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Aminoglycoside Antibiotics in Neonatal Foals

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KEY FACTS

- Gram-negative bacteria are frequently involved in equine neonatal infections.
- Because of their rapid bactericidal effects and concentration-dependent nature, aminoglycosides are very effective against gram-negative organisms.
- Safe and effective use of these drugs must include therapeutic drug monitoring, which requires the collection of at least two serum samples following administration of the first dose.
- Use of extended-interval dosing has the potential to enhance clinical efficacy while minimizing (but by no means eliminating) the risk of nephrotoxicity.

ABSTRACT: Because of the frequent involvement of gram-negative bacteria in equine neonatal sepsis, it is critical that the initial empiric antimicrobial regimen employed provide excellent gram-negative coverage. Aminoglycoside antimicrobials have rapid bactericidal effects, clinical efficacy, relatively low resistance rates, and synergism with β-lactam antimicrobials; therefore, these drugs remain a mainstay in treating gram-negative infections in neonatal foals. Aminoglycosides are classified as concentration-dependent antimicrobials because they exhibit peak concentration-dependent bactericidal activity and postantibiotic effects against susceptible organisms. High peak concentrations of aminoglycosides produce more rapid and extensive bacterial killing, prolong postantibiotic effects, and decrease the emergence of resistant strains. Because of these dose-dependent properties, the peak concentration in serum (C_{max}) and the ratio of C_{max} to the minimal inhibitory concentration (MIC) for the organism (C_{max}:MIC) are the best predictors of the efficacy of aminoglycosides. The potential for nephrotoxicity makes it important that serum concentrations be allowed to fall to trough levels for a substantial portion of the dosing interval to allow clearance of the drug from sites of accumulation within the kidney. Maximizing clinical efficacy and avoiding nephrotoxicity require monitoring of aminoglycoside serum concentrations and individualized patient dosage adjustment in critically ill equine neonates.

Managing bacterial infections in neonatal foals presents numerous challenges to equine practitioners. Bacterial infection in these patients may be localized or systemic, and the progression from acquired, localized infection to septicemia can occur very rapidly because of the presence of impaired cellular and humoral immune responses associated with age and failure of passive transfer.[1] Additionally, neonatal foals may have been exposed to bacteria in utero, with septicemia being present at birth. Therefore, when treating infections in equine neonates, therapy should be administered as early as possible. Historically, gram-positive organisms were the primary pathogens of equine neonates; in the last 20 years, however, gram-negative organisms have become predominant.[2]

Initial antimicrobial therapy should be broad-spectrum in nature, but it is imperative that adequate gram-negative coverage be provided. Although several antimicrobials have activity against gram-negative organisms, aminoglycoside antimicrobials are a mainstay in treating gram-negative infections in neonatal foals because of the rapid bactericidal effects of these drugs, clinical efficacy, relatively low resistance rates, and synergism with β-lactam antimicrobials. Maximizing clinical efficacy and avoiding nephrotoxicity require moni-

Dosage Adjustment

Because aminoglycoside pharmacokinetics are linear for clinical application of TDM, the dosage may be modified by use of proportionality.[39] If the desired C_{max} (i.e., 30 µg/ml) is twice the obtained C_{max} (15 µg/ml), the dosage is simply doubled.[39] Use of the following equation facilitates this calculation:

$$\text{Revised dose (mg/kg)} = \frac{(C_{max}\text{ desired [µg/ml]} \times \text{Original dose [mg/kg]})}{C_{max}\text{ obtained (µg/ml)}}$$

Use of this equation is demonstrated with the following example in which the original dose is 6 mg/kg:

$$\text{Revised dose (mg/kg)} = (30\ \mu g/ml \times 6\ mg/kg) \div 15\ \mu g/ml$$
$$\text{Revised dose} = 12\ mg/kg$$

However, alteration of the dosage interval cannot be based on the proportionality relationship but must be extended empirically or altered based on monitoring serum concentrations for a greater duration within the dosage interval, with dosing repeated after an adequate time period (8 to 12 hours) with serum concentrations below the trough value for the drug in question. Lowering the dosage to accommodate for prolonged clearance is not recommended because it may result in decreased efficacy.[39]

toring of aminoglycoside serum concentrations and individualized patient dosage adjustment in critically ill equine neonates (see the box above).

PHARMACOLOGY

The original member of the aminoglycoside group, streptomycin, was discovered in 1943. Other compounds have followed, and the group now includes several compounds; gentamicin and amikacin are the most commonly used in equine medicine. All members of the aminoglycoside family are structurally similar, consisting of amino sugars bound to a central hexose nucleus, and they share many pharmacokinetic properties. Aminoglycosides are poorly absorbed after oral administration and have minimal protein binding.[3] Because aminoglycosides are highly polar, they are very water soluble and widely distributed in extracellular fluid, but they cross biologic membranes poorly, resulting in low intracellular concentrations.[4] Aminoglycosides are not metabolized and are rapidly excreted (compared with other drugs) unchanged in the urine. The drug is cleared by glomerular filtration, and the urine concentration of the drug is predictably high, with concentrations 30 to 100 times those found in the serum.[3] There is reabsorption of aminoglycosides by the proximal renal tubular epithelial cells, leading to accumulation of the drug of up to 50 times the serum concentration within the renal cortex.[3,5]

Because of their high polarity, aminoglycosides do not penetrate the blood–brain barrier; in normal people and horses, aminoglycosides cannot be found in the cerebrospinal fluid following parenteral administration.[6–8] Aminoglycosides also demonstrate poor penetration into bronchial secretions of humans[9] and horses[10,11] following parenteral administration. Aminoglycosides demonstrate good soft-tissue penetration, however, and numerous studies have documented appropriate aminoglycoside concentrations in the peritoneal cavity, endometrium, and synovial tissues following IV or IM injection of gentamicin or amikacin.[7,12,13] Penetration of soft tissues depends on passive diffusion[14]; therefore, achieving therapeutic concentrations is facilitated by attaining high peak serum concentrations.[15]

Aminoglycosides are active against a wide range of aerobic gram-negative organisms of veterinary importance, whereas their gram-positive spectrum of activity is relatively limited. Aminoglycosides are bactericidal because of interference with bacterial ribosomal protein synthesis. Passage of aminoglycosides across the outer membrane of gram-negative bacteria is a self-promoted uptake process involving the drug-induced disruption of magnesium (Mg^{++}) bridges between adjacent lipopolysaccharide molecules.[16] Transport of aminoglycosides across the cytoplasmic (inner) membrane depends on oxygen and electron transport and is blocked or inhibited by low pH and anaerobiosis,[16] with anaerobiosis increasing the minimal inhibitory concentration (MIC) at least tenfold.[17] In the cytosol, aminoglycosides bind to the 30S ribosomal subunit and disrupt the mRNA translation process by impairing the proofreading process controlling translational accuracy.[16,18] The resulting aberrant proteins may be inserted into the cell membrane, leading to altered membrane permeability and enhanced aminoglycoside transport.[16] Aminoglycosides exhibit synergistic effects when administered with β-lactam antibiotics,[19,20] perhaps resulting from enhanced bacterial aminoglycoside uptake.[17]

Aminoglycosides are classified as concentration-dependent antimicrobials because they exhibit peak concentration-dependent bactericidal activity and postantibiotic effects against susceptible organisms. High peak concentrations of aminoglycosides produce more rapid and extensive bacterial killing than do lower

concentrations.[21] High concentrations of aminoglycosides also prolong postantibiotic effects, wherein bacterial growth is suppressed for a period of time after the tissue concentration of the antimicrobial has fallen below the MIC for the bacteria in question.[18] High peak concentrations of aminoglycosides (greater than eight to 10 times the MIC) have also been shown to decrease the emergence of resistant strains.[21] Because of these dose-dependent properties, the peak concentration in serum (C_{max}) and the ratio of C_{max} to the MIC for the organism (C_{max}:MIC) are the best predictors of the efficacy of aminoglycosides (consistent with an antimicrobial with concentration-dependent killing activity).[22] IV bolus administration of aminoglycosides results in higher values of C_{max} than does IM administration.[23,24]

Postantibiotic effects are critical to maintaining efficacy with dosage regimens using extended intervals between doses because the serum concentration of the drug is below the MIC for a substantial portion of the dosage interval. Some investigators have argued that the postantibiotic effects are largely an in vitro phenomenon and have little clinical relevance.[25] However, numerous studies have demonstrated the presence of the postantibiotic effects of aminoglycosides in vivo, which, in some instances, have an even greater duration than effects in vitro, likely because of the presence of a functioning immune system.[26] Factors contributing to the prolongation of the postantibiotic effects can include high aminoglycoside C_{max} and concurrent cell-wall active (β-lactam) antimicrobial therapy.[15]

Although attainment of a high aminoglycoside C_{max} reduces the development of stable resistance in bacteria,[21] there is an additional resistance phenomenon to be considered when designing aminoglycoside dosage regimens, namely the phenomenon of adaptive resistance.[27] Adaptive resistance represents the development of transient, reversible bacterial refractoriness to an antimicrobial following prior exposure resulting from down regulation of the active uptake of the drug by the organism.[27] The onset of adaptive resistance usually follows the end of the postantibiotic effects.[28] The development of adaptive resistance to aminoglycosides has been documented in vitro and in vivo and may be overcome by allowing for a period of time within the dosing interval wherein the serum concentration is negligible, during which the organisms again become susceptible.[15,28]

TOXICITY

Although aminoglycosides are important for treating many equine conditions, these drugs exhibit a low therapeutic index, wherein there is little difference between a therapeutic and toxic dose.[29] The toxic effects of aminoglycosides primarily involve the hair cells of the inner ear and the proximal tubular epithelial cells of the kidney.[18] Although there is no reason to believe that horses do not suffer from ototoxicity, the major concern is nephrotoxicity. All aminoglycoside agents are nephrotoxic, although there is variability with regard to toxic potential, with neomycin being the most toxic and streptomycin the least.[3] Aminoglycoside nephrotoxicity is manifested clinically as non-oliguric renal failure, with a gradual increase in serum creatinine and hypo-osmolar urinary output developing after several days of treatment.[30] Tubular dysfunction is the primary result of aminoglycoside toxicity, as reflected by the development of enzymuria, proteinuria, glucosuria, increased fractional excretion of electrolytes, and cast excretion.[30] Increased activity of the renin–angiotensin system and the resulting renal vasoconstriction are likely responsible for the decrease in glomerular filtration rate (GFR), whereas the development of hypo-osmotic polyuria appears to result from decreased fluid reabsorption in the proximal tubule because of the impairment of solute reabsorption.[30]

Aminoglycosides are freely filtered by the glomerulus and then bind to the brush border of the proximal tubular epithelial cell. The bound molecule is internalized by pinocytosis; this process has been shown to be saturable.[30] The saturable nature of proximal tubular epithelial cell aminoglycoside uptake means that the presence of higher intraluminal concentrations of aminoglycosides, as occurs with the administration of larger doses less frequently, does not result in increased aminoglycoside uptake by the proximal tubular epithelial cell.[31] In this situation, much of the aminoglycoside bypasses the proximal tubular epithelial cell and is excreted, with the total aminoglycoside accumulation by the proximal tubular epithelial cell being less over 24 hours than occurs with administration of smaller dosages more frequently.[31] After internalization by the proximal tubular epithelial cell, aminoglycosides inhibit lysosomal phospholipases, resulting in intracellular accumulation of phospholipids and inhibition of the sodium–potassium ATPase pump, leading to swelling, dysfunction, and necrosis.[18]

Numerous factors (e.g., dehydration, prolonged aminoglycoside therapy, preexisting kidney or liver disease, concomitant use of other nephrotoxic drugs) have been found to increase the risk of nephrotoxicity in patients treated with aminoglycosides.[18,32] Many of these conditions may be encountered when treating neonatal foals, placing them at increased risk for aminoglycoside-induced nephrotoxicity. Thus it is extremely important that neonatal foals be managed in a way that minimizes the risk of nephrotoxicity and

monitors for evidence of developing nephrotoxicity. In addition to monitoring serum aminoglycoside levels, several steps can be taken to minimize the risk of nephrotoxicity. Maintaining hydration and correcting hypotension are of utmost importance in critically ill neonates to allow for a normal GFR and adequate urine production in animals with normal renal function. Impairment of renal function requires prolongation of the aminoglycoside treatment interval or complete avoidance of aminoglycosides. Appropriate drug selection is also important because amikacin appears to have less nephrotoxic potential than does gentamicin. IV calcium supplementation has been demonstrated to decrease the risk of nephrotoxicity in adult ponies receiving toxic doses of gentamicin,[33] but the applicability of this treatment in foals is unknown.

It has become apparent that antimicrobials may be involved in the pathophysiology of septic shock because of the ability of some antimicrobials to release potent antigenic materials, such as endotoxin, from the bacterial cell wall during antimicrobial-induced bacterial growth suppression or bacteriolysis.[34] This endotoxin-releasing effect varies with different antimicrobials and is related to their mechanism of action.[35] Antimicrobials affecting cell-wall synthesis, such as β-lactams, can stimulate the release of large quantities of endotoxin, whereas rapidly bactericidal agents with intracellular killing mechanisms, such as aminoglycosides, cause relatively minor endotoxin release.[35,36] The use of aminoglycosides alone or in combination with β-lactam antimicrobials has been associated with lower levels of endotoxin release from gram-negative bacteria in vitro.[36] Although the role of endotoxin in the pathogenesis of septic shock is well accepted, much of the work documenting the endotoxin-liberating effects of antimicrobials has been done in vitro, and the clinical relevance of this phenomenon remains unclear.[35–37] Because of the possibility that antimicrobial-associated endotoxin release could worsen clinical disease in patients with gram-negative infections, the use of β-lactam drugs should be accompanied by appropriate treatment for endotoxemia[36] and/or administration of an aminoglycoside.

PHARMACOKINETIC PRINCIPLES

The distribution and elimination of drugs can be described by several mathematical expressions. The most important for basic monitoring of dosing include the volume of distribution (V_d), clearance (Cl_B), and elimination half-life ($T_{½e}$). These parameters are used in therapeutic drug monitoring (TDM), wherein the distribution and elimination of the drug in individual clinical cases is established and used to determine the most appropriate drug dosage and frequency of administration for that particular individual. Some assumptions are made in most aminoglycoside TDM paradigms, the most important being that the elimination of aminoglycosides can be adequately modeled using a one-compartment pharmacokinetic model. This is primarily a concern regarding determination of $T_{½e}$, defined as the time required for the amount of the drug in the body to decrease by 50%.[38]

The kinetics of aminoglycosides are most accurately described by a three-compartment model (i.e., α, β, and γ), with $T_{½\alpha}$ representing the distribution phase (30 minutes following IV bolus) and with $T_{½e}$ representing the combination of $T_{½\beta}$ and $T_{½\gamma}$. $T_{½\beta}$ represents the classic elimination phase primarily dependent on renal elimination (1 to 24 hours), whereas $T_{½\gamma}$ represents the slow elimination of aminoglycosides deposited in the tissues (100 to 200 hours).[18,29,39] The vast majority of the aminoglycoside dosage administered is eliminated during the β phase of elimination; therefore, $T_{½\beta}$ represents the clinically relevant $T_{½e}$ with the aminoglycosides.[39] Using the β phase as the single compartment in TDM (and assuming that this phase is accurately described by a linear model) allows straightforward estimation of the relevant pharmacokinetic parameters and modification of the dosage (Figure 1).[39]

V_d is the extent of distribution of the drug in terms of theoretical volumes of fluid. V_d is the amount of fluid that would be required to contain the amount of drug

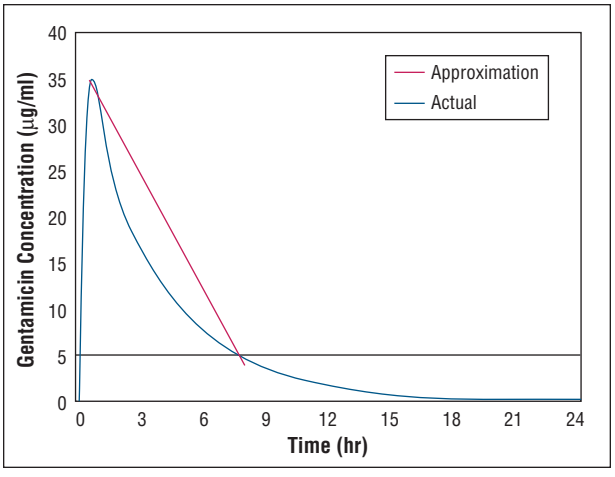


Figure 1—A representative curve demonstrating the serum concentration of gentamicin (µg/ml) versus time in hours (actual). The clinically determined line representing the β phase of elimination (an approximation) based on serum samples taken 0.5 and 8 hours after administration is also depicted. This demonstrates the reasonable approximation of the slope of the β phase elimination curve that is achieved using only two serum samples to determine gentamicin elimination. Note the *horizontal line* at 5 µg/ml representing the desired cutoff value for the 8-hour serum gentamicin concentration.

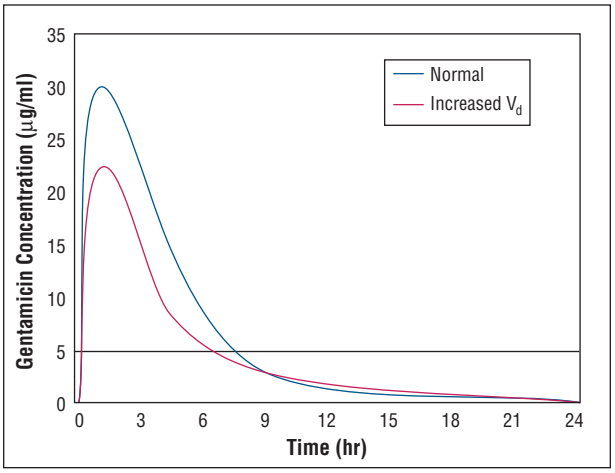


Figure 2—The serum concentration of gentamicin (µg/ml) versus time in hours in a normal patient and in one with an increased V_d. Note how the C_{max} is substantially lower (approximately 23 µg/ml) in the patient with an increased V_d versus 30 µg/ml in the patient with a normal V_d.

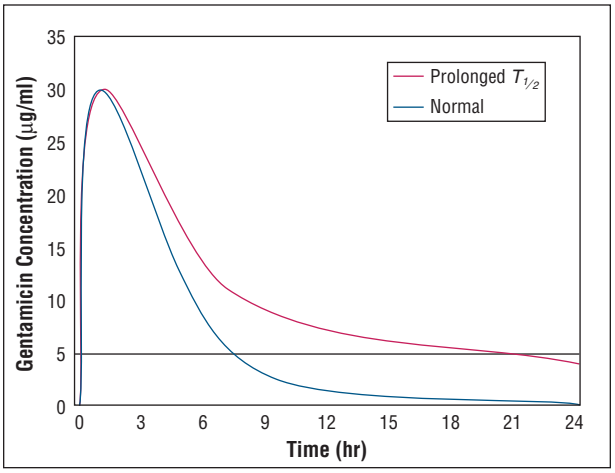


Figure 3—The serum concentration of gentamicin over time in a normal patient and in a patient with a prolonged $T_{½}$. Note that the C_{max} is the same in both patients (30 µg/ml), whereas the patient with a prolonged $T_{½}$ demonstrates persistent elevation of the serum gentamicin concentration. The serum gentamicin concentration in the patient with prolonged $T_{½}$ does not approach the 8-hour cutoff level until near the end of the 24-hour dosing interval, requiring significant prolongation of the treatment interval or discontinuation of gentamicin therapy.

in the body if it were distributed in a concentration equal to that of the drug in the plasma. V_d represents a proportionality factor relating the serum concentration of the drug to dosage administered, as determined by the following formula:

$$V_d = \frac{D \text{ (dosage in mg)}}{C_p \text{ (plasma concentration in mg/ml)}}$$

Although little can be determined about the specific (body compartment) distribution of the drug from the V_d alone, the higher the V_d, the more "widely" the drug is distributed within the body. Alternatively, a small V_d, equivalent to the plasma volume (e.g., 0.08) suggests that most of the drug is confined to the plasma. The V_d of aminoglycosides closely approximates the extracellular water volume, as these compounds achieve negligible intracellular concentrations in most tissues.[29] Conditions that increase extracellular water volume increase the V_d of aminoglycosides. Knowledge of the V_d is required to determine the dosage required to achieve a certain C_p of drug via the following formula:

$$D = V_d \times C_p$$

An increase in V_d results in a lowering of C_{max} (C_p) with a given dosage of aminoglycoside (Figure 2).

Another means of expressing elimination is Cl_B, defined as the volume of plasma cleared of the drug per unit of time[38]:

$$Cl_B = \frac{\text{Plasma volume cleared (ml)/time (min)}}{\text{Body mass (kg)}}$$

$$Cl_B = V_d \times K_{el}$$

K_{el} is the elimination rate constant, reflects all of the membrane diffusion processes involved in the elimination of the drug, and is determined using the following formula[38]:

$$K_{el} = 0.693/T_{½e}$$

Clearance differs from $T_{½e}$ in that it is not affected by the V_d of the drug. The Cl_B of drugs can be the same, whereas the $T_{½e}$ may be vastly different because of differences in V_d. Knowledge of the $T_{½e}$ and Cl_B is required to determine the likelihood of drug accumulation and the appropriate frequency of drug administration. Half-life ($T_{½}$) is related to clearance and V_d by the following equation[38]:

$$T_{½e} = (0.693 \times V_d)/Cl_B$$

As aminoglycosides are eliminated by glomerular filtration, a decrease in the GFR will prolong $T_{½e}$ and decrease Cl_B.[40] The effect of an increase in $T_{½e}$ on aminoglycoside kinetics is illustrated in Figure 3.

ALTERATIONS IN PHARMACOKINETICS

It is important to realize that neonatal foals are not miniature versions of adults, and many physiologic and pathophysiologic factors can alter the distribution and elimination of aminoglycosides in foals. There is significant interindividual variability in aminoglycoside pharmacokinetics[41]; in addition, there are effects of age,

presence of hypoxia, dehydration, fever, and sepsis.[41–44] Neonatal age was found to have numerous effects on aminoglycoside pharmacokinetics; the V_d in foals 1 to 30 days of age was 1.5 to 2.5 times that in adults (Tables 1 and 2)[7,43,45–48] because foals have a greater extracellular water volume than adults.[18] The effect of increased V_d on aminoglycoside pharmacokinetics is illustrated in Figure 2. Foals 1, 10, and 15 days of age were also found to have a decreased elimination (K_{el}) when compared with foals 30 days of age.[45] Decreases in $T_{½e}$ were associated with increasing age, with $T_{½e}$ decreasing as much as 50% from 1 day of age to adulthood (Tables 1 and 2, Figure 3).[7,43,45–48] As might be expected from the prolonged $T_{½}$, trough levels were not reached until 8 to 9 hours after administration in 1-day-old foals compared with 4 to 7 hours in foals older than 1 day.[45] These findings have significant implications for choosing the treatment interval when using aminoglycosides in neonatal foals.

Hypoxia and prematurity also have a profound impact on pharmacokinetic variables (Tables 1 and 2). The presence of hypoxia in premature foals was found to decrease K_{el}, prolong $T_{½e}$, and decrease Cl_B,[43] whereas hypoxia alone decreased Cl_B and prolonged $T_{½e}$ in a group of term foals.[42] The specific mechanism for these changes was not determined in these studies but is assumed to arise in large part from hypoxic-induced renal vasoconstriction, leading to reduced GFR.[42] The presence of sepsis also induces changes in metabolism and excretion of aminoglycoside antibiotics. One human study found that the presence of sepsis increased V_d to 165% of normal and led to a decrease in K_{el} (0.11 vs 0.24/hr).[49] These changes may be due to increased capillary permeability coupled with aggressive fluid therapy.[49,50] Although IV fluid therapy was found to have no effect on aminoglycoside kinetics in adult horses,[51] the effect of IV fluid administration has not been examined in neonatal foals being aggressively treated with fluids. Fever also has effects on aminoglycoside kinetics, with chemically induced fever being associated with a decrease in serum peak gentamicin concentration of 20% in dogs and 40% in humans.[52] Systemic inflammation is present in foals with sepsis, and the alterations of vascular permeability, vascular tone, and renal function associated with this syndrome[53] are likely responsible for much of the variability in aminoglycoside pharmacokinetics associated with critical illness.[50,54]

DOSAGE PARADIGMS

Although a variety of dosages and dosing schedules have been recommended for administering aminoglycosides to horses, two major approaches are employed. The first, called the *multiple-daily dosing (MDD) paradigm*, involves administering an aminoglycoside so that plasma levels exceed the MIC of the infecting organism for the duration of treatment.[40] Historically, MDD in horses has consisted of administering gentamicin at 2.2

Table 1. Summary of Selected Pharmacokinetic Variables for Horses and Foals Treated with Amikacin

Study	*Horses*	*Dose/Dosage*	*V_d (L/kg)*	*$T_{½e}$ (hr)*	*Clearance (ml/min/kg)*	*Area Under the Curve*
Brown et al[7]	Normal adults	7 mg/kg IM	0.26 ± 0.03	2.30 ± 0.18	1.33	Not reported
Wichtel et al[46]	Normal foals (1–2 days of age)	6.6 mg/kg IV	0.50 ± 0.02	3.73 ± 0.5	1.99 ± 0.18	3.08 ± 0.21
Wichtel et al[46]	Normal foals (4–6 days of age)	6.0–6.6 mg/kg IV	0.49 ± 0.02	3.30 ± 0.29	2.17 ± 0.12	2,948 ± 133
Wichtel et al[46]	Sick foals (n = 12)	6.0–7.6 mg/kg IV	0.39 ± 0.04	4.09 ± 0.44	1.34 ± 0.2	5,401 ± 852
Furr[a]	Sick foals (younger than 14 days of age; n = 19)	34.3 mg/kg/day IV (±15.8 SD)	0.43 ± 0.14 (0.14–0.76)	4.07 ± 1.8 (1.43–9.43)	1.66 ± 0.83 (0.21–3.5)	Not reported
Green and Conlon[43]	Sick, premature, hypoxic foals (n = 7)	7.0 ± 1.84 mg/kg/day IV	0.60 ± 0.09	5.39 ± 3.46	1.90 ± 1.13	Not reported
Green and Conlon[43]	Sick, term, nonhypoxic foals (n = 8)	7.51 ± 1.15 mg/kg/day IV	0.56 ± 0.11	2.86 ± 0.89	2.44 ± 0.73	Not reported

[a]Furr MO: Unpublished data, Marion duPont Scott Equine Medical Center, Leesburg, VA, 2002.

Table 2. Summary of Selected Pharmacokinetic Variables in Foals and Horses Given Gentamicin IV

Study	*Horses*	*Dose/Dosage*	*V_d (ml/kg)*	*$T_{½e}$ (hr)*	*Clearance (ml/min/kg)*	*Area Under the Curve*
Magdesian et al[48]	Normal adults	6.6 mg/kg	142	3.0	0.96	116.6
Pedersoli et al[47]	Normal adults	5.0 mg/kg	240	2.5	1.15	Not reported
Cummings et al[45]	Normal foals (1 day of age)	4.0 mg/kg	306 ± 30	2.1 ± 0.4	1.75 ± 0.47	Not reported
Cummings et al[45]	Normal foals (15 days of age)	4.0 mg/kg	325 ± 48	1.8 ± 0.6	2.4 ± 0.87	Not reported
Cummings et al[45]	Normal foals (30 days of age)	4.0 mg/kg	279 ± 34	1.0 ± 0.5	3.66 ± 1.93	Not reported
Furr[a]	Sick foals (younger than 14 days of age; n = 10)	6.6–18.6 mg/kg/day	510 ± 170 (300–810)	3.2 ± 0.6 (2.2–4.4)	1.93 ± 0.73 (0.83–3.5)	93.9 ± 33.2 (48.0–161.5)

[a]Furr MO: Unpublished data, Marion duPont Scott Equine Medical Center, Leesburg, VA, 2002.

mg/kg tid or 3.3 mg/kg bid IM or IV. These dosages result in adequate penetration of soft tissues, with peak concentrations of two to three times the anticipated MIC of the commonly encountered organisms. The MDD paradigm has also been advocated in critically ill equine neonates by several authors.[42,43,55,56]

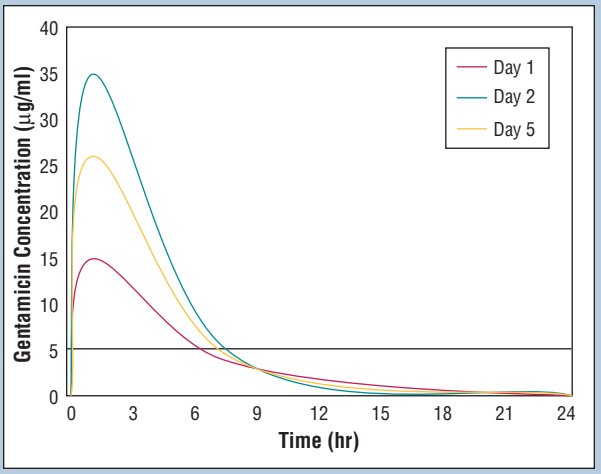
The second approach is called *extended-interval dosing (EID)*. It involves administering large, single doses at prolonged intervals (typically 24 hours) that are designed to provide a high C_{max} to enhance bacterial killing, followed by a long elimination time to minimize the risk of aminoglycoside accumulation and toxicity. The effectiveness of this method of dosing exploits the concentration-dependent bactericidal and postantibiotic effects properties of aminoglycosides and may minimize the development of antimicrobial resistance. Numerous studies in humans have found EID to be equally safe and effective compared with MDD regimens,[21] with some studies suggesting that EID is indeed associated with decreased nephrotoxicity and decreased mortality.[31,57]

EID has been evaluated in horses, and results suggest that administering gentamicin at 6.6 mg/kg IV or IM sid is safe and effective.[10,48,58] It is questionable to extrapolate this dose and interval to the neonatal foal, however, because the distribution and clearance of aminoglycosides can be quite variable in ill foals.[42,43,59] One study has examined EID of amikacin in normal neonatal foals.[60] Foals were administered amikacin at 21 mg/kg IV sid for 10 days. No renal toxicity was noted in these foals after 10 days; however, significant age-related changes were found, with amikacin $T_{½e}$ decreasing from 3.62 ± 0.79 hours at 1 day of age to 1.89 ± 0.66 hours at 10 days of age, amikacin Cl_B increasing from 1.59 ± 0.44 (ml/min)/kg at 1 day of age to 2.71 ± 0.61 (ml/min)/kg at 10 days of age, and amikacin V_d decreasing from 442.4 ± 63.1 ml/kg at day 1 to 373 ± 67.7 ml/kg at 10 days of age.[60] Similar studies have not been performed in critically ill neonates, and significant differences can exist in such patients, as already described. Furthermore, many critically ill neonates are neutropenic, a condition in which the duration of the postantibiotic effect may be less pronounced.[15] Given the numerous variables already described, extrapolation of the adult EID paradigm (i.e., 6.6 mg/kg/day of gentamicin) to the critically ill neonatal foal is not appropriate.

The use of goal-directed therapy in humans has been reported to yield superior results when compared with standard EID methods.[61] Goal-directed therapy involves pharmacokinetic dosage optimization at the start of treatment and subsequent pharmacokinetic modeling. Initially, the aminoglycoside dose is empirically set to attain a goal of either a target C_{max} (i.e., 20 µg/ml) or a target C_{max}:MIC ratio (i.e., 10:1) chosen to achieve the maximum probability of response.[62] Based on the results of subsequent pharmacokinetic modeling, the aminoglycoside dosage is modified to achieve the desired C_{max} or C_{max}:MIC ratio, and the dosage interval is modified to allow an appropriate trough concentration to be achieved. Given the interindividual variability seen in the pharmacokinetics of foals, the use of goal-directed therapy is indicated.

Case Report

A 2-day-old thoroughbred filly presented with a 10-day history of premature delivery and weakness since birth. At presentation, the filly was recumbent and approximately 5% clinically dehydrated and exhibited multiple joint effusion. Hematology revealed a normal total leukocyte count with a left shift and toxic cellular morphology. Serum creatinine concentration was normal, and failure of passive transfer was present. A blood culture obtained at admission yielded a pure growth of *E. coli*. Gentamicin was administered at 10 mg/kg IV, and the serum gentamicin concentration at 30 minutes after administration (C_{max}) was 14.5 µg/ml, with an 8-hour concentration of 3.25 µg/ml (**A**). The C_{max} was well below the targeted concentration of 25 to 35 µg/ml, and the dose was increased 120%, to 22 mg/kg, targeting a C_{max} of 32 µg/ml. Toxicity was also a concern because the apparent $T_{½e}$ was prolonged (i.e., approximately 200 minutes). The dosage interval remained at 24 hours because the 8-hour concentration was within an acceptable range. TDM was repeated following the second dose to ensure that an adequate C_{max} was achieved and to allow prolongation of the dosage interval, if necessary. The C_{max} was slightly greater than intended (i.e., 35.6 µg/ml), whereas the 8-hour concentration was within the acceptable range (i.e., 4.11 µg/ml; **A**). Because the apparent $T_{½e}$ had decreased to the normal range (i.e., 150 minutes), the dosage remained at 22 mg/kg and the dosage interval remained at 24 hours. TDM was repeated 3 days later and revealed a C_{max} (at 40 minutes) of 26.1 µg/ml and an 8-hour concentration of 3.84 µg/ml (**A**), demonstrating adequate C_{max} for efficacy and a normal $T_{½e}$ of 150 minutes, reflecting normal elimination.



A—The serum gentamicin concentration in µg/ml plotted versus time in hours as estimated based on serum concentrations obtained at 0.5 and 8 hours from the foal in this case on days 1, 2, and 5 of hospitalization.

MONITORING AMINOGLYCOSIDE THERAPY

Avoiding Nephrotoxicity

A number of diagnostic modalities may be used to monitor horses and foals for the development of aminoglycoside nephrotoxicity. The following are all valuable but vary substantially in their sensitivity: microscopically examining urinary sediment for casts (cylindruria), measuring urine enzyme concentrations (GGT), determining the urine GGT:creatinine ratio (urine GGT:urine creatinine × 100 [normal: ≤25%]), monitoring urine output, measuring serum creatinine concentration, determining creatinine clearance, and TDM. The earliest changes detected in horses with aminoglycoside nephrotoxicity are cylindruria and enzymuria, which were noted within 4 days after initiation of neomycin administration (10 mg/kg IM q12h).[63] These changes persisted throughout drug administration, resolving only after withdrawal of the drug.[63] In horses given therapeutic dosages of gentamicin, enzymuria and increased urinary GGT:creatinine ratios (i.e., >25%) are consistently present, but the magnitude of these increases cannot be used for identifying nephrotoxicity.[64] Monitoring urine output is also useful because oliguria may be present in some cases of aminoglycoside nephrotoxicity, potentially occurring before the development of azotemia, and can progress to anuria.

Determining BUN and serum creatinine are additional means of monitoring horses for the development of nephrotoxicity; however, it is important to recognize that these values do not increase until GFR has decreased by approximately 75%.[65] Because significant renal dysfunction must occur before these values change, monitoring BUN and serum creatinine represents fairly insensitive means of determining the presence of subclinical renal compromise, as demonstrated by the fact that azotemia was not detected in either of the reports already described.[63,66] Monitoring creatinine clearance requires the timed collection of urine and is cumbersome and not routinely performed. Although there is little experience with monitoring creatinine clearance in critically ill neonatal foals, catheterization

of the urinary bladder in these foals is relatively common; hence urinary creatinine clearance could easily be determined.

TDM should be performed when administering aminoglycosides using either the MDD or EID treatment paradigm to minimize the risk of nephrotoxicity and to allow individualized patient-based dosing adjustment. When using the MDD approach, TDM involves determining serum aminoglycoside concentrations following a predetermined distribution period (0.5 hours after bolus IV administration; commonly called *the peak* and considered to be representative of maximal tissue concentrations) followed by determining the aminoglycoside concentration immediately before administering the next dose (commonly called *the trough*, which is representative of the lowest tissue concentrations). 1he dose administered (mg/kg), time of peak and trough collection after administration (hours), number of doses given, and peak and trough concentrations (µg/ml) are then used to calculate the patient-specific pharmacokinetic parameters. Elevations in the trough concentration are associated with an increased risk of nephrotoxicity and suggest an excessive dosage, an insufficient dosage interval, or impaired aminoglycoside clearance.[67–69] Subtle changes in the trough concentration (C_{tr}), $T_{½e}$, or Cl_B can represent sensitive indicators of subclinical impairment of renal function, but C_{tr} and $T_{½e}$ may also be influenced by changes in the V_d. Therefore, TDM is a valuable means to ensure that nephrotoxicity has not occurred and to minimize the risk of inducing nephrotoxicity. Target trough C_p to minimize the risk of nephrotoxicity in foals administered aminoglycosides using the MDD paradigm have been proposed to be less than 2 µg/ml for gentamicin[70] and less than 3 µg/ml for amikacin.[43]

Monitoring of EID is not as straightforward as in MDD, and no established method has found universal acceptance. This is due to the fact that the trough concentration at the end of a 24-hour dosing interval should ideally fall below the lower limit of detection of the aminoglycoside assays that are most commonly used.[29,39] To minimize toxicity, a primary benefit of EID, the underlying principle is the early detection of impaired aminoglycoside elimination. To detect impaired elimination, a serum concentration must be obtained during the β phase of elimination (typically the first 12 hours) at least one $T_{1/2}$ after the peak but before the point at which the serum concentration becomes undetectable. A commonly used method in humans is to assay the serum aminoglycoside concentration at a specific time after the dose is administered (usually 6 to 14 hours). This result is then compared to a nomogram to determine if the point is above a predetermined acceptable limit, which would indicate that either the rate of elimination is decreased (first or subsequent doses) or that drug accumulation is occurring (after multiple doses).[71,72] Population pharmacokinetic information necessary to construct a similar nomogram for the foal is currently unknown. At our hospital, however, we have determined aminoglycoside concentrations at 0.5, 6, 12, 18, and 24 hours after a dose to ensure that aminoglycoside accumulation is not occurring and that additional drug can safely be given (Tables 3 and 4). We have found that dosing may proceed on schedule if serum concentrations are below 4 to 5 µg/ml (for gentamicin) or 15 to 20 µg/ml (for amikacin) at 8 hours following the previous dose or 2 to 3 µg/ml (for gentamicin) or 5 to 7 µg/ml (for amikacin) at 12 hours.

Treating Aminoglycoside Nephrotoxicity

Aminoglycoside nephrotoxicity is primarily treated with supportive care because there are no specific treatments to reverse the toxic effects of aminoglycosides. Treatment with aminoglycosides should be discontinued if at all possible following the detection of nephrotoxicity. If continued aminoglycoside therapy is absolutely necessary, close monitoring of serum aminoglycoside concentrations is required to allow adjustments in dosage and frequency to accommodate for the impairment of renal aminoglycoside elimination resulting from decreased GFR. Initial treatment should be focused on correction of volume deficits and normalization of electrolyte and acid–base abnormalities. Individuals with systemic hypotension not responsive to volume replacement fluid therapy may require inotropic and/or vasopressor therapy to restore blood pressure. Following this initial stage, it is very important to monitor the response to therapy, especially regarding urine output, because animals in oliguric or anuric renal failure will suffer from fluid retention, resulting in the development of potentially severe tissue edema. Animals that demonstrate a persistently inadequate urine output may benefit from diuretic therapy with furosemide or mannitol, although these agents are not always capable of substantially increasing urine output in these patients. Because of the effects of low-dose dopamine on renal blood flow and GFR, use of this drug has been advocated for treating oliguric renal failure; however, recent work in humans has concluded that this treatment is ineffective.[73]

Optimization of Efficacy

In addition to minimizing nephrotoxicity, TDM should be performed to ensure adequate drug concentrations for therapeutic efficacy and to allow individual-

Table 3. Serum Concentrations of Amikacin Following Various Doses Given IV on the Extended-Interval Dosing Paradigm[a]

Dose (mg/kg)	*Age (days)*	n	*0.5-hr Concentration*	*6-hr Concentration*	*12-hr Concentration*	*24-hr Concentration*
10–14.9	1–14	3	24.5 ± 6.7–8.3	—	3.34 ± 2.3	—
15–19.9	1–14	8	37.0 ± 10.1	6.7 ± 0.7	5.4 ± 4.0	4.4 (*n* = 1)
20–24.9	1–14	5	39.5 ± 8.7	8.6 ± 3.6	—	—
≥25	1–14	1	55.0	6.78	3.7	—

[a]Furr MO: Unpublished data, Marion duPont Scott Equine Medical Center, Leesburg, VA, 2002.

Table 4. Serum Concentrations of Gentamicin Following Various Doses Given IV on the Extended-Interval Dosing Paradigm[a]

Dose (mg/kg)	*Age (days)*	n	*0.5-hr Concentration (n)*	*6-hr Concentration (n)*	*8-hr Concentration (n)*	*12-hr Concentration (n)*	*24-hr Concentration (n)*
All doses[b]	1–9	13	27.5 ± 8.3 (13)	5.2 ± 1.2 (5)	4.4 ± 1.2 (7)	3.1 ± 0.9 (7)	1.6 ± 0.6 (5)
9.7–11.9	1–2	6	22.1 ± 6.0 (6)	5.1 ± 1.4 (4)	3.6 ± 0.5 (3)	2.6 ± 0.6 (4)	1.22 (1)
12–14.9	1–3	4	29.1 ± 7.6 (4)	—	5.4 ± 1.2 (3)	4.66 (1)	2.2 ± 0.4 (2)
≥15	1–9	3	40.2 ± 4.7 (3)	5.4 (1)	3.54 (1)	3.2 ± 0.2 (2)	1.2 ± 0.3 (2)

[a]McKenzie HC: Unpublished data, Marion duPont Scott Equine Medical Center, Leesburg, VA, 2002.
[b]Pooled data from the following rows.

ized patient-based dosing adjustment. Because of the increased V_d of aminoglycosides in ill neonatal foals, the initial dosing choices for these patients may result in a suboptimal C_{max} and C_{max}:MIC ratio, with the risk of a suboptimal therapeutic response or treatment failure. Target peak C_p based on the MIC of commonly isolated equine pathogens have been proposed to be 10 µg/ml for gentamicin[70] and 15 µg/ml for amikacin.[43] These values were determined based on achieving a peak that was four to five times the MIC of common equine pathogens.[43] Interestingly, in humans with gram-negative pneumonia, achieving a C_{max}:MIC ratio of 10 or higher within 48 hours of initiating aminoglycoside therapy was associated with a 90% probability of leukocyte count normalization by day 7 of therapy compared with a 68% probability associated with achieving a C_{max}:MIC ratio of 4.5.[22] Extrapolating from published MIC values for common equine pathogens, a C_{max}:MIC ratio of higher than 10 would require peak serum gentamicin concentrations of at least 25 µg/ml or peak amikacin concentrations of at least 40 to 50 µg/ml. The application of TDM based on MIC values in horses was demonstrated in one study of once-daily administration of gentamicin to adult horses. The study determined that for organisms with MIC values of 2 µg/ml or less, a dose of 4 mg/kg IV would achieve an appropriate C_{max} of 20 µg/ml, whereas for organisms with MIC values of 2 to 4 µg/ml, a dose of 6.6 mg/kg IV was required to achieve a C_{max} of 40 µg/ml.[58]

Published data[59,74] and our experience suggest that gentamicin dosages of 6 to 10 mg/kg/day in neonatal foals often result in suboptimal C_{max}:MIC ratios. Optimal concentrations in serum may best be achieved by giving a relatively large loading dose of aminoglycoside immediately followed by TDM with the first dose.[75] These doses approximate 11 to 15 mg/kg/day IV for gentamicin or 20 to 25 mg/kg/day IV for amikacin. Because the pathogen and/or the MIC are typically unknown at the time of initial TDM, target concentrations can be determined empirically by using published or institutional MIC data for potential causative bacteria. It is critical when administering high doses to use

some form of therapeutic monitoring to ensure that optimal peak concentrations are being achieved and that serum levels are adequately low before the subsequent dose is given. Additionally, the risk of nephrotoxicity can be reduced by rapidly identifying individuals with impaired elimination, allowing for modification of the dosage regimen by prolongation of the dosage interval or cessation of aminoglycoside therapy.

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ARTICLE #5 CE TEST

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. *Choose the best answer* to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium.*

1. The spectrum of activity of aminoglycosides includes
   a. gram-negative organisms only.
   b. gram-positive organisms only.
   c. gram-negative and some gram-positive bacteria.
   d. broad coverage of gram-negative and gram-positive bacteria.

2. Aminoglycosides exert their antimicrobial activity via
   a. binding to the 50S ribosomal subunit and interfering with ribosomal mRNA translation.
   b. alteration of peptidoglycan cross-linking.
   c. interference with function of bacterial DNA gyrase.
   d. binding to the 30S ribosomal subunit and interfering with ribosomal mRNA translation.

3. The microbicidal effects of aminoglycosides are enhanced by
   a. maintaining concentrations above the MIC for the duration of the treatment interval.
   b. achieving peak serum concentrations of 10 or more times the MIC of common pathogens.
   c. maintaining trough serum levels below 1 to 2 µg/ml for at least half of the treatment interval.
   d. achieving peak serum concentrations of two to four times the MIC of common pathogens.

4. The development of bacterial resistance to aminoglycosides is inhibited by
   a. achieving high peak serum concentrations.
   b. minimizing the duration of the trough period.
   c. avoiding excessively high peak serum concentrations.
   d. using aminoglycosides without other antimicrobials.

5. Neonatal foals exhibit alterations in aminoglycoside pharmacokinetics, including
   a. a shortened $T_{1/2}$.
   b. prolonged elimination.
   c. increased V_d.
   d. b and c

6. The efficacy of EID with aminoglycosides depends on
   a. their concentration-dependent microbicidal effects.
   b. the postantibiotic effect.
   c. the duration of the trough period.
   d. a and b

7. The safety of EID is maximized by
   a. therapeutic drug monitoring.
   b. using lower aminoglycoside dosages.
   c. administering IV fluid therapy.
   d. monitoring serum creatinine concentrations.

8. The effects of hypoxia and prematurity on aminoglycoside pharmacokinetics include
   a. prolongation of serum $T_{1/2}$.
   b. increased rate of elimination.
   c. decreased V_d.
   d. b and c.

9. The uptake of aminoglycosides into bacteria depends on
   a. prolonged exposure to aminoglycosides.
   b. growth phase of the bacteria.
   c. the presence of nutrients.
   d. the presence of oxygen.

10. The uptake of aminoglycosides by renal proximal tubular epithelial cells is
    a. concentration dependent.
    b. saturable.
    c. time dependent.
    d. b and c