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Erica Paige Bucki
Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida

Steeve Giguère

Margo Macpherson

Rachel E. Davis
University of South Carolina, rdavis@mailbox.sc.edu

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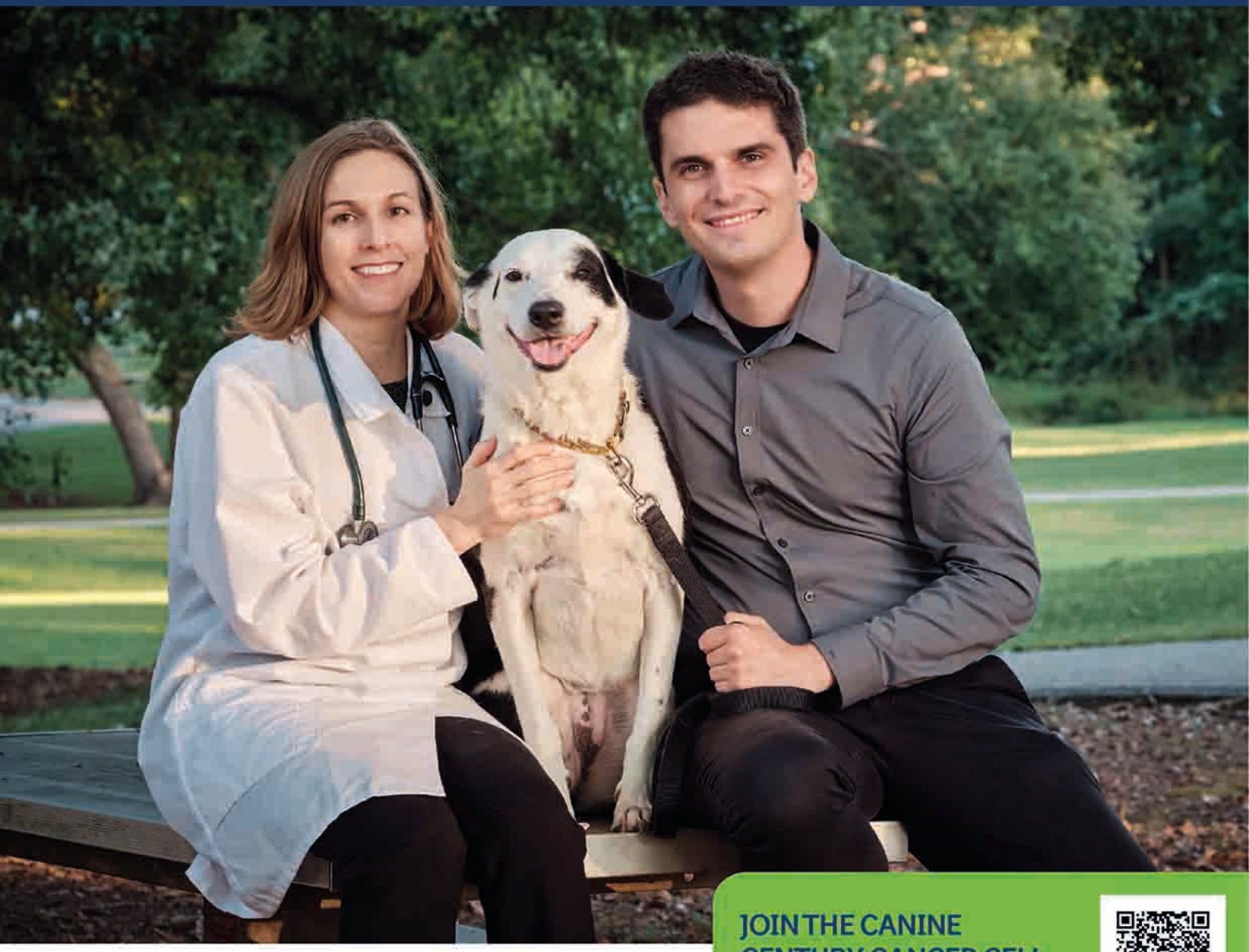

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Pharmacokinetics of Once-Daily Amikacin in Healthy Foals and Therapeutic Drug Monitoring in Hospitalized Equine Neonates

Erica Paige Bucki, Steeve Giguère, Margo Macpherson, and Rachel Davis

The objectives of this study were to investigate the pharmacokinetics of once-daily amikacin in healthy neonates, to determine amikacin concentrations in hospitalized foals, and to determine the minimum inhibitory concentrations (MICs) of amikacin against gram-negative isolates from blood cultures in septic foals. Median half-life, clearance, and volume of distribution of amikacin in healthy 2- to 3-day-old foals after administration of an intravenous bolus of amikacin (25 mg/kg) were 5.07 hours (4.86–5.45 hours), 1.82 mL/min/kg (1.35–1.97 mL/min/kg), and 0.785 L/kg (0.638–0.862 L/kg), respectively. Statistically significant ($P < .05$) decreases in area under the curve (14% decrease), mean residence time (19% decrease), and C_{24h} plasma amikacin concentrations (29% decrease) occurred between days 2–3 and 10–11. Plasma amikacin concentrations in healthy foals at 0.5 hours ($C_{0.5h}$) were significantly higher ($P = .02$) than those of hospitalized foals. Sepsis, prematurity, and hypoxemia did not alter amikacin concentrations. The MIC at which 90% of all gram-negative isolates from equine neonatal blood cultures were inhibited by amikacin was 4 μg/mL, suggesting that amikacin $C_{0.5h}$ of 40 μg/mL should be targeted to achieve a maximum serum concentration to MIC ratio of 10:1. The proportion of foals with $C_{0.5h} \geq 40$ μg/mL was significantly higher ($P < .0001$) in hospitalized foals receiving a dose of amikacin at 25 mg/kg (22/24 or 92%) than in foals receiving a dose at 21 mg/kg (9/25 or 36%), whereas no difference was found in the proportion of foals with C_{24h} concentrations ≥3 μg/mL between the 2 groups. An initial dose at 25 mg/kg is recommended for once-daily amikacin in equine neonates.

Key words: Aminoglycoside; Antimicrobial; Foals; Minimum inhibitory concentration; Sepsis.

Sepsis is the leading cause of morbidity and mortality in neonatal foals.[1,2] Infection of the foal can occur through several routes, including the placenta in utero, the respiratory tract, the gastrointestinal tract, or the umbilical stump. Gram-negative bacteria account for 70–95% of the microorganisms isolated from blood cultures, with *Escherichia coli* being the most common isolate.[2,3] Other members of the Enterobacteriaceae (*Klebsiella* spp., *Salmonella* spp., and *Enterobacter* spp.), nonenteric gram-negative rods (*Pasteurella* spp. and *Actinobacillus* spp.), and, less commonly, gram-positive cocci (β-hemolytic steptococci, *Staphylococcus* spp., and *Enterococcus* spp.) also may be isolated from sick neonatal foals.[1–3]

Antimicrobial agents provide the basis of therapy for septic foals. Broad-spectrum antimicrobial agents for systemic administration are usually selected until culture and in vitro susceptibility results are available. Given that enteric gram-negative microorganisms predominate in neonatal sepsis, aminoglycosides such as gentamicin or amikacin are commonly used in conjunction with either penicillin or ampicillin for the control of gram-positive bacteria.[4,5] Of all aminoglycosides, amikacin is considered the agent of choice for the treatment of sepsis in equine neonates because of its lower frequency of resistance among gram-negative isolates obtained from blood cultures.[2,4]

Aminoglycosides exert concentration-dependent bacterial killing characteristics. Their rate of killing increases as the drug concentration increases above the minimum inhibitory concentration (MIC) for a given pathogen, with an optimal maximum serum concentration (C_{max}) to MIC ratio of 8–12:1.[6,7] Higher C_{max} values also result in a longer postantibiotic effect and decrease selection of resistant bacterial mutants within a population.[8,9] Traditionally, amikacin has been administered to foals every 8–12 hours.[10–13] However, the considerations described above and examination of data from other species showing that nephrotoxicity may be minimized by giving larger doses less frequently, suggest that optimal dosing of aminoglycosides involves administration of high doses with long dosing intervals.[14,15]

Although multiple studies report the pharmacokinetics of multiple daily dosing of amikacin, no information is available on the disposition of once-daily amikacin in a large population of critically ill equine neonates.[10–13] A few studies have determined in vitro susceptibility of bacterial isolates from equine neonatal blood cultures by using the disk diffusion method but, to the authors' knowledge, MICs have never been reported.[2,4,5] Knowledge of the MIC of amikacin against common gram-negative isolates from septic foals would be important to determine targeted amikacin concentrations in hospitalized patients. Therefore, the objectives of this study were to investigate the pharmacokinetics of once-daily amikacin in clinically healthy neonates, to determine amikacin concentrations in hospitalized foals with various illnesses, and to determine the MICs of amikacin against gram-negative isolates obtained from blood cultures in septic foals.

Materials and Methods

Healthy Equine Neonates

Five mixed-breed pony foals (3 males and 2 females) were studied. Transfer of passive immunity was confirmed before initiation of the study by measurement of plasma immunoglobulin G concentration with a commercial immunoassay.[a] Foals were considered healthy on the basis of history, physical examination, CBC, measurement of plasma fibrinogen concentration, and plasma biochemical profile performed the day before administration of amikacin. The foals were kept with their dams at all times. They were kept at pasture between ex-

From the Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL.

Reprint requests: Steeve Giguère, DVM, PhD, DACVIM, Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, P.O. Box 100136, 2016 SW 16th Avenue, Gainesville, FL 32610; e-mail: gigueres@mail.vetmed.ufl.edu.

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periments and in individual stalls during the experiments with ad libitum access to grass hay and water. Each foal received a single bolus of amikacin at 2–3 days of age and again at 10–11 days of age. Amikacin sulfate[b] (250 mg/mL) was administered at a dosage of 25 mg/kg in a jugular vein. Blood samples were obtained from a catheter placed in the opposite jugular vein at 0 (before administration), 5, 10, 20, 30, and 45 minutes and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the foals were dosed. Heparinized blood samples were centrifuged at 2,800 × *g* for 10 minutes. Plasma was collected and kept frozen at −70°C until assayed.

Hospitalized Foal Population

Case records of all the foals less than 16 days of age admitted to the veterinary medical teaching hospital at the University of Florida between January 2000 and June 2003 were examined. Foals were included in the study only if they were treated with once-daily amikacin, 0.5-hour and 24-hour amikacin concentrations were measured at least once during hospitalization, and an exact body weight was available for accurate determination of the dose of amikacin administered. Information obtained from the medical records included length of gestation, primary and secondary diagnoses, outcome, sepsis score on admission,[16] arterial partial pressure of oxygen (Pa_{O_2}) on admission, blood culture results, age and body weight at time of measurement of amikacin concentrations, dose of amikacin, number of days of amikacin therapy, and plasma creatinine and blood urea nitrogen (BUN) concentrations throughout hospitalization. The dosage of amikacin administered was calculated retrospectively by dividing the number of milligrams of amikacin given just before sample collection by the most recent body weight. Amikacin sulfate[b] was administered as a bolus in a catheter placed in a jugular vein. Blood samples were collected in heparinized tubes from the opposite jugular or from a cephalic vein for determination of plama amikacin concentrations 0.5 hours ($C_{0.5h}$) and 24 hours (C_{24h}) after the foals were dosed. Heparinized blood samples were centrifuged at 2,800 × *g* for 10 minutes. Plasma samples obtained outside regular working hours were frozen at −20°C and analyzed the next working day.

Hospitalized foals were assigned retrospectively to one or more of the following groups. Foals were considered premature if they were born at a gestational age ≤ 320 days and displayed immature physical characteristics. Foals were considered hypoxemic if they had a Pa_{O_2} ≤ 65 mm Hg. Foals were considered septic if they had a positive blood culture or had a sepsis score of 11 or higher. Foals not meeting any of these criteria were classified as other. Evidence of nephrotoxicity was defined as a 25% increase in plasma creatinine concentration compared to baseline value or creatinine concentration ≥ 2 mg/dL in a foal with a plasma creatinine concentration previously within the reference range.

Measurement of Amikacin Concentrations

Amikacin concentrations were measured by using a fluorescence polarization immunoassay on an automated chemistry analyzer.[c] In preliminary experiments, known amounts of purified amikacin standard was added to equine plasma at concentrations ranging from 128 to 0.25 μg/mL. Measured concentrations were similar to expected concentrations. Plots of measured concentrations versus expected amikacin concentrations were linear between 1.0 and 128 μg/mL, with a correlation coefficient (*r*) of 0.999. The sensitivity of the assay, defined as the lowest measurable amikacin concentration in equine plasma that could be distinguished from 0 with 95% confidence, was 0.8 μg/mL. The interassay coefficient of variation in equine plasma was <5% at concentrations of 2–128 μg/mL and ≤10% at concentrations of 0.8–1 μg/mL. Low (5.0 μg/mL) and high (30 μg/mL) concentration standards were measured with each sample. Results were only considered valid if the low concentration standard ranged between 4.25 and 5.75 μg/mL and the high concentration standard ranged between 27.0 and 33.0 μg/mL.

Pharmacokinetic Analysis

For each healthy foal, 1-, 2-, and 3-compartment models were fit to serum concentration versus time data by using a pharmacokinetics computer program.[d] A 2-compartment model was most appropriate based on computer-assisted examination of residual plots:

$$C_t = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t},$$

where C_t is the serum drug concentration at time *t*; *e* is the base of the Naperian logarithm; A and α are the intercept and slope, respectively, of the distribution phase; and B and β are the intercept and slope, respectively, of the elimination phase. Elimination half-life ($t_{½\beta}$) was calculated as the natural logarithm of 2 divided by β. Pharmacokinetic values were calculated as reported by Gibaldi and Perrier.[17] The area under the concentration-time curve (AUC) and the area under the 1st moment of the concentration-time curve (AUMC) were calculated by using the trapezoidal rule, with extrapolation to infinity, with C_{24}/β, where C_{24} was the plasma amikacin concentration at the final time point (24 hours). Mean residence time (MRT) was calculated as AUMC/AUC. Apparent volume of distribution based on the AUC (Vd_{area}) was calculated as dose/AUC·β and clearance (CL) was calculated from dose/AUC.

MIC of Amikacin against Gram-Negative Isolates

Ninety-four gram-negative bacterial isolates from equine neonatal blood cultures submitted to the microbiology laboratory of the University of Florida Veterinary Medical Teaching Hospital from January 1998 and March 2003 were examined. Isolates included *E coli* (n = 50), *Pasteurella* spp. (n = 15), *Enterobacter* spp. (n = 11), *Klebsiella* spp. (n = 10), *Salmonella enterica* subspecies *enterica* (n = 6), and *Actinobacillus* spp. (n = 2). Before testing, isolates were subcultured, checked for purity, and identified by standard identification procedures. The MICs were determined by using microtitration strips.[e] MICs obtained by use of this technique have previously been shown to correlate closely with those of the standard broth dilution method.[18,19] Concentrations of amikacin tested were 2, 4, 8, and 16 μg/mL. Fresh isolates were grown on blood agar plates and colonies were suspended in sterile water to a turbidity equal to that of a 0.5 McFarland standard. Ten microliters of the suspension were used to inoculate 10 mL of Mueller Hinton broth for a final bacterial concentration of 1×10^5 colony-forming units/mL. Each well was then inoculated with 50 μL of bacterial suspension. Strips were sealed and incubated for 18–24 hours at 37°C. A test was considered valid only if adequate growth occurred in control wells. Control strains used to validate the assay at monthly intervals included *Staphylococcus aureus* American Type Culture Collection (ATCC) 29213, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, *E coli* ATCC 25922, and *E coli* ATCC 35218. In all instances, MICs obtained with the control stains were within the reference range proposed by the National Committee for Clinical Laboratory Standards.[20,21]

Statistical Analysis

Differences in $C_{0.5h}$, C_{24h}, and pharmacokinetic parameters between clinically healthy 2- to 3-day-old foals and the same foals at 10–11 days of age were assessed with a paired *t*-test. Data are reported as median and range.

Differences in $C_{0.5h}$ and C_{24h} concentrations between groups of foals (normal, premature, hypoxemic, septic, or other) were determined by analysis of variance. Normality and equal variance of the data were confirmed in preliminary analysis. Age at time of administration of amikacin and dose were included in the model as covariates. When indicated, multiple pairwise comparisons were done with a Student-Newman-Keuls test. In preliminary analysis, no significant differences were found in values of $C_{0.5h}$ and C_{24h} concentrations between foals considered septic based on a positive blood culture versus foals with a negative blood culture and a septic score of 11 or more. Therefore, the data were

Table 1. Pharmacokinetic variables (median and range) in 5 foals given a single intravenous dose of amikacin (at a dosage of 25 mg/kg) at 2–3 days of age and again at 10–11 days of age.

Variable	Age, days				*P*-value
	2–3		10–11		
A, μg/mL	62.6	(49.8–71.4)	77.5	(68.3–87.3)	0.002
α, 1/h	1.22	(0.970–2.52)	1.62	(0.899–2.18)	0.93
$t_{1/2\alpha}$, h	0.566	(0.275–0.715)	0.429	(0.318–0.771)	0.89
B, μg/mL	24.9	(20.6–36.2)	17.9	(11.3–35.6)	0.40
β, 1/h	0.137	(0.127–0.143)	0.133	(0.120–0.205)	0.55
$t_{1/2\beta}$, h	5.07	(4.86–5.45)	5.20	(3.38–5.76)	0.70
Vd_{area}, L/kg	0.785	(0.638–0.862)	1.05	(0.587–1.22)	0.31
CL, mL/min/kg	1.82	(1.35–1.97)	2.13	(1.45–2.68)	0.06
AUC, μg·h/mL	228	(215–308)	195	(1.55–288)	0.03
AUMC, μg·h^2/mL	1,380	(1,151–2,221)	841	(745–1,821)	0.004
MRT, h	6.17	(5.34–7.21)	4.99	(4.05–6.33)	0.004
$C_{0.5h}$, μg/mL	53.0	(46–59.9)	58.4	(43.8–61)	0.38
C_{24h}, μg/mL	1.20	(0.90–2.00)	0.85	(<0.80–1.6)	0.04

A and α, intercept and slope, respectively, of distribution phase; $t_{1/2\alpha}$, distribution half-life; B and β, intercept and slope, respectively, of elimination phase; $t_{1/2\beta}$, elimination half-life; Vd_{area}, volume of distribution based on AUC; CL, clearance; AUC, area under the concentration-time curve; AUMC, area under the first moment of the concentration-time curve; MRT, mean residence time; $C_{0.5h}$, amikacin concentration 0.5 h after administration; C_{24h}, amikacin concentration 24 h after administration.

combined under a single group designated septic foals. Pearson product moment correlations were used to determine the relationship between $C_{0.5h}$ or C_{24h} amikacin concentrations in hospitalized foals and creatinine concentration or BUN concentration. Logistic regression was used to examine the relationship between outcome (death or euthanasia versus discharge from the hospital) and amikacin $C_{0.5h}$. Differences in proportions were assessed with a Fisher exact test. All analyses were done with a statistical software.[f] For all comparisons, values of $P < .05$ were considered significant.

Results

Pharmacokinetics of Amikacin in Clinically Healthy Foals

Concentrations of amikacin 5 minutes after administration of an IV bolus were 89.5 μg/mL (81.0–97.9 μg/mL) and 100.1 μg/mL (96.2–141.9 μg/mL) for 2- to 3- and 10- to 11-day-old foals, respectively. The C_{24h} concentrations were $\leq$2.0 μg/mL for all foals on both days. A statistically significant decrease occurred in AUC, AUMC, MRT, and C_{24h} between days 2–3 and 10–11 (Table 1). A tendency ($P = .06$) toward an increase in CL occurred between days 2–3 and 10–11 (Table 1).

Therapeutic Drug Monitoring in Hospitalized Foals

Forty-nine foals met the criteria for inclusion in the study. The median age at time of measurement of amikacin $C_{0.5h}$ and C_{24h} concentrations was 3 days (range 1–15 days). The median duration of amikacin therapy was 6 days (range 3–23 days). The median dosage of amikacin administered was 23.5 mg/kg (range 16.7–28.0 mg/kg). The proportion of foals with $C_{0.5h} \geq 40$ μg/mL was significantly higher in foals receiving a dose at >23.5 mg/kg (median dosage: 25 mg/kg; 22/24 or 92%) than in foals receiving a dose at <23.5 mg/kg (median dosage 21 mg/kg; 9/25 or 36%; $P < .0001$). Seven (14%) of 49 hospitalized foals had C_{24h} lower than the limit of sensitivity of the assay. The C_{24h} amikacin concentrations were <2 μg/mL in 37 foals, 2–3 μg/mL in 7 foals, 3–4 μg/mL in 3 foals, and $\geq$4 μg/mL in 2 foals (5.0 and 9.0 μg/mL). No difference was found in the proportion of foals with $C_{24h} \geq 3$ μg/mL between foals that received a dose of amikacin at >23.5 mg/kg (3/24 or 13%) versus foals that received a dose at <23.5 mg/kg (2/25 or 8%; $P = .67$).

Forty-two (86%) of 49 foals were discharged from the hospital and 7 (14%) foals died (n = 1) or were euthanized (n = 6). Reasons for death or euthanasia included septic arthritis (n = 4), prematurity (n = 1), hypoxic ischemic encephalopathy (n = 1), and sepsis (n = 1). Gram-negative bacteria (*Klebsiella* spp.) were isolated from only 1 of the nonsurvivors. No correlation was found between $C_{0.5h}$ or C_{24h} amikacin concentrations and creatinine or BUN concentrations. No association was found between $C_{0.5h}$ and survival. Plasma creatinine concentrations were monitored during the course of amikacin therapy in 40 foals. Two (5%) of 40 foals developed evidence of nephrotoxicity.

Eight hospitalized foals were classified as premature, 10 were hypoxemic, 28 were septic, and 19 did not fall within any of these categories and were classified as other (Table 2). Most of the foals classified as other were diagnosed with hypoxic-ischemic encephalopathy, failure of transfer of passive immunity, or mild diarrhea. Clinically healthy foals had significantly higher $C_{0.5h}$ than all groups of hospitalized foals (Table 2). $C_{0.5h}$ and C_{24h} amikacin concentrations were not significantly different between groups of hospitalized foals (Table 2).

MIC of Amikacin against Gram-Negative Isolates from Equine Neonatal Blood Cultures

The MICs of amikacin inhibiting at least 90% of *E coli*, *Pasteurella* spp., *Enterobacter* spp., and *Klebsiella* spp. isolates (MIC_{90}) were 4, 4, $\leq$2, and $\leq$2 μg/mL, respectively (Table 3). The MIC_{90} for all gram-negative isolates combined was 4 μg/mL.

Table 2. Amikacin concentrations 0.5 hours ($C_{0.5h}$) and 24 h (C_{24h}) after administration (median and range) in healthy and hospitalized foals treated with amikacin intravenously at a dosage ranging between 16.7 and 28.0 mg/kg, once daily.

Group	Amikacin concentration, μg/mL	
	$C_{0.5hs}$	C_{24h}
Normal (n = 5)	54.5[a] (43.8–61.0)	0.9 (<0.8–2.0)
Premature (n = 8)	40.5[b] (32.9–47.4)	1.4 (<0.8–9.0)
Hypoxemic (n = 10)	45.5[b] (32.9–63.0)	1.3 (0.8–9.0)
Septic (n = 28)	41.3[b] (29.4–63.0)	1.5 (<0.8–9.0)
Other (n = 19)	40.0[b] (20.2–61.1)	1.4 (<0.8–4.0)

[a,b] Different letters in a column indicate a statistically significant difference between groups ($P < .05$).

Table 3. Minimum inhibitory concentrations (MICs) of amikacin against 94 gram-negative bacterial isolates obtained from blood culture in equine neonates.

Microorganism	MIC, μg/mL		
	90%	50%	Range
Escherichia coli (n = 50)	4	≤2	≤2–8
Pasteurella spp. (n = 15)	4	4	≤2–8
Enterobacter spp. (n = 11)	≤2	≤2	≤2
Klebsiella spp. (n = 10)	≤2	≤2	≤2
Salmonella enterica (n = 6)	—	4	≤2–8
Actinobacillus spp. (n = 2)	—	—	4–8
All isolates combined (n = 94)	4	≤2	≤2–8

Discussion

The combination of an aminoglycoside with a beta-lactam antimicrobial agent has been the mainstay of therapy for septic foals.[5] Studies in humans and laboratory animals have shown that a once-daily administration of aminoglycosides is more effective, decreases the emergence of resistant isolates, and results in similar or less nephrotoxicity than multiple daily dosing.[22,23] Such a dosing scheme has been investigated with gentamicin in adult horses with no evidence of nephrotoxicity.[24] In a recent study, once-daily amikacin was administered to 7 healthy equine neonates at a dosage of 21 mg/kg for 10 days with no apparent nephrotoxicity.[25] In the same study, significant age-related changes in pharmacokinetics included a decrease in $t_{1/2\beta}$, AUC, and MRT, as well as an increase in clearance between day 1 and day 10.[25] In the present study with a higher dosage (25 mg/kg), significant decreases in AUC, AUMC, MRT, and C_{24h} between days 2–3 and 10–11 were observed, whereas CL tended to increase (Table 2). Values for $t_{1/2\beta}$ (5.2 hours) and Vd (1.05 L/kg) in 10-day-old foals in the present study were slightly higher than those previously reported in foals of the same age (3.85 hours and 0.671 L/kg, respectively), whereas the CL was similar between the 2 studies.[25]

Therapeutic drug monitoring should be performed when administering aminoglycosides to minimize the risk of nephrotoxicity and allow individualized adjustment of dose or dosing interval. In one study, human patients treated with multiple daily dosing aminoglycoside monitored by a pharmacokinetic service had shorter hospital stays, shorter duration of therapy, increased antibiotic efficacy, and a 13.4% lower incidence of nephrotoxicity compared to patients who were not subjected to guided therapeutic drug monitoring.[26] However, the issue of optimal plasma concentration and timing for sample collection after once-daily aminoglycoside administration remains controversial and no established method has found universal acceptance.[22] A C_{max} is obtained after a predetermined distribution period and is considered representative of maximal tissue concentration.[22,27] In most studies, C_{max} has been obtained 0.5–1 hours after IV bolus administration.[10,27,28] Although some studies recommend collection of a 2nd sample just before administering the next dose (trough), others recommend a mid-point sample, typically 6–14 hours after administration.[22,27,29,30] Based on our results, collection of a C_{max} sample at 0.5 hours would appear too early to estimate the elimination phase of the disposition curve. In addition, collection of the 2nd sample at 24 hours resulted in undetectable amikacin concentrations in 7 (14%) of 49 foals. For these reasons, pharmacokinetic variables could not be calculated accurately from hospitalized foals in the present study. Based on our data, the 1st sample should be taken 1.5–2 hours after administration to obtain a sample in the 1st part of the elimination phase of the drug. The 2nd sample should be taken 8–16 hours after drug administration to ensure measurable drug concentrations.

Knowledge of trough amikacin concentration may be of particular importance in therapeutic drug monitoring because trough aminoglycoside concentration has been shown to be a significant factor for development of nephrotoxicity.[31] Optimal trough concentration for minimizing nephrotoxicity after administration of once-daily amikacin in humans is controversial, with recommendations ranging from <1 μg/mL to <10 μg/mL.[32–35] The present study failed to identify a correlation between C_{24h} amikacin concentration and serum creatinine concentrations or development of nephrotoxicity in hospitalized foals. This may be due to the fact that therapeutic drug monitoring was done early during amikacin therapy. Dose, dosing interval, or both were adjusted in all foals with C_{24h} concentration >3 μg/mL, thereby preventing accurate assessment of the effect of long-term high C_{24h} concentration on development of nephrotoxicity. In the present study, 2 (5%) of 40 foals in which plasma creatinine concentrations were monitored during amikacin therapy developed renal dysfunction, as evidenced by an increase in creatinine concentrations above baseline values and above the reference range for our laboratory. Monitoring serum creatinine concentration is a fairly insensitive mean of determining renal dysfunction because these values do not exceed the reference range until glomerular filtration has decreased by approximately 75%. The incidence of nephrotoxicity (also defined by an increase in creatinine concentrations) in humans treated with once-daily amikacin has ranged between 5 and 21%.[32,35]

Previous studies using multiple daily dosing of amikacin have revealed significant alterations of values of various pharmacokinetic parameters in premature, hypoxemic, and azotemic foals compared to clinically healthy animals.[10–12] In one study also using multiple daily dosing of amikacin,

sepsis score and serum creatinine concentrations were inversely correlated to amikacin clearance and appeared to be useful indicators of altered drug disposition.[12] In the present study, all groups of hospitalized equine neonates had significantly lower amikacin $C_{0.5h}$ compared to clinically healthy foals. However, prematurity, hypoxemia, and sepsis did not result in significant changes in amikacin $C_{0.5h}$ and C_{24h} concentrations compared to other hospitalized foals (Table 2). Similarly, no correlation was found between $C_{0.5h}$ and C_{24h} amikacin concentrations and creatinine concentrations or BUN concentrations. Although renal dysfunction would be expected to alter the disposition of amikacin, the lack of correlation between $C_{0.5h}$ and C_{24h} amikacin concentrations and creatinine concentrations in the present study is not unexpected for 2 reasons. First, high plasma creatinine concentrations in newborn foals may be the result of placental dysfunction and do not necessarily represent abnormal glomerular filtration.[36] In addition, it is general practice in our hospital to use a 3rd-generation cephalosporin instead of amikacin in foals with high BUN or creatinine concentrations.

Multiple in vivo and in vitro studies have shown that the rate of bacterial killing with aminoglycosides increases as the drug concentration increases above the MIC for a given pathogen with an optimal C_{max} to MIC ratio of approximately 8–12:1.[6–8,37] In addition, a C_{max} to MIC ratio of at least 10:1 may prevent the emergence of resistant pathogens.[8,9] A few studies have reported in vitro susceptibility of bacterial isolates from equine neonatal blood cultures.[2,4,5] Bacterial isolates with an MIC $\leq$ 16 μg/mL are considered to be susceptible to amikacin.[21] Maintaining a C_{max} to MIC ratio of 10:1 for all susceptible isolates would imply achieving $C_{0.5h}$ of 160 μg/mL. Based on data presented in Table 2, this approach would be impossible. It was therefore necessary to know the true MIC of amikacin against gram-negative isolates from blood cultures to make appropriate recommendations for targeted amikacin C_{max} in neonatal foals. The MIC at which at least 90% of all gram-negative isolates were inhibited by amikacin was 4 μg/mL, suggesting that amikacin $C_{0.5h}$ of 40 μg/mL should be targeted (Table 3). The proportion of foals with $C_{0.5h} \geq 40$ μg/mL was significantly higher in foals receiving a dose at approximately 25 mg/kg (22/24 or 92%) than in foals receiving a dose at approximately 21 mg/kg (9/25 or 36%), whereas no difference was found in the proportion of foals with C_{24h} concentrations ≥ 3 μg/mL between the 2 groups. The lack of association between $C_{0.5h}$ and survival in the present study may have been due to the small number of nonsurvivors and to the fact that many foals included in the study did not have confirmed bacterial infections.

In conclusion, the results of this study show that age affects the pharmacokinetics of once-daily amikacin in neonatal foals. Hospitalized foals have lower amikacin $C_{0.5h}$ than healthy foals. Sepsis, prematurity, and hypoxemia did not alter $C_{0.5h}$ and C_{24h} amikacin concentrations after once-daily administration to hospitalized foals. An initial dose at 25 mg/kg is recommended to optimize the C_{max} to MIC ratio. This dose resulted in adequate $C_{0.5h}$ and C_{24h} concentrations in most, but not all, foals. Therefore, therapeutic drug monitoring to allow individual adjustment of dose and dosing interval is strongly recommended in equine neonatal patients.

Footnotes

[a] DVM Stat, Corporation for Advanced Applications, Newburg, WI
[b] Amiglyde-V, Fort Dodge Animal Health, Fort Dodge, IA
[c] TD_x Automated System, Abbott Laboratories Diagnostic Division, Abbott Park, IL
[d] PK Solutions 2.0, Summit Research Services, Montrose, CO
[e] JustOne, AccuMed International Ltd, Westlake, OH
[f] SPSS 12.0, SPSS Inc, Chicago, IL

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