Clin. Pharmacokinet. 23 (2): 106-131, 1992
0312-5963/92/0008-0106/$13.00/0

CPK1 195

Pharmacokinetic Drug Interactions of Macrolides

Piero Periti, Teresita Mazzei, Enrico Mini and *Andrea Novelli*
Department of Preclinical and Clinical Pharmacology, University of Florence, Italy

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Summary

The macrolide antibiotics include natural members, prodrugs and semisynthetic derivatives. These drugs are indicated in a variety of infections and are often combined with other drug therapies, thus creating the potential for pharmacokinetic interactions.

Macrolides can both inhibit drug metabolism in the liver by complex formation and inactivation of microsomal drug oxidising enzymes and also interfere with microorganisms of the enteric flora through their antibiotic effects. Over the past 20 years, a number of reports have incriminated macrolides as a potential source of clinically severe drug interactions. However, differences have been found between the various macrolides in this regard and not all macrolides are responsible for drug interactions. With the recent advent of many semisynthetic macrolide antibiotics it is now evident that they may be classified into 3 different groups in causing drug interactions. The first group (e.g. troleandomycin, erythromycins) are those prone to forming nitrosoalkanes and the consequent formation of inactive cytochrome P450-metabolite complexes. The second group (e.g. josamycin, flurithromycin, roxithromycin, clarithromycin, miocamycin and midecamycin) form complexes to a lesser extent and rarely produce drug interactions. The last group (e.g. spiramycin, rokitamycin, dirithromycin and azithromycin) do not inactivate cytochrome P450 and are unable to modify the pharmacokinetics of other compounds.

It appears that 2 structural factors are important for a macrolide antibiotic to lead to the induction of cytochrome P450 and the formation *in vivo* or *in vitro* of an inhibitory cytochrome P450-iron-nitrosoalkane metabolite complex: the presence in the macrolide molecules of a non-hindered readily accessible *N*-dimethylamino group and the hydrophobic character of the drug.

Troleandomycin ranks first as a potent inhibitor of microsomal liver enzymes, causing a significant decrease of the metabolism of methylprednisolone, theophylline, carbamazepine, phenazone (antipyrine) and triazolam. Troleandomycin can cause ergotism in patients receiving ergot alkaloids and cholestatic jaundice in those taking oral contraceptives.

Erythromycin and its different prodrugs appear to be less potent inhibitors of drug metabolism. Case reports and controlled studies have, however, shown that erythromycins may interact with theophylline, carbamazepine, methylprednisolone, warfarin, cyclosporin, triazolam, midazolam, alfentanil, disopyramide and bromocriptine, decreasing drug clearance. The bioavailability of digoxin appears also to be increased by erythromycin in patients excreting high amounts of reduced digoxin metabolites, probably due to destruction of enteric flora responsible for the formation of these compounds. These incriminated macrolide antibiotics should not be administered concomitantly with other drugs known to be affected metabolically by them, or at the very least, combined administration should be carried out only with careful patient monitoring.

Josamycin, midecamycin and probably also the related compounds miocamycin, clarithromycin and flurithromycin, may have a clinically significant interaction with carbamazepine and cyclosporin, requiring close monitoring. Roxithromycin interaction with drugs such as theophylline or cyclosporin does not seem to justify a dosage reduction. No pharmacokinetic interactions have yet been described for spiramycin, rokitamycin, dirithromycin and azithromycin.

The macrolide group of antibiotics includes different members, thus named because they contain a many-membered lactone ring (from 14 to 16 carbon atoms) to which are attached 1 or more deoxy sugars.

Erythromycin, discovered in 1952 in the metabolic products of a strain of *Streptomyces erythreus*, is the prototype of all the antimicrobial agents of the macrolide class. Macrolide antibiotics have been useful drugs for the last 40 years. During this period they successfully treated *Staphylococcus* spp. and *Streptococcus pyogenes* infections and have been the drugs of choice against *Mycoplasma pneumoniae* and *Bordetella pertussis*. More recently, their use has been extended to the treatment of infections caused by *Campylobacter*, *Legionella* and *Chlamydia* spp. (Periti et al. 1990).

Over the past several years, a large effort has been made to synthesise derivatives or analogues of erythromycin that would have improved chemical, biological and pharmacokinetic properties. Indeed, since 1977, macrolides have recaptured clinical interest through the development of semisynthetic molecules with improved pharmacokinetics (Periti et al. 1989a). These drugs differ from erythromycin in their size and substitution pattern of the lactone ring system. Other approaches have also been taken in an attempt to overcome the problems of oral bioavailability of erythromycin and related natural macrolide antibiotics by converting the base to acid-stable palatable ester, salt or salt of an ester, and to an oxazine derivative like azithromycin (table I).

The new macrolides, roxithromycin, clarithromycin, azithromycin, dirithromycin and the prodrug rokitamycin, appear to have the same spectrum of activity as the natural macrolides, erythromycin, spiramycin, oleandomycin, midecamycin, josamycin and the older semisynthetic derivative miocamycin, and their advantages lie mostly in their pharmacokinetics (Fernandes 1987; Kirst & Sides 1989a,b). Additional macrolide antibiotics have been mentioned in the recent literature, but it is unknown whether any will reach clinical evaluation (Kirst & Sides 1989a).

It is well known that macrolide antibiotics may interact with several compounds with possible effects on their pharmacokinetics (Periti & Mazzei 1987; Periti et al. 1989b). During the past 20 years, a number of case reports have incriminated macrolide antibiotics as a potential source of clinically severe drug interactions.

Following the initial paper on precipitation of acute ergotism by troleandomycin (Hayton 1969), several recent reports indicate drug interaction between macrolide antibiotics and other drugs such

as natural and semisynthetic ergot alkaloids (Larcan 1979; Nelson et al. 1990), oral contraceptives (Miguet et al. 1980), carbamazepine (Dravet et al. 1977a,b; Mesdjian et al. 1980; Turner & Renton 1989; Wong et al. 1983; Wroblewski et al. 1986), theophylline (Brazier et al. 1980; Cummings et al. 1977; Descotes et al. 1985; Iliopoulou et al. 1982; May et al. 1982; Paulsen et al. 1987; Prince et al. 1981; Rieder & Spino 1988; Weinberger et al. 1977), caffeine (Descotes et al. 1985), lovastatin (Ayanian et al. 1988), the benzodiazepines triazolam (Phillips et al. 1986) and midazolam (Gascon et al. 1989), the antiarrhythmic agent disopyramide (Ragosta et al. 1989), digoxin (Friedman & Bonventre 1982), warfarin (Bachmann et al. 1984a; Bachmann 1986; Bartle 1980), phenazone (antipyrine) [Larrey et al. 1983; Paire & Lavarenne 1982; Pessayre et al. 1985], methylprednisolone (LaForce et al. 1983; Szefler et al. 1980), cyclosporin (Freeman et al. 1984, 1987; Kessler et al. 1986; Lysz et al. 1988) and the opioid analgesic alfentanil (Bartkowski et al. 1989).

However, some differences were found between macrolide derivatives and not all of them are potential sources of drug interactions. For example, troleandomycin was the most commonly incriminated agent, erythromycin ranked second, josamycin, flurithromycin, roxithromycin, midecamycin, miocamycin (ponsinomycin) and clarithromycin were seldom involved, while dirithromycin, azithromycin, rokitamycin and the older compound spiramycin have not been involved in drug interactions to date (Barzaghi et al. 1988; Debruyne et al. 1986; Descotes & Evreux 1987; Descotes et al. 1985; Periti et al. 1989b; Principi et al. 1987; Rimoldi et al. 1986; Saint-Salvi et al. 1987; Vinçon et al. 1987).

Initially, the mechanism of these interactions was unknown but the clinical course of all reported cases was consistent with the hypothesis that macrolide antibiotic-induced symptoms were related to a relative overdose of the other drug. This accounted for the widely different clinical presentations of the reported drug interactions. Available data strongly suggest that the possible mechanism of interaction may be an inhibition of hepatic drug metabolising enzymes (Pessayre et al. 1981, 1985).

1. Mechanism of Drug Interaction

Macrolides consist of a large aglycone ring and 1 or more sugars, some of which are amino sugars, bearing a tertiary amine function, $-N(CH_3)_2$. Drugs

Table I. Classification of clinically available macrolide antibiotics

Natural	Prodrugs	Semisynthetic
Erythromycin	**Erythromycin ester**	**Miocamycin**
Oleandomycin	Propionyl	Acetyl-midecamycin
Spiramycin	Ethylsuccinate	**Flurithromycin**
Josamycin	**Erythromycin salt**	Fluoro-erythromycin
Midecamycin	Stearate	**Roxithromycin**
	Erythromycin salt of an ester	Methoxyethoxy-methyloxime-erythromycin
	Estolate	**Clarithromycin**
	Propionyl-mercaptosuccinate	Methyl-erythromycin
	Acistrate	**Azithromycin**
	Acetylcysteinate	Deoxo-aza-methyl-homoerythromycin
	Troleandomycin	**Dirithromycin**[a]
	Triacetyloleandomycin	Bis-deoxo-imino-methoxyethoxy ethylidene-oxy-erythromycin
	Rokitamaycin	
	Propionyl-ester of leucomycin A5	

a Derivative of erythromycylamine (an older derivative of erythromycin).

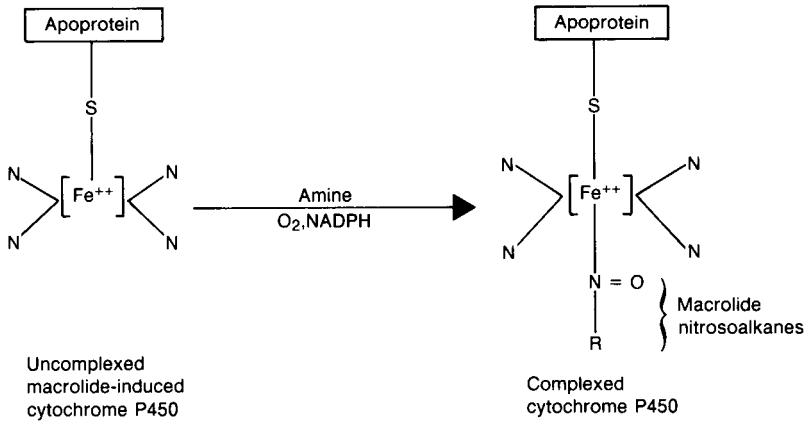


Fig. 1. Metabolism of tertiary amine drugs such as macrolides. The induced isozymes actively demethylate and oxidise the macrolide antibiotic into a nitrosoalkane which forms a stable, inactive complex with the iron [Fe^{++}] of cytochrome P450.

such as macrolide antibiotics are oxidised in the liver by a microsomal multienzymatic system with cytochrome P450 as the terminal oxidase. Cytochrome P450 is comprised of different isozymes, each with the same haeme iron oxidising centre but varying apoprotein (Pessayre et al. 1985). A drug substrate initially binds to oxidised (Fe^{+++}) cytochrome P450 and the resulting complex is reduced (Fe^{++}) by the NADPH-cytochrome P450 oxidoreductase and then combines with molecular oxygen. A second electron and 2 hydrogen ions are acquired from the donor system, and the subsequent products are oxidised metabolite and water, with regeneration of the oxidised (Fe^{+++}) cytochrome P450 (Guengerich et al. 1982). In the oxidising centre, 4 bonds unite the iron to the 4 nitrogens of the tetrapyrrole ring of haeme and a fifth bond attaches the haeme iron to the sulfur of a cysteinyl residue of the apoprotein while a sixth site remains free, permitting the binding of molecular oxygen and the subsequent oxidation of substrates (Pessayre et al. 1985) [fig. 1].

An important property of this microsomal system is that it can be induced by several drugs or chemicals and that it can be inhibited by different mechanisms. Thus, some drugs may compete with other substrates for reversible binding to cytochrome P450 and their reactive metabolites may covalently bind to a haeme nitrogen or to the apoprotein and inactivate the enzymatic system (Halpert et al. 1983; Delaforge et al. 1983). Moreover some metabolites may form inactive complexes with the iron of cytochrome P450 (Franklin 1977), in particular during the metabolism of secondary or tertiary amines (fig. 1).

It is known, on the basis of experimental *in vitro* and *in vivo* models, that macrolides selectively induce the forms of P450 belonging to group IIIA which are also involved in the oxidation of other drugs like theophylline, caffeine and cyclosporin. The same enzymes are inducible by glucocorticosteroids that could be involved in complex drug interactions when associated with macrolide antibiotics for antimicrobial chemotherapy (Pessayre et al. 1985; Watkins et al. 1986; Wrighton et al. 1985).

The effects of some macrolide antibiotics on hepatic cytochrome P450 may be explained as: (a) induction of a form of cytochrome P450 able to bind and metabolise the antibiotic; (b) oxidation to a stable iron-metabolite complex by the new form of antibiotic; (c) accumulation of the complex where cytochrome P450 is completely inactivated (Delaforge et al. 1983). A cytochrome P450/nitrosoalkane complex results from the existence of an accessible $N(CH_3)_2$ group in the molecule, steric hindrance around this group and the hydrophobicity of the molecules that is directly proportional

to their potency as metabolite-complex precursors (Delaforge et al. 1983). For example, some macrolides such as troleandomycin, followed by erythromycin estolate, erythromycin propionate, erythromycin base, erythromycin stearate and erythromycin ethylsuccinate, can induce microsomal enzymes and formation of inactive cytochrome P450 metabolite complexes in rats (Delaforge et al. 1983) and in humans (Larrey et al. 1983).

However, individual variability is to be expected in a system where drug metabolising enzymes are both induced and inactivated. Other mechanisms may contribute to the profound depression of cytochrome P450 activity observed after administration of the incriminated macrolide antibiotics that, as unchanged molecules in the liver *in vivo* or persisting in isolated microsomes, may compete with other substrates for reversible binding to the hydrophobic site of the induced cytochrome P450 isoenzymes, thereby further decreasing their affinity for other substrates.

One possibility which has not yet been confirmed experimentally is that the reactive nitrosoalkane might bind covalently to the apoprotein and produce a hypoactive form of uncomplexed cytochrome P450 (Pessayre et al. 1985).

In those macrolides where a second sugar is attached to the amino sugar, the presence of this bulky molecule may prevent, by steric hindrance, a close proximity between the tertiary amine and the iron of cytochrome P450, thereby reducing or preventing the oxidation of the macrolide substrates and the inactivation of the enzyme system. Conversely, the semisynthetic modifications of the aglycone ring can also decrease the macrolide nitrosoalkanes and consequent inhibition of cytochrome P450. Interestingly, such differences between macrolides in the formation of nitrosoalkanes may also be present with regard to hepatotoxic potential (Miura et al. 1989; Pessayre et al. 1985). In fact, the administration of erythromycin as base or in the form of different prodrugs (table I) has been reported to cause 2 different types of hepatic reactions in humans. First, in up to 10% of cases these macrolide antibiotics can induce apparently benign increases in serum transaminases, and secondly, erythromycin estolate is believed to be responsible for potentially severe but uncommon cholestatic liver injury, which may occur in as many as 2 to 4% of treated patients (Keller & Bircher 1980; Pessayre et al. 1985; Viluksela et al. 1988). In isolated cases, even erythromycin ethylsuccinate and stearate may cause cholestasis (Fraser 1980). Although the exact mechanism of cholestasis remains unknown, an immune-mediated reaction has been suggested (Pessayre et al. 1985).

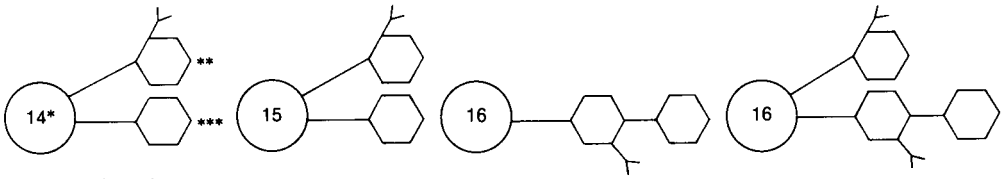
The 2'-acetyl ester structure of erythromycin acistrate resembles erythromycin estolate. However, in toxicological studies acistrate does not cause hepatotoxicity (Lehtonen et al. 1991). There is no information about the effect of other drugs on the pharmacokinetics of this new erythromycin prodrug.

In summary, there are some 14-carbon membered ring macrolides bearing an amino sugar with a tertiary amine function, i.e. troleandomycin, erythromycin and its prodrugs, which form nitrosoalkanes, decrease drug metabolism and may produce drug interactions (group 1). Others, however, including semisynthetics, rarely form (midecamycin, miocamycin, josamycin, flurithromycin, roxithromycin, clarithromycin; group 2) or do not form (spiramycin, azithromycin, rokitamycin, dirithromycin; group 3) nitrosoalkanes and do not engender these adverse effects (fig. 2).

2. *Troleandomycin*

Troleandomycin (triacetyloleandomycin, TAO) is more lipid soluble than oleandomycin. As a prodrug it is better absorbed from the intestine and is then hydrolysed to the more active oleandomycin.

Troleandomycin was the first macrolide antibiotic noted to cause clinically severe interactions with ergotamine (Bacourt & Couffinhal 1978; Franco et al. 1978; Hayton 1969; Matthews & Havill 1979). The mechanism of the interaction has not been investigated in humans, but the drug can notably increase dihydroergotamine blood concentrations in Rhesus monkeys and in the minipig (Azria et al. 1979; Martinet & Kiechel 1983).



High degree (Group 1)	Troleandomycin Erythromycin			
Low degree (Group 2)	Flurithromycin Clarithromycin Roxithromycin		Josamycin Midecamycin Miocamycin	
Not incriminated (Group 3)	Dirithromycin	Azithromycin	Rokitamycin	Spiramycin

Fig. 2. Correlations between the molecular structure and differential degree of drug interaction potential of macrolide antibiotics. *Symbols:* * = n-membered aglycone macrolide ring; ** = amino sugar bearing a tertiary amine function; *** = neutral sugar.

Following early reports of troleandomycin as a 'steroid sparing' agent in the treatment of patients with asthma (Fox 1961; Itkin & Menzel 1970; Kaplan & Godin 1959; Spector et al. 1974; Ziger et al. 1980), Szefler et al. (1980; 1982a,b) investigated a possible pharmacokinetic interaction. They demonstrated dosage- and time-related effects of troleandomycin on methylprednisolone elimination, with a significant increase in the serum half-life ($t_{1/2}$) and a decrease in clearance (CL). Troleandomycin can also cause a significant decrease in the volume of distribution (Vd) of methylprednisolone (LaForce et al. 1983; Szefler et al. 1982a,b).

Cholestatic jaundice in women receiving troleandomycin and oral contraceptives has been described in numerous reports (Belgian Centre for Drug Supervision 1979; Claudel et al. 1979; Fevery et al. 1983; Haber & Hubens 1980; Miguet et al. 1980; Rollux et al. 1979). Specific pharmacokinetic investigations are lacking but a possible inhibition of the drug on the metabolism of estrogens and progestational agents has been hypothesised.

Several studies also demonstrate the influence of troleandomycin on theophylline pharmacokinetics in patients and healthy volunteers, with a significant increase in serum $t_{1/2}$ (27 to 70%) and drug concentrations and a reduction in serum CL by 50% (Brazier et al. 1980; Lavarenne et al. 1981; Weinberger 1978; Weinberger et al. 1977). These effects are the possible cause of reported cases of theophylline toxicity during treatment with the 2 drugs.

Numerous cases of carbamazepine toxicity have been described in patients with epilepsy receiving troleandomycin (Dravet et al. 1977a,b; Mesdjian et al. 1980). Although this interaction has not been investigated in specific pharmacokinetic studies, carbamazepine serum concentrations 2 to 3 times higher than normal were measured in 6 symptomatic patients (Mesdjian et al. 1980).

The effects of troleandomycin on phenazone pharmacokinetics have been documented by Paire and Lavarenne (1982) in 6 healthy volunteers: after a 3-day treatment with 1.5g of the macrolide, there was a 44% increase in the phenazone $t_{1/2}$ and a 32% decrease in CL. Moreover, Pessayre et al. (1982b) observed a 45% decrease in phenazone CL in patients with respiratory tract infections treated with troleandomycin 2g for 7 days.

More recently, troleandomycin was found to interact pharmacokinetically with triazolam, prolonging the psychomotor impairment and amnesia produced in 7 healthy volunteers by the benzodiazepine (Warot et al. 1987). The macrolide produced a significant increase in triazolam serum concentrations, area under the plasma concentration-time curve (AUC) and serum $t_{1/2}$, with a de-

Table II. Results of clinical studies on pharmacokinetic drug interactions of the group 1 macrolides troleandomycin (TAO) and erythromycin (E)

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Troleandomycin					
Sequential	10 steroid-dependent asthmatic pts	14 mg/kg/day (1 g/day maximum) for 7 days	Methylprednisolone 1 mg/kg or 40mg IV before and after TAO therapy	Significant decrease of methylprednisolone CL and significant increase of methylprednisolone $t_{1/2}$	Szefler et al. (1980)
Sequential	5 steroid-dependent asthmatic pts	I-14 mg/kg/day for 7 days followed by 500 mg/day for 9 or 13mo	I-Methylprednisolone 40mg IV before and after 1 week on TAO, then methylprednisolone 8mg after 9mo or 4mg after 13mo	I-Lower methylprednisolone CL and Vss and higher MRT and $t_{1/2}$	Szefler et al. (1982a)
		II-250mg every other day for 7mo	II-Methylprednisolone 40mg IV before and after 7mo on TAO therapy administered on 2 consecutive days (day-on and day-off TAO)	II-During the day-on TAO there was greater impairment of steroid disposition than during the day-off TAO	
		III-long therapy for 13mo	III-Methylprednisolone 40mg IV before and after 13mo on TAO therapy administered after single or multiple 250mg dose	III-Greater impairment in steroid disposition during TAO multiple doses	
Sequential	6 steroid-dependent pts	14 mg/kg/day for 7 days	Methylprednisolone 40mg before and after 1 week on TAO (3 pts) Prednisolone 40mg IV before and after 1 week on TAO (3 pts)	Impaired elimination of methylprednisolone in the presence of TAO therapy. No effect on prednisolone elimination	Szefler et al. (1982b)
Sequential	8 pts with chronic asthma	1 g/day for 10 days	Theophylline 340mg IV qid before and after TAO	Theophylline CL was reduced by 50 ± 6% after 10 days of TAO therapy	Weinberger et al. (1977)
Sequential	5 pts	500mg	Theophylline 200mg PO	Decrease of 40% in theophylline ke and increase in $t_{1/2}$ by 70% approximately	Brazier et al. (1980)
Sequential	5 HV	1.5 g/day for 17 days	Theophylline 300mg PO	Significant increase in theophylline $t_{1/2}$ by 27% and reduced ke by 21%	Lavarenne et al. (1981)
Sequential	6 HV	1.5 g/day for 3 days	Phenazone 1g PO before and during TAO (3rd day)	Significant increase in phenazone $t_{1/2}$ (44%) and reduction in CL (32%)	Paire & Lavarenne (1982)
Randomised	18 pts with mild LRTI	2 g/day for 7 days	Phenazone 15mg/kg IV before and during TAO	Significant reduction in CL (45%)	Pessayre et al. (1982b)

Table II. Contd

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Double-blind crossover study	7 HV	2 g/day for 7 days or placebo	Triazolam 0.25mg PO after TAO or placebo treatment	Significant enhancement of the AUC, the C_{max} and the delay to t_{max} of triazolam	Warot et al. (1987)
Erythromycin					
Sequential	I-9 adolescent pts with chronic asthma	E base 1 g/day for 7 days	Methylprednisolone 40 mg/1.73m^2 IV prior and after macrolide therapy	I-Significant decrease of methylprednisolone CL (46%) and Vd. Significant increase in $t_{1/2}$ and MRT of methylprednisolone	LaForce et al. (1983)
	II-10 adolescent pts with chronic asthma	TAO 14 mg/kg/day (maximum 1 g/day) for 7 days		II-Significant decrease of methylprednisolone CL (58%) and Vd. Significant increase of MRT (95%) and $t_{1/2}$	
Unselected pts	11 paediatric asthmatic pts with infection	E ethylsuccinate (3 pts) E stearate (4 pts) E estolate (1 pt) E base (3pts) from 10.3 to 54.9 mg/kg/day	Theophylline long term (5.2-33 mg/kg/day)	4 patients had clinically significant increase in theophylline serum concentrations	Kozak et al. (1977)
Sequential	9 HV	E stearate (2 pts) E base (7 pts) 500mg for 1 day and then 1g for 1 day	Single dose aminophylline 5 mg/kg IV	No significant changes in theophylline pharmacokinetic parameters. However, in 3 of the 9 volunteers, $t_{1/2}$ was prolonged and CL reduced (20-50%)	Pfeifer et al. (1979)
Sequential	8 pts with asthma	E stearate 1 g/day for 5-7 days	Aminophylline 400-900 mg/day PO > 1 week before and after E	Significant increase in theophylline $t_{1/2}$ (18%) and trend to higher Vd. No apparent change in CL	Branigan et al. (1981)
Sequential double crossover	8 HV	E base 1 g/day for 10 days	Aminophylline 4 mg/kg PO before, after 3 and 10 days of E and 2 weeks after completing E	Significant decrease in theophylline CL (17%) and increase in $t_{1/2}$ (21%). The changes are statistically significant between the 10th day of treatment and post-study control	Zarowitz et al. (1981)
Sequential	14 adolescent asthmatic pts	E ethylsuccinate 800mg-1g (7 pts) or 30 mg/kg/day (maximum 1.5 g/day) for 1 week (7 pts)	Aminophylline 13.4-29.6 mg/kg day as constant IV infusion before and after E	Significant reduction in theophylline CL rate (25.8 ± 18.4%) and concomitant elevation in steady-state serum theophylline concentration of 40 ± 35.3%	LaForce et al. (1981)

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Table II. Contd

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Sequential	12 HV	E stearate 750mg for 10 days	Single oral dose of 200mg of oxtriphylline (equivalent to 128mg of theophylline) before and after E	Significant increase in theophylline $t_{1/2}$ and decrease in CL	Renton et al. (1981)
Sequential	8 HV	E base 1 g/day for 7 days	Aminophylline 5 mg/kg IV before and after E	Significant decrease in theophylline CL (27%) and increase in $t_{1/2}$. No changes in excretion of theophylline metabolites	Prince et al. (1981)
Sequential with placebo	23 HV	E base (6 pts) E stearate (6 pts) E ethylsuccinate (6 pts) placebo (6 pts) 1 g/day for 6 days	Theophylline oral elixir 6 mg/kg before and after E or placebo	Significant increase in theophylline $t_{1/2}$ (E base 51.7%, E stearate 21.3% and E ethylsuccinate 60.3%) and significant decrease in CL (25-31%). No changes in placebo group	May et al. (1982)
Clinical	62 pts: 46 with bronchial asthma (BA) and 16 with chronic airflow obstruction (CAO)	No antibiotic (31 pts with BA, 8 pts with CAO) E ethylsuccinate 1.95 ± 0.05 g/day for 53.1 ± 0.1 days (15 pts with BA) E ethylsuccinate 2.14 ± 0.148 g/day for 5.5 ± 1.8 days (8 pts with CAO)	Theophylline 600mg PO	Higher theophylline plasma levels bioavailability and decreased CL (30%) in patients with BA, but not with CAO	Richer et al. (1982)
Sequential	6 HV	E stearate 1.5 g/day for 5 days	Theophylline 250mg IV before and after E	Significant increase in theophylline $t_{1/2}$ and in CL	Iliopoulou et al. (1982)
Sequential	13 HV	E stearate 1 g/day for 5 days	Oral aminophylline 3 mg/kg qid for 5 days before and after E	No changes in theophylline pharmacokinetics	Maddux et al. (1982)
Randomised crossover with placebo	7 HV	E stearate 2 g/day for 2 days or placebo	Oral aminophylline 4 mg/kg qid for 3 days starting 1 day before E or placebo; after a 3-day washout the subjects were crossed over	No changes in urinary excretion of theophylline and metabolites	Melethil et al. (1982)
Sequential	15 pts with stable COPD	E stearate 2 g/day for 2 days (phase I: 11 pts) and for 7 days (phase II: 7 pts)	Uncoated aminophylline (9 pts) oxitriphylline (1 pt) sustained release theophylline (5 pts)	No significant differences in mean values. Increases in steady-state trough concentrations in 5 pts	Stults et al. (1983)

Table II. Contd

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Randomised crossover with placebo	12 pts with COPD	E stearate 2 g/day for 2 days or placebo	Oral aminophylline 4 mg/kg qid for 2 days during E or placebo; and after 7 days washout period the patients were crossed over	Significant decrease in theophylline CL (22%) and increase in C_{max}. No changes in urinary excretion of theophylline and metabolites	Reisz et al. (1983)
Sequential	11 HV	E stearate 1 g/day for 10 days (last dose was E lactobionate 300mg IV)	Theophylline 280 mg IV bolus followed by a constant infusion of 23.8 ± 4.1 mg/h for 6h before and after E	No changes in theophylline CL or $t_{1/2}$ No difference in metabolism	Hildebrandt et al. (1984)
Sequential	10 pts with exacerbated chronic asthmatic bronchitis	E stearate 2 g/day for 2 days	Theophylline 5 mg/kg IV followed by a constant infusion of 0.7 mg/kg/h for 132h before and during E	Significant increase of theophylline serum concentrations	Bartolucci et al. (1984)
Sequential	10 HV	E base 1 g/day for 9 days	Theophylline 5 mg/kg IV followed by a constant infusion of 0.5 mg/kg/h for 5h before and after E	Significant increase of theophylline AUC and plasma concentrations. No statistically significant changes in CL and CL_R	Paulsen et al. (1987)
2-way crossover	8 HV	Treatment A: E (4 pts) 1 g/day for 5 days before and 3 days after carbamazepine. Treatment B: (4 pts) no antibiotic	Carbamazepine 400mg in group A and B pts: after a 4-week washout period pts crossed	Significant decrease in carbamazepine CL (19%), but no difference in Vd, ke and ka	Wong et al. (1983)
Crossover	8 HV	E base 999 mg/day for 7 days	Phenytoin 300mg PO before and after E	No significant changes in phenytoin Vd, $t_{1/2}$ and CL	Bachman et al. (1984)
Randomised crossover	8 HV	E base 1 g/day for 7 days	Phenytoin 400mg PO before and after 4.5 days of E	No significant differences in phenytoin pharmacokinetic parameters (AUC, $t_{1/2}$, etc.)	Milne et al. (1988)
Randomised crossover	12 HV	E base 1 g/day for 8 days	Warfarin 1 mg/kg PO the fifth day of E	Significant decrease in warfarin CL by 14%	Bachman et al. (1984a)
Sequential	8 pts on long term warfarin	E base 990 mg/day for 7 days	Warfarin 2.9-9 mg/day	Modest but significant increase in plasma warfarin concentrations (<15%) and similar rise in prothrombin time (<10%)	Weibert et al. (1989)

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Table II. Contd

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Sequential	10 HV	E base 1 g/day for 7 days	Cyclosporin 10 mg/kg PO before and after E	Significant increase in cyclosporin C_{max} and AUC; decrease in t_{max} and CL No alterations in $t_{1/2}$	Freeman et al. (1987)
Sequential	8 pts on haemodialysis	E ethylsuccinate 33 mg/kg/day for 4 days (free from dialysis)	Cyclosporin 6 mg/kg PO before and after E	Significant increase in cyclosporin C_{min}, AUC and $t_{1/2}$	Vereerstraeten et al. (1987)
Sequential	4 renal transplant patients	E (NS)	Cyclosporin IV (dose NS)	Significant reduction in cyclosporin CL and Vd	Aoki et al. (1987)
Randomised crossover	6 renal transplant pts on oral cyclosporin for 6-12 months	E base 2 g/day for 3 days	Cyclosporin oral and IV (with crossover) before and after E	Significant increase in cyclosporin bioavailability with a small but significant (13%) decrease in CL	Gupta et al. (1989)
Sequential	6 HV	E 1 g/day for 7 days	Alfentanyl 50 g/kg IV before, the first day and after E	Significant increase in alfentanyl $t_{1/2}$ and decrease in CL	Bartkowski et al. (1989)
Sequential	5 HV	E estolate 1 g/day for 4 days	Bromocriptine 5mg PO before and after E	Significant increase in bromocriptine AUC and C_{max}	Nelson et al. (1990)

Abbreviations: CL = total body clearance of drug from the plasma; $t_{1/2}$ = half-life; Vd = volume of distribution; V_{ss} = volume of distribution of steady-state; MRT = mean resistance time; t_{max} = time to reach peak; AUC = area under the plasma concentration-time curve; C_{max} = maximum peak plasma concentration; BA = bronchial asthma; CAO = chronic airflow obstruction; COPD = chronic obstructive pulmonary disease; ke = elimination rate constant; ka = absorption rate constant; CL_R = renal clearance of drug from the plasma; C_{min} = minimum plasma drug concentration; NS = not stated; IV = intravenous; PO = oral; HV = healthy volunteers; qid = 4 times daily; LRTI = lower respiratory tract infection.

crease in CL (Warot et al. 1987). Table II summarises the principal studies which demonstrate a clear pharmacokinetic interference between troleandomycin and methylprednisolone, theophylline, carbamazepine, phenazone and triazolam. In view of these data and the numerous clinical reports on pharmacokinetic interactions, it is not advisable to prescribe troleandomycin in patients receiving these other agents.

In contrast to troleandomycin, no drug interaction has been reported with oleandomycin. This discrepancy may indicate that oleandomycin interferes less with microsomal enzymes than does troleandomycin. Indeed, oleandomycin is both a weaker inducer of these enzymes and a poorer substrate for the induced species of cytochrome P450 (Pessayre et al. 1982a).

3. Erythromycin

After troleandomycin, erythromycin is the macrolide most frequently implicated in pharmacokinetic drug interactions. From a clinical perspective, the most important interactions are those with methylprednisolone, theophylline, carbamazepine, warfarin, cyclosporin, digoxin (Ludden 1985; Yee & McGuire 1990) and benzodiazepines (Phillips et al. 1986).

Erythromycin, at therapeutic dosages, can decrease methylprednisolone CL and Vd (LaForce et al. 1983).

The literature on erythromycin-theophylline interaction is contradictory. In some papers significant pharmacokinetic effects are demonstrated; in others no changes were found. Ludden (1985)

accurately and critically reviewed 22 publications, case reports and pharmacokinetic studies on this topic (Branigan et al. 1981; Cummings et al. 1977; Green & Clementi 1983; Hildebrandt et al. 1984; Kimelblatt & Slaughter 1980; Kozak et al. 1977; Iliopoulou et al. 1982; La Force et al. 1981; Maddux et al. 1982; May et al. 1982; Melethil et al. 1982; Murray & Brown 1982; Parrish et al. 1983; Pfeifer et al. 1979; Pingleton et al. 1980; Prince et al. 1981; Reisz et al. 1983; Renton et al. 1981; Richer et al. 1982; Stratton 1983; Stults et al. 1983; Zarowitz et al. 1981). He concluded that many (but not all) studies did not demonstrate any interaction when employing only moderate erythromycin dosages (<1.5 g/day) for short periods of time (<5 days). The importance of the size of the erythromycin dosage and the duration of treatment has been noted previously by Jonkman and Hendells (1983).

The pharmacokinetic effects on theophylline can occur with any salt or ester of erythromycin and consist of a decrease in CL (mean values varying from 9 to 40%) and an increase in $t_{1/2}$ (15 to 60%). However, the mean intrasubject variability in theophylline CL has a coefficient of variation of about 10% and its metabolism is dependent on factors such as diet, caffeine intake, smoking and infections (Ludden 1985). Other studies published after Ludden's review suggested a significant pharmacokinetic interaction between the 2 agents (Bartolucci et al. 1984; Paulsen et al. 1987; Wiggins et al. 1986), but in only 1 study (Wiggins et al. 1986) was erythromycin used at dosages greater than 1.5 g/day (i.e. 500mg 4 times daily for 6 days). Altogether, these data indicate that careful clinical and pharmacokinetic monitoring of patients receiving both theophylline and erythromycin should be carried out. A more rational alternative for patients requiring treatment with both drugs would be to substitute a newer macrolide which does not interact pharmacokinetically with theophylline.

During theophylline coadministration, the only change in a pharmacokinetic parameter of erythromycin was increased renal clearance (Hildebrandt et al. 1987).

Erythromycin has been reported to interact with the anticonvulsant carbamazepine in children and adults, causing elevated serum concentrations of carbamazepine and signs of toxicity (confusion, somnolence, ataxia, vertigo, nausea and vomiting) [Berrettini 1986; Carranco et al. 1985; Goulden et al. 1986; Jaster & Abbas 1986; Macnab et al. 1987; Wong et al. 1983; Woody et al. 1987; Wroblewski et al. 1986]. Commonly the toxicity starts shortly after the institution of erythromycin treatment and is rapidly reversible after withdrawal of the antibiotic.

To date, only 1 controlled study has evaluated the effects of erythromycin on carbamazepine pharmacokinetics in healthy volunteers (Wong et al. 1983). CL of a single dose of carbamazepine was significantly reduced by 19% during erythromycin treatment (1g/day). Two pharmacokinetic studies in healthy volunteers indicated a lack of effects due to erythromycin on the single-dose pharmacokinetics of phenytoin (Bachmann et al. 1984b; Milne et al. 1988).

Numerous case reports describing an erythromycin-warfarin interaction have been published (Bartle 1980; Friedman & Bonventre 1982; Grau et al. 1986; Husserl 1983; Sato et al. 1984; Schwartz & Bachmann 1984). Erythromycin can increase the hypothrombinaemic effect of warfarin, causing a marked rise in prothrombin time with haemorrhage occurring in several cases.

Bachmann et al. (1984a) demonstrated a decrease in warfarin CL by 14% ($p < 0.001$) in 12 healthy volunteers treated with erythromycin. The reduction was greater in volunteers who had a lower initial CL rate. Weibert et al. (1989) confirmed these data in 8 patients on long term warfarin therapy who also received erythromycin and showed a modest but significant ($p < 0.05$) increase in plasma warfarin concentrations and a similar rise in prothrombin time. However, there is a discrepancy between the modest pharmacokinetic interaction and the clinical case reports which often told of severe results. The morbidity with this interaction can be potentiated by factors such as old age and dietary restrictions, but additional studies are needed to identify patients at major risk (Ludden 1985; Weibert et al. 1989).

Several case reports describing the increase in cyclosporin concentrations in recipients of renal or cardiac transplants were recently reviewed by Yee and McGuire (1990). This pharmacokinetic interaction has also been shown by evidence of a significant increase in cyclosporin AUC and peak plasma concentration (C_{max}), a reduction in the time to C_{max} (t_{max}) after oral cyclosporin (Freeman et al. 1987; Jensen et al. 1987; Vereerstraeten et al. 1987; Wadhwa et al. 1987) and a decrease in cyclosporin CL after intravenous administration (Aoki et al. 1987; Grino et al. 1986).

Gupta et al. (1989) studied the effects of erythromycin on cyclosporin pharmacokinetics after oral and intravenous administration. They concluded that the increase in cyclosporin plasma concentrations were principally dependent on increased absorption, probably due to the inhibition of gastrointestinal motility or of intestinal cytochrome P450 enzymes by erythromycin. The pharmacokinetic interaction is, however, complex and probably involves both increased oral bioavailability and decreased cyclosporin metabolism (Yee & McGuire 1990). Coadministration of the 2 drugs should be avoided or the cyclosporin concentrations carefully monitored to minimise the risk of toxicity.

Erythromycin increases digoxin plasma concentrations with subsequent severe nausea, vomiting and arrhythmia (Friedman & Bonventre 1982; Maxwell et al. 1989). Erythromycin and tetracycline can both decrease the urinary excretion of digoxin metabolites due to reduction of digoxin by *Eubacterium lentum*, a common constituent of normal intestinal flora. The mechanism of the erythromycin-digoxin interaction is not clear, but increased bioavailability of oral digoxin induced by enhanced gastric emptying by erythromycin has been hypothesised (Sutton & Pilot 1989). Erythromycin can also decrease digoxin metabolism with direct antimicrobial activity against *E. lentum* (Ludden 1985). It is appropriate to clinically monitor patients receiving digoxin when they require erythromycin and to consider a temporary reduction in the digoxin dose.

The effect of erythromycin on the pharmacokinetics of triazolam was studied in healthy male volunteers. Administration of the macrolide resulted in a 52% decrease in triazolam CL, higher serum concentrations, a 30% decrease in the apparent Vd and significant increase in the elimination $t_{1/2}$ (Phillips et al. 1986). Midazolam hydroxylation, monitored *in vitro* in human liver microsomes, are also inhibited by erythromycin (Gascon et al. 1989).

A 7-day course of erythromycin clearly inhibited the metabolism of alfentanil, a short acting potent narcotic, with significant change in $t_{1/2}$ and CL (Bartkowski et al. 1989).

The effects of a 4-day treatment with erythromycin on bromocriptine plasma concentrations were evaluated in 5 volunteers (Nelson et al. 1990). The macrolide caused a significant increase in bromocriptine AUC and plasma concentrations with a risk of increased adverse effects.

Other erythromycin interactions have been recently described, such as 1 case of rhabdomyolysis with concomitant lovastatin therapy (Ayanian et al. 1988) or 2 potentially fatal cases due to interactions with the antiarrhythmic agent disopyramide (Ragosta et al. 1989).

The principal pharmacokinetic studies which report pharmacological interference between erythromycin and the drugs mentioned above are outlined in table II.

In summary, while the interactions between methylprednisolone and erythromycin do not involve serious risk for the patient, nevertheless, combination of the following drugs with erythromycin should be avoided or very carefully monitored: theophylline, carbamazepine, cyclosporin, digoxin, benzodiazepine and bromocriptine.

For more recently reported interactions (i.e. with lovastatin or disopyramide), while more studies are needed to verify the mechanisms of interactions, clinicians should use prudence when administering these drugs concomitantly with erythromycin.

4. Josamycin

In the past decade several studies have been conducted with josamycin to evaluate its possible involvement in drug interactions (table III). This

Table III. Results of clinical studies on pharmacokinetic drug interactions of group 2 macrolides

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Josamycin					
Comparative	15 adult pts	500mg single dose	Theophylline 200mg single PO dose, in the absence (controls) or presence of macrolide treatment	No modification of theophylline $t_{1/2}$, ke	Brazier et al. (1980)
Sequential	27 paediatric pts with RTI	57 mg/kg/day for at least 6 days	Theophylline 13.9 mg/kg/day before (controls) and after treatment with macrolide	Statistically significant increase in theophylline serum concentrations	Vallarino et al. (1982)
Sequential	6 HV	2000 mg/day for 7 days	Theophylline 240mg single PO dose before (controls) and after treatment with macrolide	No modification of theophylline t_{max}, C_{max}, ka, ke, $t_{1/2\beta}$ CL, AUC	Selles et al. (1983)
Randomised crossover	23 paediatric pts	50-100 mg/kg/day for 4 days	Theophylline 15-20 mg/kg/day	Statistically significant increase in theophylline serum concentrations	Jiménez Baos et al. (1983)
Sequential	10 pts with COPD	1500 mg/day for 2 days	Theophylline 0.7 mg/kg/h IV over a period of 132h in the absence (controls) or presence of macrolide treatment	No modification of theophylline serum concentrations	Bartolucci et al. (1984)
Sequential	30 asthmatic pts	2000 mg/day for 5 days	Theophylline 9.95 mg/kg/day PO before (controls) and during treatment with macrolide	No statistically significant modification of theophylline serum concentrations	Ruff et al. (1984)
Sequential double crossover	6 HV	2000 mg/day for 5 days	Caffeine 2.5 mg/kg single PO dose before (controls) and after treatment with macrolide	Statistically significant increase in $t_{1/2}$ (14.6%) and decrease in CL (21.5%) of caffeine	Descotes et al. (1985)
Sequential	7 paediatric pts with LRTI	40 mg/kg/day for 7 days	Anhydrous theophylline 14-17 mg/kg/day before (controls) and during treatment with macrolide	Statistically significant increase in serum concentrations and decrease (38.7%) in CL of theophylline	Pavesio et al. (1989)
Sequential	10 HV	2000 mg/day for 7 days	Carbamazepine 200mg single PO dose before (controls) and after treatment with macrolide	Statistically significant increase in $t_{1/2}$ (17.4%), AUC and decrease in CL (18.8%) of carbamazepine	Albin et al. (1982)
Sequential	8 epileptic pts	2000 mg/day for 7 days	Carbamazepine 11.8 mg/kg/day PO before (controls) and after treatment with macrolide	Statistically significant decrease in CL of total (17%) and unbound (21.5%) carbamazepine decrease of metabolite to parent drug AUC ratio (20.2%)	Vincon et al. (1987)

Table III. Contd

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Sequential	6 HV	2000 mg/day for 5 days	Phenazone 12 mg/kg single PO dose before (controls) and after treatment with macrolide	No modification $t_{1/2}$, CL, Vd of antipyrine	Cadot et al. (1984)
Midecamycin					
Sequential	5 HV	1200 mg/day for 7 days	Theophylline 300mg single PO dose before (controls) during treatment with macrolide	No modification of theophylline $t_{1/2}$, ke	Lavarenne et al. (1981)
Sequential	18 asthmatic paediatric pts	40 mg/kg/day for 10 days	Theophylline 15 mg/kg/day PO before (controls), during and after treatment with macrolide	Slight, though not statistically significant, decrease of theophylline plasma concentrations	Lavarenne et al. (1981)
Sequential triple crossover	6 HV	1200 mg/day for 15 days	Phenazone 1g PO before (controls) and during treatment with macrolide	No modification of antipyrine $t_{1/2}$, CL, Vd at day 7 of treatment. 11% decrease of $t_{1/2}$ and 19% increase of CL at day 14 of treatment	Paire & Lavarenne (1982)
Miocamycin					
Sequential double crossover	20 pts with COPD	1200 mg/day for 10 days	Theophylline 4 mg/kg tid IV or slow release anhydrous theophylline 300mg bid PO before (controls) and during treatment with macrolide	No modification of theophylline C_{av}^{ss}, C_{max}, $t_{1/2}$, CL	Rimoldi et al. (1986)
Sequential single crossover	5 asthmatic children	35 mg/kg/day for 10 days	Theophylline 4.3 mg/kg IV single dose before (controls) and after treatment with macrolide	No modification of theophylline serum, $t_{1/2}$, CL, Vd	Principi et al. (1987)
Sequential	25 pts with COPD	1200 mg/day for 8 days	Theophylline 240mg IV single dose before (controls) and after treatment with macrolide	No modification of theophylline serum concentrations	Dal Negro et al. (1988)
Sequential	12 HV	800 mg/day for 5 days	Theophylline 200mg tid PO before (controls) and during treatment with macrolide	No modification of theophylline C_{max}, C_{min}, $t_{1/2}$, AUC, CL; 27% increase of CL_R	Couet et al. (1989)
Sequential	11 paediatric pts with LRTI	40 mg/kg/day for 7 days	Slow release anhydrous theophylline 100-200mg bid before (controls) and during treatment with macrolide	Slight, NSS, decrease of C_{av}^{ss} and 17% increase of CL of theophylline	Pavesio et al. (1989)

Continued next page

Table III. Contd

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Randomised crossover	14 adult HV	1600 mg/kg for 12 days	Single carbamazepine 200mg PO dose in the absence (controls) and on day 8 of treatment with macrolide	Statistically significant increase in $t_{1/2}$, AUC (13%) and decrease in CL of carbamazepine. Statistically significant decrease in C_{max} and AUC (26%) of metabolite	Couet et al. (1990a)
Sequential single crossover	10 renal transplant pts	1600 mg/day for 3 days	Single cyclosporine 2.67 mg/kg PO dose before (controls) and during treatment with macrolide	Statistically significant increase in C_{max}, C_{av}^{ss}, C_{min}, and AUC of cyclosporin	Couet et al. (1990b)
Clarithromycin					
Sequential	5 HV	300 mg/day for 5 days	Theophylline PO sustained release 400 mg/day PO before (controls) and during treatment with macrolide	Slight, not statistically significant increase in serum concentrations and AUC and decrease in CL (16.4%) of theophylline	Niki et al. (1988)
Sequential	10 HV	1000 mg/day for 9 days	Theophylline SR 13 mg/kg/day before (controls) and during treatment with macrolide	Consistently higher plasma theophylline concentrations	Ruff, unpublished data on file, Abbott
Randomised, placebo-controlled double-blind crossover	14 HV	1000 mg/day for 5 days	Carbamazepine 200mg single PO dose in the presence or absence of macrolide treatment	Increase in $t_{1/2}$ and AUC of carbamazepine, decrease in AUC of metabolite	Richens, unpublished data on file, Abbott
Sequential double crossover	7 HV	Flurithromycin 1500 mg/day for 10 days	Carbamazepine 400mg single PO dose before (controls) and during treatment with macrolide	Statistically significant increase in AUC of carbamazepine and decrease in C_{max} and AUC of metabolite	Barzaghi et al. (1988)
Flurithromycin					
Sequential double crossover	7 HV	1500 mg/day for 10 days	Single carbamazepine 400mg PO dose before (controls) and during treatment with macrolide	Statistically significant increase in AUC of carbamazepine and decrease in C_{max} and AUC of metabolite	Barzaghi et al. (1988)

Abbreviations: RTI = respiratory tract infections; LRTI = lower respiratory tract infections; C_{av}^{ss} = mean steady-state drug concentrations in the plasma during multiple dosing; bid = twice daily; NSS = not statistically significant; tid = 3 times daily; for other abbreviations see table II.

macrolide does not seem to inhibit hepatic enzymes (Pessayre et al. 1985) and does not interfere with the pharmacokinetics of phenazone (Cadot et al. 1984). A comparative study of the pharmacokinetics of theophylline administered alone or in combination with josamycin (500mg) showed no pharmacokinetic modification of the xanthine derivative in the presence of the macrolide (Brazier et al. 1980). Similarly, no modifications were observed after a 7-day treatment (Selles et al. 1983). Two other studies failed to demonstrate an increase in theophylline serum concentrations after josamycin administration for 2 to 5 days (0.5g 4 times daily or 1g twice daily) in patients with asthma (Bartolucci et al. 1984; Ruff et al. 1981, 1984).

Nevertheless, Descotes et al. (1985) demonstrated an influence of josamycin on caffeine disposition in healthy volunteers, with a 14.6% increase in plasma $t_{1/2}$ and a 21.5% decrease in plasma CL. These results agreed with the observation of increased serum concentrations (Jimenez Baos et al. 1983; Vallarino et al. 1982) or 38.7% reductions in theophylline CL (Pavesio et al. 1989) in paediatric patients. However, josamycin seems to cause only minimal changes in xanthine disposition in adults, although caution may be required for children. Slight but statistically significant modifications in carbamazepine pharmacokinetic parameters such as a 17 to 20% increase in both AUC and $t_{1/2}$ and a 20% decrease in plasma CL have been reported after single or multiple doses of josamycin in healthy volunteers (Albin et al. 1982) and in patients with epilepsy (Vincon et al. 1987). None of the subjects showed clinical symptoms of this interaction. However, close monitoring is recommended for patients treated with both carbamazepine and josamycin.

Finally, 3 case reports suggest that this macrolide may also inhibit hepatic metabolism of cyclosporin, requiring a reduction in the dosage of the immunosuppressive agent in order to attain adequate plasma concentrations (Azanza et al. 1990; Kreft-Jais et al. 1987).

In summary, the interaction of josamycin with theophylline seems to be clinically insignificant, at least in adults, while plasma carbamazepine and cyclosporin should be closely monitored.

5. Midecamycin and Miocamycin

These macrolide derivatives have not as yet been considered potentially hazardous from the perspective of pharmacokinetic drug interactions (Descotes et al. 1985; Periti et al. 1989b) [table III]. Midecamycin 1.2 to 2g daily administered for 5 to 7 days to healthy volunteers does not interfere with phenazone disposition, although 14 days of treatment may increase the CL and reduce the $t_{1/2}$ of phenazone (Paire & Lavarenne 1982). This macrolide does not modify significantly the pharmacokinetics of theophylline in adults and paediatric patients (Lavarenne et al. 1981). No further reports concerning other drug interactions with this compound are available in the literature. Several studies have failed to demonstrate an effect of miocamycin on theophylline disposition either in healthy volunteers (Couet et al. 1989), patients with chronic obstructive pulmonary disease (Dal Negro et al. 1988; Rimoldi et al. 1986) or in paediatric patients (Pavesio et al. 1989; Principi et al. 1987) [table III].

However, miocamycin administration seems to cause a moderate but statistically significant increase (13%) in the AUC of carbamazepine and a 26% decrease in the AUC of its metabolite in healthy adult volunteers (Couet et al. 1990a). It almost doubles cyclosporin plasma concentrations in renal transplant patients (Couet et al. 1990b). Therefore, miocamycin, and probably its related compound midecamycin, should be used carefully in combination with carbamazepine or cyclosporin and plasma concentrations of the latter drugs should be monitored.

6. Roxithromycin

Roxithromycin seems unable to form stable complexes with cytochrome P450 (Delaforge et al. 1988a,b; Villa et al. 1986c). Nevertheless, this macrolide derivative, when administered at 150mg twice daily for 4 to 9 days in combination with

theophylline, interacted slightly with the pharmacokinetics of the latter drug, leading to a small but statistically significant increase either in C_{max} and AUC in healthy volunteers (Saint-Salvi et al. 1987) or in mean trough concentrations in patients with acute exacerbations of chronic bronchitis (Bandera et al. 1988) [table III]. However, this type of interaction is not clinically relevant and does not seem to justify a change in the theophylline dosage. Monitoring theophylline plasma concentrations would be useful if pre-roxithromycin-treatment concentrations are higher than 15 mg/L.

The concomitant administration of roxithromycin with cyclosporin in heart transplant recipients led to a slight nonsignificant rise in cyclosporin concentrations and no dosage adjustment was necessary (Billaud et al. 1990).

Finally, disopyramide, unlike lidocaine, prednisone and warfarin, seems to be capable of interacting with roxithromycin *in vitro* by modifying serum protein binding and producing a notable increase in the unbound plasma concentrations of both drugs (Zini et al. 1987). This observation, although suggesting a possible increased risk of disopyramide side effects, has not yet been confirmed *in vivo*. Moreover, roxithromycin does not modify the carbamazepine pharmacokinetic profile (Saint-Salvi et al. 1987), does not interfere with the efficacy of oral contraceptives (Meyer et al. 1990) or interact with warfarin, ranitidine and antacids containing aluminium or magnesium hydroxide (Paulsen et al. 1988; Young et al. 1989).

7. Clarithromycin

When given alone, clarithromycin appears not to form complexes with cytochrome P450 *in vitro* or *in vivo*. However, this macrolide derivative, like roxithromycin, does form complexes in glucocorticoid-pretreated rats (Tinel et al. 1989).

Up to now there is only 1 publication about a possible pharmacokinetic drug interaction with clarithromycin. Niki et al. (1988) demonstrated an influence of this drug on theophylline pharmacokinetics in healthy volunteers, with a slight increase in serum concentrations and AUC and a 16.4% decrease in CL. However, these differences were not statistically significant when compared with control values (table III). Nevertheless, Ruff and coworkers found consistently higher theophylline plasma concentrations after concomitant administration of this macrolide compound in healthy adult volunteers (unpublished data on file, Abbott). The authors conclude that this increase justifies continuous monitoring of plasma concentrations of the xanthine in patients receiving clarithromycin during long term theophylline treatment. Similarly, Richens and coworkers described altered pharmacokinetic parameters of carbamazepine in healthy volunteers treated with clarithromycin (500mg twice daily) for 5 days, with increased carbamazepine concentrations, AUC and plasma $t_{1/2}$ values and a decreased AUC of the epoxide metabolite (unpublished data on file, Abbott). Thus, caution is recommended when administering theophylline or carbamazepine concomitantly with clarithromycin (Periti et al. 1990).

8. Flurithromycin

Like other macrolides, flurithromycin does not affect microsomal enzyme activity in animal models and does not form inactive complexes with cytochrome P450 *in vitro* (Villa et al. 1986a,b). Nevertheless, when administered at 500mg 3 times daily for 10 days to healthy volunteers, this fluorinated macrolide modified the disposition of a single oral dose of carbamazepine, causing a slight but significant increase in the AUC and a moderate reduction in epoxide metabolite concentrations (Barzaghi et al. 1988) [table III]. The inhibitory effect exerted by the antibiotic seems to be lower than that observed with erythromycin (Larrey et al. 1983). However, from a clinical standpoint, flurithromycin may be included among those macrolides which interfere with carbamazepine metabolism and is therefore potentially capable of enhancing the risk of toxicity of the antiepileptic drug. No data are presently available on the potential interference of flurithromycin with the biotransformation of other drugs.

Table IV. Results of clinical studies on pharmacokinetic drug interactions of group 3 macrolides

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Spiramycin					
Sequential	15 asthmatic pts	2 g/day for at least 5 days	Theophylline SR (dose not specified) for at least 10 days before, during (3rd day) and after S	No significant effect on theophylline pharmacokinetics	Debruyne et al. (1986)
Sequential	6 HV	2 g/day for 5 days	Phenazone 12 mg/kg PO before and after S	No significant alterations of phenazone pharmacokinetic parameters	Descotes & Evreux (1987)
Sequential	7 renal transplant pts	4.5-6 MIU/day for 6-30 days in 6 pts, 1 pt treated for 135 days	Cyclosporin 3.6 ± 1.3 mg/kg/day before, during and after S	No significant effect on cyclosporin pharmacokinetics	Kessler et al. (1988)
Sequential	6 heart transplant pts	6 MIU/day for 10 days	Cyclosporin 5.8 ± 1.4 mg/kg/day before, during and after S	No significant variations in pharmacokinetic parameters	Guillemain et al. (1989)
Sequential	14 kidney transplant pts	6 MIU/day for 5-25 days	Cyclosporin 4-6 mg/kg/day before, during and after S	No modifications in pharmacokinetics	Birmele et al. (1989)
Sequential	5 renal transplant pts	6 MIU/day	Cyclosporin 3.6-6.4 mg/kg/day before, during and after S	No significant modifications in cyclosporin pharmacokinetics	Vernillet et al. (1989)
Dirithromycin					
Sequential single crossover	14 HV	500 mg/day for 10 days	Theophylline SR 400 mg/day before (controls) and during treatment with macrolide	Statistically significant decrease in C_{av}^{ss} (18%) and C_{max} (26%) of theophylline	Bachmann et al. (1990)
Sequential	12 HV	500 mg/day for 7 days	Phenazone 1g PO before (controls) and after the treatment with macrolide	No kinetic modification of phenazone $t_{1/2}$, CL, Vd, AUC	Baldit et al. (1987)
Azithromycin					
Sequential	12 HV	250 mg/day for 5 days	Theophylline 4 mg/kg single IV dose before (controls) during and after treatment with macrolide	No kinetic modification (C_{max}, $t_{1/2\beta}$, AUC, ke) of theophylline	Mesure, unpublished data on file, Pfizer
Randomised, placebo-controlled, single-blind	15 HV	250 mg/day for 5 days	Warfarin 15mg single PO dose in the presence or absence of macrolide treatment	No significant differences for either the maximum response to warfarin or the AUC of prothrombin	Mesure, unpublished data on file, Pfizer

Table IV. Contd

Type of study	Subjects	Macrolide regimen	Concurrent drugs	Results	Reference
Rokitamycin					
Sequential	12 pts with COPD	800 mg/day for 7 days	Theophylline SR 600 mg/day PO or 400 mg/day IV to before (controls) and during treatment	Slight, but not statistically significant, increase in C_{max}, C_{min} and AUC of oral theophylline. No modification of intravenous theophylline, C_{max}, C_{min}, AUC	Cazzola et al. (1991)
Roxithromycin					
Sequential	12 HV	300 mg/day for 5 days	Theophylline 600 mg/day PO before (controls) and during treatment with macrolide	Statistically significant increase of C_{max}, $t_{½}$, AUC of theophylline	Saint-Salvi et al. (1987)
Sequential	16 pts with chronic bronchitis	300 mg/day for 6-9 days	Theophylline SR 300mg bid PO before (controls) and during treatment with macrolide	Slight, but statistically significant increase in C_{av}^{ss} of theophylline	Bandera et al. (1988)
Randomised crossover	12 HV	300 mg/day for 9 days	Carbamazepine 200mg single PO dose randomly allocated in the presence or absence of macrolide treatment	No modification carbamazepine, of C_{max}, t_{max}, $t_{½}$, AUC	Saint-Salvi et al. (1987)
Sequential	8 heart transplant pts	300 mg/day for 11 days	Cyclosporin 8 mg/kg/day before (controls), during and after treatment with macrolide	Slight, NSS, increase in cyclosporin plasma concentrations	Billaud et al. (1990)
Sequential	22 healthy women	300 mg/day for 20 days	Triphasic PO contraceptive 1 tablet/day before (controls) and during treatment with macrolide	No modification of serum progesterone concentrations	Meyer et al. (1990)
Randomised placebo-controlled double-blind	21 HV	300 mg/day for 14 days	Warfarin 5.2-5.7 mg/day PO in the presence or absence of macrolide treatment	No modification of warfarin C_{av}^{ss}, AUC. No difference in enantiomer S/R ratio. No difference in thrombotest concentrations	Paulsen et al. (1988)

Abbreviations: MIU = millions of international units; SR = sustained release; S = spiramycin; for other abbreviations, see tables II and III.

9. Spiramycin

Spiramycin does not seem to inhibit cytochrome P450 hepatic enzymes and there are no reports of interactions between this macrolide and other drugs (Descotes et al. 1988). A number of

pharmacokinetic studies have also clearly demonstrated the lack of effect of this drug on the pharmacokinetics of theophylline in patients with asthma (Debruyne et al. 1986), of phenazone in healthy volunteers (Descotes & Evreux 1987) and of cyclosporin in transplant recipients (Birmele et al. 1989; Guillemain et al. 1989; Kessler et al. 1988; Vernillet et al. 1989). The results of these studies are summarised in table IV.

10. Dirithromycin

Dirithromycin is a new antibiotic related to erythromycin, being a derivative of erythromycylamine. In contrast to findings for several macrolides, dirithromycin 500mg once daily for 10 days in healthy volunteers receiving a sustained release theophylline regimen had a tendency to increase theophylline oral CL and decrease both average steady-state plasma concentrations and C_{max} values by 18 and 26%, respectively (Bachmann et al. 1990) [table IV]. Therefore, it is unlikely that standard dirithromycin treatment will alter theophylline disposition. In addition, this macrolide derivative, when administered at 500mg daily for 1 week, does not modify phenazone pharmacokinetics (Baldit et al. 1987). Thus, it appears that dirithromycin produces little or no pharmacokinetic interactions. However, in the absence of more comprehensive studies, caution is required in concomitant administration of other drugs commonly involved in pharmacokinetic interactions with macrolides.

11. Azithromycin

Azithromycin does not seem to affect hepatic enzyme metabolism. One pharmacokinetic study showed no interaction between this semisynthetic macrolide and theophylline when coadministered to healthy volunteers (unpublished data on file, Pfizer) [table IV]. Similarly, azithromycin does not alter the anticoagulant effect of a single 15mg dose of warfarin (unpublished data on file, Pfizer). Possible pharmacokinetic interactions of azithromycin with carbamazepine, ergot derivatives, cyclosporin and digoxin have not been evaluated. At present, therefore, coadministration of these drugs may require an appropriate monitoring of plasma concentrations and pharmacokinetic parameters.

12. Rokitamycin

Rokitamycin is a new 16-membered ring macrolide. The possible interference of rokitamycin with theophylline has been recently investigated in patients with chronic obstructive pulmonary disease, demonstrating that this macrolide does not significantly affect the steady-state pharmacokinetics of the xanthine derivative (Cazzola et al. 1991) [table IV]. In our experience there are no other reports in the literature on possible drug interactions due to rokitamycin and therefore we must suggest the same precautions considered for dirithromycin and azithromycin.

13. Conclusions

A number of published clinical studies report pharmacokinetic drug interactions with macrolide antibiotics concurrently administered with several compounds that have metabolism partly or entirely dependent on the cytochrome P450 drug metabolising system of the liver. Clinically severe drug interactions have been reported when some macrolides were coadministered with ergot alkaloids, oral contraceptives, and less often with carbamazepine, theophylline, caffeine and lovastatin, some benzodiazepines, disopyramide, warfarin, phenazone, methylprednisolone, alfentanil, cyclosporin and digoxin.

Troleandomycin, erythromycin and its prodrugs produce frequent drug interactions and, consequently, concurrent administration with compounds whose metabolism is known to be affected or that could potentially be compromised should be avoided or undertaken with caution and with appropriate patient monitoring. However, not all macrolide antibiotics are a potential source of serious drug interactions. The other macrolide antibiotics josamycin, flurithromycin, roxithromycin, clarithromycin, miocamycin and midecamycin,

have seldom provoked drug interactions, while spiramycin, rokitamycin, azithromycin and dirithromycin have been associated with no drug interactions to date.

The following structural features of macrolide antibiotics might be of critical importance in explaining these differences of pharmacokinetic drug interactions: first, the presence of an accessible tertiary amine function and the steric hindrance around this group; secondly, but no less important, the hydrophobicity of each molecule that is proportional to its potency as metabolite-cytochrome-P450-complex precursors.

Thus, several factors could explain the fact that only some macrolide antibiotics modify plasma concentrations and therapeutic responses to drugs given in combination with them. In this respect, these antimicrobial drugs can be divided into the 3 subgroups reported in figure 2. Group 1 (troleandomycin and erythromycin) is frequently involved in drug interactions. Group 2 members (josamycin, flurithromycin, roxithromycin, clarithromycin, miocamycin and midecamycin) are unable to form iron-metabolite complexes, but act as weak inducers of cytochrome P450 and have seldom been implicated clinically in drug interactions. Group 3 (spiramycin, rokitamycin, dirithromycin and azithromycin) is unable to form cytochrome P450-metabolite complexes *in vivo* and is not associated with drug interactions in humans.

Pharmacokinetic drug interactions with macrolide antibiotics deserve attention. However, not all of these drugs are potentially hazardous in this respect. Members of the group 1 macrolides should be avoided in patients who must receive other drugs metabolised by cytochrome P450. The possibility that the macrolides of groups 2 and 3 should be avoided in patients simultaneously treated with pharmacological agents as theophylline, carbamazepine, ergot alkaloids, oral contraceptives and methylprednisolone cannot be ruled out at present. It should be underlined that the 4 compounds of group 3 (dirithromycin, azithromycin, rokitamycin and spiramycin) do not form an inhibitory P450-metabolite complex *in vivo* even at very high doses and the possibility of drug interactions should be extremely low.

Acknowledgement

We thank Marg Forrest for assistance in preparation of the manuscript.

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Correspondence and reprints: Prof. *Piero Periti*, Dipartimento di Farmacologia Preclinica e Clinica, Università degli Studi, Viale G.B. Morgagni 65, 50134 Firenze, Italy.