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Original Research

A Controlled Safety Study of Elevated Dosages of Trimethoprim Plus Sulfadiazine in Mature Horses

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ABSTRACT

A novel, proprietary, oral suspension of trimethoprim plus sulfadiazine (TMP/SDZ) had no serious adverse effects on clinical, laboratory, or pathologic parameters of mature horses when administered at up to five times the intended combined dosage of 24 mg/kg twice daily for 30 consecutive days. Loose feces was the most common observation that was likely related to TMP/SDZ treatment, and the incidence of loose feces was greater in groups treated with higher dosages of TMP/SDZ. However, all episodes were self-limiting, and no horses were treated for loose feces.

1. Introduction

Potentiated sulfonamides combine a sulfa drug with a diaminopyrimidine, exploiting the different but complementary modes of action of these drugs. Trimethoprim and sulfadiazine function as bacteriostatic antimicrobials by interfering with folate metabolism in bacterial cells. Sulfadiazine acts as a competitive inhibitor of the substrate para-aminobenzoic acid (PABA) of the bacterial enzyme dihydropteroate synthetase, which produces the essential precursor PABA. Trimethoprim acts downstream of sulfadiazine binding to dihydrofolate reductase and inhibiting the reduction of dihydrofolic acid to tetrahydrofolic acid. The two antimicrobials function synergistically to inhibit bacterial DNA synthesis, reducing the potential for the development of antimicrobial resistance to a greater extent than for either drug used alone. Potentiated sulfonamides have long been used in equine practice for broad-spectrum antibiotic therapy, particularly in the treatment of urinary and lower respiratory tract infections [1].

Antibiotic treatment can alter the gut flora of horses, potentially leading to acute colitis and diarrhea [2]. In horses, diarrhea has been the most common side effect of treatment with antimicrobials, including the potentiated sulfonamides [3,4]. However, the risk associated with potentiated sulfonamide treatment is considered low compared with that of other antibiotics [5,6]. One must weigh the advantages of oral dosing against the risk of inducing diarrhea [7,8], although parenteral treatment is not without some risk of alimentary disturbances.

Antibiotics that inhibit folate production may have prenatal effects in foals and are generally not recommended for pregnant mares [9]. Although no effects of sulfonamides on sperm quality have been documented, potential effects on hind leg agility have been reported in breeding stallions. Such effects may result in problems with sexual performance [10]. Neurologic effects on gait and agility were reported recently in a series of case studies [11] and should be considered before the use of potentiated sulfonamides in breeding stallions.

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Other side effects of potentiated sulfonamide treatment in horses are generally rare. An isolated case of anaphylaxis was reported in a Shetland pony [12], and hematopoietic effects have been reported sporadically in horses, as in other species [13,14]. Persons with known sensitivities to sulfa drugs should take precautions against contact when administering potentiated sulfonamides to animals.

Although paste formulations approved for horses are labeled for once-daily administration at 30 mg/kg body weight, pharmacokinetic data for the potentiated sulfonamides suggest that twice-daily dosing is more appropriate to maintain therapeutic plasma levels above the minimum inhibitory concentration (MIC) [8,15]. A combined study of field effectiveness and pharmacokinetics conducted in 26 horses with lower respiratory disease determined that the time-concentration profile of sulfadiazine and trimethoprim in horses did not demonstrate linearity with increasing dosage (unpublished data, Aurora Pharmaceutical, LLC; Figs. 1 and 2). Increased dosages of the potentiated sulfa did not result in a significantly greater $t >$ MIC for either active moiety, particularly for sulfadiazine, in which the plasma Cmax was actually lower for the higher dose regimen. A dosing regimen of 30 mg/kg every 12 hours had no clinical advantage over 24 mg/kg every 12 hours, and the latter was associated with fewer incidents of antibiotic-associated loose feces (Aurora Pharmaceutical, LLC; unpublished dose titration data 2012).

A proprietary oral suspension formulation of trimethoprim plus sulfadiazine (TMP/SDZ) has been developed, with label recommendations for dosing at 24 mg/kg body weight twice daily for 10 consecutive days (EQUISUL-SDT Sulfadiazine/Trimethoprim; Aurora Pharmaceutical, LLC, Northfield, MN). A controlled clinical study was performed to determine the margin of safety of the suspension at dosages of 1×, 3×, and 5× the label recommendation, administered for 30 days (three times the recommended duration).

2. Materials and Methods

2.1. Study Design

A blinded, randomized, and controlled margin of safety study was performed with 32 mature horses using a proprietary TMP/SDZ suspension at dose multiples of 0×, 1×, 3×, or 5× the recommended dosage of 24 mg/kg body weight (Table 1). Doses were administered at 12-hour intervals for a total of 30 days, three times the recommended treatment duration of 10 days.

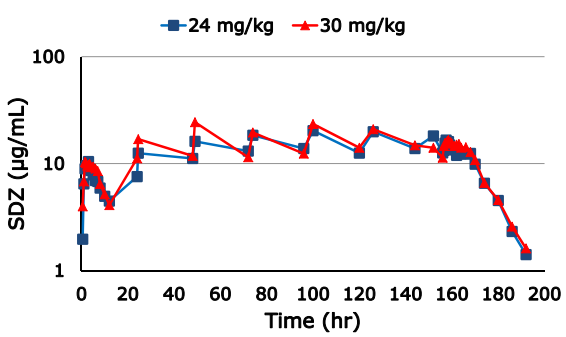

Fig. 1. Time-concentration profile for sulfadiazine.

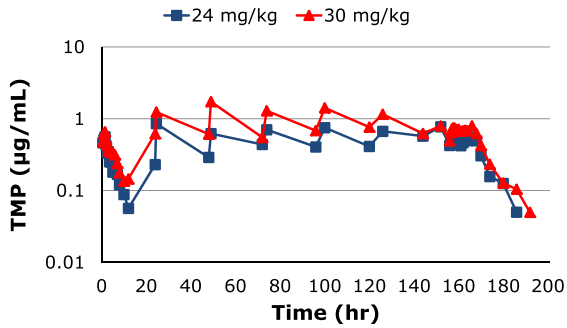

Fig. 2. Time-concentration profile for trimethoprim.

2.2. Animals and Management

Thirty-six candidate horses were acclimated to the testing facility's housing, feed, hay, and management conditions for at least 14 days. Horses were housed individually in 12 ft × 12 ft stalls within a covered pole barn and held under ambient conditions between January and March 2009. Potable water was supplied by a local utility and provided to each horse in two 14-L buckets that were filled at least twice daily. Concentrate was a 11% protein commercial horse feed (Co-Op 11% Sweet Horse Feed Coarse; Tennessee Farmers Cooperative, Lavergne, TN), provided at 0.5% body weight and divided into similar weighed portions supplied AM and PM. Orchard grass hay was offered at 1.5% body weight per day and similarly divided by weight into AM and PM portions. Individual feed, hay, and water consumption were assessed twice daily for the duration of the trial.

Candidates were light, saddle breed horses, at least aged 1 year, and of normal health as assessed by physical examinations and clinical pathology analyses. Of the 36 candidates that underwent acclimation, 16 male horses (15 geldings and one stallion) and 16 mares were enrolled. Subjects were aged 2-12 years and weighed between 329 and 484 kg. Horses were blocked by gender and ranked by descending body weight. Within gender, each four consecutively ranked horses formed a replicate, and each horse within a replicate was randomly assigned to one of the four treatment groups detailed in Table 1.

Table 1
Treatment group assignments

Group	Multiple Of Recommended Dosage	Dosage (mg/kg) Every 12 hr	Duration of Treatment (d)	Number (Male/ Female)
A	0× (control)	Saline[a]	30	4/4
B	1×	24	30	4/4
C	3×	72	30	4/4
D	5×	120	30	4/4

[a] Control horses were dosed orally with 3 mL, 0.9% sodium chloride solution per 50 kg body weight.