

## Macrolide Antibiotics

Since the discovery of **erythromycin** almost 50 years ago, New Zealand has acquired three other macrolide antibiotics (**azithromycin**, **clarithromycin** and **roxithromycin**) which may offer advantages over the original agent. This bulletin discusses the major differences between the macrolides.

### Antimicrobial activity

The macrolides inhibit RNA-dependent protein synthesis resulting in bacteriostatic antimicrobial activity.

- **Erythromycin** has activity against gram-positive cocci (eg *S.aureus*,  $\beta$ -haemolytic streptococci), and some gram-negative organisms (eg *B.pertussis*, *M.pneumoniae*, *L.pneumophila*, *Chlamydia* and *Neisseria sp.*).
- **Roxithromycin** has similar activity to **erythromycin**.
- **Clarithromycin** has greater activity against *H.influenzae*, *M.catarrhalis*, *Non TB mycobacterium*, *Mycobacterium Avium Complex (MAC)* and *H.pylori*.
- **Azithromycin** has greater activity against gram-negative organisms, particularly genitourinary pathogens (eg *C.trachomatis*, *U.urealyticum*, *N.gonorrhoeae*, and *T.pallidum*).

### Indications

- Respiratory tract infections (sinusitis, pharyngitis, LRTI and particularly atypical organisms).
- Skin and soft tissue infections.
- Cervicitis/urethritis (eg. **azithromycin** for *C.trachomatis* infections).
- Mycobacterial infections (eg. **clarithromycin**, see funding below).
- *H.pylori* infections (**clarithromycin**, as part of triple therapy).

### Precautions/Contraindications

Macrolides should be avoided in severe liver disease due to increased risk of hepatotoxicity and altered handling. A previous hypersensitivity reaction is a contraindication.

**Erythromycin** is considered safe in pregnancy and breast feeding. **Roxithromycin** and **clarithromycin** are safe in breast feeding (pregnancy unknown). The evidence for safety of **azithromycin** is lacking, and use is therefore inadvisable unless benefit is considered to outweigh potential harm.

### Pharmacokinetics

- **Erythromycin's** oral availability is affected by food in different ways depending upon the formulation used (ie. decreased with the base forms and increased with the estolate form). A short half-life (1-1.5h) means dosing four times daily is generally required.
- **Roxithromycin** has good oral availability, which is independent of food. A half-life of 12h allows administration once or twice daily.
- **Clarithromycin** has good oral availability, which is independent of food. Its half-life is 3 to 7h, allowing twice daily administration, either orally or intravenously, with similar efficacy. Dilution in 250mL of either normal saline or 5% dextrose, administered over 60 minutes into a large proximal vein is required to reduce phlebitis. In severe renal dysfunction (CrCl<0.5mL/s) the dose should be halved.
- **Azithromycin's** oral availability is independent of food. A very large Vd (2100L) results in very good tissue

penetration and a long half-life (40-60h), which allows once daily dosing.

**Erythromycin** and **Clarithromycin** are metabolised through CYP450 3A4, whereas **azithromycin** and **roxithromycin** are predominantly cleared unchanged in the bile or metabolised by non-CYP450 mechanisms.

### Adverse Effects

Macrolides do not usually have serious toxicity although gastrointestinal symptoms such as nausea, vomiting, diarrhoea and abdominal cramps may be problematical. **Erythromycin** is significantly more likely to evoke gastrointestinal side effects, largely through stimulation of motility. Co-administration with food may reduce GI upset.

High intravenous doses of **erythromycin** or **clarithromycin** have been associated with hearing loss and QT prolongation. Allergic reactions, headache, taste disturbance, eosinophilia and hepatotoxicity are an infrequent occurrence with all the macrolides.

### Drug interactions

**Erythromycin** and **clarithromycin** are strong inhibitors of cytochrome P450 3A4 and may result in elevated concentrations of many drugs (Table). **Roxithromycin** and **azithromycin** cause fewer clinically significant interactions, and may be preferred if interactions are likely.

Table: Drug interactions

#### 3A4 substrates

- Benzodiazepines  
alprazolam, midazolam, triazolam, diazepam
- Calcium channel antagonists  
felodipine, diltiazem, verapamil, nifedipine
- HMG CoA reductase inhibitors  
atorvastatin, simvastatin<sup>†</sup>
- Immunosuppressants  
ciclosporin, tacrolimus
- Psychiatric drugs  
buspirone<sup>†</sup>, clozapine, pimozide<sup>†</sup>
- Other  
carbamazepine, cisapride<sup>†</sup>, theophylline, warfarin

#### Non 3A4 substrates

fexofenadine, digoxin

<sup>†</sup>Macrolide use contraindicated due to increased ADR's

### Funding

**Erythromycin** and **roxithromycin** are fully funded. **Azithromycin** and **clarithromycin** are only fully funded under certain circumstances (eg. a special authority is available for **clarithromycin** in proven *H.pylori* infections, MAC and atypical or drug resistant mycobacterial infections. Use of **azithromycin** is restricted to uncomplicated *C.trachomatis* urethritis/cervicitis). Otherwise there is a significant cost to the patient or the hospital (approximately \$63 for a 10-day course of **clarithromycin** 500mg twice daily).

*In the Canterbury District Health Board roxithromycin is the preferred agent for oral administration in both inpatients and outpatients in the majority of clinical situations.*