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MACROLIDES

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 Î²-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- intracellulare 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 (methylasemediated 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

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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.

CHLORAMPHENICOL

Chloramphenicol is active against a wide range of gram-positive and gram-negative organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

A. Mechanism of action

The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction. Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating *chloramphenicol* levels, producing bone marrow toxicity.

B. Antimicrobial spectrum

Chloramphenicol, a broad-spectrum antibiotic, is active not only against bacteria but also againstother microorganisms, such as rickettsiae. Pseudomonas aeruginosa is not affected, nor are the chlamydiae. *Chloramphenicol* has excellent activity against anaerobes. The drug is either bactericidal or (more commonly) bacteriostatic, depending on the organism.

C. Resistance

Resistance is conferred by the presence of an R factor that codes for an acetyl coenzyme A transferase. This enzyme inactivates *chloramphenicol*. Another mechanism for resistance isassociated with an inability of the antibiotic to penetrate the organism. This change in permeability may be the basis of multidrug resistance.

D. Pharmacokinetics

Chloramphenicol may be administered either intravenously or orally.It is completely absorbedvia the oral route because of its lipophilic nature, and is widely distributed throughout the body.It readily enters the normal CSF. The drug inhibits the hepatic mixed-function oxidases. Excretion of the drug depends on its conversion in the liver to a glucuronide, which is then secreted by the renal tubule. Only about 10 percent of the parent compound is excreted by glomerular filtration. *Chloramphenicol* is also secreted into breast milk.

E. Adverse effects

The clinical use of *chloramphenicol* is limited to life-threatening infections because of the serious adverse effects associated with its administration. In addition to gastrointestinal upsets, overgrowth of Candida albicans may appearon mucous membranes.

Anemias: Hemolytic anemia occurs in patients with low levels of glucose 6-phosphate dehydrogenase. Other types of anemia occurring as a side effect of *chloramphenicol* include reversible anemia, which is apparently dose-related and occurs concomitantly with therapy, and aplastic anemia, which although rare is idiosyncratic and usually fatal.

Gray baby syndrome: This adverse effect occurs in neonates if the dosage regimen of *chloramphenicol* is not properly adjusted. Neonates have a low capacity to glucuronylate the antibiotic, and they have underdeveloped renal function. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes. This leads to poor feeding, depressed breathing,

cardiovascular collapse, cyanosis and death. Adults who have received very high doses of the drug can also exhibit this toxicity.