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Popular Article

An Overview of the Use of Aminoglycosides in Veterinary Medicine

Teja balusupati[1], Anil Kumar B*[2], Satish Kumar K[3] and Ambica G[4]
College of Veterinary Science, PVNRTVU, Rajendranagar, Hyderabad, Telangana.
[1]MVSc Scholar, Department of Veterinary Medicine,
[*2]Assistant Professor, Department of Veterinary Pharmacology & Toxicology,
[3]Professor & Univ. Head, Department of Veterinary Medicine
[4]Assistant Professor, Department of Veterinary Medicine
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Abstract

Aminoglycosides are antibiotics derived from actinomycetes that were among the first to be used clinically. However, they have been largely replaced by other antibiotics since the 1980s. They are still important for treating diseases in both humans and animals but their extensive use has led to acquired resistance, primarily through enzymatic inactivation. Resistance genes can easily spread between bacterial species, including those with zoonotic potential. Although there is no quantitative data on the contribution of animals to aminoglycoside resistance in humans, it is considered a high risk. Aminoglycosides are valuable drugs for treating gram-negative sepsis and Pseudomonas aeruginosa infections, and responsible usage is crucial to preserving their effectiveness.

Introduction

Aminoglycosides are an old class of bactericidal antimicrobials that impair bacterial protein synthesis by binding to the 30S ribosomal subunit (1). They have a restricted range of action, and their efficacy is reduced in low pH, hyperosmolar conditions, and purulent material. They are hydrophilic and poorly absorbed from the stomach (2). Aminoglycosides are effective against gram-negative bacteria, staphylococci, mycobacteria, Leptospira, and certain protozoa but perform poorly against intracellular bacteria, anaerobic bacteria, and streptococci. They are frequently used in veterinary medicine to treat infections in all major food-producing and companion animal species and are classified as veterinary critically important antimicrobials (VCIAs) and critically important antimicrobials (CIAs) for human medicine (3 &4).

Classification

Aminoglycosides can be classified based on their chemical structure as well as their spectrum of activity. Structurally, they comprise one or more amino sugars and an aminocyclitol ring linked by glycosidic bonds. The aminocyclitol ring provides antimicrobial activity by binding to the bacterial ribosome and inhibiting protein synthesis. Based on their spectrum of activity, aminoglycosides can be divided into two groups: broad-spectrum and narrow-spectrum. Broad-spectrum aminoglycosides, such as gentamicin and tobramycin, have activity against many gram-negative and gram-positive bacteria. Narrow-spectrum aminoglycosides, such as streptomycin and kanamycin, are primarily active against gram-negative bacteria. Another way to classify aminoglycosides is by their clinical use. Some aminoglycosides, such as neomycin and paromomycin, are primarily used in topical formulations due to poor systemic absorption. Other aminoglycosides, such as amikacin and netilmicin, are used for serious systemic infections, such as sepsis and pneumonia, because of their broad-spectrum activity and reduced susceptibility to resistance mechanisms.

Administration routes of aminoglycosides

Aminoglycosides are used in parenterally, oral &topical applications in veterinary Medicine. Approximately half of AG use is as oral formulations (premix, oral powder or soluble in drinking water) and about half is as injectable formulations (5); substances used for parenteral applications include (dihydro)streptomycin, gentamicin, kanamycin, framycetin, spectinomycin and neomycin. (Dihydro)streptomycin, neomycin, apramycin, gentamicin, paromomycin and spectinomycin are used in oral formulations (5) The majority of oral formulations include oral solution, oral powder, premix reused for treatments in pigs, calves, sheep, poultry and rabbits, they are often given once daily throughout 3-5 (and in rare circumstances, even 7) days as oral drenches (to newborns) or in feed or drinking water/milk. Individual drugs, such as apramycin for 21 days or up to 28 days, are approved for even longer treatment durations. Eardrops, eyedrops, topical skin treatments, intramammary preparations, and intrauterine preparations are examples of local applications. (5)(6)

Pharmacodynamics

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The pharmacodynamics of aminoglycosides refers to the relationship between the concentration of the drug and its therapeutic effect or toxicity. Aminoglycosides exhibit concentration-dependent bactericidal activity, meaning their efficacy is directly proportional to the peak serum concentration. However, their therapeutic index, which is the ratio of the toxic dose to the effective dose, is narrow. Aminoglycosides act by binding to the 30S subunit of bacterial ribosomes, inhibiting protein synthesis and ultimately, bacterial cell death (8). The concentration of aminoglycosides required to achieve bactericidal activity varies depending on the bacterial species, but generally, a peak serum concentration that is at least four to eight times the minimum inhibitory concentration (MIC) of the bacteria is required (9). The pharmacodynamics of aminoglycosides can also be influenced by other factors, including the bacterial inoculum size, the site of infection, and the duration of exposure. Higher bacterial inoculum sizes may require higher peak concentrations to achieve bactericidal activity. Aminoglycosides are also more effective against rapidly dividing bacteria and may have reduced efficacy against bacteria in stationary growth phases. Prolonged exposure to aminoglycosides can lead to the development of resistance, and combination therapy with other antibiotics may be required to prevent this. The combination of aminoglycosides with beta-lactam antibiotics, such as penicillins or cephalosporins, can result in synergistic activity against certain bacterial species (10).

Pharmacokinetics

Aminoglycosides are a class of antibiotics that are commonly used in veterinary therapeutics to treat various bacterial infections. They are usually administered intravenously or intramuscularly and have a broad spectrum of activity against gram-negative bacteria. The pharmacokinetics of aminoglycosides in veterinary therapeutics are similar to those in human medicine. They are characterized by a rapid distribution phase, a prolonged elimination phase, and a narrow therapeutic window. The pharmacokinetic properties of aminoglycosides can be affected by various factors, including the route of administration, dose, age, body weight, renal function, and co-administration with other drugs.

Aminoglycosides are not well absorbed after oral administration in veterinary medicine and are usually administered intravenously or intramuscularly. The distribution of aminoglycosides in the body is rapid, with high concentrations achieved in the kidney, liver, and lungs. However, their distribution to certain tissues, such as the central nervous system and the eye, is limited. The

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elimination of aminoglycosides in veterinary medicine is primarily via the kidneys, with a small portion eliminated via the biliary system. The elimination half-life of aminoglycosides is longer in animals than in humans, ranging from several hours to days depending on the species and dose. This prolonged elimination phase can lead to accumulation of the drug and potential toxicity, especially in animals with renal impairment.

Side effects / adverse effects

Studies of nephrotoxicity involving animal models have found that once-daily administration of gentamicin or tobramycin was significantly less toxic than more frequent (i.e., twice or three times daily) dosages or continuous infusion (12-15), Animal studies have further elucidated the probable mechanism involved in aminoglycoside nephrotoxicity, which involves an absorptive influx at proximal convoluted tubule cells and is mediated by a low-affinity, high-capacity mechanism that can be saturable, linear, or a mixture of the two(16-17) The exact mechanism is not known, but speculation has led primarily to the following hypotheses: (i) a lysosomal mechanism, with aminoglycosides causing an accumulation of myeloid bodies within lysosomes and thereby inhibiting lysosomal phospholipases with a subsequent decrease in sphingomyelinase activity, or (ii) an extra lysosomal mechanism, with inhibition of Na ,K -ATPase and phospholipase C, leading to unopposed angiotensin II activity, or (iii) a combination of these mechanisms. Animal studies that have examined ototoxicity show that the degree of cochlear damage is more related to the total daily dose of the Aminoglycoside rather than the frequency with which the drug is administered (17-18) Saturation of cochlear cells may play a role in determining ototoxicity (19-21) Discontinuous administration, as opposed to constant infusion or more frequent administration, may lead to less saturation and accumulation of aminoglycosides (21-22).

Other effects

Aminoglycosides have a low propensity to cause allergic reactions both anaphylaxis and rash rarely, streptomycin may cause peripheral neuritis optic nerve dysfunction

Clinical uses

Aminoglycosides are widely used in veterinary medicine, with neomycin and dihydrostreptomycin being the most commonly used. Other aminoglycosides, including apramycin, gentamicin, kanamycin, paromomycin, neomycin, framycetin, and streptomycin, are also used in food-producing animals where maximum residue limits have been established. Aminoglycosides are

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primarily administered to animals for clinical purposes to treat infections such as septicaemia, respiratory, digestive, and urinary tract infections. They are used in various animal species, including cattle, pigs, poultry, sheep, goats, horses, dogs, and cats. Gentamicin is indicated explicitly for Pseudomonas aeruginosa infections, for which few alternative treatments are available. It is important to note that aminoglycosides have not been authorized as growth promoters in animals.

Dosage regime

At present, the dosage of Aminoglycoside to use in a once-daily aminoglycoside strategy has not been clearly determined (Collin D. Freeman Once-daily dosing of aminoglycosides: review and recommendations for clinical practice), Dosages for gentamicin, tobramycin and netilmicin have ranged from 3 to 7 mg/kg (Collin) amikacin dosages have ranged from 11 to 30 mg/kg, calculated this dose based on the total daily dose given in the conventional regimen (1.5–2.0 mg/kg tds

Another approach to dosage selection has been based on the pharmacokinetic and pharmacodynamic parameters it suggests a 7 mg/kg dosage of either gentamicin or tobramycin. (23)

Contraindications

Aminoglycosides should not be utilized in people who are hypersensitive to them, new-borns, geriatric patients, and patients with pre-existing renal disorders. AGs may impede neuromuscular transmission, making them contraindicated during pregnancy and not administered to animals with myasthenia gravis.

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