New Macrolides

Faridah Moosdeen, PhD., MRCPath.

Macrolides are a class of antibiotics that include erythromycin, roxithromycin, clarithromycin, and azithromycin. These antibiotics are effective against a variety of bacterial and mycobacterial infections. Erythromycin is a macrolide antibiotic that is effective against many Gram-positive bacteria, including Streptococcus pneumoniae and Mycobacterium avium. Roxithromycin and clarithromycin are derivatives of erythromycin that are more resistant to acid and have a longer half-life. Azithromycin is a macrolide antibiotic that is effective against various respiratory pathogens and is used in the treatment of pneumonia and other infections.

Key words: Macrolides, erythromycin, roxithromycin, clarithromycin, azithromycin

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Synopsis

The main problem with the older macrolides was their poor pharmacokinetics and their side effect involving the gastrointestinal tract. The advent of new macrolides help overcome some of these problems. Although the spectrum of activity of most new macrolides is similar to that of erythromycin, some of them showed a better spectrum of activity against Gram negative bacteria. The activity of clarithromycin is much superior than erythromycin against streptococci and chlamydia. The peculiar pharmacokinetics ensure that these compounds are concentrated in tissues and also the polymorphonuclear cells for a long period of time. As such, the compounds may show potential success in eradicating organisms residing in tissues or in cells. These compounds have been shown to be effective in the treatment of upper and lower respiratory infections, skin and soft tissue infections and also in non-gonococcal urethritis. A few compounds are also effective against the Mycobacterium-avium-intercellulare complex (MAC) as well as against the leprae bacilli. Their pharmacokinetics also point out to better patient compliance as they produce less side effects and can be given less frequently.

INTRODUCTION

One of the more exciting developments in the antibiotic scene during this decade is the development of the macrolides; the last decade having seen the quinolones. The problem with the early macrolide, erythromycin, has been the narrow range of antibacterial activity, resistance, poor gastrointestinal tolerance and the poor compliance with multiple dose programs. In the effort to overcome some of these problems, a number of new agents with the macrocylic lactone nucleus have been synthesized. There new macrolides have been shown to be better tolerated than erythromycin and they also have much improved pharmacokinetics.

The derivation of the new macrolides from erythromycin is shown in Figures 1 and 2. Alteration of the C-9 oxime of erythromycin yields roxithromycin, erythromycylamine, and also dirithromycin. Clarithromycin is a methyl derivative. Clarithromycin is also metabolised into an active metabolite (14-OH derivative). This metabolite is however twice as active as clarithromycin against H. influenzae specifically (1,2). Azithromycin, with a different chemical entity (so called azalide) from the macrolides, is also derived from erythromycin but the lactone ring is expanded from 14-membered to 15-membered, by the incorporation of nitrogen (3). The 16-membered lactone such as josamycin is derived from Streptomyces naphonensis var. josamyceticus. Spiramycin and midecamycin are other natural 16-membered macrolides. Among the 16-membered macrolides, rokitamycin and miocamycin

**Fig. 1 Chemical structure and relationship of 14-membered macrolides**
are semi-synthetic.

**Antimicrobial activity:** The spectrum of activity of the new macrolides is comparable and similar to that of erythromycin, although some significant differences in activity has been observed (Table 1). Erythromycin resistant strains of staphylococci and streptococci will remain resistant to the new macrolides with the exception of rokitamycin and miokamycin. Against group A streptococci, clarithromycin is most active. Strep. pneumoniae strains are also particularly susceptible to clarithromycin. Enterococci are usually resistant. Against Haemophilus influenza, Moraxella catarrhalis, Mycoplasma pneumoniae, Neisseria gonorrhoeae and Campylobacter jejuni, azithromycin is most active. The new macrolides, excepting clarithromycin are not more active than erythromycin against Bordetella pertussis. Clarithromycin also show greater activity against Chlamydia pneumoniae (and also Chlamydiatrachomatis) than other macrolides.

The activity of new macrolides against Mycobacterium avium intracellulare is superior than erythromycin (MICclarithromycin 0.25-8.0 mg/l(7)). Against *M. leprae*, clarithromycin is shown to be more active than roxithromycin. Erythromycin and azithromycin were inactive(8).

The macrolides have poor activity against Enterobacteriaceae, *Pseudomonas* spp. and related Gram-negative bacteria. Azithromycin, however, has improved activity against Gram negative bacteria(9). Against *Salmonella typhi*, Metchock (10) reported azithromycin to be active at 4-16 mg/l.

**Resistance:** These compounds bind to the 50S ribosomal subunit of prokaryotic ribosomes with a specific target in the 23S ribosomal RNA involving specific sites. The binding of macrolides to these sites is influenced by particular L proteins(11-13). The compounds act primarily by stimulating the disassociation of peptidyl-tRNA from ribosomes during translocation (14). The major mechanism of resistance to the macrolides involves the modification of the target, that is, methylation of the 23S ribosomal RNA (MLS\(_B\) phenotype) due to *erm* (erythromycin resistance methylase) genes(15). Methylation prevents the drug from binding to the 50S ribosomal subunit probably as a consequence of a conformational change in the 23S rRNA(13). This mechanism confers cross-resistance in these compounds. Other mechanisms of resistance involve chromosomal mutations that affect ribosomal proteins. Mutants designated *ery A* show an alteration in protein L4 which leads to loss of macrolide binding by ribosomes. *Ery B* confers a change in protein L22. *Ery C* has been reported to affect maturation of ribo-
Table 1 Activity* of macrolides (MIC\textsubscript{90} in mg/l) against common pathogens.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Erythromycin</th>
<th>Clarithromycin</th>
<th>Roxithromycin</th>
<th>Azithromycin</th>
<th>Josamycin</th>
<th>Rokitamycin</th>
<th>Miocamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staph. aureus (MS)**</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Staph. aureus (MR)**</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>Strep. pyogenes</td>
<td>0.03</td>
<td>0.015</td>
<td>0.06</td>
<td>0.12</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Strep. pneumoniae</td>
<td>0.03</td>
<td>0.015</td>
<td>0.03</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Step. agalactiae</td>
<td>0.06</td>
<td>0.06</td>
<td>0.25</td>
<td>0.12</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>128</td>
<td>&gt;128</td>
<td>&gt;128</td>
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<tr>
<td>Haem. influenzae</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>0.5</td>
<td>16</td>
<td>16</td>
<td>&gt;16</td>
</tr>
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<td>M. catarrhalis</td>
<td>0.25</td>
<td>0.25</td>
<td>1</td>
<td>0.06</td>
<td>1</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>Bord. pertussis</td>
<td>0.03</td>
<td>0.03</td>
<td>0.25</td>
<td>0.06</td>
<td>0.25</td>
<td>0.12</td>
<td>0.25</td>
</tr>
<tr>
<td>L. pneumophila</td>
<td>2</td>
<td>0.25</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Ch. pneumoniae</td>
<td>0.06</td>
<td>0.007</td>
<td>0.25</td>
<td>0.5</td>
<td>0.25</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>0.004</td>
<td>0.03</td>
<td>(0.015)</td>
<td>0.001</td>
<td>–</td>
<td>(0.06)</td>
<td>–</td>
</tr>
<tr>
<td>List. monocytogenes</td>
<td>0.5</td>
<td>0.25</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
<td>0.06</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Camp. jejuni</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>0.12</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

*(after 4,5,6)

**MS = methicillin sensitive; MR = methicillin resistant.

somal RNA. The mechanisms of macrolide resistance conferred by \textit{ery} B and \textit{ery} C mutations are presently unclear. Plasmid-mediated mechanisms of resistance to erythromycin which involves inactivation of the compound - resulting in hydrolysis of the lactone ring have been described, and the genes \textit{ere} A and \textit{ere} B encoding esterases have been determined(16). Inactivation, however, has been restricted specifically to 14-membered macrolides.

The prevalence of resistance to macrolides such as erythromycin is variable among the different countries. Resistance of \textit{Staph. aureus} to erythromycin can range from 1 to 50 per cent dependent on whether they are community or hospital isolates. Resistance in \textit{Strep. pyogenes} to erythromycin too is varied [as low as 1\% in the USA and as high as 50\% in Japan(17)]. In Malaysia, resistance is about 2 per cent(18).

**Pharmacology:** After oral administration, macrolides are absorbed to a variable extent and pass to the liver via the portal vein. Inactivation may occur in the liver, but the compound is predominantly excreted into the bile and re-absorbed from the intestine, entering the hepatoenenteric circulation. After biliary excretion is saturated, the remainder is then distributed and retained in various organs. Many factors may affect the rate of absorption, for instance, the absorption of josamycin and roxithromycin is delayed by food(19,20). The relative bioavailability (based on the AUCs), however, was unaffected by food. The formulation of the compounds may also affect absorption, whether in the stearate or succinate form (as for erythromycin) or in the propionate form (as for josamycin).

The pharmacokinetics of the currently available macrolides show marked variation. The new macrolides have improved pharmacokinetic properties and acid stability compared with erythromycin. Roxithromycin has markedly high serum levels and has a long elimination half-life (8 to 12 hours)(21). Clarithromycin is characterised by high serum and tissue levels and still a longer half life (3 to 5 hours) compared to erythromycin(22). Dirithromycin has relatively low serum concentrations but high tissue concentrations. Its half life is extremely long (20 to 50 hours)(23). Azithromycin also produces low serum levels but high tissue concentrations which may persist for several days due to its long half-life of 11 to 14 hours(24).

Macrolides have been shown to accumulate within various cells and high concentrations have been achieved in phagocytes, macrophages and neutrophils(24,25). Both erythromycin and clarithromycin show intraphagocytic antimicrobial activity(26). The concentration of roxithromycin achieved highly significant levels in macrophages and neutrophils than erythromycin(27). Dirithromycin achieves four times the concentration achieved by erythromycin in alveolar macrophages (28). Azithromycin concentrations in macrophages is 26 fold-more than erythromycin levels (29). The ability of macrolide antibiotics to penetrate
and concentrate within phagocytes have been used to treat infections caused by intracellular pathogens. The long half-life and high tissue concentrations of these drugs also make them very attractive to be given only once or twice daily and this will most likely improve patient compliance.

**Toxicity and side-effects:** In general, erythromycin is a safe non-toxic drug. Allergic reactions are rare. Abnormalities of liver function tests were encountered following the use of erythromycin estolate, but not other erythromycin preparations. Tinnitus and transient deafness have also been described in a small number of patients after administration of erythromycin lactobionate. The most common adverse reaction of macrolides is gastrointestinal side effect. Erythromycin has been known to disrupt the gastrointestinal motility patterns after both oral and intravenous administration(30). The 16-membered macrolides such as josamycin and spiramycin produce fewer side effects than erythromycin(31-33). Studies on the newer 14-membered compounds such as roxithromycin(34), clarithromycin(35) and the azalide, azithromycin (36,37), suggested that they cause a lower incidence of side effects than erythromycin. In many of these clinical trials with clarithromycin, roxithromycin or with azithromycin, the severity of the gastrointestinal side effects was less than erythromycin, although in some cases it necessitated the discontinuation of therapy (38,39).

**Clinical applications:** The maintenance of active levels of the macrolides at the site of infection for a long time due to its unusual pharmacokinetic profile means that the drug can be administered once or twice daily, and for a shorter duration without loss of clinical and microbiological efficacy.

Table 2 shows the dosage recommendation of the various macrolides.

Worldwide data on clinical studies using these new macrolides showed much promise as they are as active as erythromycin, better absorbed with high tissue concentrations and has prolonged half-lives which means that it can be given with less frequency. In fact, there is a trend for fewer gastrointestinal problems in the elderly group.

Clinical success rates of more than 80 per cent in cases of upper and lower respiratory tract infections, soft tissue and skin infections have been achieved although there is variation amongst the different compounds. The macrolides have a clear advantage over beta-lactams against atypical pathogens and also against those pathogens resistant to penicillins and cephalosporins. In paediatric infections, the macrolides are also as effective as conventional antibiotics used in treating respiratory, skin and soft tissue infections.

In the treatment of non-gonococcal urethritis, roxithromycin and azithromycin were as effective as tetracyclines commonly used for such infections. Roxithromycin was used at 150 mg bd, over ten days, azithromycin used at 1 gram as a single dose. Azithromycin had also been used to treat chancroid at a single dose of 1 gram and the results was promising (47). Against gonococcal infections, however, the

<table>
<thead>
<tr>
<th>Table 2 Dosage of macrolides</th>
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<tbody>
<tr>
<td>Paediatric dose*</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Erythromycin</strong></td>
</tr>
<tr>
<td>Azithromycin**</td>
</tr>
<tr>
<td>Clarithromycin**</td>
</tr>
<tr>
<td>Roxithromycin</td>
</tr>
<tr>
<td>Dirithromycin</td>
</tr>
<tr>
<td>Josamycin</td>
</tr>
<tr>
<td>Rokitamycin</td>
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<tr>
<td>Miocamycin</td>
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</tbody>
</table>

*In children use of new macrolides not well established. Data from (42, 43)
**established adult doses.
clinical outcome was less satisfactory for clarithromycin(48) although azithromycin was more effective (92% cured)(36). Some strains of gonococci are resistant to the macrolides and their usefulness in the treatment of gonorrhoea will depend on the prevalence of resistant strains in the community.

The role of macrolides against Mycobacterium, whether those causing tuberculosis or those causing leprosy must be exciting in the light of increasing notification of mycobacterioses and their resistance to present day drugs. Clarithromycin may show advantage over dapsone, an antileprotic drug in terms of tolerability and resistance to present day drugs. Clarithromycin may show advantage over dapsone, an antileprotic drug in terms of tolerability and resistance to present day drugs.

REFERENCES


