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Expert Opinion

Drug interactions during therapy with three major groups of antimicrobial agents

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This review focuses on drug–drug interactions with three major groups of antimicrobial agents: macrolides (including azalides and ketolides), quinolones, which are widely used for the treatment of bacterial infections, and azoles, which are used for antifungal therapy. Macrolides and the ketolide telithromycin are potent inhibitors of CYP3A4 and thus interfere with the pharmacokinetics of many other drugs that are metabolised by this enzyme. In contrast, although closely related, azithromycin is not a cytochrome inhibitor. All quinolones form complexes with di- and trivalent cations and, therefore, the absorption of quinolones can be dramatically reduced when given concomitantly with mineral antacids, zinc or iron preparations. Ciprofloxacin exhibits an inhibitory potential for the cytochrome isoenzyme 1A2, resulting in an inhibition of theophylline metabolism. Other quinolones, such as levofloxacin or moxifloxacin, do not interfere with theophylline metabolism. The systemic azoles, such as ketoconazole, itraconazole, fluconazole and voriconazole, are inhibitors of CYP isoenzymes, such as CYP3A4, CYP2C9 and CYP2C19, to varying degrees. In addition, some are substrates of the *MDR-1* gene product, P-glycoprotein. These features are the basis for most of the interactions occurring during azole therapy (e.g., in severely ill patients in the hospital who are treated with multiple drugs).

Keywords: azoles, drug–drug interactions, ketolides, macrolides, quinolones

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1. Introduction

Antimicrobial agents are drugs that are widely used in the hospital as well as in an ambulatory setting. Often, patients who are prescribed antibiotics for an acute infection are also receiving other agents continuously for chronic diseases. Such a situation bears a significant risk for drug interactions, which can be pharmacodynamic or pharmacokinetic in nature. The results of drug–drug interactions can range from barely measurable effects up to major alterations with severe consequences. Published data suggest that the incidence of hospital admissions that are attributable to drug–drug interactions can be as high as 2.8% [1]. This review focuses on drug–drug interactions with three major groups of antimicrobial agents: macrolides, including azalides and ketolides, quinolones, which are widely used for the treatment of bacterial infections, and azoles, antifungal agents that are increasing in use.

Several mechanisms of drug interactions are known to exist. For the drugs discussed in this review, the interactions with oxidative metabolism via interference with CYP enzymes and/or transport proteins such as P-glycoprotein (Pgp) are the most important ones. In humans, a total of 57 *CYP* genes have been identified but only some of the enzymes, mainly the CYP1, CYP2 and CYP3 families, are involved in the metabolism of drugs. A single CYP enzyme may be responsible for the oxidative metabolism of a molecule, or a whole variety of isoenzymes may contribute to the

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metabolic process. Expression of the CYP3A forms is highly variable in human liver specimens, with some livers showing ≤ 60% of their total CYP as CYP3A4, whereas others contain < 10% but its distribution is continuous and unimodal. Typical substrates of this monooxygenase form are frequently used drugs such as ciclosporin, ethylmorphine, diltiazem, quinidine and others. Clinically significant polymorphisms have been described for CYP2D6, CYP2C9 and CYP2C19. For these isoenzymes, extensive and poor metabolisers can be distinguished. Poor metabolisers can be at a high risk for toxicity from drugs that are metabolised by these enzymes [2,3].

Apart from these metabolising enzymes, other systems protect the mammalian organism from the effects of xenobiotics. The transmembrane efflux protein Pgp is the product of the multi-drug resistance (*MDR*) gene, which is extensively colocalised with CYP3A in the intestine, the liver and the kidneys. In the gastrointestinal epithelium, it opposes the absorption of drugs and other xenobiotics by transporting lipophilic substances out of the enterocytes back into the gastrointestinal lumen. The individual variability of this protein is considerable and can be as large as 10-fold. The protein has a broad substrate specificity but, with respect to possible drug interactions, it is important to consider that many drugs have affinities for both the Pgp and CYP3A4/5 [4,5].

With respect to the given multitude of possible interactions, it is reasonable to distinguish these according to the clinical importance of drug interactions. A specific combination of drugs can either be absolutely contraindicated; acceptable when accompanied by drug-level monitoring or dose adjustment; or have a sufficiently low drug interaction potential allowing concomitant administration without precautions.

2. Macrolides and azalides

Interactions between erythromycin and other drugs that are metabolised by CYP-dependent monooxygenases have been described for several decades. A number of comprehensive review articles have been published on drug interactions involving macrolides [6-9]. This section will briefly summarise what is known about clinically important interactions with erythromycin and clarithromycin in comparison to the azalide azithromycin, and will also focus on telithromycin, the newest drug of this family of antimicrobial agents Table 1. Although telithromycin differs considerably from macrolides with respect to its antibacterial activity against macrolide resistant pneumococci, the drug represents a pharmacological modification of erythromycin and exhibits a similar drug interaction profile as a typical macrolide [10,11].

When these drugs are compared, it should be kept in mind that the available data basis for the classic macrolide erythromycin and the newer derivatives (such as clarithromycin, azithromycin and telithromycin) differ considerably because systematic drug interaction studies were not performed when erythromycin was developed as an antimicrobial agent ~ 50 years ago.

Theophylline is metabolised by *N*-demethylation and by 8-hydroxylation. The interaction between macrolides and theophylline has received much attention because both drugs could be prescribed concomitantly in patients with acute exacerbations of chronic bronchitis. The results of an early study in eight healthy individuals showed an increase in theophylline half-life of ≤ 72% over baseline values after a 7-day course of erythromycin 1 g/day [12]. The mean value for the half-life of the bronchodilator increased from 6.7 ± 1.9 (prior to erythromycin) to 8.1 ± 1.6 h (plus 27%). This study documents one principle problem with drug interaction studies: although major changes are demonstrated in individual subjects, the mean values are only slightly altered and variability is high. This implies that with a limited number of individuals studied, the result of such a study can be a statistically nonsignificant effect, although clinically the alterations in some individuals may be relevant depending on their individual expression of CYP isoenzymes.

Apart from the effect on theophylline metabolism, erythromycin has been reported to potentiate the effects of atorvastatin, carbamazepine, corticosteroids, ciclosporin A, digoxin, warfarin and other drugs (Table 1). Concomitant administration of erythromycin and ergotamine has been associated with the induction of ischaemia and peripheral vasospasm [13]. Several interactions between erythromycin and hypnotics have been observed [14]. The interaction of erythromycin and midazolam was investigated in volunteers treated with erythromycin or placebo and a single dose of midazolam. The antibiotic increased the AUC values of midazolam by more than fourfold, as illustrated in Figure 1 [15]. The elimination half-life of zopiclone was significantly elongated from 5 to 7 h if the hypnotic was administered simultaneously with erythromycin [16].

Roxithromycin has a less pronounced potential for drug interactions than erythromycin. However, because this macrolide is not available worldwide, the data basis is poor. Only a few data are available from direct comparative studies. A statistically significant interaction between theophylline and roxithromycin has been observed in volunteers and in patients with chronic bronchitis. The effect was judged as 'clinically insignificant' but monitoring of theophylline plasma concentrations may be reasonable. Roxithromycin did not alter the pharmacokinetics of carbamazepine and no significant interactions were observed with warfarin, ranitidine or mineral antacids [17].

Some well-designed studies indicate that the potential for drug interactions is similar for clarithromycin and erythromycin. Clarithromycin administration was associated with an increase in the elimination half-life of carbamazepine and marked increases of plasma concentrations. A total of four out of seven patients who received carbamazepine and clarithromycin coadministration developed moderate-to-severe symptoms of carbamazepine toxicity, such as drowsiness, dizziness and ataxia, which resolved within 5 days after clarithromycin discontinuation [18-20].

Table 1. Interactions of macrolides and related antibiotics with other drugs.

Drug	Clarithromycin (macrolide)	Erythromycin (macrolide)	Azithromycin (azalide)	Telithromycin (ketolide)
Atorvastatin	↑↑↑↑	?	0	?
Carbamazepine	↑	↑↑	0	?
Ciclosporin	↑↑	↑↑↑	0	?
Digoxin	↑↑	↑↑	?	↑↑ – ↑↑↑
Ergot alkaloids	Risk of ergotism	Risk of ergotism	?	Risk of ergotism
Lovastatin	↑↑↑↑	↑↑↑↑	?	?
Midazolam	↑↑	↑↑↑	0	↑↑↑↑
Simvastatin	↑↑↑↑	↑↑↑↑	?	↑↑↑↑
Tacrolimus	↑↑↑	↑↑↑	0	?
Theophylline	↑ – ↑↑	↑ – ↑↑	0	↑
Triazolam	↑↑↑	↑↑↑	0	?
Warfarin	Risk of bleeding	Risk of bleeding	0	Risk of bleeding

↑↑↑↑: > 75% change; ↑↑↑: 50 – 75% change; ↑↑: 25 – 49% change; ↑: < 25% change of the plasma concentration; 0: No significant effect was documented.

Of special interest is the interaction with digoxin because the cardiac glycoside possesses a narrow therapeutic index. Case reports on patients with digoxin intoxiciation have suggested an interaction between the glycoside and the macrolide antibiotics erythromycin and clarithromycin [21]. It has been speculated that macrolides modify the gut flora and thus decrease bacterial digoxin metabolism, leading to increased plasma levels of the glycoside. However, another mechanism may be a decrease in renal tubular digoxin secretion, which is mediated by Pgp located in the apical surface of tubular epithelia. A study in volunteers showed that oral coadministration of clarithromycin and digoxin resulted in a 1.7-fold increase of the digoxin concentrations (AUC) and a reduction of the nonglomerular renal clearance of digoxin, both probably due to inhibition of intestinal as well as the renal Pgp [22].

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are important drugs for the treatment of hypercholesterolaemia. Although well tolerated, the treatment bears a small risk of myopathy. Clinically important rhabdomyolysis is rare, and when developing it is often the result of an increased systemic exposure due to a drug interaction. Clarithromycin significantly increased the plasma concentrations of some statins, most markedly simvastatin and the active metabolite of simvastatin (~ 10- and 12-fold increase in AUC), followed by atorvastatin (> 4-fold) and then pravastatin (almost 2-fold) [23]. Renal failure requiring haemodialysis as a result of severe interaction can occur and has been recently described in a 77-year-old man, who was treated with simvastatin and clarithromycin. The creatinine kinase level in this patient increased to a peak of 99,770 U/l [24].

When volunteers were given terfenadine 60 mg plus either erythromycin, clarithromycin or azithromycin, only the subjects that were receiving erythromycin or clarithromycin showed detectable concentrations of terfenadine in plasma, which was associated with altered cardiac repolarisation. Azithromycin had no effect on terfenadine pharmacokinetics or cardiac pharmacodynamics [25]. The results of this comparative study show that the azalide azithromycin obviously differs significantly from macrolides and ketolides with respect to its potential for clinically relevant drug interactions. Azithromycin does not seem to have any effect on the pharmacokinetics of drugs that are substrates of CYP enzymes, such as theophylline, ciclosporin, the antiepileptics carbamazepine and phenytoin, terfenadine, warfarin, oral contraceptives, and others (Table 1). A possible explanation for this behaviour seems to be the inability of the drug to bind to the CYP3A enzyme [26,27].

3. The ketolide telithromycin

Ketolides are semisynthetic derivatives of erythromycin A that were designed to overcome current resistance mechanisms against erythromycin A within Gram-positive cocci. Telithromycin was the first ketolide introduced into clinical practice [10]. Because clinical experience is still limited with telithromycin, most data available result from the clinical development of the drug. The best source of information is the full prescribing information of Ketek™ (Aventis Pharmaceuticals, Inc.). Figure 3 provides a synopsis of some of these data.

Telithromycin is metabolised by CYP3A4 and acts as a strong inhibitor of this isoenzyme. Coadministration of this antibiotic and a drug that is primarily metabolised by this cytochrome may result in increased plasma concentration of the latter drug. A number of drug-interaction studies were conducted to evaluate either the effects of other CYP inhibitors or inducers on the kinetics of telithromycin, or the

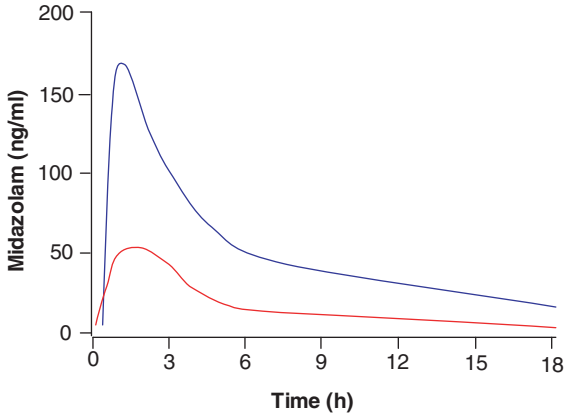

Figure 1. Schematic presentation of the plasma concentrations (mean values) of midazolam after a dose of 15 mg p.o. and pretreatment with erythromycin 500 mg t.i.d. (blue line) or placebo (red line) for 1 week in 12 healthy volunteers. Reprinted from OLKKOLA KT, ARANKO K, LUURILA H *et al.*: A potentially hazardous interaction between erythromycin and midazolam. *Clin. Pharmacol. Ther.* (1993) **53**:298-305 [15], copyright (1993), with permission from the American Society for Clinical Pharmacology and Therapeutics.

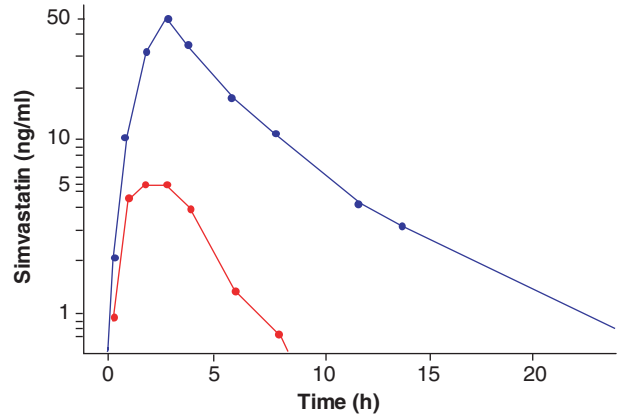

Figure 2. Mean serum concentrations of simvastatin when administered alone at a dose of 40 mg (red line) and with concomitant clarithromycin (blue line) 500 mg b.i.d. Concomitant clarithromycin increased the AUC value of simvastatin by ~ 10-fold, the effect on the active metabolite simvastatin acid was even more pronounced. Reprinted from JACOBSON TA: Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am. J. Cardiol.* (2004) **94**:1140-1146 [23], copyright (2004), with permission from Excerpta Medica, Inc.

effects of telithromycin on the concomitantly administered drugs. For example, a multiple-dose interaction study with the CYP inhibitor ketoconazole showed that the C_{max} of telithromycin was increased by 51% and the AUC by 95%. Less pronounced effects were observed with itraconazole. Grapefruit juice inhibits intestinal CYP3A enzymes but the pharmacokinetics of telithromycin were not affected when telithromycin was given together with grapefruit juice to healthy subjects.

During concomitant administration of the CYP3A4 inducer rifampin and telithromycin in repeated doses, the plasma levels of telithromycin were decreased by ~ 80%. Hence, the concomitant treatment with telithromycin and rifampin should be avoided. Concomitant administration of other CYP3A4 inducers such as phenytoin, carbamazepine, or phenobarbital is likely to result in subtherapeutic levels of telithromycin and a loss of the drug's effect.

Several statins are metabolised by CYP3A and other cytochrome enzymes. Coadministration of simvastatin with telithromycin caused a 15-fold increase in the plasma concentration (C_{max}) of the simvastatin active metabolite. Similarly, an interaction may occur with lovastatin or atorvastatin but not with pravastatin or fluvastatin. If the antibiotic is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be stopped during the course of treatment [28].

Concomitant administration of telithromycin with oral midazolam resulted in a sixfold increase in the AUC of midazolam due to the inhibition of CYP3A4-dependent metabolism of midazolam. Dosage adjustment of this benzodiazepine should be considered if necessary. Precaution should be used with other drugs of this class, which are metabolised by CYP3A4 and undergo a high first-pass effect (e.g., triazolam). Metoprolol is a CYP2D6 substrate. When this β-blocker was coadministered with telithromycin, the plasma concentrations increased by ~ 38%. Therefore, coadministration of telithromycin and metoprolol in patients with heart failure should be considered with caution [28].

The plasma peak and trough levels of digoxin were increased by 73 and 21%, respectively, in healthy volunteers when coadministered with telithromycin. Trough plasma concentrations of digoxin (when equilibrium between plasma and tissue concentrations has been achieved) ranged from 0.74 to 2.17 ng/ml. There were no significant changes in electrocardiogram parameters and no signs of digoxin toxicity. Nevertheless, monitoring of digoxin serum levels should be considered during concomitant administration of digoxin and the ketolide [28]. The peak plasma concentration of theophylline was increased by 16% when coadministered with repeated doses of telithromycin, and it is, therefore, recommended that the ketolide should be taken with theophylline 1-h apart to decrease the likelihood of gastrointestinal side effects [28]. Telithromycin did not interfere with the antiovulatory effect of oral contraceptives containing ethinyl estradiol and levonorgestrel. When such drugs were coadministered with telithromycin, the concentrations of levonorgestrel were increased by 50%, whereas ethinyl estradiol concentrations did not change. Spontaneous postmarketing reports suggest that concomitant administration of telithromycin and oral anticoagulants may

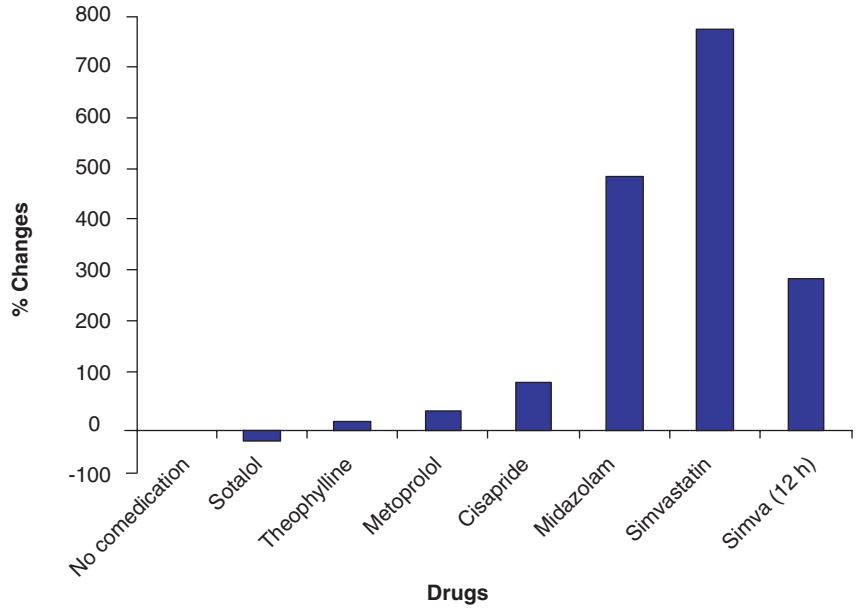

Figure 3. The changes in plasma concentrations (AUC values or steady-state concentrations) of various drugs after concomitant administration with telithromycin, presented as the percentage change in comparison to the control (that has no comedication). Concomitant administration of telithromycin causes a decrease of AUC of sotalol by 20% but an increase of the plasma concentrations of several other drugs. Among the drugs that have been studied during the clinical development of telithromycin, effects on simvastatin concentrations were most pronounced. The AUC of this statin increased 8.9-fold after coadministration. When simvastatin and telithromycin were administered 12-h apart, there was a fourfold increase of the AUC [28].
AUC: Area under the curve.

potentiate the effects of the oral anticoagulants. Prothrombin times/international normalised ratio should be closely monitored whilst patients are receiving telithromycin and oral anticoagulants simultaneously [29].

Similar drug interactions as those that have been observed with macrolides can be expected with telithromycin, although no specific studies or case reports are available so far. These drugs include carbamazepine, ciclosporin, ergotamine, tacrolimus, sirolimus and phenytoin. Because acute ergot alkaloid toxicity (ergotamine or dihydroergotamine) characterised by severe peripheral vasospasm and dysesthesia has been reported when macrolide antibiotics were coadministered, simultaneous treatment with telithromycin and these drugs is not recommended [30].

4. Quinolones

Several quinolones with an inhibitory potential for cytochrome enzymes, such as pefloxacin, enoxacin or grepafloxacin, have been removed from the market or play only a minor role in some countries. Today, the major quinolones in worldwide clinical use are ciprofloxacin, ofloxacin/levofloxacin and moxifloxacin. Among these, only ciprofloxacin exhibits a significant inhibitory effect on cytochrome enzymes. However, all quinolones show dose-dependent, clinically relevant interactions with mineral antacids and other drugs that contain divalent or trivalent cations [31-33]. For example, the concomitant administration of ciprofloxacin 500 mg and Maalox® (Cassella-med GmbH & Co.), a magnesium/aluminium containing antacid, resulted in a drastic decrease in peak plasma concentrations and the AUC (mean from 7.4 to 0.7 mg/l × h), as shown in Figure 4 [34,35]. The effect was less pronounced with ofloxacin/levofloxacin but significantly reduced absorption of any fluoroquinolones also has to be expected when it is taken together with zinc or iron preparations, or after concomitant intake with sucralfate, an aluminium-containing drug [36,37]. A similar profile of a drug–cation interaction was also observed with moxifloxacin, one of the newest fluoroquinolones. Moxifloxacin absorption was reduced by the concomitant administration of aluminium- and magnesium-containing antacids, sucralfate or an iron supplement. However, calcium supplements did not interact significantly with moxifloxacin [38].

The main reason for this class effect is the formation of chelate complexes between the antibacterials and the metal ions. As quinolones bind to a DNA/gyrase complex via a magnesium ion [39], it seems to be impossible to develop a quinolone with antibacterial activity that will exhibit no affinity to magnesium and other di- or trivalent cations. The degree of interaction between quinolones and mineral antacids is most pronounced when antacids are taken shortly before the quinolone (≤ 2 h), but is less pronounced and probably without clinical relevance if the antacid is taken ≥ 2 h after taking the quinolone [40,41].

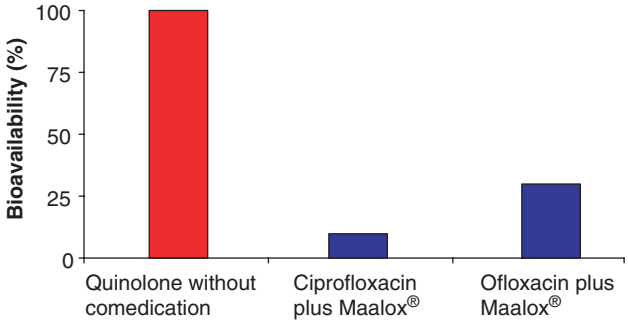

Figure 4. Effect of a mineral antacid (Maalox®) on the bioavailability of two fluoroquinolones. The left column symbolises the bioavailability of ciprofloxacin or ofloxacin without comedication (100%). Pronounced interaction between ciprofloxacin (500 mg p.o.) and an aluminium/magnesium-containing antacid. The AUC value is reduced from 7.4 to 0.7 mg/l × h, corresponding to a relative bioavailability of ~ 10%. The effect is not as pronounced with ofloxacin (500 mg) under otherwise identical conditions, but a marked reduction in bioavailability is still obvious (relative bioavailability: 30%). Adapted from [35].
AUC: Area under the curve.

During the treatment of lower respiratory tract infections with enoxacin, interactions with theophylline metabolism were first noticed. Most patients who received enoxacin plus the bronchodilator experienced serious nausea and vomiting, and some also complained of tachycardia and headaches. In a comparative study, significant increases of the theophylline plasma concentrations were seen with enoxacin (111%) and, to a lesser degree, also during the coadministration of pefloxacin (20%) and ciprofloxacin (23%) [42]. No significant influence on theophylline metabolism was found with the newer quinolones levofloxacin, moxifloxacin or gatifloxacin (Table 2). When ciprofloxacin is used, the interaction with theophylline should be considered. Interactions between quinolones have also been demonstrated with caffeine, which is closely related to theophylline [32].

Interactions between digoxin and fluoroquinolones have been described for gatifloxacin and moxifloxacin. Statistically, the changes in plasma concentrations were not significant but they showed a pronounced variability and more data are needed to elucidate the mechanism of this interaction [43,44]. As mentioned above, some quinolones interfere with the metabolism of theophylline and caffeine by the inhibition of the CYP1A2 isoenzyme. Significant interactions between fluoroquinolones and drugs that are metabolised by other isoenzymes, such as CYP3A4, are unlikely. Nevertheless, in several studies, the possible interactions between fluoroquinolones, mostly enoxacin or ciprofloxacin, have been investigated. Several reports indicate that ciprofloxacin may have significant effects on the metabolism of phenytoin. For example, a significant decrease of phenytoin concentrations to subtherapeutic levels has been described in a 61-year-old man soon after the start of concomitant ciprofloxacin treatment (750 mg b.i.d.). As the patient developed seizures, the phenytoin doses were doubled, yielding therapeutic plasma levels again. However, phenytoin intoxication ensued after discharge from the hospital when ciprofloxacin was discontinued. This case underscores the need for dose adjustment, not only when a drug is added to the medication list but also when treatment is discontinued. The mechanism of this interaction is unknown [45].

5. Azoles

In recent years, the options for antifungal therapy have been extended by the development of new compounds and improved formulations of older drugs. Apart from differences in their antimycotic spectrum, the tolerability and the potential for drug interactions are important aspects to be taken into consideration for an adequate selection of an antimycotic compound for an individual patient. Considering the patient populations typically confronted with systemic mycoses (and often receiving a variety of other drugs), the increasing clinical use of antimycotic agents in critically ill patients and the limited choice of antifungal substances underlines the importance for understanding the drug-interaction profile of these drugs. An increasing oral use of fluconazole and itraconazole for the treatment of genital mycoses and dermatomycoses in an ambulatory setting has further increased the likelihood for these interactions.

Azoles for systemic use, such as ketoconazole, itraconazole, fluconazole and voriconazole, exert a fungistatic effect by inhibiting the specific fungal CYP51A1-dependent C-14 α-demethylase (lanosterol demethylase), the enzyme necessary for the conversion of lanosterol to ergosterol. This results in the depletion of ergosterol, the essential sterol of the fungal cell membrane, and eventually compromises cell membrane integrity [46,47]. Despite significant differences in their affinity to fungal and human cytochromes, azoles are also substrates and inhibitors of human CYP isoforms to varying degrees. In addition, some azoles such as itraconazole and ketoconazole, are substrates of the *MDR-1* gene product Pgp. Therefore, it is difficult to attribute azole drug interactions observed in animal experiments or in human subjects solely to CYP inhibition [48]. It is of interest that *in vitro* and *in vivo* data indicate that voriconazole is neither a substrate nor an inhibitor of Pgp [49].

Ketoconazole, itraconazole and voriconazole are very lipophilic compounds. In contrast, fluconazole is water soluble, and these physicochemical differences explain some of the differences observed with these drugs with respect to their drug-interaction profiles. Azoles predominantly inhibit the isoenzyme CYP3A4 [48,50,51]. Fluconazole requires less biotransformation than other azoles. Fluconazole is a strong noncompetitive or mixed-type inhibitor of CYP2C9, and perhaps CYP2C19 as well [52]. The extent of enzyme inhibition

Table 2. Interactions of fluoroquinolones with other drugs.

Effect	Ciprofloxacin	Levofloxacin	Moxifloxacin	Gatifloxacin
Quinolones may interfere with the metabolism of the following:				
Increased levels of:				
Theophylline	↑↑	0	0	0
Caffeine	↑↑	0	?	?
Warfarin	slight to ↑*	0	0	0
Absorption of the quinolones is affected when administered concomitantly with the following:				
Aluminium- or magnesium- containing antacids	↓↓↓	↓↓↓	↓↓↓	↓↓↓
Calcium-containing antacids	↓↓	↓	↓‡	↓
Ferrous sulfate	↓↓↓	↓↓	↓↓↓	↓↓↓
Sucralfate	↓↓↓↓	↓↓↓§	↓↓↓§	?

↑↑↑↑: > 75% change; ↑↑↑: 50 – 75% change: ↑↑: 25 – 49% change; ↑: < 25% change; 0: no significant effect was documented.

*The effect on warfarin metabolism is variable. ‡Absorption delayed with no effect on total bioavailability. §A decrease in absorption of the fluoroquinolone is documented; however, the actual percentage decrease is not clear. Adapted from [41].

depends only on its concentration. The CYP3A4 inhibitory potential is lower than for ketoconazole and itraconazole but as fluconazole serum concentrations are ~ 30-times higher than those of itraconazole, the inhibitory potential may still be significant, particularly at higher doses [53,54].

The first data about azole drug interactions were published with ketoconazole; this drug can thus be considered as a model compound for azole–drug interactions. Notably, it has been proposed to exploit certain drug interactions with ketoconazole to reduce the dose of concomitantly given drugs and thus produce a pharmacoeconomic benefit. In contrast to the imidazole derivative ketoconazole, the other azoles for systemic use are triazole derivatives and possess a higher selectivity towards fungal cytochromes. Some of the interactions observed with ketoconazole are less pronounced with the triazole derivatives.

Voriconazole is the newest azole available for systemic antifungal therapy. Voriconazole is extensively metabolised by the CYP system, mainly by the polymorphically expressed CYP2C19 isoenzyme CYP2C9 and to a lesser extent by CYP3A4 [47]. Before launch, this azole was tested systematically to clarify its drug-interaction profile. With increasing use, the experience with voriconazole will broaden and, possibly, additional types of drug interactions will be added to the current list. Recently, it has been shown that extracts of St. John's wort (*Hypericum perforatum*) given concomitantly with voriconazole cause a short-term increase followed by a prolonged extensive reduction of voriconazole exposure, probably associated with a risk for voriconazaole treatment failure [55]. Some of the most relevant interactions with voriconazole, which are typical examples for this whole class of antifungal agents, are compiled in Table 3.

Drugs that increase gastrointestinal pH can influence the absorption of some of the azoles. Histamine (H_2)-antagonists, mineral antacids and sucralfate can markedly reduce ketoconazole absorption. Similarly, it was shown that H_2 antagonists or proton pump inhibitors reduce the absorption and oral availability of the itraconazole capsule by ~ 30 – 60% following single or multiple doses [50,56-58]. In patients receiving drugs that elevate gastric pH and who require itraconazole therapy, the oral solution rather than the capsule form should be used. If the capsule form is used, itraconazole serum concentrations (C_{min}) should be monitored periodically to document adequate oral availability. The absorption of voriconazole and fluconazole is unaffected by the concomitant administration of substances that increase gastric pH, and their absorption is unaffected by aluminium and magnesium hydroxide [59,60].

Potent inducers of CYP3A4, such as barbiturates, carbamazepine, phenytoin, rifampin and rifabutin may induce the metabolism of ketoconazole. Isoniazid has also been reported to reduce ketoconazole serum concentrations; however, the mechanism behind this interaction is unknown [51,50]. Similarly, inducers of CYP3A4 can markedly reduce itraconazole serum concentrations with sometimes delayed effects of ≤ 2 weeks after the onset or stop of concomitant therapy. Rifabutin and voriconazole coadministration not only leads to decreased voriconazole levels but also increases rifabutin concentrations to toxic levels, and so the concomitant use of these anti-infectives is contraindicated [47,61-63].

A similar two-way interaction occurs with voriconazole and phenytoin, which is a CYP2C9 substrate and CYP inducer. Phenytoin decreases voriconazole levels but repeated dose administration of voriconazole can increase the AUC of phenytoin by 80% by competing for the CYP2C9 enzyme. Therefore, during coadministration of voriconazole and phenytoin, monitoring of plasma phenytoin concentrations and appropriate dose adjustments are recommended [64]. A

Table 3. Effects of voriconazole on the pharmacokinetics of other drugs, mechanism of interaction and specific recommendations.

Drug/class	CYP isoenzyme inhibited	C_{max}	AUC	Recommendations
Astemizole	CYP3A4	(+)	(+)	Contraindicated (QTc prolongation, torsade de pointes)
Ciclosporin	CYP3A4	++	++	Drug-level monitoring and dose adjustment of ciclosporin
Cisapride	CYP3A4	(+)	(+)	Contraindicated (QTc prolongation, torsade de pointes)
Ergot alkaloids	CYP	(+)	(+)	Contraindicated
HIV protease inhibitors	CYP3A4	+	+	Drug-level monitoring and monitoring of specific AEs/ toxicity, no dose adjustment necessary for indinavir
Omeprazole	CYP2C19/3A4	++	++	If omeprazole dose > 40 mg, dose reduction of omeprazol is indicated (50%), probably similar for other proton pump inhibitors
Phenytoin	CYP2C9	++	++	Drug-level monitoring and monitoring of phenytoin-related AEs
Quinidine	CYP3A4	(+)	(+)	Contraindicated (QTc prolongation, torsade de pointes)
Rifabutin	CYP3A4	++	++	Contraindicated
Sirolimus	CYP3A4	++	++	Contraindicated
Statins	CYP3A4	+	+	Monitoring for statin-related AEs/toxicity (rhabdomyolysis) and dose adjustment
Sulfonyl urea	CYP2C9	(+)	(+)	Blood glucose monitoring and monitoring of signs of hypoglycaemia, dose adjustment may be necessary
Tacrolimus	CYP3A4	++	++	Drug-level monitoring and dose adjustment
Terfenadine	CYP3A4	(+)	(+)	Contraindicated (QTc prolongation, torsade de pointes)
Vinca alkaloids	CYP3A4	(+)	(+)	Drug-level monitoring and monitoring of specific AEs/ toxicity, dose adjustment may be necessary
Warfarin	CYP2C9	(+)	(+)	Partial thromboplastin time increased, prothrombin time/international normalised ratio monitoring and warfarin dose adjustment

++: Significantly increased; +: *In vitro* studies show potential for inhibition of metabolism and increased plasma exposure; (+): Likely to be increased, not studied; 0: No effect. Adapted from [91].

AE: Adverse event; AUC: Area under the curve; C_{max}: Maximum concentration; CYP: Cytochrome P450; QTc: Corrected QT interval.

similar recommendation can be given for the combination of fluconazole and other azoles plus phenytoin [65].

Most studies of azole interactions with another CYP3A4 substrate attribute pharmacokinetic changes of the substrate to the enzyme inhibition by the azole. Azoles are substrates and potent inhibitors of CYP3A4 and other CYP isoforms and, therefore, have the potential to influence the pharmacokinetics of other CYP3A4 substrates, such as HMG-CoA reductase inhibitors (statins) [66], benzodiazepines (midazolam, triazolam) [53,67], certain anxiolytics (buspirone) [68], sedative hypnotic agents (zolpidem) [69], antipsychotics (haloperidol) [70], immunosuppressive drugs (ciclosporin and tacrolimus) [51,71-73] and calcium channel blockers (felodipine) [74].

The inhibitory potential is not restricted to CY3A4. For example, ketoconazole also inhibits several additional isoforms to a lesser extent, including CYP1A2, CYP2E1, CYP2D6 and the CYP2C subfamily; therefore, it may interact with a wide range of medications [51]. Similarly, itraconazole and other azoles have a very broad drug-interaction profile, and many of these interactions are clinically important. For example, statin-induced skeletal muscle toxicity could ultimately progress to rhabdomyolysis and renal failure [75]. This toxicity has been reported in a case report about a patient receiving lovastatin in combination with itraconazole, and it can be likely to occur with simvastatin or other agents of this class. In addition, concomitant azole therapy with these agents may increase the risk of other adverse effects associated with HMG-CoA reductase inhibitors, such as hepatotoxicity [66]. Patients receiving statins in combination with itraconazole should be monitored closely for clinical and laboratory signs of skeletal muscle toxicity and hepatotoxicity. Empirical dose adjustments of the statins may be prudent. However, pravastatin and fluvastatin do not seem to interact with azoles and may be used as preferred HMG-CoA reductase inhibitors during concomitant itraconazole therapy.

Coadministration of azoles with midazolam or triazolam significantly alters the pharmacokinetics of these benzodiazepines. The alteration results from inhibition of primarily hepatic but also of intestinal CYP3A4, and results in significant increases in pharmacodynamic effects that are long lasting and dependent on the administered azole dose. Interactions with intravenously administered midazolam were less significant [53,76-78]. In order to avoid interactions, benzodiazepines, such as temazepam, oxazepam or lorazepam should be used instead of midazolam or triazolam. These undergo Phase II metabolism and show no clinically significant interactions. Other CYP3A4 substrates such as diazepam and zolpidem can also be used alternatively as their pharmacokinetics are not significantly affected by itraconazole [79].

The clinical significance of the interaction between azoles, ciclosporin and other immunosuppressive agents require special attention. The effect of itraconazole on ciclosporin concentrations is less pronounced than that produced by ketoconazole, and the associated nephrotoxicity is reduced [51]. The risk of an interaction between itraconazole and tacrolimus, and the subsequent tacrolimus toxicity, is likely to be high. Most data concerning ketoconazole interactions with other CYP3A4 substrates were gathered before the importance of Pgp for systemic availability was realised. However, it is now recognised that oral ciclosporin availability is determined primarily by intestinal Pgp rather than CYP3A4 [48]. Therefore, it is possible that Pgp inhibition, particularly in the gastrointestinal tract, contributes to drug interactions with ketoconazole and other azoles that were previously attributed to CYP3A4 inhibition [80]. In addition, itraconazole was identified as a Pgp substrate and a potent inhibitor of Pgp function *in vitro* and in clinical interaction studies [81-83].

In contrast, fluconazole and voriconazole do not act as inhibitors of Pgp [4,5,48], but higher doses of fluconazole can cause slow increases in ciclosporin serum concentrations [84,85] and a dose-dependent interaction has also been reported for tacrolimus [86]. These interactions were not considered as clinically significant. Mean ciclosporin AUC increased by 1.7-fold in the presence of voriconazole in renal transplant patients [87]. When voriconazole is initiated in patients already receiving ciclosporin, the ciclosporin dose should be halved. A case report about a patient after allogeneic bone marrow transplantation who received ciclosporin A and voriconazole concomitantly underlines the need for dose adjustment of the immunosuppressive agent if the azole therapy is stopped [88]. Figure 5 provides some data from this publication. If concomitant treatment with an azole and tacrolimus or ciclosporin is necessary, the dose of the immunosuppressant should be reduced, and renal function parameters and serum concentrations of the immunosuppressant should be closely monitored.

Interactions between felodipine and itraconazole can lead to clinically significant changes of the pharmacodynamic effects of felodipine associated with significantly reduced blood pressure and increased heart rates [74]. Combinations of

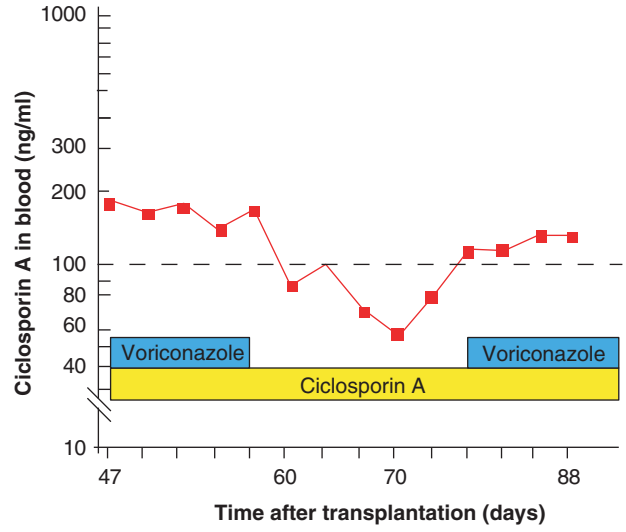

Figure 5. Time course of ciclosporin A trough levels prior, during and following discontinuation of voriconazole on day 56 with stable (2.8 mg/kg/day) dosing of ciclosporin A. When voriconazole was reinstituted on day 74, ciclosporin A levels returned to their prior concentration range [88].

itraconazole and felodipine, and chemically similar calcium channel blockers such as nifedipine, amlodipine and isradipine should be avoided. When this is not possible, the dose of calcium channel blockers should be reduced and vital signs of the patient should be monitored.

The pharmacologically active *S*-enantiomer of warfarin is metabolised almost exclusively by CYP2C9. Azoles inhibit this pathway and fluconazole, for example, causes a 38% increase in international normalised ratio in patients previously stabilised on warfarin therapy. Interactions between fluconazole and warfarin may require the discontinuation of fluconazole therapy. Significantly increased prothrombin times were also observed during coadministration of itraconazole or voriconazole with warfarin. Combinations of azoles and warfarin should be avoided, and regular monitoring of prothrombin time and appropriate warfarin dose adjustment is recommended if these drugs are coadministered. Alternatively, amphotericin B could be used [52,89,90].

Overall, macrolides, including the ketolide telithromycin, are potent inhibitors of CYP3A4 and other cytochrome enzymes. These antimicrobial agents have the ability to considerably decrease the metabolism of other concomitantly administered drugs. As a result of increased plasma levels, drug toxicity can lead to severe consequences that includes lethality. Among the currently used quinolones, only ciprofloxacin exhibits a comparatively low inhibitory potential of CYP1A2, but reduced absorption is observed with all of the quinolones when administered orally together with drugs that contain di- or trivalent cations. As a consequence, therapeutic failure of the quinolone therapy is probable. Knowledge of the possible

interactions is the essential prerequisite to deal with these risks and to improve efficacy and safety of pharmacotherapy.

6. Expert opinion

In the majority of cases, antimicrobial agents are given for a short time period only, and are often (especially in the elderly population) added to a list of continuously taken drugs. If the antimicrobial agent influences drug metabolising enzymes, a risk for a possibly serious drug–drug interaction occurs in such a situation. Physicians and pharmacists should be aware of the drug interaction potential that is associated with macrolides, ketolides, quinolones and azoles, to name only the most important antimicrobials with a pronounced drug interaction potential. By paying attention to such possibilities, the therapeutic outcome can be optimised with respect to a better efficacy, as well as to an improved tolerability.

A specific problem that is often overlooked is related to the need for dose adjustment, not only when a potentially interacting drug is added to a medication list, but also when treatment with this drug is stopped. Of special concern are the interactions with drugs that have a narrow therapeutic index because they have the capability for producing serious clinical consequences including a fatal outcome. If a drug interaction occurs, the responsible drug should be replaced with an alternative drug that is not likely to cause the side effect. In general, it cannot be expected to avoid a drug–drug interaction by simply increasing the time period between the administration of the interacting drugs. Several studies have shown that changes in the cytochrome activity can last for ≥ 24 h.

Although *in vitro* and *in silico* models provide valuable screening tools for cytochrome inhibition, *in vitro* data on the inhibitory potencies of cytochrome inhibitors do not necessarily translate directly into the extend of a drug interaction *in vivo*. In addition, animal models are of limited value due to interspecies variations in substrate specificity and other problems, making studies in human subjects the main approach to provide the necessary evidence. Certainly, besides the inhibitory potency, the drug–blood and drug–tissue levels of cytochrome inhibitors and inducers are the other major contributors for the extent of interactions but, even with the knowledge of both the potency and the concentration, a precise prediction of an interaction for an individual is not possible. This is due to the large interindividual variability in the cytochrome activities in the liver, the intestine and other organs. The clinical consequences of an inhibition of cytochromes depend on additional factors, such as plasma protein binding, the formation of inhibitory metabolites, intestinal active efflux of the drug and the inhibitor, extrahepatic metabolism as well as several others. Notably, even well-conducted studies in human volunteers cannot provide exact data for an extrapolation to the patient's situation. This aspect is often neglected, but it should be kept in mind that due to infection and inflammation major changes are induced in the mammalian organism that have potential impact on the metabolism of xenobiotics. Cytokines, such as IL-6, can affect drug metabolism by reduced expression of CYP3A4, CYP2B and CYP2C. Furthermore, cytokines regulate the activity of transport proteins. Therefore, drug interaction data obtained from studies in healthy individuals cannot be extrapolated uncritically to infected patients. The most relevant data on an interaction derives from the patient population that uses the combination. This underlines the necessity of a carefully conducted postmarketing surveillance of drug safety. Obviously, with the rapidly increasing knowledge of pharmagenomics, an enormous potential exists for molecular diagnostic approaches to become routine tools providing data that enable physicians to select medications and dose them individually on a more rational basis, and thus optimise drug therapy.

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