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### COURSE TITLE: INTRODUCTION TO PHARMACOLOGY AND TOXICOLOGY II

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

### ANSWERS

### The named bacteria protein synthesis inhibitor is: AMINOGLYCOSIDES.

* Aminoglycosides are large, highly polar antibacterial drugs that bind to the 30S subunit of bacterial ribosomes, impairing the proofreading ability of the ribosomal complex. This impairment causes mismatches between codons and anticodons, resulting in the production of proteins with incorrect amino acids and shortened proteins that insert into the cytoplasmic membrane. Disruption of the cytoplasmic membrane by the faulty proteins kills the bacterial cells.
* The aminoglycoside antimicrobials have a long and controversial history. First developed in the 1940s, they are derived from antimicrobial substances produced by the soil dwelling bacterial species *Streptomyces* and *Micromonospora.* The ‘workhorse’ of aminoglycosides, gentamicin, has been used for the treatment of serious Gram‐negative bacterial infections since the early 1960s and continues in this role today.
* The three commonly used parenteral agents are gentamicin, tobramycin and amikacin. Other routes of administration include inhalation through a nebulizer (tobramycin), intra-peritoneal and intra-ventricular administration (gentamicin). Two further agents paromomycin and neomycin are used orally for their bowel intra‐luminal activity, as they are not systemically absorbed.Streptomycin, the first aminoglycoside agent in widespread use, along with netilmicin and kanamycin are now infrequently used.

**MECHANISM OF ACTION**

* Aminoglycosides are more effective against rapidly multiplying organisms, and they affect and ultimately destroy bacteria by several mechanisms. They need only a short contact with bacteria to kill them and, as such, are concentration dependent in their actions. Their main site of action is the membrane-associated bacterial ribosome through which they interfere with protein synthesis. To reach the ribosome, they must first cross the lipopolysaccharide (LPS) covering (gram-negative organisms), the bacterial cell wall, and finally the cell membrane. Because of the polarity of these compounds, a specialized active transport process is required.
* The first concentration-dependent step requires binding of the cationic aminoglycoside to anionic components in the cell membrane. The subsequent steps are energy dependent and involve the transport of the polar, highly charged cationic aminoglycoside across the cytoplasmic membrane, followed by interaction with the ribosomes. The driving force for this transfer is probably the membrane potential. These processes are much more efficient if the energy used is aerobically generated. The efficacy of the aminoglycosides is markedly curtailed in an anaerobic environment. Aminoglycosides are associated with a post antibiotic effect in a number of bacteria, principally gram-negative (e.g. *E coli*, *Klebsiella pneumoniae*, *and P aeruginosa*). The effect generally lasts 2–8 hours after exposure and allows for dosing intervals longer than the half-lives of the drugs.
* Several features of these mechanisms are of clinical significance:

1. The antibacterial activity of the aminoglycosides depends on an effective concentration of antibiotic outside the cell.
2. Anaerobic bacteria and induced mutants are generally resistant, because they lack appropriate transport systems.
3. With low oxygen tension, as in hypoxic tissues, transfer into bacteria is diminished.
4. Divalent cations (e. g calcium and magnesium) located in the LPS, cell wall, or membrane can interfere with transport into bacteria because they can combine with the specific anionic sites and exclude the cationic aminoglycosides.
5. Passive movement of aminoglycosides across bacterial cell membranes is facilitated by an alkaline pH; a low pH may increase membrane resistance more than 100-fold.
6. Changes in osmolality also can alter the uptake of aminoglycosides.
7. Some aminoglycosides are transported more efficiently than others and thus tend to have greater antibacterial activity.
8. Synergism is common when aminoglycosides and β-lactam antibiotics (penicillin and cephalosporins) are used in combination. The cell-wall injury induced by the β-lactam compounds allows increased uptake of the aminoglycoside by the bacteria because of easier accessibility to the bacterial cell membrane.

* The intracellular site of action of the aminoglycosides is the ribosome, which is irreversibly bound by aminoglycosides, particularly at the 30 S but also the 50 S subunits (which comprise the 70 S subunit). Variability occurs between aminoglycosides with respect to their affinity and degree of binding. The number of steps in protein synthesis that are affected also varies. Spectinomycin cannot induce misreading of the mRNA and often is not bactericidal, in contrast to the other bactericidal members. However, at low concentrations, all aminoglycosides may be only bacteriostatic. Efficacy of aminoglycosides is enhanced if peak plasma or tissue drug concentrations exceed MIC by 10–12 times. Once-daily dosing has been used to enhance both efficacy and safety.
* Finally, a cell-membrane effect also occurs with aminoglycosides. The functional integrity of the bacterial cell membrane is lost during the late phase of the transport process, and high concentrations of aminoglycosides may cause nonspecific membrane toxicity, even to the point of bacterial cell lysis.

**INDICATIONS FOR USE**

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. 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. Often, hospital staff refer to this combination as "amp and gent" or more recently called "pen and gent" for penicillin and gentamicin.

**TOXICITY AND ADVERSE EFFECT**

* Ototoxicity, neuromuscular blockade, and nephrotoxicity are reported most frequently; these effects may vary with the aminoglycoside and dose or interval used, but all members of the group are potentially toxic.
* **NEPHROTOXICITY**: This is of major concern and may result in renal failure due to acute tubular necrosis with secondary interstitial damage. Aminoglycosides accumulate in proximal tubular epithelial cells, where they are sequestered in lysosomes and interact with ribosomes, mitochondria, and other intracellular constituents to cause cell injury. The greater the ionization (e.g. the more the amine groups and the lower the pH), the greater the active uptake. Kidneys must have a drug-free period to eliminate accumulated drugs. As such, persistence of aminoglycosides in plasma and thus urine is likely to predispose the tubular cells to toxicity, and the risk may be reduced by allowing plasma drug concentrations to drop below recommended concentrations (generally 1–2 mcg/mL) before the next dose. Non-oliguria renal failure is the usual observation; it is generally reversible if damage is not sufficiently extensive to harm the basement membrane, although recovery may be prolonged. Renal function should be monitored during therapy; however, no indicator of renal disease is sufficiently sensitive to prevent continued damage once nephrotoxicity is detected. Polyuria, decreased urine osmolality, enzymuria, proteinuria, cylindruria, and increased fractional sodium excretion are indicative of aminoglycoside nephrotoxicity. Later, BUN and creatinine concentrations may be increased. Early changes or evidence of nephrotoxicity can be detected in 3–5 days, with more overt signs in 7–10 days. Several factors predispose to aminoglycoside nephrotoxicosis, including age (with young [especially the newborn foal] and old animals being sensitive), compromised renal function, total dose, duration of treatment, dehydration and hypovolemia, aciduria, acidosis, hypomagnesemia, severe sepsis or endotoxemia, concurrent administration of furosemide, and exposure to other potential nephrotoxins (e. g methoxyflurane, amphotericin B, cisplatinum, and perhaps some cephalosporins). In renal insufficiency, generally the interval between doses is prolonged (rather than reducing the dose) to minimize toxicity, while avoiding a negative impact on efficacy. Dosing in the morning may decrease toxicity in diurnal animals. The risk of toxicity is less in alkaline urine. Nephro-active drugs, including those that alter renal vascular response (e.g. auto-regulation) should be avoided or used cautiously (e.g. NSAIDs, diuretics). Treatment with *N*-acetylcysteine should be considered (see ototoxicity, below).
* **OTOTOXICITY**: Aminoglycosides can cause ototoxicity, which may manifest as either auditory or vestibular dysfunction. Binding or damage to mitochondria plays a prominent role in ototoxicity. Vestibular injury leads to nystagmus, incoordination, and loss of the righting reflex. The lesion is often irreversible, although physiologic adaptation can occur. Ototoxicity is not unusual in people, but relevance to veterinary patients is not clear. Cats are particularly sensitive to the toxic vestibular effects, although occurrence at therapeutic concentrations after systemic administration is unlikely. However, aminoglycosides should not be administered topically into the ear unless the tympanic membrane is intact. Hearing impairment reflects permanent damage and loss of the hair cells in the organ of Corti. Loss of high-frequency hearing is followed by deafness, which may not be complete if sufficiently low doses or durations were used. Aminoglycosides should be avoided in working dogs that depend on hearing (e.g., guide dogs). Factors increasing the risk of vestibular and cochlear damage are the same as for nephrotoxicity but also include preexisting acoustic or vestibular impairment and concurrent treatment with potentially ototoxic drugs. The ototoxic potential is greatest for gentamicin, sisomicin, and neomycin, and least for netilmicin. In people, treatment with *N*-acetylcysteine has deceased the risk of aminoglycoside ototoxicity.
* **NEUROMUSCULAR BLOCKADE:** All aminoglycosides, when administered in doses that result in high plasma concentrations, have been associated with muscle weakness and respiratory arrest attributable to neuromuscular blockade. The effect is more pronounced when aminoglycosides are used with other drugs that cause neuromuscular blockade and with anesthetics. Neomycin, kanamycin, amikacin, gentamicin and tobramycin are listed in order of most to least potent for these neuromuscular effects. The effect is due to the chelation of calcium and competitive inhibition of the pre-junctional release of acetylcholine in most instances (there are some differences among aminoglycosides). The blockade is antagonized by calcium gluconate and somewhat less consistently by neostigmine. CNS disturbances rarely include convulsions or collapse after rapid IV administration.
* Other adverse effects include super-infection when used topically or PO, a mal-absorption syndrome due to attenuation of intestinal villous function when used PO in neonates, occasional hypersensitivity reactions, contact dermatitis, cardiovascular depression, and inhibition of some WBC functions (e. g neutrophil migration and chemo taxis and even bactericidal activity at high concentrations).
* Monitoring for toxicity can be through three mechanisms; quantitative testing of end‐organ effects (monitoring serum creatinine and audiometry), active bedside testing and passive reporting by the patient. There is no definitive evidence to inform optimal techniques for monitoring of toxicity.As a minimum standard, before the commencement of aminoglycoside therapy patients should be informed about the possible adverse effects and asked to report if they develop subjective hearing loss, tinnitus or oscillopsia, and serum creatinine should be monitored in all patients.

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