Received: 19 February 2020 | Revised: 25 October 2020 | Accepted: 6 November 2020
DOI: 10.1111/jvp.12930

ORIGINAL ARTICLE

JOURNAL OF Veterinary Pharmacology and Therapeutics WILEY

Pharmacokinetics of a sulfadiazine and trimethoprim suspension in neonatal foals

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Funding information
Aurora Pharmaceutical, Inc., Grant/Award Number: 2164151

Abstract

There is limited investigation of neonatal foal pharmacokinetic parameters for the antimicrobial combination of sulfadiazine (SDZ) and trimethoprim (TMP). Neonatal pharmacokinetic investigation of the sulfadiazine–trimethoprim combination is required to ensure safe and effective utilization in this population. The purpose of this study was to determine the pharmacokinetics of sulfadiazine–trimethoprim in five healthy neonatal foals with oral administration at 24 mg/kg every 12 hr (hrs) for 10 days. Blood samples were collected at serial time points at approximately 72 hr of age (steady-state) and at days 5 and 10 to monitor the influence of age within the neonatal period. Pharmacokinetic parameters were determined using a one-compartment model analysis, and mean ± *SD* was calculated. C_{max} was 37.8 ± 13.4 µg/ml (SDZ) and 1.92 ± 0.25 µg/ml (TMP). T_{max} was 1.4 ± 0.6 hr (SDZ) and 1.4 ± 0.4 hr (TMP). C_{min} for SDZ and TMP was 16.84 ± 8.46 µg/ml and 0.46 ± 0.24 µg/ml, respectively. Elimination half-life was 10.8 ± 6.1 hr (SDZ) and 6.5 ± 2 hr (TMP). $AUC_{0\rightarrow\infty}$ was 667 ± 424 µg × hr/ml (SDZ) and 21.1 ± 5.3 µg × hr/ml (TMP). Foals remained healthy, and the plasma concentration of sulfadiazine–trimethoprim reached levels above $MIC_{(90)}$ for *Streptococcus equi* ssp. (SDZ/TMP): 9.5/0.5 µg/ml).

KEYWORDS
foal, horse, neonatal, pharmacokinetics, sulfadiazine, trimethoprim

1 | INTRODUCTION

Neonates have known differences compared with adults in absorption, distribution, metabolism, and excretion of drugs, which may lead to inappropriate dosing and increased adverse effects if neonatal pharmacokinetic values are not established (O'Hara et al., 2015). Many drugs have higher oral bioavailability and altered pharmacokinetic profiles in foals (Baggot, 1994; Baggot & Short, 1984). Increased total body water of neonatal foals (Fielding et al., 2011) and decreased body fat content (Caprile & Short, 1987; Webb & Weaver, 1979) alter drug disposition in this population. Additionally, the neonatal pharmacokinetic profiles of drugs alter rapidly as the foal matures (Adamson et al., 1991; Swain et al., 2015). Consequently, it is commonly recommended to reduce the dose and dosing frequency to improve the safety when these drugs are used in neonates. Despite the established differences in neonates, many of the current dosage of drugs in neonatal medicine are extrapolated from adult data.

Pharmacokinetic parameters for the combination of sulfadiazine (SDZ) and trimethoprim (TMP) in neonatal foals have been limited to a study investigating a lower dose with an intravenous route of administration (Brown, et al., 1990). The spectrum of activity is moderate to broad affecting gram-positive, gram-negative, and many protozoal organisms (Reviere & Papich, 2018). Sulfadiazine–trimethoprim is used in foals to prolong the course of antimicrobial treatment following initial stabilization with beta-lactam–aminoglycoside combinations or cephalosporins or for less serious infections involving the urinary tract or umbilical infections (Magdesian, 2017). Additionally, potentiated sulfonamides have activity against *Pneumocystis carinii*, a yeast-like fungal infection associated with pneumonia in immunocompromised foals (Magdesian, 2017) and against *Streptococcus spp.* for susceptible isolates.

A commercially available formulation of sulfadiazine–trimethoprim has recently been FDA approved for use in adult horses (McClure et al., 2015; Aurora Pharmaceutical, LLC). Data from a pharmacokinetic study performed on adult horses and a mean inhibitory concentration (MIC_{90}) for *Streptococcus equi* ssp. *zooepidemicus* were utilized to identify the recommended dosage regimen (24 mg/kg, orally, q12 hr) for the treatment of lower respiratory tract infections (McClure et al., 2015). Accurate dosage regimens for neonatal foals are indicated to ensure that plasma concentrations are above MIC for common isolates in equine neonates, but minimize the risk for the development of enterocolitis secondary to antimicrobial administration.

The aim of this prospective study was to determine the pharmacokinetics of the sulfadiazine–trimethoprim suspension in healthy foals during the neonatal period (beginning 24 to 36 hr of age) when administered as serial oral doses (24 mg/kg, q12 hr). The objective was to evaluate pharmacokinetic profiles in neonatal foals at steady-state. A second objective was to determine whether age and development within the neonatal period had an influence on a plasma concentration. Additionally, the foals were monitored for the development of complications. Our hypothesis was that neonatal foals would have different pharmacokinetics for sulfadiazine–trimethoprim compared with adult horses, which would require different dose recommendations (in mg/kg) for safe and effective treatment in this population.

2 | MATERIALS AND METHODS

2.1 | Animals and housing

Six neonatal Quarter Horse colts were studied. The foals were deemed healthy based on physical examination and laboratory data. They were evaluated for adequate passive transfer (IgG concentration > 800 g/dl) at 12–18 hr of age using a commercial immunoassay (SNAP Foal IgG Test; IDEXX). Each foal had an initial complete blood count (CBC, HemaTrue® Veterinary Hematology Analyzer; Heska) and serum biochemistry analysis (SBA, DRI-CHEM® 4000 Chemistry Analyzer; Heska) performed. The foal and dam pairs were housed in box stalls with no food, water, or nursing restrictions. Each foal received a physical examination once daily. Body weight was estimated by measuring heart girth (G) prior to dosage calculation and again at day 5 to allow for dose adjustment if indicated (Rodrigez et al., 2007; power 2 formula: weight estimate (kg) = G^3 (m) × 90). An Institutional Animal Care and Use Committee approved the study.

2.2 | Study design and sample collection

Sulfadiazine–trimethoprim suspension (333 mg SDZ/67 mg TMP) was administered through the oral route at a dose of 24 mg/kg (Aurora Pharmaceutical, LLC). Calibrated dose syringes were used to ensure accurate oral administration of the antibiotic suspension. The foals received five doses of sulfadiazine–trimethoprim suspension at 12-hr. intervals beginning at 24 to 36 hr of age. At 72–84 hr of age, a commercial 16-G, 3.25-inch polyurethane catheter was placed in one jugular vein for sequential blood collection. The catheters remained in place for the 12-hr. study period and then removed. Blood waste (12 ml volume) was removed prior to collecting every blood sample. This waste sample was returned to the foal following each sample collection, and the catheter was then flushed with heparinized saline (6 ml volume). Venous blood samples (3.0 ml volume collected into a 12 ml syringe) were collected immediately prior to the 5th antibiotic dose and then at 0.5, 1, 2, 4, 6, 8, 10, and 12 hr after the fifth dose. All blood samples were transferred into evacuated blood collection tubes containing heparin and centrifuged (LWS 815 Centrifuge; LW Scientific, Lawrenceville, GA) at 600 *g* for 10 min. Plasma was then pipetted into plastic cryovials, subdivided in duplicate, and stored frozen in liquid nitrogen until shipment for assay.

Following this study period, the foals continued q12-hr. treatments for a total treatment period of 10 days. At days 5 and 10 of the treatment, the foals had additional samples drawn to assess drug concentration at the estimated trough time (12 hr after last administration). CBC and SBA were repeated at the end of the treatment course on day 10.

2.3 | Determination of plasma sulfadiazine and trimethoprim concentrations

2.3.1 | Plasma sample analysis

Samples were shipped on dry ice and stored at −80°C until assayed. A validated liquid chromatography–mass spectrometry (LC-MS) assay modified from a previously reported method (Patyra et al., 2018) was used for the determination of trimethoprim/sulfadiazine plasma concentrations at each time point. Samples were chromatographically separated using a Shimadzu Prominence HPLC System with a HTC-PAL Autosampler fitted with a Waters SunFire C18 column (4.6 × 50 mm). The mobile phases consisted of Milli-Q water with 0.1% formic acid (solvent A) and acetonitrile (B) and starting conditions of 95:5 (A:B) that was held for 1 min prior to a linear gradient resulting in 5:95 (A:B) over a 0.5-min period and maintaining this composition for 1 min prior to re-establishing initial conditions over a 1-min period. The flow rate was 1.0 ml/min, and 10 μl sample volumes was injected with a 5 μl injection loop. Samples were detected using an AB Sciex 3200 Q-Trap triple quadrupole mass spectrometer operating in positive ion mode with unit resolution in Q1 and Q3, a source temperature of 550°C, and ion spray voltage of 5,000 V. Multiple reaction monitoring was used to measure sulfadiazine (251.1 *m/z* →108.1 *m/z*, 251.1 *m/z* →156.1 *m/z*), trimethoprim (291.3 *m/z* →230.0 *m/z*, 291.3 *m/z* →261.1 *m/z*), and the internal standard (IS) naringenin (273.1 *m/z* →153.0 *m/z*) with mass spectrometer parameters optimized for each transition. Standards

TABLE 1 Multi-dose steady-state pharmacokinetic parameters calculated for sulfadiazine (SDZ) using a one-compartment model

Parameter	Unit	F1	F2	F3	F4	F5	Mean ± *SD*
C_{max}	µg/ml	33.9	21.1	35.4	58.1	40.6	37.8 ± 13.4
C_{min}	µg/ml	11.6	7.7	13.3	26.8	24.8	16.8 ± 8.5
T_{max}	hr	0.9	2.3	0.9	1.17	1.39	1.4 ± 0.6
$AUC_{0\rightarrow\infty}$	µg•hr/ml	475	243	460	830	1,325	667 ± 424
k_{abs}	hr^{-1}	4.46	1.12	4.22	3.28	3.37	3.29 ± 1.32
k_{el}	hr^{-1}	0.077	0.112	0.083	0.076	0.032	0.076 ± 0.029
$T_{1/2}$	hr	9.05	6.17	8.34	9.06	21.61	10.8 ± 6.1
V_D/F	L/kg	0.55	0.73	0.52	0.32	0.47	0.52 ± 0.15

Note: The foals at 24-36 hr of age were orally administered sulfadiazine/trimethoprim suspension (24 mg/kg q 12 hr).

Abbreviations: $AUC_{0\rightarrow\infty}$, area under the curve from time zero to infinity; C_{max}, maximum concentration; C_{min}, minimum concentration; k_{abs}, first-order absorption rate constant; k_{el} elimination rate constant from the central compartment; $t_{1/2}$, elimination half-life; T_{max}, time of maximum concentration; V_D/F, apparent volume of distribution after oral administration.

and quality control (QC) samples were generated by adding 10 µl of 10X concentrated drug prepared in Milli-Q water to 90 µl of control horse plasma. Preparation of unknown, standard, and QC samples involved adding 10 µl of 1,000 ng/ml IS prepared in Milli-Q water to 100 µl of sample followed by protein precipitation by addition of 200 µl acetonitrile, vortex mixing for 5 min followed by centrifugation at 9,500 *g* for 5 min and collection of supernatant for the analysis.

2.3.2 | Pharmacokinetic analysis

An analysis was performed on the plasma sulfadiazine and trimethoprim concentration versus time data using Phoenix® WinNonlin (Phoenix 64, Build 8.0.0.3176). Calculated pharmacokinetic parameters using a one-compartment model for the concentration data included maximum concentration (C_{max}), minimum concentration (C_{min}), time to maximum concentration (T_{max}), area under the curve from time 0 to infinity ($AUC_{0\rightarrow\infty}$), absorption rate constant (first order; k_{abs}), elimination rate constant from the central compartment k_{el} (hr^{-1}), elimination half-life ($t_{1/2}$), and apparent volume of distribution after oral administration (volume/kg; V_D/F).

The pharmacokinetic parameters calculated following the 5th dose were used to simulate time versus. concentration data using the equation: C = (FD/V)(ka/(ka − kel)[exp(−kel(t)] − exp[−ka(t) that describes the data with a one-compartment model with first-order absorption. Data for subsequent doses were calculated the same way multiplied by the accumulation factor as determined by AF = 1 − (exp(−n × kel × Tau))/1 − (exp(kel × Tau)) for each dosing interval which collapses to AF = 1/1 − (exp(kel × Tau)) at steady-state.

2.4 | Statistical analysis

The clinicopathological data were analyzed using a nonparametric method for paired data at time points of 12–18 hr of age and compared with day 10 of receiving the suspension, at the completion of the study. Wilcoxon's matched-pairs signed-rank test was used to compare all continuous clincopathological data between the drug groups. A non-parametric repeated measures Friedman's test was used to compare C_{min} (trough levels) at the time points of drug administration for Time 0, Time 72 hr, and at days 5 and 10 for sulfadiazine and trimethoprim. A post hoc Dunn's test was used to obtain adjusted *p*-value for multiple comparisons. GraphPad Prism v8.4.0 for Windows (GraphPad Software; San Diego, California, USA) was used for all statistical analysis. A *p*-value of .05 was used to determine the statistical significance.

3 | RESULTS

3.1 | Clinical and clinicopathological findings

One foal had an elevated AST of 724 mg/dl at the end of the study. Otherwise, the physical examination findings were within reference values for the duration of the study for each foal. No adverse reactions were observed throughout the study period. Mean body weight for the six foals at 24–36 hr of age and at day 5 of age was 56.8 ± 7.5 kg and 70.0 ± 7.4 kg, respectively.

3.2 | Accuracy and Precision for LC-MS analysis of Sulfadiazine and Trimethoprim in equine plasma

Assay performance for sulfadiazine was linear from 100 to 100,000 ng/ml, and analysis of QC samples at 250, 2,500, and 25,000 ng/ml showed precision and accuracy (%RSD) of 90.1% ± 4.4%. For trimethoprim, assay performance was linear from 10 to 5,000 ng/ml and analysis of QC samples at 25, 250 and 2,500 ng/ml showed precision and accuracy (%RSD) of 94.0% ± 4.8%. The accuracy is reported and calculated as

TABLE 2 Multi-dose steady-state pharmacokinetic parameters calculated for trimethoprim (TMP) using a one-compartment model

Parameter	Unit	F1	F2	F3	F4	F5	Mean ± *SD*
C_{max}	μg/ml	1.98	2.11	1.71	2.20	1.61	1.92 ± 0.25
C_{min}	μg/ml	0.44	0.62	0.38	0.75	0.12	0.46 ± 0.24
T_{max}	hr	1.2	1.9	1.2	0.8	1.8	1.4 ± 0.4
$AUC_{0 \to \infty}$	μg•hr/ml	22.4	19.5	24.7	25.9	12.7	21.1 ± 5.3
k_{abs}	hr^{-1}	2.86	1.33	3.10	4.96	1.33	3.29 ± 1.32
k_{el}	hr^{-1}	0.100	0.141	0.076	0.091	0.172	0.116 ± 0.039
Half-Life	hr	6.95	4.93	9.08	7.58	4.04	6.5 ± 2.0
V_D/F	L/kg	1.79	1.46	2.13	1.69	1.83	1.78 ± 0.24

Note: The foals at 24–36 hr of age were orally administered sulfadiazine/trimethoprim suspension (24 mg/kg q 12 hr).

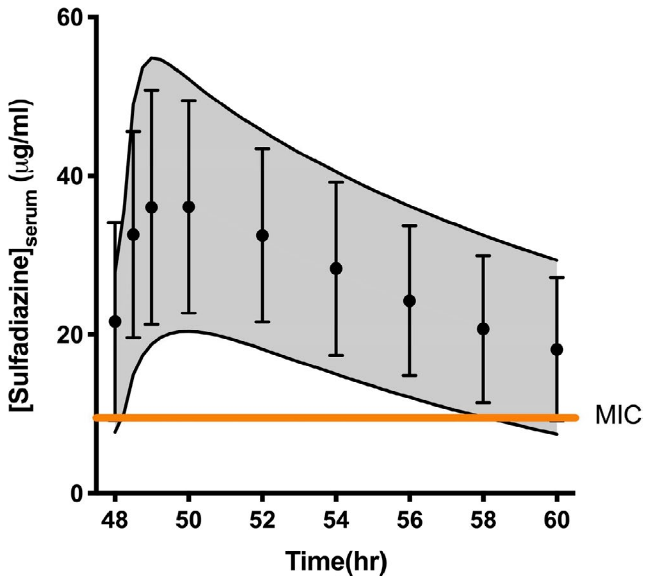

FIGURE 1 Sulfadiazine concentration over time (hr) for the fifth dosing interval. The mean inhibitory concentration (MIC_{90}) is 9.5 μg/ml for sulfadiazine as the recommended break point for *Streptococcus equi* ssp. *zooepidemicus*

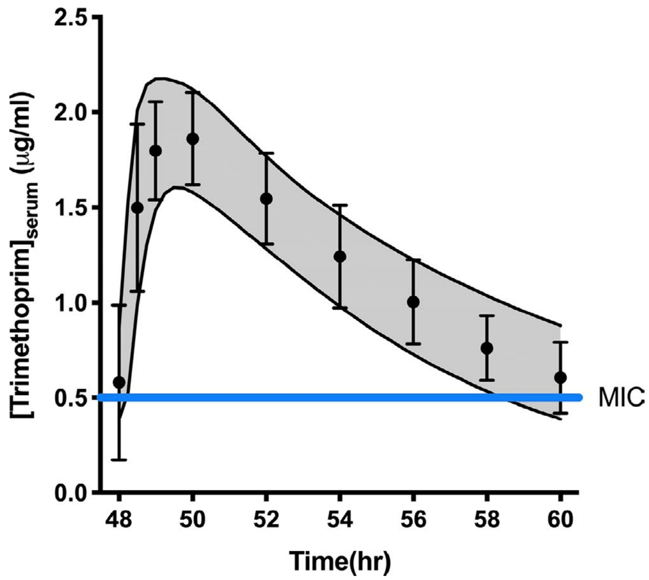

FIGURE 2 Trimethoprim concentration over time (hr) for the fifth dosing interval. The mean inhibitory concentration (MIC_{90}) is 0.5 μg/ml for trimethoprim as the recommended break point for *Streptococcus equi* ssp. *zooepidemicus*

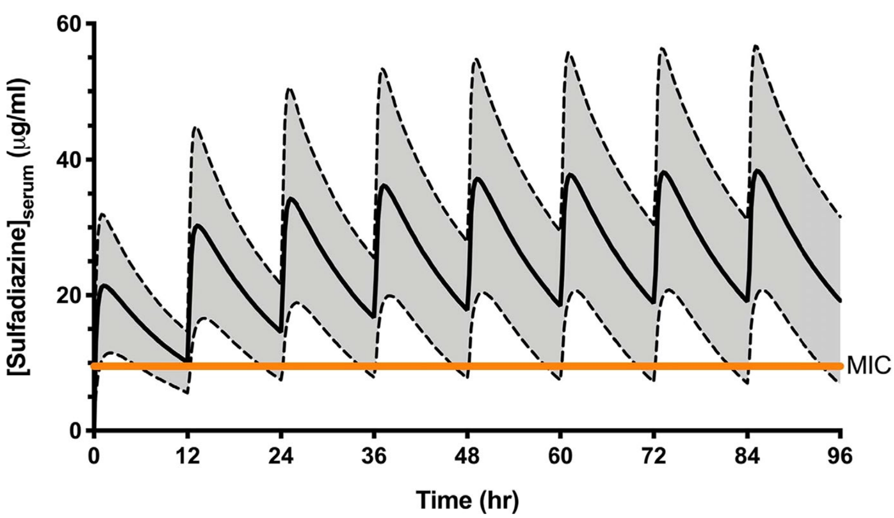

FIGURE 3 Sulfadiazine multi-dose simulation based on pharmacokinetic parameters obtained for individual foals at steady-state. The shaded area represents the 95% confidence interval based on mean values for five foals. The mean inhibitory concentration (MIC_{90}) is 9.5 μg/ml for sulfadiazine as the recommended break point for *Streptococcus equi* ssp. *zooepidemicus*

TABLE 3 Plasma concentrations for sulfadiazine (SDZ) and trimethoprim (TMP) at multi-dose trough levels. The foals at ages 5 and 10 days received orally administered SDZ/TMP suspension (24 mg/kg q 12 hr. for 10 days)

Parameter	Day	Unit	F1	F2	F3	F4	F5	Mean ± *SD*
SDZ C_{min}	5	μg/ml	22.3	3.88	7.25	21.6	31.0	17.2 ± 11.32
SDZ C_{min}	10	μg/ml	4.46	15.6	13.0	8.97	9.6	10.3 ± 4.23
TMP C_{min}	5	μg/ml	1.84	0.43	0.73	0.9	0.77	0.93 ± 0.54
TMP C_{min}	10	μg/ml	0.43	1.82	1.53	0.46	0.39	0.93 ± 0.69

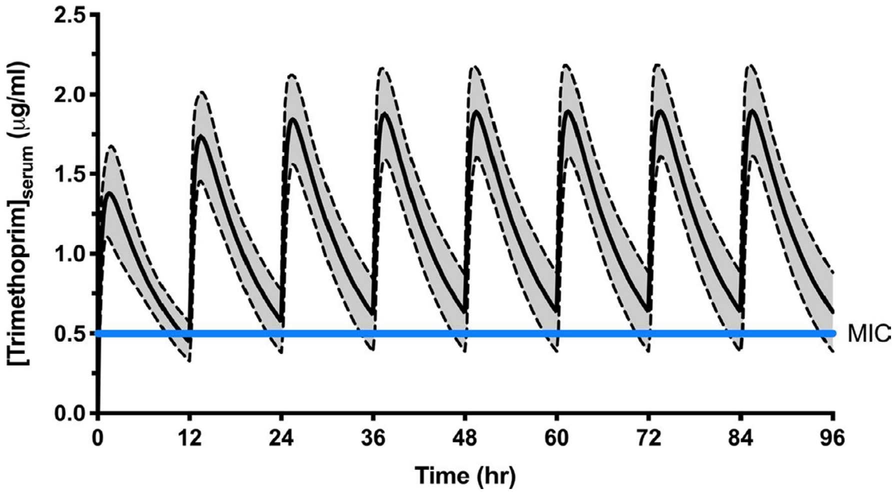

FIGURE 4 Trimethoprim multi-dose simulation based on pharmacokinetic parameters obtained for individual foals at steady-state. The shaded area represents the 95% confidence interval based on mean values for five foals. The mean inhibitory concentration (MIC_{90}) is 0.5 μg/ml for trimethoprim as the recommended break point for *Streptococcus equi* ssp. *zooepidemicus*

follows: Accuracy (%) = (1 − (abs(Theoretical − Measured)/Theoretical)) × 100. The precision is expressed as the percentage of calculated values utilizing the standard deviation of the accuracy measure. Precision is calculated as follows: Precision (RSD) = (Standard Deviation Calculated Values/mean calculated value) × 100. These are presented as accuracy ± precision (%CV). Theoretical values are the actual amount of standard added to the tube, and the measured values are what was measured in that QC sample.

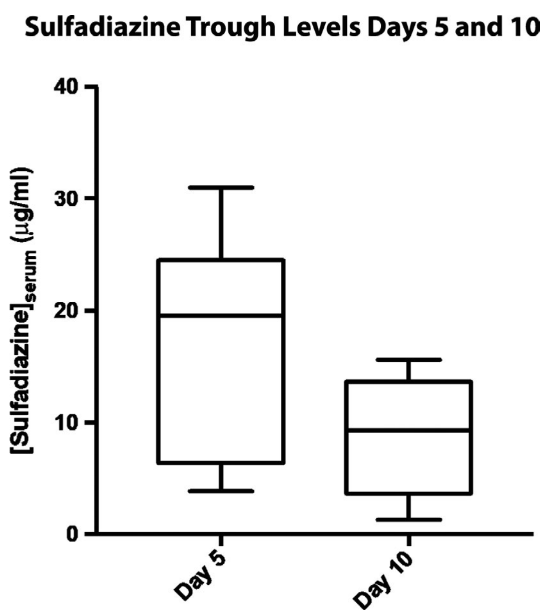

FIGURE 5 Sulfadiazine C_{min} (trough) plasma concentration at days 5 and 10

3.3 | Plasma concentrations of sulfadiazine and trimethoprim following oral administration

The pharmacokinetic parameters for the oral route of administration for sulfadiazine and trimethoprim are summarized in Tables 1 and 2. Multi-dose simulation of sulfadiazine and trimethoprim concentrations is shown in Figures 3 and 4, respectively, based on the pharmacokinetic data obtained at the estimated steady-state after the 5th dose (Rowland & Tozer, 2010). Trough concentrations at days 5 and 10 of the treatment period are depicted in Table 3. The

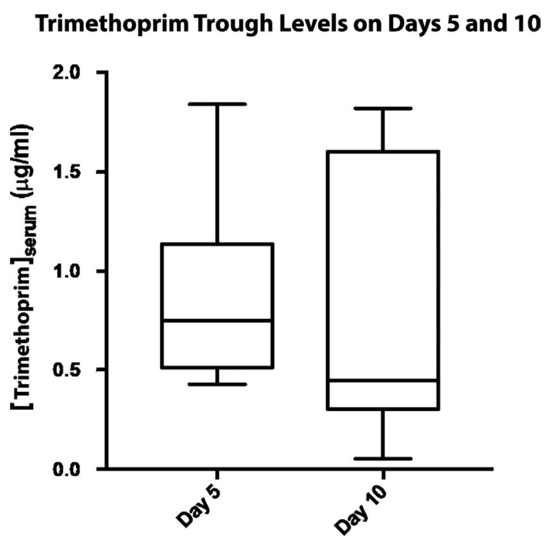

FIGURE 6 Trimethoprim C_{min} (trough) plasma concentration at days 5 and 10

TABLE 4 Clinicopathological values that significantly ($p < .05$) changed with time for six foals

	Units	<24 hr of age	Mean	After 10 days of treatment	Mean
Blood urea nitrogen (BUN)	mg/dl	(12.1–25.8 ± 4.904)	18.3	(5–7.2 ± 1.111)	5.717
Total bilirubin (Tbili)	mg/dl	(2–3.9 ± 0.6998)	2.78	(1.2–1.6 ± 0.1517)	1.45
Aspartate aminotransferase (AST)	U/L	(132–203 ± 26.72)	165.2	(264–724 ± 173.1)	469.7
Red blood cells (RBC)	×10/μl	(9.33–10.54 ± 0.4563)	9.89	(7.64–9.38 ± 0.6689)	8.612
Hematocrit (HCT)	%	(33.2–39.9 ± 2.726)	37.02	(27–33.7 ± 2.461)	31
Hemoglobin (Hb)	g/dl	(12.9–15.1 ± 0.8687)	14.07	(10.4–13 ± 0.9975)	12.05

Wilcoxon matched-pairs signed rank test (Appendix S1).

concentration data from one foal did not fit the one-compartment model. This foal was excluded from the pharmacokinetic analysis, though was still included for clinical and clinicopathological comparison. No statistical significance was identified on analysis of the pharmacokinetic data (Supplemental Materials).

4 | DISCUSSION

The steady-state mean ± *SD* C_{max} after oral administration of the fifth dose of sulfadiazine and trimethoprim was 37.8 ± 13.4 μg/ml and 1.92 ± 0.25 μg/ml, respectively. These peak or maximal plasma concentrations are elevated compared with concentrations described in adult horses (12.1–22.4 μg/ml SDZ and 0.78–1.31 μg/ml TMP) after similar oral dose administration (Gustafsson, et al., 1999; US FDA. EQ UISUL-SDT, 2014; Van Duijkeren, Vulto, Sloet van Oldruitenborgh-Oosterbaan, et al., 1994).

The mean ± *SD* C_{min} for sulfadiazine and trimethoprim was 16.84 ± 8.46 μg/ml and 0.46 ± 0.24 μg/ml, respectively. The C_{max} and C_{min} concentrations varied among individual foals. For most time points, plasma concentrations at steady-state remained at or above MIC_{90} of 9.5 μg/ml sulfadiazine and 0.5 μg/ml for trimethoprim (Figures 1-4), the recommended break point for *Streptococcus equi* ssp. *zooepidemicus* by some authors (Adamson, et al., 1985). At various time points, each foal had concentrations below the level of 9.5 μg/ml at their day 5 and day 10 trough samples for sulfadiazine and below the level of 0.5 μg/ml for trimethoprim (Figures 5 and 6). This observation of variability in individual foals should be taken into consideration prior to dose reduction, despite the elevated C_{max} compared with adult horses.

Tissue concentrations of sulfadiazine and trimethoprim were not measured in this study; however, studies in adult horses have reported plasma concentrations to be elevated compared with maximal tissue fluid concentration (Van Duijkeren, et al., 2002). This relates to protein binding of both the sulfadiazine and the trimethoprim. In infected tissues, there are changes in the permeability of the diffusion barrier between blood and tissue chamber fluid and the protein-bound drug concentrations would be expected to increase locally as it has been demonstrated in other species (Clarke et al., 1989).

The mean ± *SD* time to C_{max} (T_{max}) foals was 1.4 ± 0.6 hr for sulfadiazine and 1.4 ± 0.4 hr for trimethoprim compared with mean T_{max} in adult horses 1.7 hr and 3.5 hr, respectively. Mean trimethoprim concentrations were observed to rise to C_{max} faster in foals compared with adult horses after repeated doses (Gustafsson, et al., 1999), though this was not statistically assessed. The other pharmacokinetic parameters are comparable in foals to the adult horse parameters.

There was no significant accumulation of either sulfadiazine or trimethoprim observed in these foals. According to the initial elimination half-life, steady-state was reached. The multi-dose simulations estimate that C_{min} on days 5 and 10 will be the same once reaching steady-state. A comparison of the actual trough levels on days 5 and 10 reflects changes in the pharmacokinetics over time for the foals. The physiologic and anatomic changes in foals during the first days of life influence the C_{min} levels observed over time, suggesting that these dynamics altered individual steady-state levels.

Foals within this study did not demonstrate any adverse effects. All observed clinicopathological changes were expected maturational changes for foals during the early neonatal period compared with age-matched reference ranges (Axon & Palmer, 2008; Barton et al., 1995) with statistical significance identified between the two age groups outlined in Table 4 and Supplemental Data. The foal with the elevated AST at the end of the study was being managed with bandages for a contractual deformity, and the elevation was attributed to this condition. Potentiated sulfonamides have documented adverse effects in horses including changes in the intestinal microbiota (dysbiosis) causing diarrhea (Costa et al., 2015; Ensink, et al., 1996b; Gustafsson, et al., 1999; Magdesian, 2017). Reducing the dose of sulfadiazine–trimethoprim from the adult dose of 24 mg/kg may be recommended if there are regional concerns for gastrointestinal microbiota disturbances.

Future studies are warranted, including measurement of concentrations of sulfadiazine–trimethoprim following a reduced dosage protocol for this suspension, as well as a comparison of pharmacokinetics as the foal increases in age.

One limitation was that only male foals were available for this study; however, it was estimated that fillies and colts would have similar body composition and sex status would not bias the result. An additional limitation was that one foal was excluded from the one-compartment model analysis. He was still included for the clinical data analysis for the study period and remained healthy throughout.

5 | CONCLUSION

Data from the present study showed that the plasma concentration of sulfadiazine and trimethoprim reached levels above MIC_{90} for *Streptococcus equi* ssp. *zooepidemicus* (SDZ/TMP: 9.5/0.5 μg/ml) during the 10-day study period.

ACKNOWLEDGMENTS

This work was performed at Royal Vista Southwest, Purcell, OK. The authors thank Ryan Ferris, DVM, MS, DACT, for assisting with proposal development. We extend appreciation to the following individuals for technical and veterinary help: Ryan Coy, DVM, Renea Delhomme, DVM, Claire Freeman, DVM, Meghan Simpson, Christina Gosch, Sam Traficante, and Tori Rohwer. The funding was courtesy of Aurora Pharmaceutical, LLC.

CONFLICT OF INTEREST

This study was funded by Aurora Pharmaceuticals, LLC.

AUTHOR CONTRIBUTIONS

E.S-O contributed to study design, data collection and analysis, and manuscript preparation. P.M. and D.G. contributed to study design, data analysis, and manuscript preparation. All authors have read and approved the current manuscript.

ANIMAL WELFARE AND ETHICS STATEMENT

The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at Colorado State University, (IACUC #17-7232, approval date February 2018).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Swain O'Fallon E, McCue P, Rao S, Gustafson DL. Pharmacokinetics of a sulfadiazine and trimethoprim suspension in neonatal foals. *J Vet Pharmacol Therap*. 2020;00:1–8. https://doi.org/10.1111/jvp.12930