The development of macrolides and related compounds

One could be forgiven for thinking that the development of new antimicrobials is almost a matter of fashion. The early seventies were the years of the aminoglycosides; the early eighties—the broad spectrum penicillins; the late eighties—the quinolones. Possibly the nineteen nineties will be the era of the macrolides.

In the UK at least, the macrolides are often considered, somewhat unfairly and rather patronizingly, as general practice drugs. This seems to imply that they should be used in a wide range of infections of modest severity. However this is a very large potential worldwide market. In addition, erythromycin is widely considered to be a drug free from severe adverse effects—with a few well known exceptions (Inman & Rawson, 1983)—but it is often poorly tolerated by patients. Therefore any pharmaceutical company which could produce a more active agent, or one with superior pharmacokinetics or a better tolerated agent could expect to reap considerable rewards.

The race is on. As witness to this are two recent supplements of this journal. Erythromycin acistrate (Davey & Williams, 1987) is a new 2-acetyl ester prodrug of erythromycin base; although it has a certain resemblance to the 2-propionyl ester (the estolate), animal studies suggest that it is less hepatotoxic. The acistrate undergoes extravascular hydrolysis: hence tissue levels are fairly high. Roxithromycin (Phillips et al., 1987) is an oxime derivative of erythromycin and has similar activity to its parent. It is, however, excreted more slowly (the half-life being 13 h), and the serum levels are considerably greater than one would expect from a similar dose of erythromycin (Wise et al., 1987). Both of these compounds have been extensively studied in man.

Clarithromycin (A-56268, TE-031) is the 6-0-methyl derivative of erythromycin and has generally a similar potency to its parent but is somewhat less active against Haemophilus influenzae (Fernandes et al., 1986). Animal studies suggest that tissue levels, particularly in the lung, are greater than those in serum and that the half-life is twice that of erythromycin: hence once daily dosing is a possibility.

Also under evaluation is dirithromycin, an oxazine derivative of erythromycin which was synthesized by Boehringer-Ingelheim. This compound is metabolized to another active macrolide, erythromyclamine, which has a range of activity similar to that of erythromycin but is more active against staphylococci. This agent has a considerably greater terminal half-life (in excess of 24 h) compared with erythromycin's. Tissue levels are stated to be 10-50-fold greater than those in serum (Bozler, Heinzel & Busch, 1988). Studies in man are under way.

Another agent being studied is azithromycin, which has the virtue of being a different chemical entity, by some called an azalide, in distinction from the macrolides. It is derived from erythromycin but the lactone ring is expanded from 14-membered to 15-membered, by the incorporation of nitrogen (Bright et al., 1988). Azithromycin is four-fold more active than erythromycin and eight-fold more active than roxithromycin against H. influenzae (Barry, Jones & Thornsberry, 1988). The poor activity of erythromycin against this important respiratory pathogen I have always considered to be one of the greater weaknesses of this agent. Azithromycin is four-fold less active than erythromycin against Gram-positive cocci, but it does have modest activity against some of the Enterobacteriaceae, for example Escherichia coli (MIC 4 mg/l). The pharmacokinetics of azithromycin are markedly different from those of erythromycin. The former has a serum half-life of 12-14 h (although elimination is not log-linear) as against erythromycin's two hours, and high levels of azithromycin are reported in tissues, although serum levels are low; for example prostate levels are ten times greater than serum. These high tissue levels are reflected in the large volume of distribution of azithromycin, in excess of 20 l/kg (information from Pfizer Ltd). This suggests that such an agent might be very useful in the therapy of intracellular pathogens.

What the distinct differences between the various macrolides, and between the macro-
lides and the azalides, mean in clinical practice we have yet to learn by careful clinical trials. What is certain is that those interested in antimicrobial therapy will now have to turn their attention more and more to this expanding group of agents.

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References


