Macrolide – induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin

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Introduction

The oxidative phase of the biotransformation of drugs is a function of hepatic or intestinal cytochromes P-450, also called the mixed-function oxidase system. Three families of cytochromes – CYP1, CYP2, and CYP3 – perform the oxidative metabolism of drugs in humans. Within these families, five isoforms – CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, and CYP 3A4 – account for nearly all the side-effects related to drug interactions [1, 2].

The ability of macrolide antibiotics to interact with the biotransformation of some other drugs has been widely recognized, mostly with erythromycin and troleandomycin because these compounds have been marketed decades ago. Macrolides can induce their own hepatic biotransformation into nitrosoalkanes. These metabolites are derived from the metabolic oxidation of the –N(CH3)2 group of the antibiotic to the corresponding –NO group. Nitrosoalkanes subsequently form inactive CYP 3A4-iron-metabolite complexes (Figure 1) resulting in inhibition of the CYP 3A4-mediated catalytic activity [3]. This mechanism accounts for most of the drug interactions produced by macrolides [4].

Macrolides differ in their abilities to bind to and inhibit the cytochrome P-450 isoform CYP 3A4 [3, 5–7]. These differences prompted von Rosenstiel & Adam [8] to classify macrolide antibiotics into three groups on the basis of data provided by *in vitro* experiments:

- Group 1 agents include erythromycin and troleandomycin. Both drugs bind strongly to and inhibit markedly CYP 3A4. Since troleandomycin was withdrawn from the market many years ago, this drug will not be discussed further in the present paper;
- Clarithromycin belongs to Group 2 agents. This drug exhibits lower affinity for CYP 3A4 as compared with erythromycin, and form complexes to a lesser extent;
- Group 3 include azithromycin and dirithromycin. These compounds have been shown to interfere poorly with cytochrome P-450 system *in vitro*.

Clarithromycin has recently appeared to be similar to erythromycin in some drug interactions (e.g. with psychotropic agents), on the basis of the results of some clinical studies. Furthermore, a number of recent clinical case reports demonstrate that azithromycin and dirithromycin still exhibit some potential for drug interactions, although to a much lesser extent than that with erythromycin.

The discrepancy between what is expected from *in vitro* data and what may be observed in clinical practice underscores the well-known interindividual variability in the extent of cytochrome P-450 catalytic activity (as much as 10- to 20-fold). This pattern provides some explanation for why some patients appear to be more susceptible than others to a given drug–drug interaction.

It is now clear that the heterogeneity among patients in the ability to perform P-450 metabolism of some drugs is largely the result of genetic factors [1]. Aside from the drug-induced induction/inhibition enzymatic processes, some other nongenetic factors probably contribute to interpatient differences in the liver content or activity of individual P-450:

- for example, dietary differences may contribute significantly [9, 10].
- CYP 3A4 activity may be non specifically depressed by debilitation or disease, e.g. liver cirrhosis [11] or celiac disease [12].
- importantly the infectious process by itsef can affect the activity of CYP; viral or bacterial pulmonary infections have been shown to depress CYP activity. In a sequential study conducted in 14 patients with fever and clinical pneumonia, antipyrine clearance was on average impaired by 36% [13]. Antipyrine elimination proceeds almost exclusively through hepatic biotransformation, and its

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metabolites are formed by at least 6 hepatic cytochrome P-450 isoforms, namely CYP 1A2, CYP 2B6, CYP 2C8, CYP 2C9, CYP 2C18 and CYP 3A4 [14]. Hence, the infection is likely to induce global inhibition of cytochrome P-450 catalytic activities. This stems probably from the release of endotoxin or interferon during the infection [15, 16]. Conceivably, the combination of interferon- or endotoxin-related CYP depression and the macrolide-induced inhibition of the CYP 3A4 isoform might result in an enhanced metabolic interaction.

An additional factor that may contribute to individual variability in the extent of drug interactions of pharmacokinetic type is the involvement of P-glycoprotein (P-gp). Drug-induced changes in expression of this protein may overlap changes at the level of CYP catalytic activities.

P-gp is an ATP-dependent efflux drug transporter that is constitutively expressed in normal tisues including the gastrointestinal epithelium, the canalicular membrane of the liver, the kidney and capillary endothelial cells in the central nervous system [17, 18]. P-gp appears to play a key role in absorption, distribution and elimination of many anticancer agents as well as other drugs such as digoxin or cyclosporin [19, 20]. Many P-gp inhibitors are also inhibitors of CYP 3A [21]. However, Wandel *et al.* [22] have demonstrated recently that there is no significant correlation between the ability of the P-gp inhibitors to inhibit P-gp and their ability to inhibit CYP 3A. In the case of macrolide antibiotics, erythromycin has been shown to reverse significantly multidrug resistance in cell-lines, which retain a higher expression of P-gp than the drug-sensitive parental cells [23], suggesting an inhibitory effect of the macrolide on P-gp expression. Also, clarithromycin appears capable of reducing the renal clearance of digoxin through inhibition of P-gp in the kidney epithelial cell [24].

While the involvement of P-gp in some pharmacokinetic drug interactions is an emerging issue, there is no further information at present on the role of this protein in macrolide–associated drug interactions. However, the interaction of some macrolides with cyclosporin might be partially explained by inhibition of P-gp (see below).

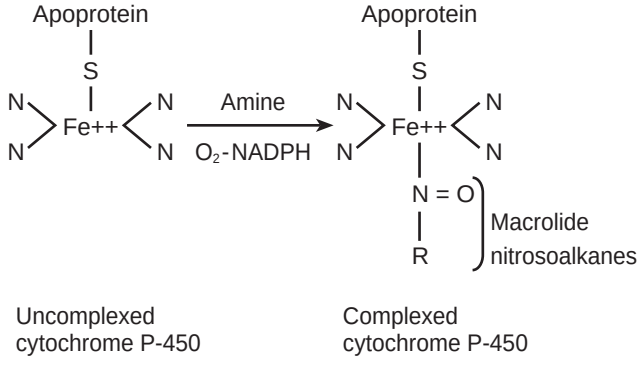

Figure 1 Metabolism of macrolides.

The present review addresses those macrolide–induced drug interactions (at the CYP level) that have been reported recently and shown to result in potentially serious side-effects in patients. Emphasis is placed on drug interactions involving the relatively recent and widely used macrolides clarithromycin, dirithromycin, and the azalide azithromycin because the last comprehensive reviews available on drug interactions of macrolides were published in 1995 [8, 25]. Following these reports, important drug interactions have emerged (e.g. with cisapride or pimozide) and some others, initially thought to be rare or dubious, have been substantiated or clarified (e.g. with benzodiazepines or HMG-CoA reductase inhibitors).

Recently emerged or substantiated drug interactions

Psychotropic agents

1a Benzodiazepines

Alprazolam, midazolam, temazepam, and triazolam are among the known substrates of CYP 3A4 [26].

Triazolam: Using *in vitro* preparations of human liver microsomes, Greenblatt *et al.* [27] showed that erythromycin and clarithromycin are potent inhibitors, with similar IC_{50} values, of triazolam biotransformation. In contrast, azithromycin is a weak inhibitor. Consistent with these findings are data from a controlled clinical study conducted by the same authors in healthy volunteers [27]: both erythromycin and clarithromycin significantly increased triazolam peak plasma concentrations and area under the serum concentration-time curve (AUC), prolonged elimination half-life, and decreased markedly the apparent oral clearance of this benzodiazepine to 33% and 22% of the control value, respectively (characteristics of macrolide regimen are indicated in Table 1). The inhibitory effect of clarithromycin was greater than that of erythromycin, especially on triazolam half-life and AUC. All of the pharmacodynamic effects of triazolam were enhanced by coadministration of erythromycin and clarithromycin. The dynamic interactions are consistent with an increase in triazolam plasma concentrations. The greatest impairment, as assessed by an electro-encephalogram and the digit symbol substitution test, was associated with the triazolam-clarithromycin combination. In contrast, azithromycin produced no effect on the kinetics or dynamics of triazolam.

This study demonstrates that clarithromycin is at least as potent an inhibitor of CYP 3A4 as erythromycin.

Table 1 Summary of recently recognized drug interactions or noninteractions associated with the macrolide antibiotics erythromycin, clarithromycin, azithromycin, or dirithromycin.

Substrate	*Interacting macrolide [ref]*	*Subjects Type of study*	*Macrolide regimen*	*Results*	*Action*
Alprazolam	Erythromycin [31]	healthy volunteers randomized crossover	400 mg tid × 10 days	62% increase in AUC no change in psychomotor function variables (alprazolam was given as a single oral dose)	monitor effects
Midazolam	Erythromycin [28]	healthy volunteers randomized crossover	500 mg tid × 6 days	fourfold increase in AUC significantly altered psychomotor performances	avoid combination with erythromycin or clarithromycin, or reduce midazolam dosage by 75%
	Clarithromycin [29]	healthy volunteers sequential	500 mg bid × 7 days	2.4-fold increase in oral midazolam availability	
	Clarithromycin [30]	healthy volunteers randomized	250 mg bid × 5 days	3.5-fold increase in AUC, enhanced pharmacodynamics	
	Azithromycin [30]	crossover	500 mg od × 3 days	no significant pharmacokinetic or dynamic change	
Triazolam	Erythromycin [27]	healthy volunteers randomized	500 mg bid × 2 days	threefold increase in AUC, enhanced monitor dynamic effects	monitor effects
	Clarithomycin [27]	crossover	500 mg bid × 2 days	fivefold increase in AUC, enhanced effects	
	Azithromycin [27]		500 mg day1, 250 mg day2	no kinetic or dynamic change	
Clozapine	Erythromycin [32]	case-report	333 mg tid × 3 days	increased serum clozapine conc. leukocytosis, somnolence, disorientation	avoid combination or halve clozapine dosage and monitor for side-effects
	Erythromycin [33]	case-report	250 mg qid × 7 days	twofold increase in serum clozapine conc. tonic-clonic seizure	
Pimozide	Clarithromycin [35]	healthy volunteers randomized crossover	500 mg bid × 5 days	113% increase in AUC significant increase in QT interval	combination contraindicated
Carbamazepine	Clarithromycin [25]	healthy volunteers randomized crossover	500 mg bid × 5 days	significant decrease in AUC and C_{max} of carbamazepine epoxide metabolite	reduce carbamazepine dosage by 25%–50%
	Azithromycin [25]	healthy volunteers	500 mg od × 3 days	no kinetic change	
Disopyramide	Clarithromycin [52]	case report	250 mg bid × 6 days	ventricular fibrillation marked QT prolongation (625 ms)	monitor closely ECG and plasma drug conc
Quinidine	Erythromycin [49]	healthy volunteers sequential	250 qid × 7 days	34% decrease in total clearance C_{max} increased by 39%	monitor ECG, serum drug conc. and factors predisposing to torsade de pointes
Cisapride	Clarithromycin [40]	case-report	500 mg bid × 3 days	polymorphic ventricular tachycardia QT interval increased to 640 ms	combination contraindicated
	Clarithromycin [41]	healthy volunteers randomized crossover	500 mg bid × 5 days	threefold increase in AUC 25 ms increase in QT interval	
Simvastatin	Erythromycin [45]	healthy volunteers randomized crossover	500 mg tid × 2 days	6.2 fold increase in AUC	avoid combination, or monitor serum creatine kinase and occurence of muscle aches

Table 1 Summary of recently recognized drug interactions or noninteractions associated with the macrolide antibiotics erythromycin, clarithromycin, azithromycin, or dirithromycin (continued).

Substrate	*Interacting macrolide [ref]*	*Subjects Type of study*	*Macrolide regimen*	*Results*	*Action*
Lovastatin	Clarithromycin [46]	case report	500 mg bid ×10 days	acute rhabdomyolysis	same as simvastatin
	Azithromycin [46]	case report	250 mg oid ×5 days	acute rhabdomyolysis	
Ergotamine	Clarithromycin [88]	case report	500 mg bid ×5 days	clinical ergotism, lingual ischaemia	combination contraindicated
Loratadine	Erythromycin [84]	healthy volunteers randomized crossover	500 mg tid ×10 days	40% and 46% increase in the AUC of loratadine and its active metabolite respectively, no significant change in QT interval	no dosage adjustment required
	Clarithromycin [85]	healthy volunteers randomized crossover	500 mg bid ×10 days	36% and 76% increase in steady-state C_{max} and AUC respectively, no significant change in QT interval	no side-effects, no dosage adjustment required
Theophylline po	Clarithromycin [25]	healthy volunteers sequential	500 mg bid ×4 days	20% increase in steady-state values of C_{max}, trough conc. and AUC	monitor drug conc in patients with baseline values in the upper therapeutic range
	Dirithromycin [79]	patients with COPD sequential	500 mg od ×10 days	no significant kinetic change	safe utilization in patients with COPD
	Azithromycin [25]	healthy volunteers sequential	250 mg od ×5 days	no significant kinetic change	
Warfarin	Clarithromycin [60]	case report	500 mg tid ×3 days	INR increased to 7.3	monitor INR carefully
	Clarithromycin [59]	case report	500 mg bid ×14 days	INR increased to 16.8	
	Azithromycin [62]	case report	250 mg/d ×5 days	INR too high to quantify	
	Azithromycin [61]	case report	250 mg/d ×3 days	INR increased to 4.9	
	Dirithromycin [42]	healthy volunteers sequential	500 mg/d ×10 days	no significant kinetic or dynamic (INR) change	
Cyclosporine po	Clarithromycin [70]	case-report	500 mg tid ×21 days	serum conc. increased 10 times the baseline values, twofold increase of serum creatinine level	monitor trough steady-state conc.
	Dirithromycin [42]	kidney transplant patients, sequential	500 mg/d ×14 days	17% decrease in mean apparent clearance, 13% increase in trough steady-state conc.	
Tacrolimus	Erythromycin [73]	case report	1g qid ×2 days	trough conc. increased by sixfold	monitor drug conc.

Abbreviations: AUC = area under the serum concentration-time curve; conc. = concentration; C_{max} = maximal concentration in serum; INR = international normalized ratio; COPD = chronic obstructive pulmonary disease.

This finding is further substantiated by studies on the midazolam–macrolide interaction.

Midazolam: The interaction between erythromycin and orally administered midazolam was investigated in a randomized, crossover study in healthy volunteers [28]. Pretreatment with erythromycin (500 mg) three times daily for 6 days resulted in an almost threefold increase in C_{max} and more than a fourfold increase in AUC of midazolam. This interaction resulted in undesirably severe and excessively long-lasting hypnotic effects and was ascribed to the inhibition of CYP 3A4-mediated metabolism of midazolam by erythromycin.

Clarithromycin reduces the clearance of midazolam [29]. Following pretreatment with clarithromycin (500 mg) twice daily for 7 days, the clearance of midazolam was reduced by 64% following iv administra-

tion, and by 86% after oral dosing. Oral bioavailability of midazolam was increased significantly from 0.31 to 0.75 (mean values) after dosing with clarithromycin. Using a stable isotope of the benzodiazepine, the authors showed that besides the liver, the intestine is a major site of interaction between oral midazolam and clarithromycin. Additionally, they concluded that interindividual variability in first-pass extraction of high-affinity CYP 3A substrates, such as midazolam, is primarily a function of intestinal enzyme activity.

This drug interaction was described earlier by Yeates *et al.* [30] who reported a 3.6-fold increase in the AUC of oral midazolam (given as a single dose), with enhancement of psychomotor effects, after a 5-day twice daily treatment with clarithromycin (250 mg). In contrast, the authors found no interaction of azithromycin (500 mg once a day for 3 days) with the pharmacokinetics or pharmacodynamics of midazolam.

Alprazolam: Alprazolam is another benzodiazepine where the metabolic clearance is impaired by erythromycin. In healthy volunters, erythromycin (400 mg) three times daily for 10 days produced a 62% increase in the AUC(0,48 h), a 60% decrease in oral clearance and a more than twofold increase in elimination half-life of alprazolam when given orally as a single dose [31].

In summary, coadministration of a macrolide antibiotic (with the exception of azithromycin) with one of the highly metabolized benzodiazepines mentioned above should be avoided, or the dose of the benzodiazepine should be substantially reduced.

1b Neuroleptics

Clozapine is a new antipsychotic agent used in the management of schizophrenia resistant to other neuroleptic medications. Erythromycin has been reported to interact with this agent, presumably through inhibition of its metabolic clearance; case-reports of serious side-effects – including seizure, somnolence, disorientation, difficulty in coordination and ambulation – associated with the coadministration of erythromycin and clozapine (Table 1) have been published [32, 33]. This drug combination should therefore be avoided.

Pimozide is a neuroleptic agent used in the treatment of delusion, schizophrenia, and other psychiatric disorders. Two fatal cases of ventricular dysrhythmia have been ascribed to the drug association pimozide × clarithromycin, presumably due to excessive prolongation of QT interval [34]. In a controlled pharmacokinetic study, clarithromycin (500 mg) twice daily for 5 days inhibited the metabolic clearance (CYP3A-mediated) of pimozide, resulting in elevation of plasma concentrations, significant prolongation of the QT interval, thereby increasing the risk of pimozide cardiotoxicity [35]. Accordingly, this drug association is contraindicated.

2 Cisapride

Cisapride is a widely used drug for gastro-oesophageal reflux, gastroparesis, and dyspepsia. The drug undergoes extensive first-pass metabolism in both the liver and the intestine [36].

Cisapride caused tachycardia and extrasystoles in a review of records of over 13000 patients receiving the agent [37]. The first report of an arrhythmic drug interaction with cisapride was with erythromycin [38]; the patient developed a QT interval of 550 ms from a normal baseline value with progression to polymorphic nonsustained ventricular tachycardia. Over 50% of the reports of torsade de pointes, prolonged QT intervals, and deaths associated with cisapride are due to interactions with drugs known to inhibit the CYP3A4 and, consequently, the metabolism of cisapride [39]. Risk factors for dysrhythmia were identified as history of coronary disease and dysrhythmia, renal insufficiency, and electrolyte imbalance (including hypokalaemia, hypomagnesaemia, and hypocalcemia) [39].

Clarithromycin seems to exhibit a similar adverse reaction when coadministered with cisapride [40]. Data from a case-report and results from a controlled trial on this drug interaction are summarized in Table 1. Potentiation of the cardiotoxic effect of cisapride resulting from the inhibition of the CYP 3A4 – mediated metabolism of the drug by clarithromycin [40, 41] is probably the mechanism underlying the adverse drug reaction.

No studies have yet been reported regarding the potential of the other macrolides for such an interaction with cisapride [42, 43]. Until additional data are available, however, concomitant use of cisapride with any macrolide antibiotic should be avoided.

3 HMG-CoA reductase inhibitors

These agents are metabolized by CYP 3A4 and have dose-related toxic effects on skeletal muscle that may range from diffuse myalgia and myopathy to severe rhabdomyolysis [44].

In a clinical pharmacokinetic study, erythromycin (500 mg) twice daily for 2 days increased the AUC of simvastatin in serum sixfold [45], due presumably to an inhibitory effect of erythromycin on CYP 3A4. Accordingly, concurrent administration of erythromycin and simvastatin should be avoided.

Rhabdomyolysis is a complication known to be associated with concomitant use of lovastatin and erythromycin. In order to reduce this risk, limiting the daily dose of lovastatin to 20 mg has been advocated [8].

Rhabdomyolysis has also been ascribed to the concomitant administration of lovastatin and clarithromycin or azithromycin (one case-report each, Table 1) [46]. Therefore, possible adverse effects, such as elevated serum creatine kinase and muscle tenderness, should be closely monitored when a combination of simvastatin or lovastatin with erythromycin (and probably other macrolides) is used.

4 Class IA antiarrhythmic drugs

Quinidine is eliminated from the body primarily through hepatic biotransformation, and approximately 50% of its metabolism is catalysed by CYP 3A4 [47]. Spinler *et al.* [48] reported that addition of intravenous erythromycin lactobionate (1 g) four times daily to chronic quinidine therapy resulted in a 50% decrease of the total clearance of quinidine after 5 days of macrolide therapy. In an open clinical study in healthy volunteers, the pharmacokinetics of a single oral dose of quinidine (200 mg) was evaluated before and during administration of erythromycin (250 mg) 4 times daily for 7 days [49]. Erythromycin reduced the total clearance of quinidine and its partial clearance by 3-hydroxylation and *N*-oxidation by 34, 50 and 33%, respectively, as the median C_{max} increased by 39%, inhibition of both hepatic and intestinal CYP 3A4 activity by erythromycin was considered to account for these observations, while the role of P-gp was thought to be ancillary.

Therefore, quinidine concentrations should be monitored closely if quinidine and erythromycin are coadministered. Additionaly, given the antiarrhythmic activity of both drugs [50], electrocardiograms (ECG) should be performed and other factors that may predispose to a prolonged QT interval and torsades de pointes should be treated.

Two cases of life-threatening ventricular dysrhythmia resulting from the interaction between disopyramide-erythromycin have been reported [51].

One case involving the interaction with clarithromycin (Table 1) has been reported recently [52]. In all of these cases, serious ventricular dysrhythmia was induced by a marked prolongation of QT interval, i.e. ≥ 600 ms. This effect was ascribed to the rise in serum disopyramide concentrations, resulting from the impaired clearance of the drug (primarily metabolized through CYP 3A4) during macrolide treatment.

The aforementioned recommendations regarding quinidine hold true also for disopyramide in the case of concurrent administration of erythromycin or clarithromycin.

5 Warfarin

There are reports describing an increase in the hypoprothrombinaemic effect of warfarin sodium following the administration of erythromycin [8, 25]. Prothrombin times increased up to twofold after 7 days of therapy and were occasionally associated with bleeding complications. However, there is a discrepancy between such data and the changes observed in pharmacokinetic studies [53, 54]. For example in the trial by Bachman *et al.* [53], erythromycin decreased warfarin clearance by 14% in healthy volunteers. Warfarin is a racemic mixture of R-and S-warfarin, with the S-form two-to five-fold more potent. Both forms are metabolized by cytochrome P-450 with predominant involvement of CYP 1A1, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 3A4 [55]. S-warfarin is metabolized primarily by CYP 2C9, while CYP 1A2 and CYP 3A4 account for most of the metabolism of R-warfarin.

The relatively limited changes in the pharmacokinetics of warfarin in healthy volunteers under treatment with erythromycin is consistent with inhibition of CYP 3A4, and to a lesser extent CYP 1A2 by erythromycin [2, 56]. Hence, this drug interaction is likely to be potentiated by other factors, particularly the disease state [57, 58]. As indicated earlier in this review, the process of infection, especially of pulmonary infection, can reduce substantially overall cytochrome P-450 catalytic activity [13].

Regarding the semisynthetic macrolides, only four cases of an interaction with warfarin have been published involving clarithromycin and azithromycin (2 cases each) [59–62]. Dirithromycin has no effect on prothrombin time in healthy volunteers receiving warfarin [42] (Table 1). Nevertheless, the unpredictability of this drug interaction demands careful monitoring of prothrombin time in patients treated concomitantly with warfarin and a macrolide.

Updated overview of previously well-recognized and clinically relevant drug interactions induced by macrolides

1 Immunosuppressive agents

Cyclosporin is extensively metabolized by CYP 3A pathway so there is considerable potential for interaction with macrolides [63]. This is of particular relevance since cyclosporin has low therapeutic index and its renal toxicity is concentration-related. Numerous clinical reports of significant increases in AUC and decreases in the clearance of cyclosporin following the administration of erythromycin are available [63]. This drug interaction seems to result from erythromycin-induced inhibition of CYP 3A4 in both liver and intestine [1, 64, 65]. It is thought that presystemic metabolism in the gastro-intestinal tract plays a

leading role in the total metabolic clearance of cyclosporin and may explain the well-known erratic bioavailability of the drug [66].

In addition to CYP 3A4, it has emerged recently that P-gp is involved in the pharmacokinetic behaviour of cyclosporin. The drug is a substrate of P-gp [20] and some drug interactions with this immunosuppressive agent are mediated by P-gp [67]. Gupta *et al.* [68] reported that erythromycin increases the absolute bioavailability of orally administered cyclosporin. This effect might be ascribed to impairment of the presystemic metabolism of cyclosporin in the intestine as a result of erythromycin-induced inhibition of the intestinal CYP 3A4. However, given that P-gp is also present in the intestinal epithelial cells [17, 69] and that erythromycin has been shown to inhibit the expression of P-gp in tumoral cell lines *in vitro* [23], the increased bioavailability of cyclosporin during erythromycin treatment might be accounted for by inhibition of both CYP and P-gp in the intestine.

Cases of interaction between clarithromycin and cyclosporin with subsequent cyclosporin toxicity have been reported [8, 70]. According to Spicer *et al.* [70] (Table 1) the underlying mechanism is the macrolide-related inhibition of CYP 3A4, leading to decreased clearance and increased blood concentrations of cyclosporin. However, given that clarithromycin can inhibit P-gp [24], involvement of this protein in this drug interaction is conceivable.

The effect of dirithromycin on the steady-state pharmacokinetics of cyclosporin was evaluated in 15 stable kidney transplant patients [71]. Administration of dirithromycin (500 mg) daily for 14 days resulted in a 17% decrease in the apparent clearance of cyclosporin, a 16% increase in the average steady-state cyclo-sporin concentration, and a 13% increase in trough steady-state cyclosporin concentrations. All of these alterations were statistically significant. Although this interaction is limited, it still appears that a 17% decrease in cyclosporin clearance may be clinically significant.

A possible clinical interaction between cyclosporin and azithromycin was reported in a kidney transplant recipient [72].

In summary, when macrolides are used in patients under cyclosporin therapy, trough serum cyclosporin concentrations and serum creatinine concentrations must frequently be monitored to allow appropriate adjustment of the cyclosporin dosage.

Tacrolimus is a new immunosuppressive agent that is extensively metabolized by the CYP 3A4 and like cyclosporin is transported by P-gp [20]. The drug appears interact with erythromycin, as described in several case-reports [73]. For example, Desmond Padhi *et al.* [73] reported a clinical case where the addition of erythromycin (1 g) twice daily in a patient under chronic therapy with tacrolimus induced a sixfold increase in trough concentrations of tacrolimus after only 2 days of erythromycin therapy. The extent of the interaction seems to be similar to that between erythromycin and cyclosporin.

Accordingly, management of this situation is identical to that advised for the cyclosporin–macrolide interaction.

2 *Theophylline*

Interactions of macrolides with theophylline are fairly well-documented. In most studies, erythromycin and clarithromycin decreased theophilline clearance by 20–25% after 7 days of concomitant administration [8, 25]. The interaction is most likely to occur in patients receiving relatively high erythromycin dosages (>1.5 g day^{-1}) and in those receiving prolonged therapy [74].

Theophylline is metabolized in man by *N*-demethylation and by 8-hydroxylation. A number of studies has been published during the past 10 years directed toward the characterization of the CYP isoforms involved in the metabolism of theophylline. It is generally agreed that CYP 1A2 catalyses the *N*-demethylation [75–77] and is also involved in 8-hydroxylation [76, 77]. It seems that, in addition to CYP 1A2, CYP 2E1 and CYP 3A4 play a role in 8-hydroxylation [77, 78]. Inhibitors of CYP 3A4 (including troleandomycin) inhibit both *N*-demethylation [56] and 8-hydroxylation *in vitro* [77]. However, these experiments showed that CYP 3A4 inhibitors reduced *N*-demethylation by a maximum of 16%. On this basis, the well–known interaction of macrolide antibiotics with theophylline *in vivo* could be explained by the inhibition of CYP 1A2 and CYP 3A4. However, given the relatively weak inhibitory effect of macrolides on the CYP 1A2 activity *in vitro*, the inhibitory effect of macrolides on theophylline metabolism may be enhanced in subjects who exhibit low CYP 1A2 activity and subsequently higher CYP 3A4 activity, the latter isoenzyme standing as a substitute metabolic pathway [1]. This hypothesis has been substantiated recently in an *in vitro* study [77]. Such a pattern might explain why a number of prospective clinical trials fail to show a statistically significant reduction in theophylline clearance when this drug is coadministrated with erythromycin [4].

In two controlled studies, dirithromycin therapy did not appear to alter significantly the disposition of theophylline in healthy subjects or patients (Table 1) [42, 79]. The kinetics of iv aminophylline or oral theophylline were not altered in healthy volunteers after, respectively, a 3 or 5 day treatment with azithromycin (250 mg day^{-1}). However, a case-report has been published of a moderate interaction of this macrolide with theophylline [80].

From a practical viewpoint, given the relative unpredictability of the extent of the theophylline–macrolide

interaction, it remains necessary to monitor serum theophylline concentrations whatever the macrolide being used, especially in those patients with baseline theophylline concentrations in the upper therapeutic range (15–20 mg l^{-1}).

3 Carbamazepine

Numerous case-reports and several pharmacokinetic studies document the well–known interaction between erythromycin and carbamazepine.

Following oral administration of this macrolide, a two- to fourfold increase in carbamazepine serum concentration is observed, with the extent of the interaction related to the dose of erythromycin [8]. In carbamazepine-treated patients, serious manifestations of toxicity occur within the 3 days of the start of erythromycin therapy. A number of case-reports have also been published regarding the interaction with clarithromycin [8]. The mechanism underlying this drug interaction is assumed to be the macrolide-induced inhibition of the CYP 3A4 isoform for which carbamazepine is a substrate [81].

Azithromycin and dirithromycin appear to be free from interaction with carbamazepine [42, 43].

In summary, serum carbamazepine concentrations should be closely monitored and patients observed for signs of toxicity in case of coadministration of erythromycin or clarithromycin.

4 Non sedating antihistamines

Terfenadine is a non sedating antihistamine that undergoes nearly complete first-pass biotransformation through CYP 3A4 pathway to form an acid metabolite. In susceptible individuals, accumulation of the parent compound can cause QT interval prolongation that may result in torsade de pointes [82]. Hazardous drug interactions involving this agent and some macrolides have been described [8]. Given that the drug is essentially withdrawn from the market, it will not be discussed further.

Loratadine, another H1-receptor antagonist, is metabolized primarily by CYP 3A4 and, to a lesser extent, by CYP 2D6 [83]. Erythromycin (500 mg) three times daily for 10 days reduced the metabolic clearance of loratadine [84] in a controlled clinical study. However, no changes in the QT interval and safety profile of loratadine were observed.

Carr *et al.* [85] evaluated the potential for an interaction between clarithromycin (500 mg) twice daily for 10 days and loratadine in a randomized crossover study in healthy volunteers. Clarithromycin increased the steady-state maximum observed plasma concentration and AUC over a dosing interval for loratadine (+36% and +76%, respectively) and for descarboethoxy-loratadine, the active metabolite of loratadine (+69% and +49%, respectively). No corresponding electrocardiographic pharmacodynamic interaction was observed. The authors concluded that given the wide margin of safety associated with loratadine, the observed pharmacokinetic interaction is probably unimportant.

Astemizole undergoes extensive first-pass metabolism to active metabolites and, like terfenadine, the parent compound is the cardiotoxic entity [82]. In many cases, drug interactions with terfenadine have been extrapolated to astemizole. Warnings about the concomitant use of terfenadine and macrolides apply also for astemizole [86].

5 Ergot alkaloids

Clinical ergotism has resulted from the coadministration of ergots and erythromycin [87]. This adverse effect is ascribed to the macrolide-induced inhibition of CYP 3A4, which is responsible for the metabolism of the ergots. Recently, a clinical case of ergotism with lingual ischaemia induced by a clarithromycin–ergotamine interaction has been described [88]. Accordingly, concomitant use of ergot alkaloids with erythromycin or clarithromycin is contraindicated. Until now, no case of such an interaction has been reported with azithro-mycin or dirithromycin. However, avoiding coadministration of ergot alkaloids with any of the macrolide antibiotics appears sensible.

Conclusions

A limiting factor of most controlled studies reviewed above is that they are conducted in healthy volunteers. Although these studies give initial indication of potential clinically significant drug interactions, the most accurate description of an interaction comes from conducting the study in the patient population that will use the combination and are receiving one of these drugs on a long-term basis. This underscores the importance of postmarketing surveillance of drug safety profiles. In this regard, reporting adverse events encountered in clinical practice appears to be essential, especially for recently available drugs. A knowledge of drug interactions, for example those induced by macrolides, contributes to safer management of patients.

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