

Inhibitors of Bacterial Protein Synthesis

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- 1. Aminoglycosides**
- 2. Tetracyclines**
- 3. Macrolides**
- 4. Clindamycin**
- 5. Chloramphenicol**
- 6. Linezolid**
- 7. Glycylcyclines: Tigecycline**

Aminoglycosides (AG)

- Mechanism of action:
- These are bactericidal antibiotics that inhibit bacterial protein synthesis by an action on ribosome 30S resulting in abnormal proteins & killing of bacteria
- They are effective against aerobic bacteria only (their entry into bacteria is oxygen-dependent)

- Aminoglycoside antibiotics had been mainstays for treatment of **serious infections due to aerobic gram -ve bacilli**
- Because their use is associated with **serious toxicities**, they have been replaced to by safer antibiotics, such as:
 - **3ed & 4th generation cephalosporins**
 - **Fluoroquinolones**
 - **Carbapenems**

- **Gentamicin**
- **Amikacin**
- **Tobramycin**
- **Streptomycin**
- **Spectinomycin**
- **Neomycin**
- **Framycetin**

Mechanisms of Bacterial resistance

- **Enzymes formation** (about 9 enzymes are isolated; transferred by plasmids)
- **Decrease uptake of drugs**
- **Anaerobic bacteria infections**

Therapeutic Uses & Spectrum of Activity

- AG are active against **aerobic Gram –ve bacilli** & also are active against **staphylococci**

AG are indicated in the following conditions:

- **Serious Gram –ve bacillary infections** like **UTI**, **septicemia** & **pelvic infections** caused by E.coli, Proteus, Klebsiella & Pseudomonas aeruginosa

- **Some serious Gram +ve infections** like **bacterial endocarditis** (combined with penicillin G or vancomycin)
- **Streptomycin** (Tuberculosis)
- **Topical therapy** including:
 - **Eye, ear & skin infections** (using topical neomycin, gentamicin & framycetin)
 - **Prepare bowel prior surgery (oral neomycin)**

Pharmacokinetics

- AG are **water-soluble** agents that are **poorly absorbed from GIT**
- Therefore, they should be given **parenterally** or **topically**
- AG are **eliminated by kidneys** by glomerular filtration **with no significant metabolism**
- Accumulation occurs in **renal cortex, endolymph & perilymph of inner ear**

Aminoglycosides & renal disease

- In renal impairment, AG t $\frac{1}{2}$ increases & therefore, intervals between doses should be increased or daily doses should be reduced
- Doses can be obtained from tables according to patient's weight & renal function
- The following formula helps to calculate daily dose in renal disease:

$$\text{Dose (mg/day)} = \frac{\text{Daily dose/creatinine}}{\text{creatinine}} = \frac{300}{\text{creatinine}}$$

Aminoglycosides & renal disease

- Blood levels have also to be checked e.g. twice weekly
- Single daily dose administration of AG is recommended nowadays rather than 2-3 doses daily to reduce risk of ototoxicity & nephrotoxicity

Adverse effects

- These are more in elderly, in renal & liver diseases & with prolonged therapy
- **Adverse effects are dose-related**
(therapy should not exceed 7 days)
- **Monitor plasma levels**

Adverse effects

- **Nephrotoxicity:**
- AG may accumulate in proximal tubular cells
- Kidney damage ranging from **mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible**
- being highest with **kanamycin** & least with **streptomycin**

Adverse effects

➤ Ototoxicity:

- Irreversible in the form of vestibular damage (patients presented with vertigo) or cochlear damage (presented with deafness & tinnitus) or both. **AG ear drops** may also produce ototoxicity

➤ Neurotoxicity: AG may reduce acetylcholine release & may produce neuromuscular blockade & muscle weakness

- Others like allergic reactions, fever & blood disorders

Contraindications & precautions of AG

- Pregnancy as AG may cause ototoxicity in newborn
- Allergy
- Avoid AG in:
 - Myasthenia Gravis
 - Prolonged use (more than one week)

Drug interactions with AG:

- **Loop diuretics** (frusemide, bumetanide): increase ototoxicity & nephrotoxicity of AG
- **β -LA** (penicillins & CSs): potentiate their antibacterial activity
- **Neuro-muscular blockers**: potentiation of effect

Gentamicin



- It is mainly used in **serious aerobic Gram -ve infections** (E. coli, Proteus, Klebsiella & Pseudomonas) & some **Gram +ve infections** (endocarditis)
- can also be used **topically in eye, ear & skin infections**
- **In septicemia**, it is combined with a **penicillin & metronidazole**

Tetracyclines

- **Tetracycline, Doxycycline, Minocycline, Demeclocycline**
- These **broad spectrum (gram +ve, -ve bacteria), bacteristatic** antibiotics contain 4 rings in their structure
- They **inhibit bacterial protein synthesis** by binding to bacterial ribosome 30S

Pharmacokinetics

- Tetracyclines are usually given orally
- Their absorption from GIT is impaired by antacids, iron & by food particularly calcium-containing food like milk. Therefore, they are better taken on empty stomach
- Unabsorbed fraction alters bacterial flora & causes diarrhea
- They are distributed throughout body but have poor entry into CSF (except minocycline)
- They cross placenta and are excreted in milk

- Tetracyclines are eliminated mainly unchanged in urine and should be avoided in renal disease
- Doxycycline & minocycline are excreted only in bile & are therefore, safe in renal disease
- Tetracyclines bind to calcium of teeth & bones

Therapeutic uses

- Brucellosis
- Cholera
- Mycoplasma pneumonia
- Chlamydia infections like pelvic inflammatory disease, urethritis, trachoma, psittacosis
- Syphilis
- Chronic bronchitis exacerbations
- Acne (inhibit *Corynebacterium acnes* bacteria)

Contraindications

- Pregnancy
- Breast feeding women
- Renal disease because they accumulate in renal disease (**except doxycycline & minocycline**)
- Children because of yellow discoloration of teeth

Tetracycline-Induced Discoloration of Teeth



Adverse effects

- **GI:** Epigastric pain or discomfort, nausea, vomiting, diarrhea or even antibiotic-associated colitis
- Sore throat, black hairy tongue & dysphagia
- **Photosensitivity, burn**, rash & blue gray discolouration (with minocycline)
- **Yellow discolouration & hypoplasia of teeth in children**
- Renal impairment

Macrolides

- **Erythromycin, Clarithromycin & Azithromycin**
- These are bacteriostatic agents that inhibit protein synthesis by acting on ribosome 50S

Pharmacokinetics

- Route of administration is usually **orally**
- They are well absorbed & widely distributed in tissues but **do not cross BBB into the CSF**
- **Elimination is in bile through liver**

Therapeutic uses

- **Alternative to penicillin** in presence of penicillin allergy
- **Mycoplasma pneumonia** (called atypical pneumonia)
- **Helicobacter infections** like gastro-enteritis
- **Chlamydia infections**
- **Diphtheria**
- **Whooping cough** (pertussis)
- **Legionnaire's disease** (characterized by respiratory, GIT & CNS manifestations)

Contraindications

➤ Liver disease

Adverse effects:

- GI upset
- Liver damage (cholestatic jaundice)
- Inhibition of hepatic drug metabolism

Erythromycin (Erythrocin)



- Effective against gram +ve organisms
- Antibacterial spectrum is similar to that of penicillin
- **It is used in patients allergic to penicillin**

Clarithromycin (Klacid)



- It acts like erythromycin & with similar spectrum of activity mainly against Gram +ve organisms & also against H. influenzae
- It is rapidly & better absorbed than erythromycin and produces less GIT upset
- It is used in respiratory tract infections & soft tissue infections
- It is useful in peptic ulcer therapy to eradicate Helicobacter pylori with other anti-ulcer drugs

Azithromycin (Zithromax)



- It is active against many **Gram -ve organisms** like H. influenzae & N. gonorrhoea & against **chlamydia** but less effective than erythromycin against **Gram +ve organisms**
- It is useful to **treat respiratory TI (mycoplasma pneumonia), soft tissue infections & sexually transmitted chlamydial disease**
- Long half-life (40 hrs)
- **Orally or intravenous infusion**

Clindamycin (Dalacin)



- It is a **bacteriostatic agent** that acts by **inhibiting bacterial protein synthesis**
- It has similar spectrum of activity to **erythromycin, penicillin & anaerobes**
- It is well absorbed after **oral** administration

Therapeutic uses

- **Anaerobic infections** like in abdomen, teeth (dental infections), pelvis & septic abortion
- **Osteomyelitis** (infection of bone caused by staphylococci) because of **good bone penetration & good anti-staph** activity
- In **serious Gram +ve infections**

Adverse effects

- **Diarrhoea, antibiotic-associated colitis, allergy & liver dysfunction**

Chloramphenicol

- It is a **bacteriostatic agent**, but sometimes, may be **bactericidal** (H.influenzae, strep pneumonia)
- It has a **broad spectrum** of activity against **Gram +ve & Gram -ve bacteria & anaerobes**
- Because of its **serious adverse effects**, **it has limited uses** mainly in **serious infections**

Pharmacokinetics

- The drug can be given orally or parenterally
- It is widely distributed in tissues & **crosses BBB** into the CSF
- It is metabolized in liver and its excretion is in urine (**smaller doses in liver disease**)

Therapeutic uses

- **Salmonellosis**
- **H. influenza meningitis**
- **Meningococcal meningitis in penicillin allergic patients**
- **Anaerobic infection in CNS**
- **Topically in ocular infections (bacterial conjunctivitis)**

Adverse effects

- **Bone marrow depression** includes:
 - Reversible dose-dependent depression (anemia)
 - **Idiosyncratic irreversible** depression (aplastic anemia)
- **Gray baby syndrome** (cyanosis, hypotension, death) because of inability of newborn liver to metabolize drug efficiently resulting in its accumulation & toxicity
- **Optic & peripheral neuritis**
- **Inhibition of hepatic metabolism of drugs like warfarin & phenytoin**

Contraindications

- **Late pregnancy**
- **Newborn babies** (risk of grey baby syndrome)
- **Breast feeding women**

Linezolid

- Its main clinical use in **resistant gram-positive organisms** such as:
 - **Methicillin- and vancomycin-resistant staphylococcus aureas**
 - **Vancomycin- resistant Enterococcus**
 - **Penicillin– resistant streptococci**
- Oral & iv administration
- **Adverse effects:** nausea, diarrhea, headache, rash, thrombocytopenia

Glycylcyclines

- **Tigecycline**
- Structure similar to tetracyclines
- **Has extended broad spectrum activity against:**
- **Multidrug-resistant gram +ve:**
- - methicillin-resistant staphylococci, multi-drug resistant streptococci, vancomycin-resistant enterococci
- **Extended- spectrum B-lactamase producing gram – ve**
- *Acinetobacter baumannii*
- Anaerobic organisms

- Not active against Proteus & Pseudomonas
- **Is indicated for:**
 - complicated skin & soft tissue infections
 - complicated intra-abdominal infections
- Given iv infusion every 12 hrs
- Eliminated via biliary/fecal excretion
- No dose adjustment in renal impairment

- **Adverse effects:**
- Similar to tetracyclines
- Nausea & vomiting
- Photosensitivity
- Discoloration of teeth in children
- Contraindicated during pregnancy