

Protein Synthesis Inhibitors

Introduction

- A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome, which has components that differ structurally from those of mammalian cytoplasmic ribosome.
- In general, the bacterial ribosome is smaller(70s) than the mammalian ribosome (80s)

Classes

Tetracyclines

- Demeclocycline
- Doxycycline
- Minocycline
- Tetracycline

Glycylglycine

- Tigecycline

Aminoglycoside

- Amikacin
- Gentamicin
- Neomycin
- Streptomycin
- Tobramycin

Macrolide

- Azithromycin
- Clarithromycin
- Erythromycin
- Telithromycin

Others

- Chloramphenicol
- Linezolid
- Clindamycin
- quinupristin

Tetracycline

- Tetracycline are commonly broad spectrum antibiotics having bacteriostatic antimicrobial activity.
- **Chemistry:**

All tetracycline have shown the basic structure of 4 cyclic rings with different substituents of 3R groups.

Tetracyclines are available as hydrochlorides which are more soluble than free tetracyclines.

Mechanism of Action

- Tetracycline are bacteriostatic
- They act by inhibiting bacterial protein synthesis.
- Tetracycline enter microorganisms partly by passive diffusion and partly by an energy dependent process of active transport.
- Tetracycline binds to 30S subunit of bacterial ribosome and inhibit attachment of aminoacyl-tRNA to acceptor site on the mRNA-ribosome complex.
- This prevent the addition of amino acids to growing polypeptide chain and inhibit protein synthesis and activity of microorganisms.

Antibacterial Spectrum

- As broad spectrum bacteriostatic antibiotic the tetracyclines are effective against gram +ive and gram-ive bacteria as well as against organisms other than bacteria.

Tetracyclines are drug of choice for:

1. Lyme Disease (spirochetal disease caused by bite of infected ticks) Skin lesion,headach, fever followed by meningoencephilitis and eventually arthritis. (a single 200mg dose of doxycycline given within 72hr after a bite, can prevent disease).

2. *Mycoplasma pneumoniae*: is a common cause of community acquired pneumonia in young adults. Treatment with doxycycline.

3. Cholera: cholera is caused by *Vibrio cholerae* ingested in fecally contaminated food and water, where it secretes enterotoxin which causes diarrhea. Treatment with doxycycline reduces the number of intestinal vibrios and fluid replacement.

Resistance

- Wide spread resistance to tetracycline limit their clinical use the most commonly encountered, naturally occurring resistance (R) factor confers an inability of organism to accumulate the drug thus producing resistance.
- Decrease intracellular accumulation owing to either impaired influx or increase efflux by an active transport protein pump.
- Ribosome protection owing to production of proteins that interfere with tetracycline binding to target site
- Enzymatic inactivation of tetracycline.

Pharmacokinetic

Absorption:

- all tetracycline are adequately, yet incompletely absorbed after oral ingestion
- Dairy food decrease absorption due to formation of non absorbable chelates of tetracycline
- Doxycycline and minocycline are almost totally absorbed on oral administration.
- Currently, doxycycline is preferred tetracycline for parenteral administration but minocycline is available IV as well.

Distribution

- Tetracycline are distributed throughout the body. They cross the placenta to reach the fetus. Concentration in CSF is low
- Tetracycline concentrate in liver, kidney, spleen, skin and they bind to tissue undergoing calcification (for example teeth and bone) or tumors that have high calcium content for example gastric carcinoma.
- Minocycline enter the brain in absence of inflammation and also appears in tear and saliva.

Elimination

- All tetracycline are concentrate in liver, where they are in part metabolized and conjugated to form soluble glucouronide.
- Most tetracycline are reabsorbed in intestine via enterohepatic circulation and enter urine by glomerular filtration
- Unlike other tetracyclines, doxycyclines can be employed for treating infections in renally compromised patient because it is preferable excreted via a bile into feaces.

Adverse Effects

- Gastric discomfort
- Effect on calcified tissue
- Fatal hepatotoxicity
- Phototoxicity
- Vestibular problem
- Pseudotumor cerebri
- Superinfections

Contraindication

- Renally impaired patients should not be treated with any of tetracycline except doxycycline
- Shouldnot employed in pregnancy or breast feeding women or In children less than 8 years of age.

Glycylcycline

- Tigecycline is first available member of new class of antimicrobial agents called glycylcycline.
- Tigecycline is a derivative of minocycline, structurally similar to tetracycline and has a broad spectrum activity against multidrug resistant gram +ive pathogen, some gram –ive organism and anaerobic organism.
- Tigecycline is indicated for treatment of complicated skin and soft tissue infection as well as complicated intrabdominal infection.

Mechanism of Action

- Tigecycline exhibit bacteriostatic broad spectrum activity and is a protein synthesis inhibitor by binding to 30S ribosomal sub unit of bacteria and thereby blocking entry of aminoacyl tRNA and inhibiting protein translation.

Pharmacokinetic

- Following a 30-60 min IV infusion every 12hr tigecycline rapidly distribute in body tissue.
- It does not undergo significant liver metabolism but primarily excreted via biliary and fecal excretion
- No dose adjustment is necessary for renal impaired. However, required in hepatic dysfunction.

Adverse Effects

- Nausea
- Vomiting
- Photosensitivity
- Pseudotumor cerebri
- Discoloration of permanent teeth
- Fatal harm during pregnancy