Aminoglycoside antibiotics

Aminoglycosides

- Streptomycin – 1944
- Actinomycetes – *Streptomyces griseus*
- Used to treat aerobic Gram –ve bacteria
- Interfere with protein synthesis
- Bactericidal
- Resemble each other in mode of action, pharmacokinetic, therapeutic and toxic properties

Chemistry

- Streptomycin family – Streptomycin & dihydro-streptomycin
- Neomycin family – Neomycin, Framycetin, Paromomycin
- Kanamycin family – Kanamycin, Tobramycin, Amikacin
- Gentamicin family – Gentamicin, Sisomicin, Netilmicin

Antimicrobial activity

- Narrow spectrum antibiotics
- Gram –ve bacilli
- Enterobacteriaceae – E.coli, Proteus, Klebsiella, Shigella
- *Pseudomonas aeruginosa*, *Yersinia pestis*, *Pasturella tularensis*
- Haemophilus and Neisseria
- *Mycobacterium tuberculosis*
- MIC – 0.25 to 130 μg/ml

Mode of Action

- Rapidly bactericidal
- Inhibit protein synthesis
- Bacterial killing conc. dependent
- Residual bactericidal activity
- Act inside the cell
- Misreading and premature termination of mRNA at ribosome
- Primary site of action is 30s ribosome subunit
- Resulting abnormal proteins are fatal to microbes

Bacterial resistance

- Very poor GIT absorption
- Rapid IM absorption
- Peak plasma conc. 30 to 90 minutes
- Poor penetration in Eye, CNS
- High conc. in renal cortex & inner ear
- PPB negligible
- Excretion in glomerular filtration

Common features

- Poorly absorbed from GIT
- Distribution extra cellular
- CSF and Eye penetration is poor
- High conc. in renal cortex → **nephrotoxicity**; &
  In endolymph & perilymph of inner ear → **ototoxicity**
- Excreted rapidly by glomerular filtration
- Bacterial resistance develops rapidly and cross-resistance exists
- Highly active against Gram –ve bacilli inactive against anaerobes
- Synergistic with penicillin or cephalosporin

Adverse effects

All aminoglycosides can produce nephrotoxicity & ototoxicity.

OTOTOXICITY – *Both vestibular and auditory damage*, causing loss of hearing, vertigo & tinnitus, due to auditory nerve damage

- Early signs of vestibular toxicity – motion related headache, dizziness or nausea
- Serious ototoxicity can occur with ear drops
- Risk of toxicity depends upon high dose, long duration, inefficient renal clearance and dehydration
- Streptomycin, Gentamicin – Vestibular dysfunction
- Amikacin, Kanamycin – Auditory dysfunction

Adverse effects

NEPHROTOXICITY- Reversible renal impairment occurs in who receive drugs for more than 10 days due to accumulation and high retention in proximal tubular cells

- Mild proteinuria and appearance of hyaline and granular casts
- ↓GFR
- Acute tubular necrosis (Rare)
- Risk factors – Low B.P., Loop diuretics and advanced age

Adverse effect

- Neuromuscular blockade – Intrapleural and intraperitoneal administration produces neuromuscular blockade & apnea (resp. arrest)
- May aggravate or reveal myasthenia gravis or cause transient myasthenic syndrome
- Blockade antagonized by neostigmine
- Rashes
- Haematological abnormalities
- Bleeding
- Superinfection

Preparations

- Streptomycin sulphate injection
- Kanamycin sulphate injection
- Neomycin sulphate cap
- Gentamicin sulphate injection
- Tobramycin injection
- Amikacin injection
- Netilmicin injection
- Paromomycin cap
- Framycetin ointment, cream or solution

Clinical uses

- Gram –ve bacillary infection – septicaemia, pelvic & abdominal sepsis
- Bacterial endocarditis – enterococcal, streptococcal or staphylococcal injection of heart valves
- Pneumonias, Tuberculosis
- Tularemia
- Plague, Brucellosis
- Topical – Neomycin, Framycetin.
- Infections of conjunctiva or external ear
- To sterilize the bowel of patients who receive immunosuppressive therapy, before surgery & in hepatic coma

Clinical uses

Streptomycin

- Combination of chemotherapy of tuberculosis
- Plague
- Brucellosis
- Tularemia
- Streptococcal endocarditis- combined with Penicillin-G

ADRs:- Optic nerve dysfunction

- Peripheral neuritis
- Perioral paraesthessia

Gentamicin

- Useful bactericidal for serious G -ve bacillary infection
- First choice Aminoglycosides due to low cost, reliable activity and long experience of use
- Tobramycin, amikacin and interchangeably
- Used in infected burns, otitis externa, acute pyelonephritis
- Trough plasma drugs conc. > 2μg / ml - toxic

Gentamicin

- U.T.I
- Pneumonia
- Meningitis
- Endocarditis
- Peritonitis
- Intraabdominal and pelvic infection and septic states caused by sensitive bacteria, pseudomonas, entrobacter, klebsiella
- Skin, eye and ear infection

Tobramycin

- Pseudomonas infections
- Bacteremia
- Osteomyelitis
- Pneumonia
- Tobramycin + Piperacillin
- Tobramycin + Ceftzidime
- Ophthalmic ointment & solution

Amikacin

- Broadest antibacterial spectrum
- Similar to gentamicin and tobramycin in therapeutic uses
- Resistant to Aminoglycosides inactivating enzymes
- Preferred in serious nosocomial G -ve bacillary infection in hospitals where Tobramycin & Gentamicin have developed resistance
- Effective against M. tuberculosis & atypical mycobacteria in AIDS patients

Netilmicin

- Serious aerobic G-ve bacillary infections due to enterobacteriacaea
- Effective against Gentamicin resistant except entrococci pathogens

Neomycin

- Broad spectrum antibiotics
- Orally used intestinal antiseptic before colonic surgery
- Suppression of intestinal flora in hepatic coma
- Topically used in skin, eye and ear infection combined with other antibiotics like bacitracin or polymyxin-B to widen antibacterial spectrum and to prevent emergence of resistant strains

Neomycin

- Neomycin and polymyxin B used for bladder irrigation in solution containing 40mg neomycin and 2 lac units of polymyxin-B per ml.
- 1 ml added to 1 liter of 0.9% sodium chloride solution and is used for continuous irrigation of bladder in order to prevent bacteremia and bacteriurea associated with use of indwelling catheters at the rate of 1000 ml/day.
- Neomycin cream, ointment alone and combination with other antibiotics and corticosteroids.
- Used in burns, wounds, ulcers

Kanamycin

- Reserve drug for Tuberculosis- combined with other antitubercular drugs
- Most toxic
- Orally used in therapy of hepatic coma.

Alogrithm for Dose Reduction of Aminoglycosides Based on Calculated Creatinine Clearance

Creatinine clear. (ml/min)	% Maximal daily dosing	Frequency of dosing
100	100	Every 24 hr
75	75	,,
50	50	,,
25	25	,,
20	80	Every 48 hr
10	60	,,
< 10	40	,,

Maximum Daily Dose

- For Amikacin, Kanamycin and Streptomycin is 15 mg/ kg
- For Gentamicin and Tobramycin is 5.5 mg/kg
- Netilmicin is 6.5 mg/ kg

Cochlear Toxicity

- High pitched tinnitus- first symptom
- Auditory impairment after a few days if drug continues
- Tinnitus persists upto 2 weeks after discontinuation
- Sound perception lost first outside conversational range
- Individual may be unaware of impairment
- Detected on audiometric examination
- Loss of hearing may progress

VESTIBULAR- Toxicity

- Moderately intense headache lasting 1 to 2 days
- Onset of labyrinthine dysfunction
- Acute stage: Nausea, vomiting and difficulty in equilibrium persists for 1 to 2 weeks
- Upright vertigo
- Difficulty in sitting and standing
- Eye focusing and reading difficult

- Acute stage followed by chronic labyrinthine dysfunction:- ataxia, difficulty in sudden movements persists for 2 months
- Later on symptom appear only on closing eyes
- Recovery in 12 to 18 months
- Permanent residual damage may occur
- EARLY DISCONTINUATION OF DRUG PREVENTS DAMAGE AND PERMIT RECOVERY

Nephrotoxicity

- Reversible renal damage in 8% to 26% patients
- Renal proximal tubular cells accumulate and retain drug
- Mild proteinuria, appearance of casts, hyaline or granular

- Proximal tubular cells have regenerative capacity
- Neomycin highly toxic- systemic administration contraindicated
- Reduced excretion predisposed to ototoxicity
- Monitor plasma drug conc. in prolonged and high dose therapy