Aminoglycoside antibiotics

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Aminoglycosides

- Streptomycin – 1944
- Actinomycetes – *Streptomyces griseus*
- Bactericidal antibiotics
- Interfere with protein synthesis
- Used to treat aerobic Gram –ve bacteria
- Resemble each other in MOA, pharmacokinetic therapeutic and toxic properties
- Relatively low margin of safety
- Exhibit ototoxicity and nephrotoxicity

Chemistry

Amino sugar -O- 2-deoxystreptamine -O- Amino sugar

Aminoglycosides Structure

Streptidine -O- Streptose amino sugar -O- N-Methyl-L glucosamine amino sugar

Streptomycin structure

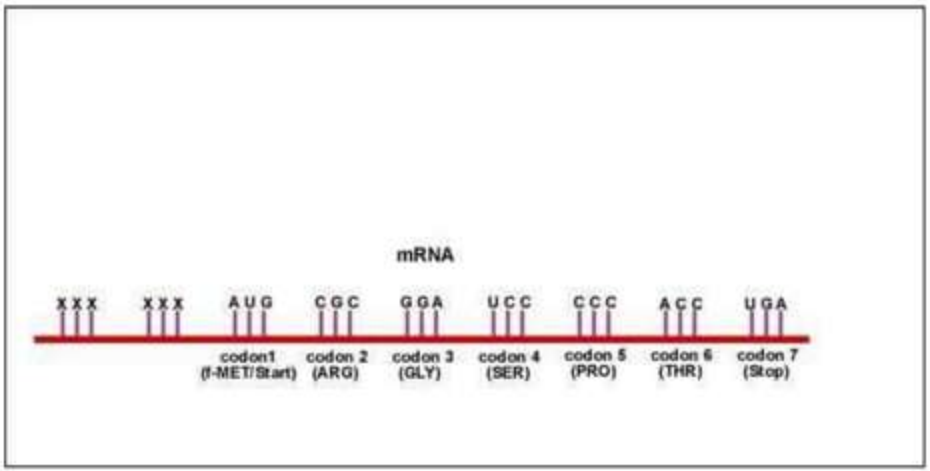
Streptobiosamine

Aminoglycosides

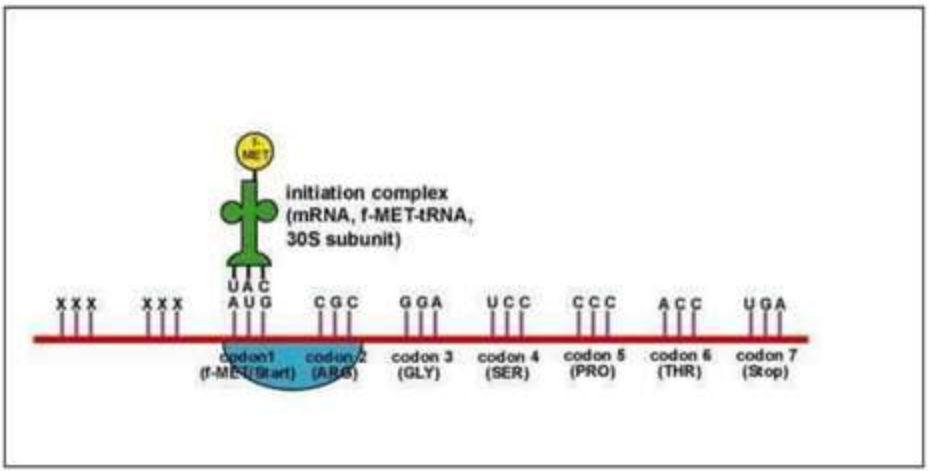
- Systemic
  - Streptomycin
  - Gentamicin
  - Kanamycin
  - Amikacin
  - Sisomicin
  - Tobramycin
  - Netilimicin
- Topical
  - Neomycin
  - Framycetin

Mechanism of Protein synthesis

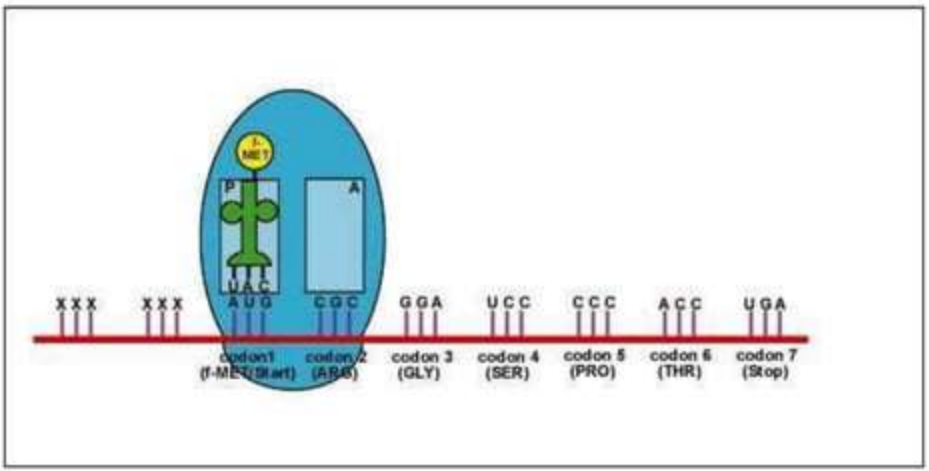
Formation of the Initiation Complex



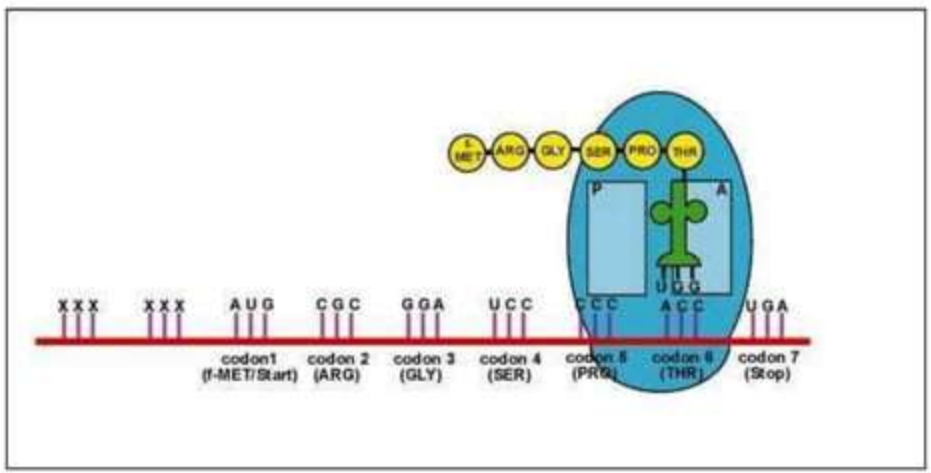
Joining of 50S Ribosomal Subunit



Protein Elongation

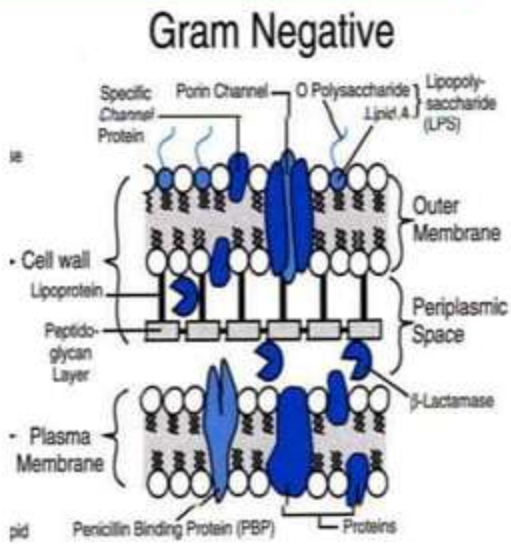


Termination of Translation



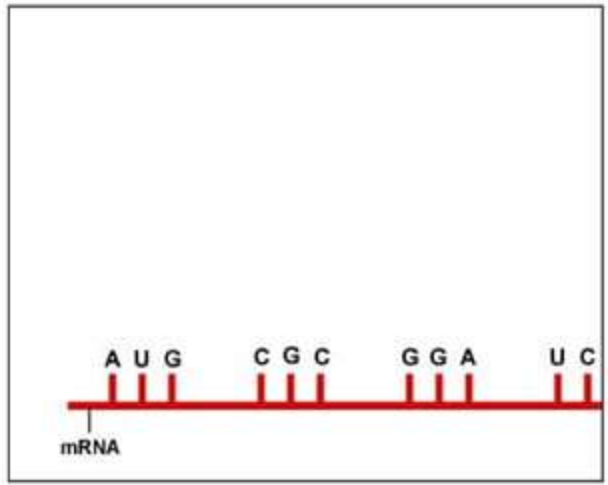
Mechanism of action

- Initially they penetrate bacterial cell wall, to reach periplasmic space through porin channels (passive diffusion)
- Further transport across cytoplasmic membrane takes place by active transport by proton pump; an oxygen-dependent process



Mechanism of Action

- Bind 30S ribosomal subunits and interfere the initiation complex
- Induce misreading of genetic code on mRNA
- Breakup of polysomes into monosomes



Post antibiotic effect

- Aminoglycosides exhibit concentration dependent killing.
- They also possess significant Post-antibiotic effect.
- Single daily dosing at least as effective as and no more toxic than multiple dosing.

Mechanism of resistance

- Synthesis of plasmid mediated bacterial transferase enzyme: Inactivate aminoglycosides
- ↓ transport into bacterial cytosol
- Deletion/alteration of receptor protein on 30 S ribosomal unit by mutation: prevents attachment

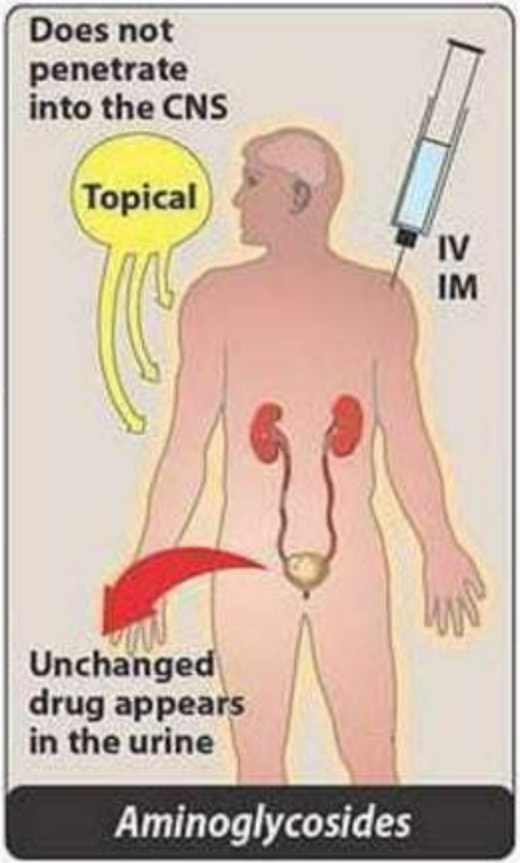
Antibacterial spectrum

- Primarily against Gm –ve aerobic bacilli
  - Proteus, pseudomonas
  - E.Coli,enterobacter
  - Klebsiella
  - Shigella
- Only few Gm +ve cocci:
  - staph aureus, strepto viridans
- Not effective against Gm +ve bacilli, Gm-ve cocci and anaerobes

Pharmacokinetics

- Highly polar basic drugs: poor oral BA
- Administered parenterally or applied locally
- Poorly distributed and poorly protein bound
- Do not undergo any significant metabolism
- Nearly all IV dose is excreted unchanged in urine
- Dose adjustment is needed in renal insufficiency

Pharmacokinetics



Dose for a case of renal insufficiency

= Normal therapeutic dose

Sr creatinine value (mg/dl)

Dose for a case of renal insufficiency

- Cockroft gault formula:

$$CrCl = \frac{(140\text{-age}) \times \text{weight [kg]}}{(sCr \times 72)}$$

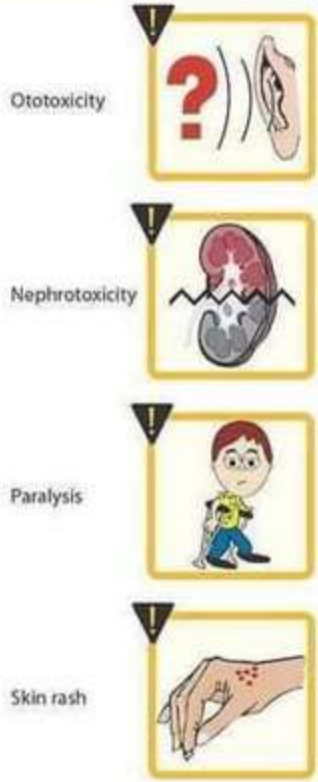
  - For females multiply above value by 0.85
  - Corrected dose = $\frac{\text{Normal dose} \times \text{pt CrCl}}{\text{Normal CrCl}}$

Clinical uses

- Gram –ve bacillary infection
  - Septicaemia, pelvic & abdominal sepsis
- Bacterial endocarditis –
  - enterococcal, streptococcal or staphylococcal infection 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

Shared toxicities

- Ototoxicity
  - Vestibular damage
  - Cochlear damage
- Nephrotoxicity
- Neuromuscular blockade



Ototoxicity

- Impairment of VIII cranial nerve function
- May be irreversible
- Cochlear damage
  - Hearing loss and tinnitus
  - More with neomycin , amikacin and kanamycin
- Vestibular damage
  - Vertigo, ataxia, loss of balance
  - More with Streptomycin, gentamycin
- Tobramycin has both types of toxicity
- Netilimycin claimed to have low ototoxicity

Nephrotoxicity

- Gentamicin, amikacin and tobramycin are more toxic than streptomycin
- Responsible for 10-15% of all renal failure cases
- Reversible if drug promptly discontinued
- ↓ GFR, ↑ sr creatinine
- ↓clearance of antibiotic → ↑ ototoxicity

Neuromuscular blockade

- Cause N-M junction blockade by
  - Displacing Ca^{2+} from NM junction
  - By blocking post synaptic N_M receptors
  - Inhibiting Ach release from motor nerve
- Neomycin & streptomycin: more propensity
- Tobramycin least likely to produce it
- Myasthenic weakness ↑by these drugs

Precautions / Contraindications

- Pregnancy: foetal ototoxicity
- With other ototoxic drugs: furosemide, minocycline
- With nephrotoxic drugs: vancomycin ,cisplatin
- Elderly patients
- Those with kidney disease
- Cautious use of muscle relaxants
- Do not mix with any other drug in same syringe

Streptomycin

- Ribosomal resistance develops fast
- Limited usefulness as single agent
- Plague, tularemia and brucellosis
  - In combination with tetracycline

- Reserve first line drug for tuberculosis used only in combination

Gentamicin

- Obtained from Micromonospora purpurea
- Most commonly used aminoglycoside
  - More potent than Streptomycin
  - Broader spectrum: pseudomonas, proteus, E.coli, klebsiella, enterobacter, serratia
  - Low cost, reliability of use, long experience
  - Acts synergistically with ampicillin, penicillin G, Ticarcillin, ceftriaxone, Vancomycin
- Ineffective against M.tuberculosis
- Relatively more nephrotoxic

Gentamicin (Uses)

- Use restricted to serious Gm-ve bacillary infections
- Septicaemia, sepsis, fever in immunocompromised patients
  - Used with penicillins
- Pelvic infections : with metronidazole
- Coliform infection: with ampicillin or ceftriaxone
- Pseudomonal infections: with ticarcillin
- Meningitis by Gm-ve bacilli : III generation cephalosporin alone or with gentamicin

Guideline for adjustment of dose in renal insufficiency

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	,,

Tobramycin

- Identical to gentamicin
- Used in pseudomonas and proteus infections
- Ototoxicty and nephrotoxicity probably lower

Sisomicin

- Identical to gentamicin
- More potent on pseudomonas and β-hemolytic streptococci
- Used interchangeably with gentamicin

Amikacin

- Less toxic semisynthetic derivative of kanamycin
- Resistant to enzymes that inactivate gentamicin and tobramcyin
- Widest spectrum of activity
- Uses:
  - Same as gentamicin
  - Reserve drug for hospital acquired Gm-ve bacillary infections
  - Multidrug resistant TB along with other drugs
- Dose : 15mg/kg/day in 1-3 doses

Netilimicin

- Semisynthetic derivative of sisomicin
- Relatively resistant to aminoglycoside inactivating enzymes
- More active against klebsiella, enterobacter & staphylococci
- Less active against pseudomonas aeruginosa
- Doses and pharmacokinetics similar to gentamicin

Neomycin

- wide spectrum active against Gm-ve bacilli and some gm+ve cocci
- Pseudomonas and strep.pyogenes not sensitive
- Too toxic for parenteral use , limited to topical use

Neomycin (uses)

- Topically used in skin, eye and external ear infections combined with bacitracin or polymyxin-B to widen antibacterial spectrum and to prevent emergence of resistant strains
- Orally
  - Preparation of bowel before surgery 1 gm TDS
  - Hepatic coma: Supresses ammonia forming coliforms prevents encephalopathy (Lactulose more preferred)
- Bladder irrigation along with polymyxin B

Framycetin

- Very similar to neomycin
- Too toxic for systemic administration
- Used topically on skin, eye ear