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PHARMACOLOGY ASSIGNMENT

QUESTION 1 : Write on a named bacterial protein synthesis inhibitor, stating its mechanism of action, indication for use, toxicity and adverse effect

AMINOGLYCOSIDES

Aminoglycosides are bactericidal inhibitors of protein synthesis that interfere with ribosomal function. They are useful mainly against aerobic Gram-negative microorganisms. The aminoglycosides include streptomycin, neomycin, kanamycin, amikacin, gentamicin, tobramycin, sisomicin, netilmicin, and others. They are used most widely in combination with other agents to treat drug-resistant organisms

PHARMACOKINETICS

Aminoglycosides are absorbed very poorly from the intact gastro-intestinal tract, and almost the entire oral dose is excreted in feces after oral administration. minoglycosides are usually administered intravenously.After intramuscular injection, aminoglycosides are well absorbed, giving peak concen-trations in blood within 30–90 minutes. Aminoglycosides are highly polar compounds that do not enter cells readily. They are largely excluded from the central ner-vous system and the eye.Even after parenteral administration, concentrations of aminoglycosides are not high in most tissues except the renal cortex.

When administered with a cell wall-active antibiotic (a β-lactam or vancomycin), aminoglycosides may exhibit synergistic killingagainst certain bacteria. The effect of the drugs in combination is greater than the anticipated effect of each individual drug; ie, the killing effect of the combination is more than additive. This synergy may be important in certain clinical situations, such as endocarditis.Adverse effects from aminoglycosides are both time- and concentration-dependent. Toxicity is unlikely to occur until a certain threshold concentration is reached, but, once that concentra-tion is achieved, the time beyond this threshold becomes critical.

Aminoglycosides are cleared by the kidney, and excretion is directly proportional to creatinine clearance.

CLINICAL USES

Aminoglycosides are mostly used against aerobic Gram-negative bacteria, especially when there is concern for drug-resistant patho-gens or in critically ill patients. They are almost always used in combination with a β-lactam antibiotic to extend empiric cover-age and to take advantage of the potential synergism between these two classes of drugs. Penicillin-aminoglycoside combinations have also been used to achieve bactericidal activity in treatment of enterococcal endocarditis and to shorten duration of therapy for viridans streptococcal endocarditis. Due to toxicity, these com-binations are used less frequently when alternate regimens are available. For example, in the case of enterococcal endocarditis, studies suggest that the combination of ampicillin and ceftriaxone is an effective regimen with less risk for nephrotoxicity. When aminoglycosides are used, the selection of agent and dose depends on the infection being treated and the susceptibility of the isolate

INDICATION

Aminoglycosides are useful primarily in infections involving aerobic, Gram-negative bacteria, such as Pseudomonas, Acinetobacter, and Enterobacter. In addition, some Mycobacteria, including the bacteria that cause tuberculosis, are susceptible to aminoglycosides. Streptomycin was the first effective drug in the treatment of tuberculosis, though the role of aminoglycosides such as streptomycin and amikacin has been eclipsed (because of their toxicity and inconvenient route of administration) except for multiple-drug-resistant strains.The most frequent use of aminoglycosides is empiric therapy for serious infections such as sepsis, complicated intra-abdominal infections, complicated urinary tract infections, and nosocomial respiratory tract infections. Usually, once cultures of the causal organism are grown and their susceptibilities tested, aminoglycosides are discontinued in favor of less toxic antibiotics.

As noted, aminoglycosides are mostly ineffective against anaerobic bacteria, fungi, and viruses.[2] Infections caused by Gram-positive bacteria can also be treated with aminoglycosides, but other types of antibiotics are more potent and less damaging to the host. In the past, the aminoglycosides have been used in conjunction with beta-lactam antibiotics in streptococcal infections for their synergistic effects, in particular in endocarditis. One of the most frequent combinations is ampicillin (a beta-lactam, or penicillin-related antibiotic) and gentamicin.

## CONTRAINDICATION

Aminoglycosides can exacerbate weakness in patients withmyasthenia gravis, and use is therefore avoided in these patients.

Aminoglycosides are contraindicated in patients with mitochondrial diseases as they may result in impaired mtDNA translation, which can lead to irreversible hearing loss, tinnitus, cardiac toxicity, and renal toxicity. However, hearing loss and tinnitus have also been observed in some patients without mitochondrial diseases

MECHANISM OF ACTION

The drug is passively diffused across the outer membrane via porin channels.Drug is then actively transported across the cell me-brane into the cytoplasm by an oxygen-dependent process. The transmembrane electrochemical gradient supplies the energy for this process, and transport is coupled to a proton pump. Low extracellular pH and anaerobic conditions inhibit transport by reducing the gradient. Transport may be enhanced by cell wall-active drugs such as penicillin or vancomycin; this enhancement may be the basis of the synergism of those antibiotics with aminoglycosides.Inside the cell, aminoglycosides bind to 30S-subunit ribosomal proteins. Protein synthesis is inhibited by aminoglycosides in at least three ways :

 (1) interference with the initiationcomplex of peptide formation;

(2) misreading of mRNA, which causes incorporation of incorrect amino acids into the peptide and results in a nonfunctional protein

(3) breakup of polysomes into nonfunctional monosomes. These activities occur more or less simultaneously, and the overall effect is irreversible and leads to cell death

MECHANISMS OF RESISTANCE

Three principal mechanisms of resistance have been established:

(1) production of a transferase enzyme that inactivates the amino-glycoside by adenylylation, acetylation, or phosphorylation. This is the principal type of resistance encountered clinically.

 (2) There is impaired entry of aminoglycoside into the cell. This may result from mutation or deletion of a porin protein involved in transport and maintenance of the electrochemical gradient or from growthconditions under which the oxygen-dependent transport process is not functional.

(3) The receptor protein on the 30S ribosomal subunit may be deleted or altered as a result of a mutation.

DRUG INTERACTIONS

Some products that may interact with this drug include: amphotericin B, high doses of aspirin/NSAIDs such as ibuprofen/naproxen.

TOXICITY

Ototoxicity refers to damage usually caused by medications that damage the inner ear, including the cochlea, vestibule, semicircular canals and otoliths .The results of this toxic damage include hearing loss, tinnitus, dizziness, and balance impairment

Damage can occur both to the peripheral vestibular system and the central vestibular system. The central vestibular system includes parts of the brain and brainstem that process information obtained from the peripheral vestibular system regarding balance and spatial orientation. Those with damage to the central vestibular system may not experience vertigo, but instead have more difficulty with balance and exhibit ataxia, which is the medical term for an abnormal gait when walking

Aminoglycosides are also well known to cause nephrotoxicity (kidney damage) although this can usually be reversed.

Encephalopathy is a term used to describe a malfunction in the brain caused by some other agent, such as a neurotoxin, infection, impaired liver function, or other condition.

ADVERSE EFFECTS

**Adverse Effects**  from Gentamicin and Other **Aminoglycosides**. **Aminoglycosides** are known to cause ototoxic damage, vestibulo-toxic impairments, nephrotoxicity (kidney damage), and encephalopathy

STREPTOMYCIN

Streptomycin was isolated from a strain of Streptomyces griseus. The antimicrobial activity of streptomycin is typical of that of other aminoglycosides, as are the mechanisms of resis-tance. It is a broad spectrum antibiotic. It has the chemical formula C21H29N7O12. It consists of 3 components linked glycosidically by ether bonds

It has a bioavailability of 84% to 88% intramuscularly. It has a half-life of 5-6 hours and it is excreted by the kidneys.

PHARMACOKINETICS

Absorption:it is well absorbed intramuscularly and it is not absorbed in the gut

Distribution: it is well distributed to extracellular fluid including serum, synovial abcesses etc; crosses placenta; small amounts enter breast milk.

Excretion: it is excreted mainly in the urine as unchanged drug ,

CLINICAL USES

1. Mycobacterial Infections: Streptomycin is mainly used as a second-line agent for treatment of tuberculosis
2. In plague, tularemia, and sometimes, brucellosis, streptomycin, 1 g twice daily (15 mg/kg twice daily for children), is given intra-muscularly in combination with an oral tetracycline.
3. Penicillin plus streptomycin is effective for enterococcal endo-carditis and 2-week therapy of viridans streptococcal endocarditis;
4. Streptomycin remains a useful agent for treating gentamicin non-susceptible enterococcal infections

CONTRAINDICATIONS OF STREPTOMYCIN

1. the risk of severe neurotoxic reactions is sharply increased in patientswith impaired renal function or pre-renal azotemia. these include disturbances of vestibular and cochlear function, optic nerve dysfunction, peripheral neuritis, arachnoiditis, and encephalopathy may also occur. the incidence of clinically detectable, irreversible vestibular damage is particularly high in patients treated with streptomycin.
2. renal function should be monitored carefully; patients with renal impairment and/or nitrogen retention should receive reduced doses. the peak serum concentration in individuals with kidney damage should not exceed 20 to 25 mcg/ml.
3. the concurrent or sequential use of other neurotoxic and/or nephrotoxic drugs with streptomycin sulfate, including neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin b, colistin, tobramycin and cyclosporine should be avoided.
4. the neurotoxicity of streptomycin can result in respiratory paralysis from neuromuscular blockage, especiallywhen the drug is given soon after the use of anesthesia or muscle relaxants
5. the administration of streptomycin in parenteral form should be reserved for patients where adequate laboratory and audiometric testing facilities are available during therapy

ADVERSE EFFECTS OF STREPTOMYCIN

1. Fever, skin rashes, and other allergic manifestations may result from hypersensitivity to streptomycin. This occurs most frequently with a prolonged course of treatment (eg, for tuberculosis).
2. Pain at the injection site is common but usually not severe.
3. The most serious toxic effect with streptomycin is disturbance of vestibular function—vertigo and loss of balance. The frequency and severity of this disturbance are in proportion to the age of the patient, the blood levels of the drug, and the duration of administration.
4. Vestibular dysfunction may follow a few weeks of unusually high blood levels (eg, in individuals with impaired renal function) or months of relatively low blood levels. Vestibular toxicity tends to be irreversible.
5. Streptomycin given during pregnancy can cause deafness in the newborn.