AMINOGLYCOSIDE ANTIBIOTICS

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AMINOGLYCOSIDE ANTIBIOTICS

→ These are a group of natural and semisynthetic antibiotics having polybasic amino groups linked glycosidically to two or more amino sugar residues.

Classification:-

1. Systemic aminoglycosides: - Ex. Streptomycin, Kanamycin, Tobramycin, Amikacin, etc.
2. Topical aminoglycosides:-Neomycin, Framycin.

They have following Characteristics:-

→ They have 2 or more aminosugars joined in glycosidic linkage to a hexose nucleus.
→ They are poorly absorbed from g.i.tract on oral administration.
→ They poor penetration into CNS.
→ They are excreted through the kidneys by glomerular filtration.
→ All of them develop fast resistance against various organisms.
→ They produce ototoxicity, nephrotoxicity and curaremimetic effects.
→ They are highly effective against gram negative bacteria.

Streptomycin:-

Streptomycin is obtained from Streptomyces griseus.

Mechanism of Action:-

Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. The antibiotic then binds to the 30S ribosomal subunit prior to ribosome formation. There, it interferes with assembly of the functional ribosomal apparatus and/or can cause the 30S subunit of the completed ribosome to misread the genetic code. Polysomes become depleted, because the aminoglycosides interrupt the process of polysome disaggregation and assembly. [Note: The aminoglycosides synergize with Î²-lactam antibiotics because of the latter's action on cell wall synthesis, which enhances diffusion of the aminoglycosides into the bacterium.]

Antibacterial Spectrum:-

Very Sensitive Microbes:- Actinomyces, B.anthrus, P.pestis, H.influenzae, M.tuberculosis, Shigella, E.coli, Aerobacteria, H.duczeyii and Brucella.

Moderately Sensitive Microbes:- Proteus vulgaris, Pseudomonas aeroginosa, Vibrio comma, Listeria, Nocardia.

Other Less sensitive microbes:- Staphylococci, streptococci, D.pneumoniae, Salmonella etc.

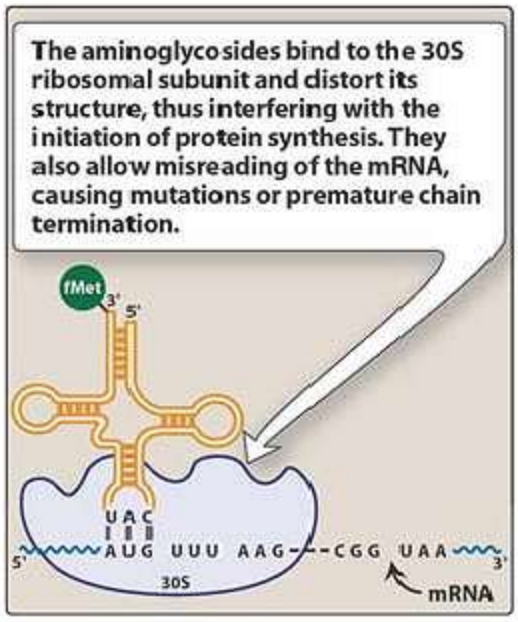

Figure: - Mechanism of action of the aminoglycosides.

Resistance:-

→ As streptomycin does not affect the vital metabolic processes, resistance is developed more rapidly than what it is with penicillin.

→ Some microbes utilize streptomycin in their metabolic processes, thus developing streptomycin dependence.

→ Simultaneous administration of another tuberculostatic drug reduces this bacterial resistance.

→ PAS and isoniazide are very widely used along with streptomycin for their synergistic action.

The mechanisms by which resistance may develop to streptomycin are as follow:

A. **Mutation:** Bacteria may undergo genetic changes and hence streptomycin fails to bind with 30s ribosomes.
B. **Inability to transport:** streptomycin from extracellular site to intracellular site.
C. **Induction of enzymes:** In bacteria such as adenylate synthetase phosphorylase, acetylase. These enzymes may digest even streptomycin.

Pharmacokinetics:-

A. **Administration:**

→ The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. Therefore, all aminoglycosides (except neomycin) must be given parenterally to achieve adequate serum levels.

→ [Note: The severe nephrotoxicity associated with neomycin precludes parenteral administration, and its current use is limited to topical application for skin infections or oral administration to prepare the bowel prior to surgery.]

→ The bactericidal effect of aminoglycosides is concentration and time dependent; that is, the greater the concentration of drug, the greater the rate at which the organisms die. They also have a post-antibiotic effect.

→ Because of these properties, once-daily dosing with the aminoglycosides can be employed. This results in less toxicity and is less expensive to administer. The exceptions are pregnancy, neonatal infections, and bacterial endocarditis, in which these agents are administered in divided doses every 8 hours. [Note: The dose that is administered is calculated based on lean body mass, because these drugs do not distribute into fat.]

B. **Distribution:**

→ Levels achieved in most tissues are low, and penetration into most body fluids is variable.

→ Concentrations in CSF are inadequate, even when the meninges are inflamed. Except for neomycin, the aminoglycosides may be administered intrathecally or intraventricularly.

→ High concentrations accumulate in the renal cortex and in the endolymph and perilymph of the inner ear, which may account for their nephrotoxic and ototoxic potential.

→ All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

C. **Fate:**

→ Metabolism of the aminoglycosides does not occur in the host.

→ All are rapidly excreted into the urine, predominantly by glomerular filtration.

→ Accumulation occurs in patients with renal failure and requires dose modification.

Adverse Effects:-

→ It is important to monitor plasma levels of gentamicin, tobramycin, and amikacin to avoid concentrations that cause dose-related toxicities.

→ Patient factors, such as old age, previous exposure to aminoglycosides, and liver disease, tend to predispose patients to adverse reactions.

→ The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. **Ototoxicity:** Ototoxicity (vestibular and cochlear) is directly related to high peak plasma levels and the duration of treatment. The antibiotic accumulates in the endolymph and perilymph of the inner ear, and toxicity correlates with the number of destroyed hair cells in the organ of Corti. Deafness may be irreversible

and has been known to affect fetuses in utero. Patients simultaneously receiving another ototoxic drug, such as cisplatin or the loop diuretics, furosemide, bumetanide, or ethacrynic acid, are particularly at risk. Vertigo and loss of balance (especially in patients receiving streptomycin) may also occur, because these drugs affect the vestibular apparatus.

2. **Nephrotoxicity:** Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes, and this results in kidney damage ranging from mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible.
3. **Neuromuscular paralysis:** This side effect most often occurs after direct intraperitoneal or intrapleural application of large doses of aminoglycosides. The mechanism responsible is a decrease in both the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site. Patients with myasthenia gravis are particularly at risk. Prompt administration of calcium gluconate or neostigmine can reverse the block.
4. **Allergic reactions:** Skin rash, eosinophilia, pericarditis, angioneurotic edema and anaphylaxis, Contact dermatitis is a common reaction to topically applied neomycin.
5. **Curaremimetic effects** i.e skeletal muscle relaxant effect leading to respiratory arrest.

Therapeutic Uses:-

1. Tuberculosis
2. Plague
3. Urinary tract infections
4. Meningitis due to H.influenzae
5. Bacteraemia
6. Endocarditis
7. Respiratory tract infections
8. Gonorrhoea
9. Granuloma venerium infection
10. Tularemia
11. Brucellosis