Pharmacokinetics and In Vitro Effects of Tegaserod, a Serotonin 5-Hydroxytryptamine 4 (5-HT₄) Receptor Agonist with Prokinetic Activity in Horses

Michelle L. Delco, DVM, DACVSᵃ,*
Jorge E. Nieto, MVZ, PhD, DACVSᵇ
Arthur L. Craigmill, PhDᶜ
Scott D. Stanley, PhDᵈ
Jack R. Snyder, DVM, PhD, DACVSᵇ

ᵃVeterinary Medical Teaching Hospital
ᵇDepartment of Surgery and Radiology
ᶜDepartment of Environmental Toxicology
ᵈK. L. Maddy Equine Analytical Chemistry Laboratory
University of California, Davis
Davis, California 95616

CLINICAL RELEVANCE

Tegaserod, a serotonin agonist, has been shown to have prokinetic effects in horses, but pharmacokinetic information is not currently available. The pharmacokinetics and in vitro effects of tegaserod were evaluated. Tegaserod increased the contractile activity of smooth muscle preparations of the equine pelvic flexure. Pertinent pharmacokinetic parameters for a single IV and oral dose were determined. Therapeutic plasma concentrations of tegaserod were achieved with a single oral dose at 0.27 mg/kg. These findings indicate that further clinical studies are warranted to investigate potential benefits in cases of functional gastrointestinal motility disorders in horses.

INTRODUCTION

Colic resulting from functional gastrointestinal (GI) motility disorders is common in horses; examples include small intestine (SI) ileus, small and large colon impactions, and cecal impactions. Postoperative ileus is one of the most frequently encountered and potentially fatal complications after colic surgery.¹⁻⁸ The treatment of horses with postoperative ileus remains controversial, but prokinetic drugs are frequently used⁹ and may decrease the morbidity associated with this disease entity.¹⁰⁻¹⁴ Unfortunately, drug choices are limited, and many of those available to equine practitioners have the potential for serious adverse effects.¹⁰

Serotonin, or 5-hydroxytryptamine (5-HT), plays a critical role in the GI tract, influencing secretory, motor, and sensory function. Serotonin subtype 4 receptors are found through-
out the GI tract and act to initiate the peristaltic reflex and modulate visceral sensitivity. Cisapride, a second-generation substituted benzamide, acts as a 5-HT receptor agonist and was shown to increase GI motility in horses in experimental models in vitro and in clinical trials. However, because the use of cisapride was related to fatal cardiac arrhythmias in humans, it was removed from the US market in July 2000.

Tegaserod is a potent selective 5-HT₄ partial agonist. Tegaserod is approved for the treatment of irritable bowel syndrome and chronic idiopathic constipation in humans and has been shown to have promotile effects and visceral analgesic properties in various species. Limited information regarding the use of tegaserod in horses is available. Recently, tegaserod was shown to increase in vitro motility of the equine pelvic flexure and accelerate GI transit time in normal horses, but information about the pharmacokinetics of tegaserod in horses is lacking. The objectives of this study were to determine the effects of tegaserod on the in vitro contractile activity of the equine jejunum and pelvic flexure and to determine the pharmacokinetic profile of tegaserod after a single oral, rectal, and IV dose in normal horses.

**MATERIALS AND METHODS**

**Muscle Strip Preparations (In Vitro)**

Segments of mid-jejunum and pelvic flexure were collected from four horses between the ages of 3 and 15 years euthanized for reasons other than GI problems or systemic disease. Ingesta was removed by rinsing with modified Krebs–Ringer’s buffer solution; segments were pinned flat in a dissecting dish containing oxygenated modified Krebs–Ringer’s buffer solution, and full-thickness muscle strips were cut parallel to the circular smooth muscle fibers and placed in organ baths as previously described. After 60 minutes’ normalization, baseline isometric force was recorded using force transducers connected by a grass transducer cable to an eight-channel polygraph chart recorder. Tegaserod maleate (Topharman Shanghai Co., Ltd., Shanghai, China) was dissolved in 0.6 mM tartaric acid and further diluted in distilled water. Briefly, 4.175 mg of tegaserod maleate was dissolved in a 0.6 mM solution of tartaric acid and further diluted in 950 µl of distilled water to make a stock solution of 10⁻² M; 10 µl of this stock solution was added to 990 µl of Krebs–Ringer’s buffer solution to make a second stock solution of 10⁻⁵ M concentration. These two stock solutions were used to achieve the desired concentration in the tissue bath by adding 2, 20, or 200 µl to 20 ml of tissue bath. Increasing molar concentrations (10⁻⁹ to 10⁻⁴ M) of tegaserod or vehicle were added cumulatively to the tissue baths every 3 minutes, and the data were recorded (Power Lab, AD Instruments Pty Ltd., Castle Hill, Australia). Active contractile force was adjusted for cross-sectional area as previously described. Statistical analysis was performed using a one-way analysis of variance followed by the Bonferroni test using a commercial software package (SPSS, Chicago, IL). Significance was set at \( P < .05 \).
and then further diluted in 250 ml of 0.09% sodium chloride. An IV catheter was placed in the jugular vein using aseptic techniques, and tegaserod was administered as a slow bolus (over 2 minutes). Blood samples (20 ml) were obtained from the IV catheter and placed in sterile heparinized Vacutainers at 0 (baseline), 5, 10, 15, 20, 30, 45, and 60 minutes, and 2, 3, 4, 6, 8, 10, 12, and 24 hours. Samples were centrifuged at room temperature, and the plasma was collected and stored at –80˚C until analysis.

A total of 14 normal horses received a single administration of tegaserod orally (0.09 mg/kg, \( n = 6 \); 0.18 mg/kg, \( n = 2 \); and 0.27 mg/kg, \( n = 6 \)). Tegaserod maleate (Zelnorm, Novartis Pharmaceuticals) from the commercially available tablets was pulverized using a mortar and pestle, suspended in 30 ml of distilled water, and administered via nasogastric tube. The tube was flushed with 120 ml of water and removed.

For rectal administration, horses were restrained in standing stocks and feces were evacuated from the rectum manually. Tegaserod (prepared as for oral dosing; 0.09 mg/kg, \( n = 6 \); 0.18 mg/kg, \( n = 2 \)) was administered rectally approximately 30 to 40 cm orad to the anal sphincter using a syringe and plastic extension set, and the extension set tubing was flushed with 30 ml of air. Blood was collected and stored as previously described.

Horses from a herd of research

**Figure 1.** A. Contractile force in smooth muscle preparations of the equine pelvic flexure exposed to increasing concentrations of tegaserod (squares) and control samples (diamonds). Concentrations are expressed as mean ± SEM. Asterisks indicate significant increase in contractile force versus control samples (\( P < .05 \)). B. Contractile force in smooth muscle preparations of the equine jejunum exposed to increasing concentrations of tegaserod (squares) and control samples (diamonds). Concentrations are expressed as mean ± SEM. No significant difference is demonstrated between tegaserod-treated samples and controls.
animals maintained by the Center for Equine Health at the University of California, Davis were randomly assigned to each treatment group. The two horses used for IV administration were also used for the oral dosing, and a 2-month washout period was allowed between studies. Horses were housed in round pens and fed free choice grass hay beginning 1 hour after tegaserod administration. They were monitored for attitude, appetite, signs of colic, and passage of feces continuously for the first 4 hours, then at intervals coinciding with sample collection.

### Sample Analysis

Plasma concentrations of tegaserod were determined by liquid chromatography–mass spectrometry (LC-MS). The plasma samples were subjected to solid-phase extraction, and tegaserod was identified and quantified by LC-MS operated under electrospray ionization conditions in the multiple reaction monitoring mode using a triple quadrupole LC-MS/MS (liquid chromatography/mass spectrometry/mass spectrometry) system. Plasma samples and calibrators were processed for analysis by diluting 1.0-ml aliquots with water (HPLC grade); internal standard solution (5.0 ng/ml azaperone) was added, followed by centrifugation (1,300 × g for 3 minutes). Solid-phase extraction was performed by using CleanScreen DAU columns (3 ml, 130 mg; United Technologies, Bristol, PA). The columns were conditioned sequentially with 3 ml each of methanol and 0.1-M phosphate buffer (pH 6.0). The plasma samples were loaded onto the column at a flow rate of 1 to 2 ml/min using low-pressure nitrogen gas. The columns were rinsed with 3 ml each of water and methanol. Each column cartridge was dried using low-pressure (20 psi) nitrogen gas for 2 minutes. To collect the tegaserod, 3 ml of a 78:20:2 methylene chloride:isopropanol:ammonium hydroxide solution was applied to the column and the fraction collected. The eluent was dried in a nitrogen evaporator at 40°C ± 5°C.

Plasma quantitative measurements were conducted in duplicate on a TSQ Quantum triple quadrupole mass spectrometer (Thermo Electron, San Jose, CA) with electrospray interface connected with a 1100 Series HPLC (Agilent Technologies, Palo Alto, CA). Chromatography used a C-18 column (internal diameter: 10 × 2.1 mm; particle size: 3 μm) (Mac-Mod Analytical, Chadds Ford, PA) and a linear gradient of acetronile in water with a constant 0.2% formic acid at a flow rate of 0.4 ml/min. The acetronile concentration was held at 10% for 1.0 minute, ramped from 10% to 90% over 5.0 minutes, and held at 90% for an additional 1.0 minute. Before analysis, the extracts of all samples, controls, and calibrators were redissolved in 150 µl of the initial mobile phase. For each plasma sample, 10 µl was injected onto the analytical column. Tegaserod was detected by positive mode ionization with fragment m/z (mass:charge ratio) = 302.1 for tegaserod with MS-MS transitions of 173, 158, 285, and 145 and fragment m/z = 328.4 for the azaperone internal standard. Calibration curves consisted of seven standard concentrations ranging from 0.10 to 10 ng/ml. The concentration of tegaserod was determined by the internal standard method using the peak area ratio and linear regression analysis. The limit of quantitation of this method in plasma was approximately 0.1 ng/ml. The method accuracy was determined by replicate analysis of samples containing 0.1, 0.2, 0.5, 1.0, 2.0 5.0, 10.0, and 20.0 ng/ml of tegaserod. All mean values were within 15% of the actual value, except the LOQ (0.10 ng/ml), which was within 20% of the actual value. Six positive control samples at 1.0 ng/ml were run with every batch of plasma samples. The intra-day
and inter-day precision for the peak area ratios ranged from 2% to 12% and 3% to 11%, respectively. The results indicated that the method has acceptable precision.

**Pharmacokinetic Analysis**

Data were analyzed using a commercial pharmacokinetic data analysis software package (WinNonLin Pro 5.0, Pharsight, Mountain View, CA). A two-compartment open model was used initially to fit the IV data. The PO data were first fitted to a one-compartment model with first order absorption. A two-compartment model was found to be the best for both the IV and PO routes based on visual examination of the line fit, residual plots, and Akaike's information criterion. Weighting of the data using the inverse square of the concentration improved the line fit and residual plots and was used for all of the data. The primary compartmental parameters calculated were A and B (i.e., zero time intercept of the distribution and elimination phases, respectively) and alpha and beta (i.e., the rate constants for the distribution and elimination phases). For the oral route, the rate constant of absorption (Kabs) and the lag time were also calculated. The secondary compartmental parameters calculated were the alpha and beta half-lives for the IV route. A noncompartmental analysis of the plasma concentration–time data was performed for both routes of administration. The parameters estimated include the lambda z half-life, the area under the curve from 0 to infinity (AUC_{0→∞}), the mean residence time (MRT), the volume of distribution at steady-state (Vd_{ss}), the observed clearance (Cl), and
the maximum observed plasma concentration ($C_{\text{max}}$) and the time at which it was observed ($T_{\text{max}}$). The mean absorption time was calculated by subtracting the MRT calculated for the IV route from the area under the first moment curve (AUMC)/AUC for the PO route. Bioavailability ($F$) was calculated by dividing the mean $AUC_{\text{IV}}$ by mean $AUC_{\text{oral}}$ after normalizing for dosage ($F = AUC_{\text{oral}} \times \text{Dose}_{\text{IV}} / AUC_{\text{IV}} \times \text{Dose}_{\text{oral}}$). Values for IV administration were expressed as the mean of the two values. Values for oral administration were expressed as mean ± SD.

### RESULTS

#### In Vitro Studies

Tegaserod caused a concentration-dependent increase in isometric stress response in the pelvic flexure smooth muscle preparations. A significant increase ($P < .05$) was observed in the smooth muscle preparations of the pelvic flexure at concentrations of tegaserod above $10^{-5}$ M (Figure 1A). No significant increase was observed in the preparations of the jejunum (Figure 1B).

#### Pharmacokinetic Studies

The plasma concentration–time profiles of tegaserod after a single IV and oral dose are shown in Figures 2A and 2B, respectively. The pertinent pharmacokinetic parameters are summarized for the IV route in Table 1 and the oral route in Table 2.

After IV dosing, the mean predicted maximum concentration at $t = 0$ was 9.27 ng/ml; the distribution was rapid with a mean half-life of 0.125 hours, and the elimination rate was moderate with a mean half-life of 4.08 hours. The mean area under the plasma concentration–time curve ($AUC_{\text{IV}}$) was 2.88 hr × ng/ml, the mean clearance was 15.9 L/hr/kg, the mean $V_d$ was 60.4 L/kg, and the MRT was 3.41 hours. The mean percentage of the AUC, which was extrapolated, was 23.7%.

The observed mean peak plasma concentration of 4.95 ng/ml was obtained at a mean of 1.25 hours after a single oral dose of 0.27 mg/kg, and the mean $AUC_{\text{oral}}$ was 14.67 hr × ng/ml. After a lag time of 0.81 hour, tegaserod was rapidly absorbed, maintained plasma concentrations above 1 ng/ml for approximately 5 hours, and demonstrated a prolonged terminal elimination phase. The mean percentage of the AUC, which was extrapolated, was 19.4%. The mean elimination half-life was 8.45 hours, and the mean absorption time was 6.64 hours. The oral bioavailability was calculated to be 55%.

Rectal administration at 0.09 mg/kg resulted in a mean maximum plasma concentration of 1.4 ng/ml at 52.5 minutes after administration; however, when a dose of 0.18 ng/ml was tested in two horses, the mean $C_{\text{max}}$ achieved was only 0.77 ng/ml. Because of the erratic plasma levels that occurred after rectal dosing, kinetic analysis was not performed.

All dosages and routes of administration were well tolerated by all horses.

#### DISCUSSION

Tegaserod increased the in vitro contractile activity of smooth muscle preparations of the equine pelvic flexure. This finding is similar to that reported by Weiss and colleagues, which was the first study to demonstrate in vitro evidence for prokinetic properties of tegaserod in horses. In that study, tegaserod increased the contractile activity of smooth muscle preparations of the pelvic flexure but not the ileum. Our goal was to use the pelvic flexure as a positive control and to test a different segment of the small intestine. No significant effect of tegaserod on the contractile force of jejunal smooth muscle preparations was observed in our experimental model. Tegaserod has, however, been shown to stimulate small intestinal motility and gastric emptying in multiple oth-
er species examined, including humans, rats, guinea pigs, and dogs.\textsuperscript{22,26,27} Furthermore, another specific 5-HT\textsubscript{4} agonist was recently shown to increase myoelectric activity in the equine jejunum in vivo.\textsuperscript{28} Conflicting information exists regarding the in vitro characterization of 5-HT receptors in the equine small intestine.\textsuperscript{21,23,29} Weiss and associates\textsuperscript{23} demonstrated that horses may possess 5-HT\textsubscript{4} receptors in the ileum; in that study, cumulative application of serotonin induced contractions in equine ileal smooth muscle preparations, which were antagonized (by approximately 45\%) by a specific 5HT\textsubscript{4} antagonist (SB 203-186). Nevertheless, application of tegaserod caused no significant increase in the amplitude or frequency of contractions in the ileal preparations. One suggested explanation for this finding is potential heterogeneity among 5-HT\textsubscript{4} receptors within a species or in different segments of the GI tract.\textsuperscript{23} Nieto et al\textsuperscript{21} found that a different 5-HT\textsubscript{4} antagonist (SDZ-205,557) did not alter response to 5-HT in equine jejunal smooth muscle preparations. This may support the theory of heterogeneity among 5-HT\textsubscript{4} receptor subtypes, be related to different selectivity of the compounds used, or indicate that horses lack 5-HT\textsubscript{4} receptors in the jejunum. Most recently, receptor agonist–antagonist studies by Delesalle and coworkers\textsuperscript{29} suggest that the contractile effects of serotonin on the equine jejunum are not mediated by any of the currently known classes of 5-HT receptors. Interestingly, Lillich and associates\textsuperscript{30} demonstrated that the serotonin agonist cisapride may modulate intestinal motility via nonserotonergic receptors, namely ether-a-go-go (ERG) voltage-gated ion channel proteins.

**TABLE 1. Pharmacokinetic Data for Tegaserod after a Single IV Administration (0.04 mg/kg; \( n = 2 \))**

<table>
<thead>
<tr>
<th></th>
<th>Units</th>
<th>Horse 1</th>
<th>Horse 2</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Two-compartment analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>ng/ml</td>
<td>4.3</td>
<td>13.8</td>
<td>9.02</td>
</tr>
<tr>
<td>B</td>
<td>ng/ml</td>
<td>0.269</td>
<td>0.239</td>
<td>0.254</td>
</tr>
<tr>
<td>Alpha</td>
<td>1/hr</td>
<td>3.7</td>
<td>11.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Beta</td>
<td>1/hr</td>
<td>0.148</td>
<td>0.198</td>
<td>0.2</td>
</tr>
<tr>
<td>Alpha HL</td>
<td>hr</td>
<td>0.19</td>
<td>0.06</td>
<td>0.125</td>
</tr>
<tr>
<td>Beta HL</td>
<td>hr</td>
<td>4.67</td>
<td>3.49</td>
<td>4.08</td>
</tr>
<tr>
<td><strong>Noncompartmental analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL lambda (_{z})</td>
<td>hr</td>
<td>3.79</td>
<td>4.12</td>
<td>3.96</td>
</tr>
<tr>
<td>AUC(_{\text{HL}})</td>
<td>hr (\times) ng/ml</td>
<td>3.89</td>
<td>1.86</td>
<td>2.88</td>
</tr>
<tr>
<td>Cl</td>
<td>ml/hr/kg</td>
<td>10,260</td>
<td>21,480</td>
<td>15,870</td>
</tr>
<tr>
<td>MRT</td>
<td>hr</td>
<td>2.58</td>
<td>4.39</td>
<td>3.49</td>
</tr>
<tr>
<td>Vd(_{\text{ss}})</td>
<td>ml/kg</td>
<td>26,430</td>
<td>94,300</td>
<td>60,365</td>
</tr>
</tbody>
</table>

A = zero-time intercept of the distribution phase; alpha = negative slope of the distribution phase; alpha HL = half life of the distribution phase; AUC\(_{\text{HL}}\) = area under the tegaserod plasma concentration–time curve; B = zero-time intercept of the elimination phase; beta = negative slope of the elimination phase; beta HL = half-life of the elimination phase; MRT = mean residence time; Cl = body clearance; HL lambda \(_{z}\) = half life of the final phase; Vd\(_{\text{ss}}\) = volume of distribution at steady state.
In our study, concentrations of tegaserod above $5 \times 10^{-5}$ M were not tested in the jejunum because, above this concentration, baseline motility of the control preparations was significantly inhibited by the vehicle. We hypothesize that the tartaric acid (used to dissolve tegaserod) was likely responsible for the decline in baseline motility, but this was not investigated further. The concentration of tegaserod that produced an increase in contractions in the in vitro study is orders of magnitude higher than the $C_{\text{max}}$ obtained after the oral administration of tegaserod. It is possible that the strips of smooth muscle required longer exposure time to the tegaserod to stimulate contractions; we allowed only 3 minutes at each concentration. Tegaserod maleate is practically insoluble in water and ethanol, and the solvent used to prepare our stock solution may well have a negative effect on contractility, moving the concentration-response curve to the right. Based on this and previous studies, in vivo models to test gastric emptying and small bowel transit may be more useful in investigating the effect of tegaserod on the upper GI tract in horses.

In the pharmacokinetic studies, increasing doses corresponded with increasing plasma concentrations of tegaserod when administered orally. The dosages used in this study were extrapolated from human literature and recent work in horses. Tegaserod administered orally at 0.09 and 0.18 mg/kg resulted in plasma concentrations below the therapeutic levels reported in humans; these data were not included in our analysis. The recommended dose in humans is 6 mg PO bid, resulting in a $C_{\text{max}}$ of $2.9 \pm 1.1$ ng/ml, which compares favorably with the values we obtained (4.95 ng/ml) after a single oral dose at 0.27 mg/kg. Lippold and coworkers observed a significant decrease in intestinal transit time in horses at a dose comparable to that studied here. Based on our findings, 0.27 mg/kg PO bid appears to be an appropriate dose for horses, although establishing a true therapeutic plasma concentration would require a large-scale clinical efficacy trial.

Bioavailability of tegaserod in horses was calculated to be approximately 55%, which contrasts to an approximate bioavailability of 10% in humans. This finding may be a reflection of the major differences in GI physiology between humans and horses. Alternatively, this discrepancy may be a result of individual variation owing to the small sample size of our IV group. The small sample size is a principal limitation of this study. The volume of distribution is large, implying extensive extravascular distribution, likely because of the drug’s high lipid solubility. After IV administration to human subjects, the terminal half-life of tegaserod was approximately 11 hours versus 4.08 hours in horses.

Tegaserod in the form of crushed tablets is stable in and compatible with water; the suspension is homogenous and, in humans, the complete dose is delivered in this form. As a suspension, tegaserod appeared to be well absorbed by the horses in our study and is therefore an acceptable form for oral administration.

Preliminary data on rectal administration of tegaserod (0.09 mg/kg, $n = 6$) were promising in that peak plasma concentrations were higher than those obtained with the same dose administered orally. However, based on the finding that a higher rectal dose (0.18 mg/kg, $n = 2$) resulted in a lower mean plasma concentration, we concluded that rectal absorption is not predictable under these conditions. The reason for this finding is unclear but may have been the result of confounding factors (e.g., individual horse variation, increased defecation caused by stress, external or environmental factors, mixing of drug with feces). Similarly disappointing results have been demonstrated with rectal application of cisapride. It is possible
that a rectal bolus, a lipophilic suspension, or a different solvent (such as DMSO) could improve the rectal absorption. The latter approach was not evaluated based on one author’s (J. E. N.) experience, indicating that DMSO did not improve rectal absorption of cisapride.

In addition to its effect on motility, tegaserod has been shown to decrease sensitivity to colorectal distension in animal models and decrease pain and bloating associated with constipative irritable bowel syndrome in humans. Prokinetics are not routinely used to treat impactions of the large colon; however, if it is shown to decrease visceral sensitivity in horses, tegaserod may prove a useful tool in the management of nonsurgical large and small colon impactions; agents commonly used to provide analgesia in these cases (such as α2 agonists and opioids) may negatively impact motility. If shown to be safe, beneficial, and cost effective, tegaserod may improve primary therapy, potentially expediting resolution and decreasing the number of patients that develop gas distension, remain persistently colicky, and require surgical intervention. Of further interest would be the use of tegaserod in clinical cases of chronic, intermittent, idiopathic colic in which a primary dysmotility of the large intestine is suspected. These potential applications are clearly speculative and would require further investigation.

**CONCLUSION**

Tegaserod increased the in vitro contractile activity of the smooth muscle of the equine pelvic flexure. Therapeutic plasma concentrations of tegaserod can be achieved in normal horses by a single oral administration at 0.27

---

**TABLE 2. Pharmacokinetic Data for Tegaserod after a Single Oral Administration (0.27 mg/kg body weight; n = 5)**

<table>
<thead>
<tr>
<th>Two-Compartment Analysis</th>
<th>Units</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ng/ml</td>
<td>39.61</td>
<td>14.81</td>
<td>6.63</td>
</tr>
<tr>
<td>B</td>
<td>ng/ml</td>
<td>0.912</td>
<td>0.72</td>
<td>0.32</td>
</tr>
<tr>
<td>Kabs</td>
<td>1/hr</td>
<td>3.76</td>
<td>3.68</td>
<td>1.65</td>
</tr>
<tr>
<td>Alpha</td>
<td>1/hr</td>
<td>2.02</td>
<td>0.65</td>
<td>0.29</td>
</tr>
<tr>
<td>Beta</td>
<td>1/hr</td>
<td>0.114</td>
<td>0.15</td>
<td>0.07</td>
</tr>
<tr>
<td>Tlag</td>
<td>hr</td>
<td>0.806</td>
<td>0.39</td>
<td>0.18</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>hr</td>
<td>1.252</td>
<td>0.19</td>
<td>0.08</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>ng/ml</td>
<td>4.95</td>
<td>5.43</td>
<td>2.43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Noncompartmental Analysis</th>
<th>Units</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL lambda z</td>
<td>hr</td>
<td>8.45</td>
<td>5.93</td>
<td>2.65</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>hr × ng/ml</td>
<td>14.7</td>
<td>8.67</td>
<td>3.88</td>
</tr>
<tr>
<td>AUMC/AUC</td>
<td>hr</td>
<td>10.0</td>
<td>4.92</td>
<td>2.2</td>
</tr>
<tr>
<td>MAT</td>
<td>hr</td>
<td>6.64</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

A = zero-time intercept of the distribution phase; alpha = negative slope of the distribution phase; AUC<sub>0-∞</sub> = area under the tegaserod plasma concentration–time curve; B = zero-time intercept of the elimination phase; beta = negative slope of the elimination phase; Cl = body clearance; C<sub>max</sub> = peak plasma concentration; HL lambda z = half-life of the final phase; Kabs = rate constant of absorption; MAT = mean absorption time; Tlag= lag phase for absorption; T<sub>max</sub> = time to peak plasma concentration.
mg/kg. Additional clinical studies are warranted to investigate potential clinical benefits in horses suffering from functional GI motility disorders.

ACKNOWLEDGMENTS

These findings were presented as an abstract at the Eighth International Equine Colic Research Symposium, August 3, 2005, Quebec City, Canada. This project was supported by the Center for Equine Health with funds provided by the Oak Tree Racing Association, the State of California satellite wagering fund, and contributions by private donors.

REFERENCES


