

Drugs inhibiting Protein Synthesis

Aminoglycosides and Macrolides

Tetracycline and Chloramphenicol

Protein Synthesizing machinery

Ribosome

bacteria has 50S and 30 S subunit which forms 70 S polysome that slides on mRNA

has A, P and E sites for binding with tRNA

mRNA

forms template for protein synthesis

transcribed from DNA

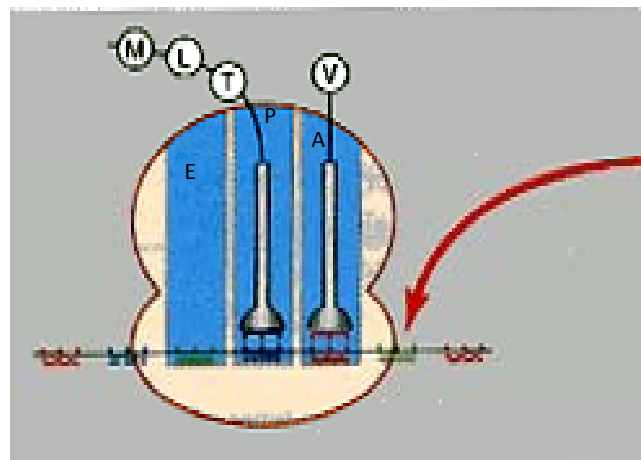
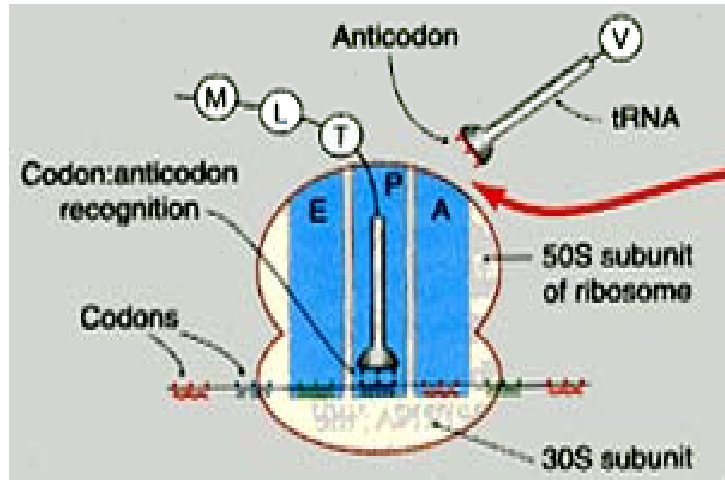
attaches to 30s ribosomes

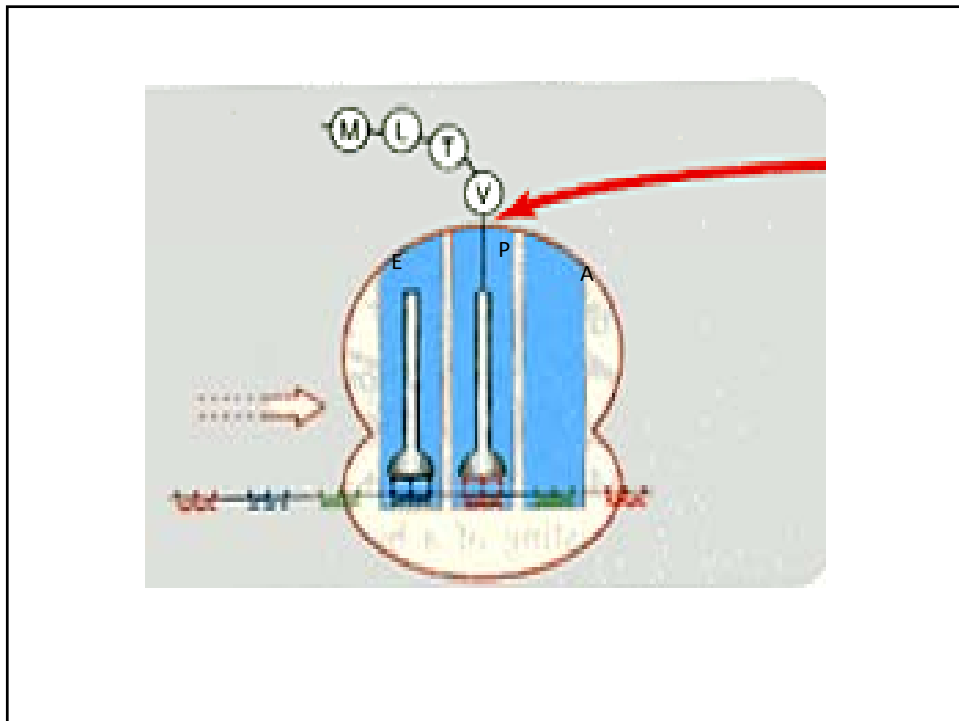
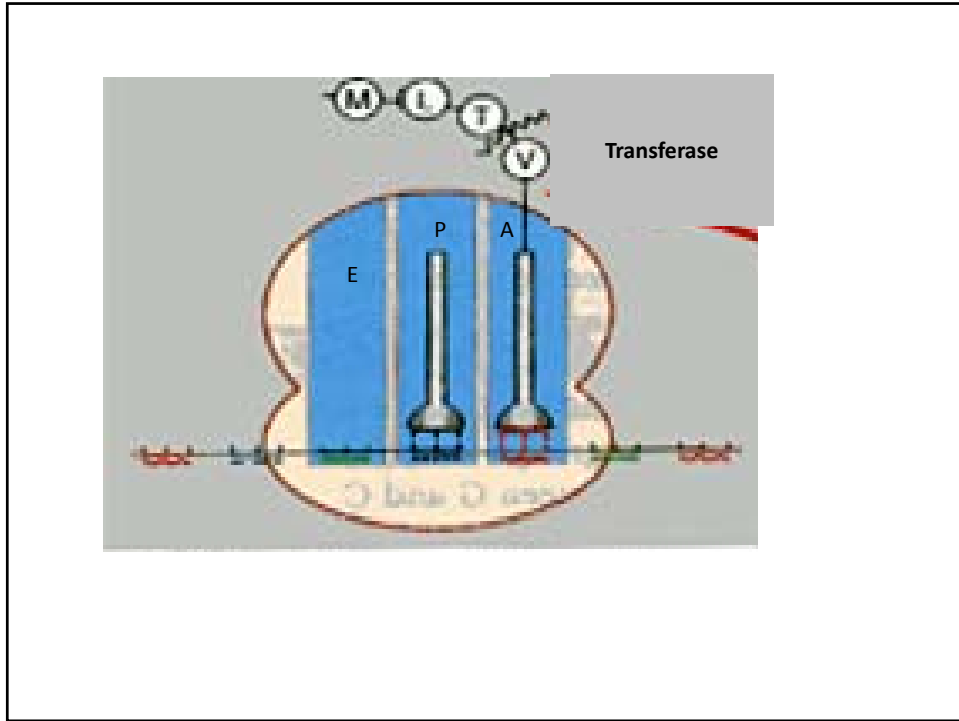
tRNA

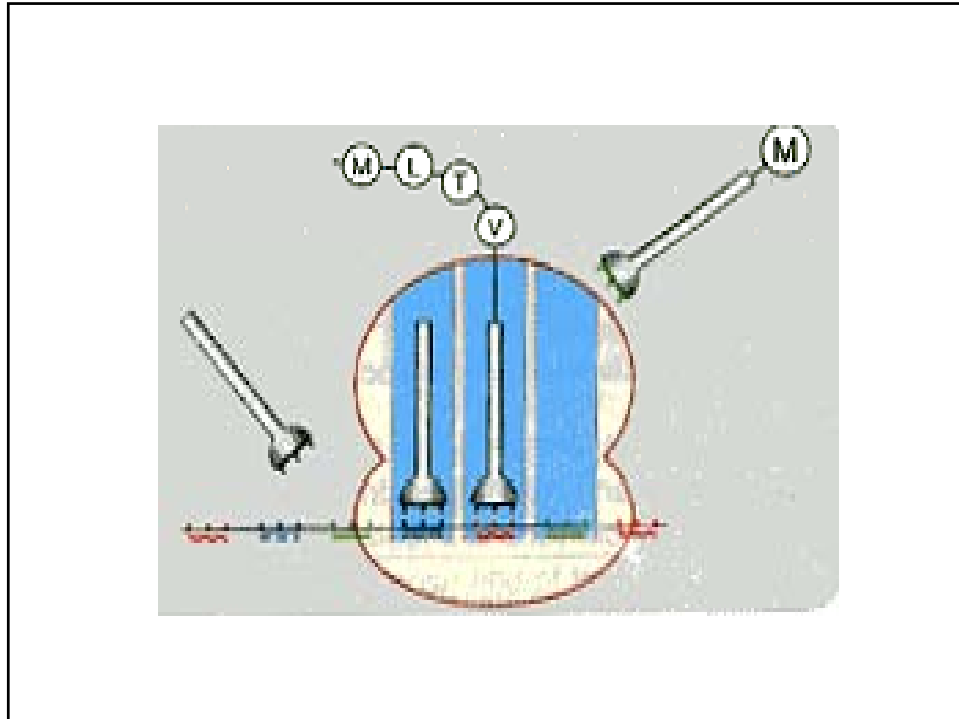
brings amino acids

attaches to A, P and E sites of ribosomes

Overview:







Why antibiotic drugs do not inhibit mammalian protein synthesis??

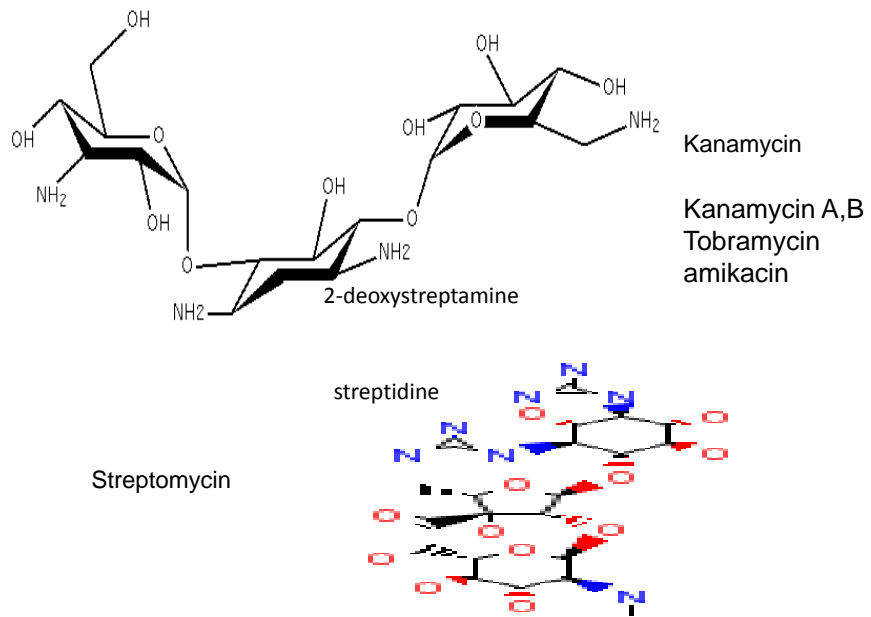
Eukaryotes : 60S and 40 S subunit

Difference in ribosomal units is the basis of selectivity of antimicrobial drugs against bacteria

Aminoglycosides

Gentamicin
 Tobramycin
 Amikacin
 Netilmicin
 Kanamycin
 Streptomycin

composed of amino-sugars
 water-soluble (hydrophilic)
 highly polarized



Bacterial killing → concentration dependent

Post-antibiotic effect persists after the serum conc < **minimum inhibitory concentration (MIC)**

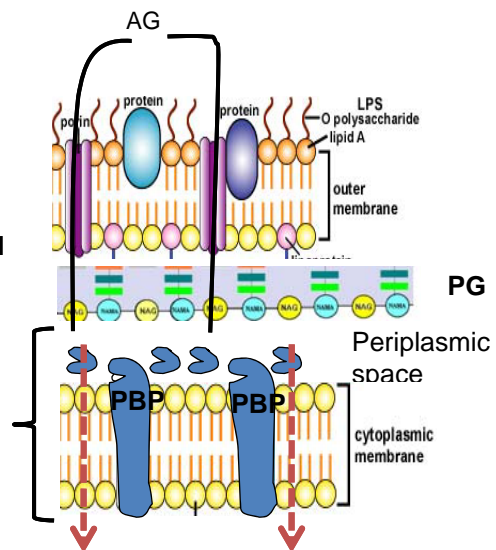
Once daily dose of aminoglycosides is therefore efficacious

Aminoglycosides Entry

a. Diffusion through **porins**

b. **Energy-Dependent Phase 1 (EDP1)**

rate limiting requires
negative inner membrane
potential
electron-transport chain



c) Create fissure inducing bacterial damage (**contrast from Tetra or Chloram**) further enhancing **AG uptake (EDP2 phase)**

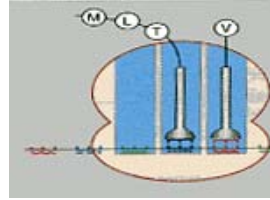
Entry/effectiveness

↓ pH
Ca²⁺/Mg²⁺
Hyperosmolarity
Anearobic conditions

(Abscess, hyperosmolar acidic urine)

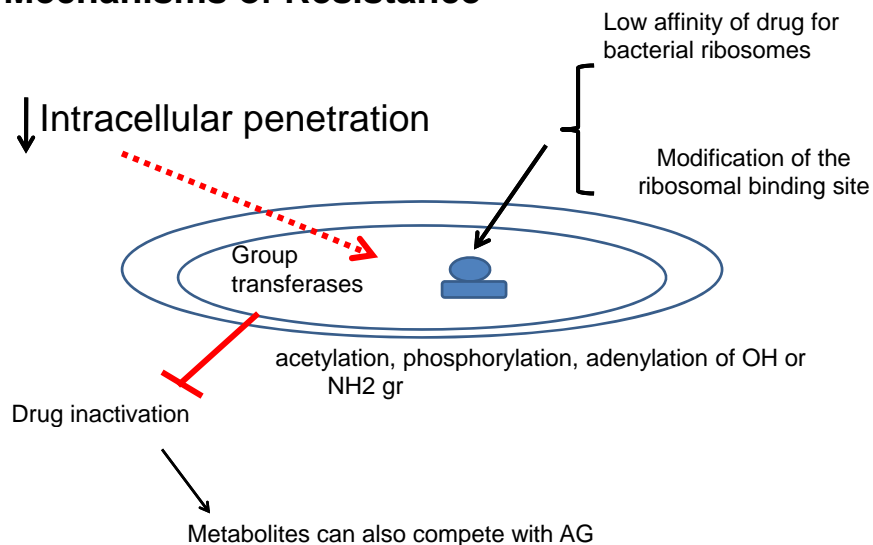
Mechanism of Action:

a) binds to A site of 30s of ribosome subunit



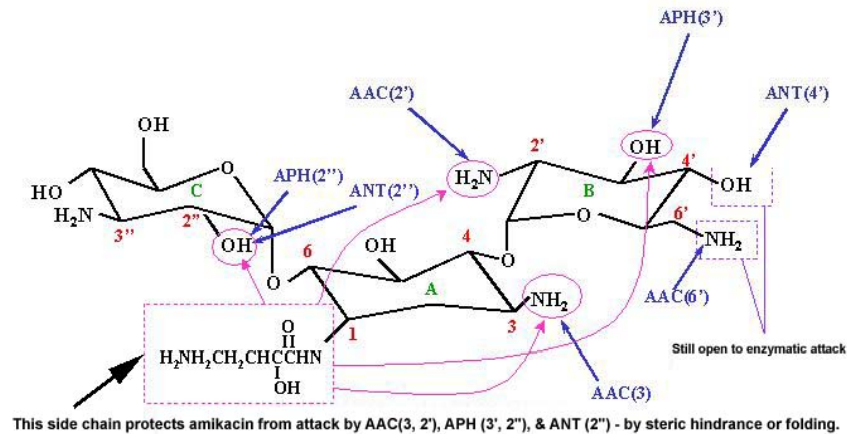
- i. interfere with the formation of the initiation complex
- ii. induce misreading of the mRNA template
- iii. Premature termination of mRNA translation
- iv. cause polysomes to break up into monosomes

Mechanisms of Resistance



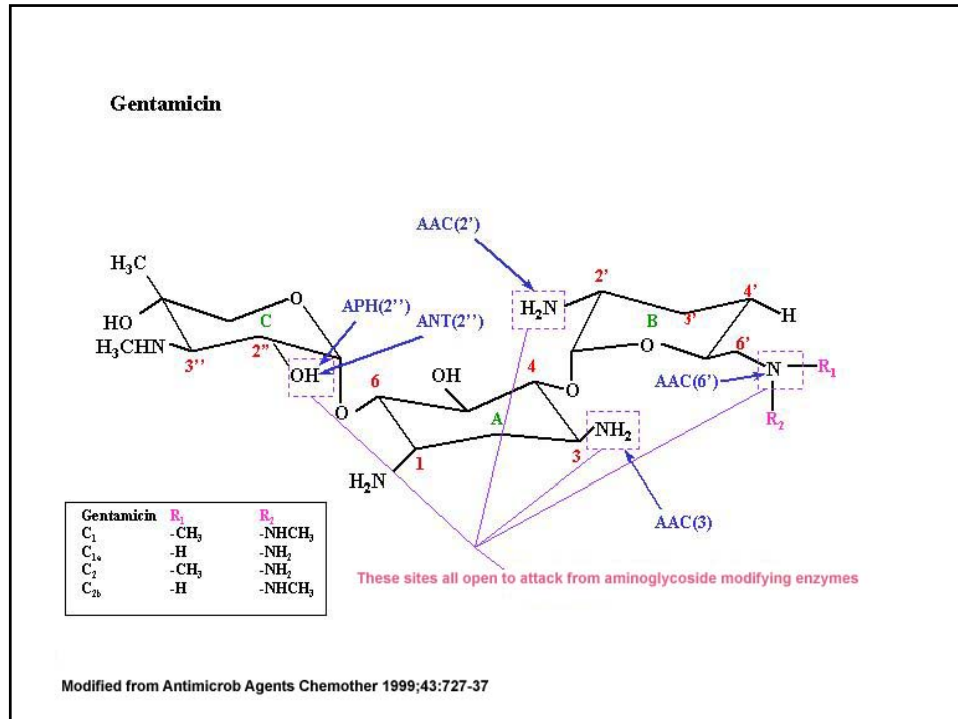
Cross-resistance by other aminoglycosides
 i.e. gentamicin → tobramycin, amikamicin, kanamycin and
 netilmycin.
 No effect on Steptomycin

Amikacin



AAC: acetylases; ANT: adenylase; APH, phosphorylase

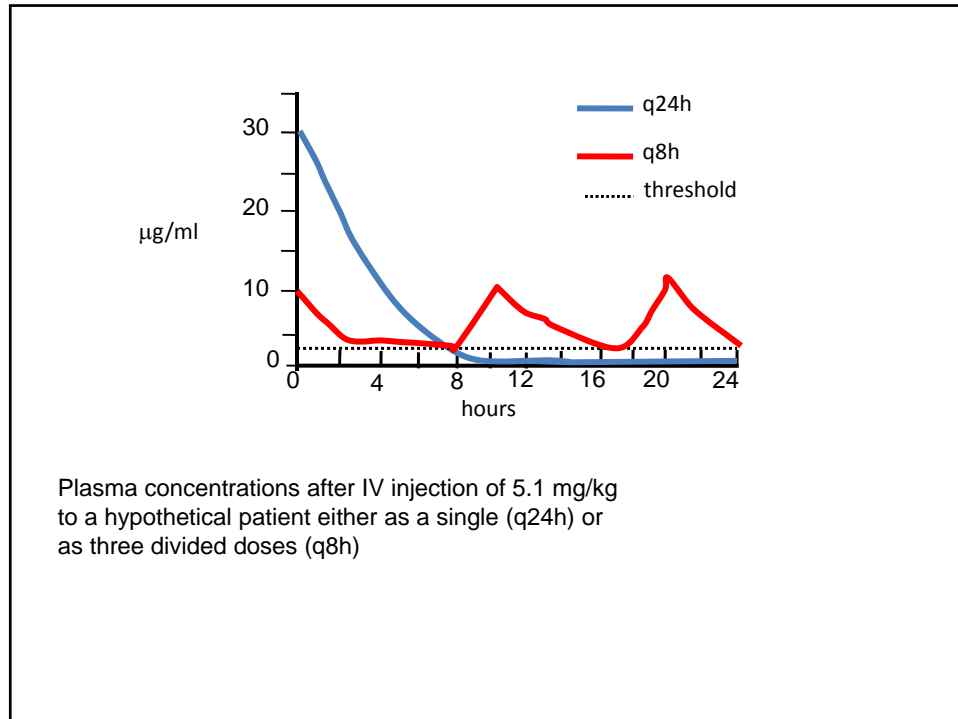
Modified from Antimicrob Agents Chemother 1999;43:727-37



VI. Absorption

Oral or rectal administration: <1% of dose is absorbed

Rapidly absorbed from I.M; peak conc. in plasma occur after 30-90 min period 4-12 ug/ml following 1.5-2 mg/kg dose



Distribution

Do not cross BBB and do not achieve high distribution in body fluids.

Can cross placenta

Excretion

Excreted entirely via the kidneys and urine conc of 50-200 ug/ml are achieved.

Clearance faster from plasma as compared to tissues

Clearance similar in adults and children older than 6 months; half life is prolonged in

The dosage must be adjusted for renal function.
Should not be administered to patients in renal failure

V. Spectrum:

Aerobic Gram (-) bacilli.

Kanamycin and Streptomycin: limited spectrum
Should not be used for infections caused by Serratia or P.aeruginosa

1st -line drug for pseudomonas.

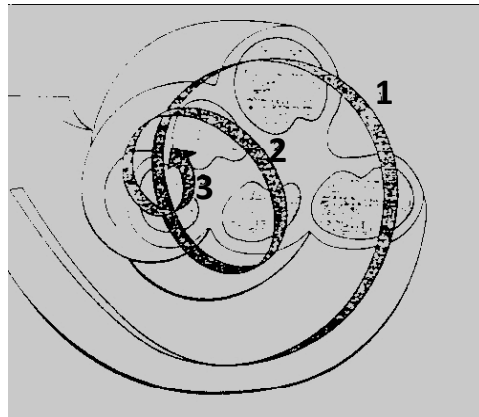
May be given with penicillin in infections caused by streptococci, Listeria sp.

Anaerobic or facultative anaerobic bacteria are resistant

IX. Side Effects

Ototoxicity (vestibular and auditory dysfunction)

Largely irreversible



Cochlea, normally lined with hair cells that are destroyed by **high concentrations of aminoglycosides**. Aminoglycosides damage hair cells, especially in turn No. 1 and part of turn No. 2. Hairs are shed by the damaged cells to give loss of high-frequency response first (associated with turn No. 1) and low-frequency loss later (associated with turn to. 3).

amikacin, kanamycin, neomycin



cochlear damage



loss of high frequency tones

streptomycin and gentamicin



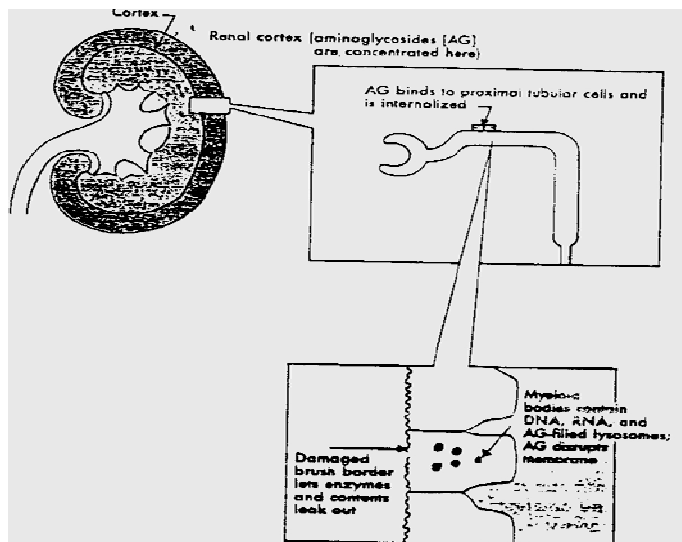
vestibular damage



loss of low frequency tones

Loop diuretics (furosemide and ethacrynic acid) potentiate the ototoxicity

Rotoxicity (reversible)



mild rise in serum creatinine

proteinuria, casts

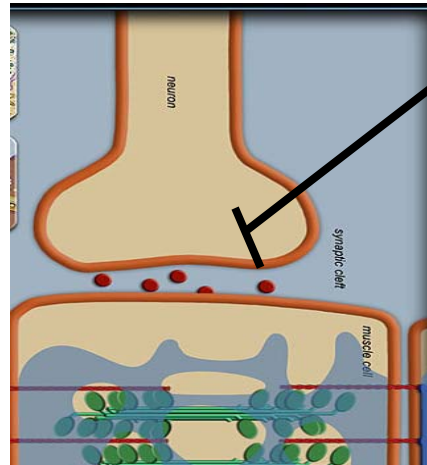
Leakage of enzymes-- alkaline phosphatase and aminopeptidase.

In severe cases, produces renal tubular necrosis

Nephrotoxic potencies: Neomycin > tobramycin
= gentamicin > streptomycin

antagonize factor V resulting in bleeding

Muscular blockade
(tobra<genta<amika<kana<neomy)



AG (curare-like)

Caution:
Myasthenia gravis
patients

calcium gluconate or neostigmine reverses this effect

VII. Therapeutic Use:

Streptomycin

unusual mycobacterial infections in combination
with other antimicrobial agents (**toxic**)
1000 mg/single or 500 mg double dose → serum
concentration of 50-60 and 15-30 hg/ml

Tuberculosis

Plague

Bacterial endocarditis (strep + Penn G) replaced by
(genta + PennG)

Tularemia (Strep or Genta)

Gentamicin: *1st choice; low cost, and reliable activity* agnst all Gram (-) bacilli including infections caused by pseudomonas aeruginosa

IT or IV: used rarely as cuases local inflammation

β -lactum-insensitive UTI's

Bacterial endocarditis

Sepsis

Topical as in burn patients

Tobramycin (Tobrex) (~ Gentamicin)

Amikacin

Broadest spectrum, absobed rapidly after IM injection;
Peak plasma concentration ~20ug/ml after 7.5 mg/kg injection

Nosocomial Gram (-) infections

Netilmicin~Gentamicin

can be used for Gentamicin resistant bacteria

Neomycin:

frequently used in topical ointments;
administered oral to clean the bowel prior to
bowel surgery (not absorbed, eliminated in the
feces, very toxic if administered I.M.)

Summary: Aminoglycosides

Requires **oxygen** and changes in transmembrane potential to act on 30S ribosome

Most toxic; **ototoxicity, rototoxicity, muscular blockade**, conc in serum should be monitored

Limited spectrum **Gram(-) Aerobes**
ineffective in anerobes
will work in facultative bact in aerobe enviroment

Use diminished as other Antibts became avl

Use for historical dis: **Plague, TB**