Pharmacokinetics of pentoxifylline and its 5-hydroxyhexyl metabolite after oral and intravenous administration of pentoxifylline to healthy adult horses

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Objective—To determine serum pharmacokinetics of pentoxifylline and its 5-hydroxyhexyl metabolite in horses after administration of a single IV dose and after single and multiple oral doses.

Animals—8 healthy adult horses.

Procedures—A crossover study design was used with a washout period of 6 days between treatments. Treatments were IV administration of a single dose of pentoxifylline (8.5 mg/kg) and oral administration of generic sustained-release pentoxifylline (10 mg/kg, q 12 h, for 8 days). Blood samples were collected 0, 1, 3, 6, 12, 20, 30, and 45 minutes and 1, 2, 4, 6, 8, and 12 hours after IV administration. For oral administration, blood samples were collected 0, 0.25, 0.5, 0.75, 1, 2, 4, 8, and 12 hours after the first dose and 0, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, and 24 hours after the last dose.

Results—Elimination of pentoxifylline was rapid after IV administration. After oral administration, pentoxifylline was rapidly absorbed and variably eliminated. Higher serum concentrations of pentoxifylline and apparent bioavailability were observed after oral administration of the first dose, compared with values after administration of the last dose on day 8 of treatment.

Conclusions and Clinical Relevance—In horses, oral administration of 10 mg of pentoxifylline/kg results in serum concentrations equivalent to those observed for therapeutic doses of pentoxifylline in humans. Twice daily administration appears to be appropriate. However, serum concentrations of pentoxifylline appear to decrease with repeated dosing; thus, practitioners may consider increasing the dosage if clinical response diminishes with repeated administration. (Am J Vet Res 2006;67:1621–1627)

Pentoxifylline is a methylxanthine derivative that was initially identified as an agent that increases flexibility of RBCs. It has been investigated for its anti-inflammatory and immune-modulating effects. Pentoxifylline can suppress the production of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6. Pentoxifylline also has the ability to inhibit activation of B and T cells, decrease adhesion and aggregation of leukocytes, and modify properties of fibroblasts by increasing fibroblast collagenase and decreasing fibroblast collagen, which positively affects wound healing.

Pentoxifylline has been used as a therapeutic option for humans with various clinical conditions, in humans, including but not limited to peripheral vascular disease, alcoholic hepatitis, and mental dementia. Pentoxifylline has also been evaluated for its capacity to optimize survival of skin flaps, enhancement of healing after radiation therapy, and treatment of vasculitis. Similarly, pentoxifylline has been used in an extralabel manner for the treatment of dogs with various conditions. Pentoxifylline has been used anecdotally for treatment of horses with laminitis, endometritis-placentitis, and dermal vasculitis and ulcers with septicemia. It is unknown whether these clinical conditions share 1 therapeutic concentration or whether they differ. In 1 study, an in vitro whole-blood model of endotoxemia in horses revealed that...
pentoxifylline suppressed production of tumor necrosis factor-α in a dose-related manner, with an optimal concentration of pentoxifylline for suppression between 1 and 10 μg/mL. Another study revealed that IV infusion of pentoxifylline resulted in plasma concentrations of pentoxifylline between 1 and 10 μg/mL.

The pharmacokinetics of pentoxifylline have been defined in humans and dogs. After oral administration in these species, pentoxifylline is rapidly absorbed and eliminated. Pentoxifylline is primarily metabolized by reduction to form the pharmacologically active 5-hydroxyhexyl metabolite. This metabolism is reversible, and both pentoxifylline and the 5-hydroxyhexyl metabolite reportedly bind to erythrocyte membranes.

The pharmacokinetics of pentoxifylline in horses is less clearly defined. More specifically, in 1 study, concentrations of pentoxifylline and 5-hydroxyhexyl metabolite were determined after oral (6.8 to 7.5 mg/kg) and IV (6.68 mg/kg) administration. Analysis of the results of that study suggested that pentoxifylline is absorbed in horses after oral administration but that the rate of absorption can vary tremendously. Because of the variability of oral absorption and the limited number of animals in that study, no recommendations were made as to the appropriate dose, dosing interval, or formulation for administration. As a consequence, practitioners are left to speculate on the appropriate dose, which leads to the use of a number of regimens (4.4 to 35 mg/kg administered 2 or 3 times daily) with variable success.

To further complicate the situation, various generic formulations are available on the market, in addition to the proprietary product. The only published serum pharmacokinetic study in horses of which we are aware used the proprietary product, which is rarely used by practitioners because of its high cost. Because of the availability of generic formulations and the substantial difference in price ($0.78/tablet for the proprietary product vs $0.11/tablet for generic products), practitioners primarily use generic formulations for which no information is available. For this reason, and before additional pharmacodynamics studies can be completed, it is important to define the pharmacokinetics of generic pentoxifylline. Therefore, the objective of the study reported here was to determine the pharmacokinetics of pentoxifylline and its major 5-hydroxyhexyl metabolite after a single dose administered IV and after single and multiple doses administered orally.

**Materials and Methods**

**Animals**—Eight adult horses from a university research herd were used for the study. The horses comprised 4 Thoroughbred mares between 3 and 3 years of age; 3 Thoroughbred geldings, all of which were 6 years old; and 1 Quarter Horse gelding that was 3 years old. Horses were determined to be healthy on the basis of housing requirements. Each group was randomly assigned to initially receive IV or oral administration of pentoxifylline; thus, horses of group 1 were initially administered pentoxifylline orally, whereas horses of group 2 initially were administered pentoxifylline IV. Treatments were reversed so that group 1 then was administered pentoxifylline IV and group 2 was administered pentoxifylline orally. There was at least a 6-day washout period between treatments.

Hay and grain were withheld for 2 hours before and until 2 hours after IV and oral administration of pentoxifylline. Indwelling catheters were inserted bilaterally in the jugular veins of all horses. Catheters were inserted in accordance with standard aseptic techniques and sutured in place with 2-O nylon. Catheters were removed 4 hours after drug administration.

**IV administration of pentoxifylline**—Pentoxifylline for IV administration was prepared by use of analytical-grade pentoxifylline in sterile water to create a solution with a concentration of 50 mg/mL at 21°C. The pentoxifylline solution was filtered through a 2-μm filter, and a dose of 8.5 mg/kg was administered slowly as a bolus via the catheter inserted in the right jugular vein of each horse. Duration of the infusion ranged from 2 to 3 minutes, depending on the volume injected. Timing for collection of blood samples began when administration of the bolus was completed. Each horse was ausculted by use of a stethoscope to monitor cardiac response.

**Oral administration of pentoxifylline**—Generic sustained-release pentoxifylline tablets were administered orally (10 mg/kg) every 12 hours for 8 days. Tablets were crushed with a mortar and pestle and added to 25 mL of molasses. The mixture was then administered orally to each horse. Blood samples were obtained for a CBC and serum biochemical analysis at the end of the 8-day oral administration phase of the study.

**Collection of blood samples**—Blood samples were collected immediately before (time 0) and 1, 3, 6, 12, 20, 30, and 45 minutes and 1, 2, 4, 6, 8, 12 hours after IV administration of pentoxifylline. Blood samples were collected immediately before (time 0) and 0.25, 0.5, 0.75, 1, 2, 4, 8, 12 hours after oral administration of the first dose and 0, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, and 24 hours after the last dose of pentoxifylline (the last dose of pentoxifylline was administered on day 8). Blood samples were collected from the right jugular vein of each horse. While the catheter was in place, blood was collected by use of extension tubing fitted with a 3-way stopcock into 10-mL syringes. Samples were immediately placed into evacuated collection tubes. Sterile saline (0.9% NaCl) solution was then used to flush the tubing and catheter. After the catheter was removed, blood samples were collected directly into evacuated collection tubes by venipuncture of the left jugular vein.

Blood samples were allowed to sit at 21°C until clotted; they then were centrifuged at 2,300 X g for 15 minutes. Serum was harvested and frozen immediately in freezer vials until HPLC analysis could be completed.

**Pentoxifylline assay**—Serum concentrations of pentoxifylline and the 5-hydroxyhexyl metabolite were determined by use of HPLC, as described elsewhere. Stock solutions of pentoxifylline, 1-(5-hydroxyhexyl)-3,7-dimethylxanthine, and caffeine were prepared by dissolving solid drug standards in HPLC-grade methanol to yield solutions with a final concentration of 0.1 mg/mL. Calibration samples and
positive control samples were prepared by diluting appropriate volumes of stock solutions in drug-free serum to create the desired concentrations. Calibration curves for pentoxifylline and the 5-hydroxyhexyl metabolite ranged from 60 to 25,000 ng/mL for samples collected after IV administration and 20 to 5,000 ng/mL for samples collected after oral administration. Quality-control samples for pentoxifylline and the 5-hydroxyhexyl metabolite were prepared in triplicate for at least 3 concentrations (ranging from 50 to 20,000 ng/mL, depending on the calibration curve).

Aliquots (0.5 mL) of experimental, calibrant, and quality-control samples were pipetted into 13 × 100-mm test tubes containing 400 mg of NaCl. The stock solution of caffeine was added as an internal standard to each tube at a final concentration of 200 ng/mL. One milliliter of cold HPLC-grade acetonitrile was added to each tube, and the mixture was vortexed for 1 minute and incubated at 2,160 rpm for 15 minutes, and the organic supernatant was transferred to a fresh set of 13 × 110-mm tubes. The organic supernatant was evaporated under a constant stream of nitrogen at 60°C, and residues were reconstituted with 0.15 mL of an 86:14 solution of 50mM phosphate buffer (pH 4.0):acetonitrile. Samples were stored at 21°C in rubber-capped glass vials until analyzed by use of HPLC.

The HPLC system consisted of a quaternary pump, autosampler, and diode-array detector set to a wavelength of 275 nm. Separation of the compounds of interest was accomplished by use of a reverse-phase, C-8, 4.6 × 150-mm column and a flow rate of 1 mL/min. The gradient method used consisted of an initial mobile phase of 14% organic solution for 6 minutes, a linear gradient to 20% organic solution at 12 minutes, a second linear gradient to 34% organic solution at 14 minutes, a hold for 0.5 minutes, and then equilibration at starting conditions for 3 minutes. For these conditions caffeine, the 5-hydroxyhexyl metabolite, and pentoxifylline eluted at 3.3, 10.3, and 10.8 minutes, respectively.

The lower LOQ was 20 and 60 ng/mL for samples collected after oral and IV administration, respectively. Interday variability for IV administration was 10.3%, whereas interday variability for oral administration was 12.6%. Intraday coefficient of variation for positive control samples was required to be < 20% for the data set to be considered acceptable.

Pharmacokinetic analysis—Pharmacokinetic variables were determined by use of standard noncompartmental analysis; commercially available software was used for the analysis. After oral administration, observed Cmax and time of Cmax for pentoxifylline and the 5-hydroxyhexyl metabolite were estimated directly from the data. Linear trapezoidal areas were used to calculate AUC values for pentoxifylline and the 5-hydroxyhexyl metabolite. After IV administration and the first oral administration of pentoxifylline, AUCO-∞,PTX and AUCO-∞,MTX were calculated. After the final oral administration of pentoxifylline, AUCO was calculated. Oral bioavailability of pentoxifylline was determined from the ratio of the dose-adjusted AUC and AUC determined after oral administration of the first and last doses of pentoxifylline, respectively, to the AUC determined after IV administration of pentoxifylline.

Statistical analysis—Results were expressed as mean ± SD. The harmonic mean was calculated for t 1/2. Pharmacokinetic variables obtained after oral administration of the first dose were compared with values obtained after oral administration of the last dose by use of a 2-tailed, paired-difference t test. Values were considered significantly different at P < 0.05.

Results

Adverse effects—Mild transient muscle fasciculations and sweating evident on the shoulders and flanks were observed in 6 horses after IV administration of 8.5 mg of pentoxifylline/kg. Although mild transient increases in heart rate were detected, no arrhythmias were evident. No adverse events were evident after oral administration of 10 mg of sustained-release pentoxifylline/kg.

CBC and serum biochemical analysis—Laboratory variables evaluated before initiation of the study were within the respective reference ranges. All values were also within their respective reference ranges when evaluated after commencement of oral administration of pentoxifylline.

Kinetics of IV and oral administration of pentoxifylline—Mean serum concentration-versus-time curves for pentoxifylline and the 5-hydroxyhexyl metabolite after IV administration to healthy adult horses were plotted (Figure 1). Pharmacokinetic variables were calculated and summarized (Table 1). Elimination of pentoxifylline from serum was rapid, with a mean ± SD MRT of only 37 ± 23.4 minutes and a mean t 1/2 of 22.8 ± 13.8 minutes.

Serum concentrations of pentoxifylline and the 5-hydroxyhexyl metabolite after oral administration of a single dose and after oral administration of the final

Figure 1—Mean ± SD serum concentrations of pentoxifylline (black circles) and the 5-hydroxyhexyl metabolite (white circles) at various time points after IV administration of a single dose (8.5 mg/kg) to 8 healthy adult horses. Time 0 = End of IV administration of pentoxifylline.

Table 1—Mean ± SD values for pharmacokinetic variables determined after IV administration of a single dose of pentoxifylline (8.5 mg/kg) to 8 healthy adult horses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>11.70 ± 3.64</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>5.60 ± 1.73</td>
</tr>
<tr>
<td>5-Hydroxyhexyl metabolite</td>
<td>4.44 ± 1.97</td>
</tr>
<tr>
<td>AUCO∞,PTX (mg·h)/L</td>
<td>9.32 ± 4.47</td>
</tr>
<tr>
<td>Ratio of AUCO∞,MTX to AUCO∞,PTX</td>
<td>2.4 ± 1.1</td>
</tr>
<tr>
<td>t1/2 for pentoxifylline (h)</td>
<td>0.38 ± 0.03*</td>
</tr>
<tr>
<td>MRT for pentoxifylline (h)</td>
<td>3.62 ± 0.28</td>
</tr>
<tr>
<td>CL for pentoxifylline (L/kg/h)</td>
<td>2.28 ± 1.28</td>
</tr>
<tr>
<td>Vdss for pentoxifylline (L/kg)</td>
<td>1.15 ± 0.30</td>
</tr>
</tbody>
</table>

*Value expressed as the harmonic mean ± SD. CL = Total body clearance.
administration of the first and last dose (10 mg/kg) to 8 horses. Pharmacokinetic variables for pentoxifylline after oral administration of the final dose. Detects in serum samples collected immediately time. For example, serum concentrations of pentoxifylline decreased rapidly over 5 of 7 horses by 12 hours after pentoxifylline administration. After twice-daily administration for 8 days, low concentrations (< 0.2 μg/mL) of pentoxifylline were detected in serum samples collected immediately before oral administration of the final dose. Pharmacokinetic variables for pentoxifylline after oral administration of the first and last dose (10 mg/kg) were summarized (Table 4). Mean ± SD Cmax of pentoxifylline was significantly lower after oral administration of the last dose (1.58 ± 0.99 μg/mL), compared with the value after oral administration of the first dose (2.41 ± 1.61 μg/mL). In a similar manner, mean values for AUC (2.20 ± 1.24 [mg*h]/L) and bioavailability (44 ± 17%) were significantly lower after oral administration of the last dose, compared with values after oral administration of the first dose (3.14 ± 1.96 [mg*h]/L).

### Table 2—Values for serum concentrations of pentoxifylline and the 5-hydroxyhexyl metabolite measured after oral administration of a single dose of pentoxifylline (10 mg/kg) to 8 horses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time after pentoxifylline administration (h)</th>
<th>0.25</th>
<th>0.50</th>
<th>0.75</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline (μg/mL)</td>
<td>Mean</td>
<td>2.23</td>
<td>1.60</td>
<td>1.07</td>
<td>0.74</td>
<td>0.46</td>
<td>0.26</td>
<td>0.07</td>
<td>&lt;LOQ</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.68</td>
<td>1.08</td>
<td>0.71</td>
<td>0.54</td>
<td>0.26</td>
<td>0.12</td>
<td>0.07</td>
<td>&lt;LOQ</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>0.77</td>
<td>0.39</td>
<td>0.46</td>
<td>0.00</td>
<td>0.13</td>
<td>0.04</td>
<td>0.02</td>
<td>&lt;LOQ</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>5.41</td>
<td>3.49</td>
<td>2.48</td>
<td>1.48</td>
<td>0.88</td>
<td>0.35</td>
<td>0.09</td>
<td>&lt;LOQ</td>
</tr>
<tr>
<td>5-Hydroxyhexyl metabolite (μg/mL)</td>
<td>Mean</td>
<td>1.33</td>
<td>1.06</td>
<td>1.09</td>
<td>1.13</td>
<td>0.38</td>
<td>0.11</td>
<td>0.01</td>
<td>&lt;LOQ</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.51</td>
<td>0.38</td>
<td>0.29</td>
<td>0.44</td>
<td>0.55</td>
<td>0.15</td>
<td>0.09</td>
<td>&lt;LOQ</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>0.62</td>
<td>0.56</td>
<td>0.80</td>
<td>0.60</td>
<td>0.28</td>
<td>0.11</td>
<td>0.04</td>
<td>&lt;LOQ</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>2.29</td>
<td>1.57</td>
<td>1.60</td>
<td>1.74</td>
<td>1.96</td>
<td>0.54</td>
<td>0.26</td>
<td>&lt;LOQ</td>
</tr>
</tbody>
</table>

*Represents results for 4 horses; the remaining 4 horses had values less than the LOQ. 1Represents results for 4 horses; the remaining 4 horses had values less than the LOQ.

### Table 3—Values for serum concentrations of pentoxifylline and the 5-hydroxyhexyl metabolite measured after oral administration of the last dose of pentoxifylline (10 mg/kg, PO, q 12 h for 8 days) to 8 horses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time after pentoxifylline administration (h)</th>
<th>0</th>
<th>0.25</th>
<th>0.50</th>
<th>0.75</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline (μg/mL)</td>
<td>Mean</td>
<td>0.08</td>
<td>1.23</td>
<td>1.02</td>
<td>1.07</td>
<td>0.76</td>
<td>0.47</td>
<td>0.16</td>
<td>0.06</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.07</td>
<td>1.12</td>
<td>0.72</td>
<td>0.82</td>
<td>0.45</td>
<td>0.21</td>
<td>0.11</td>
<td>0.05</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>0.02</td>
<td>0.01</td>
<td>0.32</td>
<td>0.19</td>
<td>0.26</td>
<td>0.19</td>
<td>0.02</td>
<td>0.02</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>0.18</td>
<td>2.52</td>
<td>2.10</td>
<td>2.55</td>
<td>1.50</td>
<td>0.78</td>
<td>0.28</td>
<td>0.11</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>5-Hydroxyhexyl metabolite (μg/mL)</td>
<td>Mean</td>
<td>0.19</td>
<td>0.90</td>
<td>1.10</td>
<td>1.19</td>
<td>1.27</td>
<td>1.16</td>
<td>0.43</td>
<td>0.08</td>
<td>0.03</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.15</td>
<td>0.56</td>
<td>0.62</td>
<td>0.48</td>
<td>0.48</td>
<td>0.33</td>
<td>0.20</td>
<td>0.07</td>
<td>0.01</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>0.42</td>
<td>0.20</td>
<td>0.47</td>
<td>0.46</td>
<td>0.68</td>
<td>0.77</td>
<td>0.16</td>
<td>0.01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>0.95</td>
<td>1.68</td>
<td>1.93</td>
<td>1.96</td>
<td>2.20</td>
<td>1.71</td>
<td>0.79</td>
<td>0.22</td>
<td>0.05</td>
<td>—</td>
</tr>
</tbody>
</table>

*Represents results for 7 horses; the remaining horse had values less than the LOQ. 1Represents results for 7 horses; the value was not determined for the remaining horse. 1Represents results for 3 horses; the remaining 5 horses had values less than the LOQ. 1Represents results for only 1 horse; the remaining 7 horses had values less than the LOQ. 1Represents results for 4 horses; the remaining 4 horses were less than the LOQ. NA = Not applicable. — = Values for all 8 horses were less than the LOQ.

### Table 4—Mean ± SD values for pharmacokinetic variables determined after the first and last dose of orally administered pentoxifylline (10 mg/kg, PO, q 12 h for 8 days) to 8 healthy adult horses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>First dose</th>
<th>Last dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (μg/mL)</td>
<td>2.41 ± 1.61</td>
<td>1.58 ± 0.99*</td>
</tr>
<tr>
<td>5-Hydroxyhexyl metabolite</td>
<td>1.51 ± 0.50</td>
<td>1.49 ± 0.46</td>
</tr>
<tr>
<td>Time of Cmax (h)</td>
<td>26.3 ± 17.8</td>
<td>30.1 ± 15.3</td>
</tr>
<tr>
<td>5-Hydroxyhexyl metabolite</td>
<td>37.5 ± 35.9</td>
<td>72.1 ± 24.0*</td>
</tr>
<tr>
<td>AUC (mg*h/L)</td>
<td>3.14 ± 1.96</td>
<td>2.20 ± 1.24*</td>
</tr>
<tr>
<td>Pentoxifylline metabolite</td>
<td>5.19 ± 1.54</td>
<td>4.92 ± 1.59</td>
</tr>
<tr>
<td>Ratio of AUC∞ to AUC∞</td>
<td>2.2 ± 1.0</td>
<td>2.7 ± 1.3</td>
</tr>
<tr>
<td>Bioavailability for pentoxifylline (%)</td>
<td>68 ± 40</td>
<td>44 ± 17*</td>
</tr>
<tr>
<td>MRT for pentoxifylline (h)</td>
<td>2.2 ± 1.3</td>
<td>2.1 ± 0.9</td>
</tr>
<tr>
<td>MAT for pentoxifylline (h)</td>
<td>1.7 ± 1.5</td>
<td>1.6 ± 1.0</td>
</tr>
</tbody>
</table>

*Within a row, value differs significantly (P < 0.05; paired-difference f-test) from the value for the first dose. MAT = Mean absorption time.
and 68 ± 40%, respectively). However, the ratio of AUC$_{0→\infty}$ to AUC$_{0→\text{PTX}}$ remained similar after oral administration of the first and last dose (2.7 ± 1.3 vs 2.2 ± 1.0, respectively).

**Discussion**

Pentoxifylline was rapidly absorbed, and $C_{\text{max}}$ was achieved within 1 hour after oral administration. In humans and dogs, the observed time until $C_{\text{max}}$ for pentoxifylline is between 1 and 2 hours after oral administration. Oral administration of a single dose of pentoxifylline resulted in a mean $C_{\text{max}}$ of 2.41 μg/mL, which is similar to that reported after oral administration of a single dose of pentoxifylline to dogs from which food was not withheld (1.95 μg/mL) and dogs from which food was not withheld (2.18 μg/mL). Similarly, twice-daily administration of pentoxifylline for 8 days in the study reported here resulted in a mean $C_{\text{max}}$ of 1.58 μg/mL, which is similar to that reported after twice-daily administration to dogs from which food was withheld (1.34 μg/mL) and dogs from which food was not withheld (1.77 μg/mL).

Findings after IV administration in the study reported here are consistent with results for studies in horses and other species. For example, in our study, the mean Vdss was 1.15 L/kg. In dogs in another study, the mean Vdss for pentoxifylline after IV administration was of similar magnitude (1.04 L/kg). In contrast, the values reported here are smaller than those reported in a study of pentoxifylline in horses in which the Vdss was 2.81 L/kg. The extensive total body clearance observed in the horses in our study (mean, 2.38 [L/kg]/h) was similar to that observed in such studies of horses, which revealed a mean clearance of 3.06 (L/kg)/h. Mean clearance rates for humans and dogs were also similar at 3.62 and 2.22 (L/kg)/h, respectively.

Despite these similarities, there were substantial differences between some kinetic variables determined in the studies. For example, the mean AUC after IV administration in the study reported here was 4.44 (mg·h)/L, which was higher than the value of 2.46 (mg·h)/L reported in a study of horses. Bioavailability after a single oral dose also differed from the value reported in that study of horses. The authors of that study of horses hypothesized that the high bioavailability (>100%) resulted from certain characteristics of pentoxifylline distribution and elimination and suggested that plasma AUC determinations for calculation of bioavailability were inappropriate for the drug. More specifically, those authors suggested that substantial amounts of the 5-hydroxyhexyl metabolite bound to erythrocytes could serve as a reservoir for pentoxifylline after oral administration. Other possible explanations for their findings include the immediate loss of pentoxifylline from the serum compartment as a result of rapid binding of pentoxifylline to erythrocytes or intravascular precipitation of pentoxifylline when administered IV to horses at high concentrations. Because mean bioavailability was <100% in the study of horses reported here and in studies of pentoxifylline disposition in other species, the final hypothesis seems the most plausible.

The concentration of pentoxifylline administered IV in the study reported here was 50 mg/mL, which was prepared at 21°C, whereas in another study in horses, a more concentrated preparation (154 mg/mL) warmed to 37°C was administered IV. Because the latter concentration approaches the limits of pentoxifylline solubility at 37°C, precipitation may have happened when the drug solution contacted the plasma, resulting in the administration of a dose that was lower than expected.

Values for several variables determined after oral administration of the first dose of pentoxifylline were significantly different from values determined after repeated oral administrations. For example, the AUC and $C_{\text{max}}$ decreased significantly with repeated administration during the study reported here and in dogs of another study. One possible explanation for this change is reduced absorption of pentoxifylline with repeated administration. However, no changes in feed or the feeding schedule were introduced, and no other drugs were administered concurrently. Additionally, mean absorption time and MRT did not differ significantly after oral administration of the first and last dose of pentoxifylline.

Although apparent bioavailability also decreases significantly with repeated administration in horses and dogs, this does not necessarily indicate that absorption decreases. A crucial assumption in computing bioavailability is that clearance is constant for both IV and oral administration. Therefore, if clearance were increased after oral administration of multiple doses, then the computation for bioavailability would no longer be valid and cannot be used to determine whether absorption is decreasing with repeated administrations.

Circadian variation in $C_{\text{max}}$ and absorption of pentoxifylline has been reported in humans and suggested in dogs. However, in the horses of the study reported here, the time of day of drug administration was consistent and serial blood collection was initiated at the same time after both the first and last dose of pentoxifylline.

Another possible explanation for the decrease in AUC, $C_{\text{max}}$, and bioavailability observed with repeated oral administrations in the study reported here is autoinduction of metabolic enzymes by pentoxifylline. Autoinduction has been reported in humans after administration of theophylline, another methylxanthine derivative. Metabolism of pentoxifylline is primarily through reduction to form the 5-hydroxyhexyl metabolite, but 6 additional metabolites have been detected in humans, and 2 additional metabolites have been detected in the plasma of dogs treated with pentoxifylline. Only 1 additional metabolite has been reported in horses.

It has been proposed that the ratio of AUC$_{0→\infty}$ to AUC$_{0→\text{PTX}}$ can serve as an indicator of autoinduction, and in the study reported here, the ratio of AUC$_{0→\infty}$ to AUC$_{0→\text{PTX}}$ did not differ significantly with repeated administrations. However, autoinduction may have increased the metabolism of 5-hydroxyhexyl metabolite in parallel with that of the parent drug, which resulted in no change in the ratio. The cause of the
decreased drug exposure after repeated oral administration of pentoxifylline cannot be determined from the study design used here; however, this topic does warrant further investigation.

Pentoxifylline and the 5-hydroxyhexyl metabolite are considered to have therapeutic activity. The therapeutic concentration in humans is reportedly 0.06 to 1.6 μg/mL. In horses, the decreased drug exposure after administration of pentoxifylline for 8 days may not decrease the efficacy of this dosage regimen because pentoxifylline and the 5-hydroxyhexyl metabolite still reach serum concentrations that are considered therapeutic in humans and therapeutic in horses with endotoxemia.3,16 In the experience of several of the authors, oral administration of 10 mg of pentoxifylline/kg twice daily for 30 days results in clinical response in horses with cutaneous vasculitis. Additional studies are needed to investigate pentoxifylline pharmacokinetics after treatment for several weeks to months, which is often clinically necessary for animals with cutaneous vasculitis, laminitis, and severe wounds. Pharmacodynamic studies are needed to determine therapeutic concentrations of pentoxifylline for the aforementioned clinical conditions.

The sustained-release formulation of pentoxifylline has been tolerated well by most human patients. Clinical signs associated with the gastrointestinal tract are the most common complaint in humans. To our knowledge, only 1 fatality in humans has resulted from an overdose of pentoxifylline. That person was an adult male who had a plasma pentoxifylline concentration of 32.5 μg/mL, which is approximately 32 times the therapeutic concentration in humans. The IV administration of pentoxifylline to horses in the study reported here caused muscle fasciculations, sweating, and tachycardia, which are similar to clinical signs reported in another study. 3 These reactions may be attributable to pentoxifylline or a contaminant, such as endotoxin, because the solution for IV injection was prepared from a drug standard and was not a commercial product formulated for parenteral administration. We do not advise the routine administration of a bolus of analytical-grade pentoxifylline because of adverse reactions. Pentoxifylline reportedly causes substantial leukocytosis in horses 2 through 6 hours after IV administration of a bolus injection.36

Although we did not specifically investigate the short-term effects of IV administration of pentoxifylline on WBCs in the study reported here, no differences were detected in WBC counts conducted before initiation of the study and after oral administration. No adverse effects were reported after oral administration of pentoxifylline to dogs from which food was withheld or that were allowed access to food.3 In addition, no adverse effects were detected after oral administration of pentoxifylline to the horses of our study.

Analysis of results of the study reported here indicated that pentoxifylline was rapidly and extensively absorbed in horses and was tolerated well after oral administration. Oral administration of a dose of pentoxifylline (10 mg/kg) every 12 hours yielded serum concentrations of pentoxifylline equivalent to those observed after administration of therapeutic doses of pentoxifylline to humans and horses. Because drug exposure appears to decrease by approximately 30% with administration of multiple doses of pentoxifylline, it is possible that the efficacy of pentoxifylline in a particular horse will wane with time. When a decrease in clinical response is evident with repeated administration of pentoxifylline, practitioners may consider increasing the rate to approximately 30 mg/kg/d by increasing the dosage for twice-daily administration or by increasing the dosing frequency to 3 times daily.

References
5. Berman B, Duncan MR. Pentoxifylline inhibits normal human dermal fibroblast in vitro proliferation, collage, glycosaminoglycan, and fibronectin production, and increases collage

a. Seminole Blue Ribbon 12, Seminole Feed, Ocala, Fla.
c. Ethilon, Ethicon Inc, Sommerville, NJ.
d. Pentoxifylline, Lot No. 022K1348, Sigma Chemical Co, St Louis, Mo.
e. Acrodisc syringe filter, Gelman Sciences, Ann Arbor, Mich.
f. PTX, 400 mg, extended release, Apotex Corp, Weston, Fla.
g. Molasses, Fortner Feed, Williston, Fla.
h. Novex extension tubing, Baxter, Deerfield, Ill.
j. Vacutainer Brand evacuated collection tubes, Becton-Dickinson, Franklin Lakes, NJ.
l. Pentoxifylline, Hoechst-Roussel Pharmaceuticals, Trenton, NJ.
m. 1-(5-hydroxyhexyl)-3,7-dimethylxanthine, Hoechst-Roussel Pharmaceuticals, Trenton, NJ.
n. Caffeine, Hoechst-Roussel Pharmaceuticals, Trenton, NJ.
o. HP series 1100 HPLC, Hewlett-Packard, Avondale, Pa.
q. WinNonlin Professional, version 4.1, Pharsight Corp, Mountain View, Calif.

1626 AJVR, Vol 67, No. 9, September 2006


