

# Pharmacology of Aminoglycosides in Cattle

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## Abstract

Aminoglycosides (e.g. gentamicin, neomycin, dihydrostreptomycin) are potent and in many instances highly effective antibiotics that are available for parenteral administration; their use in cattle is only by prescription, and in most instances only in an extralabel situation, for systemic gram-negative infections. Oral absorption is minimal except in neonatal animals; distribution of drug out of the bloodstream into tissues is proportional to extracellular fluid, and is greater in young animals that have a higher extracellular fluid volume. Their propensity for accumulation and slow release from renal tissues makes their use in feedlot cattle unwise because of the likelihood of violative tissue residues. Spectinomycin is not an aminoglycoside but rather is an aminocyclitol, with less propensity for accumulation and slow release from kidneys.

## Introduction

Aminoglycosides are potent antibiotics that are available for parenteral administration; their use in cattle is only by prescription, and in most instances only in an extralabel situation. Aminoglycosides are two or more sugars linked to central sugar, and are commercially available as the sulfate salt in nearly all instances. They are highly water soluble, resistant to heat, and are not metabolized appreciably.

## Spectrum

Aminoglycosides have a primarily aerobic, gram-negative spectrum, with poor activity against facultative anaerobes or anaerobes in a low oxygen environment; this low activity against anaerobe is because transport of aminoglycosides into the bacteria is oxygen-dependent. Most gram-positive bacteria are resistant; *Staph aureus* is sensitive although aminoglycosides are not used alone for *S. aureus* infections. Nosocomial infections now are often resistant to gentamicin and tobramycin, so amikacin is becoming more widely used. Amikacin does not have resistance develop to it as fast as other aminoglycosides, because only 1 of the sites for enzymatic degradation is available for the bacterial enzymes on amikacin.

## Mechanism of action, resistance, degradation

Aminoglycosides interfere with bacterial protein synthesis by binding tightly to the 30S ribosomal sub-

unit. Later stages of protein synthesis may also be inhibited. In addition, there is an altered specificity of codon reading during transcription and translation, and they have been shown in some studies to interfere with DNA synthesis as well, the reason for aminoglycosides being bactericidal.

## Resistance

Although bacterial ribosomes can be altered by mutation to have reduced affinity for aminoglycosides, most bacterial resistance to aminoglycosides is due to plasmid-borne inactivation of the aminoglycosides by enzymatic alteration, yielding inactive forms of the aminoglycosides. Other bacteria (e.g., *Pseudomonas*) may be less likely to accumulate some aminoglycosides because of their unique cell wall structure.

## Pharmacokinetics

Aminoglycosides are poorly absorbed into the systemic circulation when administered orally in either monogastrics, or particularly ruminants. In normal adult animals, less than 10% cross the normal intestine, but that has been shown to increase greatly in cases of intestinal disease. In addition, recent studies have shown that oral absorption of aminoglycosides in neonatal calves (less than 48 hours of age) is several-fold higher than in 21-day old cattle; other studies have confirmed a similar finding in swine as well. This may be one of the reasons that oral gentamicin appears to be effective in neonatal pigs with systemic signs arising from colibacillosis.

Distribution of aminoglycosides is relatively low into tissues, in large part because of their aqueous and positively charged nature. The volume of distribution of most aminoglycosides is approximately 25% of body weight, similar to that of extracellular fluid volume. Infant animals typically have a larger volume of extracellular fluid (often 40-45% of body weight), and hence have a larger volume of distribution for aminoglycosides. The result of this difference in volume of distribution is lower peak concentrations in plasma or serum after injection of aminoglycosides, and less amount of drug presented to the organ of elimination, the kidneys, per volume of blood flow and hence a slower half-life. Pro-

tein binding of most aminoglycosides is less than 20%, and there is very little into erythrocytes (less than 10%).

Although aminoglycosides do not penetrate cells passively to any extent because of their physicochemical properties, the renal cortex actively accumulates aminoglycosides, a major factor in the nephrotoxicity, but more importantly for this discussion, in the tissue residues of aminoglycosides. The renal depletion half-life of all aminoglycosides studied, if the right sample times and analytical methods are used, is several days to several weeks, and it appears to get longer the farther from the last dose the samples are obtained (that is, the half-life is not constant). In other tissues, aminoglycosides are found at concentrations approximately proportional to tissue blood flow. There is good penetration into pleural and peritoneal fluids and bronchial secretions, some penetration into synovial fluids, but very little penetration into the CNS.

### Fate and elimination

Aminoglycosides are not significantly metabolized, but rather are eliminated almost exclusively by renal glomerular filtration, with some reabsorption (active renal cortical accumulation) and slight tubular secretion. Approximately 80-90% of the dose is eliminated in the urine within 24 hours of the dose. Because of this nearly total reliance on renal elimination, the dose must be in patients with impaired renal function using a general rule of thumb to increase the interval between doses by the same factor that the serum creatinine is above 1.5 mg/dl. The elimination half-life, different from the tissue residue depletion half-life, is inversely proportional to GFR, and is approximately 1 hour in dogs and 2-3 hours in herbivores including cattle, sheep, and horses.

### Toxicity

Aminoglycosides can cause 8th cranial nerve damage, nephrotoxicity, and/or neuromuscular paralysis. Although the 8th cranial nerve toxicity and nephrotoxicity are both caused by accumulation of aminoglycosides in those tissues and both are predictably dose and duration dependent, nephrotoxicity is reversible if detected early whereas vestibular and cochlear damage is irreversible. Toxicity is more related to maintenance of trough concentrations above a threshold concentration (i.e., 2 µg/mL for gentamicin) rather than peak concentrations, whereas efficacy against most microorganisms is correlated most closely with high peak concentrations. Because of this, a recent development in human medicine has been to dose aminoglycosides less frequently with larger individual doses. As an aside, this same dosing strategy will produce lower tissue residues than more

frequent dosing with smaller individual doses; however, it does not alter the residue picture substantially.

Clinical signs of nephrotoxicity include (in order of onset) enzymuria, proteinuria, cylindruria, decreased creatinine clearance, increased serum creatinine and serum urea nitrogen, uremia, acute renal failure. The incidence of nephrotoxicity increases dramatically if the duration of therapy is greater than 5-7 days, if there is preexisting renal dysfunction and/or azotemia, if the patient is dehydrated, or if concurrent nephrotoxic drugs are administered. Very young and very old animals may also be more susceptible to aminoglycoside nephrotoxicity, although studies addressing this have often confounded age with altered renal function, yielding results that are difficult to interpret.

Neuromuscular paralysis can occur with all aminoglycosides, but is usually only seen after intrapleural or intraperitoneal instillation of large doses of aminoglycosides. Because they interfere with prejunctional calcium-mediated release of acetylcholine, the antidote for neuromuscular blockade caused by aminoglycosides is calcium infusion (calcium gluceptate).

### Specific Aminoglycosides

#### *Streptomycin*

Although once active against many gram-negative bacilli, many isolates are now resistant to streptomycin and its close counterpart, dihydrostreptomycin. It can only be rationally recommended for the treatment of the carrier state of leptospirosis, and is the drug of choice for tularemia. It still is being used with some success against the more sensitive strains of *Mycobacterium tuberculosis*. Resistance is widespread because of one-step mutation that can produce resistant strains within 24 hours of initial drug exposure. Recently, the parenteral combination products containing dihydrostreptomycin and procaine penicillin G have been taken off the market, in large part because efficacy superior to that with procaine penicillin alone was never confirmed in well-controlled clinical studies.

#### *Gentamicin*

One of the most widely used antibiotics in human and veterinary medicine, gentamicin is an excellent antibiotic for treatment of many serious gram-negative infections. It is approved for use in baby pigs both as a parenteral injection and for oral usage, but the withdrawal time that was approved for baby pigs is not appropriate for feedlot cattle. Most recommendations for an appropriate withdrawal time for gentamicin in cattle, aside from a novel concept of selective condemnation of the kidneys alone, is from 6 months to one year after the last injection. Because of the high likelihood of violative residues in bovine kidney tissue after parenteral

use, it cannot be recommended for use in feedlot cattle. Its use in veal calves for scours is also suspect because of the increased absorption of aminoglycosides after oral administration in both neonatal calves and in animals with certain forms of diarrhea.

#### *Amikacin*

The first semisynthetic aminoglycoside available commercially, amikacin is perhaps the most effective and the least toxic of the aminoglycosides. It is more effective and has less resistance developed to it, in large part because the sites of bacterial inactivation are protected on amikacin by portions of its molecule. It has the broadest antibacterial spectrum of any of the aminoglycosides, and because of the limited resistance that has developed to it, is the drug of choice for serious nosocomial gram-negative bacillary infections in hospitals and many veterinary schools. It has a very limited literature in food-producing animals, and its residue profiles is virtually unknown. Furthermore, it is the most expensive of the aminoglycosides available as a veterinary pharmaceutical.

#### *Neomycin*

Neomycin continues to be used orally for scours in calves and pigs, although its nephrotoxicity is the worst of any aminoglycoside commercially available when administered parenterally. Because of the latter point, it is rarely recommended as a parenteral antibiotic. In humans, it produces an intestinal malabsorption syndrome characterized by diarrhea, steatorrhea, and azotorrhea. The mechanism for this syndrome may be breakdown and absorption of a large variety of substances, but histologically the intestinal villi are altered. This syndrome has not been demonstrated in any animal species, and may very well be specific to human beings.

#### *Spectinomycin*

An aminocyclitol, which is a broader chemical class than aminoglycosides; very different from the aminoglycosides, but as close to them as to anything else. Its mechanism of action is the same as aminoglycosides (inhibition of bacterial protein synthesis at the 30S ribosomal subunit), but it is not bactericidal as are aminoglycosides, but rather bacteriostatic. Spectinomycin is active against many important bovine pathogens, both gram positive and gram-negative; it is also effective in poultry for *Mycoplasma* infections, and occasionally for *E. coli*, *Pasteurella multocida*, and *Salmonella*. It is unique compared to aminoglycosides in that there is no ototoxicity or nephrotoxicity, and the renal depletion half-life is shorter than aminoglycosides because of less accumulation in the renal cortex. After intramuscular injection, spectinomycin is rapidly absorbed (peak concentrations in less than 1 hour), and the elimination half-life from plasma in calves is approximately 2 hours. Like all aminocyclitols, spectinomycin is not substantially metabolized and is eliminated primarily by the kidneys. It is commercially available both as a single drug entity and combined with lincomycin.

#### **Withdrawal times**

The following withdrawal times are recommended for the label-prescribed dose, route, and duration of therapy in the approved species.

- A. Streptomycin -- 30 days after injection
- B. Gentamicin -- tolerance level of 0.1 ppm in muscle, 0.3 ppm in liver, and 0.4 ppm in fat and kidney
  - 1. oral -- 3 days for baby pigs
  - 2. parenteral to baby pigs -- 40 days
- C. Neomycin -- 5 days when fed at 400 g/ton in feed
- F. Spectinomycin -- 21 days in swine
- G. Apramycin -- 28 day withdrawal in swine

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