

Aminoglycosides*

Overview

Included in this group of bactericidal agents are streptomycin, dihydrostreptomycin, neomycin, framycetin (neomycin B), paromomycin (aminosidine), kanamycin, gentamicin, tobramycin, amikacin, sisomicin and netilmicin. Streptomycin, the first aminoglycoside, was introduced in 1942 for treatment of tuberculosis. Aminoglycosides are characterized by an aminocyclitol ring with aminosugars attached in a glycoside linkage. Because of minor differences in molecular substitutions, aminoglycoside antibiotics may actually consist of several forms of a single aminoglycoside. For example, gentamicin is made up of gentamicins C₁ and C₂, and neomycin is composed of neomycin B, C and fradiomycin. Removal of hydroxyl groups on the aminosugar components markedly increases antibiotic activity. Although not structurally identical, spectinomycin and apramycin are also considered to be aminoglycosides. Aminoglycosides are usually quite stable chemicals and are very poorly absorbed (<10%) from a healthy gastrointestinal tract. Inflammation and other pathology in the gut may significantly increase absorption. Subcutaneous administration may also result in protracted absorption. Intramuscular, intraperitoneal and intravenous administration usually results in rapid and almost complete absorption of the drug, but intraperitoneal and intravenous injections are characterized by a high risk of toxicity.

The site of action of aminoglycosides is the membrane associated bacterial ribosome, specifically the 30S subunit where irreversible binding takes place, thus limiting protein synthesis. Irreversible binding may explain the bactericidal nature of the drugs, whereas other inhibitors of protein synthesis are generally bacteriostatic. Aminoglycosides enter the cell through a specialized concentration and energy dependent transport process; therefore the drug must be present in a high concentration outside of the cell. The aminoglycoside binds to anionic components of the cell membrane (concentration dependent), and then is transported across the cytoplasmic membrane (energy dependent) to eventually interact with the ribosomes and alter protein synthesis. Aminoglycosides are more effective against aerobic organisms because these specialized processes are more efficient when the energy utilized is produced aerobically. Poor oxygenation in hypoxic tissues, as is seen in the presence of purulence and abscess formation, also interferes with effectiveness. Cations, such as calcium and magnesium, can interfere with aminoglycoside transport into the cell by binding to anionic sites and excluding the cationic aminoglycosides. The transport also is facilitated by alkaline pH. Acid environments may dramatically increase membrane resistance. In addition, aminoglycosides have a direct effect on the cell membrane. High concentrations often result in membrane toxicity and cell lysis, as well as a prolonged postantibiotic effect that continues to kill bacteria after serum concentrations fall below the minimum inhibitory concentrations. Aminoglycosides are often used in conjunction with β -lactams and glycopeptides. These synergists act by damaging the bacterial cell wall, thus allowing easier accessibility to the cell membrane and increased uptake of the aminoglycoside.

Little change in patterns of resistance to aminoglycosides among Gram-negative aerobes has been noted, however resistance does occur. Mechanisms of resistance to

aminoglycosides may be mutational or plasmid mediated. One non-plasmid mediated mechanism of resistance is impaired transport due to reduced oxygen tension. Anaerobic bacteria such as *Bacteroides fragilis* and *Clostridium perfringens* and facultative anaerobes such as enterobacteria and *Staphylococcus aureus*, under anaerobic conditions, are often resistant. This resistance through impaired transport can be precipitated by exposure to sub-lethal concentrations of these antibiotics, as has been observed in streptomycin resistance in some strains of *P. aeruginosa*, low level resistance to aminoglycosides among enterococci and gentamicin resistance in *Streptococcus faecalis*.

Resistance can also be due to presence of enzymes that reduce the activity of, or destroy aminoglycosides. There are three major types of enzymes that are produced: acetyltransferases (acetylating enzymes), nucleotidyltransferases (adenylating enzymes) and phosphotransferases (phosphorylating enzymes). These enzymes are encoded on plasmids or transposons. Chromosomally or plasmid mediated enzymatic modification or destruction of aminoglycosides is an important mechanism of resistance. The enzymes can be produced by both Gram-positive and Gram-negative organisms, but the susceptibility of the different aminoglycoside antibiotics is quite variable.

Excessive cell membrane protein and impaired ribosomal binding are other mechanisms of resistance. Some *P. aeruginosa* mutants can produce H1, an excess of outer cell membrane protein that can confer resistance to gentamicin. Impaired ribosomal binding from a single step mutation is a mechanism of resistance in some *E. coli* strains and *Pseudomonas aeruginosa*. Resistance by impaired ribosomal binding, however, is not considered clinically significant.

Aminoglycosides are commonly used in veterinary medicine to treat local and systemic infections caused by susceptible aerobic bacteria, especially Gram-negative aerobes. These antimicrobials are used in infections of the gastrointestinal tract and skin, and in cases of osteoarthritis, pneumonia, septicemia and tracheobronchitis. Aminoglycosides are also used topically in the ear and eyes and can be infused into the uterus and teats. In pediatrics aminoglycosides are utilized in the treatment of neonatal sepsis resulting from Gram-negative bacteria, urinary tract infections, intra-abdominal infections, infections occurring in cystic fibrosis and as empiric therapy in febrile neutropenic patients. When antibiotic therapy is necessary, aminoglycosides can be used to treat cat scratch disease. However in human medicine, due to the relatively narrow spectrum and risk of toxicity, aminoglycosides should not be used as single agent therapy in empirical treatment of sepsis.

Narrow spectrum aminoglycosides, such as streptomycin and dihydrostreptomycin are primarily effective against aerobic Gram-negative organisms, such as strains of *Actinomyces bovis*, *Pasteurella* species, *E. coli*, *Salmonella* species, *Campylobacter fetus*, *Leptospira* species and *Brucella* species, but are also effective against some staphylococci. *Mycobacterium tuberculosis* is often sensitive to streptomycin. Streptomycin is useful in therapy for tularemia, plague and multi-drug resistant tuberculosis and is used on occasion against strains of *Enterococcus* that exhibit high level resistance to gentamicin. Bacterial resistance is, however, becoming prevalent. Paromomycin is effective against *Cryptosporidium*, *Entamoeba*, and *Giardia*. Extended spectrum aminoglycosides such as neomycin, kanamycin, gentamicin, tobramycin and

amikacin exhibit a broader spectrum of activity. These aminoglycosides are also effective against some Gram-positive organisms, like *Staphylococcus aureus* and more of the aerobic Gram-negative organisms. In addition gentamicin, tobramycin and amikacin are also effective against *Pseudomonas aeruginosa*. Although in vitro tests indicate streptococci to be sensitive to aminoglycosides, these organisms are intrinsically resistant in vivo. However, aminoglycosides act synergistically with penicillin and vancomycin to be largely effective against *Enterococcus* and other Gram-positive cocci. Aminoglycosides are frequently combined with a fluoroquinolone, carbapenem, cephalosporin, vancomycin or extended spectrum penicillin as antimicrobial therapy in severe life threatening sepsis. Aminoglycosides are not effective against anaerobic bacteria or fungi. Most streptococci are either highly resistant or only moderately sensitive.

Aminoglycosides are distributed well in the extracellular space but, with the exception of the renal cortex and the endolymph of the inner ear, they poorly penetrate tissues. Therapeutic levels are not reached in the CSF, respiratory system, intestinal fluids, milk, ocular fluids or prostatic secretions; however aminoglycosides attain effective concentrations in synovial, pleural and peritoneal fluids, especially when inflammation is present. The drugs are, however, sometimes infused into the CNS by intrathecal or intraventricular infusion. Concentrations in fetal tissues and amniotic fluid are also very low in most species. The proportion of the body comprised of the extracellular fluid compartment is about 25%, but this volume changes in several physiologic and pathologic conditions, as well as under the influence of several pharmaceuticals. Variations in the extracellular fluid compartment influence the concentration of aminoglycosides.

Eighty to ninety percent of Aminoglycosides are excreted unchanged in the urine by glomerular filtration. A small, variable proportion of the chemical is absorbed into the renal cortex and, when excessively concentrated, may lead to acute tubular necrosis. Glomerular filtration rates are lower in neonates, which may explain greater sensitivity to the drug in young animals, especially newborn foals and puppies. Due to this potential problem with renal toxicity, renal function and plasma aminoglycoside concentrations should be monitored during therapy. The treatment interval should be increased in neonates, patients with renal failure and in obese patients. Hypotension, dehydration, liver disease and concurrent use of other nephrotoxic agents are additional risk factors for tubular necrosis. The potential for nephrotoxicity may also be increased with concurrent administration of furosemide, methoxyflurane, amphotericin B, cis platinum and possibly some cephalosporins. Nephrotoxicity from aminoglycosides is often reversible.

Accumulation in the endolymph of the inner ear may result in ototoxicity, specifically irreversible vestibular or cochlear injury. Hearing loss precipitated by loss of hair cells in the organ of Corti may also result in hearing loss. Cats are particularly sensitive to aminoglycoside ototoxicity. Due to potential problems with ototoxicity, these drugs are not recommended for use in service animals when alternative therapy is available. Topical infusion of an ear canal with a non-intact tympanum may also increase the likelihood of ototoxicity. Therefore aminoglycosides should never be instilled

topically in the ear unless the tympanum is intact. Once daily dosing in humans minimizes the chances of toxicity.

Use of aminoglycosides has been associated with neuromuscular blockade causing muscle weakness and respiratory distress. Care should be exercised when utilizing gas anesthetics as well as other drugs that potentiate neuromuscular blockade. Calcium gluconate and, less consistently, neostigmine may antagonize this effect.

CNS disturbances, collapse after rapid intravenous administration, malabsorption in neonates when used per os, superinfection after topical use, hypersensitivity reactions, contact dermatitis, cardiovascular depression and inhibition of white blood cell function are other side effects that have been associated with aminoglycosides. Aminoglycoside administration may also elevate BUN, serum creatinine, serum transaminases and alkaline phosphatase values. Proteinuria is frequently observed.

***References available by request. Call the Infectious Disease Epidemiology Section, Office of Public Health, Louisiana Department of Health and Hospitals (504-219-4563)**