KUCERS' THE USE OF ANTIBIOTICS

A CLINICAL REVIEW OF ANTIBACTERIAL, ANTIFUNGAL, ANTIPARASITIC AND ANTIVIRAL DRUGS

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60 Roxithromycin

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1. DESCRIPTION

Roxithromycin (CAS number: 80214-83-1) is a semisynthetic macrolide derived from erythromycin A (9-[O-[(2-methoxyethoxy)-methyl]oxime]) (Chantot *et al.*, 1986; Kirst and Sides, 1989a). The empirical formula is $C_{41}H_{76}N_2O_{15}$ and the molecular weight is 837.05. Its chemical structure is shown in Figure 60.1. Its *in vitro* antibacterial activity is similar to that of erythromycin, with similar or slightly higher minimal inhibitory concentrations (MICs) (Pechére and Auckenthaler, 1987; Barry *et al.*, 1988), and complete cross-resistance with erythromycin (Barlam and Neu, 1984; Pechére and Auckenthaler, 1987; Barry *et al.*, 1988).

Roxithromycin differs from erythromycin by an improved pharmacokinetic profile, characterized by (1) higher acid stability, due to replacement of the keto group in position 9 by an N-oxime side chain which prevents the intramolecular hemiketalization reaction (Kirst and Sides, 1989b); (2) improved oral bioavailability and higher serum levels; and (3) a prolonged half-life allowing for once-daily (300 mg) or twice-daily (150 mg bid) administration (Nilsen, 1987; Puri and Lassman, 1987).

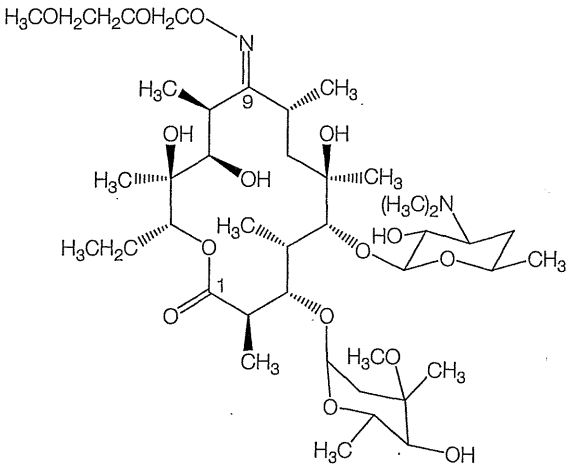

Figure 60.1 Chemical structure of roxithromycin. Chemical stability in acid medium is due to the replacement of the keto group in position 9 of erythromycin by an N-oxime.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

Similar to other macrolides, roxithromycin has a moderately broad spectrum of activity, including intracellular pathogens such as *Mycobacteria* spp., *Chlamydia* spp., or *Legionella* spp. Table 60.1 summarizes the susceptibility of wild-type strains of key pathogens to roxithromycin.

Gram-positive bacteria

Roxithromycin is active against organisms such as *Staphylococcus aureus* (including β-lactamase-producing strains) and coagulase-negative staphylococci, *Streptococcus pyogenes*, groups B, C, and G streptococci, *S. pneumoniae*, *S. viridans*, *S. bovis*, and *Enterococcus faecalis*, with MICs close to those of erythromycin. However, most of the hospital-acquired methicillin-resistant *S. aureus* (MRSA) strains have now acquired resistance to macrolides. There is complete cross-resistance between all macrolides, such that erythromycin-resistant organisms are also roxithromycin resistant (Barlam and Neu, 1984; Pechére and Auckenthaler, 1987; Barry *et al.*, 1988).

Gram-positive bacilli, such as *Listeria monocytogenes*, are slightly less susceptible to roxithromycin than to erythromycin (Barlam and Neu, 1984). *Nocardia asteroides* is resistant (Pechére and Auckenthaler, 1987).

Gram-positive anaerobic bacteria

Peptococcus and *Peptostreptococcus* spp. are usually roxithromycin susceptible. *Clostridium perfringens* is usually slightly less susceptible to roxithromycin than to erythromycin. Some *C. difficile* strains are susceptible, but others are completely resistant (Dubreuil, 1987).

Gram-negative bacteria

Roxithromycin is active with MICs equal or 2- to 4-fold higher than those for erythromycin, against some Gram-negative bacteria responsible for respiratory tract infections, (*Moraxella catarrhalis*, *Legionella* spp., *Bordetella pertussis*), genital infections (*Neisseria gonorrhoeae*, *Haemophilus ducreyi*, and *Gardnerella vaginalis*), digestive tract infections (*Helicobacter pylori* and *Campylobacter jejuni*), or meningitis (*Neisseria meningitidis*). However, *Haemophilus influenzae* is only moderately susceptible (Righter and Luchsinger, 1988), and *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., *Salmonella* spp., and *Shigella* spp. are not susceptible (Jones *et al.*, 1983; Barlam and Neu, 1984; Dubreuil, 1987; Ridgway, 1987; Barry *et al.*, 1988; Hardy *et al.*, 1988; Kirst and Sides, 1989b; Liebers *et al.*, 1989; Kitsukawa *et al.*, 1991; Vaara, 1993).

Gram-negative anaerobic bacteria

Only some 50% of the bacteria of the *B. fragilis* group are roxithromycin susceptible. Other *Bacteroides* spp. are more susceptible, but most *Fusobacteria* are resistant (Jones *et al.*, 1983; Barlam and Neu, 1984; Dubreuil, 1987; Ridgway, 1987; Barry *et al.*, 1988; Hardy *et al.*, 1988; Kirst and Sides, 1989b; Liebers *et al.*, 1989; Kitsukawa *et al.*, 1991; Vaara, 1993).

Table 60.1 Susceptibility (MIC, mg/l) of key pathogens to roxithromycin as compared with susceptibility breakpoints.

Bacterium	Wild-type strains (EUCAST distributions of MIC)			Clinical isolates	Breakpoint (S≤/R>)		Resistance issues
	Range	MIC_{51}	MIC_{90}		CLSI	EUCAST	
Staphylococcus aureus (MSSA)	0.25–0.5	0.5	0.5	There are no recent epidemiologic studies of roxithromycin MIC distributions as there is complete cross-resistance with erythromycin (see Chapter 59, Erythromycin)		1/2	
Staphylococcus aureus (MRSA)	0.25–0.5	0.5	0.5			1/2	Hospital-associated strains of MRSA are frequently multiresistant
Haemophilus influenzae	4–16	8	16			1/16	
Moraxella catarrhalis	0.032–0.25	0.064	0.0125			0.5/1	

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibtory concentration; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

Others

Roxithromycin is also active against *Chlamydia*, *Chlamydophila*, *Borrelia*, and *Mycoplasma* spp., and *Ureaplasma urealyticum*, as well as some species of *Rickettsia* (Drancourt and Raoult, 1989) and of *Mycobacteria*, including M. *avium* complex. However, roxithromycin is poorly effective against M. *tuberculosis* (Bermudez and Young, 1988; Naik and Ruck, 1989; Hansen *et al.*, 1992; Rastogi *et al.*, 1993; Rumpianesi *et al.*, 1993; Rastogi *et al.*, 1994; Rastogi *et al.*, 1995; Struillou *et al.*, 1995). Roxithromycin is active against M. *leprae* infections in mouse footpads, but clarithromycin shows superior activity (Franzblau and Hastings, 1988; Gelber *et al.*, 1991). *Toxoplasma gondii* infections in mice were successfully treated by roxithromycin, but the drug often did not eradicate the organisms from the brain (Chang and Pechère, 1987). Also, *in vitro* studies showed that roxithromycin had activity against this parasite, but high concentrations of the drug were needed to have a killing effect on T. *gondii* (Chang and Pechère, 1988). In animal studies, roxithromycin alone was also relatively ineffective for toxoplasmosis, but its efficacy was improved if it was combined with either sulfadiazine or pyrimethamine (Romand *et al.*, 1995).

2b. Emerging resistance and cross-resistance

Resistance to macrolides has become a major issue for most of the bacteria originally described as susceptible, including *Staphylococcus* spp., *Streptococcus* spp., *Bacteroides* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Lactobacillus* spp., M. *pneumoniae*, *Campylobacter* spp., *Corynebacterium diphteriae*, and *Propionobacterium*, as well as many members of the Enterobacteriaceae (Leclercq and Courvalin, 1991; Bandak *et al.*, 2000). There is complete cross-resistance between erythromycin and roxithromycin. The main mechanisms of resistance are similar to erythromycin and include target modification, antibiotic inactivation, and efflux mechanisms (see Chapter 59, Erythromycin).

3. MECHANISM OF DRUG ACTION

The mechanism of action of roxithromycin is similar to erythromycin (see Chapter 59, Erythromycin).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

Roxithromycin is available as an oral formulation only. Its absorption is minimally affected by food intake (Puri and Lassman, 1987).

4a. Adults

The daily dose is 300 mg either given once daily or divided into two doses of 150 mg (Puri and Lassman, 1987; Paulsen *et al.*, 1992).

4b. Newborn infants and children

The pediatric dosage is 2.5–5 mg/kg, divided into two administrations (Kafetzis and Blanc, 1987; Stenberg and Mardh, 1991).

4c. Altered dosages

Impaired renal function

It is commonly accepted that no dosage adjustment is needed in patients with severe renal insufficiency (Periti and Mazzei, 1987; Puri and Lassman, 1987). Significant delays in elimination have, however, been reported in patients with a creatinine clearance <15 ml/min, so that a doubling of the dosage interval has been recommended for these patients (Halstenson *et al.*, 1990). Very little roxithromycin is eliminated by continuous ambulatory peritoneal dialysis (Lam *et al.*, 1995).

Impaired hepatic function

In patients with severe hepatic dysfunction, the manufacturer recommends halving the roxithromycin dosage. No dosage adjustment is needed in patients with cirrhosis (Periti and Mazzei, 1987; Puri and Lassman, 1987). In patients with alcoholic cirrhosis, the increase in renal clearance of roxithromycin offsets the reduction in hepatic clearance, and no dosage modification is considered necessary in most patients (Periti and Mazzei, 1987).

Elderly

The pharmacokinetics of macrolides is modified in elderly patients. Dosage adjustment for roxithromycin is usually not required with conventional doses, but closer than usual clinical monitoring of the older patient has been advocated (Periti *et al.*, 1989).

5. PHARMACOKINETICS AND PHARMACODYNAMICS

The main pharmacokinetic properties of roxithromycin are summarized in Table 60.2.

5a. Bioavailability

The absorption of roxithromycin is rapid (T_{max} ~2 hours) and its oral bioavailability (72–85%) significantly higher than that of erythromycin (Puri and Lassman, 1987). Serum half-life (8–13 hours) is much longer than that of erythromycin, allowing for an administration every 12 hours (Puri and Lassman, 1987). The absorption of roxithromycin is minimally affected by food intake (increase of 15–20% in oral bioavailability when taken after a meal or with milk), but this is not considered as clinically significant (Puri and Lassman, 1987). Likewise, bioavailability of roxithromycin is not affected by antacids or anti-H_2 agents (Boeckh *et al.*, 1992). Serum protein binding is high (73–96%). When the serum concentration is 10 μg/ml, the drug is 86–91% serum protein bound (Wise *et al.*, 1987) – the free serum fraction of roxithromycin increases with increasing serum levels (Puri and Lassman, 1987).

5b. Drug distribution

When 150 mg of roxithromycin was given to normal adults every 12 hours for 3 days, the mean peak levels (attained 1.5 hours after the dose) increased from 4.4 μg/ml on day 1 to 5.9 μg/ml on day 2, and to 7.4 μg/ml on day 3 (Wise *et al.*, 1987). Steady-state serum levels were usually reached by day 4. The minimum plasma concentrations of roxithromycin at steady state (days 4–11) ranged from 3.22 to 3.69 μg/ml. The maximal serum level during this time was about 9.3 μg/ml. The drug is eliminated with a half-life of about 10 hours. Doubling the dose increases, but does not double, the peak serum level (Puri and Lassman, 1987; Kirst and Sides, 1989a).

Roxithromycin is distributed in the total body water and penetrates easily in tissues, where it persists longer than in the blood. Roxithromycin penetrates well into blister fluid; in one study the mean percent penetration was 85% (Wise *et al.*, 1987). After oral dosing, a very high concentration was achieved in pulmonary, prostatic, epididymal, tonsillar, and skin tissue, tear fluid and aqueous humor, as well as periodontal and synovial tissues. However, roxithromycin was not detected in the cerebrospinal fluid (CSF) of subjects with noninflamed meninges (Chastre *et al.*, 1987; Puri and Lassman, 1987; Campa *et al.*, 1990; Costa *et al.*, 1992; Van Bambeke and Tulkens, 2002). Overall, macrolide penetration into the central nervous system (CNS) is generally low – thus these findings, specifically for roxithromycin, are consistent with this observation (Kearney and Aweeka, 1999). Roxithromycin crosses the placental barriers and less than 0.05% of a single 300-mg dose is excreted in the breast milk of lactating women (Puri and Lassman, 1987). Roxithromycin accumulates in the cells to higher levels than erythromycin (Carlier *et al.*, 1987). Roxithromycin is concentrated in human monocytes (Hand and King-Thompson, 1989), neutrophils, and macrophages (Labro *et al.*, 1989), and it stimulates human neutrophil migration *in vitro* (Anderson, 1989).

5c. Clinically important pharmacokinetic and pharmacodynamic features

The cure rate for macrolides mainly depends on the AUC/MIC ratio (Andes *et al.*, 2004), based on their time-dependent effect coupled with a postantibiotic effect, both *in vitro* and in animal models (Rolin and Bouanchaud, 1989; Novelli *et al.*, 2002). The high level of tissue diffusion is considered an advantage for the treatment of serious infections, including those in the respiratory tract; however, increasing rates of resistance in some regions limit the use of roxithromycin in some countries (Bergogne-Berezin, 1987; Chastre *et al.*, 1987; Puri and Lassman, 1987). However, conclusions with respect to tissue concentrations should be drawn with great caution (Mouton *et al.*, 2008).

5d. Excretion

Liver metabolization of roxithromycin is limited (~25% of the dose), the main metabolite being the decladinose derivative (Puri and Lassman, 1987; Zhong *et al.*, 2000). The unchanged form is excreted in the urine (7–12%), the feces (~25–54%) and the expired air (~13%) (Bergogne-Berezin, 1987; Puri and Lassman, 1987; Lassman *et al.*, 1988). About 30% of the drug eliminated in the feces consists of inactive metabolites (Periti and Mazzei, 1987; Puri and Lassman, 1987).

5e. Drug interactions

Drug interactions with macrolides can be an important problem, which in some cases can seriously limit their use in at-risk patients. The main mechanism involved in these interactions is the ability of macrolides to bind to cytochrome P450 (group 3A4), thereby impairing the subsequent metabolization of other substrates of the same cytochrome (Periti *et al.*, 1992). The elimination of these co-administered drugs is therefore reduced, causing a potential risk of toxicity (Periti *et al.*, 1992; von Rosensteil and Adam, 1995). The risk of interactions with roxithromycin is lower than with erythromycin. The main clinically relevant interactions are summarized in Table 60.3.

Although roxithromycin is a 14-membered lactone ring macrolide, it is unlike erythromycin in that it does not interfere with the metabolism of theophylline and carbamazepine (Saint-Salvi *et al.*, 1987). Ergotamine and drugs that prolong the QT interval (e.g. tamoxifen, fluoxetine, salmoterol, cisapride, astemizole, terfenadine, grepafloxacin) should not be co-administered with roxithromycin (see Chapter 61, Clarithromycin) (Curtis *et al.*, 2003). Conversely, co-administration of inducers of the cytochrome P4503A4, such as

Table 60.2 Pharmacokinetic parameters of roxithromycin.

Pharmacokinetic parameter	Roxithromycin (150 mg bid)
C_{max} (mg/l)	6.8
T_{max} (h)	2
$t_{1/2}$ (h)	8–13
Bioavailability (%)	72–85
Protein binding (%)	73–96
Tissue/serum concentration	1–2
AUC (mg · h/l)	70

Reproduced with permission from Puri and Lassman (1987).

Table 60.3 Drug interactions with roxithromycin.

Contraindicated drugs	Drugs to use with caution (require dose reduction and/or other parameter monitoring)
Astemizole	Benzodiazepines
Cisapride	Bromocriptine
Ergotamine and ergot derivatives	Theophylline
Terfenadine	Digoxin
	Fentanyl

Adapted with permission from Periti *et al.* (1992) and Amsden (1995).

rifampicin or rifabutin, may cause a reduction in macrolide plasma levels, which can lead to therapeutic failure or to selection of resistant strains.

Roxithromycin does not influence the pharmacokinetics of lovastatin, such that no dosage alteration is needed when these agents are given concomitantly (Bucher *et al.*, 2002).

6. TOXICITY

6a. Gastrointestinal adverse effects

These are the most common side-effects and easily observed by patients (Periti *et al.*, 1993). Abdominal pain, nausea and vomiting, diarrhea, and anorexia are observed in 5–15% of patients treated with roxithromycin (Worm *et al.*, 1989; Worm, 1990). In adults, the gastrointestinal tolerance of roxithromycin compares favorably with that of doxycycline and erythromycin ethylsuccinate. Roxithromycin therapy has caused vomiting in a few children (Kafetzis and Blanc, 1987).

6b. Hepatotoxicity

Transaminase elevation may occur in ~1–2% of patients receiving roxithromycin, but it is reversible on drug cessation. Fulminant acute hepatitis has been rarely reported (Blanc *et al.*, 1987; Paulsen *et al.*, 1992; Vial *et al.*, 1997). Concomitant acute renal failure and hepatotoxicity have been associated with roxithromycin therapy (Akcay *et al.*, 2004).

6c. Hypersensitivity reactions

Allergic reactions, including eosinophilia, fever, and skin eruptions, are rarely reported for macrolides. They usually disappear upon treatment cessation (Periti *et al.*, 1993). Roxithromycin-induced eosinophil pneumonitis has been reported by a number of authors (Pérez-Castrillón *et al.*, 2002; Chew *et al.*, 2006).

6d. Other adverse reactions

Reversible and mild itching and headache are other side-effects observed in more than 1% of patients (Worm *et al.*, 1989; Worm, 1990). *Candida* overgrowth occurs rarely (Blanc *et al.*, 1987; Peterslund *et al.*, 1989; Paulsen *et al.*, 1992).

Macrolides have been associated with prolongation of cardiac repolarization (prolongation of the QT interval). The molecular mechanism appears to be a blockade of the human ether-a-go-go related gene (hERG channel-dependent potassium current in myocyte membranes (Roden, 2008). These interactions may give rise to polymorphic ventricular tachycardia, torsades de pointes, or ventricular fibrillation. In a rat model, the potency of macrolides to induce QTc prolongation was ranked as follows: erythromycin > clarithromycin > roxithromycin > azithromycin (Ohtani *et al.*, 2000). However, few human data are available for roxithromycin.

6e. Risk in pregnancy

Roxithromycin belongs to the B category. There is insufficient clinical experience in pregnancy to confirm its safety.

7. CLINICAL USES OF THE DRUG

Overall, the various indications for roxithromycin are somewhat limited, since, despite a favorable pharmacokinetic profile, it does not have a major advantage in intrinsic activity over other newer macrolides, such as clarithromycin (see Chapter 61, Clarithromycin) or azithromycin (see Chapter 62, Azithromycin). Clarithromycin and azithromycin both demonstrate lower MICs than erythromycin, have high bioavailability and prolonged half-lives, and are therefore often preferred to roxithromycin. In those countries where roxithromycin is used regularly, it is generally for respiratory tract infections, especially mild to moderate cases of community-acquired pneumonia, often in combination with a β-lactam agent.

7a. Respiratory tract infections

Roxithromycin is a potential alternative to erythromycin for the treatment of pharyngitis. In patients with group A β-hemolytic streptococcal pharyngitis, its efficacy is similar to or lower than that of erythromycin (Herron, 1987; Melcher *et al.*, 1988).

Roxithromycin has been effective in the treatment of sinusitis, otitis media, bronchitis, and pneumonia caused by pathogens such as *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *M. pneumoniae*, and *Chlamydophila psittaci*. Its performance in these indications was attributed to its favorable pharmacokinetic profile, which can compensate for MICs that are sometimes higher than those of erythromycin (Kirst and Sides, 1989b; Peterslund *et al.*, 1989; Paulsen *et al.*, 1992; Chatzimanolis *et al.* 1998). Roxithromycin (300 mg once daily) has been compared with amoxicillin–clavulanate (875 + 125 mg twice daily) for a mean of 7 days for acute otitis media, pharyngotonsillitis, or rhinosinusitis. Outcomes were similar with clinical cure/improvement in 82% and 78%, respectively (Mira and Benazzo, 2001). Roxithromycin (150 mg daily for three months) appears to be more effective than placebo in the treatment of chronic rhinosinusitis (Wallwork *et al.*, 2006).

Macrolides have long been considered as an alternative to β-lactams for the treatment of respiratory tract infections. However, the increasing rates of resistance among common respiratory pathogens, other than *Mycoplasma* and *Chlamydophila* spp., to macrolides has meant that roxithromycin and other similar agents should be used with caution in countries where resistance rates are high (Brunton and Iannini, 2005; Lode, 2007). Hopstaken *et al.* (2002) found that amoxicillin (500 mg three times a day) and roxithromycin (300 mg once daily) both had similar clinical efficacy among 196 patients with acute lower respiratory tract infections treated for 10 days in a double-blind randomized controlled trial. In a small study, Tatsis *et al.* (1998) found that roxithromycin (300 mg once daily) demonstrated similar efficacy to clarithromycin (500 mg twice daily) in patients with lower respiratory tract infections.

Compared with broad-spectrum fluoroquinolones, roxithromycin appears inferior. In a study by Örtqvist *et al.* (1996) comparing roxithromycin (150 mg twice daily) with sparfloxacin (400 mg on day 1, followed by 200 mg daily) for 10–14 days in 304 adults with community-acquired pneumonia (CAP), cure rates were 79% for roxithromycin versus 94% for sparfloxacin among evaluable patients at follow-up. Asymptomatic prolonged QTc interval was noted in 1% and 3% of patients, respectively, whereas mild to moderate phototoxicity was noted in 5% of sparfloxacin recipients. Overall, sparfloxacin was superior to roxithromycin for moderately severe CAP. Similarly, once-daily moxifloxacin (400 mg) appears to have similar efficacy to amoxicillin–clavulanate (1000/125 mg three times a day) plus

roxithromycin (150 mg twice a day) for adults with nonsevere CAP (Portier *et al.*, 2005).

In an open-label, randomized study comparing once-daily oral regimens of roxithromycin (300 mg) to cefixime (400 mg) in 60 patients with mild to moderate CAP, cure rates were similar (100 *vs* 94%, respectively) and both agents were well tolerated (Salvarezza *et al.*, 1998).

7b. Skin infections

Roxithromycin can be effective for impetigo and erysipelas caused by susceptible *S. aureus* or *S. pyogenes* (Agache *et al.*, 1987; Bernard *et al.*, 1992). However, roxithromycin offers little advantage over clarithromycin or azithromycin (Parsad *et al.*, 2003). A 4-week treatment proved effective in decreasing inflammatory acne (Ferahbas *et al.*, 2004).

7c. Lyme disease

Limited data suggest that roxithromycin can be effective in borreliosis and Lyme arthritis (Pedersen and Friis-Moller, 1991), but therapeutic failures have also been reported (Weber, 1996). The efficacy is much lower than would be anticipated based on *in vitro* susceptibility data (Hansen *et al.*, 1992). Overall, macrolides, including roxithromycin, are considered second-line therapy behind β-lactams and tetracyclines for this disease owing to their lower rates of efficacy (Loewen *et al.*, 1999).

7d. Sexually transmitted diseases

In the treatment of nongonococcal urethritis in males, roxithromycin in a dosage of 150 mg 12-hourly cured 97% of *C. trachomatis* infections, 88% of *Ureaplasma urealyticum* infections, and 73% of infections due to *M. homini* (Lassus and Seppala, 1987). Chlamydial conjunctivitis in newborns and adults has also been treated with some success with oral roxithromycin (Stenberg and Mardh, 1991).

7e. Gastrointestinal infections

In the treatment of *H. pylori* gastritis, initial studies with roxithromycin alone or in combination with metronidazole were encouraging (Cellini *et al.*, 1991; Stolzle, 1994). In triple-therapy studies, roxithromycin was shown to be less effective than clarithromycin in one study (Svoboda *et al.*, 1997), but another one did not find such a difference (Pohle *et al.*, 1998). In a quadruple-therapy study of omeprazole, amoxicillin, metronidazole, and roxithromycin, however, cure rates as high as 95% were recorded (Okada *et al.*, 1998). No reinfection after apparent successful eradication of *H. pylori* with 20 mg of omeprazole once daily, 500 mg of amoxicillin three times per day, 250 mg of metronidazole three times per day, and 150 mg of roxithromycin twice a day for 1 week was seen (Seo *et al.*, 2002).

A number of uncontrolled studies have suggested that roxithromycin 300 mg twice daily for 4 weeks may be effective in the treatment of AIDS-related cryptosporidial diarrhea, with 79–95% of patients improving and 50–68% achieving complete recovery (Sprinz *et al.*, 1998; Uip *et al.*, 1998).

7f. Chemoprophylaxis in neutropenic patients

In a prospective, randomized, open trial, the efficacy of oral roxithromycin (150 mg 12-hourly) as additional chemoprophylaxis to ofloxacin was evaluated in 131 adult patients with acute leukemia or adult bone marrow transplant recipients. In comparison with patients given ofloxacin alone, fewer patients receiving both drugs developed bacteremia caused by *S. viridans*. The authors considered that routine use of roxithromycin prophylaxis was not justified, but that it may be valuable in areas where there is a high risk of streptococcal infections (Kern *et al.*, 1994). Other authors have also used a quinolone, such as ciprofloxacin, plus roxithromycin as chemoprophylaxis in neutropenic patients with some success (Verhoef, 1993). Similarly, a reduction in chemotherapy-induced febrile neutropenia has been observed among patients with small cell lung cancer given prophylaxis with ciprofloxacin plus roxithromycin in a double-blind placebo-controlled phase III study conducted by the EORTC group (Tjan-Heijnen *et al.*, 2001).

7g. Coronary artery and other arteriovascular diseases

Macrolides have been suggested to play a protective role against coronary artery disease, as a result of their antichlamydial or an anti-inflammatory effect on atheromata. Studies with roxithromycin for this indication suggest contradictory results (Gurfinkel *et al.*, 1997; Gurfinkel, 2000; Leowattana *et al.*, 2001). Until recently, no large randomized trials had been conducted with roxithromycin (Muhlestein, 2003), but studies with azithromycin (Grayston *et al.*, 2005) or clarithromycin (Gluud *et al.*, 2008) found no change in cardiac risk or increased mortality in macrolide-treated patients. A meta-analysis of studies examining macrolide benefit in the secondary prevention of coronary artery disease did not support the routine use of antichlamydial therapy (Etminan *et al.*, 2004).

Recently, Zahn *et al.* (2003) assessed 872 patients with acute myocardial infarction (AMI) who were randomly assigned to receive double-dummy treatment with either roxithromycin (300 mg daily) or placebo for 6 weeks. The primary end point was mortality at 12 months. More patients in the roxithromycin group interrupted their therapy before completion of at least 4 weeks' treatment (18% *vs* 11%; $p = 0.003$). Among the 868 patients followed up at 12 months, there was no difference in mortality (6.5% *vs* 6.0%, respectively). Thus, these findings are contrary to those of Gurfinkel *et al.* (1997) and do not support the routine use of roxithromycin therapy in patients with AMI. Similarly, Sander *et al.* (2002) found no benefit in the combined incidence of stroke, AMI, and vascular death among *Chlamydophila pneumoniae*-seropositive patients aged >55 years who were treated with roxithromycin for 30 days. Subsequently, in a long-term follow-up program, these authors (Sanders *et al.*, 2004) found ongoing progression of vascular disease among roxithromycin recipients with no difference in cardiovascular events compared with the placebo group.

For patients who have undergone cardiac vascular stenting, Neumann *et al.* (2001) found no difference between patients receiving roxithromycin or placebo in the rate of angiographic restenosis (31% *vs* 29%, respectively), nor any difference in the rate of death or AMI at one-year follow-up. However, among patients with very high titers of antibody to *C. pneumoniae*, restenosis rates appeared to be lower in roxithromycin recipients. The interpretation of these data remains unclear. Interestingly, Kaehler *et al.* (2005) found similar results in terms of roxithromycin therapy having no association with any reduction in symptomatic restenosis. However, they noted that during follow-up a marked increase in antichlamydial antibodies, TNF-α and eotaxin occurred, suggesting that angioplasty-induced plaque rupture may induce a specific immunologic response without activation of inflammatory mechanisms such as C-reactive protein.

For peripheral vascular disease, a number of authors have suggested that reduced rates of disease progression are associated with roxithromycin (300 mg once daily) compared with placebo for 28 days (Wiesli *et al.*, 2002; Krayenbuehl *et al.*, 2005). However, Joensen *et al.* (2008) recently demonstrated in a large, randomized, double-blinded, placebo-controlled study of 507 patients with established peripheral vascular disease that 28 days' therapy with roxithromycin 300 mg is ineffective in preventing death, amputation, peripheral revascularization, AMI, stroke, transient cerebral ischemic attacks, thrombosis, and decline in ankle–brachial blood pressure index.

A randomized, double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm (AAA) expansion among 92 patients suggested that, compared with placebo, roxithromycin 300 mg once daily for 4 weeks reduced the expansion rate of AAAs (Vammen *et al.*, 2001). However, additional studies are needed to confirm these findings before such therapy can be routinely recommended (Baxter *et al.*, 2008).

7h. Immunomodulatory and anti-inflammatory uses

Similar to clarithromycin and azithromycin, roxithromycin appears to have an anti-inflammatory effect that is independent of dose and results in a reduction in the secretion of proinflammatory cytokines, ameliorates the infiltration of inflammatory cells into the airways, and reduces mucus secretion. Improvements in pulmonary function and quality of life have been observed when these agents are given to some patients with chronic inflammatory diseases of the airways, including diffuse panbronchiolitis, cystic fibrosis, asthma (including aspirin-intolerant asthma), and bronchiectasis (Shoji *et al.*, 1999; Siddiqui, 2004; Amsden, 2005).

7i. Other uses

Long-term roxithromycin (300 mg daily) appears to have been effective in the treatment of nine patients with chronic diffuse sclerosing osteomyelitis of the mandible – seven of the nine had resolution of symptoms after 1–12 months (Yoshii *et al.*, 2001).

Roxithromycin has been used successfully in the treatment of cutaneous *M. chelonae* infection, but other macrolides such as clarithromycin are generally preferred (Sodemoto *et al.*, 2007).

Owing to the perceived possible association between *C. pneumoniae* infection and multiple sclerosis (MS), a randomized, placebo-controlled, double-blind study involving 28 patients with confirmed MS was undertaken with roxithromycin (300 mg daily) and placebo given over 12 months in three cycles of 6 weeks' oral therapy. No difference in clinical outcomes was identified – suggesting that a causative role for *C. pneumoniae* in this condition seems unlikely (Woessner *et al.*, 2006).

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