PHARMACOLOGY

Modified slides no.5
Writer: Sra'a Ali
Corrector: Abdallah Aburoman
Doctor: Suheil Zmeili

■ **Every note in this lecture is additional**

Macrolide antibiotics

■ NOTE: memorize memorize memorize the slides to get the full mark.

Static, contain lactone ring + sugars (12-22 carbon lactone ring linked to sugars)

Include:

■ It has a unique chemical structure

Erythromycin; Clarithromycin; Azithromycin

Oleandomycin; Telithromycin; Roxithromycin; Spiramycin…etc

Erythro. has high activity against G+ve bacteria, little effect against G-ve bacteria

■ due to their different cell wall structure and composition.

■ **Additional information: The structural modifications in clarithromycin and azithromycin allow enhanced activity against a wider range of pathogens, and increased effectiveness against certain bacteria that were less responsive to erythromycin.**

Clarithromycin and Azithromycin are more active than erythromycin against several gram negative bacteria as well as Mycoplasma pneumonia, Helicobacter pylori, Toxoplasma gondii, cryptosporidia and several atypical mycobacteria

Macrolides differ in their pharmacokinetic properties ($t_{1/2}$)

■ **Additional information: Macrolide antibiotics do indeed differ in their pharmacokinetic properties, including half-life (t1/2). Azithromycin, for instance, has an extended half-life ,clarithromycin has a moderate half-life, while erythromycin generally has a shorter half-life.**

■ NOTE: A solution is a homogeneous mixture, While a suspension is a heterogeneous mixture

Erythromycin is available in 250 and 500 mg tab. and 125mg, 200mg, 400mg/5ml susp. and topical gels and solutions. (dose 250mg x 4 daily or 500mg x 2 for 10-14 days)

Azithromycin is available in 250 & 500 mg tablet & 100 & 200mg/5ml suspension dosage forms

Total dose of azithromycin=1.5-2.5g (3days therapy or 5 days therapy)

■ Additional information: The dosing regimen of azithromycin often allows for a shorter course of treatment due to its extended half-life, which allows for longer drug concentrations in the body even after the completion of the dosing regimen.

■ NOTE: This is just to give you an idea of how the half-life of the drug affects the dosage

Macrolides are considered drugs of choice to treat Corynbacteria diphtheria and mycoplasma pneumonia (along with tetracyclines)

■ NOTE: both macrolide antibiotics and tetracyclines are considered effective treatment options.

- Macrolides mechanism of action:

Reversibly bind 23S rRNA of the 50S subunit of the ribosome inhibiting translocation during protein synthesis

■ NOTE: So it interferes with the translocation process.

Considered alternatives to PNC's (particularly erythromycin) (second line drug) to treat Strep. and Staph. infections e.g. tonsillitis in patients with penicillin allergy

Considered 2nd line therapy to PNC's for Rx of dental infections (never 1st line because they are static; resistance develops easily to them, less effective than PNC's in orodental infections and more toxic)

Given orally; distribute well but cross well inflamed meninges

- For patients with penicillin allergy, penicillin alternatives, especially erythromycin, are second-line (alternative) treatments for various infections caused by streptococcal, staphylococcal bacteria and in some cases of dental infections.

■ **NOTE: Side effects are very important in the exam so memorize them well.**

▶ Side effects to macrolide antibiotics:

- **GIT irritation (major & most frequent)**
- **Allergy**
- **Cholestatic hepatitis (direct toxic effect or hypersensitivy reaction; reversible; more common in adults; more common with estolate form of erythromycin=the gastric acid resistant form of erythromycin)**

Chloramphenicol

Bacteriostatic

Broad spectrum (G+ve & -ve bacteria and anaerobes)

The drug of choice to treat H. influenza meningitis and epiglotitis, brain abscesses and Salmonella infections (typhoid and paratyphoid fever) (recent restriction due to toxicity)

■ **Additional information: Chloramphenicol associated with potential toxicity. One of the most significant concerns is the risk of bone marrow suppression, which can lead to aplastic anemia.**

▶ Chloramphenicol mechanism of action:

Binds to rRNA of 50S subunit of the ribosome inhibiting transpeptidation during protein synthesis

Highly lipid soluble, orally effective and widely used locally on eye

The best antibiotic that crosses BBB

Metabolized to inactive metabolites by conjugation (glucuronide)

■ **Additional information**: Chloramphenicol metabolism occurs in the liver.

■ After metabolism, Chloramphenicol is converted into inactive metabolites primarily through conjugation processes, such as glucuronidation. These inactive metabolites are then excreted from the body through urine or bile.

- **Cholramphenicol side effects:**

- Reversible dose-related bone marrow depression
- Aplasic anemia (allergic in nature; fatal; none dose-related)
- Gray-baby syndrome (fatal toxic reaction; abdominal distension, severe vomiting, cyanosis (bluish discoloration of a skin) hypothermia, collapse)
- Optic neuritis, nausea, vomiting, diarrhea

■ **Affects the bone marrow!! So it will affect the formation of RBC, WBC, and platelets**

Spectinomycin

Bacteriostatic

Chemically related to aminoglycoside

- It shares structural and chemical similarities with aminoglycoside antibiotics.

It binds to the 30S subunit of the bacterial ribosome and inhibits protein synthesis

Alternative to PNC's and cephalosporins to treat uncomplicated gonococcal infection in pts allergic to PNC's and cephalosporins

A single IM injection is adequate

- only a single intramuscular (IM) injection for effective treatment!

Tetracyclines

Bacteriostatic

Broad spectrum (antibacterial, antiparasitic…)

Have different structure but similar MOA

Inhibitors of bacterial protein synthesis (bind to the 30S ribosomes)

Somewhat selective since they penetrate bacterial plasma membrane by energy dependent mechanism which is absent in human cells

- involves active transport through specialized channels or transporters present in bacterial membranes. This mechanism of entry is absent in human cells, providing some selectivity in targeting bacteria while minimizing the impact on human cells.

▶ Mechanisms of bacterial resistance to tetracyclines:

- Altered bacterial permeability to tetracycline

■ **Reduced permeability limits the entry of the antibiotic into the bacterial cell, reducing antibiotic efficacy in inhibiting bacterial growth.**

- Increased efflux of tetracyclines by bacterial energy dependent mechanism leading to lower intracellular antibiotic concentration

- Altered bacterial protein structure

■ **pump tetracycline antibiotics out of the bacterial cell**

■ **Additional information:** **Bacteria can alter their protein structures as a mechanism of resistance through genetic mutations. One common way is by acquiring mutations in the genes that code for the target proteins of antibiotics. This can lead to changes in the structure of these proteins, making them less susceptible to the inhibitory or killing effects of the antibiotics.**

- **Tetracyclines include:**

Tetracycline

Chlortetracycline

Oxytetracycline

Demeclocycline

Doxycycline

Minocycline

Methacycline

▶ Tetracyclines spectrum of activity:

Effective against G+ve and -ve bacteria

Considered drugs of choice to treat:

- **Rickettsia**
- **Mycoplasma pneumonia (erythromycin 2nd line)**
- **Clamydia**

Also effective against certain protozoal infections, long term treatment of acne and vibrio cholera

- **NOTE: The first-line treatment for cholera is rehydration**
- **Acne includes some bacteria that produce lipase, which contributes to skin irritation and inflammation, leading to redness and swelling.**

■ **Doxycycline has a longer duration of action compared to some other tetracyclines, allowing for once-daily dosing.**

▶ Pharmacokinetics of tetracyclines:

- Differ in DOA, Doxycycline has the longest DOA (given once daily); available also in topical dosage forms (creams; lotions; oint.; ophthalmic, ear & nasal drops…)
- Could be given orally and parenterally (IV)
- Food, Mg^{++}, AL^{+++} and Ca^{++} (milk) form complexes with tetracyclines ↓ absorption of tetracyclines

■ **The formation of these complexes reduces the availability of free tetracycline in the GIT, decreasing its absorption into the bloodstream. As a result, the effectiveness of the antibiotic can be compromised when taken simultaneously or close in time to these substances.**

- Distribution good but do not cross BBB
- Excretion

  In feces (Mino-"minocycline", Oxy- "oxytetracycline"& chlortetracycline)

  In urine (other tetracyclines)

- **Tetracyclines toxicity & side effects:**

- Dental staining; yellowish to brownish (irreversible) (incorporate into growing teeth & bones) (contraindicated during pregnancy & in children <8yrs old)

■ nausea (N), vomiting (V), and diarrhea (D). These symptoms might occur due to the antibiotics effect on the gastrointestinal tract.

■ can increase sensitivity to sunlight, leading to an exaggerated sunburn response.

- N, V, D
- Hepatotoxicity
- Photosensitivity; more with Demeclo- and Doxycycline
- Nephrotoxicity; more in patients with renal disease and with administration of other nephrotoxic antibiotics; least with Doxy- and Minocycline
- Increased intracranial pressure
- Superinfection with Candida albicans and C. difficile

Lincomycin & Clindamycin

Static

Inhibitors of protein synthesis (bind exclusively to the 50S subunit of bacterial ribosomes, thus suppressing protein synthesis by disrupting the formation of the 70S initiation complex and by inhibiting the aminoacyl translocation step of peptide bond formation)

Have good activity against G+ve (Strep; Staph), Enterobacteriaceae (Salmonella, Shigella, Escherichia, Klebsiella, Proteus); Vibrioaceae (Vibrio Cholera); Pasteurellaceae (Pasteurella, Haemophilus)…

■ These antibiotics have demonstrated efficacy in treating bone and dental infections.

Demonstrate good effect against bone and teeth infections and Corynebacteria acne

- Side effects (limit their uses):

■ bacterium associated with acne.

- Skin rashes
- Hepatotoxicity
- Pseudomembraneous colitis

Rx: stop drug & give vancomycin ± metronidazole

- Contraindications:

Hepatic impairment, previous history of pseudomembranous colitis

■ because they may exacerbate these conditions.

Locally effective antimicrobials

- **Antimicrobial agents are known for their bactericidal activity against some Gram-negative bacteria.**

Polymyxins (Polymyxin B & Polymyxin E = Colistin)

Cidal

Interfere with function or permeability of the plasma membrane

Have good activity against G-ve bacteria & high activity against Pseudomonas

Very nephrotoxic (more than aminoglycosides)

Their use is restricted to topical preparations in combination with Bacitracin (cell wall inhibitor) & neomycin (creams, oint's, eye & ear drops…)