic in nature, involving inhibition of enzyme systems by the former, especially the CYP450 superfamily.[46]

3.1.1 Phenytoin

Murray[47] first reported clinical phenytoin toxicity in patients who received isoniazid concomitantly, and the neurological dysfunction disappeared on isoniazid cessation. Subsequently Kutt et al.[48-50] confirmed this interactive toxicity and suggested that the likely responsible mechanism was that of inhibition of phenytoin metabolism by isoniazid, particularly in patients who are slow ac-

etylators. Miller et al.[51] also reported similar findings. The neurological toxicity could be severe enough to result in fatality.[52] In patients who are rapid acetylators, it seemed that phenytoin toxicity occurred more readily in the presence of isoniazid-induced hepatic dysfunction.[53] As rifampicin is a potent inducer of the CYP450 enzymes, this effect was found to probably outweigh the inhibitory effect of isoniazid on the metabolism of phenytoin when both antituberculous drugs were given together.[54]

3.1.2 Carbamazepine

Valsalan and Cooper.[55] reported features of carbamazepine toxicity in patients who received isoniazid concomitantly. When the dose of carbamazepine was reduced, the signs of toxicity subsided. Subsequently, other authors also reported elevated serum cabamazepine levels in patients receiving isoniazid treatment.[56,57] The additional potentiality of drug-drug interaction leading to liver toxicity due to isoniazid also deserves attention.[56,58] This could be due to complex enzyme inhibition and induction involving both the CYP450 family and other systems.[56]

3.1.3 Valproic Acid (Sodium Valproate)

To date, there have been limited reports on an interaction between isoniazid and valproic acid (sodium valproate); in one reported case the interaction lead to isoniazid hepatoxicity and in this case and a second there was valproic acid toxicity.[59,60] The likely responsible mechanisms might be similar to those in operation for carbamazepine.[59]

3.1.4 Levodopa

Concomitant isoniazid and levodopa therapy has been reported to result in flushing, palpitation and elevation of blood pressure.[61] Isoniazid can act as a monoamine oxidase inhibitor, thus causing excess catecholamine stimulation when coadministered with the dopamine precursor levodopa. Furthermore, inhibition of both peripheral and central dopa decarboxylase aggravate the adverse effects.

3.1.5 Theophylline

Reports of reduced clearance of theophylline in patients coadministered isoniazid have been reported in the literature,[62,63] affecting the slow acetylators more.[63] Clinical theophylline toxicity has also been reported.[64] The interaction of isoniazid with theophylline is more likely to be clinically relevant when a higher dosage of isoniazid is administered i.e. ≥10 mg/kg/day. When rifampicin is administered together with isoniazid, the serum theophylline concentration is most likely to decrease,[46] though reports of reduced clearance[65,66] and even consequential toxicity[65] are also available.

3.1.6 Paracetamol (Acetaminophen)

Increased susceptibility to paracetamol (acetaminophen) toxicity in patients receiving isoniazid has been well reported.[67-69] It has been hypothesised that isoniazid induces the CYP450 system, resulting in increased metabolism of paracetamol, formation of toxic metabolites, depletion of glutathione stores and subsequent hepatocellular injury.[70] Biphasic effect of inhibition-induction on one CYP450 isoform enzyme, CYP2E1, may also explain the increased risk of hepatotoxicity.[67] Patients with slow acetylator phenotype when given isoniazid 300mg daily for 7 days along with paracetamol 500mg at different times during this period actually were found to excrete lower amounts of oxidative metabolites.[46] However, 24 hours after the last dose of isoniazid, when another dose of paracetamol was administered, a marked increase (about 50%) in oxidative metabolites over baseline was observed, followed by a return to normal values when the next dose of paracetamol was given 48 hours later.[71] A significant increase of oxidative metabolites was also found when rapid acetylators were given paracetamol only 12 hours after their daily isoniazid dose.[72]

3.1.7 Warfarin

Rosenthal et al.[73] first reported a clinical case of warfarin toxicity when isoniazid was accidentally administered at a dosage of 600mg once daily instead of the usual 300mg once daily. A consistent

report on an animal model was in fact made somewhat earlier.[74]

3.1.8 Benzodiazepines

Isoniazid was found to impair the hepatic demethylation of diazepam.[75] However, when rifampicin and ethambutol were also administered, the overall result was enhanced clearance of diazepam due possibly to the overriding induction of hepatic microsomal enzyme mediated oxidation.[75] In another study, isoniazid was found to decrease the clearance of triazolam but not oxazepam.[76] Other benzodiazepines like chlordiazepoxide and clonazepam that are hepatically metabolised may also have reduced clearance by isoniazid treatment although studies are needed to confirm the impression.[46]

3.1.9 Antacids

Some studies have shown that antacids, but not histamine H_2 receptor antagonists can impair the absorption of isoniazid.[77,78] However, others[79,80] have shown little effect. A higher dose of aluminium hydroxide used in the early study might account for the discrepancy.[77]

3.1.10 Other Drugs

Prednisolone was found to reduce serum concentrations of isoniazid in both slow and rapid acetylators, but the underlying mechanism is unclear.[81] Pretreatment with isoniazid has been reported in some cases to increase the hepatic metabolism of enflurane, a volatile anaesthetic, thereby increasing the concentration of fluoride ions and the resulting risk of nephrotoxicity.[82] The effect of long-term antituberculous treatment on vitamin D metabolism was not found to be significant, albeit the study was confounded by failure to control for dietary calcium and vitamin D intake.[83] Thus, the short-term effect of isoniazid on lowering serum concentrations of 25-hydoxy vitamin D and 1, 25-dihydroxy vitamin D reported earlier[84] carries unclear significance. As isoniazid is a weak monoamine oxidase inhibitor, there is a potential for interacting with antidepressant medications. The pertinent clinical data, however, have been conflicting.[85,86] Isoniazid when used at high dose, has also been found to interact with hydralazine and other vasodilators, irrespective of their mechanisms of action. The interaction often resulting in hypotension could be due to the influence of the drug on γ-aminobutyric acid (GABA) levels at cardiovascular regulatory sites.[87]

3.1.11 Food

Basically all food can impair absorption of isoniazid, particularly those with high fat or carbohydrate content.[80,88] Case reports on 'cheese' and 'wine' reaction in patients who received isoniazid might presumably be due to accumulation of monoamines (tyramine) as isoniazid can be a monoamine oxidase inhibitor.[89-91] Because isoniazid is also an inhibitor of histaminase[90,91] reports of adverse reactions representing histamine overdose, resulting from ingesting fish with high histamine content and isoniazid have been reported.[91,92]

3.2 Interactions of Rifampicin (Rifampin)

Food affects the oral absorption of rifampicin, but probably not antacids.[93]

Most interactions involving rifampicin are pharmacokinetic in nature. Rifampicin is a potent inducer of many CYP450 isoenzymes, particularly CYP2C and CYP3A as previously discussed.[18-24] Drugs metabolised by these isoenzymes will be clearly affected with therapeutic effects attenuated or opposed.[5,18-24] Other drugs with routes of metabolism less clearly understood can also be metabolised more rapidly in patients receiving rifampicin, and their pharmacological effects can thus be altered. Some, like morphine may involve phase II biotransformation pathways such as glucuronidation,[94] and others, like digoxin may even involve the P-glycoprotein elimination mechanism.[31] Table II depicts some examples of such potentially or overtly significant clinical interactions of varying severity.[31,54,75,93-202]

Aside from the interactions discussed which are largely due to induction of liver microsomal enzymes and intestinal enzymes by rifampicin,[203] a number of intriguing interactions involving rifampicin and other drugs are also worthwhile mentioning. The underlying mechanisms for some of

Table II. Examples of clinically significant interactions of rifampicin (rifampin) mostly related to its enzyme induction action. For all induction interactions, special attention is needed when initiating and discontinuing rifampicin therapy.

Drug	Clinical significance	Comments/Recommendations	References
Antacids	*	Advise to take rifampicin 1 hour before or 2 hours after meal; antacids have uncertain, but probably little interference with its absorption	93, 95
Anticoagulants, oral			
Warfarin	***	Increase warfarin dose according to results of international normalised ratio and prothrombin time	96-98
Anticonvulsants			
Hexobarbital	**	Monitor clinical state and plasma hexobarbital level (with prudence in interpreting plasma concentration of racemic drug); increase in dose may be required	99, 100
Phenytoin	**	The increase in phenytoin clearance is more marked when rifampicin is used alone than when its is used together with isoniazid and ethambutol; monitoring serum phenytoin concentration is required	54
Valproic acid (sodium valproate)	*	Studies required to evaluate clinical impact of lowered serum valproic acid concentration; monitoring of clinical state and serum concentration of valproic acid needed; effect of coadministration of isoniazid is not known	101
Anti-infectives (excluding anti-retroviral agents)			
Atovaquone	*	More investigation required, avoid coadministration of drugs; if absolutely necessary, then monitor for loss of atovaquone efficacy	102
Clarithromycin	*	Further studies required to evaluate clinical impact of reduced serum concentration of clarithromycin	103
Chloramphenicol	**	Avoid coadministration of drugs; if not, monitor chloramphenicol serum concentration	104, 105
Dapsone	**	Further studies required to evaluate clinical impact especially in patients with *Pneumocystis carinii* pneumonia	106-108
Doxycycline	**	Avoid coadministration of drugs; monitor patient's clinical response to doxycycline therapy if absolutely indicated	109
Fluconazole	***	Monitor clinical response and serum fluconazole concentration; may need to escalate fluconazole dosage; less reduction in serum concentration compared with itraconazole	110-112
Itraconazole	***	Same as for fluconazole; avoid use together with rifampicin if possible	111, 113, 114
Ketoconazole	***	Same as for fluconazole; space ketoconazole and rifampicin by 12 hours or avoid use of the two drugs concomitantly if possible	115-117
Cardiovascular therapeutic agents			
Amiodarone	***	Monitor clinical state and serum amiodarone concentration if coadministration unavoidable	118
Bisoprolol	*	Monitor clinical response to bisoprolol	119
Bunazosin	**	Monitor clinical response and serum bunazosin concentration; adjust dose for antihypertensive effect as needed	120
Carvedilol	***	Monitor clinical response and increase dose if needed	121
Clofibrate	**	Monitor for clinical efficacy and serum lipid level and increase dose if needed	122
Digitoxin	***	Monitor serum digitoxin concentration plus heart failure and arrythmia control; increase dose if needed	123-125
Digoxin	**	Monitor serum digoxin concentration and clinical control of heart failure/arrhythmia; interaction complicated by renal failure	31, 126-128
Diltiazem	***	Monitor for attenuation of effective control of hypertension or angina	129-131
Disopyramide	**	Monitor clinical response	132, 133
Enalapril	**	More studies required; careful monitoring of clinical response especially blood pressure on coadministration	134

Table II. Cont'd

Drug	Clinical significance	Comments/Recommendations	References
Fluvastatin	*	Monitor clinical efficacy and serum cholesterol level; adjustment of dose may be required	135
Lorcainide	**	Monitor for decreased lorcainide effectiveness	136
Losartan	**	Monitor for reduced clinical efficacy of losartan. Further study on clinical relevance required	137
Metoprolol	**	Monitor for reduced efficacy of blood pressure control and also angina; may need dosage increase	138
Mexiletine	***	Monitor for arrhythmia control if combination is unavoidable	139, 140
Nifedipine	***	Use alternative agent or class of drug if possible; monitor clinical response, may need increase of dose	141, 142
Propafenone	***	Monitor plasma propafenone concentration and arrhythmia control; increase dose if necessary	143-145
Propanolol	***	Monitor blood pressure control, may need increased dose	146
Quinidine	***	If combination unavoidable, monitor arrhythmia control and serum concentration; increase dose if needed	128, 147, 148
Tertatolol	**	Monitor for possible attenuation of clinical efficacy	149
Tocainide	**	Monitor arrthymia control; may need increase in dose	150
Verapamil	***	Use alternative agent or class of drug if possible; monitor serum concentration and clinical response to guide required increase in drug dose	151-155
Contraceptives, oral	***	Change to other forms of contraception together with counselling (because unplanned pregnancy well documented with coadministration of oral contraceptives and rifampicin)	156-158
Glucocorticoids			
Cortisone	***	Increase in dose, roughly twice according to clinical and biochemical response parameters	159, 160
Dexamethasone	***	Same as above	161
Methylprednisolone	***	Same as above	162
Prednisone, prednisolone	***	Same as above	163, 164
Immunosuppressants			
Cyclosporin	***	Effect on oral preparation greater than intravenous preparation; rifampicin-containing antituberculous regimen when used concomitantly necessitates increase in dose ± thrice instead twice daily administration; guidance by therapeutic drug monitoring mandatory to avoid toxicity. Loss of graft due to interaction possible	165-171
Sirolimus	**	Most likely similar to cyclosporin; more clinical data required	172
Tacrolimus	***	Similar to cyclosporin; more clinical data desirable	173-175
Leflunomide	**	Monitor for hepatotoxicity due to metabolites; more clinical data required	176
Levothyroxine	***	Monitor clinically and biochemically for hypothyroidism for patients on L-thyroxine replacement	177, 178
Montelukast	*	More clinical data required to assess possibility of worsening of asthma control	179
Opioids			
Methadone	***	Increase dose to prevent opioid withdrawal as indicated	180, 181
Morphine	**	Monitor for pain control and increase dose as needed; more clinical data required	94
Psychotropic Agents			
Benzodiazepines			
diazepam	**	Monitor clinical effect and increase dose as needed; possible circumvention by substitution with lorazepam or oxazepam	75, 182, 183
midazolam	**	Same as above	184

Table II. Cont'd

Drug	Clinical significance	Comments/Recommendations	References
nitrazepam	**	Same as above	185
triazolam	**	Same as above	186
Haloperidol	***	Monitor control of psychosis; escalate dose if needed	187, 188
Nortriptyline	***	Monitor for loss of antidepressant effect and escalate dose as needed; therapeutic monitoring of serum antidepressant concentration possible	189, 190
Sertraline	**	Same as for nortriptyline	191
Zopiclone	**	Monitor clinical hypnotic effect; may need dosage increase	192
Zolpidem	**	Monitor as for zopiclone	193
Rofecoxib	*	Monitor clinical anti-arthritis efficacy; more clinical data required	194
Sulphasalazine	*	Monitor clinical effects; more data required	195
Sulphonylureas			
Chlorpropamide	***	Monitor blood glucose control and adjust dosage accordingly	196
Glibenclamide (glyburide)	***	Same as above	197-199
Tolbutamide	***	Same as above	123
Theophylline	***	Monitor clinical effect and rarely toxicity (due to isoniazid coadministration and other confounding variables); monitor serum theophylline concentration; increase of dose and rarely decrease of dose may be required	46, 65, 66, 200-202

* = possible; ** = likely; *** = definite.

these interactions have not been totally unravelled. Serum concentrations of rifampicin were undetectable when the drug was given simultaneously with both isoniazid and ketoconazole, and decreased by about half when just ketoconazole was given concurrently with rifampicin.[115] However, serum concentrations similar to those attained with rifampicin alone were achieved when rifampicin was administered 12 hours after ketoconazole.[115] An interaction at the level of absorption of rifampicin might be in operation. Rifampicin was speculated to exert an alternative role, aside from enzyme induction to potentiate the anticoagulant effect of warfarin.[204] This might be due to a change in warfarin binding, a differential effect on warfarin stereoisomer metabolism or through another obscure pharmacodynamic effect.[204] However, the confounding influence of isoniazid-related interaction could not be totally excluded. Coadministration of cotrimoxazole (trimethoprim-sulfamethoxazole) with rifampicin could escalate the serum levels and half-life of the latter[205] and this may lead to hepatotoxicity. Levamisole when given simultaneously with rifampicin was found to cause an approximately 3-fold rise in the free fraction of rifampicin and led to increase in its clearance with decrease in serum rifampicin concentration.[206] A displacement of drug at the binding sites of protein might have occurred.

3.3 Interactions of Fluoroquinolones

The discussion on interactions between fluoroquinolones and other drugs/dietary components will be restricted largely to those pertinent to ciprofloxacin, ofloxacin and levofloxacin. This is because these are currently the three fluoroquinolones that are recommended for long-term use in tuberculosis treatment based on their satisfactory safety profile.[207] The interactions include those which result in altered absorption, metabolism and renal excretion of the fluoroquinolones or the other agents, and those which result in potential CNS toxicity. It is important to note that extrapolation of the drug interactions observed with one fluoroquinolone to another can be inappropriate. Indeed, ciprofloxacin has been found to be a stronger inhibitor of CYP1A2 activity than ofloxacin.[208,209]

3.3.1 Pharmacokinetic Interactions

Absorption

Food usually has little or no impact on the principal pharmacokinetic parameters of ciprofloxacin, ofloxacin and levofloxacin.[210-212] Aluminium-, magnesium- and calcium-containing antacids are well known for their potential to reduce the absorption of oral fluoroquinolones (by ≤85% decrease in AUC or C_{max}), though to different degrees depending chiefly on the metal cation, aluminium and magnesium being more potent.[213-215] The proposed mechanism of this interaction lies in the chelation between the cation and 4-keto oxygen, 3-carboxyl group of the fluoroquinolone.[213] Ranitidine, a H_2 antagonist, has no effect on the absorption of concurrently administered ciprofloxacin,[213] ofloxacin[216] or levofloxacin.[215] Sucralfate (an aluminium salt of a sulphated disaccharide) is known to markedly diminish the absorption of most fluoroquinolones (≤90% decrease) if no adequate spacing of doses is carried out.[212,217,218] This can be prevented by giving the fluoroquinolone 2 to 3 hours before the administration of sucralfate.[212] The iron supplement ferrous sulphate can impair the absorption of fluoroquinolones.[215,219] The decrease in AUC and C_{max} can be ≤90%. Studies have shown ciprofloxacin can have reduced oral bioavailability when coadministered with didanosine.[220,221] It is likely that other fluoroquinolones will behave similarly. Many multivitamin preparations contain minerals such as zinc, magnesium and copper. They can also impair the absorption of fluoroquinolones when these antimicrobials are coadministered.[219] The preparations probably act through a similar chelation mechanism as for the antacids. The oral bioavailabilities of ofloxacin and ciprofloxacin were significantly reduced when given with nutritional supplements in one study,[222] but another study by Yuk et al.[223] demonstrated no such effect.

Metabolism

Ciprofloxacin, by inhibiting CYP450 enzymes, appeared to have significant negative impact on caffeine and theophylline clearance,[224-226] possibly leading to undesirable gastrointestinal and neurological toxicity.[227,228] On the other hand, ofloxacin and levofloxacin have not been shown to significantly interfere with the clearance of theophylline or caffeine.[224,227,229,230] Minor alteration in theophylline clearance did not produce clinical effects.[231]

Although there have been a number of clinical reports on potentiation of the hypoprothrombinaemic effect of warfarin by ciprofloxacin and ofloxacin,[232-234] the evidence of a pharmacokinetic interaction due to liver microsome enzyme inhibition by a fluoroquinolone leading to accumulation of the anticoagulant has been controversial.[235-237] However, results of studies performed in healthy volunteers might not be fully extrapolatable to the elderly or malnourished patients.[233] Sometimes only the pharmacologically less active *R*-isomer was in fact found to accumulate.[235] Thus, the mechanism of interaction may be beyond a pharmacokinetic issue.

Elevation of serum concentrations of cyclosporin have been reported with the concomitant use of cyclosporin with certain fluoroquinolones like norfloxacin,[238,239] and ciprofloxacin.[240] Nephrotoxicity was reported to occur when fluoroquinolones and cyclosporin were coadministered.[238,240,241] Conversely, there have been reports of lack of disturbance of cyclosporin pharmacokinetics when either ciprofloxacin or levofloxacin was coadministered.[242-246] Thus, the clinical significance of the interaction between some fluoroquinolones and cyclosporin appears not yet fully known, nor is its mechanism if it is indeed present.

More reports and studies of lowered serum phenytoin concentrations, on coadministration of the anticonvulsant and ciprofloxacin, are available rather than of the contrary occurrence.[247-252] This can be of clinical significance as the propensity to seizure is much increased as a result of this putative interaction between the two drugs.[248,252] The underlying mechanisms have not been fully elucidated. Possible ones such as ciprofloxacin-mediated induction of liver enzymes or suppression of gut flora–related deconjugation have been suggested.[250,252]

Renal Excretion

Cimetidine and probenecid have been shown to reduce the renal clearance of ofloxacin and levofloxacin.[253-255] Probenecid was also reported to reduce the renal clearance of ciprofloxacin, though there was no significant changes in the total clearance of the drug presumably due to activation of nonrenal elimination pathways.[256]

3.3.2 Pharmacodynamic Interactions

Nonsteroidal Anti-Inflammatory Drugs

The likely attributable mechanism for CNS proexcitation is a concentration-dependent competitive inhibition of GABA binding at post-synaptic receptor sites.[257] Certain nonsteroidal anti-inflammatory drugs (NSAIDs) and their metabolites can enhance the inhibition of GABA receptor binding by fluoroquinolones.[258,259] While in laboratory studies, the combination of NSAIDs and ciprofloxacin could produce convulsions in mice,[260,261] this effect has not been significantly observed with ofloxacin and levofloxacin.[261,262]

Others

When ciprofloxacin was combined with theophylline, GABA binding to receptors could be decreased in a dose-related fashion leading to neurotoxicity, even in the absence of a significant increase in serum concentrations of theophylline.[263] The previously discussed nephrotoxicity that might result from interaction of cyclosporin with ciprofloxacin,[240,241] could also be pharmacodynamic in nature as the levels of cyclosporin were only found to be therapeutic. As ofloxacin has not been shown to be a significant inhibitor of CYP450 enzymes, the interaction of ofloxacin and warfarin could again result from a pharmacodynamic, rather than pharmacokinetic interaction.[232] The postulated mechanisms have included suppression of vitamin-K producing gut bacteria and displacement of warfarin from albumin binding sites. However, there is yet no consensus on these hypothesised mechanisms.[264,265] When ofloxacin and cycloserine were coadministered, adverse neurological reactions could occur.[266,267] At the moment, there are no convincing data on an unequivocal pharmacokinetic interaction between these two antimycobacterial agents.[268] One possible mechanism is a pharmacodynamic interaction. Finally, Lucet et al.[269] reported two cases of increased neurotoxicity when metronidazole was coadministered with pefloxacin. Unfortunately, serum drug concentrations were not clearly reported. The interaction was suspected to be pharmacodynamic in nature. No similar data exist for other fluoroquinolones.

3.4 Interactions of Other Antitubreculous Drugs

Streptomycin has ototoxic and nephrotoxic potential and, when practical, should not be given with drugs with similar toxicity profiles. These include other aminoglycosides, some cephalosporins, vancomycin, amphotericin B, cyclosporin and cisplatin.[5] Streptomycin may also potentiate the effect of neuromuscular blocking agents used during the administration of an anaesthetic.[5]

Pyrazinamide was reported to have drug interaction with allopurinol.[270] The latter induced marked changes in levels of pyrazinamide metabolites and accumulation of pyrazinoic acid. These could cause inhibition of renal urate secretion and might negate the favourable effect of allopurinol as a hypouricaemic agent. Pyrazinamide was also suspected to contribute to lowering of serum level of cyclosporin when used with isoniazid and rifampicin.[271]

Ethambutol was reported to increase the unbound fraction of diazepam when patients received coadministration of these two drugs, but the change in clearance was not significant.[75] Ethambutol C_{max} was reduced by about 30% by aluminium-magnesium antacid,[272,273] thus avoidance of antacids has been recommended near timing of ethambutol administration.[273]

4. Drug Interactions in the Treatment of HIV-Related Tuberculosis

4.1 Drug-Disease Interactions

Among others, the most important aspect of drug-disease interactions is malabsorption of anti-

mycobacterial agents[274,275] due to HIV enteropathy and other HIV-associated opportunistic infections of the gut. Rifampicin, ethambutol and to a lesser extent pyrazinamide appeared more readily affected, unlike isoniazid.[274,275] Malabsorption could become increasingly common and severe with progression in the immunodeficiency.[274,275] Rifabutin, a drug with equivalent antituberculous activity in patients with HIV,[276] appeared to be less frequently malabsorbed in this patient population compared with rifampicin.[277] Better bioavailability of rifapentine was also documented in another study.[278] The absorption of fluoroquinolones appeared to be reasonably preserved.[279]

4.2 Drug-Drug Interactions

As the therapy for HIV and its associated infections is becoming increasingly complex, the potential for drug interactions can be extremely high. A few important groups of possible drug interaction during antituberculous chemotherapy are briefly discussed below.

4.2.1 Interactions of Rifamycins with Nucleoside Reverse Transcriptase Inhibitors

The nucleoside reverse transcriptase inhibitors such as zidovudine and lamivudine are not metabolised by the CYP450 enzymes. Furthermore, the pharmacokinetic parameter most closely associated with the activity of these analogues is the intracellular concentration of the active form, the triphosphate derivative,[280] and a close relationship between the serum concentration of the analogue and its triphosphate metabolite is lacking.[281,282] The plasma concentration of zidovudine, which is metabolised mainly by glucuronidation,[283] is decreased it is when coadministered with rifampicin.[284] Plasma concentration lowering, however, has not been shown to reduce the concentration of the intracellular metabolite;[282] thus the clinical efficacy of these antiretroviral agents can still be preserved.

4.2.2 Interactions of Rifamycins with HIV Protease Inhibitors

The currently available rifamycins are all inducers of the CYP3A isoform enzymes, with rifampicin having greater activity than rifabutin.[45] Thus, rifampicin has been shown to decrease serum concentrations of protease inhibitors by 35 to 92%, whereas rifabutin decreases them by only 15 to 45%.[6] Although the clinical relevance of these findings have not been established as the interaction studies were conducted in human volunteers, the efficacy of these antiviral agents can be attenuated as their activity in the recommended dosage ranges appears to depend heavily on their serum concentrations.[6] Intermittent administration of rifampicin does not seem to reduce the enzyme inducing capacity could impair the therapeutic efficacy of the protease inhibitors.

The clinical relevance of modest reduction in serum concentrations of the protease inhibitors when coadministered with rifabutin remains unclear. It has been suggested that increased dosage of indinavir and nelfinavir might enable the maintenance of therapeutic efficacy.[6] Furthermore, as the protease inhibitors are CYP450 enzyme inhibitors, the serum concentration of rifabutin would be increased. This might result in toxicity such as uveitis and leucopenia.[285] This phenomenon has led to the initial recommendation that ritonavir, which has the strongest enzyme inhibition, should preferably not be used together with rifabutin.[6,286] However, there have been more recent suggestions that appropriate dosage reduction of rifabutin when coadministered with indinavir, nelfinavir and perhaps even ritonavir might circumvent this interaction toxicity.[287-290] Furthermore, as a comparison, for the patient who is treated with saquinavir soft gelatin capsules, with relatively weak CYP450 inhibition, and two nucleoside reverse transcriptase inhibitors, the usual dosage of rifabutin should probably not be decreased.[290] In contrast, the protease inhibitors have little known effects on serum rifampicin concentrations.[6] These phenomena can be exploited advantageously in therapeutic terms for enabling the use of ritonavir together with rifampicin and saquinavir, and perhaps even other protease inhibitors.[291] The strong inhibiting effect of ritonavir on saquinavir metabolism might compensate

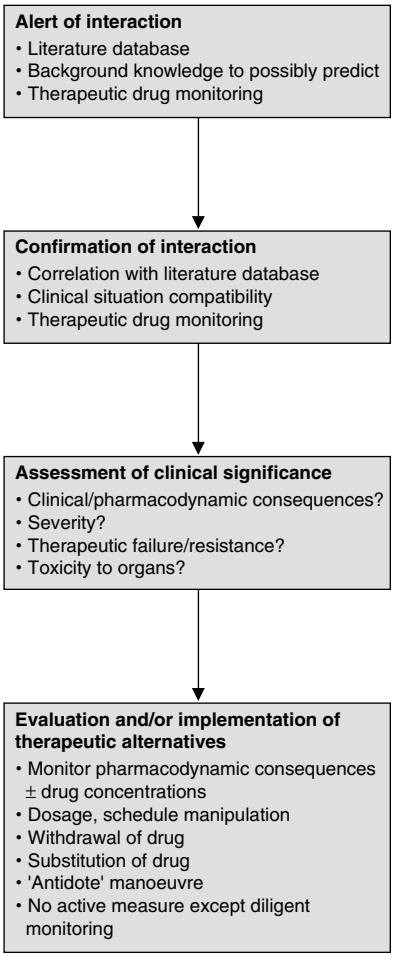

Fig. 1. Proposed algorithm for the management of drug interactions during antituberculous chemotherapy.

for the enzyme inducing effect of rifampicin, thus preserving their combined antiretroviral activity.

4.2.3 Interactions of Rifamycins with Non-Nucleoside Reverse Transcriptase Inhibitors

The non-nucleoside reverse transcriptase inhibitors are metabolised hepatically, but there are major differences in their actions on the CYP3A enzymes and the degree to which they act as substrates of these enzymes. As a result, their interactions with rifamycins cannot be generalised as a class.[6] Delavirdine acts much like protease inhibitors. Its coadministration with rifampicin can result in marked reduction in the serum concentration of the antiretroviral agent with little change in the serum concentration of the antituberculous drug.[292] Delavirdine concentrations were also reduced by 80% when given with rifabutin,[293] and rifabutin concentrations were raised by 300%.[294] Thus, the use of delavirdine with either rifamycin is not recommended.[290] It appears that nevirapine and efavirenz can be used with either rifabutin or rifampicin.[290] Increase in dosage of rifabutin is required when used together with efavirenz. Preliminary data also have suggested that intermittent rifampicin administration might incur less interaction with nevirapine,[295] and this could have potential therapeutic implications.

4.2.4 Interactions of Other Antituberculous Drugs with Antiretroviral Agents

Isoniazid has been evaluated and was found to have no interaction with indinavir.[6] However, an increased incidence of peripheral neuropathy with coadministration of stavudine and isoniazid has been reported.[296] Ethionamide might be primarily metabolised by CYP3A isozymes,[297] and hence can interact potentially with protease inhibitors. A major obstacle in prediction of drug interactions among the other antituberculous drugs and the antiretroviral agents, particularly regarding the second-line drugs, is the lack of full knowledge of their pharmacokinetics.

5. Management of Drug Interactions During Antituberculous Chemotherapy

Figure 1 presents a proposed algorithm for the management of drug interactions between antituberculosis drugs. To begin with a readily available and constantly updated literature database for consultation is of paramount importance, since new therapeutic agents are continually emerging and it is virtually impossible to maintain an ever fully comprehensive vocabulary by oneself. An example of such a source of comprehensive reference is the 'P-450 and P-glycoprotein drug interactions websites' compiled by Dr J Oesterheld and Dr DN Osser, MD (http://www.mhc.com/cytochromes/, http://mhc.com/PGP/ and others). However, one

should be familiar with the basic pharmacokinetic and pharmacodynamic characteristics of the agents in question to help in predicting the likelihood of interactions. When in doubt, and if therapeutic drug monitoring (TDM) is available, this should be prudently utilised early on to help prevent toxicity resulting from an interaction. If an interaction is suspected to have already occurred, one should check the clinical situation compatibility particularly regarding the time course. In addition to data retrieved from the literature, TDM can be used also to confirm the presence of pharmacokinetic interactions. The data in literature must also be appropriately interpreted, considering such factors as disease population versus healthy volunteers, design and strength of the clinical report or study, and the drug dosage used. But the greatest concern would be the clinical or pharmacodynamic relevance and consequence, especially the seriousness of the interaction in terms of a change in efficacy or the production of toxicity by one or both drugs. Finally, one needs to evaluate and/or implement alternative therapeutic strategy. Most of the time, change in scheduling or frequency of administration of the drug(s) may be the only change required. However, if this cannot be optimised to meet the goals of treatment or satisfactory alternative drugs are readily available, drug withdrawal and substitution would be the solution. In fortunate settings, despite definitely quantifiable interactions, the clinical impact is mild. Then only vigilant monitoring is required.

With advancement of knowledge, technology and expertise, it is sincerely hoped that TDM can emerge as a new paradigm of care for some patients during antituberculous chemotherapy by optimising the management of a wide variety of pharmacokinetic drug interactions.

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