CHAPTER II

REVIEW OF ROXITHROMYCIN

1. Physicochemical Properties (Young, Gonzales, and Sorkin, 1989; Reynolds, 1996)

Roxithromycin is a semisynthetic acid-stable macrolide antibacterial drug. Figure 1 shows the chemical structure of roxithromycin, which can be seen to be an ethyl-oxime derivative of erythromycin A. Roxithromycin has a 14-membered macrolide nucleus, a neutral and an amino sugar, and an esterified oxime grouping, which confer improved pharmacokinetic properties on the compound over other macrolides.

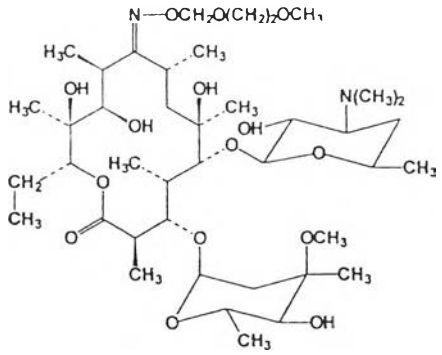

Figure 1 Chemical structure of roxithromycin

Chemical name	: Erythromycin 9-{O-[(2-methoxyethoxy)methyl)]oxime}
Empirical formula	: $C_{41}H_{76}N_2O_{15}$
Molecular weight	: 837.1
Synonym	: RU-965, RU-28965
Appearance	: white crystalline powder

2. Antibacterial Activity (Markham and Faulds, 1994)

Roxithromycin is an ether oxime derivative of erythromycin with *in vitro* activity resembling that of the parent compound. MIC_{90} (minimum concentration required to inhibit 90% of strains) value of ≤2 mg/L and 2 to 4 mg/L are indicative, respectively, of full and moderate susceptibility to the drug. Roxithromycin has variable activity against methicillin-susceptible *Staphylococcus aureus* but methicillin-resistant *S. aureus*, as well as *S. epidermidis*, *S. haemolyticus* and *S. hominis*, are not susceptible to the drug. Erythromycin-susceptible isolates of coagulase-negative staphylococci are susceptible to roxithromycin but erythromycin-resistant isolates are not.

Roxithromycin is active against *Streptococcus agalactiae*, *S. pneumoniae, S. pyogenes*, Lancefield group C and viridans group streptococci. It is generally inactive against Lancefield group G *Streptococcus* and enterococci. The activity of roxithromycin against *Listeria monocytogenes* is broadly similar to that of erythromycin, with most isolates being inhibited at a concentration of 1 or 2 mg/L.

Roxitromycin MIC_{90} values for *Neisseria gonorrhoeae* are similar to those of erythromycin; *Neisseria meningitidis* is slightly less susceptible with an MIC range of 0.3 to 4 mg/L.

Roxithromycin has borderline activity *in vitro* against *Haemophilus influenzae* when measured using current susceptibility guideline; however, a higher susceptibility breakpoint of ≤16 mg/L has recently been proposed. The drug has good *in vitro* activity against *Bordetella pertussis*, *B. parapertussis*, *Borrelia burgdorferi*, *Moraxella catarrhalis* and *Legionella pneumophila.* Roxithromycin MIC_{90} values against *Chlamydia trachomatis* range between 0.25 and 1 mg/L.

Roxithromycin had a MIC_{90} value of 16 mg/L against 28 *Mycobacterium avium* complex strains isolated from patients with acquired immune deficiency

syndrome, compared with values of 8, 32, and ≥64 mg/L for clarithromycin, azithromycin and erythromycin, respectively.

Roxithromycin MIC_{90} values against *Bacteroides* spp. and *Clostridium difficile* are high.

Roxithromycin exerts its action by disrupting bacterial protein synthesis. It is also concentrated in human polymorphonuclear leucocytes and macrophages. The drug has demonstrated good activity in animal models of Gram-positive and other infections such as toxoplasma encephalitis, Legionnaires' disease, *Mycobacterium leprae* infection, syphilis and chlamydial urogenital infection.

3. Pharmacokinetics

3.1 Absorption and Plasma Concentrations

Peak concentrations of orally administered roxithromycin in plasma (C_{max}) ranged between 6.61 and 7.9 mg/L following a 150 mg oral dose (Kees et al., 1988 and Zini et al., 1988), and between 9.1 and 11.02 mg/L following a single 300 mg dose. C_{max} was generally reached 1.3 to 2.2 hours after a 300 mg dose (Nilsen et al., 1992). Administration of roxithromycin 15 minutes after a standard meal may result in reduced bioavailability (Tremblay, Meyer et al., 1986) and it is thus recommended that the drug be given at least 15 minutes before food.

The improvement in pharmacokinetic parameters of roxithromycin relative to erythromycin has been quantified in a direct comparison. C_{max} after a single 150 mg dose of roxithromycin was 3.3-fold greater than that produced by a single 250 mg dose of erythromycin. The area under the plasma concentration versus time curve (AUC) produced by roxithromycin was 16.2-fold greater than that produced by erythromycin. Similar differences were observed after multiple doses. A single dose of roxithromycin (300 mg) produced a higher peak plasma concentration than single

dose of clarithromycin (500mg) and azithromycin (500mg) when directly compared in volunteers (Markham and Faulds, 1994).

3.2 Distribution

Concentrations of roxithromycin in tissue and body fluids are generally higher than MIC_{90} values for susceptible bacteria (Markham and Faulds, 1994). The mean peak roxithromycin concentration in bronchial secretions was 4.71 mg/L and occurred after 2 to 4 hours in 7 intensive care patients who received a 300 mg loading dose followed by six 12 hourly 150 mg doses. The corresponding mean peak serum level was 8.74 mg/L after 1 hour (Boccazzi and Langer, 1991).

Roxithromycin is weakly and nonspecifically bound to albumin (15.6 to 26.7 %) but is strongly, specifically and saturably bound to α_1-acid glycoprotein (Zini et al., 1988).

3.3 Metabolism and Elimination

Descladinose, N-didemethyl and N-monodemethylated derivatives of roxithromycin have been identified in urine and faeces. Other faecal metabolites have also been detected but have not yet been identified. 74.2% of a radiolabelled roxithromycin dose was accounted for after administration to volunteers: 53.4 % in faeces; 13.4% as expired carbon dioxide and 7.4% in the urine (McLean et al., 1988) and plasma clearance appears to be dose- or plasma concentration-dependent (Wise et al., 1987).

The mean elimination half-life of roxithromycin 150 or 300 mg was 8.4 to 15.5 hours in volunteers (Kees et al., 1988; Tremblay, Jaeger et al., 1988), considerably longer than that recorded for erythromycin (1.5 to 3 hours) (Nilsen, 1987). Studies suggest that the pharmacokinetics of roxithromycin are nonlinear and

may include a saturable process involving release of plasma α_1-acid glycoprotein-bound roxithromycin for distribution and elimination (Markham and Faulds, 1994).

3.4 Effect of Age and Disease on Pharmacokinetics

Roxithromycin has a similar pharmacokinetic profile in children to that reported in adults (Demotes-Mainard, Vincon, and Albin, 1989). Dosage adjustment is not required in patients with renal impairment or in the elderly (Markham and Faulds, 1994). Roxithromycin urinary recovery, maximum plasma concentrations, AUC and clearance were similar in 8 dialysis patients and 8 patients with renal failure who were not on dialysis, after administration of a single 150 mg oral dose.

A 50% reduction in daily roxithromycin dosage to 150 mg/day has been recommended for patients with liver cirrhosis because of the significantly increased roxithromycin half-life in this patient group (Markham and Faulds, 1994).

4. Therapeutic Use (Markham and Faulds, 1994)

Roxithromycin has produced efficacy rates of between 71 and 96% in patients with tonsillitis or sinusitis and resolved or improved the signs and symptoms of pharyngotonsillitis and sinusitis significantly more effectively than clarithromycin in 1 study.

Clinical efficacy rates were >90% in almost 10,000 patients with acute bronchitis who received roxithromycin in noncomparative studies. The clinical efficacy of roxithromycin was very similar to that of amoxicillin/clavulanic acid, cefaclor and azithromycin in comparative studies. Roxithromycin is also an effective treatment for exacerbations of chronic bronchitis, producing clinical efficacy rates ranging between 83.3 and 89% in 4 noncomparative trials involving >4,000 patients, and having clinical efficacy similar to that of amoxicillin/clavulanic acid, doxycycline, cefaclor and azithromycin in comparative studies.

Roxithromycin has demonstrated similar clinical efficacy to amoxicillin/ clavulanic acid, azithromycin, clarithromycin, cefaclor, erythromycin and midecamycin acetate in patients with pneumonia. The drug is also an effective treatment for patients with pneumonia caused by atypical organisms such as chlamydia, mycoplasma, *Legionella* spp., rickettsia and *Coxiella burnetii*.

Roxithromycin 300 mg/day was equally effective administered either once or twice daily to 1,588 patients with various infections.

One study has shown roxithromycin to be as effective as josamycin in treatment for patients with suppurative skin and soft tissue infections and as effective as penicillin in patients with erysipelas.

The clinical efficacy of roxithromycin was similar to that of amoxicillin, erythromycin and josamycin in treatment for orodental and odontological infections and was also comparable with spiramycin in prophylaxis prior to dental surgery.

In patients with urogenital or gynaecological infections, roxithromycin has produced clinical response rates ranging between 71 and 100%, and was as effective as doxycycline and minocycline in comparative studies. The drug was equally effective administered either once or twice daily in patients with nongonococcal urethritis.

Roxithromycin has good *in vitro* activity against *Borrelia burgdorferi* and, in combination with cotrimoxazole (trimethoprim/sulfamethoxazole), was an effective treatment for late Lyme disease. In a pilot study the drug effectively prevented pneumocystosis and cerebral toxoplasmosis in human immunodeficiency virus (HIV)-positive patients, either alone or in combination with pentamidine aerosol. Roxithromycin 300 mg/day in combination with omeprazole and bismuth subnitrate eradicated confirmed *Helicobacter pylori* infection in patients with peptic ulcers and gastritis more effectively than omeprazole monotherapy.

Although recent paediatric studies are limited, roxithromycin 5 to 10 mg/kg/ day has demonstrated efficacy in the treatment of respiratory tract and skin and soft tissue infections in children and, compared with placebo, has significantly reduced the duration of diarrhoea and faecal excretion of *Campylobacter* in children with campylobacter-associated enteritis.

5. Adverse effects

Clinically significant adverse effects from roxithromycin are uncommon. Few adverse effects were noted from the published literature, and out of 2,917 adults, only 4.1% of patients reported adverse effects that were possible or probably related to treatment with roxithromycin. The most common adverse effects encountered were gastrointestinal in nature with nausea, abdominal pain, and diarrhoea being the most frequently reported (Blanc et al., 1987).

In 304 infants and children aged 2 months to 14 years, the incidence of adverse effects following treatment with roxithromycin 2.5 to 5 mg/kg every 12 hours was 6.9%. These reactions were mild and transient (Kafetzis and Blanc, 1987). Included in the multicenter review described above was a safety evaluation in 480 elderly patients aged 65 and over who were treated with roxithromycin. 15(3.1%) was reported to develop adverse effects. These led to the discontinuation of treatment in 9 patients (1.9%) (Blanc et al., 1987).

In the comparative study of respiratory tract infections with roxithromycin 150 mg twice daily produced fewer adverse effects than erythromycin ethylsuccinate 400 mg 4 times daily ($p<0.05$) (Herron, 1987). Similarly, in another double-blind study comparing roxithromycin 150 mg twice daily with doxycycline 200 mg daily, gastrointestinal complaints were more frequent in the doxycycline group ($p=0.075$) (Young, Gonzalez, and Sorkin, 1989).

Some abnormalities in liver function tests for subjects with normal values at baseline have been reported. Less than 0.7% of 2,917 patients treated with roxithromycin had changes in serum total bilirubin, alanine aminotransferase, aspartate aminotransferase and serum alkaline phosphatase. In addition, there is no evidence to suggest that roxithromycin produces hepatitis (Blanc et al., 1987).

6. Drug Interaction

Roxithromycin appears unable to form stable complexes with cytochrome P450 enzymes (Delaforge, Sartori, and Mansuy, 1988). However, a clinical insignificant interaction betweeen roxithromycin and theophylline, leading to slight but statistically significant increases in theophylline C_{max} and AUC, has been reported in healthy volunteers (Saint-Salvi et al., 1987). Bandera et al. reported a similar effect with respect to mean theophylline trough concentrations in patients with acute exacerbations of chronic bronchitis. These findings do not justify alterations to theophylline dosages, although monitoring of plasma theophylline concentrations may be prudent if they exceed 15 mg/L before administration of roxithromycin (Periti et al., 1992). In contrast, Hashiguchi et al. found that roxithromycin did not increase serum theophylline concentrations in volunteers (Marhkam and Faulds, 1994).

Although the antiarrhythmic drug disopyramide appears to interact with roxithromycin in vitro by modifying serum protein binding, producing notably increased unbound plasma concentrations of both drugs (Zini et al., 1988), this observation has not been confirmed in vivo (Periti et al., 1992). Roxithromycin does not affect the pharmacokinetic profile of carbamazepine or the efficacy of oral contraceptives (Meyer et al., 1990) and does not interact with warfarin, ranitidine or antacids containing aluminium or magnesium hydroxide (Young, Gonzales and Sorkin, 1989).

7. Dosage and Administration (Markham and Faulds, 1994)

The recommended daily oral dosage of roxithromycin for adults is 300 mg; this may be administered either as 150 mg every 12 hours or 300 mg once daily. Dosage adjustments are not necessary in elderly patients or those with mild or moderate renal impairment but a reduced dose of 150 mg is recommended for patients with severe hepatic insufficiency. The recommended dose for infants and children is 5 to 8 mg/kg of body weight administered in 2 divided doses for a maximum of 10 days.