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Pharmacokinetic and pharmacodynamic properties of orally administered torsemide in healthy horses

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Background: Diuretic treatment is the mainstay for management of congestive heart failure in horses, and its use has been restricted to injectable medications because no currently data supports the use of PO administered loop diuretics.

Objectives: To determine the pharmacokinetic and pharmacodynamic properties of PO administered torsemide and, determine if PO administered torsemide, could be used as an alternative to injectable diuretics in the horse.

Animals: Six healthy adult mares.

Methods: A 2-phase, prospective study, that consisted of pharmacokinetic profiling of a single dose (6 mg/kg PO) and pharmacodynamic effects of long-term torsemide administration (2 mg/kg PO q12h) for 6 days in healthy horses.

Results: Pharmacokinetic analysis identified a peak concentration (C_{max}) of 10.14 μg/mL (range, 6.79–14.69 μg/mL) and elimination half-life ($T_{1/2}$) 9.2 hours (range, 8.4–10.4 hours). The area under the plasma drug concentration over time curve (AUC) was 80.7 μg × h/mL (range, 56.5–117.2 μg × h/mL). A statistically significant increase in urine volume and decrease in urine specific gravity were found from day 0 (baseline) to day 6 ($P < .0001$). Significant alterations in biochemical variables included hyponatremia, hypokalemia, hypochloremia, and increased serum creatinine concentration. Mean arterial blood pressure significantly decreased on day 6 (57.7 ± 8.8 mm Hg, $P = .001$) as compared with baseline (78 ± 6.1 mm Hg). Serum aldosterone concentrations significantly increased after 6 days of torsemide administration ($P = .0006$).

Conclusions and Clinical Importance: PO administered torsemide (4 mg/kg/day) successfully reached therapeutic concentrations in blood, induced clinically relevant diuresis, and resulted in moderate pre-renal azotemia and electrolyte disturbances.

KEYWORDS
congestive heart failure, diuretic, fluid overload, loop of Henle, torsemide

1 | INTRODUCTION

Fluid overload occurs with various conditions in the horse including congestive heart failure (CHF), pulmonary edema,[1] distal limb cellulitis,[2] head trauma,[3] and respiratory distress syndrome in foals.[4] Loop

Abbreviations: CHF, congestive heart failure; EIPH, exercise induced pulmonary hemorrhage; HPLC, high performance liquid chromatography; MAP, mean arterial pressure; RAAS, renin-angiotensin-aldosterone system; USG, urine specific gravity.

diuretics (eg, furosemide, torsemide) have been used for clinical conditions in horses, humans, dogs, and cats to remove excessive fluid from the body by blocking the Na-K-2Cl transporters in the thick ascending loop of Henle. Once the active reabsorption of sodium, potassium, and chloride is blocked, diuresis is promoted by excretion of water, sodium, potassium, and chloride. Intravenously administered furosemide is commonly used to resolve pulmonary edema secondary to acute CHF,[5] whereas PO administered diuretics are the mainstay for successful long-term management of CHF.[6] Diuretics also are indicated to increase urine output in horses with acute renal failure, oliguria, anuria,[7] poisoning, envenomation,[8] and severe hypercalcemia[4] or hyperkalemia.[9]

Torsemide is a high ceiling loop diuretic that is 10 times more potent than furosemide, and has a consistently high bioavailability after PO administration in humans and dogs.[10] Torsemide has been widely used in humans and dogs with CHF, and shown less diuretic resistance.[8] Although torsemide is proven to be safe and effective with good PO absorption in humans, dogs, cats, and rats.[2,11–13] pharmacokinetic and pharmacodynamic studies have not been reported in horses.

In the horse, diuretic treatment is restricted to injectable furosemide because of a lack of current data on the use of PO furosemide. Frequent IM or IV administration of furosemide can lead to complications such as local infection, perivascular administration of the drug, thrombosis and accidental injection into the carotid artery.[14] A pharmacokinetic and pharmacodynamic study of PO furosemide in healthy horses indicated that the bioavailability of PO furosemide using a single dose of 1 mg/kg was only 5%.[1] In the same study, no differences in urine volume and plasma electrolyte concentrations were noted after PO furosemide administration when compared with control horses.

The absorption of PO administered torsemide is nearly complete in humans, dogs and rats.[7,13] A formulation of torsemide for PO administration was rapidly absorbed in human patients with CHF, and similar results were observed in a pharmacokinetic study of torsemide in healthy human volunteers and patients with renal failure.[15,16] Loop diuretics activate the renin-angiotensin-aldosterone system (RAAS) by decreasing plasma volume, and its long-term administration may lead to diuretic resistance.[17,18] In a study performed in healthy dogs, plasma aldosterone concentrations were significantly increased from baseline after long-term furosemide and torsemide administration.[19] In the same study, long-term administration of torsemide markedly increased 24 hours urine volume, whereas furosemide induced only modest diuresis, suggesting that long-term administration of torsemide might lead to less diuretic resistance despite an increase in plasma aldosterone concentration.

The use of torsemide has several pharmacological advantages over furosemide. In a study comparing diuretic effects of equivalent dosages of torsemide and furosemide in small animals, less potassium loss was observed in animals treated with torsemide.[12] In humans, torsemide has considerably high bioavailability which allows an immediate switch from IV to PO formulation without changing the dosage.[10] A half-life that allows dosing every 12 hours, good PO absorption, and low risk of diuretic resistance are potential advantages of PO administered torsemide for long-term diuretic treatment, which may contribute to clinical and prognostic improvement in patients with fluid overload.

We hypothesized that torsemide would be well-absorbed when administered PO, and produce clinically relevant diuresis in healthy horses. The study aims were to determine the pharmacokinetic profile after single PO administration of torsemide and to evaluate the pharmacodynamic effects of long-term administration of torsemide PO in healthy horses. To our knowledge, this study constitutes the first pharmacokinetic and pharmacodynamic investigation of PO administered torsemide in the horse.

2 | MATERIALS AND METHODS

2.1 | Animals and criteria

Six healthy, adult mares (5 Quarter horses and 1 draft-cross horse) from the teaching herd of the Auburn University Large Animal Teaching Hospital were enrolled. Their average body weight and age were 594 kg (range, 477–541 kg) and 15 years (range, 11–23 years), respectively. All horses were used in a 2-phase study with a minimum of 90 days washout period between phases. All horses were deemed clinically healthy based on physical examination, baseline echocardiography, indirect blood pressure, CBC, plasma fibrinogen concentration, and results of serum biochemical profiles. This experiment was approved by the Institutional Animal Care and Use Committee of Auburn University.

2.2 | Plasma torsemide concentration determination

Plasma concentrations of torsemide were determined by a high performance liquid chromatography (HPLC) method as previously described.[20] The HPLC equipment included Agilent 1100 series pumps, temperature controlled auto-injection, ultraviolet detector, and interface. A C-18 column (Phenomenex; 2.6 u; 100 × 4.6 mm; Torrance, California) was used with a mobile phase of acetonitrile and potassium dihydrogen orthophosphate buffer (0.05M) at a ratio 40 : 60 by volume. Detection was at 290 nm and the flow rate was 1 mL/min. To 1 mL of equine plasma sample or plasma standard, 0.8 mL of 10% perchloric acid in methanol was added and the samples were centrifuged at 1048 × *g*. A 20 μL volume was injected into the HPLC system. The assay was evaluated in plasma with respect to recovery, linearity, selectivity, limit of quantification, precision, and accuracy. Standards were prepared with equine plasma by spiking with aliquots of torsemide to yield concentrations of 0.01, 0.04, 0.1, 0.4, 1.0, 4.0, 10.0, and 20.0 μg/mL. Plasma standards stored for 4.5 months at −80°C showed no evidence of drug degradation. Drug concentrations were determined from equine plasma standard curves based on a peak area. The limit of quantification was 0.04 μg/mL and the limit of detection was 0.01 μg/mL. Intraday and interday variations were <5.5%.

2.3 | Experiment phase I (pharmacokinetic profiles)

Each horse was stalled for 3 days (1 day acclimatization and 2 days of blood collection). Before torsemide administration (6 mg/kg, PO, once), a 14-gauge IV catheter was aseptically placed in the left jugular vein for blood collection. Access to hay and water was restricted for 2 hours before and 4 hours after the single dose administration of torsemide.

Thereafter, free choice hay and water was offered. Torsemide tablets were crushed and mixed in 500 mL of water, and administered via a nasogastric tube. The tube was irrigated with 500 mL of water and removed after drug administration. Ten milliliter of blood was collected into lithium heparin tubes to measure plasma torsemide concentrations. Blood was collected before treatment ($T = 0$), and at times 5, 10, 20, 30, 45, and 60 minutes, and 2, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration. Blood was centrifuged for 10 minutes at 1200 rpm, and the supernatant plasma was harvested and stored at −80°C for a total of 3 days before batch analysis.

2.4 | Experiment phase II (pharmacodynamic profiles)

The 6 horses employed for the phase I study were used in the phase II study after a wash-out period of 90 days. Each horse was stalled for 8 days (1 day acclimatization and 7 days of data collection). The tablets (100 mg/tablet) were crushed and mixed with 60 mL of water and administered PO at a dosage of 4 mg/kg/day for 6 days. Horses had access to free choice water, free choice hay, and 1.4 kg of a 10% pelleted feed once daily throughout the study period. All horses were weighed daily. A 28 Fr Foley urinary catheter was aseptically placed into each mare's bladder and connected to a urine collection bag. Urine bags were maintained using a truss so that the mares could move freely in the stall. Urine was collected over the course of 12 hours on day 0 (before drug administration), and on days 1 and 6 (after drug administration). Urinary catheters were removed after 12 hours of urine collection. Collection bags were emptied hourly, and urine specific gravity (USG) and volume were measured. Blood samples were collected at 8 AM daily for determination of packed cell volume (PCV), total protein (TP) concentration, and serum biochemical profiles. Mean arterial pressure (MAP) was measured with a tail cuff using an oscillometric monitor device (SurgiVet Advisor [Smiths Medical, Norwell, Massachusetts]) as previously described.[21] Mean arterial pressure was measured daily at $T = 0$ (before drug administration), and 1, 5, and 9 hours after drug administration. Echocardiographic parameters were evaluated by a board-certified cardiologist (SWJ), using a digital cardiovascular ultrasound imaging system (Philips HD-11) with a S3-1 (3–1 MHz) cardiovascular transducer. Standard long- and short-axis views were used to obtain echocardiographic images.[22] Parameters measured included mitral and tricuspid inflow pattern, chamber dimensions of the left ventricle and the left atrium, transaortic flow velocity, transpulmonary flow velocity, and left ventricular volume measured by a modified Simpson's method.[23] All echocardiographic data obtained was normalized to body weight as previously described.[24] Echocardiography was performed on day 0 (baseline) and then on day 6 of torsemide administration. Samples for plasma aldosterone concentration were obtained daily 1 hour after torsemide administration in the morning. Plasma aldosterone concentrations were measured by radioimmunoassay (Coat-A-Count Aldosterone Radioimmunoassay) as previously validated for horses.[25,26]

2.5 | Pharmacokinetic data analysis

Torsemide pharmacokinetic parameters were estimated by noncompartmental analysis using Phoenix WinNonlin Ver. 7 (Pharsight). The terminal decrease in the natural log plasma concentrations was used to calculate the elimination rate constant (λz) and the $t_{1/2}$ was determined as 0.693/λz. The AUC and its first moment (AUMC), were assessed by the linear/log trapezoidal rule method. The apparent total body clearance after PO administration (Cl/*F*), the apparent volume of distribution (V_{area}/F), and mean residence time (MRT) were estimated from individual values of AUC, AUMC, and $t_{1/2}$. Pharmacokinetic data were expressed as mean, median, geometric mean, standard deviation (SD), and coefficient of variation (% CV).

2.6 | Statistical analysis

Assessment of data distribution in regard to normality was determined using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± SD. A Student's *t*-test with Bonferroni correction was used to analyze differences in pharmacodynamic parameters between day 0 (baseline before torsemide administration) and day 6 of torsemide administration. Central tendency and dispersion for non-normally distributed data were expressed as median and interquartile range (IQR). A 1-way analysis of variance was used to determine differences between pharmacodynamic variables across different time points: day 0 (before drug administration), day 1 (first day of torsemide administration), and day 6 (last day of torsemide administration). If a statistically significant difference was detected among 3 time points, a Tukey's test was used to compare differences between 2 time points. A commercial software (GraphPad Prism 6 [La Jolla, California]) package was used for all statistical analyses, and a corrected P value $< .05$ was set as statistically significant.

3 | RESULTS

3.1 | Pharmacokinetic profile of torsemide after a single PO dose (phase I)

Torsemide was absorbed after intragastric administration with wide kinetic variability among individuals (Figure 1). Average duration to peak plasma concentration (T_{max}) was approximately 3 hours (range, 1.7–4 hours; Table 1). Peak torsemide plasma concentration (C_{max}) was 10.1 μg/mL (range, 6.8–14.7 μg/mL). The excretion half-life of the terminal phase ($T_{1/2}$) was 9.2 hours (range, 8.4–10.4 hours). The area

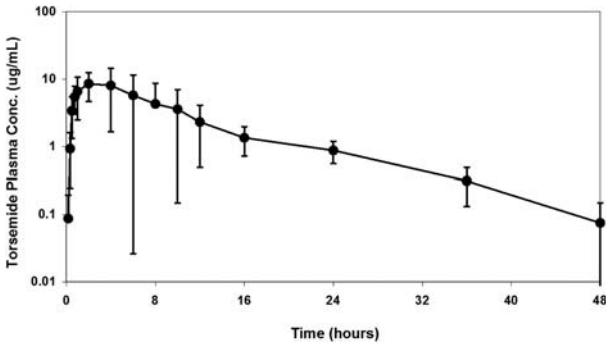

FIGURE 1 Mean plasma concentrations of torsemide over time after a single intragastric administration with 6 mg/kg in 6 healthy adult mares. Bars represent SD

TABLE 1 Pharmacokinetic parameters after PO administered torsemide (6 mg/kg)

Parameter	Median	25% Percentile	75% Percentile	Mean	SD	CV%
C_{max} (μg/mL)	10.1	6.79	14.6	11.0	5.26	47.6
T_{max} (h)	3	1.75	4	2.83	1.33	46.9
AUC (μg × h/mL)	80.7	56.5	117	92.2	48.9	53
λ (1/h)	0.07	0.06	0.08	0.07	0.01	18
$T_{1/2}$ (h)	9.20	8.38	10.4	9.27	1.65	17.8
V_{area}/F (L/kg)	0.89	0.74	1.56	1.08	0.55	51.3
Cl/F (L/h/kg)	0.07	0.05	0.10	0.07	0.02	37.8
MRT (h)	11.5	9.16	14.3	11.6	2.53	21.8

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; Cl/F, apparent total body clearance; MRT, mean residence time; T_{max}, time of maximum concentration; λ, slope of the terminal phase; $T_{1/2}$, half-life of the terminal phase; V_{area}/F, apparent volume of distribution.

under the plasma drug concentration over time curve (AUC) was 80.7 μg × h/mL (range, 56.5–117.2 μg × h/mL).

3.2 | Pharmacodynamic profiles after torsemide given PO for 6 days (phase II)

3.2.1 | Urine volume, USG, and body weight

Oral torsemide administration significantly changed USG, and no statistical difference was observed in body weight when compared between baseline (day 0; before torsemide administration) and day 6 (Figure 2). A significant increase in urine volume (median; IQR) was noted: day 0 (2204; 1881–3874 mL), day 1 (26665; 23185–31225 mL), and day 6 (11525; 9140–14170 mL). A statistically significant increase in urine volume occurred from day 0 to day 6 ($P < .0001$). Urine specific gravity (median; IQR) significantly decreased after torsemide treatment (day 0: 1.046; 1.033–1.048) and (day 1: 1.010; 1.009–1.011; $P < .0001$).

3.3 | Plasma electrolyte, BUN, creatinine, TP, and plasma aldosterone concentrations, and PCV (%)

Serum electrolyte, BUN, creatinine, and TP concentrations, and PCV were significantly altered by the prolonged administration of torsemide (Figure 3). Hyponatremia (median; IQR) was noted on day 6 with a significant decrease in serum sodium concentration (129; 128.8–131.0 mmol/L; $P < .0001$) from baseline (137; 136.8–139.5 mmol/L). Similarly, hypochloremia was observed on day 6 (79.1 ± 3.4 mmol/mL; $P < .0001$) from baseline (101.2 ± 1.7 mmol/L). Moderate hypokalemia was noted on day 6 (3.7 ± 0.2 mmol/L; $P < .0001$) when compared with baseline (1.9 ± 0.2 mmol/L). Metabolic alkalosis was noted with a significant increase in bicarbonate concentration on day 6 (32.3 ± 3.8 mmol/L; $P < .0003$) from baseline (23.2 ± 1.1 mmol/L). Azotemia was noted with a significant increase in serum creatinine concentration (baseline, 1.4 mg/dL ± 0.1; day 6, 2.0 ± 0.1 mg/dL) and BUN (baseline, 14.5 ± 1.8 mg/dL; day 6, 23.5 ± 6.0 mg/dL; $P < .0001$ and $P = .0058$, respectively). A significant increase in TP was noted on day 6 (7.5 ± 0.5 g/dL, $P < .0130$) from baseline (6.6 ± 0.3 g/dL). Increased PCV was noted after long-term torsemide administration (baseline, 35 ± 2%; day 6, 43 ± 3%; $P = .0005$). A significant increase was identified in plasma aldosterone concentrations over the course of torsemide administration ($P = .0006$): day 0 (14.6 ± 9.6 pg/mL), day 1 (59.2 ± 38.2 pg/mL), and day 6 (100.2 ± 27.5 pg/mL; Figure 4).

3.4 | Echocardiography and MAP

The effects of PO torsemide on echocardiographic variables and MAP are shown in Figure 5. Normalized left atrium maximal diameters were significantly decreased on day 6 (1.5; 1.4–1.5, $P = .0046$) when compared with the baseline (1.7; 1.5–1.7). Mean arterial pressures decreased significantly on day 6 (57 ±9 mm Hg, $P = .001$) as compared with baseline (78 ± 6 mm Hg).

4 | DISCUSSION

Orally administered torsemide administration caused significant diuresis with an increase in urine volume and a decrease in USG in all horses. Results also indicated that torsemide reached therapeutic concentrations in blood, resulting in persistent diuresis and changes in biochemical and hemodynamic test results.

Torsemide has less diuretic resistance and anti-aldosterone effects in dogs.[8] Although bioavailability could not be calculated in our study because of unavailability of a torsemide formulation for IV use, it was absorbed after PO administration in all horses, reaching plasma concentrations similar to those observed in previous studies in dogs, rabbits,

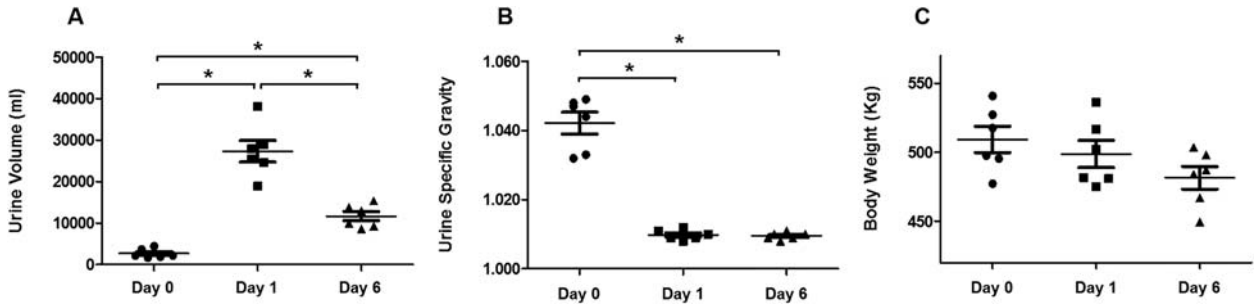

FIGURE 2 A, Total urine volume; B, USG; and C, Body Weight (kg) in each horse before and after oral torsemide administration with 2 mg/kg q12h at three different time points (day 0, circle; day 1, squares; day 6, triangles). The asterisk indicates statistical significance (corrected P value < .05)

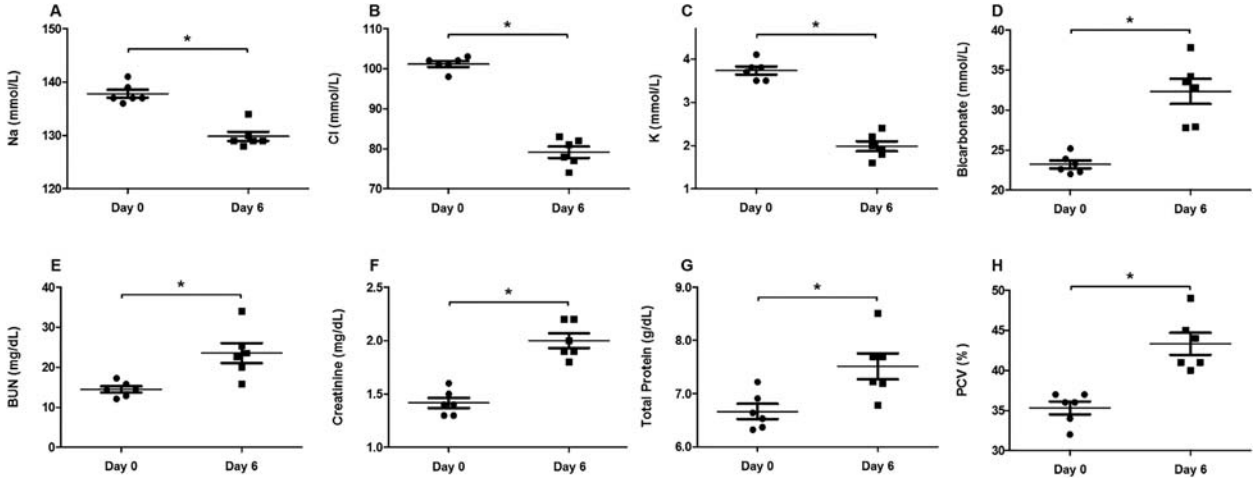

FIGURE 3 Serum electrolytes, biochemistry changes, TP, and PCV before and after oral torsemide administration with 2 mg/kg q12h at day 0 and 6. A, Sodium; B, chloride; C, potassium; D, bicarbonate; E, BUN; F, creatinine; G, TP; H, PCV. The asterisk indicates statistical significance between the different time points (corrected P value $< .05$)

rats and humans.[2,11,13,27,28] Our results showed that after a single dose of 6 mg/kg, plasma torsemide concentration reached a median C_{max} of 10.14 μg/mL and time to reach peak plasma concentration was approximately 3 hours. In humans, peak plasma concentrations are obtained approximately 1 hour after PO torsemide administration[2] and in dogs, peak plasma concentrations were observed at 1.5 hours after drug administration.[11] For the single PO torsemide dose of 6 mg/kg, plasma torsemide concentrations over time showed great variability, and could not be fitted to a compartmental model. Plasma concentration of torsemide after a single PO dose was variable among individuals over the initial 14 hours with an AUC that had a high CV (53%). The high variability for torsemide concentration among individuals and the late onset of peak plasma concentration in our study could be explained by several factors. The nature and amount of ingesta in the gastrointestinal tract of each horse could have played a role and explained the different onset of peak plasma concentration and the differences in drug absorption (eg, drug binding to ingesta). All horses had hay and water restricted for 2 hours before and 4 hours after the single PO dose administration of torsemide (Phase I), and then free choice hay and water were offered. It is likely that the amount of ingesta in the gastrointestinal tract of each horse was different, which could have interfered with drug absorption. The influence of diet, anatomy, and physiology of the equine gastrointestinal tract in the absorption of PO administered torsemide is unknown. However, in humans, simultaneous administration of food with torsemide led to a decrease in drug absorption as indicated by a decrease in C_{max} and a delay in reaching peak plasma drug concentration with no influence on total drug bioavailability and diuretic effects.[29] In our study, a single PO dose of torsemide resulted in an elimination half-life 3 times longer than what was observed in humans and slightly shorter than what was observed after

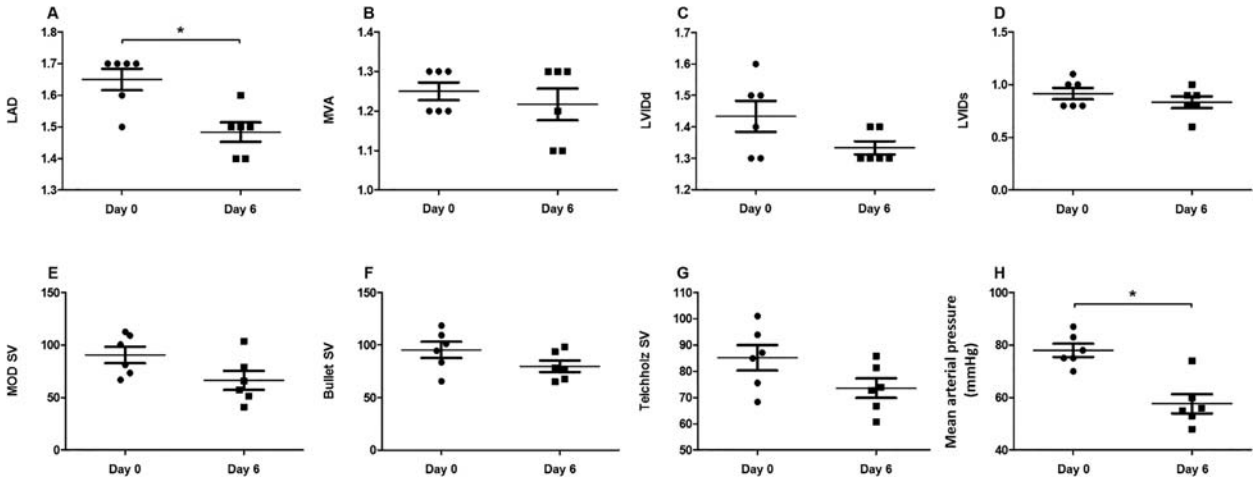

FIGURE 4 Normalized echocardiographic parameters, noninvasive SV measurements, and noninvasive mean arterial systolic blood pressure before and after oral torsemide administration with 2 mg/kg q12h, at day 0 and 6. A, LAD; B, mitral valvular annulus; C, left ventricular internal diameter at end-diastole; D, left ventricular internal diameter at end-systole; E, SV measured by a modified Simpson's method; F, Bullet stroke volume, Bullet SV; G, Teichholz stroke volume, Teichholz SV; H, noninvasive mean arterial systolic blood pressure. The asterisk indicates statistical significance between the different time points (corrected P value $< .05$)

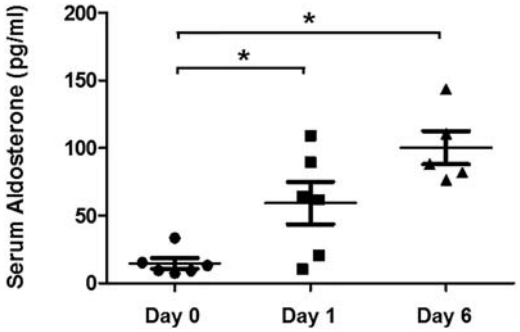

FIGURE 5 Serum aldosterone concentrations before and after oral torsemide administration with 2 mg/kg q12h at 3 different time points (day 0, circle; day 1, squares; day 6, triangles). A significant increase in aldosterone levels was noted when comparing the baseline (day 0) with day 1 and with day 6. No statistical difference was observed between day 1 and day 6. The asterisk indicates statistical significance (corrected P value $< .05$)

IV torsemide administration in dogs.[2,11] The terminal elimination half-life is influenced by drug clearance, but plasma drug decay also can be influenced by the tissue distribution rate. Based on the low CV% for the termination half-life (17.8%), it is likely that the variation among individuals was caused by drug absorption and clearance. Although the CV was high (37.8%), PO torsemide administration resulted in a low apparent total body clearance with a mean of 0.07 L/h/kg, and this finding could be the reason why PO torsemide showed a relatively long terminal half-life in our study. Another important factor is that the pharmacokinetic data reported in our study was obtained from healthy individuals. Physiologic changes seen in CHF, such as a decrease in mesenteric and portal blood flow and increased sympathetic and decreased parasympathetic activity, may have a negative influence on drug absorption, distribution and clearance.[30] Despite this, absorption of PO administered torsemide seems to be similar in healthy and diseased individuals. In a previous pharmacokinetic study,[15] PO and IV formulations of torsemide resulted in similar plasma concentrations in patients with CHF, reaching C_{max} in 1 hour after administration and an absolute bioavailability of 89% was observed. These results indicate that the pharmacokinetics of torsemide in patients with CHF are comparable with those in healthy individuals.[2] Similar results were obtained in a pharmacokinetic study of torsemide in healthy volunteers and patients with renal failure.[16] As previously reported in humans, furosemide has considerable variability with regard to its absorption, which makes it difficult to predict how much furosemide will be absorbed by a given patient. In contrast, the absorption of torsemide in humans, dogs, and rabbits is nearly complete.[13,16,27] By comparison, a previous pharmacokinetic study reported bioavailability ranging from 26 to 65% after a single PO dose of furosemide when compared with a higher bioavailability of 96% after PO administration of torsemide.[2] A recent pharmacokinetic and pharmacodynamic study of PO administered furosemide at 1 mg/kg in healthy horses showed extremely low bioavailability (approximately 5%), absorption was erratic, and diuresis was not induced.[1] It is possible that the furosemide dose used in the study was subclinical, and perhaps therapeutic plasma concentrations and clinical diuresis would have been observed if higher doses had been used. Although torsemide was considered 5–10 times more potent than furosemide on a weight basis,[31] we elected to use a considerably high dose (6 mg/kg) to increase the chances of absorption after a single PO administration during phase I. Based on drug accumulation theory and the pharmacokinetic data obtained in our study, it was speculated that PO dose of 2 mg/kg q12h would result in clinically meaningful drug concentrations in plasma. Therefore, this dosage regimen was applied for the pharmacodynamic study (Phase II).

In a pharmacodynamic study of torsemide in neonatal rabbits, a significant decrease in body weight was observed and related to the forced diuresis.[28] An accurate measurement of feed intake was not obtained, but subjectively it was observed that all horses maintained their dry matter intake. This observation could indicate that torsemide had good palatability among the horses, but our data did not allow a definitive conclusion in this regard. Loop diuretics activate RAAS by decreasing intravascular volume.[17] Aldosterone is an important regulator of renal reabsorption of sodium and effects blood pressure and volume.[18] The aldosterone concentrations measured in our study indicated that PO administered torsemide activated the RAAS as shown by an increase in plasma aldosterone concentration, proving that PO administered torsemide was sufficiently absorbed and induced significant diuresis, likely with a subsequent decrease in plasma volume.

Drugs that inhibit the action of aldosterone on the distal renal tubule potentially can decrease potassium loss during diuretic treatment. Torsemide has been shown to have an inhibitory effect on aldosterone secretion by adrenal cells in rats, guinea pigs, and cows.[32] It was hypothesized that aldosterone secretion was decreased by torsemide, and decreased potassium excretion would be expected in response to the drug. In a study comparing the diuretic effects of torsemide and furosemide in dogs and cats, less potassium wastage was observed in the animals treated with torsemide.[12] Also, in a study evaluating in vivo aldosterone receptor binding activity after administration of furosemide and torsemide to rats, the torsemide group experienced inhibition of aldosterone binding to its receptor in the cytoplasmic fraction of the kidney, whereas the furosemide group did not.[33]

In our study, prolonged PO torsemide at 2 mg/kg q12h induced a significant decrease in serum potassium concentration with moderate to severe hypokalemia noted in all horses during phase II. The marked decrease in serum potassium concentration required supplementation in all horses. After PO potassium chloride supplementation (0.1 g/kg, PO q12h), the decrease in serum potassium concentration reached a plateau, indicating that the electrolyte imbalance observed after PO torsemide can be managed and controlled using PO electrolyte supplementation.

The excessive potassium wastage observed in our study could have been related to the dosage that was employed. The dosage used in our study was relatively high, and might not be appropriate for the treatment of horses with CHF. The decision to use a high dosage was made with the intention of inducing marked diuresis, volume depletion, and activation of the RAAS. In a previous study performed with dogs and cats, torsemide at approximately 1/10 of

the dose of furosemide induced longer diuretic effects. We believe that a reasonable dosage of torsemide for horses with CHF should be lower than used in our study. Based on clinical experience (data not published), we recommend a dosage of 0.5–1 mg/kg PO q12h, but further clinical studies are necessary to determine the optimal PO dosage of torsemide for the treatment of fluid retention in horses. The metabolic alkalosis noted in all horses, likely as compensation from the hypochloremia, also could have contributed to the marked hypokalemia observed in our study. Alkalosis has a direct influence on excretion of potassium mainly by affecting the Na^+/K^+-ATPase pump in the cortical collecting ducts.[34]

The effects of loop diuretics on systemic blood pressure and volume are of interest in the management of diseases such as systemic hypertension, exercise-induced pulmonary hemorrhage (EIPH) and CHF in the horse. Loop diuretics can to attenuate increased right atrial, venous, pulmonary arterial, and capillary pressures, which are evident in the development of pulmonary capillary stress failure during exercise.[9] Although the mechanism of EIPH is not yet fully understood, loop diuretics such as furosemide have been used for more than 40 years to decrease the occurrence or severity of EIPH in horses.[35] Although a decrease in MAP was observed, which could be beneficial in the treatment of EIPH, further research with this new potent diuretic agent in EIPH is necessary before clinical use can be recommended. In our study, prolonged PO administration of torsemide induced a significant decrease in left atrial maximal diameter when comparing baseline to day 6. Although a direct measure such as lithium dilution technique was not used to obtain stroke volume (SV) measurements in our study, noninvasive methods to determine SV in horses using echocardiography have been described and provided reliable results.[23] The decrease in the left atrial diameter (LAD) likely was related to the hypovolemia induced.

In an open-label study performed in human patients with CHF secondary to left ventricular systolic dysfunction, patients assigned to treatment with torsemide were less likely to be hospitalized for CHF, were less fatigued, and reported better quality of life when compared to patients being treated with furosemide.[36] In a study evaluating the effects of different diuretics on cardiac function in rats with induced CHF, animals being treated with torsemide showed decreased cardiac aldosterone synthase, less remodeling of the left ventricle and echocardiographic evidence of improved cardiac function when compared with rats being treated with furosemide.[37] In dogs with CHF being treated with torsemide for 28 days, no evidence of weakness, fatigue, hypotension, severe electrocardiographic alterations or skin rash were observed.[38] With the current availability of effective formulations of other cardiovascular medications, such as ACE inhibitors, for PO use, and the tendency to keep horses long term as companion animals, horse owners maybe more amenable to treat chronic medical conditions such as CHF.[39] A diuretic drug such as torsemide, which potentially can provide better quality of life, less risk of cardiac remodeling, less diuretic resistance, and better owner compliance without the need for an injectable treatment regimen, can be an important addition in the treatment of CHF in the horse.[1]

5 | CONCLUSION

The use of PO administered torsemide has several pharmacological advantages. Torsemide is relatively inexpensive and available in a wide range of tablet sizes (from 5 to 100 mg per tablet). Some of the electrolyte imbalances observed in our study were likely related to the high dosage used. As with other diuretics, horses being treated with torsemide should be closely monitored for any signs of dehydration and electrolytes imbalances. Based on the pharmacokinetic data and the pharmacodynamic effects observed, we recommend 0.5–1 mg/kg PO q12h as a starting dosage and recommend titrating the dosage to effect for horses with fluid overload. Good absorption after PO administration, a reasonable excretion half-life, and persistent diuresis may make PO torsemide an attractive alternative to furosemide for prolonged diuretic treatment in the horse.

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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

This experiment was approved by the IACUC of Auburn University.

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