Medicinal Chemistry **BP601TP**

Aminoglycosides

Prepared by:
Ms. Krutika Poshiya
Assistant Professor
M.Pharm

Aminoglycosides

- It includes Gentamicin ,Tobramycin , Amikacin, Netilmicin , Kanamycin ,Paromomycin, Streptomycin (systemic) & Neomycin, Framycetin (topical)

(Paromomycin- It is used orally for intestinal amebiasis and in the management of hepatic coma.)

- Primarily used to Tt inf.s caused by aerobic G-ve bact. & Streptomycin is an important agent for the Tt of Tuberculosis.

Aminoglycosides

- In contrast to most inhibitors of microbial protein synth. which are bacteriostatic the Amgl.s are bactericidal .
- Mutations affecting proteins in bact. ribosomes can confer marked resist. to their action

Aminoglycosides

These agents contain amino-sugars linked to an aminocyclitol ring by glycosidic bonds .

-They are polycations

- There polarity is responsb. in part for pharmacokinetic property shared by all memb.s of the gp. e.g.- **none is abs. adequately after oral administration.**
- Inadequate conc.s are found in CSF.

Aminoglycosides

- All are excreted rapidly by normal kidney.
- Amgl.s are widely used but their toxicity limits their usefulness (esp. **nephrotoxicity & ototoxicity**).

History :

-They are natural prod.s or semisynth.

Aminoglycosides

derivatives of compd.s produced by variety of soil Actinomycetes .

- Streptomycin first isolated from **Streptomyces griseus**.
- Gentamicin & Netilmicin are broad spect. antb.s derived from sp. of the Actinomycetes - Micromonospora .

Aminoglycosides

The difference in spelling :

-micin ,antb.s originate from Genus- Micromonospora

-mycin, antb.s originate from Genus- Streptomyces

-semisynth. derivatives e.g. Netilmicin also end with suffix "micin"

-Tobramycin is one of several components of an Amgl. complex that is produced by S. tenebrarius. It is ≡ Gentamicin .

- Amikacin a derivative of Kanamycin

Aminoglycosides

& Netilmicin a derivative of Sisomicin are semisynth. product .

Chemistry :

Amgl.s consists of two or more amino sugars joined in glycoside linkage to a hexose nucleus . This hexose or aminocyclitol is either **streptidine**

Aminoglycosides

(found in Streptomycin) or **2-deoxy streptamine** (found in all other Amgl.s)

-Amgl. family is distinguished by the aminosugar attached to the aminocyclitinol .

Mech. of action :

Amgl. antb.s are rapidly bactericidal

Aminoglycosides

- It is conc. dependent. The higher the conc. the greater is the rate at which bact.s are killed (**Conc. Dependent Killing**)

-The **post antibiotic effect** i.e. residual bactericidal action persist after the serum conc. falls below the MIC (**minimum inhibitory concentration)** also a

Aminoglycosides

a characteristic of Amgl.s (accounts for once daily dosing regimen of Amgl. antb.s).

- Amgl.s diffuse through aq. channels formed by Porin protein in the outer membrane of G-ve bact. to the periplasmic space.

Aminoglycosides

-Transport of Amgl. across cytoplasmic (inner) memb. depends on electron transport . This phase of transport has been termed as ***energy dep. phase I*** **(EDP I)** . {It can be blocked by divalent cations e.g. Ca++ & Mg ++ ions (rate limiting) , hyperosmolarity , low pH and & anaerobic conditions }

Aminoglycosides

(thus the AM action of Amgl. is reduced markedly in the anaerobic environment of an abscess & in hyperosmolar acidic urine) .

- Once inside the cell it binds to polysomes & interfere with protein synthesis by causing misreading &

Aminoglycosides

premature termination of mRNA transl.

→ aberrant protein prod. & insertion into the cell membrane → altered permeability & ↑ further transport of Amgl.

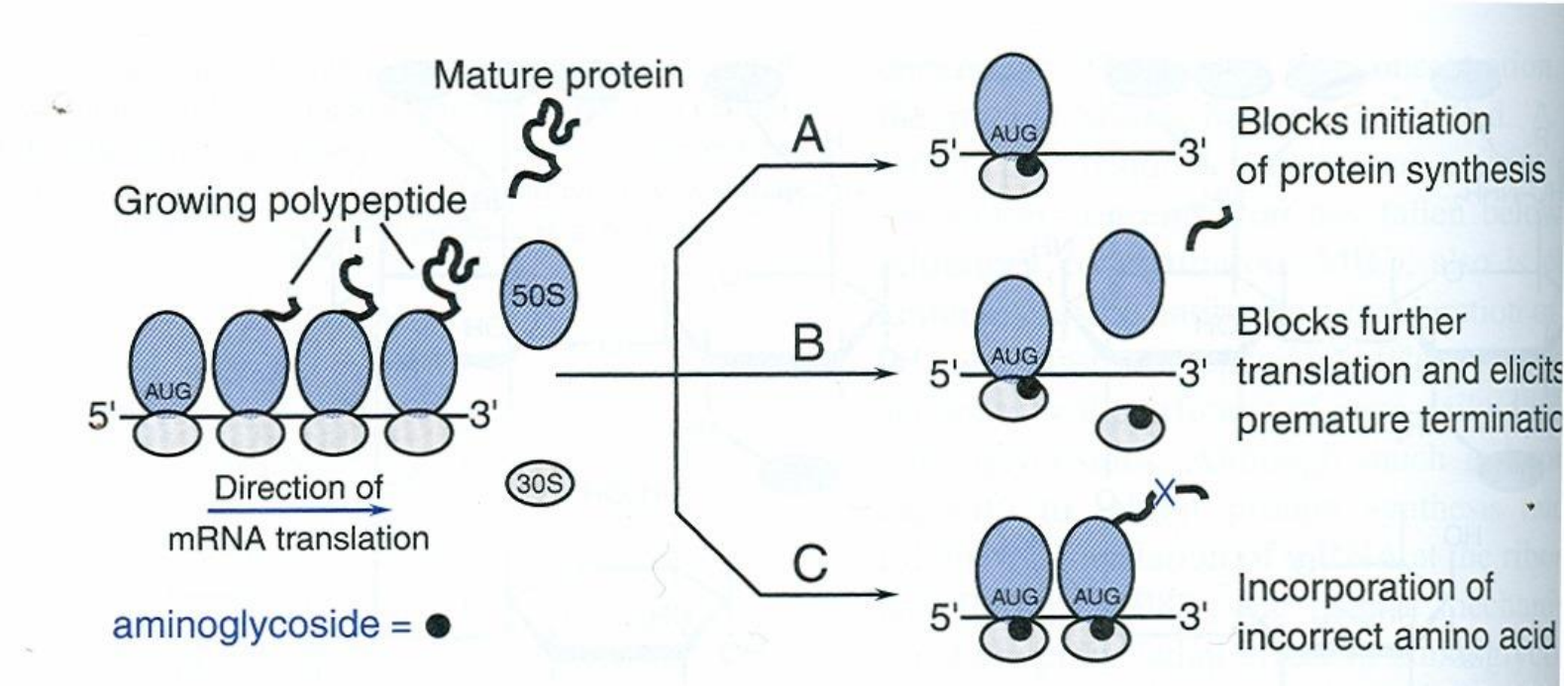
This is termed as ***energy dep. phase II*** **(EDPII)** which is ≈ disruption of cell membrane by aberrant protein.

Aminoglycosides

- This progressive disruption of the cell envelop , as well as other vital processes may help in explaining the lethal action of Amgl.s .

(**The primary intracellular site of action of the aminoglycoside is 30 S ribosomal subunit)**

Aminoglycosides



Aminoglycosides

Spectrum of Amgl.s :

-AM activity of Gentamicin ,Tobramycin, Kanamycin , Netilmicin & Amikacin is directed primarily against **aerobic G- ve bacilli** .

Aminoglycosides

- Kanamycin & Streptomycin has limited spectrum compared with other Amgl.s (not used in inf. caused by Serratia or P. aeruginosa).
- Amgl.s has little effect against anaerobic micro-organisms.

Aminoglycosides

or facultative bacteria under anaerobic conditions .

- Action against most G +ve bact. is limited & they should not be used as single agents to treat them (**G- ve cocci are also not sensitive**)

e.g. in comb. with Penicil. & Vancomy.

Aminoglycosides

The Amgl. Gentamicin & Streptomycin are tested extensively , they produce synergistic bactericidal effect in vitro against Enterococci , Streptococci & Staphylococci.

- the aerobic G- ve bacilli vary in their susceptibility to the Aminoglycosides

Aminoglycosides

- Tobramycin & Gentamicin exhibit similar activity against most G-ve bacilli .
- Tobramycin > active against

  P. aeruginosa & some proteus spec.

  (**Amikacin** & in some instances Netilmicin retain their act. against Gentamicin resistant strains because they are a poor substrate for many of the Amgl. inactivating enzymes.)

Aminoglycosides

Absorption ,Distribution ,Dosing & Elimination of the Amgl. :

-Amgl. are highly polar cations & hence poorly abs. from GIT .

-The drugs are not inactivated in the intestine & are eliminated in the feces

Aminoglycosides

(**Long term oral or rectal administration of Amgl.s may result in accumulation up to toxic concentration in pts with renal impairment** .) .

-Installation of these drugs into body cavities with serosal surfaces also may result in rapid absorption &unexpected toxicity (**recurrent muscular blockade**).

Aminoglycosides

-Similarly topical application for long periods (in large wounds , cut ulcers & burns) causes toxicity .

-All are absorb rapidly from I.M. site of inj.s .(**Peak conc. reaches after 30-90 min.s**)

Aminoglycosides

Distribution :

-Polar nature so not penetrate into **most cells , CNS & eye** .

-They do not bind to pl. albumin (except Streptomycin)

-Conc. of Amgl.s in secretions & tissues are also low.

Aminoglycosides

- High conc.s are found only in the **renal cortex , endolymph & perilymph** of the inner ear (**& likely contribute to nephrotoxicity & ototoxicity respectively**) .
- Bile represents only minor route of elimination.

Aminoglycosides

- inflam. ↑ the penetration of Amgl. in the peritoneal & pericardial fluids .
- Conc. of Amgl.s in CSF with parenteral administ. usually are sub-therapeutic (**Concentration in CSF is< 10% of plasma & ↑ to 25% in meningitis and intrathecal & intraventricular administration** of **Amgl.s and can achieve therapeutic levels**) .

Aminoglycosides

-Administ. in women in late pregnancy may result in accumulation of drug in fetal plasma & amniotic fluid & can cause hearing loss (e.g. Streptomycin & Tobramycin).

So they are used with caution during pregnancy & only for strong clinical indication.

Aminoglycosides

Dosing :

Current procedure is to give total daily dose as a single injection

(**It is associated with less toxicity & as effective as multiple doses**)

Aminoglycosides

-Once daily dosing also cost less &

administered more easily .so it is better to give single daily dose.

(exception is use in pregnancy , neonates & pediatric infection & combination low dose therapy in endocarditis)

Aminoglycosides

- Once daily dose should be avoided in pt with Creatinine clearance< 20 - 25 ml/min because accumulation can occur so less frequent dosing (**48hrly**) is more appropriate .

Aminoglycosides

Creatinine Cl.	% of max. daily dose	Freq. of dosing
100	100	every 24 hr
75	75	
50	50	
25	25	
20	80	every 48 hr
10	60	
< 10	40	

Aminoglycosides

-The maximum daily dose for

-Amikacin ,Kanamycin & Streptomycin

-**15mg/kg**,

-Gentamicin & Tobramycin is

-5.5mg/kg

-Netilmicin **-6.5 mg/kg**

(Monitoring will be done in multiple daily dosing where renal function test are compromised or impaired .)

Aminoglycosides

Elimination :

eliminated almost entirely by glomer.

filtrate.(**renal cl. of Amgl. is ⅔ of creatinine cl.).**

- Amgl.s can be remove from the body by either hemodialysis or peritoneal dialysis .

Aminoglycosides

S/E –

All Amgl.s have the potential to prod. reversible or irreversible

vestibular /cochlear & **renal toxicity**.

These side effects complicate the use of these compounds .

Aminoglycosides

Ototoxicity -

- Vestibular & auditory dysfunction is because of accumulation of drug in perilymph & endolymph .

- The t ½ is 5-6 times high in otic fluid than in plasma . (Ototoxicity has been linked to mutation in the mitochondrial ribosome RNA gene - **genetic predisposition.**) .

Aminoglycosides

- It is largely irreversible (more resistant in Cochlear changes & results from prolong destruction of vestibular or cochlear sensory cells .
- Repeated course of Amgl. can probably resulting in the loss of nerve cells which leads to deafness & ataxia.

Aminoglycosides

(Drug e.g. **Ethacrynic acid & Furosemide** potentiates the ototoxic effect of Amgl.s if given simultaneously).

- More in pts having preexisting auditory impairment .

(**Streptomycin** & **Gentamicin** predominantly produces **vestibular toxicity** whereas **Amikacin** ,**Kanamycin** & **Neomycin** affects **auditory function** ,**Tobramycin** affects **both equally**).

Aminoglycosides

- **Cochlear Toxicity-**

  First symptom is tinnitus & if drug is not discontinued then impairment of auditory function occurs after a few days .

Aminoglycosides

Vestibular toxicity-

headache in 1-2 days → nausea ,vomiting & diff. in equilibrium (if persists for 1-2 wks)⟶ vertigo in upright position , diff in standing & sitting (**+ve Romberg test**).

Rarely spontaneous Nystagmus & Chronic labrynthitis leads to **ataxia** in in walking .

Aminoglycosides

Nephrotoxicity :

-Mild renal impairment. – if Amgl.s are given for more than several days & is **reversible**

-Late effect- mild proteinuria & appearance of hyaline & granular cost in microscopic examination of urine → ↓↓ **GFR .**

Aminoglycosides

- Severe acute tub. necrosis may occur rarely (mild ↑ in creatinine cl.) .
- The impairment in renal functions is almost always revers. (**because the prox. renal tubular cells have the capacity to regenerate**).
- Neomycin is highly nephrotoxic & not given systemically .

Aminoglycosides

- Streptomycin does not conc. in renal cortex so **least nephrotoxic.**

- AmphotericinB , Vancomycin, ACEIs, Cisplatin & cyclosporin may pot. Amgl induced nephrotoxicity.

Aminoglycosides

Neuromuscular blockade :

Order of decreasing potency for this is

Neomycin > Kanamycin > Amikacin >

Gentamicin & Tobramycin (**especially after intra pleural or intra peritoneal instillation in high doses** .)

- Pts of myasthenia gravis are more susceptible to Amgl.s for this effect.

Aminoglycosides

-It is due to ↓ in prejunc. release of **Ach** & also due to ↓ in post synaptic sensitivity to transmitter. (**Tt. is – IV Ca-gluconate / IV Neostigmine)**

Others –

-Streptomycin can cause **optic nerve damage .**

-H/S react.s are rare – skin rash, eosinophilia , fever , blood dyscrasia

Aminoglycosides

angiodema , exfoliative dermatitis & stomatitis.

1.) **Streptomycin** :

Used for the Tt of certain unusual inf. gen. in comb with other AM agents.

it is less active than other memb.s against aerobic G -ve rods .

Aminoglycosides

- Given deep I.M. / I.V. & I.M may be painful at the site of injection.

(**dose – 10-15mg/kg/day**)

Uses :

1. **Bact. endocarditis** (**Streptomycin + Penicillin produces synergistic & bactericidal effect**)
2. **Tularemia** -DOC (Gentamicin, Fluroquinolones & Tetracyclines are also given)

Aminoglycosides

3. **Plague** – effective in all forms –(2gm I.M./ day in 2div.doses x7-10 days≡ Gentamicin & Tetracyclines)
4. **Tuberculosis** – always used in combination with at least one or two other drugs.

(**dose- with normal renal function is 15 mg/kg/day OD. X 2-3 months or 2-3 times a week.** .)

Aminoglycosides

2.) **Gentamicin** (& other Amgl.s):

(**dose- 2mg/kg , ⅓ given 8 hourly or single daily dose -5-7 mg/ kg**)

Uses :

- **UTI** – not indicated in uncomplicated inf.
- **Pneumonia** – in comb. with β- lactum
- **Meningitis** – with G- ve org. (**resistant to β-lactum e.g.- Pseudomonas , Acinobacter** .)

Aminoglycosides

- **Bact. endocarditis -** synergistic effect with Penicillin or Vancomycin.
- **Sepsis** : febrile patient with granulocytopenia. & infection with P. aeruginosa

Topical use –

Gentamicin absorb slowly when applied topically (**but more rapidly when applied as cream**) .

Aminoglycosides

3.)**Tobramycin** ≡ Gentamicin (**also as ophthalmic oint. & soln.**) > effective in inf. with P. aeruginosa

4.) **Amikacin** : broadest spectrum (**because resistant to many Amgl. inactivating enzymes**).

Aminoglycosides

-Specific role in **hospital acquired infection** **(dose- 10 mg/kg/day)**

DOC in serious nosocomial G -ve infection of hospitals.

- Not effective against most G-ve anaerobic bacteria.

Aminoglycosides

- Active against **M. tuberculosis** including Streptomycin resist. cases & atypical mycobacteria in **AIDS** pts .

5.) **Netilmicin** : Latest ≡ Gentamicin

- not metabolize by Amgl.s inactivating enzymes like Amikacin.

Aminoglycosides

- UTI – in complicated infection

  (**Dose – 1.5-2 mg / kg 12 hrly .**)

- Useful in Tt . of aerobic G- ve bacilli inf. & inf. with Enterobacteriaceae.

6.) **Neomycin**:

Broad spectrum antibiotic

(**G- ve** - highly sensitive species are – E.coli , Enterobacter , Klebsiella , Pneumococci , Proteus vulgaris , **G+ve** - S.aureus & M. tuberculosis –**acid fast rods**)

Aminoglycosides

Uses :

- Topical- skin & mucous memb. Infect.

(Neomycin sulfate- **burns , wounds ,ulcers & infective dermatosis**) **.**

-Oral with Erythromycin (for bowel prepr.) or Polymixin (**40 mg Neomycin + 2 lack Unit of Polymixin** for irrigation of bladder)

-In hepatic encephalopathy (**4-10 gm orally if renal functions are normal**)

Aminoglycosides

It kills the ammonia producing org.s in the large gut, but now Lactulose is preferred .

S/E – Hypersensitivity react . in topical use,

renal impairment & nerve deafness

oral – intestinal malabsorption. & superinfection

Aminoglycosides

7.) **Kanamycin** :

most toxic & spectrum of activity is limited (**Dose – 1.5 mg/kg /day)**

- **almost obsolete** .

(only in India – in resistant Tuberculosis with comb. of other drugs)

-prophylactic use -in hepatic encephalopathy **(6 gm /day)** .

Aminoglycosides

Framycetin: ≡ **Neomycin-**

It is also very toxic so used only for topical purpose (as ointment) – Skin inf. , otitis externa , furunculosis , burns & scalds & also as eye drops .

Aminoglycosides

Spectinomycin (produced by *Streptomyces spectabilis*) **:**

It is Aminocyclitol related to aminoglycosides , which is used as **single dose treatment** for –

-Penicillinase producing **Neisseria gonorrhoea (PPNG).**

-For gonorrhoea in Penicillin allergic patients

MCQs

1.Tick the drug belonging to antibiotics- Aminoglycosides:

- a) Erythromycin
- b) Gentamicin
- c) Vancomycin
- d) Polymyxin

. 2. Aminoglycosides are effective against**:**

- a) Gram positive microorganisms, anaerobic microorganisms, spirochetes
- b) Broad- spectrum, except Pseudomonas aeruginosa
- c) Gram negative microorganisms, anaerobic microorganisms
- d) Broad- spectrum, except anaerobic microorganisms and viruses

3. Aminoglycosides have the following unwanted effects**:**

- a) Pancytopenia
- b) Hepatotoxicity
- c) Ototoxicity, nephrotoxicity
- d) Irritation of gastrointestinal mucosa

4. The most important mechanism of bacterial resistance to an Aminoglycoside antibiotic is :

- (a) Plasmid mediated acquisition of aminoglycoside conjugating enzyme
- (b) Mutational acquisition of aminoglycoside hydrolyzing enzyme
- (c) Mutation reducing affinity of ribosomal protein for the antibiotic
- (d) Mutational loss of porin channels

5. Which toxic effect of aminoglycoside antibiotics is most irreversible in nature ?

(a) Vestibular damage

- (b) Hearing loss
- (c) Neuromuscular blockade
- (d) Kidney damage

6.Select the antibiotic whose dose must be reduced in patients with renal insufficiency :

- (a) Ampicillin (b) Chloramphenicol
- (c) Tobramycin (d) Erythromycin

7. The aminoglycoside antibiotic which is distinguished by its resistance to bacterial aminoglycoside inactivating enzymes is :

- (a) Kanamycin (b) Sisomicin
- (c) Amikacin (d) Tobramycin

8. An aminoglycoside antibiotic should not be used concurrently with the following drug :

- (a) Ampicillin (b) Vancomycin
- (c) Ciprofloxacin (d) Rifampin

9. The aminoglycoside that can be used in amoebiasis is :

- (a) Paromomycin (b) Framycetin
- (c) Amikacin ((d) Netilmicin

10. Streptomycin sulfate is not absorbed orally because it is :

- (a) Degraded by gastrointestinal enzymes
- (b) Destroyed by gastric acid
- (c) Highly ionized at a wide range of pH values
- (d) Insoluble in water

11. Aminoglycoside antibiotics have the following common property **:**

- (a) They are primarily active against gram negative bacilli
- (b) They are more active in acidic medium
- (c) They readily enter cells and are distributed in total body water
- (d) They are nearly completely metabolized in Liver

12. Which aminoglycoside antibiotic causes more hearing loss than vestibular disturbance as toxic effect **?**

- (a) Streptomycin
- (b) Gentamicin
- (c) Kanamycin
- **(**d) Sisomicin

- 13. Single dose of Aminoglycoside administration is more preferable than 8 hourly dose because of:
- a) Post antibiotic effect
- b) Increase perfusion of renal cortex
- c) MIC
- d) Time dependent killing

Answer Key

- 1-a ,2-d, 3-c, 4-a, 5-b , 6-c , 7-c, 8-b, 9-a , 10-c, 11-a, 12-c, 13-a

Bibliography

1.Goodman & Gilman's ,The Pharmacological Basis of Therapeutics (12th Edition).

2. Principles of Pharmacology by H. L. Sharma & K K Sharma (Latest Edition)

3. A complete Textbook of Medical Pharmacology by S. K. Srivastava (Latest Edition)

4. Essentials of Medical Pharmacology by K. D. Tripathi (7th edition)