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Drug interactions with azithromycin and the macrolides: an overview

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Evidence interactions between individual macrolides and a number of pharmacologically active compounds that are frequently co-administered to patients with bacterial infections is reviewed. Theophylline is strongly associated with erythromycin interaction; clarithromycin may also interact with this drug. Azithromycin, spiramycin and rokitamycin, however, do not appear to have any effect on theophylline pharmacokinetics. The other therapeutic agents considered are cyclosporin, the antiepileptics, carbamazepine and phenytoin, terfenadine, warfarin, oral contraceptives, agents used in the management of gastritis and peptic ulcer and zidovudine. With the exception of interaction with antacids, there is no evidence that azithromycin, unlike most other macrolides, interacts with any of these agents to produce clinically significant adverse effects. The explanation for this variation appears to be azithromycin's inability to induce and bind to the cytochrome P450 IIIA enzyme system.

Introduction

The rapid expansion of the macrolide class of antibiotics in recent years has resulted in a growing potential for drug interactions between them and other pharmacologically active agents. Clinicians are generally aware of such interactions and exercise appropriate caution when prescribing. However, interactions may be associated with widely used or widely available compounds, including over-the-counter preparations. This increases the burden of responsibility, with all patients being questioned carefully and cautioned before antibiotics are prescribed.

Erythromycin, the first marketed macrolide, is noted for a wide range of interactions with other therapeutic agents. Many of these interactions can be severe and have resulted in erythromycin's use being restricted among certain patient groups receiving concomitant therapies. Erythromycin also has the disadvantages of a relatively narrow spectrum of activity and far from ideal pharmacokinetic and safety profiles. Since 1952 when erythromycin was developed, there has been a search for structurally related compounds with a wider spectrum of activity. Modifications of the macrocyclic lactone ring structure and of the substituent groups have resulted in compounds with varying antibacterial activities and pharmacokinetic properties. These structural changes have also led to alterations in the potential for interactions with other drugs. This review considers the nature of common drug interactions and highlights variations among the different macrolides.

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Theophylline

The bronchodilator theophylline is widely used in the management of patients with bronchospasm associated with asthma or chronic obstructure pulmonary disease including chronic bronchitis. Patients with chronic bronchitis frequently experience acute infectious exacerbations, necessitating the use of antibacterial agents. Macrolides are included among the drugs prescribed for this purpose. The therapeutic range of theophylline serum concentrations, however, is narrow and should be maintained within the therapeutic range of 10–20 mg/L, to avoid the side-effects of nausea, vomiting, convulsions and supraventricular tachycardia which are concentration-dependent.

Theophylline is extensively metabolized in the liver by the cytochrome P450 isoenzymes to produce the metabolites 1,3-dimethyluric acid, 3-methylxanthine and 1-methyluric acid. Co-administration of other agents metabolized via the same system can competitively inhibit the conversion of theophylline, thus influencing this complex biotransformation and altering the pharmacokinetic profile of the bronchodilator.

In 1976, Weinberger reported that the macrocyclic compound troleandomycin had an inhibitory effect on theophylline metabolism (Weinberger, 1976). A series of letters rapidly ensued reporting an apparent interaction between theophylline and erythromycin (Cummins, Kozak & Gillman, 1976, 1977; Kozak, Cummins & Gillman, 1977). Cummins and co-workers described how children receiving concurrent erythromycin were found to have markedly increased serum concentrations of theophylline, and this was often associated with bouts of vomiting.

Following these initial publications, there have been numerous case reports and controlled clinical trials confirming this interaction. Although the literature on erythromycin–theophylline interaction remains contradictory, the general consensus is that the plasma concentration of theophylline increases when erythromycin is co-prescribed and may result in the characteristic adverse effects. These effects have been observed with erythromycin base and the various salts and esters of the drug (Ludden, 1985).

Ludden (1985), Upton (1991) and Periti *et al.* (1992) have all highlighted the difficulties in reconciling the various apparently disparate conclusions. Rieder & Spino (1988) adopted a pragmatic approach to the problem by categorizing the literature with respect to study design and then posing four questions regarding erythromycin–theophylline interaction: does it occur? Does it occur in all patients? What is the magnitude of the interaction? and is the interaction clinically significant? These authors cited the duration of erythromycin treatment as a potential reason for the varying results. They suggested that a 7 to 10 day course of erythromycin can have a significant impact on theophylline clearance in as many as 25% of patients and that there may be up to a 45% change in theophylline concentrates compared with control values. Based on these findings, they have advocated the importance of individualizing patient management to ensure effective, non-toxic bronchodilator therapy.

The mechanism by which erythromycin alters the pharmacokinetics of theophylline is related to the fact that both agents are metabolized by cytochrome P450 enzymes. Although erythromycin and some other macrolides initially induce cytochrome P450 enzymes, they rapidly form a stable complex with the cytochrome, rendering it inactive (Amacher, Schomaker & Retsema, 1991; Periti *et al.*, 1992). As a consequence, cytochrome P450 is unavailable for theophylline oxidation. Clearance is therefore

compromised and theophylline accumulates in the plasma. This view is consistent with the clinical observation that erythromycin–theophylline interactions present as a relative overdose of theophylline.

The literature suggests that there are appreciable differences between macrolides in terms of their potential, to interact with theophylline. Periti *et al.* (1992) identified three separate groups of macrolides with differing potentials for interaction. Those with low potentials include spiramycin (Debruyne *et al.*, 1986), rokitamycin (Cazzola *et al.*, 1991) and the structurally related azalide, azithromycin (Periti *et al.*, 1992).

In a recent placebo-controlled, parallel-group study conducted in normal subjects, Gardner *et al.* (1996) demonstrated that azithromycin given orally once daily for 5 days (500 mg on day 1 and 250 mg on days 2–5) had no significant effect on maximum theophylline concentrations in plasma, the time taken to reach the maximum theophylline concentration or the area under the plasma theophylline concentration–time curve. In addition, the same authors performed an open study which demonstrated that this azithromycin dosing regimen had no influence on the total systemic clearance, volume of distribution at steady-state or elimination half-life of intravenously administered theophylline. The lack of an effect of azithromycin on theophylline may be explained by the absence of cytochrome P450 interactions with azithromycin, as shown in rats (Amacher *et al.*, 1991). Although periodic monitoring of plasma theophylline concentrations remains prudent, the results of this study suggest that azithromycin can be administered to asthmatic patients receiving theophylline without adjusting the theophylline dosage.

Clarithromycin and roxithromycin belong to another group of macrolides in terms of their effects on theophylline. When repeated doses of clarithromycin (Ruff *et al.*, 1990) or roxithromycin (Saint-Salvi *et al.*, 1987) were administered, reductions in the clearance of theophylline were noted in normal adults. However, in the opinion of Ruff *et al.* (1990), this small, but nevertheless significant, effect of roxithromycin did not justify changes in theophylline dosages on clinical grounds.

In contrast to the other macrolides, dirithromycin may increase theophylline oral clearance and decrease both average and maximum steady-state plasma concentrations (Bachmann *et al.*, 1990). On the basis of this study, Periti *et al.* (1992) suggested that the standard dosage of dirithromycin is unlikely to alter theophylline disposition. Once again, however, a policy of monitoring patients would appear wise.

Cyclosporin

As an immunosuppressant, cyclosporin is commonly used to prevent rejection following transplantation, and it can also be useful as treatment of certain autoimmune diseases. Since immunosuppressants reduce the ability of the body to fight infection, antibiotic therapy is often required by patients treated with these compounds. Cyclosporin is extensively metabolized by the cytochrome P450 system (Watkins, 1990) and so, as with theophylline, there is considerable potential for interaction with the macrolides. This is particularly important since cyclosporin has a low therapeutic index and its renal toxicity is concentration-related.

There have been several case reports of markedly increased cyclosporin concentrations in transplant patients receiving concomitant erythromycin, as reviewed by Yee & McGuire (1990). Other pharmacokinetic studies confirm this drug interaction (Periti *et al.*, 1992). Nevertheless, the mechanism of this interaction has remained

unclear since Gupta *et al.* (1989) postulated that the increased plasma cyclosporin concentrations they observed in renal transplant patients were due to increased cyclosporin absorption in the presence of erythromycin. Whatever the mechanism, cyclosporin concentrations should be monitored when erythromycin is co-administered.

Unlike erythromycin, there have been no reports of interactions between cyclosporin and azithromycin (Hopkins, 1991). In a study of 3995 patients treated with azithromycin, no cases of cyclosporin–azithromycin interaction were detected. Similarly, there have been no reports of clarithromycin interacting with cyclosporin, and spiramycin, administered to five renal transplant patients, did not affect the pharmacokinetics of cyclosporin (Vernillet *et al.*, 1989).

Some macrolides, including erythromycin, appear to increase cyclosporin concentrations. A review of three case studies by Azanza *et al.* (1992) suggests that josamycin may inhibit cyclosporin metabolism, thus elevating the plasma concentrations of the immunosuppressant. Miocamycin has been reported to double the blood concentrations of cyclosporin in renal transplant patients (Couet *et al.*, 1990). Concomitant administration of roxithromycin to heart transplant patients brought about a non-significant rise in cyclosporin concentrations (Billaud *et al.*, 1990).

Antiepileptics

Phenytoin and carbamazepine are anticonvulsants used mainly in the management of patients with epilepsy; both have the potential to interact with antibiotics. Since the rate of phenytoin metabolism is saturable at therapeutic dosages and the therapeutic range for carbamazepine is relatively narrow, any compound that markedly alters the pharmacokinetics of either anticonvulsant can produce unwanted side-effects.

Phenytoin

A single-dose crossover study in healthy volunteers receiving erythromycin indicated that the clearance of phenytoin is unaffected by this macrolide antibiotic (Milne *et al.*, 1988). Thus it may be suggested that the clinician is unlikely to encounter any problems in patients receiving concomitant phenytoin and macrolide therapy.

Carbamazepine

A number of cases of carbamazepine toxicity have been described in both adults and children with epilepsy who were also receiving erythromycin (Carranco *et al.*, 1985; Woody, Kearns & Bolyard, 1987). Signs of toxicity, including confusion, somnolence, ataxia, vertigo, nausea and vomiting, were experienced. The adverse events started shortly after commencing erythromycin therapy and disappeared rapidly on withdrawal of the antibiotic (Periti *et al.*, 1992). In a pharmacokinetic study, Wong, Ludden & Bell (1983) showed that erythromycin significantly decreased the clearance of oral carbamazepine. Thus, if avoidance of this drug combination is not possible, modification of the carbamazepine dosage and/or monitoring blood concentrations is desirable.

Concomitant administration of clarithromycin, josamycin, miocamycin or flurithromycin to volunteers has been shown to significantly alter the pharmacokinetic profile of carbamazepine (Periti *et al.*, 1992). In a case report, a 10-day course of

clarithromycin led to increased serum carbamazepine concentrations, despite a dosage reduction of carbamazepine (Albani, Riva & Baruzzi, 1993).

In contrast, in the case of azithromycin, Rapeport *et al.* (1991) were unable to find any evidence of interaction, with carbamazepine in studies conducted in healthy volunteers. In clinical studies involving more than 6000 patients (Hopkins, 1994), 45% of whom were receiving some form of concomitant medication, there was no clinical or laboratory evidence of drug interactions with azithromycin. Roxithromycin also appears not to interact with carbamazepine (Saint-Salvi *et al.*, 1987).

Terfenadine

The non-sedating antihistamine terfenadine is used widely in the treatment of patients with allergies and, in some countries, it is available without prescription. Terfenadine undergoes rapid first-pass metabolism in the liver, where cytochrome P450IIIA enzyme converts it to the active form, terfenadine carboxylate. If metabolism is inhibited, then the unmetabolized terfenadine accumulates and cardiotoxicity may ensue. This includes the development of *torsade de pointes*, a potentially fatal cardiac arrhythmia (Woosley *et al.*, 1993).

Co-administration of erythromycin and terfenadine to healthy volunteers has been shown to result in ECG changes in some subjects (Honig *et al.*, 1993). In a subsequent three-way comparison, the same authors found that clarithromycin, as well as erythromycin, altered the pharmacokinetics of terfenadine (Honig *et al.*, 1994).

Harris *et al.* (1995) demonstrated in a double-blind, placebo-controlled study in healthy males that the situation with azithromycin differs. The azalide did not affect the pharmacokinetics of terfenadine carboxylate, and there was no significant effect on the rate-corrected QT interval. They concluded that potentially life-threatening disorders experienced as a result of the interactions of other macrolides with terfenadine are unlikely to occur in patients receiving simultaneous azithromycin–terfenadine therapy.

Warfarin

Widely used in the prophylaxis and therapy of thrombosis and embolism, warfarin acts by inhibiting the formation of certain clotting factors. The therapeutic range is narrow, so warfarin treatment needs to be monitored carefully. There is a risk of haemorrhage if serum concentrations are too high. Numerous drugs interact with warfarin, among them a variety of antibiotics. Most of these enhance the anticoagulant effects of warfarin, probably by interfering with metabolic clearance.

Several case reports describing an erythromycin–warfarin interaction have been published. These have shown that erythromycin can markedly increase the prothrombin time, while two pharmacokinetic studies have demonstrated that erythromycin decreases warfarin clearance (Periti *et al.*, 1992). In reviewing these findings, Periti *et al.* (1992) pointed to a discrepancy between the modest pharmacokinetic interaction observed and some severe clinical results and suggested that factors such as old age and dietary restrictions might also play a part.

Information on other macrolides is limited. A lack of interaction between the azalide azithromycin and warfarin was found in a study involving 23 healthy volunteers (Mesure, unpublished data). Azithromycin did not affect the prothrombin time response to a single dose of warfarin. Similarly, in a double-blind, placebo-controlled study,

Paulsen *et al.* (1988) showed that roxithromycin did not affect the pharmacokinetics or anticoagulant effects of warfarin. Despite these findings, it is recommended that the prothrombin times be monitored in patients receiving concomitant therapy.

Hormonal contraceptives

Controversy concerning interactions between certain antibiotics and oral contraceptives remains unresolved. The contraceptive pill, whether progestogen-only or an oestrogen–progestogen preparation, is a highly effective means of birth control in worldwide use. Over the past 20 years, there have been numerous reports of unintended pregnancies in women taking the pill who had also been given broad-spectrum antibiotics (Back & Orme, 1990). Tetracyclines and ampicillin have been implicated most frequently with decreased oral contraceptive efficacy (Barnett, 1985). However, there is still no firm pharmacokinetic evidence to support the view that macrolides alter the concentrations of contraceptive steroids in the blood. Alternative mechanisms for apparent pill failure might include interpatient variability in susceptibility to broad-spectrum antibiotics, therapy preventing hormone absorption, and in hepatic metabolism. A study of 22 healthy women taking a triphasic oral contraceptive preparation showed that a 20-day course of roxithromycin did not modify serum progesterone concentrations (Meyer *et al.*, 1990). Information regarding the other macrolide antibiotics remains limited, but Hopkins (1994), in a review of clinical experience of the treatment of 6655 patients, did not detect any interactions between azithromycin and oral contraceptives.

Gastrointestinal agents

Acid-peptic disease, in the form of ulcers, gastritis and dyspepsia, is responsible for much morbidity. Pharmacological approaches to treatment include antacids, H_2-receptor antagonists and cytoprotectants, many of the preparations being available without prescription. Various interactions between this broad family of agents and antibiotics have been reported. These seem to result mainly, but not exclusively, in impaired absorption of the antibiotic in question, in contrast to the types of antibiotic–drug interactions already discussed.

The macrolides clarithromycin and roxithromycin do not appear to be adversely affected by the concurrent administration of antacids, although the data remain limited. A preliminary communication by Zundorf, Wischmann & Fassbender (1992) indicated that neither ranitidine nor an antacid caused decreased bioavailability of clarithromycin when it was co-administered. In a study conducted in healthy subjects and reported by Boeckh *et al.* (1992), there was high inter- and intra-individual variability in the pharmacokinetics of roxithromycin when co-administered with either an antacid or ranitidine. Despite this, the authors concluded that the bioavailability of roxithromycin is unaffected by either of these agents.

In a single-dose crossover study, ten volunteers took either azithromycin alone or immediately following a dose of an aluminium/magnesium combination antacid (Foulds *et al.*, 1991). Although the mean maximum serum concentrations of azithromycin were significantly reduced by concurrent antacid administration, the extent of total azithromycin absorption was unaffected. This finding probably has little clinical implication as azithromycin's activity is not directly dependent on serum

concentration. In the same study, when oral cimetidine was given 2 h before azithromycin, there were no changes in the serum concentrations of the antibiotic.

Zidovudine

Azithromycin demonstrates favourable in-vitro activity against a range of pathogens responsible for opportunistic infections in HIV-infected subjects, including *Toxoplasma gondii*, *Cryptosporidium parvum* and the *Mycobacterium avium-intracellulare* complex. Such patients are also frequently receiving zidovudine therapy. Thus, it is important to establish that there is no interaction between the two agents.

In a study conducted by Chave *et al.* (1992) in HIV-infected patients, the administration of azithromycin (1 g/week) 2 h before their usual morning dose of zidovudine did not affect the disposition of the latter agent. Also, the pharmacokinetics of azithromycin were similar after the first and repeated administrations of the antibacterial agent. These results, therefore, indicate that azithromycin may be used in HIV-infected patients receiving zidovudine, and clinical trials are currently being conducted to assess its efficacy in this patient population.

Miscellaneous interactions

There are several reports of erythromycin interacting with a range of other drugs, including corticosteroids, bromocriptine, digoxin, ergot alkaloids and benzodiazepines (Periti *et al.*, 1992; Polk, 1993). However, it is unlikely that azithromycin will cause clinically significant interactions with these agents (Hopkins, 1994).

Conclusions

The investigation of possible drug interactions is usually conducted in healthy volunteers, so that experimental conditions are controlled and confounding factors avoided. However, clinical practice can present a different picture. There are several groups of patients in whom the risks of interactions are greater, and it is for this reason that the medical community is often first alerted to a potential interaction through a case report.

In the management of elderly patients, polypharmacy is frequently necessary to control underlying problems, such as cardiac disease chronic lung disease or arthritis, while simultaneously treating acute infections. In addition, compromised renal or hepatic clearance is not uncommon in the elderly. These factors together mean that the chances of observing an antibiotic-related drug interaction are increased in older patients.

Patients who require immunosuppressive therapy to prevent transplant rejection, as well as other immunocompromised patients, are particularly prone to infections. Since prompt introduction of therapy for difficult-to-treat pathogens may require aggressive antibiotic regimens, these patients are also at increased risk of antibiotic-related interactions.

This review demonstrates that, although the first macrolide, erythromycin, interacts with a wide range of other pharmacological agents, this does not necessarily preclude the use of other macrolides in patients who might be at risk of drug interactions. Structurally-related, 14-membered ring compounds also appear to be associated with a tendency to interact with other drugs, whereas, with the 16-membered ring

compounds, the incidence of clinically significant interactions is generally reduced. Azithromycin, the 15-membered ring azalide, does not appear to cause any clinically significant interaction with antacids and, to date, evidence is lacking for any clinically significant interaction with other concomitantly administered drugs.

Increased understanding of the mechanisms of drug interactions makes it possible to predict those antibiotics that will adversely affect the metabolism of other drugs. Macrolide drug interactions are generally associated with the induction and binding of the hepatic cytochrome P450IIIA isoenzyme system. As azithromycin does not interact with this enzyme system, the clearances of concomitantly administered drugs that are metabolized by this system are not affected. This is in contrast to certain other macrolides which affect cytochrome P450IIIA to varying degrees.

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