Anti-Microbial Drugs

Lecture 5

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Macrolides:
Erythromycin was the 1\textsuperscript{st} of macrolides to find clinical application, both as a drug of choice and as an alternative to penicillin in individuals who are allergic to B-lactam antibiotics. The newer members of this family are clarithromycin and azithromycin. Telithromycin is the first ketolide that has been approved.

Mechanism of Action:
The macrolides bind irreversibly to a site on the 50s subunit of 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.

Antibiotic Spectrum:
1. Erythromycin: this drug is effective against many of the same organisms as penicillin G. Erythromycin is effective against gram +ve organisms, especially Staphylococci, Streptococci, Pneumococci and Corynebacteria. Gram –ve organisms such as Neisseria species, bordetella and legionella are susceptible. Spirochetes (Treponema pallidum), mycoplasma pneumoniae, Chlamydia pneumoniae and Chlamydia trachomatis are also susceptible.
2. **Clarithromycin**: this antibiotic has a spectrum of antibacterial activity similar to that of Erythromycin, but:
   a. It's also effective against Haemophilus influenzae.
   b. It has a higher activity against Chlamydia, Legionella, Moraxella, Ureaplasma species and Helicobacter pylori.
   c. It's active against Mycobacterium-avium intracellular complex (MAC) in AIDs patients with disseminated infections.

3. **Azithromycin**: Azithromycin and erythromycin are virtually identical with respect to antimicrobial activity except that Azithromycin is:
   a. Less active against streptococci and staphylococci.
   b. Far more active against respiratory infections due to H. influenzae and Moraxella catarrhalis.
   c. The preferred therapy for urethritis caused by Chlamydia trachomatis.
   d. Active against mycobacterium avium intracellular complex (MAC) in AIDs patients with disseminated infections.

4. **Telithromycin**: this drug has an antibacterial spectrum similar to that of azithromycin. The structural modification within ketolides neutralizes the most common resistance mechanisms that make macrolides ineffective.
Resistance:

Resistance:

Resistance to erythromycin became a serious clinical problem. Several mechanisms have been identified: (1) the inability of the organism to take up the antibiotic or the presence of an efflux pump, (2) a decreased affinity of the 50s ribosomal subunit for the antibiotic (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.

Pharmacokinetics:

1. **Administration:**
   The erythromycin base is destroyed by gastric acid, thus either enteric coated tablets or esterified forms of the antibiotic are administrated. 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 IV infusion.

2. **Distribution:**
   Erythromycin distributes well to all body fluids except the CSF. It's one of the few antibiotics that diffuse into prostatic fluid and it has the unique characteristics of accumulating in macrophages. 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 (>40 hours) and largest volume of distribution among the four drugs.

3. **Fate:**
   Erythromycin, clarithromycin and telithromycin are metabolized and are known to inhibit the oxidation of a number of drugs through their interaction with cytochrome p450 system.

4. **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 in urine.

**Adverse effects:**

1. **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 GIT problems are their most common side effects.
2. **Cholestatic jaundice:** this side effect occurs especially with estolate form of erythromycin, presumably as the result of a hypersensitivity reaction to the estolate form.
3. **Ototoxicity:** transient deafness has been associated with erythromycin, especially at high doses.
4. **Contraindications:** patients with hepatic dysfunction should be treated with caution with erythromycin, azithromycin or telithromycin because these drugs accumulate in the liver.
5. **Interactions:** Erythromycin, clarithromycin and telithromycin inhibit the hepatic metabolism of some drugs which can lead to toxic accumulation of these compounds e.g. astemizole, terfenadine, carbamazepine, valporate, theophylline, warfarin and cyclosporine. An interaction with
digoxin may occur. In this case the antibiotic eliminates a species of intestinal flora that ordinarily inactivates digoxin, thus leading to greater reabsorption of the drug from the enterohepatic circulation. No interactions have been reported for azithromycin.

**Chloramphenicol:**

It's active against a wide range of gram +ve and gram –ve organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

**Mechanism of Action:**

The drug binds to the bacterial 50s ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction. Protein synthesis in mammalian mitochondrial ribosome may be inhibited at high circulating levels, producing bone marrow toxicity.

**Antibacterial Spectrum:**

Chloramphenicol, a broad spectrum antibiotic, is active not only against bacteria but also against other 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.

**Resistance:**

1. Clinically significant resistance is due to production of chloramphenicol acetyl transferase, a plasmid encoded enzyme that inactivates the drug.
2. Inability of the antibiotic to penetrate the organism.

**Pharmacokinetics:**

Chloramphenicol is completely absorbed via the oral route, widely distributed throughout the body and readily enters the normal CSF. The drug inhibits the hepatic cytochrome P450 system. Excretion of the drug depends on its conversion in the liver to a glucuronide, which is then secreted by the renal tubule. Chloramphenicol is also secreted into breast milk.

**Adverse Effects:**

The clinical use of chloramphenicol is limited to life-threatening infections because of the serious adverse effects associated with its administration.

1. **GIT upsets.**
2. Overgrowth of *Candida albicans* may appear on mucous membrane.
3. **Anemia:**
   a. Hemolytic anemia occurs in patients with low levels of glucose-6-phosphate dehydrogenase.
   b. Reversible anemia, which is apparently dose-related and occurs concomitantly with therapy.
c. Aplastic anemia, which although rare is idiosyncratic and usually fatal. It's independent of dose and may occur after therapy has been ceased.

4. Gray Baby Syndrome: occurs in neonates if the dosage regimen of chloramphenicol is not properly adjusted. Neonates have a low capacity to glucuronylate the antibiotic and they've underdeveloped renal function. The drug accumulates to the levels that interfere with the function of mitochondrial ribosomes. This leads to depressed breathing, cardiovascular collapse, cyanosis and death.

5. Interactions: Chloramphenicol inhibits some of the hepatic mixed-function oxidase and thus blocks the metabolism of many drugs, thereby elevating their concentration and potentiating their effects.

Clindamycin:

Clindamycin has a mechanism of action and resistance similar to those of erythromycin. Clindamycin is employed primarily in the treatment of infections caused by anaerobic bacteria, such as Bacteriodes fragilis, which often causes abdominal infections associated with trauma. However, it's also significantly active against non-enterococcal gram +ve cocci. It distributes well into all body fluids except CSF. Penetration into bone occurs even in the absence of inflammation. The most serious adverse effect is potentially fatal pseudomembranous colitis caused by overgrowth of Clostridium difficile, which elaborates necrotizing toxins. Oral administration of either metronidazole or vancomycin is usually effective in controlling this serious problem.

Metronidazole is the drug of choice to treat pseudomembranous colitis.
**Quinupristin/Dalfopristin:**

Quinupristin/Dalfopristin is a mixture of 2 streptogramines. The drug is reserved for the treatment of vancomycin resistant Enterococcus faecium (VRE). The combination drug is bacteriostatic and has a long post antibiotic effect (PAE). It is active primarily against gram-positive cocci.

Adverse effects include venous irritation, arthralgia and hyperbilirubinemia. Quinupristin/Dalfopristin inhibits cytochrome P450 isozyme.

**Linezolid:**

Linezolid was introduced recently to combat resistant gram +ve organisms, such as methicillin and vancomycin resistant Staphylococcus aureus, vancomycin-resistant Enterococcus faecium and Enterococcus faecalis, and penicillin-resistant streptococci. Linezolid is completely absorbed on oral administration. It is well tolerated, with some reports of GIT upset.
Summary of Protein Synthesis Inhibitors:
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