Macrolides*

Overview

The macrolide class antibiotics include erythromycin, clarithromycin and azithroymcin. The prototypical macrolide, erythromycin, became available in the 1950s. Macrolide antibiotics are characterized typically by a large lactone ring within their structure. Macrolides are classed according to the number of lactone ring components; the 12-membered, 14-membered and 16-membered groups. Erythromycin, oleandomycin and troleandomycin belong to the 14-membered group. Spiramycin, josamycin and tylosin are the only 16-member macrolides in clinical use. None of the 12-member macrolides are used clinically.

Azithromycin (technically an azolide) and clartihromycin are semi-synthetic derivatives of erythromycin that are characterized by increased tissue penetration and improved gastrointestinal tolerance. These newer derivatives also enjoy an increased spectrum of activity, especially against Gram-negative organisms. Macrolide preparations are in reality, complex mixtures of related antibiotics. They vary from one another by the chemical substitutions on the carbon atoms within their structure and the substitutions on the aminosugars and neutral sugars. These substances are chemically alkaline due to the presence of a dimethylamino group in the structure. They are poorly soluble in aqueous solutions but dissolve in more polar organic solvents. They are inactivated in highly acidic and highly basic environments (pH <4 or >10), but are most active in a pH range of 7.8 to 8. Pharmaceutical preparations are usually supplied in more stable ester forms, such as acetylates, estolates, lactobionate, succinates, propionates and stearates.

Macrolides inhibit protein synthesis by reversibly binding to the 50S ribosomal subunit, also targeted by the lincosamides and chloramphenicol. Bacterial growth is inhibited by induction of the separation of peptidyl transfer RNA from the ribosome during the elongation phase. This effect is confined to rapidly dividing bacteria and mycoplasmas. For the most part, the macrolides are bacteriostatic.

Ribosomal methylase, encoded by the *erm* gene, can precipitate resistance to macrolides by alteration of the ribosomal binding site. This mechanism has resulted in development of highly resistant enterobacteriaceae, enterococci, *S. aureus* and streptococci. High levels of resistance of *S pneumoniae* mediated by this mechanism have been noted within the United States. In fact 20% to 25% of *S. pneumoniae* isolates are now resistant to macrolides in some areas of the country. Increased resistance to *S. pneumoniae* and *S. pyogenes* is likely the result of increased macrolide use, especially the use of azithromycin. The gene that encodes for an efflux mechanism, *mef*, also brings about a moderate degree of resistance by *S. pneumoniae*. Increases in macrolide resistance in *H. influenzae* (in some cases over 90% of the strains are resistant), have also been reported in recent years. This resistance is brought about by an efflux pump that actively rids the cells of the macrolide. This efflux pump is chromosomally mediated by genes referred to as *acrAB* genes. Resistance of Pseudomonas species and other Gram-negative bacteria, enterococci and staphylococci may be precipitated by chromosomally controlled alteration of permeability or uptake of the drug. Generally, macrolides cannot

penetrate the cell walls of Gram-negative organisms. Cross resistance both among macrolides and with clindamycin has been reported.

Macrolides are used in therapy for systemic and local infections. In veterinary medicine these drugs are indicated for treatment of upper respiratory tract infections, bronchopneumonia, bacterial enteritis, metritis, pyodermatitis, urinary tract infections and arthritis. Formulations for mastitis therapy are available. The high concentrations in milk and short withdrawal times render the macrolides a practical choice in therapy for mastitis. Macrolides are effective against most aerobic and anaerobic Gram-positive organisms. They are sometimes considered penicillin alternatives for the treatment of staphylococci and streptococci. In general these drugs are not effective against Gram-negative bacteria, protozoa or fungi, but are active against mycoplasmas, treponemes, some rickettsiae and some strains of *Pasteurella, Haemophilus* and *Neisseria* species (azithromycin is the most effective against *Neisseria* species). *Bacteroides fragilis* exhibits moderate susceptibility to the macrolides. Macrolides are active also against atypical mycobacteria and *Mycobacterium* species. Newer macrolides have a broader spectrum of activity than erythromycin (see erythromycin section), especially against *Mycobacterium avium* (particularly clarithromycin), non-tuberculous mycobacteria, *Hemophilus influenzae, Chlamydia trachomatis* and *Chlamydophila pneumoniae.* Azithromycin is the macrolide with the best Gram-negative activity of the group and is effective against *Shigella* and *Salmonella* species. However azithromycin is less active than erythromycin against staphylococci and streptococci, but more active against *Legionella* species and *Haemophilus influenzae*, although resistance in *H. influenzae* is increasing. In vitro synergism is seen when macrolides are used with cefamandole (against *Bacteroides fragilis*), ampicillin (against *Nocardia asteroides*), rifampin (against *Rhodococcus equi*), and ceftriaxone (along with azithromycin against community acquired pneumonia). Clarithromycin is used in combination with other drugs in therapy for disseminated *Mycobacterium avium-intracellulare* (MAC) in AIDS patients and in therapy for *Helicobacter pylori*. Clarithromycin is also used alone for prophylaxis for MAC in patients at risk.

Macrolides can be inactivated by gastric acid. Accordingly, oral preparations are often stable salts, esters, or they feature enteric coatings. The drug, however, is readily absorbed from the gastrointestinal tract, although in ruminants absorption from the ruminoreticulum is delayed and unreliable. Macrolides are distributed well in tissues; in fact macrolides are concentrated in macrophages and some other cells, often reaching greater than twenty times the plasma concentration. Macrolides also concentrate in the spleen, liver, kidney and especially the lungs. They are well distributed in pleural and ascitic fluids, but not in the cerebrospinal fluid unless meningeal inflammation is present. In addition, macrolides accumulate in bile and milk. The concentration in milk can exceed that in plasma, especially in the presence of mastitis. Macrolides are excreted primarily in bile (> 60%), but the proportion excreted in urine can increase when administered parenterally.

Side effects and toxicities are rare for most macrolides, however fatal gastrointestinal disturbances have occurred in horses. Hypersensitivity has also been infrequently reported. Tilmicosin is the most toxic of the macrolides. Cardiac toxicity with tilmicosin

has occurred and the drug is contraindicated in swine. Cows have died after intravenous administration of tilmicosin. It is recommended that macrolides not be used concurrently with chloramphenicol or the lincosamides due to competition for the same ribosomal target site. Macrolide use may affect certain laboratory tests, possibly causing increases in alkaline phosphatase, bilirubin, sulfobromophthalein (BSP®), total white blood cell count, eosinophil count, AST and ALT. Decreases in cholesterol are also possible.

***References available by request. Call the Infectious Disease Epidemiology Section, Office of Public Health, Louisiana Department of Health and Hospitals (504-219-4563)**