Received: 16 September 2022 | Accepted: 7 July 2023

DOI: 10.1111/jvim.16821

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

The effects of orally administered trazodone on ambulation and recumbency in healthy horses

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Abstract

Background: Trazodone, a serotonin receptor antagonist and reuptake inhibitor, might be a useful adjunctive treatment in the initial management of horses with acute laminitis if it minimizes ambulation or encourages recumbency.

Objectives: (1) Evaluate the effects of PO trazodone on ambulatory activity and recumbency in healthy horses; and (2) assess the pharmacokinetics of multiple PO doses of trazodone.

Animals/Methods: In a randomized cross-over design, 8 healthy horses received placebo or trazodone at 2 doses (2.5 and 7.5 mg/kg) PO q12h for 48 hours with a 14-day washout period between treatments. Forelimb step frequency was measured using a hoof-mounted accelerometer and continuous video monitoring was used to detect recumbency. Groups were compared using repeated measures analysis of variance with Tukey's post hoc test. Trazodone and m-chlorophenylpiperazine (m-CPP) plasma concentrations were determined by ultra-high performance liquid chromatography-tandem mass spectrometry and pharmacokinetics were analyzed using noncompartmental methods.

Results: Step frequency was lower in horses receiving 7.5 mg/kg trazodone than in the control group (mean step reduction: 44% ± 11%). Steps-area under the curve were significantly lower in the 7.5 mg/kg group (mean ± SD: 3375 ± 525 steps × hour) as compared to the 2.5 mg/kg group (mean ± SD: 5901 ± 2232; $P = .02$) and compared to control (mean ± SD: 6590 ± 1241; $P = .001$). No difference was found in the number of recumbent episodes ($P = .92$) or total duration of recumbency ($P = .9$). Trazodone and m-CPP achieved steady-state concentrations, with an accumulation ratio of 1.45 ± 0.2.

Conclusions and Clinical Importance: Although it did not affect recumbency, trazodone at 7.5 mg/kg q12h decreased step frequency by approximately 44%.

KEYWORDS
laminitis, orthopedic, pharmacokinetics, sedation

Abbreviations: AUC, area under the curve; m-CPP, m-chlorophenylpiperazine; PK, pharmacokinetics; steps-AUC, area under the curve of steps; UPLC-MS/MS, ultra-high performance liquid chromatography-tandem mass spectrometry.

1 | INTRODUCTION

Laminitis is a common and debilitating disorder often associated with sepsis, insulin dysregulation, and orthopedic injury in equids.[1] Though the pathophysiology of laminitis is not yet completely understood, mechanical forces play an important role in the progression of laminitis.[2] These distractive forces, associated with weight bearing and ambulation, are a common element in all cases and have a major influence on the progression of laminitis.[3]

Currently, a major limitation when treating acute laminitis is our inability to completely relieve load on the feet and therefore prevent mechanically induced damage during the period when the lamellar tissue is weakened. Orthotics and certain stall surfaces may redistribute weight-bearing load from hoof wall to frog and sole and facilitate break-over, thereby partially decreasing lamellar strain. However, techniques intended to completely remove weight-bearing load, including slings or forced recumbency, are impractical in clinical cases.[3] Furthermore, although stall confinement is a common strategy aimed at restricting ambulatory activity, more specific means to limit the number of steps and direct means to encourage recumbency in the stall-confined horse could more effectively limit mechanically induced progression of laminitis. Although medications such as reserpine and fluphenazine have been used, they both have adverse effects such as erratic behavior and gastrointestinal ileus, which can further exacerbate laminitis.[4,5] Alpha-2 agonists, opioids and acepromazine are other commonly used medications, but they require frequent dosing and have similar undesirable effects. Trazodone, a serotonin receptor antagonist and reuptake inhibitor used as an anxiolytic in human and small animal veterinary medicine, recently has been reported for use in horses requiring long-term stall rest because of ocular injury, with minimal adverse effects.[6] In previous pharmacokinetics (PK) studies, 94% of horses treated with trazodone showed positive modification of adverse behaviors associated with stall rest.[7]

Our objective was to evaluate the effects of PO trazodone on ambulatory activity and recumbency in healthy horses. We hypothesized that trazodone would decrease step frequency and increase time spent in recumbency in horses. A secondary objective was to report the PK of multiple PO doses of trazodone.

2 | MATERIALS AND METHODS

2.1 | Animals

Eight healthy adult Thoroughbred horses from the University of Florida College of Veterinary Medicine research herd were included in a 3-period randomized cross-over study, structured such that each horse would receive each treatment once. Horses were moved into box stalls 24 hours before the start of the study, bedded on shavings, and allowed free access to hay and water. Horses were placed in the same stall and adjacent to the same horses for each study period.

2.2 | Drug administration

Horses were randomly assigned to receive PO trazodone at 2.5 mg/kg q12h for 48 hours (low-dose trazodone), PO trazodone at 7.5 mg/kg q12h for 48 hours (high-dose trazodone), or PO placebo q12h for 48 hours (control) with a 14-day washout between each treatment period. Trazodone tablets (100 mg tablets, Zydus Pharmaceuticals USA, Pennington, New Jersey) were dissolved in 60 mL water and molasses approximately 5 minutes before administration. The control group received 60 mL water and molasses. Horses had free-choice access to hay and were not withheld from feed before drug administration.

2.3 | Accelerometers

Accelerometers were placed at baseline and data were recorded continuously for 48 hours during each study period. Horses were instrumented using an inertial measurement unit (IMU) that included a single tri-axial accelerometer and gyroscope (Mbientlab, San Francisco, California) attached to the dorsal hoof wall of the right forelimb with adhesive. The accelerometer continuously logged hoof acceleration data. The data then was downloaded wirelessly at 6-hour intervals. Raw data from the IMU was analyzed using a custom-designed machine-learning algorithm that was trained to detect steps in the individual limb using a k-nearest neighbor (KNN) algorithm running on Stata 15.1MPh (Stata Corp, College Station, Texas). This system had been validated previously using video analysis in 6 horses over a 1-hour period in stalls and showed excellent correlation ($r = 0.99$; $P < .0001$) for detection of steps (Figure S1). The data were expressed as number of steps in each hour of the 48-hour study periods.

2.4 | Behavior monitoring

The horses' stalls were fitted with a 24-hour video monitoring system (GoPro Hero4, GoPro Inc., San Mateo, California). Video was recorded continuously for 48 hours beginning 1 hour before the time of drug administration (time 0). For each treatment hour and blood collection time, horses were scored by unblinded observers using a previously published sedation scoring system (Table S1).[7]

2.5 | Heart rate monitoring

Horses receiving the 7.5 mg/kg dose were fitted with a telemetric, continuously recording 3-channel 5-lead ECG monitor (Trillium 5000, Forest Medical, Syracuse, New York), with data recorded onto a compact flash memory card. The ECG monitors were placed 1 hour before dose 1 and monitoring continued for 48 hours. Telemetric recordings were analyzed for the presence of arrhythmias using Holter software (Trillium Platinum Vet Software, Forest Medical, Syracuse, New York),

with manual review and correction performed by a board-certified internist (DL).

To determine whether trazodone caused QT interval prolongation as described in humans,[8] QT intervals were measured 30 minutes before the 1st trazodone dose and 1 hour after the 4th trazodone dose. The QT interval was measured in milliseconds from the start of the Q wave to the end of the T wave where it intersects baseline, as previously described.[9] The QT interval (ms) was corrected for heart rate (HR) as previously described and validated in horses, where corrected QT (QTc) = measured QT + $\text{slope}_{\text{resting}}$ × (1000 − measured RR interval) and using the slope for Thoroughbred horses.[9,10]

2.6 | Pharmacokinetic analysis

A 14-gauge catheter (Angiocath, Becton Dickinson, Sandy, Utah) was placed into a jugular vein for collection of blood samples. After the 1st drug administration, blood samples were collected at 0, 15, 30, and 45 min, 1, 2, 4, 8, and 12 hours post administration into lithium heparin-containing blood tubes. Additionally, blood samples were collected immediately before and 1 hour after the 2nd and 3rd drug administration. After the last (4th) drug administration, blood samples were collected at 0, 15, 30, and 45 minutes, 1, 2, 4, 8, 12, 24, 48, and 72 hours post administration. Blood samples were processed within 15 minutes of collection by centrifugation at 3000 rpm (1207*g*) for 15 minutes. Plasma was harvested within 5 minutes of centrifugation and 3 mL aliquots were immediately frozen and stored at −80°C until analysis. Quantitative analysis was performed by the Analytical Chemistry Research Laboratory at the Virginia-Maryland College of Veterinary Medicine. Concentrations of trazodone and its metabolite m-chlorophenylpiperazine (m-CPP) were determined by ultra-high performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS). Full method details are available in Item 2 (Supporting Information). Using this method, calibration curves made using blank equine plasma were linear over a plasma concentration range of 2-3200 ng/mL for trazodone and 0.5-200 ng/mL for m-CPP. The coefficient of determination (R^2) for each curve was >0.99. The system had a limit of detection (LOD) of approximately 0.2 ng/mL for trazodone and 0.02 ng/mL for m-CPP as determined by a signal-to-noise ratio of 3 using blank plasma. The limit of quantification (LOQ) was set at the lowest concentration on the individual calibration curves (2 and 0.5 ng/mL for trazodone and m-CPP, respectively). Quality control samples for trazodone were run at 2, 200, and 3200 ng/mL. Interassay accuracy at these concentrations was 3.61 ± 2.78, 4.61 ± 0.88, and 1.11 ± 0.6%, respectively, with an interassay coefficient of variation (CV) of 1.66 ± 0.91. Quality control samples were run at 2, 200, and 3200 ng/mL for trazodone and 0.5, 10, and 200 ng/mL for m-CPP. Results of inter- and intraday accuracy and precision are presented in Table 1.

Drug concentrations were analyzed using commercially available software (Phoenix WinNonlin version 6.2, Certara USA, Inc., Princeton, New Jersey) to determine PK variables for each horse. Noncompartmental analysis was used to determine total area under the curve (AUC), half-life of the terminal phase ($t_{½\lambda}$), terminal rate constant (λ_z), maximum plasma concentration (C_{max}), and time to C_{max} (T_{max}) for trazodone and m-CPP. The accumulation ratio after dose 4 was determined for trazodone and m-CPP using the equation $AR = 1/1-e^{-k\times tau}$ where *k* is the te rminal elimination rate constant and tau is the dosing interval. Proportionality of PK within the dose range studied was determined by dividing the C_{max} and AUC for the dose interval (AUC_{tau}) by the dose administered after dose 1 and comparing the results using a paired *t* test.

TABLE 1 Intraday and interday average (avg) precision and accuracy assessed at 3 concentrations (low, medium, and high) 4 times (intraday) in 5 different analytical runs (interday) for trazodone and m-CPP.

Trazodone			
	2 ng/mL	**200 ng/mL**	**3200 ng/mL**
Intraday precision	1.3%	0.67%	2.2%
Interday precision	2.8%	1.1%	1.1%
Intraday accuracy	102.9%	94.5%	100.6%
Interday accuracy	103.9%	95.7%	100.5%
m-CPP			
	0.5 ng/mL	**10 ng/mL**	**200 ng/mL**
Intraday precision	2.9%	2.4%	1.1%
Interday precision	3.9%	2.6%	2.1%
Intraday accuracy	115%	93.7%	101.3%
Interday accuracy	110.7%	96.6%	100.5%

Abbreviation: m-CPP, m-chlorophenylpiperazine.

2.7 | Statistical analysis

A statistical a priori power analysis (Type II error = 0.2; Type I error = 0.05, www.openepi.com and G*Power software) showed that 8 horses were necessary to detect a clinically relevant (50%) difference in step frequency, based on results of preliminary findings in healthy adult horses (mean ± SD step frequency of 81 ± 30 steps/h). Statistical analysis was performed using commercially available software (Graph Pad Prism v9.4.0, GraphPad Software, LLC, San Diego, California). Because there was hourly variation in step frequency, the AUC for hourly steps (steps-AUC) was calculated for individual horses for each study arm for the following time periods: total 48 hours, day 1 (1st 24 hours), day 2 (2nd 24 hours), daytime hours (6:00 am-5:00 pm), and nighttime hours (6:00 pm-5:00 am). The steps-AUC was compared between each cohort of horses using either repeated-measures analysis of variance (ANOVA; normally distributed continuous data) with Tukey's post hoc tests or Friedman test with Dunn's multiple comparisons test (non-normally distributed data). Comparison between pre- and post- trazodone QTc values was assessed using a 2-tailed paired *t* test. Dose-corrected PK variables to determine dose proportionality were compared using paired *t* test. All results are reported as means ± SD unless otherwise noted.

3 | RESULTS

3.1 | Animals

Eight horses were used in the study, 5 geldings and 3 mares. Mean weight was 522 ± 39 kg and mean age was 8 ± 4 years.

3.2 | Step frequency

Figure 1 shows hourly step frequency by group over the full 48-hour study period. Mean hourly step frequency was significantly lower in horses receiving 7.5 mg/kg trazodone than in the control group (median [range]: 64 [56-91] steps/h vs 128 [101-181] steps/h; $P = .01$), with a mean step reduction of 44 ± 11% between the 7.5 mg/kg dose and control (Figure 2). No difference was found in mean hourly step frequency between horses receiving 2.5 mg/kg trazodone vs horses receiving 7.5 mg/kg trazodone ($P = .07$) or control horses ($P > .99$).

Over the entire 48-hour treatment period, steps-AUC for horses receiving 7.5 mg/kg trazodone (3375 ± 525 steps × hour) was significantly decreased as compared to the 2.5 mg/kg group (5901 ± 2232 steps × hour; $P = .02$) and to control (6590 ± 1241 steps × hour; $P = .001$; Figure 3A). During the 1st 24-hour period (Day 1), steps-AUC for horses receiving 7.5 mg/kg trazodone (1483 ± 456 steps × hour) was significantly decreased as compared to the 2.5 mg/kg group (2679 ± 1158 steps × hour; $P = .04$) and to control (2950 ± 765 steps × hour; $P = .01$; Figure 3B). During the 2nd 24-hour period (Day 2), steps-AUC for horses receiving 7.5 mg/kg trazodone (1670 ± 394 steps × hour) was significantly decreased as compared to the 2.5 mg/kg group (3069 ± 1218 steps × hour; $P = .03$) and to control (2947 ± 1179 steps × hour; $P = .04$; Figure 3C). During daytime hours, steps-AUC for horses receiving 7.5 mg/kg trazodone (4512 ± 588 steps × hour) was significantly decreased as compared to control (7601 ± 1198 steps × hour; $P = .0003$), but not different from the 2.5 mg/kg group (7278 ± 3528 steps × hour; $P = .08$; Figure 3D). During nighttime hours, steps-AUC for horses receiving 7.5 mg/kg trazodone (1722 ± 296 steps × hour) was significantly decreased as compared to control (3872 ± 1423 steps × hour; $P = .01$), but not different from the 2.5 mg/kg group (3105 ± 1813 steps × hour; $P = .14$; Figure 3E).

3.3 | Recumbency

No significant difference was found in time spent in recumbency ($P = .9$) or number of recumbency episodes between any of the groups ($P = .92$; Table S2).

3.4 | Behavioral monitoring

All horses that received 7.5 mg/kg trazodone experienced variable degrees of sedation as indicated by eyelid droop, lack of response to stimuli, and mild ataxia, beginning as early as 30 minutes after drug administration and continuing until 8 hours after administration. Two horses experienced mild sedation after receiving 2.5 mg/kg trazodone. Subjective sedation scores are reported in Table S3.

Horses in the control group were noted to be more anxious, exhibited increased stall walking and adverse behaviors to being handled (eg, walking to back of stall, spinning, and lifting head to avoid handlers). Two of the study horses had needle-aversive behaviors (shying, striking) that were subjectively improved at the 7.5 mg/kg dose, characterized by a lack of shying away from blood draws from the catheter. Additionally, 1 of the 2 horses during the control and 2.5 mg/kg study periods was noted to run, rear, and try to break free from handlers when being returned to pasture after the final dose. This behavior was not noted after receiving the 7.5 mg/kg dose, which was the 3rd study period for this horse.

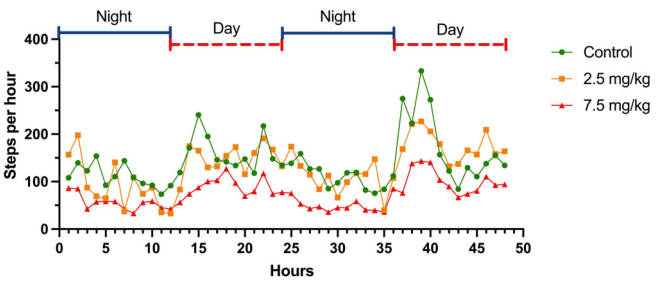

FIGURE 1 Mean hourly step frequency by group of 8 healthy adult horses over the 48-hour study period. Circles represent the control group (n = 8), squares represent 2.5 mg/kg trazodone PO q12 (n = 8), and triangles represent 7.5 mg/kg trazodone PO q12 (n = 8). Day (6:00 am-5:00 pm) and night (6:00 pm-5:00 am) are shown.

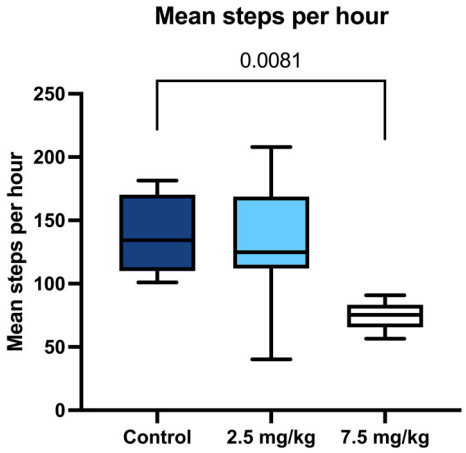

FIGURE 2 Mean steps per hour by group of 8 healthy adult horses receiving placebo or trazodone. Solid line represents mean, box represents interquartile range, and whiskers represent minimum and maximum.

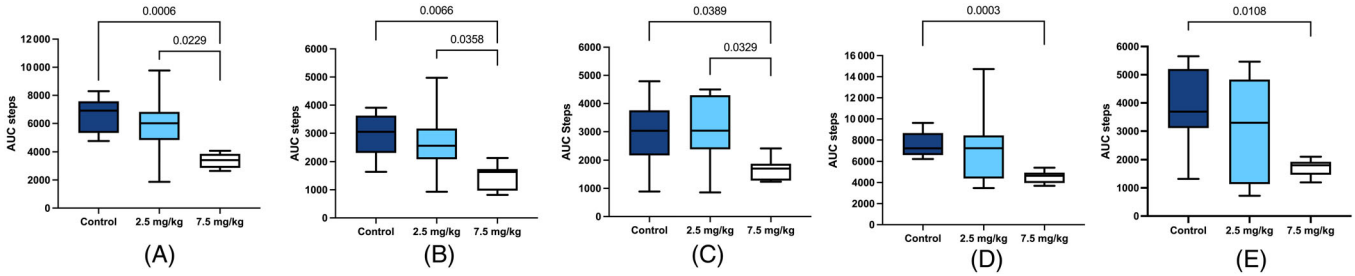

FIGURE 3 Area under the curve of steps by group of 8 healthy adult horses. (A) Total 48-hour study period. (B) First 24 hour period (Day 1). (C) Second 24-hour period (Day 2). (D) Daytime hours (6:00 am-5:00 pm). (E) Nighttime hours (6:00 pm-5:00 am). Solid line represents mean, box represents interquartile range, and whiskers represent minimum and maximum.

TABLE 2 Noncompartmental pharmacokinetics for trazodone and its metabolite m-CPP after administration of trazodone to 8 healthy adult horses at 7.5 mg/kg PO q12h or 2.5 mg/kg PO q12h for 4 doses (n = 8).

	7.5 mg/kg (mean ± SD)		2.5 mg/kg (mean ± SD)	
Trazodone	**Dose 1**	**Dose 4**	**Dose 1**	**Dose 4**
T_{max} (h)	0.5 ± 0.09	36.9 ± 1.27	0.28 ± 0.09	36.3 ± 0.13
C_{max} (ng/mL)	2421 ± 1357	3037 ± 1058	981 ± 685	1718 ± 367
C_{avg} (ng/mL)	…	1078 ± 314	…	338 ± 84.9
λ_z (1/h)	0.2 ± 0.1	0.108 ± 0.042	0.18 ± 0.11	0.106 ± 0.062
T½ (h)	4.12 ± 1.84	7.01 ± 1.91	5.01 ± 2.79	7.92 ± 3.16
AUC_{Tau} (h × ng/mL)	6986 ± 2715	13 641 ± 3705	2057 ± 798	4053 ± 953
$AUC_{0-\infty}$ (h × ng/mL)	…	17 354 ± 5912	…	4798 ± 1574
AUC_{total} (h × ng/mL)	…	51 027 ± 12 347	…	13 990 ± 3520
Accumulation ratio	…	1.45 ± 0.2	…	1.35 ± 0.18
	7.5 mg/kg (mean ± SD)		**2.5 mg/kg (mean ± SD)**	
m-CPP	**Dose 1***	**Dose 4**	**Dose 1**	**Dose 4**
T_{max} (h)	0.54 ± 0.09	38.7 ± 2.401	7.53 ± 5.07	37.2 ± 0.55
C_{max} (ng/mL)	33.46 ± 26.05	43.7 ± 21.6	4.68 ± 1.73	16.1 ± 7.44
C_{avg} (ng/mL)	…	26.6 ± 15.9	…	2.65 ± 0.99
λ_z (1/h)	0.18 ± 0.08	0.138 ± 0.022	0.16 ± 0.04	0.171 ± 0.023
T½ (h)	5.38 ± 4.9	5.14 ± 0.903	4.67 ± 1.21**	4.13 ± 0.571
AUC_{Tau} (h × ng/mL)	141 ± 111	319 ± 191	31.2 ± 12.3	74.61 ± 40.64
$AUC_{0-\infty}$ (h × ng/mL)	…	450 ± 303	…	86.3 ± 50.03
AUC_{total} (h × ng/mL)	…	1077 ± 583	…	254 ± 137
Accumulation ratio	…	1.23 ± 0.22	…	1.1 ± 0.06

Note: * n = 7 and ** n = 4 because of inadequate numbers of samples in the terminal elimination curve. Abbreviations: AUC_{Tau}, area under the concentration versus time curve for the dosing interval (0-12 h dose 1 and 36-48 h dose 4); AUC_{total}, AUC for the entire dosing interval (0-108 h); $AUC_{0-\infty}$, AUC extrapolated from administration of the last dose to infinity; C_{avg}, average concentration over the dosing period; C_{max}, maximum concentration; m-CPP, m-chlorophenylpiperazine; T_{max}, time to maximum concentration; T½, elimination half-life; λ_z, terminal rate constant.

3.5 | Electrocardiography

One horse experienced a 55-minute episode of sinus tachycardia (HR range, 66-185 bpm) that started 30 minutes after administration of the 2nd dose of 7.5 mg/kg trazodone, which resolved without intervention. Concurrently, the horse exhibited muscle fasciculations, profuse sweating, and flight behavior (running around the stall). Sinus tachycardia and concurrent behavioral changes did not occur with the 3rd and 4th doses in this horse.

Mean ± SD QTc before trazodone administration was 432 ± 22 ms. Mean ± SD QTc 1 hour after the 4th dose of trazodone was 476 ± 25 ms. No significant difference was found between pre- and post-trazodone QTc intervals ($P = .06$; $t = 2.367$; degrees of freedom = 5).

4 | PHARMACOKINETICS

Table 2 shows PK measurements for trazodone and m-CPP after doses 1 and 4. Data from 1 horse in the 7.5 mg/kg dose 1 group was excluded from the m-CPP PK analysis because plasma drug concentrations continued to increase throughout the entire dose interval. Data for half-life from 4 horses in the 2.5 mg/kg dose 1 group were excluded from m-CPP PK because drug concentrations did not change or were increasing at the terminal sample points. Unchanged or increasing concentrations result in an inability to accurately characterize elimination, and consequently, the data were omitted. Trazodone was rapidly absorbed at both the 7.5 mg/kg and 2.5 mg/kg doses. Dosing was carried out beyond 5 half-lives of the drug, indicating both trazodone and m-CPP likely achieved steady-state concentrations during the study period. Trazodone had an accumulation ratio of 1.45 ± 0.2 after 7.5 mg/kg q12h. Plasma concentrations of trazodone and m-CPP for both doses are shown over time in Figure 4. The dose-corrected C_{max} and AUC_{tau} for the 7.5 mg/kg group were 931 ± 362 ng/mL and 323 ± 181 h × ng/mL, respectively. The dose-corrected C_{max} and AUC_{tau} for the 2.5 mg/kg group were 823 ± 319 ng/mL and 392 ± 274 h × ng/mL, respectively. When evaluating the dose-adjusted C_{max} and AUC_{tau} for the 7.5 and 2.5 mg/kg doses, no significant differences were detected ($P = .37$ and .46, respectively), supporting linear kinetics within this dose range.

5 | DISCUSSION

Although it did not increase time spent in recumbency, trazodone at 7.5 mg/kg PO q12h decreased step frequency in healthy horses, an effect that might be clinically useful to minimize the mechanical strains associated with ambulation during acute laminitis.[1,2] Additionally, although horses that received 2.5 mg/kg trazodone experienced a decrease in step frequency for the overall study period, when accounting for differences in step frequency between daytime hours and nighttime hours, a difference from control horses was not observed. Also, large variation in step frequency was observed at the 2.5 mg/kg dose, suggesting intra-horse variability that could make this dose unreliable if a decrease in step frequency in the stall is the goal of treatment. Because the 7.5 mg/kg dosage caused a more reliable decrease in step frequency, a higher dose might be necessary to provide the magnitude of decreased ambulation needed in hospitalized patients for adjunctive management of laminitis.

Our findings are similar to studies in other species. In a recent study, use of PO trazodone in goats at 10 mg/kg resulted in a 49% decrease in movement as well as a 31% decrease in activity level.[11] In dogs, owners reported a substantial decrease in activity and acceptance of crate confinement after orthopedic surgery after receiving PO trazodone at 7-10 mg/kg q8-12h.[12] In both studies, no relevant adverse effects of the medication at these high doses were reported.

Horses were monitored for sedation and deviations from normal behavior. None of the horses exhibited a decrease in foraging behavior or fecal output during the study. One horse experienced a period of muscle fasciculations, sweating and sinus tachycardia after the 2nd 7.5 mg/mg dose of trazodone. The horse recovered without intervention and clinical signs did not return with subsequent doses of trazodone. No other horses exhibited anxiety or changes in behavior at the same time as this horse, suggesting it was not a reaction to environmental changes. However, determination of the association of PO trazodone with behavioral changes is difficult to assess from the results of our study. In prior studies of trazodone given IV, excitability has been noted in dogs and horses.[13,14] Trazodone administered PO has been reported to cause excitability in horses, but in those studies, the relationship between trazodone and the observed behavioral changes also could not be clearly determined.[7] Of note, trazodone often is used in dogs and cats to minimize anxiety associated with veterinary visits and medical procedures, and the excitability seen in 1 horse in our study as well as in previous reports could represent an idiosyncratic response to the drug.[12,15]

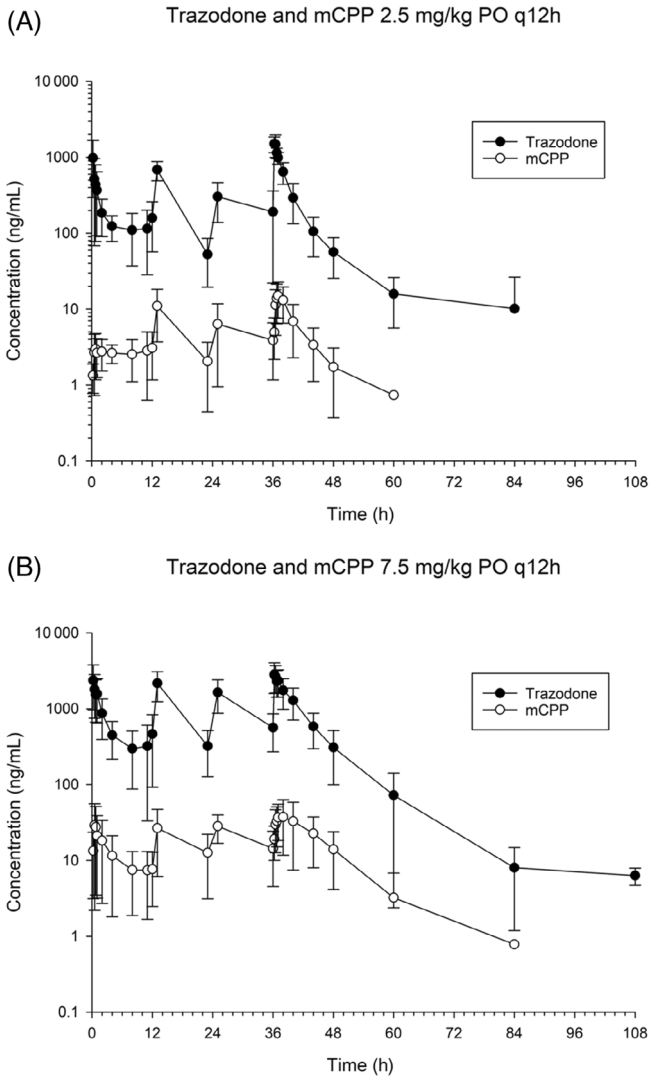

FIGURE 4 Plasma trazodone and m-chlorophenylpiperazine (m-CPP) concentrations in healthy adult horses (n = 8) after multiple PO doses of trazodone hydrochloride at either 2.5 mg/kg q12 (A) or 7.5 mg/kg q12 (B).

The horses used in our study were from a group of research horses that had minimal experience with stall confinement. During the control portions of the study, these horses were noted to be more anxious, exhibiting increased stall walking and adverse behaviors to being handled (eg, walking to back of stall, spinning, lifting head to avoid handlers). Two of the study horses had needle-aversive behaviors (eg, shying, striking) that were subjectively improved at the 7.5 mg/kg dosage, characterized by a lack of shying away from blood draws from the catheter. Additionally, 1 of the 2 horses during the control and 2.5 mg/kg study period was noted to run, rear, and try to break free from handlers when being returned to pasture after the final dose; this behavior was not noted after receiving the 7.5 mg/kg dose. However, it was also the horse's 3rd study period and the improvement also might be attributed to more familiarity with the procedures. Although these observations are subjective, we believe trazodone might have benefits in horses with behavioral problems.

Trazodone followed linear kinetics after repeated doses, consistent with a previous single-dose PK study in horses.[7] Half-life was approximately 4-6 hours after the 1st administration of the 2.5 and 7.5 mg/kg doses and approximately 7-9 hours after the 4th dose 2.5 and 7.5 mg/kg doses. These differences in half-life most likely represent better ability to characterize the terminal elimination phase of trazodone after the final dose, because samples were collected for 48 hours beyond drug administration. The use of a q12h dosing interval resulted in an accumulation ratio of almost 1.5 after the 4th 7.5 mg/kg dose, resulting in an increase in maximum plasma concentration with subsequent doses. This effect was observed in the 2.5 mg/kg dose group as well, but to a lesser extent. Anecdotal reports in dogs and horses indicate that tolerance to trazodone's sedative and anxiolytic effects might develop with dosing for >2-4 weeks, but studies have not been performed to evaluate this possibility in horses. Although no significant differences in PK variables were noted between the 1st and 4th doses of trazodone in the horses of our study, the dosing period was likely too short to determine if this finding is related to changes in drug absorption or metabolism, or pharmacodynamic tolerance.

The active metabolite m-CPP was present in all horses after both the 2.5 mg/kg and 7.5 mg/kg doses at both dose 1 and dose 4. At both dose time points, the relative ratio of m-CPP to trazodone was low, suggesting that the metabolite is unlikely to contribute substantially to the drug's overall effect. This finding is consistent with previous studies.[7,14]

The therapeutic concentration of trazodone in horses is unknown. In humans, commonly prescribed doses result in plasma concentrations between 130 and 2000 ng/mL,[16] but therapeutic antidepressant effects are associated with a threshold concentration of at least 700 ng/mL.[17] Toxic concentrations are proposed to be >4000 ng/mL.[18] In humans, m-CPP concentrations are not correlated to effect. Using that guideline, 7 of 8 horses in the 7.5 mg/kg dose group reached trazodone concentrations >700 ng/mL at the 1st and 4th dose, whereas only 4 of 8 horses in the 2.5 mg/kg dose group reached this target after the 1st dose. Because of drug accumulation, all horses in the 2.5 mg/kg dose group did reach target concentrations after dose 4. In the 7.5 mg/kg dose group, average plasma concentrations were >700 ng/mL over the entire dosing period, but not in the 2.5 mg/kg group. One horse in the 7.5 mg/kg dose group had trazodone concentrations >4000 ng/mL after both the 1st and 4th dose; this horse had no apparent adverse effects on ECG or clinical examination. Because the extent of sedation and ataxia was highly variable among horses at 2.5 mg/kg but more predictable at 7.5 mg/kg over all 4 doses, individualized dose ranges might be necessary in horses. This situation is similar to what is found in dogs, because published doses range from 1.7 to 19.5 mg/kg/day PO and dose frequencies range from q8h to q24h. Because the 7.5 mg/kg dose resulted in a more reliable decrease in step frequency, this finding suggests that horses that require decreased step frequency for management of their orthopedic conditions should be started at the higher dose range of 7.5 mg/kg because horses at the 2.5 mg/kg dose did not experience a reliable decrease in step frequency over time.

In a prior study, trazodone caused episodic arrhythmias in horses based on auscultation after a single PO dose of 10 mg/kg.[7] However, ECGs were not performed to diagnose the arrhythmias and continuous telemetry was not used to evaluate the frequency or duration of the arrhythmias and therefore a determination of the clinical relevance of the arrhythmia could not be made from that study. In humans, trazodone has been reported to induce prolonged QT intervals, ventricular premature depolarizations, and torsade de pointes.[19] In our study, horses receiving 7.5 mg/kg trazodone experienced no clinically relevant cardiac arrhythmias during the 48-hour monitoring period, although 1 horse did exhibit sinus tachycardia that resolved without treatment. Although the QTc intervals subjectively appeared longer after the 4th trazodone dose than before any drug administration, the difference was not significant. Additional studies are needed to evaluate the effects of longer-term PO administration of trazodone on ECG findings, as well as in systemically ill horses.

Our study had some limitations. Continuous telemetric monitoring only was performed on horses in the 7.5 mg/kg trazodone group. The primary goal of the ECG monitoring was to ascertain safety in regard to development of life-threatening arrhythmias. Although no arrhythmias were noted in these horses, comparisons of the effect of trazodone on HR variables and HR variability could not be made without monitoring in the other groups. Additionally, behavioral monitoring and determination of sedation and ataxia scores were performed by unblinded observers. The use of unblinded observers was not ideal, but staff availability limited the number of individuals who could be present at treatment times for observations. An additional limitation is the use of healthy horses. It is possible the effects of PO trazodone on horses with laminitis or systemic illness might be different. Horses with systemic illness or laminitis could have altered PK variables, and horses with laminitis might already be less likely to ambulate because of pain. Finally, PO administration of trazodone, rather than intragastric administration, might have resulted in additional variability in PK variables among horses. However, this route of administration was chosen based on previous PK studies as well as clinical applicability.

Trazodone at 7.5 mg/kg PO q12h decreased step frequency and ambulation in healthy horses, an effect that may be useful in treatment of conditions such as acute laminitis. Pharmacokinetic analysis indicated that trazodone establishes a steady-state concentration over repeated doses. Our findings support the use of PO trazodone for modification of ambulatory activity in horses.

ACKNOWLEDGMENT

No funding was received for this study. The authors thank R. McAlister Council-Troche for his work with UPLC-MS/MS method development and sample analysis and Kasey Cockefair for her assistance during the study periods.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the University of Florida IACUC (protocol number 202111447).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hobbs K, Luethy D, Davis J, et al. The effects of orally administered trazodone on ambulation and recumbency in healthy horses. *J Vet Intern Med*. 2023;37(5):1899-1906. doi:10.1111/jvim.16821