Pharmacokinetics of voriconazole following intravenous and oral administration and body fluid concentrations of voriconazole following repeated oral administration in horses

Carmen M. H. Colitz, DVM, PhD; Federico G. Latimer, DVM, MS; Hao Cheng, PhD; Ken K. Chan, PhD; Stephen M. Reed, DVM; Genneth J. Pennick, BA

Objective—To determine the pharmacokinetics of voriconazole following IV and PO administration and assess the distribution of voriconazole into body fluids following repeated PO administration in horses.

Animals—6 clinically normal adult horses.

Procedures—All horses received voriconazole (10 mg/kg) IV and PO (2-week interval between treatments). Plasma voriconazole concentrations were determined prior to and at intervals following administration. Subsequently, voriconazole was administered PO (3 mg/kg) twice daily for 10 days to all horses; plasma, synovial fluid, CSF, urine, and preocular tear film concentrations of voriconazole were then assessed.

Results—Mean ± SD volume of distribution at steady state was 1,604.9 ± 406.4 mL/kg. Systemic bioavailability of voriconazole following PO administration was 95 ± 19%; the highest plasma concentration of 6.1 ± 1.4 µg/mL was attained at 0.6 to 2.3 hours. Mean peak plasma concentration was 2.57 µg/mL, and mean trough plasma concentration was 1.32 µg/mL. Mean plasma, CSF, synovial fluid, urine, and preocular tear film concentrations of voriconazole after long-term PO administration were 5.16 ± 1.32 µg/mL, 3.07 ± 2.09 µg/mL, 4.42 ± 0.8095 µg/mL, and 3.37 ± 1.297 µg/mL, respectively.

Conclusions and Clinical Relevance—Results indicated that voriconazole distributed quickly and widely in the body; following a single IV dose, initial plasma concentrations were high with a steady and early decrease in plasma concentration. Absorption of voriconazole after PO administration was excellent, compared with absorption after IV administration. Voriconazole appears to be another option for the treatment of fungal infections in horses.


A variety of systemic or localized fungal infections in horses has been described including keratomycosis, endophthalmitis, meningitis, mycosis of the auditory tube diverticula, metritis, rhinitis, and dermatitis.18 Effective antifungal treatment for affected horses is restricted to a few drugs because of unfavorable pharmacokinetics, limited absorption, or potential toxicity. Pharmacokinetic and therapeutic data for antifungal drugs in horses are limited, although several antifungal drugs have been used systemically or topically, including fluconazole,1 itraconazole,10,12 miconazole,13,14 nata-mycin,9 amphoterin C,15 and ketoconazole.16

Received August 23, 2006.
Accepted March 14, 2007.
From the Department of Veterinary Clinical Sciences, College of Veterinary Medicine (Colitz, Latimer, Reed) and the Division of Pharmaceutical Sciences, College of Pharmacy (Cheng, Chan). The Ohio State University, Columbus, OH 43210; and the Department of Pathology, University of Texas Health Science Center, San Antonio, TX 78229-3900 (Pennick). Dr. Colitz’s present address is Animal Eye Specialty Clinic, 3421 West Palm Beach, FL 33406.
Supported by the USA Equestrian Federation Incorporated.
The authors thank Pfizer Limited for providing the voriconazole used in the project. In addition, the authors thank Craig Aldinger, Dr. Heather Chandler, Curtis Barden, Amanda Johnson, and Megan Hoyt for technical assistance.
Address correspondence to Dr. Colitz.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>Minimum concentration required to inhibit 90% of microbial growth</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the plasma concentration curve</td>
</tr>
<tr>
<td>MRT</td>
<td>Mean residence time</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Time to maximum plasma concentration</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>Css</td>
<td>Plasma concentration at steady state</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
</tbody>
</table>

The azole antifungal medications are synthetic compounds and are classified as imidazoles (miconazole and ketoconazole) or triazoles (itraconazole, fluconazole, and voriconazole) depending on the number of nitrogen atoms on the azole ring.17 The azole agents inhibit ergosterol synthesis in fungal cell membranes by interfering with the cytochrome P-450 enzyme system. The triazoles have a lower affinity for mammalian cytochrome P-450 enzymes than do the imidazoles.18 Miconazole is toxic when administered IV, and it is therefore limited to topical ophthalmic and dermatologic formulations.17 Following oral administration in horses, ketoconazole is poorly absorbed16 whereas itraconazole is moderately well absorbed. > 98% of the agent remains protein bound, and the drug has poor tissue distribution.10 Itra-
conazole has been variably effective in the treatment of mycotic infections in horses.\textsuperscript{11,18,19} Fluconazole is approximately 100\% bioavailable when administered orally to horses; via that route of administration, the drug has excellent distribution and attains high plasma and tissue concentrations, but similar to most azole antifungal agents, it has poor activity against Aspergillus spp.\textsuperscript{15,20}

Voriconazole is a new triazole antifungal agent that was developed via modification of the structure of fluconazole to extend its spectrum of antifungal activity, compared with those of itraconazole and fluconazole.\textsuperscript{21,22} The mechanism of action remains the induction of cytochrome P-450, but it has greater activity against Aspergillus spp than itraconazole and amphoterin C, the mainstays of treatment against severe fungal infections for years.\textsuperscript{12,13} The effectiveness of voriconazole against yeast, filamentous fungi, and dimorphic fungi has been evaluated, and the drug has activity against a wide variety of clinically important fungal organisms.\textsuperscript{23-28} Most fungi are susceptible to voriconazole when the MIC\textsubscript{90} is < 4 \mu g/mL and are considered resistant when the MIC\textsubscript{90} is > 8 \mu g/mL. In vitro, voriconazole’s activity against Aspergillus spp was high (MIC\textsubscript{90} 0.01 to 2 \mu g/mL) and the drug has fungicidal activity rather than fungistatic activity against those organisms.\textsuperscript{19}

In 2 recent studies,\textsuperscript{27,28} another research group has evaluated experimental use of voriconazole in horses. In 1 study,\textsuperscript{28} the pharmacokinetics of voriconazole in horses following a single dose of the drug administered PO (4 mg/kg) or IV (1 mg/kg) were determined. Findings of that study indicated that a dose of 4 mg of voriconazole/kg administered PO once daily would result in plasma concentrations that would achieve a minimum inhibitory concentration \leq 1 \mu g/mL, which is adequate for treatment of most fungal infections in horses. However, that investigation did not include a long-term PO dosing experiment, which is necessary for the determination of plasma and body fluid distribution of voriconazole in horses after prolonged PO administration. The second study\textsuperscript{27} revealed that following topical and PO administration in horses, detectable concentrations of voriconazole in aqueous humor were attained; these concentrations were > 0.3 \mu g/mL, which is typically considered the minimum concentration for potential clinical efficacy.

The purpose of the study of this report was to determine the pharmacokinetics of voriconazole following IV and PO administrations of a single dose and assess the distribution of voriconazole into body fluids following repeated PO administration in horses. To achieve the latter, a dosing regimen for potential clinical use in horses was derived from the pharmacokinetic data; after multiple PO administrations of voriconazole during a 10-day period, concentrations of the drug in plasma, synovial fluid, CSF, urine, and precorneal tear film were measured.

**Materials and Methods**

**Animals and initial evaluations**—Six clinically normal horses weighing 400 to 500 kg were included in the study. Use of the horses was approved by The Ohio State University Institutional Animal Care and Use Committee. No abnormalities were detected in any horse via physical and ophthalmologic examinations performed prior to study commencement. A CBC and serum biochemical analysis were also performed for each horse, and results were within reference limits. Horses were maintained in individual stalls for most of the study period. Water and grass hay were available ad libitum, and a commercial grain ration (2.2 kg/50 kg of body weight) was provided twice daily. Horses were weighed and randomly assigned to receive a dose of voriconazole via IV or PO administration (3 horses/group). All horses were fed approximately 2 hours prior to drug administration.

**Dosing procedures for pharmacokinetic analyses**—A 14-gauge, 8.98-cm catheter was placed in the right jugular vein for collection of blood samples, and a 10-gauge, 8.98-cm catheter was placed in the left jugular vein for drug administration. Voriconazole\textsuperscript{29} was administered as a bolus through the catheter in the left jugular vein to yield a final dose of 10 mg of voriconazole/kg. Immediately following drug administration, the left jugular vein catheter was removed. For oral administration, voriconazole\textsuperscript{29} was suspended in 2 L of water and administered as a bolus by gravity flow through a nasogastric tube to yield a final dose of 10 mg of voriconazole/kg.

**Blood sample collection**—Blood samples (10 mL) were obtained from the right jugular catheter of each horse immediately prior to and at 10, 20, 30, 40, and 60 minutes and 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours after voriconazole administration. Catheters were flushed with sterile saline (0.9\% NaCl) solution containing heparin immediately before and after blood collection. The first 6 mL of blood obtained at each sample collection was discarded prior to obtaining the 10-mL sample for pharmacokinetic determinations. Blood samples were placed in tubes containing lithium heparin and centrifuged in a refrigerated centrifuge immediately after collection. Plasma samples were stored at –70°C until determination of voriconazole concentrations.

**Crossover procedure**—At the conclusion of the first period of blood collections, horses were returned to pasture for 2 weeks. Following this washout period, the same 6 horses were administered a single dose of voriconazole via the other route of administration and blood sample collections were repeated.

**Determination of voriconazole pharmacokinetics**—Plasma samples for voriconazole analysis were assayed by use of a previously described analytical method.\textsuperscript{32} The assay used solid-phase extraction and high-performance liquid chromatography. The lowest limit of quantitation was 0.2 \mu g/mL, and the range of linearity tested was 0.2 to 10 \mu g/mL. Among control samples analyzed for the purposes of the study, the interday coefficients of variation for 0.5, 4.0, and 8.0 \mu g of voriconazole/mL were 8.50\%, 4.54\%, and 3.09\%, respectively. The intraday coefficients of variation for control samples containing 0.5, 4.0, and 8.0 \mu g of voriconazole/mL were 7.70\%, 6.52\%, and 3.33\%, respectively.

**Pharmacokinetic analysis**—Plasma concentration–time data were fitted to an appropriate model by use of...
computer software. Because the lowest limit of quantitation of the high-performance liquid chromatography assay was 0.2 µg/mL, voriconazole concentrations < 0.2 µg/mL were not used in the analyses. The decision to fit a selected model versus other models for all the data was made on the basis of the sum of squares of the weighted residuals and measurement of the Akaike information criteria after data were fit to those models. The model with the lowest Akaike information criterion was selected to describe data obtained from each individual horse. A weighting factor of 1/\(Y^2\) was used, where \(Y\) is the plasma concentration of voriconazole. The noncompartmental model was used to calculate the total AUC area under the curve from zero to infinity, MRT, and clearance. Clearance was calculated as the dose divided by AUC. The AUC was more accurate when noncompartmental analysis was used.

Pharmacokinetic parameters were then estimated; those for IV administration were estimated from a 2-compartment model, and those for PO administration were estimated from a 1-compartment model. The data obtained after IV administration of voriconazole were analyzed by use of a 2-compartment model with bolus input and first-order elimination. Plasma concentration (\(C\)) of voriconazole after IV administration was described by use of an equation as follows:

\[
C(t) = A e^{-\alpha t} + B e^{-\beta t}
\]

where \(e\) is the base of the natural logarithm; \(t\) is time after drug administration; \(A\) and \(B\) are the y-axis intercepts for the distribution and elimination phases of the curve, respectively; and \(\alpha\) and \(\beta\) are the slopes for the distribution and elimination phase of the curve, respectively. Data obtained after PO administration of a single dose of voriconazole were described by use of a 1-compartment model with first-order input. Plasma concentration of voriconazole after PO administration was described by use of an equation as follows:

\[
C(t) = D \cdot \frac{K_{01}}{V}(e^{-K_{10} t} - e^{-K_{01} t}) \cdot (e^{-\alpha t} - e^{-\beta t})
\]

where \(D\) is the dose that the horse received, \(K_{01}\) is the absorption rate constant, \(V\) is volume of distribution of the central compartment, and \(K_{10}\) is the elimination rate constant. Values of \(K_{01}\), \(K_{10}\), \(A\), and \(B\) and the corresponding \(t_{\text{1/2}}\) of each of these variables were generated by computer software. Bioavailability of voriconazole after PO administration (%F) was calculated by use of an equation as follows:

\[
\%F = \frac{\text{AUC}_{\text{po}}}{\text{AUC}_{\text{iv}}}
\]

where \(\text{AUC}_{\text{po}}\) is the AUC determined after PO administration and \(\text{AUC}_{\text{iv}}\) is the AUC determined after IV administration. Time to maximum plasma concentration and \(C_{\text{max}}\) of voriconazole after PO administration were determined from actual datum points. The simulation for multiple PO dosing was also conducted by use of the parameters generated from the single-dose pharmacokinetic experiments. The mean concentration at steady state was set at 2 µg/mL with a dosing interval of 12 hours, and the dose for PO administration was set at 3 mg/kg. The target Css of 2 µg/mL was chosen because voriconazole’s activity against Aspergillus spp is 0.01 to 2 µg/mL in vitro. The maintenance dose was calculated by use of an equation as follows:

\[
\text{Dose} = \text{Css} \times Cl \times \frac{1}{\tau F}
\]

where \(Cl\) is total clearance, \(\tau\) is the dosing interval, and \(F\) is the oral bioavailability. A lag time was used as appropriate. This equation was used to estimate the dose required to generate a desired Css with an input dose frequency.

**Repeated oral administration**—On the basis of the \(t_{\text{1/2}}\) data obtained following PO administration, a twice-daily dosing regimen was calculated by use of computer software for kinetic modeling. By use of twice-daily dosing and the pharmacokinetic parameters, a dose administered PO twice daily that would achieve a steady-state plasma concentration of 2 µg/mL (voriconazole’s MIC\(_{90}\) against Aspergillus spp) was determined. Thus, a dose of 3 mg of voriconazole/kg was administered PO twice daily to the 6 horses for 10 days. At the conclusion of the 10-day dosing period, plasma, synovial fluid, CSF, urine, and tear fluid were collected from the horses for determination of voriconazole concentration. Synovial fluid, CSF, urine, and tear fluid were collected from standing horses that had been sedated with detomidine (0.02 mg/kg, IV) and butorphanol (0.02 to 0.03 mg/kg, IV). Briefly, following aseptic preparation, synovial fluid was collected from a proximal intercarpal joint, and CSF was collected from the lumbosacral space in all 6 horses. Urine was collected via catheterization from all but 1 horse. That horse was catheterized twice but did not provide urine at the beginning or end of the collection period. To collect sufficient tears for evaluation, tear fluid was collected from both lacrimal lakes of each horse by use of sterile small bulb syringes. One horse’s tear fluid became diluted with eyewash and was not used in the study.

**Other assessments**—During the study, horses were examined for signs of adverse effects associated with voriconazole administration. For each horse, a physical examination, CBC, and serum biochemical analyses were performed following the initial IV or PO administration of a single dose of voriconazole as well as following the chronic oral dosing phase of the study. During the 10-day treatment period, horses also underwent physical examinations daily.

**Results**

None of the horses had any adverse effects following IV or PO administration of voriconazole. Heat, swelling, or signs of pain at the site of catheter placement did not develop at any time during or following catheterization. There were also no signs of abdominal pain, diarrhea, or change in appetite or attitude detected following IV or PO administration of a single dose of voriconazole or following repeated PO administrations of the drug. Rectal temperature, pulse rate, and respiratory rate immediately following IV or PO administration of the single dose of voriconazole did not vary from the values recorded prior to drug administration. During
Figure 1—Mean ± SD plasma concentrations of voriconazole at intervals following a single IV (circles) or PO (diamonds) administration (10 mg/kg) in each of 6 horses. The solid line represents the plasma voriconazole concentration-time profile after IV administration that was predicted by use of a 2-compartment model. The dashed line represents the plasma voriconazole concentration-time profile after PO administration that was predicted by use of a 1-compartment model.

Discussion

Similar to findings of a recent study, the pharmacokinetic data obtained in the present study indicated that absorption of voriconazole after a single dose of 10 mg/kg administered PO was excellent; $C_{\text{max}}$ values were 4.7 to 8.5 µg/mL at 1 to 4 hours following administration. From the pharmacokinetic data obtained after IV administration, the short initial $t_{1/2}$ (0.13 to 0.83 hours) indicated that voriconazole distributed quickly and widely in the body, as evidenced by high initial plasma concentrations with a steady and early decrease in plasma concentrations prior to and following the study.

Table 1—Pharmacokinetic parameters of voriconazole after IV and PO administration of a single dose (10 mg/kg) to 6 clinically normal adult horses.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IV</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>0.13–0.83*</td>
<td>NA</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>11.0–15.7</td>
<td>NA</td>
</tr>
<tr>
<td>$AUC_{\text{ss}}$ (µg·h/mL)</td>
<td>5.7 ± 3.7</td>
<td>NA</td>
</tr>
<tr>
<td>$\beta$ (µg/mL)</td>
<td>8.2 ± 1.3</td>
<td>NA</td>
</tr>
<tr>
<td>$\alpha$ (h)</td>
<td>NA</td>
<td>7.8–12.9*</td>
</tr>
<tr>
<td>$t_{\text{1/2}}$ (h)</td>
<td>NA</td>
<td>1–4*</td>
</tr>
<tr>
<td>$C_{\text{ss}}$ (µg/mL)</td>
<td>13.0 ± 4.7</td>
<td>NA</td>
</tr>
<tr>
<td>$V_{\text{ss}}$ (mL/kg)</td>
<td>1.30 ± 0.33</td>
<td>1.20 ± 0.30</td>
</tr>
<tr>
<td>$R_{\text{t}}$ (µg/mL)</td>
<td>130.2 ± 38.3</td>
<td>120.2 ± 33.0</td>
</tr>
<tr>
<td>$V_{\text{Cl}}$ (mL/h/kg)</td>
<td>1,604.9 ± 406.4</td>
<td>NA</td>
</tr>
<tr>
<td>$MRT$ (h)</td>
<td>87.2 ± 30.7</td>
<td>83.8 ± 21.6</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>17.9 ± 2.3</td>
<td>16.4 ± 2.8</td>
</tr>
<tr>
<td>$C_{\text{ss}}$ (µg/mL)</td>
<td>NA</td>
<td>95 ± 19</td>
</tr>
</tbody>
</table>

Except where noted, data are reported as mean ± SD.

*Reported as range.

α = Rate constant of distribution phase of curve. β = Rate constant of elimination phase of curve. $V_{\text{ss}}$ = Apparent volume of distribution at steady state. $C_{\text{ss}}$ = Plasma concentration at time zero. $AUC_{\text{ss}}$ = Area under the concentration versus time curve from zero to infinity. $V_{\text{Cl}}$ = Total clearance. $C_{\text{ss}}$ = Not applicable.

The 10-day treatment period, physical examinations revealed no abnormalities and clinical variables remained within reference ranges throughout the study. Results of CBCs and serum biochemical analyses were within reference ranges prior to and following the study.

In horses, both PO and IV administration of voriconazole achieved therapeutic concentrations in the plasma quickly. Ten minutes following IV administration of a single dose of 10 mg/kg, mean plasma concentration of voriconazole reached 10.40 µg/mL; the value remained > 2 µg/mL until 24 hours after administration. Twenty minutes after PO administration of a single dose of 10 mg/kg, mean plasma concentration of voriconazole was > 2 µg/mL; the value remained ≥ 2 µg/mL until 24 hours after administration. Via either route of administration, peak concentrations (4.69 to 8.54 µg/mL) were reached in 1 to 4 hours.

The plasma concentration-time profiles of voriconazole after IV and PO administrations were plotted (Figure 1). According to the Akaike information criterion, data obtained after IV administration of voriconazole were best fitted with a 2-compartment model, whereas data obtained after PO administration of voriconazole were best fitted with a 1-compartment model.

Pharmacokinetic parameters for voriconazole were calculated by use of a computer program (Table 1). Following IV administration, the drug was rapidly distributed in the body with an initial $t_{1/2}$ of distribution of 0.13 to 0.83 hours. The achievable $C_{\text{ss}}$ at 10 minutes following IV administration was 7.4 to 13.3 µg/mL. The elimination was relatively slow with a terminal $t_{1/2}$ of elimination of 11.0 to 15.7 hours. The $MRT$ ± SD was 17.9 ± 2.3 hours after IV administration. Mean AUC for IV administration of voriconazole was 130.2 ± 38.3 µg·h/mL. The apparent volume of distribution at steady state was 1,604.9 ± 406.4 mL/kg, and the mean clearance was 87.2 ± 30.7 mL/h/kg. Following PO administration, $C_{\text{max}}$ values of 4.7 to 8.5 µg/mL were detected at 1 to 4 hours ($T_{\text{max}}$); these values declined exponentially with a $t_{1/2}$ of 7.8 to 12.9 hours. Mean AUC for PO administration of voriconazole was 120.2 ± 33.0 µg·h/mL. The MRT was 16.4 ± 2.8 hours after PO administration, and mean clearance was 83.8 ± 21.6 mL/h/kg. The oral bioavailability was 95 ± 19%. The simulation results indicated that a maintenance dose of 2.23 µg of voriconazole/kg administered at a 12-hour dosing interval can maintain the mean plasma drug concentration at steady state at 2 µg/mL. The $C_{\text{ss}}$ and trough plasma concentration were 2.57 and 1.32 µg/mL, respectively.

Samples of plasma, CSF, and synovial fluid were obtained from all 6 horses. However, samples of urine and precorneal tear fluid were obtained from only 5 horses. Although one of the horses was catheterized at the beginning and at the end of the fluid collection period, no urine was collected. For 1 horse, the eyes had been rinsed with eyewash and the tears became diluted; therefore, the tear fluid could not be used for evaluation. Plasma concentrations of voriconazole in each horse after PO administration of 10 days’ duration ranged from 3.110 to 6.780 µg/mL (mean concentration, 3.163 ± 1.594 µg/mL). Voriconazole concentrations in samples of CSF ranged from 1.370 to 3.680 (mean, 2.508 ± 1.330 µg/mL). Voriconazole concentrations in synovial fluid ranged from 1.730 to 4.100 µg/mL (mean, 3.073 ± 2.093 µg/mL). Voriconazole concentrations in the urine ranged from 2.520 to 6.750 (mean, 4.422 ± 0.8095 µg/mL). Voriconazole concentrations in precorneal tear film ranged from 2.110 to 5.330 µg/mL (mean, 3.376 ± 1.297 µg/mL).
that achieved after IV administration. Compared with horses, humans have a similar \( T_{\text{max}} \) for voriconazole of approximately 2 hours, whereas other species have a \( T_{\text{max}} \) of \( \leq 8 \) hours.\(^{33} \) The bioavailability of voriconazole in horses was 99% (as calculated from the AUC value), which is lower than the value reported by Davis et al.\(^{30} \) (> 100%). Oral bioavailability of voriconazole in guinea pigs is 75%; in mice, rats, rabbits, and dogs, the value is > 81%;\(^{31} \) and in humans, the value is > 90%.\(^{23,34} \) In addition, voriconazole is not affected by the pH of gastric contents,\(^{23} \) but administration of voriconazole with food, especially high-fat meals, delays oral absorption in humans.\(^{23} \) The short \( T_{\text{max}} \) and high bioavailability for voriconazole determined in the present study support the conclusions that orally administered voriconazole is quickly absorbed and that most of the administered dose is readily available in plasma and target tissues in horses. These findings are similar to data obtained previously in various species including mice, rats, rabbits, dogs, guinea pigs, and humans, all in which absorption is essentially complete.\(^{33} \) The AUC values obtained after IV and PO administrations of a 10 mg/kg dose of voriconazole were not significantly different because each had 95% bioavailability; the similarity was also evident from the model fitting curves.

From data obtained after PO administration of a single dose of voriconazole, a PO treatment regimen that incorporated a dose that would maintain steady-state plasma concentrations at approximately 2 \( \mu \text{g/mL} \) was determined. The dosing regimen of 3 mg/kg of voriconazole administered PO twice daily maintained voriconazole concentrations at 2 \( \mu \text{g/mL} \) in plasma obtained from the study horses. A dose of 3 to 5 mg of voriconazole/kg is used in humans with fungal infections and achieves the targeted therapeutic concentration necessary for antifungal activity.\(^{24,25} \) Voriconazole is cleared from the plasma almost exclusively via hepatic metabolism (oxidation). As many as 16 metabolites of voriconazole have been isolated in a variety of species;\(^{25,33} \) similar drug metabolism should be expected in horses, although it has not yet been evaluated.

Voriconazole has high solubility and permeability as indicated by the extent of drug distribution into synovial fluid, preocular tear film, urine, and CSF collected from the study horses. The mean voriconazole concentrations achieved in these fluids were each > 2.5 \( \mu \text{g/mL} \), which is greater than the therapeutic target of 0.5 \( \mu \text{g/mL} \) that is typically considered the minimum concentration for potential clinical efficacy against most susceptible fungi.\(^{31} \) Results of the present study have indicated that the dose chosen for use in the long-term dosing regimen appears to be adequate for achieving the targeted MIC\(_{90}\) for Aspergillus spp (ie, 2 \( \mu \text{g/mL} \)). A recent study\(^{39} \) to evaluate the in vitro activity of voriconazole against 448 clinical isolates of filamentous fungi revealed that voriconazole inhibited > 95% of Aspergillus spp at a concentration of \( \leq 1 \mu \text{g/mL} \), compared with 83% and 91% inhibition of those organisms by itraconazole and amphotericin B, respectively. Voriconazole also inhibited 90% of Penicillium spp at a dose of 2 \( \mu \text{g/mL} \), 50% of Rhizopus and Mucor spp at a dose of 2 \( \mu \text{g/mL} \), and Paecilomyces spp at a dose range of 0.03 to 2 \( \mu \text{g/mL} \).\(^{39} \) The same study\(^{39} \) did, however, reveal that voriconazole had no in vitro activity against Fusarium spp or the zygomycetes, although there are clinical reports\(^{26,35} \) of humans with Fusarium infections who were successfully treated with voriconazole, probably because of its excellent tissue distribution. Results of another study\(^{36} \) indicated that voriconazole had potent in vitro inhibitory activity against Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, Cladowphialophora carrioni, Fonsecia pedrosi, and Sporothrix schenckii, many of which are pathogens of clinical importance in veterinary medicine. In that same study, voriconazole had variable inhibitory activity against Fusarium spp as well as Paecilomyces lilacinus and Pseudallescheria boydii.\(^{39} \) Voriconazole has fungistatic activity against Candida spp and fungicidal activity against Aspergillus spp.\(^{23} \)

Voriconazole is available for oral and parenteral use in humans; has been proven effective in the treatment of aspergillosis (including cerebral and ocular infections); and, to date, has been proven safer for use in humans than many other antifungal medications.\(^{23} \) The reported incidence of adverse effects in humans receiving voriconazole is \( \geq 10\% \).\(^{38} \) The drug-associated adverse effects include visual abnormalities, skin reactions, and increases in liver enzyme activities that can lead to hepatotoxicosis; its use should be avoided in pregnant females.\(^{25} \) In dogs receiving voriconazole, visual problems were transient and there were no long-term morphologic, morphometric, or histologic changes in the retina associated with administration of the drug, even after 12 months of treatment.\(^{38} \) In human clinical trials, visual abnormalities including photophobia, blurred vision, and color or visual perception alterations developed in < 0.5% of patients and resolved when administration of the drug was discontinued. In the present study, no visual abnormalities were evident in any of the horses, although electrodagnostic evaluation and histologic examination of ocular tissues were not performed. In humans, skin reactions attributable to alterations in retinol metabolism occur when exposed to sunlight during treatment, and these include rash, photosensitivity, and erythema.\(^{39} \) Skin abnormalities were also not detected in the horses used in the present study, although the time of year and lack of exposure to sun would not have induced such reactions. Treatment with voriconazole has been associated with increases in serum total bilirubin concentration and hepatic enzyme activities including alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase in humans.\(^{25,38} \) In clinical trials involving humans, the risk of drug-induced hepatic toxicosis (liver insufficiency or failure) is greater for voriconazole than the risk associated with fluconazole, but less than the risk associated with amphotericin B. No changes in serum biochemical variables (including liver enzyme activities) were detected in the horses of the present study. Clinical use of voriconazole in animals with compromised hepatic function warrants careful monitoring of liver function during treatment or avoiding use of the drug if further hepatic compromise is considered to have serious clinical consequences. Similar to treatment with fluconazole, the risk of renal toxicosis associated with voriconazole administration is minimal. However, rats and
rabbits treated with voriconazole during gestation had offspring with skeletal abnormalities, increased risk of embryo death, and reduced fetal weight. Use of voriconazole in pregnant mares should be limited on the basis of these findings.

Coadministration of voriconazole with omeprazole in humans increases the available plasma and tissue concentrations of voriconazole because of competitive inhibition of the cytochrome P-450 enzyme system. Administration of voriconazole in humans already receiving 40 mg or more of omeprazole significantly increased the plasma concentration of omeprazole, compared with findings after omeprazole was administered in humans who were not receiving voriconazole. For humans receiving omeprazole, it is recommended that the dose of omeprazole is reduced by 50% on commencement of voriconazole treatment. Similarly, in horses treated with omeprazole for treatment of gastric ulcers, the orally administered dose of voriconazole may require adjustment if both drugs are to be used concurrently over a long period. The exact dose adjustment required would have to be determined experimentally; the recommendations for human patients would only be a guideline to minimize toxic effects. Concurrent use of omeprazole, especially generic forms, may allow reduction of the dosing schedule of voriconazole, which would minimize the cost associated with long-term PO treatment of an adult horse with voriconazole.

In humans receiving doses of 3 to 6 mg of voriconazole/kg, IV, every 12 hours or 200 to 400 mg of voriconazole/kg, PO, every 12 hours, plasma concentrations of voriconazole of 2 to 7 µg/mL were achieved. In the horses of the present study; a similar plasma concentration range (3.110 to 6.780 µg/mL) was achieved via administration of 3 mg of voriconazole/kg, PO, every 12 hours. At an MIC₉₀ of < 4 µg/mL, most fungi are susceptible to voriconazole; at an MIC₉₀ > 8 µg/mL, most fungi are considered resistant. The activity of voriconazole against Aspergillus spp has been reported to be high (MIC₉₀, 0.01 to 2 µg/mL), and the drug appears to have fungicidal rather than fungistatic activity against those organisms. Elimination of voriconazole occurs primarily via hepatic metabolism (oxidation); 80% of the original dose is excreted as inactive metabolites in the urine, and 20% is excreted in the feces. Only 2% of the original dose of voriconazole is excreted unchanged in the urine, unlike fluconazole that undergoes minimal hepatic transformation and is excreted mostly unchanged in the urine.

Results of the present study indicated that administration of voriconazole at a dose of 3 mg/kg, PO, twice daily achieves excellent tissue bioavailability and penetration in horses. Because of its spectrum of activity against most filamentous fungi, this drug appears to be an effective treatment option for several mycoses in horses, particularly Aspergillus infections that develop in neonates or in the eyes and respiratory tracts of older horses. Given that adverse effects after single or multiple doses were not detected in the present study, voriconazole appears to be safe to administer to horses.

c. Dormosedan injectable, 10 mg/mL, Pfizer Animal Health, Exton, Pa.
d. Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa.

References
23. de Lastours V, Lefort A, Zappa M, et al. Two cases of cerebral...