FARAD Digest

Aminoglycoside residues in food of animal origin

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The aminoglycoside antimicrobials are polar organic bases with bactericidal activity mostly against aerobic gram-negative bacteria. The group includes dihydrostreptomycin, streptomycin, neomycin, kanamycin, gentamicin, and amikacin. Use of this group of antimicrobials has declined because of resistance, particularly in the older drugs, and problems with toxicity, but they still remain important in the treatment of serious gram-negative infections in animals.[1] They are also a common source of violative antimicrobial residues in food of animal origin. A number of veterinary organizations, including the Academy of Veterinary Consultants, the Society for Theriogenology, the American Association of Bovine Practitioners, the AVMA, and several state veterinary medical associations, have established or support policies that discourage the extralabel use of aminoglycosides. The purpose of this digest is to give an overview of the pharmacokinetics and other properties of the aminoglycosides that contribute to these residues so that practitioners can better understand the food-safety risks of using these antimicrobials in food-producing animals.

Overview of Aminoglycoside Pharmacokinetics

Aminoglycosides are poorly absorbed from the gastrointestinal tract, except in animals in which there is substantial disruption of the intestinal mucosa (eg, severe hemorrhagic diarrhea), but absorption is rapid and complete after parenteral administration. Distribution is rapid and mostly limited to extracellular fluids, and there is a small amount of plasma protein binding (< 25%). Elimination is entirely by renal excretion (glomerular filtration), and the drug in the urine is unchanged. Aminoglycosides are sequestered in certain organs, most importantly the kidneys, but other organs with large volumes such as the liver also contain substantial amounts of drug.[1]

There is considerable interindividual variation in the pharmacokinetics of aminoglycosides in healthy and diseased animals. Some of these fluctuations can be attributed to factors that influence extracellular fluid volume (and hence volume of distribution) and impair renal function (and hence rate of elimination), such as age, dehydration, pregnancy, sepsis, and kidney disease.[1]

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Cellular Mechanisms of Aminoglycoside Accumulation and Toxicity

After glomerular filtration, renal tubular reabsorption occurs and the epithelial cells of the proximal renal tubules retain a small but important proportion of the administered dose (approx 5%).[2] Aminoglycosides bind to acidic phospholipids in the brush-border membrane and are transferred to the transmembrane protein megalin, from which the drug molecules are then internalized in endosomes. Megalin binds to polybasic drugs and is expressed in the renal tubular epithelium and some other specialized epithelial cell types including retinal and inner ear epithelia. This accounts for the selective accumulation and toxicity of aminoglycosides in these tissues. Interestingly, this uptake process is saturable at clinically relevant doses, suggesting that repeated smaller doses might lead to a higher level of accumulation than higher doses administered less frequently.[2]

Human Food Safety Concerns

The main toxic effects of the aminoglycoside antimicrobials are nephrotoxicity and ototoxicity. These are not of great concern regarding human food safety because of the low oral bioavailability of these drugs. Results of genotoxicity, mutagenicity, and reproduction studies indicate that the aminoglycosides are unlikely to be carcinogenic or teratogenic, although fetotoxicity was observed for gentamicin. The most relevant adverse effect of exposure to residues of this group of antimicrobials would therefore seem to be those on the human intestinal microflora.[3] The tolerances (ie, allowable residue concentrations in tissues of slaughtered animals in the United States) for the various aminoglycosides in kidney tissue are listed (**Table 1**).

Patterns of Extralabel Use and Residue Violations

Most questions submitted to the **Food Animal Residue Avoidance Databank (FARAD)** about aminoglycosides have concerned parenteral administration of gentamicin to cattle (dairy and beef) and goats. For swine, questions are usually about higher-than-label

Table 1—Aminoglycoside antimicrobials presently approved for use in food-producing species in the United States.

Aminoglycoside	Approved species	Route of administration	Dose	Renal tissue tolerance (ppm)*	Withdrawal time
Dihydrostreptomycin	Dry dairy cows	Intramammary	1,000 mg	2.0	60 days (meat) 96 hours (milk)
Streptomycin	Calves	PO	33 mg/kg	2.0	2 days (meat)
Streptomycin	Swine	PO	33 mg/kg	2.0	0 days (meat)
Streptomycin	Chickens	PO	33 mg/kg	2.0	4 days (meat)
Gentamicin	Swine	PO	1.1 mg/kg	0.4	3 days (meat)
Gentamicin	Swine (up to 3 days old)	IM	5 mg	0.4	40 days (meat)
Gentamicin	Swine (up to 3 days old)	PO	5 mg	0.4	14 days (meat)
Gentamicin	Turkeys (1–3 days old)	SC	1 mg	0.4	63 days (meat)
Gentamicin	Chickens (1 day old)	SC	0.2 mg	0.4	35 days (meat)
Gentamicin	Cattle	Topical	0.75 mg	0.4	0 days (meat)
Neomycin	Cattle (not veal calves)	PO	22 mg/kg	7.2	1 day (meat)
Neomycin	Goats	PO	22 mg/kg	7.2	3 days (meat)
Neomycin	Sheep	PO	22 mg/kg	7.2	2 days (meat)
Neomycin	Swine	PO	22 mg/kg	7.2	3 days (meat)
Neomycin	Turkeys	PO	22 mg/kg	7.2	0 days (meat)
Apramycin	Swine	PO	12.5 mg/kg	0.1	28 days (meat)

*Maximum allowable concentration of aminoglycosides in tissue at slaughter (United States). To convert dose to mg/lb, divide by 2.2.

doses administered orally to animals at ages older than 3 days. Unapproved intramammary formulations and topical administration to wounds are other queries that have been received. There have also been many inquiries for general information, which may reflect a heightened awareness of the regulatory priority afforded to extralabel aminoglycoside use.

The results of the National Residue Program of the Food Safety Inspection Services of the USDA for the year 2000 indicate that in certain groups of food-producing animals (dairy cows, veal calves, roaster pigs, and young chickens), a high proportion of violative antimicrobial residues in meat and other edible tissues (but not milk) can be attributed to aminoglycoside antimicrobials (**Figure 1**).[4] Because there is only 1 approved product for topical use in adult cattle, these violative residues are most likely the consequence of extralabel drug use.

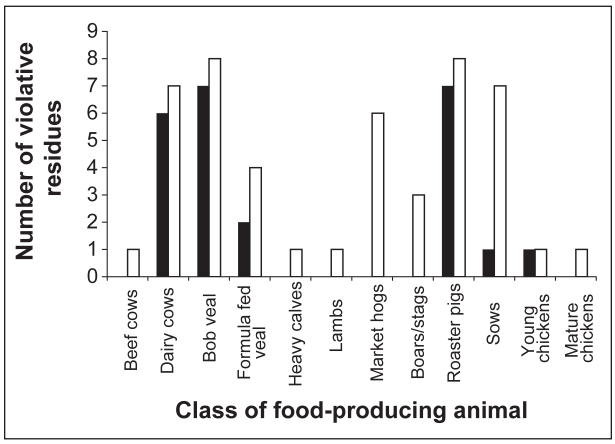

Figure 1—Number of violative residues attributed to aminoglycoside antimicrobials (solid bars) and total residue violations (open bars) detected via the Monitoring Plan of the USDA Food Safety and Inspection Service in various classes of food-producing animals during the year 2000.

Residue Studies Applicable to Patterns of Extralabel Use in the United States

Persistence of aminoglycoside residues appears to be variable and dependent on numerous factors such as the formulation used, the dose administered, the dosage interval, and the health and physiologic features of the animal. Unfortunately, there are few residue studies in the published literature that make it possible to determine reliable extralabel **withdrawal intervals (WDIs)**.

IV, SC, and IM routes—The published literature supports the observation that aminoglycosides persist in the kidneys, despite relatively rapid disappearance from the plasma and most other edible tissues. Results of many published pharmacokinetic and residue studies[5-8] indicate the continued presence of residue concentrations greater than tolerance limits in the kidneys, particularly the renal cortex, up to the last sampling time, but sampling times are not long enough to fully characterize the elimination of these drugs from the renal tissues. Residues > 400 µg/kg (182 µg/lb) were measured in kidney tissue up to the last day of sampling (80 days) after IM administration of gentamicin to calves at 4 mg/kg (1.8 mg/lb) for 3 days.[3] Dihydrostreptomycin and gentamicin residues were also detected at the injection site for a prolonged period (45 days).[6,9]

Brown et al[10] studied the depletion of gentamicin from the kidneys of sheep by performing serial percutaneous biopsies and detected residues up to the termination of the study at 74 hours after administration (3 mg/kg [1.4 mg/lb], IM, q 12 h, for 10 days). A renal tissue terminal elimination half-life of 59 days was calculated by use of this technique. This would suggest a

WDI of at least 5 months if it were assumed that 5 half-lives are required for the concentration of a drug to deplete to concentrations safe for human consumption (approx 97% eliminated). To wait 10 tissue half-lives, and hence allow 99.9% of the drug to be eliminated, would require an even longer WDI of 18 to 19 months. In an unpublished feedlot study,[a] trace amounts of gentamicin were detected for 4 to 5 months in the renal tissues of calves treated with 4 mg of gentamicin/kg once daily, IM, for 3 days.

In a study[6] that investigated the effects of dose on plasma concentrations of gentamicin in sheep, an additional slower elimination phase was identified at the higher doses because the resulting higher plasma concentrations could be detected by the analytic technique. This phase is possibly linked to the slow release of drug from tissue-binding sites. The plasma half-life of the drug during this terminal elimination phase was prolonged, compared with the other phases (between 120 and 160 hours, compared with approx 3 hours). Also, clearance was increased at higher doses, suggesting saturation of renal tubular binding sites and an increase in the fraction of filtered gentamicin eliminated in the urine. Furthermore, a decrease in clearance was detected if a second dose was administered within 21 days of the first. This could be attributed to an increase in the total amount of drug sequestered in the tissues attributable to the availability of binding sites during the second dose administration (as opposed to the saturation of these sites at higher single doses). Release of drug sequestered in the tissues would then contribute to plasma concentrations and prolong the elimination of the drug. This is further supported by the results of other studies[5,6] conducted by the same authors, in which it was found that the half-life of the terminal elimination phase increased significantly if multiple doses were administered to animals and tissue residues increased as the total dose of gentamicin increased but also as the duration of gentamicin administration was increased.

Residues of aminoglycosides were detected in milk after parenteral administration. These residues were detected for variable periods, depending on the dose and the formulation used. For dihydrostreptomycin, 1 study[11] detected residues for 18 hours after administration at 2.25 mg/kg (1 mg/lb), whereas another study[12] detected residues for 30 hours after administration at 2.25 mg/kg once and for 54 hours after 2.25 mg/kg was administered 3 times. The second study[12] used a product that was combined with procaine benzylpenicillin, which may have delayed the absorption of the dihydrostreptomycin from the administration site, although elimination is still faster than for the benzylpenicillin component. Gentamicin residues were detected for 48 to 72 hours after IV administration at 4.4 mg/kg (2.0 mg/lb)[13] and for 48 hours after both IV and IM administration at 5 mg/kg (2.3 mg/lb).[14,15]

Intrauterine administration—Assigning appropriate WDIs is problematic after extralabel intrauterine treatment in food-producing animals because a variety of factors (eg, hormonal status, degree of uterine involution, and drug vehicle) may influence drug absorption into the systemic circulation.[16,17] For intrauterine administration of gentamicin doses of 0.25 to 2.5 g, systemic bioavailability of 30% to 80% has been reported.[16,18,19] Blood and urine concentrations in those experiments suggest the presence of tissue residues, which is consistent with a report of gentamicin kidney residues detected 20 to 30 days after intrauterine administration of only 200 mg.[20] In 2 studies,[12,19] gentamicin milk residues were detected after intrauterine administration for up to 48 hours.

Intramammary administration—Milk residues after intramammary administration are highly variable and appear to be dependent on the vehicle, dose, and duration of treatment as well as concurrently administered active ingredients. In various studies, the time required for milk samples to be free of measurable residues varied from 72 hours to > 256 hours for dihydrostreptomycin[21,22]; 120 hours for gentamicin[13,15]; and 84 hours for neomycin.[23] Simultaneous intramammary and parenteral administration of gentamicin results in prolonged residues (approx 228 hours after the last treatment).[15]

After intramammary treatment with 100 mg of gentamicin combined with procaine penicillin, residues were less than the US safe concentration of 0.030 µg/mL within 60 hours. When tested, residues were not detected in milk from untreated quarters.[3] Systemic absorption is not expected because of the hydrophilic nature of these drugs, but extensive absorption did occur in cows with experimentally induced coliform mastitis (bioavailability mean ± SD, 87.9 ± 15.1%).[13,24]

Current FARAD WDI Recommendations After Extralabel Use

FARAD discourages the extralabel use of aminoglycosides because of the lack of specific residue data coupled with prolonged and variable persistence of aminoglycoside residues in tissues such as the kidney and repeated reports of violative residues even after very long withdrawal periods. If the drug has already been administered to the animal, FARAD will recommend a conservative slaughter WDI of 18 months. This is for all cases of extralabel use in all species after parenteral administration or administration via any route with the potential for systemic absorption, regardless of dose. This does not refer, however, to products approved for parenteral administration when used according to label directions in the approved species, in which case the WDI appears on the label (Table 1). An extended WDI of 1 day is recommended for all topically administered aminoglycosides for which systemic absorption is not expected.

For gentamicin, a milk WDI of 5 days is recommended after parenteral administration at 5 mg/kg every 24 hours and 10 days after intramammary administration in dairy cows. These recommendations are based on the times required for depletion to safe concentrations reported in the literature, which have been doubled as a precautionary measure. Testing may begin earlier to determine whether the cows can reenter the herd. For goats, the recommended milk WDI after parenteral administration of gentamicin is 10

days. Testing the milk with a commercially available screening test before the animal is allowed to reenter the milking herd is recommended in all instances. The screening test should be selected and the results interpreted on the basis of its sensitivity with relation to the milk tolerance (dihydrostreptomycin, 0.125 µg/mL; neomycin, 0.15 µg/mL) or unofficial safe concentration (gentamicin, 0.03 µg/mL).

It should be remembered that AMDUCA prohibits the extralabel use of drugs in feed, which would preclude the extralabel use of most orally administered aminoglycoside formulations except those that are administered as a solution.

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