

AMINOGLYCOSIDES

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Aminoglycosides - Properties

- Contain two or more aminosugars joined in glycoside linkage
- Are highly polar compounds, hence not adequately absorbed orally from the GI tract
- Are administered by parenteral (i.v., i.m.) route for systemic effect
- Mainly distributed into extracellular fluid.
- Poorly penetrate into CSF, but crosses placenta thereby increases risk of foetal toxicity

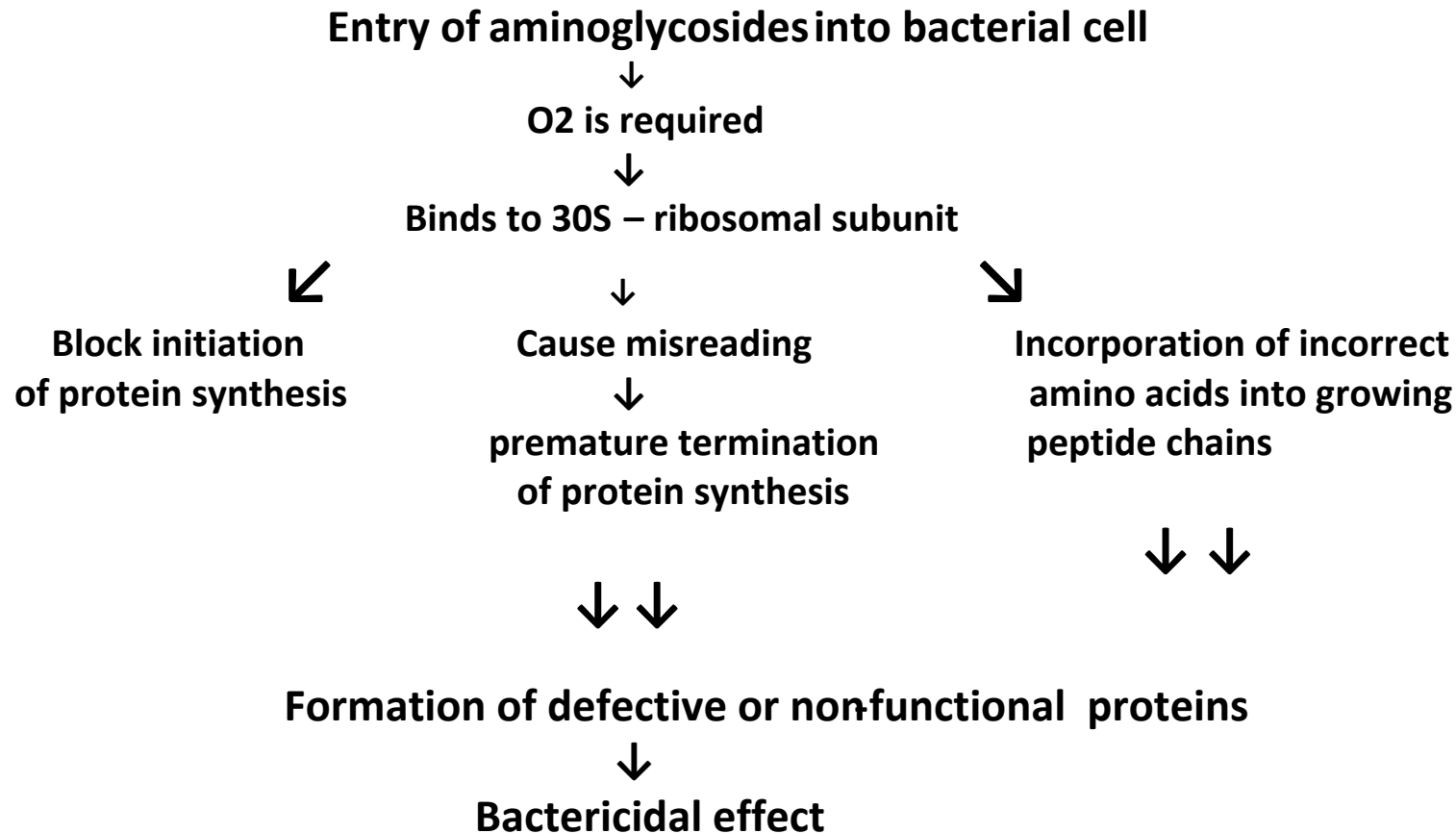
Aminoglycosides – Properties (Contd..)

- Are not metabolized in the body
- Are excreted unchanged in the urine
- Have Bactericidal action against Gm –ve aerobes (Narrow antibacterial spectrum). Streptomycin & Kanamycin are active against Mycobacterium Tuberculosis, hence used in the treatment of Tuberculosis
- Are more active at alkaline pH
- They exhibit ototoxicity, nephrotoxicity and neuromuscular blocking effects
- They exhibit partial cross-resistance among them

Aminoglycosides – Properties (Contd..)

- Transport of aminoglycosides into the bacterial cell requires oxygen, hence anaerobes are resistant to aminoglycosides
- They exhibit synergism when combined with Beta-lactam antibiotics
- **Examples :-**
- Streptomycin, Gentamicin, Amikacin, Kanamycin, Tobramycin, Netilmicin, Neomycin & Framycetin....

Aminoglycosides – Mechanism of Action



Aminoglycosides – Mechanism of Action (Contd..)

- **Aminoglycosides exhibits :-**
 1.) **A concentration – dependent killing effect** – Higher the plasma concentration, greater is the bacterial killing effect.
 2.) **A postantibiotic effect** – Bactericidal effect is present even when serum concentration falls below MIC value. **Hence**, once- daily dosing regimen is effective.

Aminoglycosides – Bacterial Resistance

- Bacteria **develop resistance to aminoglycosides** by following mechanisms :-
 - **1) Inactivation by microbial enzymes which inactivates aminoglycosides** (Amikacin & Netilmicin are not affected by these aminoglycosides inactivating enzymes, hence used when Gentamicin has developed resistance)
 - **2) Failure of Penetration** (can be overcome by concomitant use of Penicillins or Vancomycin)

Dosing of Aminoglycosides

- **1) Multiple – daily dosing regimen** – the total daily dose is administered in two or three equally divided doses
- **2) Once – daily dosing regimen** – total daily dose is given as a single injection.
- **It is preferred because :-**
 - ** is as effective as multiple – dose regimen
 - ** is as safe as multiple – dose regimen
 - ** is more convenient
 - ** is less expensive and cost effective
 - ** Better patient compliance

Aminoglycosides – Adverse Effects

- **1) Ototoxicity :-** due to progressive irreversible destruction of cochlear & vestibular sensory cells, resulting into VIIIth cranial nerve damage (degeneration of auditory nerve)
- **Cochlear dysfunction :-**
- Aminoglycosides get concentrated in the perilymph and endolymph of the inner ear -à which leads to the progressive damage to cochlear hair cells -à loss of high density sound first followed by low density sound à damages VIIIth cranial (auditory) nerve à causing degeneration and precipitate irreversible loss of hearing (permanent deafness). Manifestations of cochlear dysfunctions are tinnitus and deafness.
- **Cochlear dysfunction :** Amikacin, kanamycin, Neomycin

Aminoglycosides – Adverse Effects (Contd...)

- **Vestibular Dysfunction :-**
- Aminoglycosides get concentrated in the perilymph and endolymph of the inner ear -à which leads to progressive damage of vestibular hair cells -à Vestibular dysfunction causes à intense headache, dizziness, nausea, vomiting, vertigo, nystagmus and ataxia.
- **Vestibular dysfunction :-** Gentamicin, streptomycin
- **Risk Factors for Ototoxicity :-** Old age, diuretics like Furosemide & Ethacrynic acid, repeated drug administration

Aminoglycosides – Adverse Effects (Contd...)

- **2) Nephrotoxicity :-**
- Aminoglycosides get concentrated in the renal cortex & produce nephrotoxicity → Reversible
- **Nephrotoxicity (High) :** Neomycin & Gentamicin
- **Nephrotoxicity (Low) :** Streptomycin
- **Risk Factors for Nephrotoxicity :-**
- Elderly Pts, pre-existing renal disease & concurrent use of other nephrotoxic drugs like AMB, Vancomycin, Cisplatin, Cyclosporine etc...

Aminoglycosides – Adverse Effects (Contd...)

- **3) Neuromuscular Blocking Effect :-**
- Apnoea & muscular paralysis occur à due to inhibition of release of Acetylcholine from the motor end plate of the nerve by aminoglycosides
- Myaesthenic pts more susceptible to aminoglycosides , hence C/I.
- **4) Hypersensitivity reactions :-** skin rashes, drug fever, eosinophilia can occur
- **5) Ototoxicity in foetus :-** if given during pregnancy.

Aminoglycosides :Therapeutic Uses

- 1) Severe gram – negative aerobic bacillary infections :-
Gentamicin can be combined with Penicillin / Third Generation Cephalosporins for UTI with Pyelonephritis, pneumonia, meningitis, septicaemia, peritonitis, osteomyelitis, infected burns due to Pseudomonas, Klebsiella, E.Coli & Proteus..
- 2) Bacterial endocarditis due to S. Viridans, Enterococcus :-
Combination drugs preferred are :-
 - i) Gentamicin + Penicillin G à S. Viridans
 - li) Gentamicin + Vancomycin à Enterococcus (Pen. Allergy)
 - lii) Gentamicin + Ampicillin à Enterococcus ; For prophylaxis of endocarditis in high-risk patients before surgical procedures

Aminoglycosides :Therapeutic Uses

- **3) Tuberculosis** :- Streptomycin, Kanamycin and Amikacin are used in the treatment of T.B, MDR-T.B.
- **4) Other Gram – Negative Infections** :-
 - **i) Plague** : Stretomycin / Gentamicin + Tetracyclines
 - **ii) Brucellosis** : Streptomycin /Gentamicin + Doxycycline
 - **iii) Tularaemia** : Streptomycin/Gentamicin are DOC. Alternatively, Fluoroquinolones & Tetracyclines are effective
- **5) Topical Infections of Eyes & Skin** : Framycetin, Neomycin, Sisomycin, Tobramycin, Gentamicin used as ointments & eye drops.

Amikacin : Advantages

- 1) Effective against organisms producing aminoglycosides inactivating enzymes and hence does not develop resistance to microorganisms & are less toxic
- 2) Effective against nosocomial (Hospital-acquired) infections
- 3) Effective against Mycobacterium Tuberculosis and Atypical Mycobacteria
- 4) Disseminated atypical mycobacterium infection in AIDS patients
- 5) Used as an alternative to Gentamicin in resistance cases.

Streptomycin : Uses

- 1) Tuberculosis by i.m. Inj.
- 2) Plague with Tetracyclines
- 3) Tularaemia
- 4) Brucellosis with Doxycyline
- 5) Endocarditis with Penicillin

Gentamicin : Uses

- To treat Gm–ve aerobic infections like :-
 - 1) Bacteremia
 - 2) Meningitis
 - 3) Otitis media
 - 4) Pneumonia
 - 5) Peritonitis
 - 6) Enteric fever
 - 7) UTI
 - 8) Osteomyelitis
 - 9) Eye Infections (Eye drops)
 - 10) Enterococcal Endocarditis (Gm +ve) with Penicillin

Neomycin : Uses

- 1) Topically for various dermatological (ulcers, wounds, burn) and ophthalmic & ear infections (in combination with Bacitracin or Polymyxin B)
- 2) For irrigation of Bladder
- 3) For sterilization of the gut prior to bowel surgery (Neomycin + Erythromycin)
- 4) In patients with hepatic coma to reduce intestinal bacteria and to reduce blood concentration of ammonia (Neomycin, Kanamycin).