Macrolides

— A L Heyns

Summary

The author discusses and evaluates the different Macrolides, a large group of antibiotics; how they were discovered and improved over the years. He deals with the spectrum of activity, chemical structure, the pharmacokinetics, toxicity, and when and where most effectively used in general practice.

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Curriculum vitae

Dr Andre L Heyns studied at the University of Stellenbosch where he obtained the MB ChB in 1973. In 1978 he obtained the Diploma in Anaesthesiology at the College of Medicine (S.A.) after which he went into private practice in Northcliff, Johannesburg, for 7 years. He studied part time at the Department of Pharmacology at the University of Pretoria (from 1983) and obtained the M.Pharm Med in 1985. He is currently a part time lecturer at the University of Pretoria and is the medical advisor at a pharmaceutical company in Johannesburg.

The macrolides form part of a large group of antibiotics which have in common a large macrocyclic lactone ring containing 12 to 16 atoms (hence the generic name macrolide) to which sugars are attached via glycosidic bonds.

Etymologically "macro" comes from Greek meaning large, and "olide" is the suffix for the lactose function. Macrolide means therefore large lactone.[1]

A number of new macrolides have been discovered over the past several decades but the first representative of this family was isolated from the Streptomyces species in 1950 and was called pikromycin. Subsequently, erythromycin (the reference drug with which other macrolides are compared) was discovered by Mc Guire in 1952. Others include oleandomycin (1954), josamycin (1966), spiramycin (1954) and midecamycin (1971).

All the macrolides act as antibiotics by inhibiting protein synthesis in the bacterial cell. They bind to the so-called 50-S component of the ribosome and, in doing so, disrupt the construction of amino acids carried to the ribosome by the transfer RNA[3,4].

The large family of macrocylic antibiotics[2], can be divided into different groups:

- Macrolactams or ansamycins
- Polyene macrolides characterized by their size, the presence of several double bonds and their antifungal activity
- Unusual macrocyclic lactoses, so-called "macrolide-like" compounds produced by micro-organisms. From this class the avermectin family exhibit high anti-parasitic activity.

Spectrum of activity

In general, the macrolides show a relatively narrow antibacterial spectrum and they are active against Gram-positive cocci, Gram-negative cocci, Gram-positive bacilli and anaerobic bacilli[6]. Most Gram-negative bacilli are naturally resistant to macrolides. However, Bordetella species, Pasteurella species and Haemophilus species are sensitive to a limited extent and Campylobacter and Legionella species are highly susceptible. It is for this reason that macrolides are used extensively in treating lung infections in Europe. The macrolides are also active against Mycoplasma pneumoniae, Ureaplasma urealyticum, Rickettsia and Chlamydia species.

other forms of erythromycin. Deafness has been reported after high doses of intravenous erythromycin in patients with dimininished renal function; it appears to be transient and completely reversible. Allergic reactions are uncommon and the macrolides are safe to use where patients present with allergies to penicillin.

The different macrolides

Erythromycin

The only form of natural erythromycin which has antibacterial activity is erythromycin base. Unfortunately, it is difficult to administer the drug in this form because the base is not very soluble in water and is destroyed by the acid in the stomach. Several different formulations of erythromycin have therefore been developed with the aim of achieving satisfactory levels of the active drug in the body. Normally the drug is administered as an ester:

erythromycin ethyl succinate
erythromycin propionate
erythromycin estolate

or as a salt:

erythromycin stearate
erythromycin lactobionate (for intravenous administration).

These are converted into the active base after they have been administered.

Like the other macrolides, erythromycin rarely causes serious side effects. However, erythromycin estolate can influence liver functions.

Another problem associated with erythromycin is its potential to interact with other drugs. It is known to interact with theophylline, carbamazepine and digoxin to potentiate their effects, probably by interfering with their metabolism.

Spiramycin

Spiramycin has a spectrum of activity which differs only slightly from that of erythromycin. Its MICs are generally higher and some strains of certain bacteria (notably strains of Bordetella pertussis and Neisseria gonorrhoea) have become resistant. Unlike erythromycin, spiramycin is very active against the vegetative and non-cystic forms of Toxoplasma gondii, the protozoan which causes toxoplasmosis.

Spiramycin base is relatively resistant to stomach acid and is well absorbed from the small intestine. After absorption the drug becomes concentrated in many tissues (particularly in the lungs, spleen and tonsils) and in many body secretions (notabably saliva and breast milk). The high tissue concentrations of the drug persist for a long time, which means that spiramycin need only be administered twice a day.

Apart from those indications which are common to all the macrolides, spiramycin may be prescribed for the treatment of extra-ocular toxoplasmosis in otherwise healthy subjects or in pregnant women. It is moderately effective but has the advantage of being tolerated much better than the alternative treatment of pyrimethamine and a sulphonamide.

Oleandomycin

Oleandomycin is usually administered in the form of its triacetyl ester, troleandomycin. This compound is better absorbed than oleandomycin base.

Troleandomycin poses problems of prescription because it can interact with certain other drugs. If it is used at the same time as the ergotamine-type antimigraine drugs, the vasoconstricting effects of these drugs are potentiated. This may result in ischaemia of the extremities and, in the worst instances, in gangrene. When co-prescribed with theophylline or carbamazepine, troleandomycin raises their blood levels. This increases the incidence of side effects eg with theophylline namely nausea, headache and convulsions. When used with preparations containing oestrogens and progestogens, troleandomycin increases the risk of liver damage. Troleandomycin may also cause liver damage when used on its own, especially if treatment is prolonged for more than ten days.

All macrolides have the NB property of good tissue penetration

Josamycin

Josamycin has a spectrum similar to that of the other macrolides. It is also active, at low concentrations, against Clostridium perfringens and Bacteroides fragilis.

Josamycin does not appear to interact with theophylline. However, the drug does slow the elimination of carbamazepine administered to healthy subjects and a case of ischaemia has been reported following the simultaneous administration of josamycin and ergotamine tartrate.

Midecamycin

The spectrum and indications of midecamycin are the same as those of the other macrolides. Midecamycin is secreted in breast milk and breast feeding might therefore have to be suspended during treatment with this drug.

To date, no drug interactions with midecamycin have been reported. It should be noted that the drug is not used extensively at present and little has been published about its tolerance and its efficacy.

Roxithromycin

From research done at the laboratories of Roussel Uclaf, this recently developed new ether-oxime derivative of erythromycin-A displays an antibacterial

activity similar to that of erythromycin[5]. Due to its excellent pharmacokinetic profile (with a significantly improved bioavailability and relatively long half-life)[15] and better safety and tolerability, roxithromycin should play an important role as effective, safe treatment of many important infectious diseases including respiratory tract infections, sexually transmitted diseases and skin infections.

● *The mode of action of roxithromycin*

Roxithromycin exerts antibacterial effects by interfering with protein synthesis by the ribosomes in the bacterial cell [3 4 16]. Its clinical effects against many bacteria are enhanced because it concentrates inside phagocytic cells.

The mode of action of roxithromycin has been found to be the same as that of the other macrolide antibiotics. It inhibits the synthesis of proteins inside the bacterial cell by interfering with the reactions at the ribosomes in which amino acids brought in by transfer RNA are built up into the protein chains specified by messenger RNA.

A study carried out with ribosomal preparations from *Escherichia coli* and *Staphylococcus aureus* has shown that roxithromycin binds specifically to the 50-S component of the ribosome. It does not bind to the 30-S component, in contrast to tetracyclines and aminoglycosides.

● *Intracellular activity*

Certain micro-organisms are able to survive and develop inside phagocytic cells. Clearly, antibiotics which can penetrate phagocytes[16 17] will have an advantage in the treatment of infections caused by such micro-organisms.

Few antibiotics accumulate to any extent inside phagocytic cells. For example, the concentrations of penicillins, cephalosporins and aminoglycosides which occur in polymorphonuclear leucocytes and macrophages are no greater than their extracellular concentrations. However, macrolide antibiotics are found to penetrate phagocytes well. In particular, roxithromycin is highly concentrated inside polymorphonuclear leucocytes[16 17]. Its intracellular concentrations are about thirty times greater than its extracellular concentrations. In comparison, intracellular concentrations of erythromycin are only about ten times the extracellular levels.

It has been found that, once inside the phagocytic cell, roxithromycin tends to concentrate in the *lysosomes*. These are the structures which contain the destructive enzymes normally used in phagocytosis. The pathogens which survive inside phagocytes are also bound to these structures so that roxithromycin could be brought into close contact with them.

We should therefore expect roxithromycin to be particularly effective against those micro-organisms which are able to develop intracellularly including Chlamydiae, Rickettsiae, Toxoplasma, *Legionella, Campylobacter, Listeria* and *Brucella* Species.

Conclusion

The macrolides are used to treat many of the infections commonly encountered in general practice and some other clinically important organisms such as Legionella, Mycoplasma, Rickettsiae, Chlamydia and others.

They are popular because they are effective and well tolerated by a wide range of patients including children and pregnant women.

Recent developments (such as with roxithromycin) offer additional benefits due to improved safety profiles and special pharmacokinetic properties.

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