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 (e.g. *S. aureus*, β-haemolytic streptococci), and some gram-negative organisms (e.g. *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 (e.g. *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 (e.g. azithromycin for *C. trachomatis* infections).
- Mycobacterial infections (e.g. 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 (i.e. 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

<table>
<thead>
<tr>
<th>3A4 substrates</th>
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<tbody>
<tr>
<td>• Benzodiazepines</td>
</tr>
<tr>
<td>alprazolam, midazolam, triazolam, diazepam</td>
</tr>
<tr>
<td>• Calcium channel antagonists</td>
</tr>
<tr>
<td>felodipine, diltiazem, verapamil, nifedipine</td>
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<tr>
<td>• HMG CoA reductase inhibitors</td>
</tr>
<tr>
<td>atorvastatin, simvastatin†</td>
</tr>
<tr>
<td>• Immunosuppressants</td>
</tr>
<tr>
<td>ciclosporin, tacrolimus</td>
</tr>
<tr>
<td>• Psychiatric drugs</td>
</tr>
<tr>
<td>buspirone¾, clozapine, pimozide¹</td>
</tr>
<tr>
<td>• Other</td>
</tr>
<tr>
<td>carbamazepine, cisapride¹, theophylline, warfarin</td>
</tr>
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</table>

Non 3A4 substrates
- fexofenadine, digoxin

Funding
Erythromycin and roxithromycin are fully funded. Azithromycin and clarithromycin are only fully funded under certain circumstances (e.g. 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.