Disposition of orally administered cefpodoxime proxetil in foals and adult horses and minimum inhibitory concentration of the drug against common bacterial pathogens of horses

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Objectives—To determine the disposition of orally administered cefpodoxime proxetil in foals and adult horses and measure the minimum inhibitory concentrations (MICs) of the drug against common bacterial pathogens of horses.

Animals—6 healthy adult horses and 6 healthy foals at 7 to 14 days of age and again at 3 to 4 months of age.

Procedure—A single dose of cefpodoxime proxetil oral suspension was administered (10 mg/kg) to each horse by use of a nasogastric tube. In 7- to 14-day-old foals, 5 additional doses were administered intragastrically at 12-hour intervals. The MIC of cefpodoxime for each of 173 bacterial isolates was determined by use of a commercially available test.

Results—In 7- to 14-day-old foals, mean ± SD time to peak serum concentration (T_{max}) was 1.7 ± 0.7 hours, maximum serum concentration (C_{max}) was 0.81 ± 0.22 µg/mL, and elimination half-life (harmonic mean) was 7.2 hours. Disposition of cefpodoxime in 3- to 4-month-old foals was not significantly different from that of neonates. Adult horses had significantly higher C_{max} and significantly lower T_{max}, compared with values for foals. The MIC of cefpodoxime required to inhibit growth of 90% of isolates for *Salmonella enterica*, *Escherichia coli*, *Pasteurella* spp, *Klebsiella* spp, and β-hemolytic streptococci was 0.38, 1.00, 0.16, 0.19, and 0.09 µg/mL, respectively.

Conclusions and Clinical Relevance—Oral administration at a dosage of 10 mg/kg every 6 to 12 hours would appear appropriate for the treatment of equine neonates with bacterial infections. (*Am J Vet Res* 2005;66:30–35)

Bacterial septicemia is the leading cause of morbidity and mortality in neonatal foals.[1,2] Foals can be infected via various routes, including the placenta in utero, respiratory tract, gastrointestinal tract, or umbilical stump. Gram-negative bacteria account for 70% to 95% of the microorganisms isolated from cultures of blood samples, with *Escherichia coli* being by far the most common isolate.[2,3] Other 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 streptococci, *Staphylococcus* spp, and *Enterococcus* spp) may also be isolated.[1,2]

Antimicrobial agents provide the basis of treatment for septic foals. Systemically administered (IV or IM) broad-spectrum antimicrobial agents are usually selected until results of microbial culture and in vitro susceptibility testing are available. A minimum of 2 weeks of treatment is required for patients with positive results on culture of blood samples that do not have evidence of localized infections.[4] A longer course of treatment is often required when the infection has localized, particularly in the joints or lungs.[4] Availability of orally administered antimicrobial agents with good activity against gram-negative and gram-positive bacteria would represent a major advantage in the treatment of neonates with infections, including septicemic foals. Such orally administered antimicrobial agents used as a follow-up treatment would substantially shorten the duration of hospitalization in many foals by allowing treatment on the farm, therefore considerably decreasing the cost of treatment.

Currently, the only orally administered broad-spectrum antimicrobial product routinely administered to horses is a combination of trimethoprim-sulfonamide. However, more than 60% of Enterobacteriaceae are resistant to this drug combination.[2,5] Fluoroquinolones such as enrofloxacin can be administered orally to adult horses and are highly active against gram-negative bacteria.[6] However, fluoroquinolones can induce arthropathy in foals, and as a result, they should only be used when other alternatives are not available.[7,8] In other pharmacokinetic studies,[9-12] it has been determined that although poorly absorbed in adult horses, aminobenzyl penicillins (eg, ampicillin and amoxicillin) and first-generation cephalosporins (eg, cefadroxil and cephradine) have good oral bioavailability in foals. Unfortunately, only 40% of Enterobacteriaceae isolated from horses are susceptible to these drugs in vitro.[5] In contrast, 90% of Enterobacteriaceae and virtually all streptococci of equine origin are susceptible to the third-generation cephalosporins cefotaxime and ceftiofur.[5] Currently, none of the third-generation cephalosporins studied in horses have an oral formulation.

Cefpodoxime proxetil is an orally administered third-generation cephalosporin available for treatment of people with infections attributable to various bacterial agents.[13] Cefpodoxime proxetil is readily absorbed

Received March 5, 2004.
Accepted May 17, 2004.
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Supported by the Morris Animal Foundation and the College of Veterinary Medicine Resident Award Competition.
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and de-esterified by the intestinal mucosa to release the active metabolite, cefpodoxime.[13] Cefpodoxime has a potent antibacterial effect against numerous gram-negative and gram-positive bacterial isolates of human origin.[13] Studies[13-16] in humans have revealed that cefpodoxime has good oral bioavailability, good penetration in tissues, and a low incidence of adverse effects. The need for broad-spectrum, orally administered antimicrobial agents for use in foals makes cefpodoxime proxetil an attractive alternative. Therefore, the objectives of the study reported here were to determine the disposition of orally administered cefpodoxime in foals and adult horses and measure the **minimum inhibitory concentrations (MICs)** of the drug for common bacterial pathogens of horses.

Materials and Methods

Animals—Six foals (4 males and 2 females; 5 Thoroughbreds and 1 Quarter horse) between 7 and 14 days of age and weighing between 64.0 and 80.5 kg were selected for use in the study. The same 6 foals were used again when they were between 3 and 4 months of age. In addition, 6 adult horses (1 male and 5 females; 5 Thoroughbreds and 1 Warmblood-Thoroughbred crossbred horse) between 3 and 18 years of age and weighing between 499 and 615 kg were also included in the study. Foals and horses were considered healthy on the basis of results of a thorough physical examination as well as a CBC and biochemical analysis conducted the day prior to beginning the experiments. Foals were kept with their dams at all times. All horses were kept on pasture between experiments and housed separately in stalls during the experiments with ad libitum access to grass hay and water.

Experimental design—A single dose of cefpodoxime proxetil oral suspension[a] (10 mg/kg) was administered to each horse by use of a nasogastric tube. A catheter was inserted in a jugular vein, and blood samples were obtained before (time 0); 3, 6, 10, 20, 30, 60, and 90 minutes after; and 2, 3, 4, 6, 8, 12, and 24 hours after administration of the drug.

In 7- to 14-day old foals, 5 additional doses were administered intragastrically at 12-hour intervals. Blood samples were collected before each of those doses and 0.5, 1, 2, 3, 4, 6, and 8 hours after administration of the second and fourth doses. Blood samples were also collected 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after the last dose (dose 6).

Samples of synovial fluid, peritoneal fluid, CSF, and urine were aseptically collected 2 and 12 hours after administration of the last dose of the drug for the 7- to 14-day-old foals. Foals were sedated by administration of xylazine hydrochloride (1.0 mg/kg, IV), diazepam (0.1 mg/kg, IV), and butorphanol tartrate (0.07 mg/kg, IV). Abdominal fluid was collected by use of an 18-gauge needle, as described elsewhere.[17] Immediately after collection of peritoneal fluid, general anesthesia was induced by IV administration of ketamine (2.5 mg/kg). Samples of synovial fluid were obtained from the intercarpal or radiocarpal joint by use of a 20-gauge needle. Samples of CSF were collected from the atlantooccipital space by use of a 3.5-inch, 20-gauge spinal needle. A flexible 8-F Foley catheter was used to collect urine directly from the bladder.

Clotted blood samples as well as samples of body fluids were centrifuged at 2,800 × *g* for 10 minutes. Supernatant was collected and stored frozen at –70°C until assayed. Standard solutions made from purified cefpodoxime powder (concentrations ranged from 0.03 to 5.0 µg/mL) were frozen at the same time as the samples to assess stability of frozen compounds and compensate for the possible loss of antimicrobial activity.

Cefpodoxime concentrations—Concentrations of cefpodoxime in serum and body fluids were determined by use of an agar-well diffusion microbiological assay with *Providencia alcalifaciens* (**American Type Culture Collection [ATCC]** 9886) as the assay microorganism.[18,19] One milliliter of a bacterial suspension was grown overnight in trypticase soy broth and adjusted to an optical density of 0.5 at 550 nm. This suspension was added to tempered Mueller-Hinton agar and distributed evenly over the assay plates. The plates were allowed to solidify for 45 minutes, and 0.5-mm wells were punched in the agar. Each well was filled with 50 µL of sample or cefpodoxime standard. Known amounts of purified cefpodoxime were added to equine serum, synovial fluid, urine, CSF, and peritoneal fluid to produce standard curves for each type of substrate. The agar plates were incubated for 24 hours at 30°C. Zones of bacterial inhibition were measured to the nearest 0.1 cm. Each sample or standard was assayed in triplicate, and mean values for 3 measurements of the zone diameters were calculated. The lower limit of quantitation of the assay was 0.03 µg/mL for sera and samples of body fluids. Negative-control samples did not cause bacterial inhibition. Plots of zone diameters versus standard cefpodoxime concentrations were linear and between 0.03 and 5.0 µg/mL, with a mean correlation coefficient of 0.994 (range, 0.978 to 0.998). The coefficient of variation for repeated assay of samples was < 10% for solutions, with concentrations ranging between 0.03 and 5.0 µg/mL.

Pharmacokinetic analysis—For each foal, 1-, 2-, and 3-component mathematic models were fit to serum concentration-versus-time data by use of a weighted nonlinear regression analysis with a computer algorithm that minimizes the sum of the squared deviations.[20] Best fit of the data was for the following equation:

$$C_t = (C_1 \times e^{-\lambda_1 \times t}) + (C_2 \times e^{-\lambda_2 \times t}) + (C_3 \times e^{-\lambda_3 \times t}) - ([C_1 + C_2 + C_3] \times e^{-\lambda_4 \times t}),$$

where C_t is the serum drug concentration at time t for each respective dose; e is the base of the natural logarithm; C_1, C_2, and C_3 are preexponential terms; and λ_1, λ_2, λ_3, and λ_4 are exponential terms generated by the computer algorithm to fit the data. The value for λ_3 is the **elimination rate constant (K_{el})**. **Elimination half-life ($t_{1/2}$)** was calculated as the natural logarithm of 2 divided by K_{el}. Pharmacokinetic values were calculated on the basis of noncompartmental kinetics.[21]

The **area under the concentration-time curve (AUC)** was calculated from the model curve by use of the following equation:

$$AUC = (C_1/\lambda_1) + (C_2/\lambda_2) + C_3/\lambda_3) - ([C_1 + C_2 + C_3]/\lambda_4).$$

The **area under the first moment of the concentration-time curve (AUMC)** was calculated by use of the following equation:

$$AUMC = (C_1/[\lambda_1]^2) + (C_2/\lambda_2]^2) + (C_3/[\lambda_3]^2) - ([C_1 + C_2 + C_3]/[\lambda_4]^2).$$

Mean residence time (MRT) was calculated as MRT = AUMC/AUC.

For each 7- to 14-day-old foal, a pharmacokinetic computer program[b] was used to simulate steady-state cefpodoxime concentration-versus-time plots for a dosage of 10 mg/kg administered every 6 or 8 hours. These simulations were used to calculate the amount of time (ie, number of hours) for which cefpodoxime concentrations were greater than the MIC of a given pathogen and the percentage of the dosing interval for which cefpodoxime concentrations were greater than the MIC of a given pathogen.

MIC of cefpodoxime for bacterial pathogens of horses—Bacterial isolates from all equine clinical samples

submitted to the Clinical Microbiology Laboratory of the University of Florida Veterinary Medical Teaching Hospital between November 2002 and July 2003 were used. The MIC of cefpodoxime for bacterial isolates of horses was determined by use of an antimicrobial resistance testing kit.[c] The kit was used as described by the manufacturer and in accordance with the **National Committee for Clinical Laboratory Standards (NCCLS)**.[22] Cefpodoxime concentrations between 0.016 and 256 µg/mL were used for testing. Briefly, fresh isolates were grown on blood agar plates, and colonies were suspended in sterile water to achieve turbidity equal to that of a 0.5 McFarland standard (final bacterial concentration of approx 1×10^5 CFUs/mL). A sterile swab was dipped into the inoculum suspension and used to inoculate the entire surface of a 100-mm Mueller-Hinton plate 3 times by rotating the plate approximately 60° for each inoculation to ensure an even distribution. After allowing the excess moisture to dry (approx 10 to 15 minutes), test strips were applied to the agar. The plates were incubated for 18 to 24 hours at 37°C. A test was considered valid only when there was adequate growth on the plate. Control strains used weekly to validate the assay were *Staphylococcus aureus* ATCC 29213 and *E coli* ATCC 25922. Results were considered valid only when MICs obtained with the control stains were within the reference range proposed by the NCCLS.[23] The MIC required to inhibit growth of 50% of isolates and the **MIC required to inhibit growth of 90% of isolates (MIC_{90})** were determined for each bacterial species.

Statistical analysis—The Mann-Whitney *U* test was used to assess differences in pharmacokinetic variables between foals and adult horses. The Wilcoxon signed rank test was used to assess differences in pharmacokinetic variables between 7- to 14-day-old foals and the same foals when they were between 3 and 4 months of age. For all comparisons, values of $P < 0.05$ were considered significant.

Results

Measurable concentrations of cefpodoxime were found in all foals and 4 of 6 adult horses at 6 minutes after intragastric administration and in all horses at 10 minutes after intragastric administration. Mean ± SD **time to peak serum concentration (T_{max})** in 7- to 14-day-old foals was 1.7 ± 0.7 hours (**Table 1**). Mean **maximum serum concentration (C_{max})** was 0.81 ± 0.22 µg/mL, and harmonic mean $t_{1/2}$ was 7.2 hours. The C_{max} detected after multiple intragastric administrations at 12-hour intervals (0.65 ± 0.19 µg/mL) was not significantly different from that detected following administration of the first dose (**Figure 1**). The disposition of cefpodoxime in 3- to 4-month-old foals was not significantly different from that of neonates. Adult horses had significantly higher C_{max} and significantly lower AUMC, MRT, and T_{max}, compared with values for foals.

Table 1—Mean ± SD values for pharmacokinetic variables of cefpodoxime after intragastric administration at a rate of 10 mg/kg to 6 foals when they were 7 to 14 days old and again when they were 3 to 4 months old and to 6 adult horses.

	Foals		
Variable	**7–14 days of age**	**3–4 months of age**	**Adults**
K_{el} (/h)	0.10 ± 0.05[a]	0.13 ± 0.07[a,b]	0.18 ± 0.07[b]
$AUC_{0-\infty}$ ([µg × h]/mL)	4.8 ± 2.4	4.6 ± 1.4	3.4 ± 0.6
AUMC (µg × h^2/mL)	34.5 ± 19.7[a]	42.5 ± 23.6[a]	15.6 ± 6.4[b]
MRT (h)	7.3 ± 1.7[a]	8.9 ± 3.8[a]	4.6 ± 1.7[b]
T_{max} (h)	1.7 ± 0.7[a]	2 .0 ± 0.7[a]	0.8 ± 0.4[b]
$t_{1/2abs}$ (h)*	0.5[a]	0.6[a]	0.3[b]
$T_{1/2}$ (h)*	7.2	6.2	3.8
$C_{max\ 0-24}$ (µg/mL)	0.81 ± 0.22[a]	0.74 ± 0.29[a]	1.27 ± 0.40[b]
$C_{max\ 72-84}$ (µg/mL)	0.65 ± 0.19	ND	ND

*Value reported is the harmonic mean.

K_{el} = Elimination rate constant. $AUC_{0-\infty}$ = Area under the serum concentration-versus-time curve (time 0 [time of administration of cefpodoxime] to infinity). AUMC = Area under the first moment of the serum concentration-versus-time curve. MRT = Mean residence time. T_{max} = Time to peak serum concentration. $t_{1/2abs}$ = Absorption half-life. $t_{1/2}$ = Elimination half-life. $C_{max\ 0-24}$ = Peak serum concentration after a single intragastric dose. $C_{max\ 72-84}$ = Peak serum concentration after multiple intragastric doses administered at 12-hour intervals. ND = Not determined.

[a,b]Within a row, values with different superscript letters differ significantly ($P \leq 0.05$).

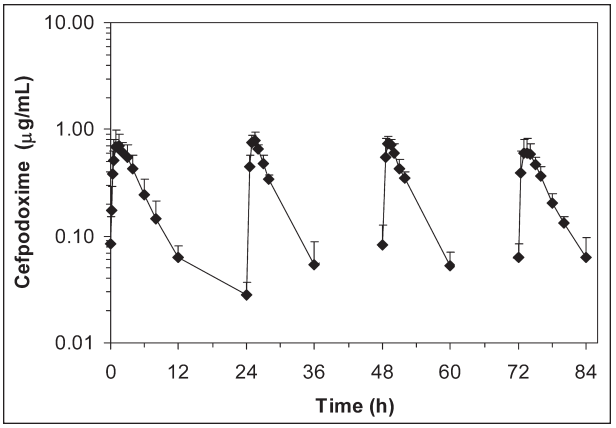

Figure 1—Mean ± SD serum concentrations of cefpodoxime for 6 foals at various time points after intragastric administrations of cefpodoxime proxetil (10 mg/kg). Time 0 was the time of administration of the first dose, and subsequent doses were administered at 24, 36, 48, 60, and 72 hours.

Table 2—Mean ± SD concentration of cefpodoxime in body fluids of six 7- to 14-day-old foals after 6 intragastric administrations (10 mg of cefpodoxime/kg, q 12 h).

	Time after cefpodoxime administration (h)	
Sample	**2**	**12**
Serum (µg/mL)	0.58 ± 0.14	0.07 ± 0.06
Synovial fluid (µg/mL)	0.42 ± 0.15	0.05 ± 0.02
Peritoneal fluid (µg/mL)	0.53 ± 0.09	0.08 ± 0.04
Urine (µg/mL)	15.61 ± 8.21	0.53 ± 0.19
CSF (µg/mL)	0	0

Table 3—Minimum inhibitory concentration (MIC) of cefpodoxime for 173 bacterial isolates cultured from horses.

	MIC (µg/mL)		
Isolates (n)	**50%**	**90%***	**Range**
Gram-negative organisms			
Salmonella enterica (25)	0.250	0.380	0.032 to > 256
Escherichia coli (21)	0.50	1.00	0.19 to > 256
Klebsiella spp (12)	0.125	0.190	0.094– 0.190
Pasteurella spp (11)	< 0.016	0.160	< 0.016–0.750
Pseudomonas spp (10)	> 256	> 256	> 256
Enterobacter spp (7)	0.50	ND	0.19–2.00
Gram-positive organisms			
β-hemolytic streptococci (54)	0.064	0.094	0.016–0.160
α-hemolytic streptococci (6)	0.125	ND	< 0.016–8
Rhodococcus equi (12)	6	12	4–12
Staphylococcus spp (8)	1.00	ND	0.38 to > 256
Enterococcus spp (7)	> 256	ND	0.19 to > 256

*The MIC required to inhibit growth of 90% of isolates (MIC_{90}) is only reported when at least 10 isolates are available.

See Table 1 for remainder of key.

Table 4—Mean ± SD amount of time that serum concentrations of cefpodoxime exceeded the MIC_{90} of common bacterial pathogens of horses after oral administration of the drug to six 7- to 14-day-old foals at the rate of 10 mg/kg for various dosing intervals and percentage of various dosing intervals for which drug concentrations would exceed the MIC_{90}.

	12-hour intervals*		8-hour intervals†		6-hour intervals†	
Isolate	**MIC_{90} (h)**	**%**	**> MIC_{90} (h)**	**%**	**> MIC_{90} (h)**	**%**
Salmonella spp	4.0 ± 1.9	33.2 ± 15.7	5.5 ± 2.1	69.3 ± 26.1	5.2 ± 1.3	86.1 ± 22.2
E coli	0.2 ± 0.4	3.5 ± 3.4	0.8 ± 0.9	9.4 ± 12.3	1.0 ± 1.1	15.9 ± 18.3
Klebsiella spp	7.1 ± 1.8	58.9 ± 14.7	7.4 ± 0.9	92.7 ± 11.5	6.0 ± 0	100 ± 0
Pasteurella spp	8.1 ± 2.4	67.3 ± 19.9	7.8 ± 0.3	97.9 ± 3.2	6.0 ± 0	100 ± 0
β-hemolytic streptococci	9.6 ± 2.1	67.6 ± 17.4	8.0 ± 0	100 ± 0	6.0 ± 0	100 ± 0

*Determined on the basis of data measured in the study reported here. †Determined on the basis of a computer simulation of predicted steady-state concentrations.

Concentrations of cefpodoxime in synovial and peritoneal fluids of 7- to 14-day-old foals were similar to the concurrent serum concentrations (**Table 2**). Urine concentrations were 12 to 72 times higher than concurrent serum concentrations. The drug could not be detected in CSF.

Adverse reactions were not detected during or after intragastric administration to foals. Mild colic developed in 2 of the adult horses 24 to 48 hours after administration of cefpodoxime. An impaction of the pelvic flexure was detected during per rectal palpation in both horses.

The MIC_{90} of cefpodoxime for *Salmonella enterica*, *E coli*, *Pasteurella* spp, *Klebsiella* spp, and β-hemolytic streptococci was 0.38, 1.00, 0.16, 0.19, and 0.09 µg/mL, respectively (**Table 3**). Oral administration of cefpodoxime to 7- to 14-day-old foals at a rate of 10 mg/kg every 12 hours resulted in serum concentrations greater than the MIC_{90} of *Klebsiella* spp, *Pasteurella* spp, and β-hemolytic streptococci for more than 50% of the dosing interval (**Table 4**). On the basis of computer simulations, the same dose administered at 8-hour intervals would have resulted in serum concentrations greater than the MIC_{90} of *S enterica* for more than 50% of the dosing interval. Administration at 8-hour intervals also would have resulted in serum concentrations greater than the MIC of 75% of *E coli* isolates (0.5 µg/mL) for 50.0 ± 21.0% of the dosing interval. Administration at 6-hour intervals would have resulted in serum concentrations greater than the MIC of 75% of *E coli* isolates for 74.3 ± 26.9% of the dosing interval.

Discussion

The need for better orally administered broad-spectrum antimicrobial agents for the treatment of neonatal foals with sepsis led us to investigate the disposition of cefpodoxime by use of a microbiological assay to measure drug concentrations. Microbiological assays cannot differentiate between a drug and its active metabolite or metabolites. Cefpodoxime proxetil is a prodrug that is absorbed from the gastrointestinal tract and deesterified to its only active metabolite, cefpodoxime. As a result, there is an excellent correlation between cefpodoxime concentrations measured by use of high-performance liquid chromatographic assays and by microbiological assays.[15,19] Therefore, the total antimicrobial activity measured by use of the microbiological assay in the study reported here was adequate to evaluate the disposition of cefpodoxime in foals and adult horses.

A solution intended for IV administration was not available for use in this study; consequently, bioavailability could not be determined. Therefore, pharmacokinetic variables such as clearance and volume of distribution could not be calculated accurately. Cefpodoxime $t_{1/2}$ for foals in the study reported here (7.2 hours) was considerably higher than values reported in adult volunteers and pediatric human patients (2.1 to 3.3 hours),[15] whereas the $t_{1/2}$ in adult horses (3.8 hours) was similar to values reported in people.[13,16,24] The ranges for mean C_{max} (0.74 to 1.27 µg/mL) and AUC (3.4 to 4.8 [µg × h]/mL) obtained in the study reported here were considerably lower than values of healthy human volunteers receiving a similar orally administered dose (5.31 µg/mL and 35.8 [µg × h]/mL, respectively).[15] Oral bioavailability of cefpodoxime in people is approximately 50%.[16] The low C_{max} and AUC obtained in our study suggest poor oral bioavailability of cefpodoxime in foals and adult horses.

Pharmacokinetic studies[9-12] have determined that although aminobenzyl penicillins (eg, ampicillin and amoxicillin) and first-generation cephalosporins (eg, cefadroxil and cephradine) are poorly absorbed in adult horses, they have good oral bioavailability in foals. In 1 study,[11] the bioavailability of cefadroxil, a first-generation cephalosporin, was 99% in 2-week-old foals and progressively decreased to 14% in 5-month-old foals. In that same study, C_{max} also decreased progressively with increasing age. In contrast, adult horses in the study reported here had significantly higher C_{max} than foals, whereas AUC was not significantly different between age groups (Table 1). Some of these differences in drug disposition may be explained by the larger extracellular fluid space of foals versus adult horses. Food was not withheld from foals or adult horses prior to administration of cefpodoxime in the study to more closely simulate a clinical situation. In humans, oral administration of cefpodoxime with food significantly increases C_{max} and AUC.[25] Oral absorption of cefpodoxime in humans is a pH-dependent event. Thus, compared with results for fasted volunteers, bioavailability is significantly decreased following treatment with aluminum hydroxide or H_2-receptor antagonists, all of which increase gastric pH.[25,26] Suckling in foals is associated with an abrupt increase in gastric pH, and conversely, gastric pH becomes highly acidic when foals do not suckle for a period of > 20 minutes.[27] Intragastric pH of adult horses

is also considerably higher when they are fed hay ad libitum, compared with intragastric pH of horses from which food is withheld.[28] Therefore, it is possible that feeding in horses, as opposed to the situation in people, may decrease oral absorption of cefpodoxime by increasing gastric pH.

With the exception of *Streptococcus* spp, bacterial isolates with an MIC ≤ 2 µg/mL are considered susceptible to cefpodoxime as established by NCCLS guidelines.[23] Streptococcal isolates susceptible to penicillin should also be considered susceptible to cefpodoxime.[23] Adhering to the NCCLS guidelines, at least 90% of *S enterica*, *E coli*, *Klebsiella* spp, *Pasteurella* spp, *Enterobacter* spp, and β-hemolytic streptococci of equine origin were susceptible to cefpodoxime in the study reported here. In contrast, *Pseudomonas* spp, *Enterococcus* spp, and *Rhodococcus equi* isolates were resistant. In vitro activity of cefpodoxime against equine bacterial isolates in our study was similar to that of 2 other third-generation cephalosporins, with the exception that cefpodoxime was more active against *S enterica* (MIC_{90}, 0.38 µg/mL) than was ceftazidime (MIC_{90}, 32 µg/mL) or ceftiofur (MIC_{90}, > 4 µg/mL).[29]

The optimal dosing of antimicrobial agents is dependent on the pharmacokinetics as well as the pharmacodynamics of the drug. Pharmacodynamic properties of a drug address the relationship between drug concentration and antimicrobial activity. The most important factor determining the efficacy of β-lactam antimicrobials such as cefpodoxime is the amount of time that serum concentrations exceed the MIC of a given pathogen.[30] The amount of time for which the antimicrobial concentration in serum exceeds the MIC of a given pathogen, when expressed as a percentage of the dosing interval, is referred to as the coverage.[30] Dosing intervals should maintain serum concentrations greater than the MIC of a pathogen for at least 50% of the dosing interval to maximize therapeutic efficacy and prevent the development of antimicrobial resistance.[31] Therefore, favorable pharmacokinetics and a low MIC are essential for optimal therapeutic success. On the basis of the serum concentration-versus-time curve in 7- to 14-day-old foals and MIC data obtained in the study reported here, oral administration at the rate of 10 mg/kg every 12 hours would provide sufficient coverage against at least 90% of *Klebsiella* spp, *Pasteurella* spp, and β-hemolytic streptococci isolates. The same dose administered at 8-hour intervals would provide adequate coverage against 90% of *S enterica* isolates and 75% of *E coli* isolates in some, but not all, foals. Administration at 6-hour intervals would provide coverage against *E coli* isolates with an MIC ≤ 0.5 µg/mL (ie, 75% of isolates). Alternatively, the dosage could be increased to achieve higher serum concentrations. Additional studies are required to determine the safety and disposition of cefpodoxime at higher dosages.

Adverse effects in humans receiving orally administered cefpodoxime are usually related to the gastrointestinal tract, with nausea, abdominal pain, and diarrhea evident in 4% to 15% of patients.[13] In the study reported here, no adverse reactions were detected during or after intragastric administration to foals. Two adult horses developed mild colic 24 to 48 hours after administration of cefpodoxime. Per rectal palpation revealed an impaction of the pelvic flexure in both horses, which responded to withdrawal of food and intragastric administration of mineral oil. Development of colic in these horses may have been the result of feed changes (from pasture to hay available ad libitum) and restriction of exercise, rather than an adverse effect of cefpodoxime. Administration of other third-generation cephalosporins, such as ceftriaxone, cefepime, and ceftiofur, to adult horses has infrequently resulted in severe diarrhea.[32-34] Additional studies with multiple doses will be required to assess the safety of orally administered cefpodoxime in adult horses.

On the basis of serum concentration-versus-time curve data and MICs of common equine bacterial isolates, oral administration at a rate of 10 mg/kg every 6 to 12 hours would appear appropriate for the treatment of equine neonates with bacterial infections. Additional studies are required to confirm the clinical efficacy and safety of these dosages in a clinical setting.

a. Vantin, Pharmacia & Upjohn, Kalamazoo, Mich.
b. PK Solutions 2.0, Summit Research Services, Montrose, Colo.
c. E test, AB Biodisk North America Inc, Piscatawa NJ.

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