

# Pharmacokinetics of sulfamethoxazole and trimethoprim in donkeys, mules, and horses

Kenneth E. Peck, MS; Nora S. Matthews, DVM; Tex S. Taylor, DVM; Katrina L. Mealey, DVM, PhD

**Objective**—To compare serum disposition of sulfamethoxazole and trimethoprim after IV administration to donkeys, mules, and horses.

**Animals**—5 donkeys, 5 mules, and 3 horses.

**Procedure**—Blood samples were collected before (time 0) and 5, 15, 30, and 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 24 hours after IV administration of sulfamethoxazole (12.5 mg/kg) and trimethoprim (2.5 mg/kg). Serum was analyzed in triplicate with high-performance liquid chromatography for determination of sulfamethoxazole and trimethoprim concentrations. Serum concentration-time curve for each animal was analyzed separately to estimate noncompartmental pharmacokinetic variables.

**Results**—Clearance of trimethoprim and sulfamethoxazole in donkeys was significantly faster than in mules or horses. In donkeys, mean residence time (MRT) of sulfamethoxazole (2.5 hours) was less than half the MRT in mules (6.2 hours); MRT of trimethoprim in donkeys (0.8 hours) was half that in horses (1.5 hours). Volume of distribution at steady state ( $V_{d_{ss}}$ ) for sulfamethoxazole did not differ, but  $V_{d_{ss}}$  of trimethoprim was significantly greater in horses than mules or donkeys. Area under the curve for sulfamethoxazole and trimethoprim was higher in mules than in horses or donkeys.

**Conclusions and Clinical Relevance**—Dosing intervals for IV administration of trimethoprim-sulfamethoxazole in horses may not be appropriate for use in donkeys or mules. Donkeys eliminate the drugs rapidly, compared with horses. Ratios of trimethoprim and sulfamethoxazole optimum for antibacterial activity are maintained for only a short duration in horses, donkeys, and mules. (*Am J Vet Res* 2002;63:349–353)

Equine practitioners use many combinations of trimethoprim and sulfonamides because of their wide range of bactericidal activity.<sup>1</sup> In the United States, trimethoprim-sulfadiazine is approved for use in horses, although the combination of trimethoprim-sulfamethoxazole approved for use in humans is also used in horses. Sulfadoxine with trimethoprim is available in Canada,<sup>1</sup> and the use of trimethoprim-sulfachloropyridazine has been reported in horses.<sup>2</sup> These

combination products are relatively inexpensive and can be administered orally.

Pharmacokinetics of various antimicrobials have been documented in donkeys, including tetracycline,<sup>3</sup> ampicillin,<sup>4</sup> gentamicin,<sup>5</sup> norfloxacin,<sup>6</sup> penicillin,<sup>7</sup> amikacin,<sup>8</sup> and sulfadimidine.<sup>9</sup> However, despite studies<sup>10,11</sup> on the use of trimethoprim in horses, we were unable to find any references on use of trimethoprim in mules and only 1 reference<sup>12</sup> on use of trimethoprim in donkeys. Therefore, the purpose of the study reported here was to determine the disposition of sulfamethoxazole and trimethoprim in donkeys and mules and to compare these pharmacokinetic variables with those in horses.

## Materials and Methods

**Animals**—Five clinically normal standard donkeys (3 males and 2 females) that ranged from 8 to 11 years old (mean, 9.2 years) and weighed between 191 and 295 kg (mean, 237 kg), 5 clinically normal mules (1 male and 4 females) that ranged from 7 to 18 years old (mean, 12.2 years) and weighed between 409 and 555 kg (mean, 467 kg), and 3 clinically normal horses (2 males and 1 female) that ranged from 3 to 19 years old (mean, 9 years) and weighed between 386 and 477 kg (mean, 447 kg) were used in the study. Animals were considered clinically normal on the basis of results of physical examination, CBC, and serum biochemical analyses. Animals were acclimatized to their surroundings and allowed ad libitum access to water. The study protocol was approved by an institutional laboratory animal use and care committee.

**Experimental design and collection of samples**—Sulfamethoxazole<sup>a</sup> (12.5 mg/kg) and trimethoprim<sup>b</sup> (2.5 mg/kg) were administered IV as a bolus injected during approximately a 1-minute period through a 14-gauge 13-cm fluoride-coated catheter<sup>c</sup> inserted in a jugular vein. The catheter was flushed with heparinized saline (0.9% NaCl) solution after drug administration and after collection of each blood sample. Bolus administration of each drug was performed through the catheter because of the relatively large volume of each drug. For all animals, blood samples were collected before (time 0) and 5, 15, 30, and 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 24 hours after administration of sulfamethoxazole and trimethoprim. Blood samples were transferred into evacuated tubes; tubes were centrifuged, and serum was harvested and frozen at  $-20^{\circ}\text{C}$  until analyzed.

**Preparation of samples**—For solid-phase extraction, samples were loaded onto a previously conditioned (5 ml of methanol, then 5 ml of high-performance liquid chromatography [HPLC]-grade water, followed by 3 ml of 1N acetic acid<sup>d</sup>) 500 mg C8/aromatic sulfonic acid mixed-bed solid-phase extraction column.<sup>e</sup> The column was rinsed with 5 ml of 0.2M phosphate buffer (pH 6.0)<sup>f</sup> and then with 3 ml of 1N acetic acid. It was dried for 15 minutes under vacuum (250 to 375 mm Hg) and then washed with 5 ml of hexanes.<sup>g</sup> Sulfamethoxazole and sulfachloropyridazine were eluted

Received Jul 16, 2001.

Accepted Oct 9, 2001.

From the Texas Veterinary Medical Center, Texas A&M University, College Station, TX 77843-4474 (Peck, Matthews, Taylor); and the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Washington State University, Pullman, WA 99163 (Mealey).

Supported by a grant from the American Donkey and Mule Society, Denton, Tex.

Address correspondence to Mr. Peck

with dichloromethane<sup>b</sup> containing 5% (vol:vol) methanol. The column was washed with 10 ml of methanol; trimethoprim and antipyrine were eluted with dichloromethane:isopropanol:ammonium hydroxide<sup>c</sup> (80:20:2 [vol:vol:vol]). Samples were dried under nitrogen at 45 °C. Sulfamethoxazole fractions for samples obtained between 0 and 5 hours were suspended in 400 µl of a 1:1 (vol:vol) mixture of acetonitrile:water; fractions for samples obtained between 6 and 24 hours were suspended in 100 µl of the acetonitrile:water mixture. All trimethoprim fractions were suspended in 150 µl of the acetonitrile:water mixture.

Following solid-phase extraction, serum concentrations of sulfamethoxazole and trimethoprim were determined by use of HPLC. Samples were extracted in triplicate and randomly analyzed for each species because of species-specific calibration curves. Internal standards (sulfachloropyridazine,<sup>1</sup> 21.9 µg for samples collected between 0 and 5 hours and 6.57 µg for samples collected between 6 and 24 hours in a stock solution containing 219 mg in 100 ml of methanol<sup>m</sup>; antipyrine,<sup>n</sup> 3.43 µg for all samples in a stock solution containing 34.3 mg in 100 ml of methanol) were added to 1 ml of serum followed by addition of 5 ml of 0.2M phosphate buffer (pH 6.0).

**Calibration curve**—Serum calibrators were prepared in duplicate by addition of appropriate volumes of trimethoprim<sup>o</sup> and sulfamethoxazole<sup>p</sup> to 1 ml of blank serum (pooled serum obtained at time 0) for each species. Internal standards were added to calibrators, and the extraction protocol described previously was performed. Two sulfamethoxazole curves were prepared. For samples obtained between 0 and 5 hours, calibrators for sulfamethoxazole were prepared by addition of the appropriate volume of a solution with a high concentration of sulfamethoxazole (252.5 mg in 50 ml of methanol) to produce final concentrations of 5.05, 15.15, 25.25, 30.3, 40.4, 50.5, and 75.75 µg/ml. For samples obtained between 6 and 24 hours, calibrators were prepared by addition of the appropriate volume of a solution with a low concentration of sulfamethoxazole (102.5 mg in 100 ml of methanol) to produce final concentrations of 1.025, 3.075, 5.125, 6.15, 8.2, 10.25, and 15.375 µg/ml. Calibrators for trimethoprim were prepared by addition of the appropriate volume of trimethoprim solution (47.3 mg in 100 ml of methanol) to the sulfamethoxazole calibrators prepared for analysis of the samples obtained between 0 and 5 hours to produce concentrations of trimethoprim of 0.473, 1.419, 1.892, 2.365, 2.838, 3.784, and 4.73 µg/ml. Linear regression was > 0.996 for all curves generated for calibration samples. Quality-control samples were prepared by addition of the appropriate amount of the high-concentration sulfamethoxazole solution to obtain concentrations of 15.15 and 35.35 µg/ml, low-concentration sulfamethoxazole solution to obtain concentrations of 3.08 and 7.18 µg/ml, and trimethoprim solution to obtain concentrations of 1.42 and 3.31 µg/ml. In addition, to evaluate curve parallelism, sulfamethoxazole quality-control samples of 7.18 µg/ml were calculated on the curve for the high-concentration solution, and samples of 15.15 µg/ml were calculated on the curve for the low-concentration solution. Resulting values for both sets of samples were between 87 and 113% of target values.

**High-performance liquid chromatography**—The HPLC instruments<sup>q</sup> were equipped with a 7-µm mixed-mode RP18 cation 100 Å (4.6 × 250 mm) column<sup>r</sup> for sulfamethoxazole analysis or a 5-µm C-18 (4.6 × 250 mm) column<sup>s</sup> for trimethoprim analysis. Mobile phase for sulfamethoxazole was 10 mM phosphate buffer (pH 4.2):acetonitrile (79:21), and the injection volume was 35 µl. Wavelengths monitored for sulfamethoxazole and sulfachloropyridazine were 267 nm (used for quantification) and 240 nm. Sulfamethoxazole and

sulfachloropyridazine were resolved; there was baseline separation and no interference from other coextracted compounds. Mobile phase for trimethoprim was 5 mM phosphate buffer (pH 7.8) with 2% (vol:vol) tetrahydrofuran:acetonitrile (76:24), and the injection volume was 40 µl. Wavelengths monitored for trimethoprim and antipyrine were 230 nm (used for quantification) and 270 nm. Trimethoprim and antipyrine were resolved; there was baseline separation and no interference from other coextracted compounds. Flow rate for both systems was 1 ml/min. Peak identities were confirmed by comparison of the UV light spectrum with that of authenticated standards. Internal standards for calibration of peak area were used in the computer-generated report of sulfamethoxazole or trimethoprim.

**Quality control and recovery**—Estimates of within-day coefficient of variation, as determined by use of 1-way ANOVA, for sulfamethoxazole at concentrations of 15.15, 35.35, 3.08, and 7.18 µg/ml were 2.5, 4.2, 6.0, and 3.3%, respectively; similar estimates for trimethoprim at concentrations of 1.42 and 3.31 µg/ml were 3.8 and 4.1%, respectively. Between-day coefficient of variation for sulfamethoxazole at concentrations of 15.15, 35.35, 3.08, and 7.18 µg/ml was 3.3, 8.4, 8.4 and 8.4%, respectively; similar estimates for trimethoprim at concentrations of 1.42 and 3.31 µg/ml were 7.6 and 9.7%, respectively. Mean ± SD recovery (spiked in 1 ml of blank horse serum and extracted as described previously, compared with the corresponding amount injected directly onto the HPLC; n = 9) for sulfamethoxazole (40.4 and 3.075 µg/ml) and sulfachloropyridazine (21.9 µg/ml) was 94.2 ± 6.3, 96.3 ± 5.9, and 94.9 ± 6.4%, respectively. Mean recovery of trimethoprim (1.892 µg/ml) and antipyrine (3.43 µg/ml) was 88.9 ± 5.1 and 90.0 ± 6.0%, respectively. Limit of quantification (20% limit from target value) for sulfamethoxazole (high- and low-concentration solutions) and trimethoprim was 0.7 and 0.9 µg/ml, respectively.

**Pharmacokinetic analysis**—Concentration-versus-time data for IV administration of trimethoprim and sulfamethoxazole were analyzed, using nonlinear least-squares regression analysis. Noncompartmental analysis of the data was performed, using statistical moment theory. The area under the serum concentration-versus-time curve (AUC; calculated to infinity by use of the trapezoidal method), mean residence time (MRT), and area under the moment curve (AUMC) were calculated by use of a computer software program.<sup>1</sup> Apparent volume of distribution at a steady state (Vd<sub>ss</sub>) was calculated, using the following equation:

$$Vd_{ss} = (\text{dose} \cdot \text{AUMC}) / (\text{AUC})^2$$

Total body clearance (Cl<sub>T</sub>) was calculated, using the following equation:

$$Cl_T = \text{dose} / \text{AUC}.$$

**Statistical analysis**—A nonparametric unpaired test (Mann-Whitney) was used to compare noncompartmental pharmacokinetic values between donkeys and horses, donkeys and mules, and mules and horses. Significance was defined as values of *P* < 0.05.

## Results

Mean serum concentration of sulfamethoxazole-versus-time curves for horses, donkeys, and mules were plotted (Fig 1). Similarly, mean serum concentration of trimethoprim-versus-time curves were plotted for horses, donkeys, and mules (Fig 2). Pharmacokinetic variables were determined (Table 1). For sulfamethoxazole, several significant differences in pharmacokinetic variables were detected among horses, mules, and donkeys.

Median AUC was highest in mules (3.8  $\mu\text{g}/[\text{ml}\cdot\text{min}]$ ), intermediate in horses (2.4  $\mu\text{g}/[\text{ml}\cdot\text{min}]$ ) and lowest in donkeys (1.6  $\mu\text{g}/[\text{ml}\cdot\text{min}]$ ). Median value for MRT was longest in mules (372 minutes), intermediate in horses

(234 minutes), and shortest in donkeys (150 minutes). Median  $\text{Cl}_T$  was slowest in mules (0.93 ml/kg/min) and most rapid in donkeys (2.19 ml/kg/min), whereas horses were intermediate (1.46 ml/kg/min). We did not detect significant differences in  $\text{Vd}_{ss}$  among horses, mules, and donkeys.

For trimethoprim, median AUC was significantly greater in mules (0.05  $\mu\text{g}/[\text{ml}\cdot\text{min}]$ ) than in horses (0.03  $\mu\text{g}/[\text{ml}\cdot\text{min}]$ ) or donkeys (0.03  $\mu\text{g}/[\text{ml}\cdot\text{min}]$ ). Median value for MRT was longest in horses (90 minutes) and mules (84 minutes) and shortest in donkeys (48 minutes). Median  $\text{Cl}_T$  was significantly slower in mules (15.6 ml/kg/min), compared with horses (21.2 ml/kg/min) or donkeys (25.8 ml/kg/min), whereas  $\text{Vd}_{ss}$  was significantly larger in horses (1,756 ml/kg), compared with mules (1,296 ml/kg) or donkeys (1,387 ml/kg).

## Discussion

Although only 3 horses were used in the study reported here, we believe that this was an adequate number for statistical comparison for 2 reasons. First, our calculated pharmacokinetic values for trimethoprim and sulfamethoxazole are in agreement with those reported in another study<sup>13</sup> in which a trimethoprim-sulfamethoxazole combination was administered IV to 6 horses. Second, there was little variation among pharmacokinetic values calculated for each of the 3 horses in our study.

Several significant differences existed among pharmacokinetic values calculated for sulfamethoxazole in horses, donkeys, and mules. Total body clearance of sulfamethoxazole was slowest in mules (0.93 ml/kg/min), intermediate in horses (1.46 ml/kg/min), and most rapid in donkeys (2.19 ml/kg/min). Clearance of the drug is dependent on renal and hepatic routes. Because the rate of clearance of sulfamethoxazole was most rapid in donkeys, it follows that renal or hepatic elimination of sulfamethoxazole in donkeys is greater than in horses or mules. Renal clearance of sulfamethoxazole is by filtration and active tubular secretion. We reported elsewhere<sup>5</sup> that the clearance of gentamicin, a drug that is eliminated almost exclusively by glomerular filtration, in donkeys does not differ from that in horses. This suggests that donkeys may have a greater

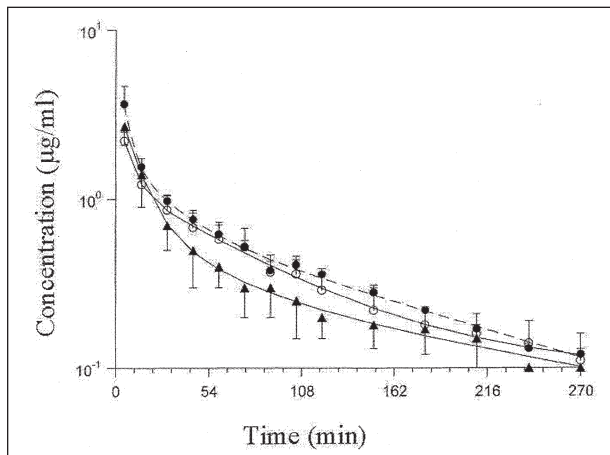


Figure 1—Mean  $\pm$  SD serum concentrations of sulfamethoxazole in mules (solid circle), horses (open circle), and donkeys (solid triangle) after IV administration of trimethoprim at a rate of 2.5 mg/kg of body weight. Time 0 = Time of administration.

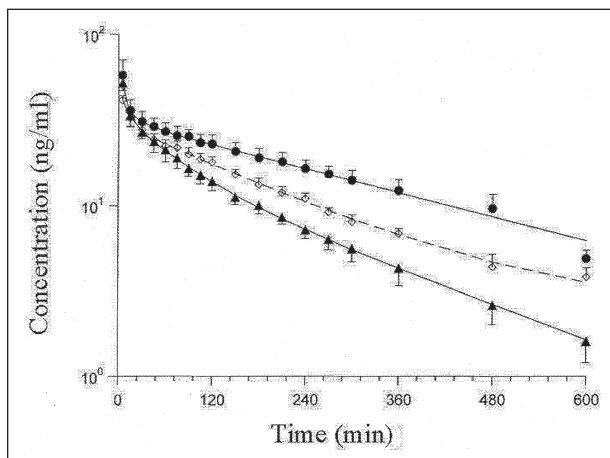


Figure 2—Mean  $\pm$  SD serum concentrations of trimethoprim in mules (solid circle), horses (open diamond), and donkeys (solid triangle) after IV administration of sulfamethoxazole at a rate of 12.5 mg/kg. Time 0 = Time of administration.

Table 1—Pharmacokinetic values for horses, donkeys, and mules after IV administration of a bolus of sulfamethoxazole (12.5 mg/kg) and trimethoprim (2.5 mg/kg)

Variable	Horses (n = 3)			Donkeys (n = 5)			Mules (n = 5)		
	Range	Mean $\pm$ SD	Median	Range	Mean $\pm$ SD	Median	Range	Mean $\pm$ SD	Median
<b>Sulfamethoxazole</b>									
AUC ( $\mu\text{g}/[\text{ml}\cdot\text{min}]$ )	2.2–2.4	2.3 $\pm$ 0.10	2.4 <sup>a</sup>	1.4–1.8	1.6 $\pm$ 0.15	1.6 <sup>b</sup>	2.5–4.7	3.6 $\pm$ 0.90	3.8 <sup>c</sup>
MRT (min)	222–240	234 $\pm$ 6	234 <sup>a</sup>	138–198	162 $\pm$ 24	150 <sup>b</sup>	252–456	354 $\pm$ 78	372 <sup>c</sup>
$\text{Vd}_{ss}$ (ml/kg)	278–316	301 $\pm$ 20	308	272–400	335 $\pm$ 46	337	240–487	337 $\pm$ 94	308
$\text{Cl}_T$ (ml/kg/min)	1.44–1.57	1.5 $\pm$ 0.1	1.46 <sup>a</sup>	1.99–2.42	2.2 $\pm$ 0.2	2.19 <sup>b</sup>	0.7–1.4	1.0 $\pm$ 0.3	0.93 <sup>c</sup>
<b>Trimethoprim</b>									
AUC ( $\mu\text{g}/[\text{ml}\cdot\text{min}]$ )	0.03–0.04	0.04 $\pm$ 0.005	0.03 <sup>a</sup>	0.02–0.05	0.030 $\pm$ 0.01	0.03 <sup>a</sup>	0.04–0.05	0.04 $\pm$ 0.003	0.05 <sup>a</sup>
MRT (min)	84–96	90 $\pm$ 6	90	42–114	60 $\pm$ 30	48	66–120	84 $\pm$ 24	84
$\text{Vd}_{ss}$ (ml/kg)	1,669–2,031	1,819 $\pm$ 189	1,756 <sup>a</sup>	1,160–1,673	1,426 $\pm$ 209	1,387 <sup>a</sup>	948–1,818	1,351 $\pm$ 358	1,296 <sup>b</sup>
$\text{Cl}_T$ (ml/kg/min)	17.1–22.9	20.4 $\pm$ 3.0	21.2 <sup>a</sup>	15.0–39.0	28.0 $\pm$ 9.0	25.8 <sup>a</sup>	14.3–17.2	15.7 $\pm$ 1.1	15.6 <sup>b</sup>

<sup>a,b,c</sup>Within a row, values with different superscript letters differ significantly ( $P < 0.05$ ).

AUC = Area under the concentration-versus-time curve as determined by use of the trapezoidal method. MRT = Mean residence time.  $\text{Vd}_{ss}$  = Volume of distribution at a steady state.  $\text{Cl}_T$  = Total body clearance.

capacity for active tubular secretion of sulfamethoxazole than do horses or mules. However, the contribution of hepatic metabolism to clearance must also be considered. We reported elsewhere<sup>14,15</sup> that donkeys metabolize several drugs more rapidly than do horses and mules. Hepatic metabolism of sulfamethoxazole in mules and horses may be slower than in donkeys. It is interesting that in previous pharmacokinetic studies, clearance of hepatically metabolized drugs in mules was, as would be predicted, between the values for donkeys and horses.

A significant difference was not detected in  $V_{d_{ss}}$  for sulfamethoxazole among horses, donkeys, and mules. Approximately 60% of sulfamethoxazole is bound to protein in people.<sup>16</sup> Although not measured, our results suggest that protein binding of sulfamethoxazole is similar in horses, mules, and donkeys.

Several significant differences existed among pharmacokinetic variables calculated for trimethoprim in horses, donkeys, and mules. The  $V_{d_{ss}}$  for trimethoprim in horses was significantly greater than in donkeys or mules, suggesting that the degree of serum protein binding of trimethoprim in horses may be less than that in donkeys or mules. Similar to the situation for sulfamethoxazole,  $Cl_T$  for trimethoprim was slower in mules than in donkeys or horses. Trimethoprim elimination depends on renal and hepatic mechanisms. Naturally, it would be expected that renal tubular secretion or hepatic metabolism of trimethoprim is slower in mules than in donkeys or horses.

Recommended intervals for IV administration of trimethoprim-sulfonamide combinations in horses range from 8 to 24 hours.<sup>1</sup> Because serum concentrations of trimethoprim and sulfamethoxazole decreased more rapidly in donkeys than in mules or horses, the appropriateness of a 24-hour dosing interval in donkeys is questionable. Mean residence time can be considered similar to elimination half-life in terms of biological relevance. The advantage when MRT and AUC are used is believed to be the independence of the specific kinetic structure of the linear kinetic system considered.<sup>17</sup> For mules, the low  $Cl_T$  and long MRT suggested that a 12- or 24-hour dosing interval may be appropriate. However, additional studies that include multiple dosing intervals and determination of tissue concentrations are necessary to determine the optimum dosing interval for donkeys and mules.

Finally, clinicians must consider the antibacterial effects of the drug combination. Although each drug alone is bacteriostatic, trimethoprim-sulfamethoxazole in combination is considered bactericidal. There is an optimal ratio of the concentrations of the 2 agents for synergistic bactericidal activity. Although this ratio varies among bacteria, the most effective ratio for the greatest number of microorganisms is 1 part trimethoprim to 20 parts sulfamethoxazole.<sup>18</sup> For horses, mules, and donkeys, a ratio of 1:20 was evident within the first 15 minutes after administration, but by 2 hours after administration, the ratio decreased to 1:63, 1:62, and 1:66 for mules, horses, and donkeys, respectively. The ratio did not approach 1:20 for the duration of the study period. Analysis of these results, in addition to the pharmacokinetic results, suggests that a dosing

interval for IV administration of trimethoprim-sulfamethoxazole that is more frequent than every 24 hours may be necessary in donkeys, mules, and horses.

<sup>a</sup>Sulfamethoxazole USP concentrate for injection, Gensia Laboratories LTD, Irvine, Calif.

<sup>b</sup>Trimethoprim USP concentrate for injection, Gensia Laboratories LTD, Irvine, Calif.

<sup>c</sup>Angiotech, Becton-Dickinson, Sandy, Utah.

<sup>d</sup>Acetic acid, Mallinckrodt Baker, Phillipsburg, NJ.

<sup>e</sup>XRDA-F515, United Chemical Technologies, Bristol, Pa.

<sup>f</sup>Potassium phosphate monobasic, EM Science, Gibbstown, NJ.

<sup>g</sup>HPLC grade hexane, EM Science, Gibbstown, NJ.

<sup>h</sup>HPLC grade dichloromethane, EM Science, Gibbstown, NJ.

<sup>i</sup>Isopropanol, reagent grade, EM Science, Gibbstown, NJ.

<sup>j</sup>Ammonium hydroxide, EM Science, Gibbstown, NJ.

<sup>k</sup>HPLC grade acetonitrile, EM Science, Gibbstown, NJ.

<sup>l</sup>Sulfachloropyridazine, Sigma Chemical Co, St Louis, Mo.

<sup>m</sup>HPLC grade methanol, EM Science, Gibbstown, NJ.

<sup>n</sup>Antipyrine, Sigma Chemical Co, St Louis, Mo.

<sup>o</sup>Trimethoprim, Sigma Chemical Co, St Louis, Mo.

<sup>p</sup>Sulfamethoxazole, Sigma Chemical Co, St Louis, Mo.

<sup>q</sup>Model 1090, Agilent Technologies, Palo Alto, Calif.

<sup>r</sup>Column No. 12459, Alltech Associates, Deerfield, Ill.

<sup>s</sup>Column No. 288145, Alltech Associates, Deerfield, Ill.

<sup>t</sup>PK Analyst, MicroMath, Salt Lake City, Utah.

## References

1. Plumb DC. Drug monographs—sulfa/trimethoprim. In: *Veterinary drug handbook*. 3rd ed. Ames, Iowa: Iowa State University Press, 1999:586–589.
2. Van Duijkeren E, Vulto A, Sloet Van Oldruitenborgh-Oosterbaan M, et al. Pharmacokinetics of trimethoprim/sulphachloropyridazine in horses after oral, nasogastric and intravenous administration. *J Vet Pharmacol Ther* 1995;18:47–53.
3. Horspool L, McKellar Q. Disposition of oxytetracycline in horses, ponies and donkeys after intravenous administration. *Equine Vet J* 1990;22:284–285.
4. Horspool L, Sarasola P, McKellar Q. Disposition of ampicillin sodium in horses, ponies and donkeys after intravenous administration. *Equine Vet J* 1992;suppl 11:59–61.
5. Welfare R, Mealey K, Matthews N, et al. Pharmacokinetics of gentamicin in donkeys. *J Vet Pharmacol Ther* 1996;19:167–169.
6. Lavy E, Ziv G, Glickman A. Intravenous disposition kinetics, oral and intramuscular bioavailability and urinary excretion of norfloxacin nicotinate in donkeys. *J Vet Pharmacol Ther* 1995;18:101–107.
7. Horspool L, McKellar Q. Disposition of penicillin G sodium following intravenous and oral administration to equidae. *Br Vet J* 1995;151:401–412.
8. Horspool L, Taylor D, McKellar Q. Plasma disposition of amikacin and interactions with gastrointestinal microflora in equidae following intravenous and oral administration. *J Vet Pharmacol Ther* 1994;17:291–298.
9. Saini N, Chaudhary R, Rampal S, et al. Pharmacokinetics and dosage regimen of sulphadimidine in donkeys following intravenous administration. *Indian J Anim Sci* 1997;67:406–407.
10. Brown M, McCartney J, Gronwall R, et al. Pharmacokinetics of trimethoprim-sulphamethoxazole in two-day-old foals after a single intravenous injection. *Equine Vet J* 1990;22:51–53.
11. Van Duijkeren E, Vulto A, Sloet Van Oldruitenborgh-Oosterbaan M, et al. A comparative study of the pharmacokinetics of intravenous and oral trimethoprim/sulfadiazine formulations in the horse. *J Vet Pharmacol Ther* 1994;17:440–446.
12. Oukessou M, Alsoussi I. Pharmacokinetics of sulfonamides and trimethoprim in the donkey (*Equus asinus*). *J Vet Med Assoc* 1998;45:191–198.
13. Brown MP, Gronwall R, Castro L. Pharmacokinetics and body fluid and endometrial concentrations of trimethoprim-sulfamethoxazole in mares. *Am J Vet Res* 1998;49:918–922.
14. Matthews NS, Peck KE, Mealey KL, et al. Pharmacokinetics and cardiopulmonary effects of guaifenesin in donkeys. *J Vet Pharmacol Ther* 1997;20:442–446.

15. Mealey KL, Matthews NS, Peck KE, et al. Comparative pharmacokinetics of phenylbutazone and its metabolite oxyphenbutazone in clinically normal horses and donkeys. *Am J Vet Res* 1997;58:53–55.

16. Benet LZ, Oie S, Schwartz JB. Design and optimization of dosage regimens; pharmacokinetic data (appendix II). In: Hardman JG, Limbird LE, eds. *The pharmacological basis of therapeutics*. New York: McGraw-Hill Book Co, 1996;1707–1792.

17. Veng-Pederson P. Mean time parameters in pharmacokinetics: definition, computation and clinical implications (part II). *Clin Pharmacokinet* 1989;17:424–440.

18. Mandell GI, Petri WA. Sulfonamides, trimethoprim-sulfamethoxazole, quinolones, and agents for urinary tract infections. In: Hardman JG, Limbird LE, eds. *The pharmacological basis of therapeutics*. New York: McGraw-Hill Book Co, 1996;1057–1072.