

PHARMACOLOGY-III

UNIT-II

TOPIC: Macrolides



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*Shaping Lives...
Empowering Communities...*

Prepared By

Sucharita Babu

Assistant Professor

School of Pharmacy and Life Sciences,

Centurion University of Technology and Management

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. Erythromycin [er-ith-roe-MYE-sin] was the first of these drugs to find clinical application, both as a drug of first choice and as an alternative to penicillin in individuals who are allergic to β -lactam antibiotics. The newer members of this family,

clarithromycin (a methylated form of erythromycin) and azithromycin (having a larger lactone ring), have some features in common with, and others that improve on, erythromycin.

A. Mechanism of action

The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis. They may also interfere at other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be bactericidal at higher doses. Their binding site is either identical or in close proximity to that for clindamycin and chloramphenicol.

B. Antibacterial spectrum

Erythromycin: This drug is effective against many of the same organisms as penicillin G therefore, it is used in patients who are allergic to the penicillins. Clarithromycin: This antibiotic has a spectrum of antibacterial activity similar to that of erythromycin, but it is also effective against *Haemophilus influenzae*. Its activity against intracellular pathogens, such as *Chlamydia*, *Legionella*, *Moraxella*, and *Ureaplasma* species and

Helicobacter pylori, is higher than that of erythromycin.

3. Azithromycin: Although less active against streptococci and staphylococci than erythromycin, azithromycin is far more active against respiratory infections due to *H. influenzae* and *Moraxella catarrhalis*. Azithromycin is now the preferred therapy for urethritis caused by *Chlamydia trachomatis*. It also has activity against *Mycobacterium avium* intracellular are complex in patients with acquired immunodeficiency syndrome and disseminated infections.

4. Telithromycin: This ketolide drug has an antibacterial spectrum similar to that of azithromycin. Moreover, the structural modification within ketolides neutralizes the most common resistance mechanisms (methylase-mediated and efflux-mediated) that make macrolides ineffective.

C. Resistance

Resistance to erythromycin is becoming a serious clinical problem. For example, most strains of staphylococci in hospital isolates are resistant to this drug. Several mechanisms have been identified:

1) the inability of the organism to take up the antibiotic or the presence of an efflux pump, both of which limit the amount of intracellular drug;

2) a decreased affinity of the 50S ribosomal subunit for the antibiotic, resulting from the methylation of an adenine in the 23S bacterial ribosomal RNA; and

3) the presence of a plasmid-associated erythromycin esterase. Both clarithromycin and azithromycin show cross-resistance with erythromycin, but telithromycin can be effective against macrolide-resistant organisms.

Administration: The erythromycin base is destroyed by gastric acid. Thus, either enteric-coated Tablets or esterified forms of the antibiotic are administered. All are adequately absorbed upon oral administration. Clarithromycin, azithromycin, and telithromycin are stable to stomach acid and are readily absorbed.

Food interferes with the absorption of erythromycin and azithromycin but can increase that of clarithromycin.

Azithromycin is available for intravenous infusion, but intravenous administration of erythromycin is associated with a high incidence of thrombophlebitis.

Distribution:

Erythromycin distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuses into prostatic fluid, and it has the unique characteristic of accumulating in macrophages.

All four drugs concentrate in the liver. Inflammation allows for greater tissue penetration. Similarly, clarithromycin, azithromycin, and telithromycin are widely distributed in the tissues. Serum levels of azithromycin are low; the drug is concentrated in neutrophils, macrophages, and fibroblasts. Azithromycin has the longest half-life and largest volume of distribution of the four drugs.

Fate: Erythromycin and telithromycin are extensively metabolized and are known to inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system. Interference with the metabolism of drugs such as theophylline and carbamazepine has been reported for clarithromycin. Clarithromycin is oxidized to the 14-hydroxy derivative, which retains antibiotic activity.

Excretion: Erythromycin and azithromycin are primarily concentrated and excreted in an active form in the bile. Partial reabsorption occurs through the enterohepatic circulation. Inactive metabolites are excreted into the urine. In contrast, clarithromycin and its metabolites are eliminated by the kidney as well as the liver, and it is recommended that the dosage of this drug be adjusted in patients with compromised renal function.

Adverse effects

Epigastric distress: This side effect is common and can lead to poor patient compliance for erythromycin.

Clarithromycin and azithromycin seem to be better tolerated by the patient, but gastrointestinal problems are their most common side effects

Cholestatic jaundice: This side effect occurs especially with the estolate form of erythromycin, presumably as the result of a hypersensitivity reaction to the estolate form (the lauryl salt of the propionyl ester of erythromycin). It has also been reported for other forms of the drug.

Ototoxicity: Transient deafness has been associated with erythromycin, especially 3. at high dosages.