

Aminoglycosides



Dr Ipseeta Ray

Dept of Pharmacology

MGM Medical College



Outline

- Classification
- General features
- Antibacterial Spectrum
- MOA , Resistance
- Pharmacokinetics
- Shared toxicities
- Individual aminoglycosides



Aminoglycosides in clinical use

Aminoglycosides	The year of development	Origin
Streptomycin	1944	Streptomyces griseus
Neomycin	1949	Streptomyces fadiae
Kanamycin	1957	Streptomyces kanamyceticus
Gentamicin	1963	Micromonospora purpurea
Tobramycin	1968	Micromonospora tenebrarius
Amikacin	1972	Semisynthetic derivative of kanamycin A
Sisomicin	1970	Micromonospora inoensis
Dibekacin	1971	Dideoxy derivative of Kanamycin B
Netilmicin	1975	N-ethyl derivative of Kanamycin B
Micromonicin	1975	Micromonospora samamiensis
Astromicin	1977	Micromonospora olivasterospora
Isepamicin	1978	Gentamicin B derivative
Arbekacin	1990	Kanamycin B derivative



Source of Aminoglycosides

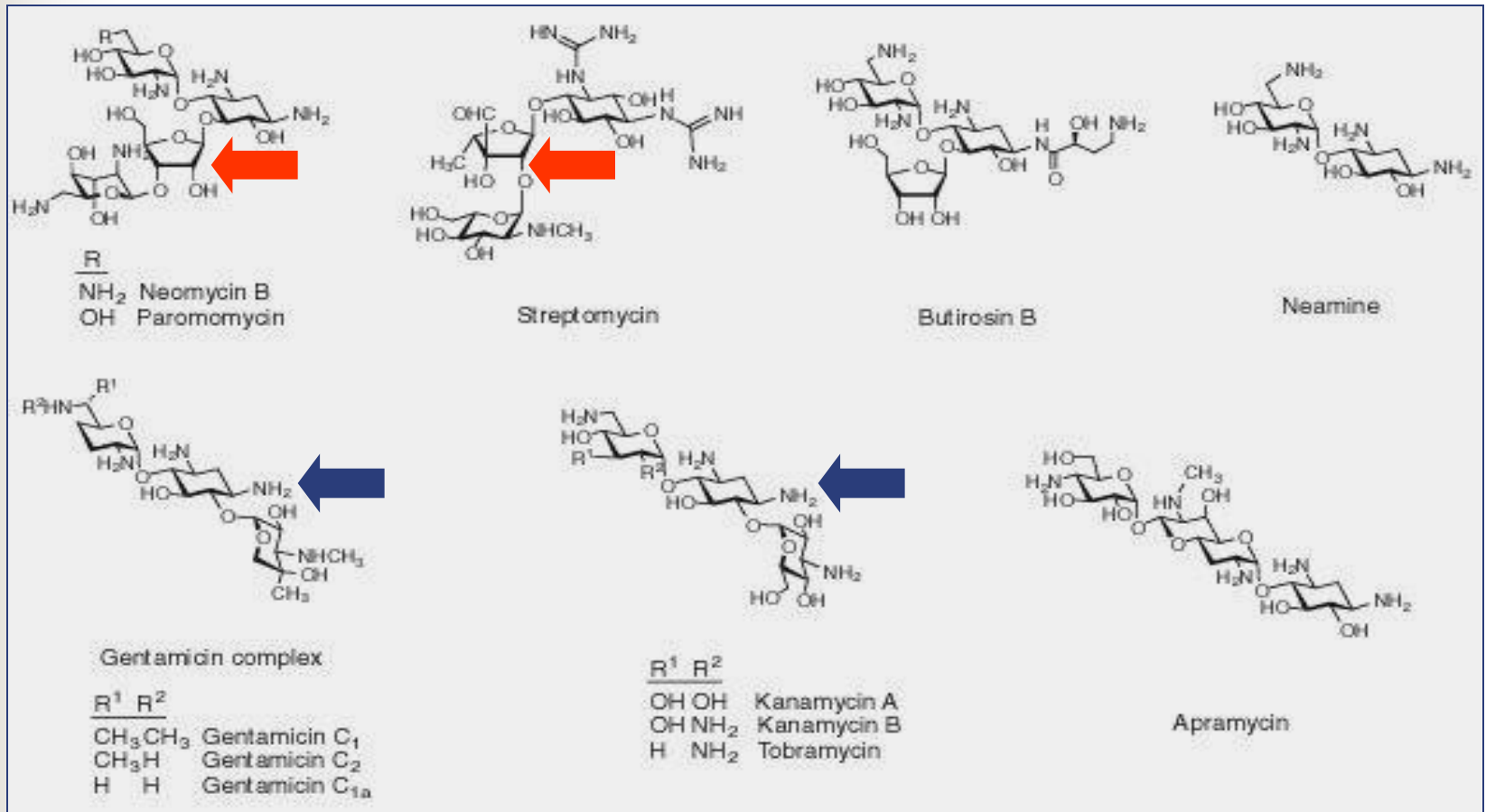
- Semisynthetic antibiotic derivatives from cultures of *Streptomyces* or *Micromonospora*.
- Classification
 - *Micromonospora actinomycetes*
 - Gentamicin
 - Netilmicin
 - *Streptomyces spp.*
 - Streptomycin
 - Kanamycin
 - Neomycin



Classification

- **Streptomycin family** – Streptomycin & dihydrostreptomycin
- **Gentamicin family** – Gentamicin, Sisomicin, Netilmicin
- **Kanamycin family** – Kanamycin, Tobramycin, Amikacin
- **Neomycin family** – Neomycin, Framycetin, Paromomycin

Structures of Aminoglycosides



Have polybasic amino groups linked glycosidically to two or more **aminosugars** (streptadine, 2-deoxy-streptadimine, garosamine)



General Features

1

- Bactericidal, activity maximum at alkaline pH

2

- Highly polar

3

- Extracellular distribution

4

- High conc. in renal cortex and inner ear

5

- Toxic to neuromuscular junction

6

- Bacteria develop resistance very rapidly

7

- Combined with beta lactum antibiotics



Clinical use

- **Parenteral use:**

Streptomycin, Gentamicin, Kanamycin, Amikacin,
Tobramycin, Netilmicin

- **Topical use**

Neomycin, Framycetin, Gentamicin

- **Inhalation use**

Tobramycin

- **Oral use**

Neomycin, Paromomycin



Antibacterial Spectrum

✓ Gram-negative aerobic bacteria

	Gentamicin	Tobramycin	Amikacin	Netilmicin
N. gonorrhoeae	0	0	0	0
N. meningitidis	0	0	0	0
M. catarrhalis	+	+	+	+
H. influenzae	+	+	+	+
Aeromonas	0			
E. coli	+	+	+	+
Klebsiella sp.	+	+	+	+
Enterobacter sp.	+	+	+	+
Salmonella sp.				
Shigella sp.	+	+	+	+
Proteus vulgaris	+	+	+	+
Acinetobacter sp.	0	+	0	
Ps. aeruginosa	+	+	+	+
S. maltophilia	0	0	0	0
Brucella sp.	+			



Antibacterial Spectrum

✓ Gram-positive aerobic bacteria

	Gentamicin	Tobramycin	Amikacin	Netilmicin
Strep. species	0	0	0	0
Enterococcus faecalis	S	S	S	S
Enterococcus faecium	S	0	0	0
MSSA	S	S	S	S
MRSA	0	0	0	0
Staph. epidermidis	±	±	±	±
C. jeikeium	0	0	0	0
L. Monocytogenes	S	S	S	S



Antibacterial Spectrum

✓ Miscellaneous

	Gentamicin	Tobramycin	Amikacin	Netilmicin
Chlamydia sp.	0	0	0	0
M. pneumoniae	0	0	0	0
Rickettsia sp.	0	0	0	0
Mycobacterium avium	0	0	+	0
Anaerobes	0	0	0	0

Mycobacteria: Streptomycin, Kanamycin, Amikacin

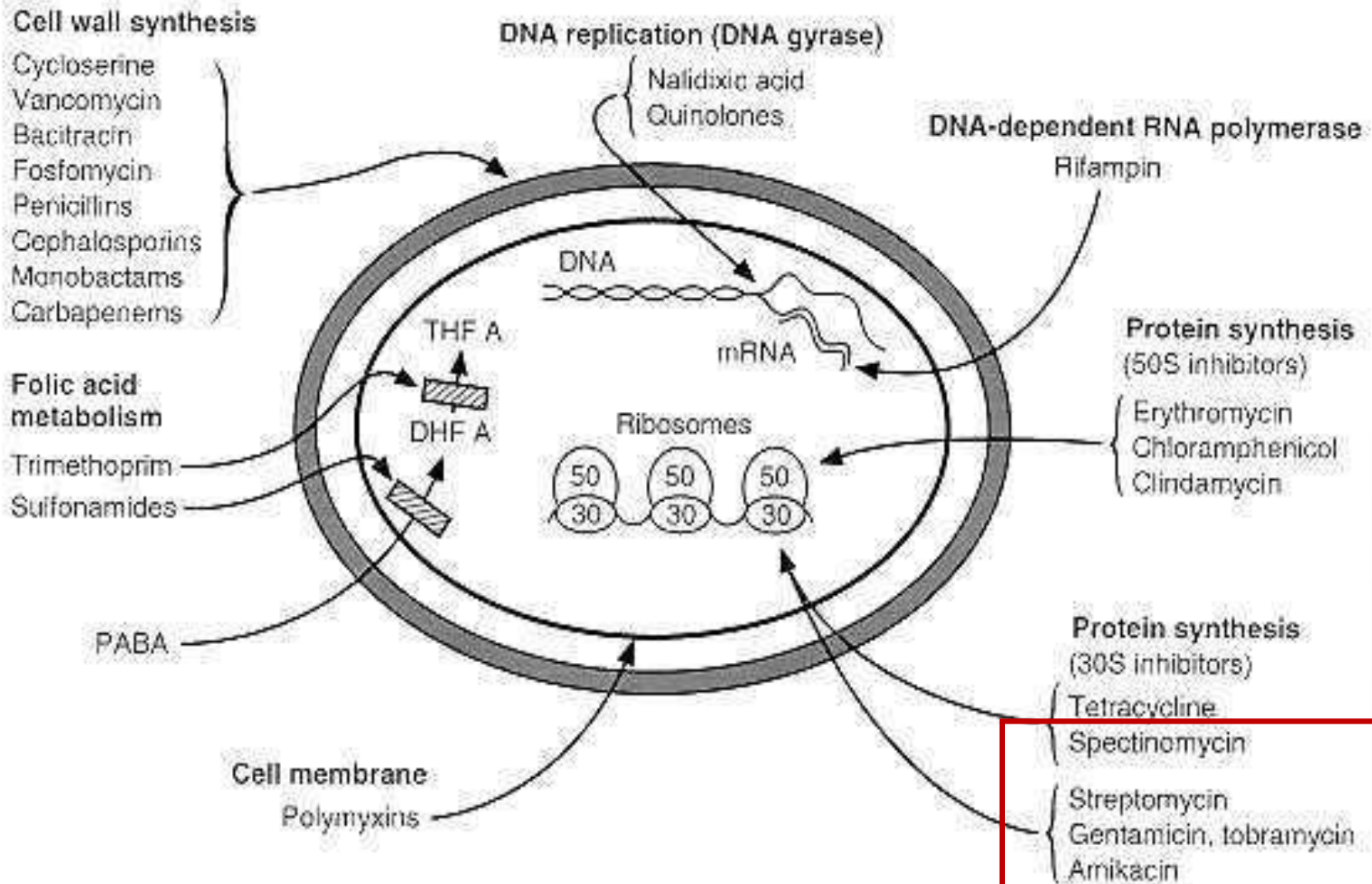
Parasites: Paromomycin



Mechanism of action

- Transportation across bacterial cell wall
- Inhibit protein synthesis
 - irreversibly binding to 30S ribosomal subunits
 - Interfere with the initiation of protein synthesis**
 - Premature termination of translocation**
 - Incorporation of incorrect amino acid**
- Bactericidal, Concentration dependent killing
- **Post antibiotic effect:** persistent suppression of bacterial growth after a brief exposure (1 or 2 h) of bacteria to an antibiotic

MOA of Aminoglycosides





Resistance

M. tuberculosis, Proteus, E. Coli, Aerobacter, H. influenza, S. aureus, Pseudomonas

- **Low level resistance:** Decreased cell permeability: Pseudomonas
- **High level resistance:** single step mutation in ribosomes: E.Coli
- **'R' factor mediated resistance:** enzymes which destroy the AG. Nosocomial inf.



Pharmacokinetics: Absorption

- Polycationic nature
 - Water soluble and poorly lipid soluble
- All are given as water soluble sulfate salts
 - Infusion
 - IM injected dose is rapidly absorbed
 - Strong tissue binding. residual amounts can be found at the injection site for long periods of time



Distribution

- Minimally protein bound (10%)
- Therapeutic concentrations are produced only in ECF.
 - Do not penetrate into the CNS or eye
 - May cross the placenta
- High concentrations in kidney, the cochlea, and vestibular apparatus.
 - Elimination half life from these tissues is much longer than that from plasma



Metabolism

Elimination

- >90% of injected drug is eliminated from the kidney via glomerular filtration
- **Renal dysfunction**
 - Dosage adjustment
 - Lowering the dose
 - Increasing the interval
 - Both
 - Therapeutic drug monitoring



Adverse effects

- Dose related!!!!
- Concentration dependence
 - Proximal tubular cell damage
 - Destruction of sensory cells in cochlea
 - Destruction of sensory cells in vestibular apparatus
 - Neuromuscular paralysis



Nephrotoxicity

- 5% ~ 10 %, Dose-related, prolonged therapy (>10 days)
- Pathophysiology
 - More poly-cationic like gentamicin and neomycin , enter proximal tubular cells by pinocytosis.
 - Inhibit lysosomal enzymes, the vesicles accumulate and take on a whorl-like appearance
 - Excessive numbers of these apparently kill the cells, producing severe toxicity.



Nephrotoxicity

- Proximal tubular necrosis
- Medullar region (Henle loop and collecting duct) of the nephron.
- Manifestations
 - Loss of urinary concentrating power
 - Low gfr: PG mediated
 - Nitrogen retention
 - Albuminuria
 - Casts
 - Ototoxicity



Risk Factors

- Advanced age
- Reduced aminoglycoside clearance
- Prolonged aminoglycoside usage
- Underlying renal insufficiency
- Co-administration of other nephrotoxic agents
- Leukemia, Sepsis, Shock
- Liver or kidney disease



Which one is the most Dangerous ??

- Based on dose-response data
 - Gentamicin > Tobramycin & Amikacin > Netilmicin
- Number of free amino groups & relative nephrotoxicity
- Initial presentation
 - Proteinuria and cylindruria (casts in urine), Creatinine elevation

How to Minimize Nephrotoxicity

Drug	Therapeutic Concentration (mcg/mL)	Maximum Peak Concentration (mcg/mL)	Maximum Trough Concentration (mcg/mL)
Amikacin	15-25	35	5
Gentamicin	4-10	10	2
Kanamycin	15-30	30-35	5
Netilmicin	6-12	16	2
Streptomycin	--	20-25*	--
Tobramycin	4-10	10	2

* In patients with renal damage. Peak concentrations greater than 50 mcg per mL are associated with increased risk of toxicity. [USPD195,71]

- Peak and trough levels
- Renal function tests
- Serum creatinine levels
- Once-daily Dose ???



Ototoxicity

- Concentration & Duration
 - High concentration within a short duration
 - Long durations of therapy at lower conc.
- Progressively damage the sensory cells of the cochlea and vestibular apparatus
 - Killed sensory cells do not regenerate
- Manifested as cochlear and vestibular damage



Vestibular Damage

- Headache, Nausea, Vomiting
- Vertigo, Ataxia
- Nystagmus

Cochlear Damage

- Hearing frequency loss
 - High frequency tones first
 - Lower frequency tones
- Tinnitus
- Complete deafness



Ototoxicity

■ Antibiotic	Vestibular	Auditory
■ Streptomycin	+++	+
■ Tobramycin	+	+
■ Gentamicin	++	+
■ Netilmicin	+	+
■ Kanamycin	+	+++
■ Amikacin	+	+++
■ Neomycin	+	++++

ALL affect both, however!!



Risk factors for ototoxicity

- Impaired renal function
- Intrinsic ototoxic drug or combinations

How to avoid ototoxicity ??

- Renal, auditory, and vestibular function
- Aminoglycoside serum concentrations
- Avoid prolonged therapy and ototoxic agents



Neuromuscular paralysis

- Inhibit Ca^{++} from motor nerve ending
 - Interfere with mobilization of centrally located synaptic vesicles to fuse with the terminal membrane
 - Decrease the sensitivity of the muscle end plate to ACh
- Streptomycin, Neomycin > Kanamycin, Gentamicin, Amikacin > Tobramycin
- NM Blockers should be cautiously used with aminoglycosides



STREPTOMYCIN

- **Source:** Streptomyces griseus
- **AMS :** Narrow
- Myco. tuberculosis. E.coli, Proteins, Shigella, pseudomonas, H.influenzae, H.ducreyi, Y. pestis, Brucella, Nocardia, Klebsiella
- **ADR**
 - NT, OT, NMB, HT :rashes, eosinophilia, lymphadenopathy, dermatitis, Superinfection



STREPTOMYCIN

Preparation : Inj : 0.75, 1 gm powder /vial, I.M

USES :

- Tuberculosis
- Plague: 30 mg/kg/day IM for 10 days
- Tularaemia: 1-2 g IM daily for 7-10 days
- Brucellosis: doxycycline 200 mg + rifampicin 600 mg OD for 6 weeks
- SAGE: combination with penicillin for 4-6 weeks



GENTAMICIN

- **Source:** Micromonospora purpurea in 1964
- Differences from Streptomycin
 - More potent
 - AMS: E.coli, Proteus, Klebsiella, Enterobacter
Streptococcus faecalis, S. aureus
 - Ineffective against M. tuberculosis, S. pneumonia, S. pyogens
 - More nephrotoxic



GENTAMICIN

Preparations

- Inj : 20mg /ml , 80mg/ ml vial
- Drops : 0.3%
- Ointment : 0.1%
- Dose : 1-1.5 mg /kg /8th hrly I.M / I.V

Uses

- Topically : burns, conjunctivitis
- Urinary and respiratory tract infection
- SABE: *S. viridans* and *S. fecalis*
- Nosocomial infections, Meningitis



AMIKACIN

- Semisynthetic der. of kanamycin A
- Broadest spectrum
- **AMS:** Klebsiella, Proteus, E.Coli, Pseudomonas
- Resistant to inactivating enzymes that degrade aminoglycoside
- **Inj :** 100, 250, 500 mg in 2ml inj
- **Uses:** MDR TB, Hospital acquired infections



NEOMYCIN

- **Source:** *Streptomyces fradiae*
- **AMS:** Wide. Pseudomonas , S. pyogens insensitive
- Not used systemically
- **Preparations:** 0.3 % ointment, 0.5 % cream, 350, 500 mg tab,
- **Uses**
 - Topical application to skin and eye (NEOSPORIN powder)
 - Intestinal antiseptic: colonic surgery
 - Hepatic coma: reduce ammonia levels



FRAMYCETIN

- **Source:** *Streptomyces lavendulae*
- Preparations
 - Cream 1%, 0.5 % (Soframycin)
 - Eye drops : 0.5 %
- **Uses**
 - Staphylococcal skin infections
 - Nasal carriers of Staphylococci