**Pharmacokinetics of voriconazole after oral administration of single and multiple doses in African grey parrots (Psittacus erithacus timneh)**

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**Objective**—To determine the pharmacokinetics and safety of orally administered voriconazole in African grey parrots.

**Animals**—20 clinically normal Timneh African grey parrots (Psittacus erithacus timneh).

**Procedures**—In single-dose trials, 12 parrots were each administered 6, 12, and 18 mg of voriconazole/kg orally and plasma concentrations of voriconazole were determined via high-pressure liquid chromatography. In a multiple-dose trial, voriconazole (18 mg/kg) was administered orally to 6 birds every 12 hours for 9 days; a control group (2 birds) received tap water. Treatment effects were assessed via observation, clinicopathologic analyses (3 assessments), and measurement of trough plasma voriconazole concentrations (2 assessments).

**Results**—Voriconazole’s elimination half-life was short (1.1 to 1.6 hours). Higher doses resulted in disproportional increases in the maximum plasma voriconazole concentration and area under the curve. Trough plasma voriconazole concentrations achieved in the multiple-dose trial were lower than those achieved after administration of single doses. Polyuria (the only adverse treatment effect) developed in treated and control birds but was more severe in the treatment group.

**Conclusions and Clinical Relevance**—In African grey parrots, voriconazole has dose-dependent pharmacokinetics and may induce its own metabolism. Oral administration of 12 to 18 mg of voriconazole/kg twice daily is a rational starting dose for treatment of African grey parrots infected with Aspergillus or other fungal organisms that have a minimal inhibitory concentration for voriconazole ≤ 0.4 µg/mL. Higher doses may be needed to maintain plasma voriconazole concentrations during long-term treatment. Safety and efficacy of various voriconazole treatment regimens in this species require investigation. (Am J Vet Res 2008;69:114–121)

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Infection with Aspergillus spp, especially *Aspergillus fumigatus*, is a common cause of respiratory and disseminated disease in birds. Current methods of treatment involving amphotericin B, itraconazole, or terbinafine are not uniformly successful, and mortality rates among infected birds remain high. Voriconazole is a second-generation triazole antifungal drug that is derived from fluconazole and is available in preparations for IV and oral administration. Like other triazoles, voriconazole inhibits cytochrome P<sub>450</sub>-dependent 14α-sterol demethylase, which is an enzyme essential for ergosterol synthesis in fungal cell walls. The drug is highly active against *Aspergillus* spp, *Candida* spp, and a variety of other fungal pathogens.

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Definition</th>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-pressure liquid chromatography</td>
</tr>
<tr>
<td>Vd/F</td>
<td>Volume of distribution requiring correction for bioavailability</td>
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<tr>
<td>CI/F</td>
<td>Clearance requiring correction for bioavailability</td>
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<tr>
<td>AUC</td>
<td>Area under the plasma concentration-versus-time curve</td>
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<td>MIC</td>
<td>Minimum inhibitory concentration</td>
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<tr>
<td>AUC&lt;sub&gt;0−24&lt;/sub&gt;</td>
<td>Area under the plasma concentration-versus-time curve from time 0 to 24 hours</td>
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Voriconazole has become the preferred drug for treatment of respiratory and disseminated aspergillosis in humans<sup>9,10</sup>, results of a clinical trial have indicated that voriconazole (2 doses administered IV followed by oral treatment) is more effective than amphotericin B administered IV<sup>11</sup>. It has also proved efficacious for treatment of bone and CNS infections<sup>12,13</sup>. Voriconazole may be useful for treatment of aspergillosis and other fungal diseases in birds; however, clinical trial and pharmacokinetic data in avian species are lacking to our knowledge.
Pharmacologic aspects of voriconazole have been studied in several mammalian species, including mice, rats, rabbits, guinea pigs, dogs, horses, and humans. In these mammals, voriconazole is absorbed well and distributed widely after IV and oral administration. Protein binding varies from 38% to 67%. Voriconazole is extensively metabolized in the liver and has dose-dependent pharmacokinetics that are dependent on the administered dose; metabolites have limited antifungal activity. Voriconazole is generally tolerated well by humans, although visual disturbances, liver function abnormalities, skin rashes, and gastrointestinal tract irritation can develop in some patients. Most of these adverse effects are transient and do not require discontinuation of the drug treatment. As with other azoles, severe hepatitis can develop but is rare.

To our knowledge, there are few reports of clinical use of voriconazole in nonhuman species and published data regarding voriconazole use and pharmacology in birds are currently limited to preliminary reports. In chickens receiving doses of 5 to 15 mg of voriconazole/kg orally, drug elimination was rapid and achieved plasma concentrations low (Cmax approx 0.4 µg/mL). No adverse effects or accumulation of voriconazole in plasma were detected in chickens treated with 10 mg of voriconazole/kg orally once daily for 30 days. In falcons treated with 12 mg of voriconazole/kg orally twice daily for 14 days, median plasma drug concentration at 1 hour after administration was maintained at approximately 2 µg/mL; however, trough plasma voriconazole concentrations at 12 hours after administration were 0.2 µg/mL. No adverse effects were detected in the birds of that study. Results of those reports suggest that the pharmacokinetics of voriconazole may vary in different avian species. For psittacine birds, a single case report describes a cockatiel (Nymphicus hollandicus) that was treated with voriconazole at a dose of 10 mg/kg orally once daily for 2 months without notable adverse effects. The purpose of the study reported here was to determine the pharmacokinetics and safety of orally administered voriconazole (single and multiple doses) in African grey parrots.

Materials and Methods

Parrots—Twenty adult Timneh African grey parrots (Psittacus erithacus timneh) that weighed 290 to 339 g and belonged to an aviculturist were included in the study. The owner gave informed consent prior to study commencement. Birds were available for a 1.5-month period during their nonbreeding seasons, and this series of experiments was completed over a period of 3 years. Each year, the birds were judged healthy on the basis of results of physical examination and assessment of PCV and total plasma solids concentration. The birds were housed as surgically sexed pairs in suspended wire cages in rooms maintained at 20° to 23°C with a 12-hour photoperiod. They were fed water and a commercial pelleted parrot diet ad libitum. The birds were acclimated for 2 weeks prior to each year’s experiments. The experimental protocol was approved by the North Carolina State University Institutional Animal Care and Use Committee.

Experimental design for single-dose trials—Four single-dose trials were performed involving voriconazole administered orally at different doses or in different compounded formulations to 12 birds. In the first experiment, voriconazole tablets were crushed with a mortar and pestle and the powder was transferred to a capped centrifuge tube. Deionized water was added to create a solution of 0.5 mg of voriconazole/mL, and the compounded solution was vortex-mixed for 10 minutes. At the end of mixing, no visible particulate matter remained. The drug solution was vortex-mixed again for 15 seconds just prior to administration; a dose of 6 mg of voriconazole/kg was delivered into the crop of each of the 12 birds by use of a 12-F rubber feeding tube that was attached to a 3-mL syringe. The birds were rested for 21 days, and the experiment was repeated with a drug solution at a final drug concentration of 0.6 mg of voriconazole/mL; a dose of 12 mg of voriconazole/kg was administered by use of a 6-mL syringe. The birds were returned to the aviculturist until the following year. At that time, 2 additional single-dose trials were completed at an interval of 14 days. For these trials, crushed voriconazole tablets were compounded at a concentration of 2.5 mg of voriconazole/mL in a commercial suspension agent and mixed 75:25 (vol/vol) with deionized water; on each of the 2 occasions, a dose of 12 or 18 mg of voriconazole/kg was administered by use of 6-mL syringes. The compounded formulation contained methylcellulose and simethicone and was mixed well. No visible settling of drug occurred within a 48-hour observation period.

To avoid collection of excessive volumes of blood from individual birds, the 12 birds in each single-dose trial were assigned to groups of 4, and samples of blood were collected from a different group at specified time points after drug administration (2 or 3 collections/bird/group). Samples were collected from birds in group A at 0.5, 4, and 12 hours after drug administration; group B at 1, 6, and 24 hours after drug administration; and group C at 2 and 8 hours after drug administration. Naïve pooling of datum points was used to generate a mean plasma voriconazole concentration at each time point, and these mean values were used for pharmacokinetic analysis. Blood samples (0.7 to 1.0 mL) were collected via venipuncture of the basilic or right jugular vein with syringes containing heparin. Samples were centrifuged at 6,600 × g for 2 minutes, and plasma was decanted within 1 hour of collection. Plasma samples for voriconazole assay were stored at −70°C until analyzed.

Experimental design for the multiple-dose trial—For the multiple-dose trial, 8 parrots were used. These birds had not been used in the single-dose trials and had not previously received voriconazole. Six birds were allocated to the treatment group and 2 birds to the control group. The treatment group received voriconazole (18 mg/kg, PO, q 12 h) for 9 days; the drug was administered by use of a 16-F curved feeding needle. A drug suspension (2.5 mg/mL) was prepared by mixing 1 crushed 200-mg voriconazole tablet with 60 mL of commercial suspending agent and 20 mL of deionized water. The mixture was vortex-mixed for 5 minutes and then quickly transferred to capped centrifuge tubes. The mixed suspension was stored at 5°C.
and protected from light until administered. The control group received an equivalent volume of tap water administered in the same manner. The day of the first dose of the drug or water was designated day 0. Plasma samples for assay of trough concentrations of voriconazole were collected immediately prior to administration of the next dose (ie, 12 hours after the previous dose) on days 3 and 10.

All birds were monitored for signs of adverse effects. They were weighed and examined each morning. Packed cell volume; plasma total solids, albumin, total bile acids, calcium, cholesterol, glucose, phosphorus, total protein, and uric acid concentrations; and plasma activities of aspartate aminotransferase, creatine kinase, and lactate dehydrogenase were assessed during the week before treatment and on days 3 and 10. Biochemical analyses of plasma samples were performed by use of an automated (wet chemistry) analyzer.1 The birds were also observed twice each day at the time of drug or water administration. Their activity level and condition of their droppings were scored by means of a 4-point and 6-point scale, respectively. Investigators doing the scoring (KF, JAN, and EE) were not blinded to the group allocation. Activity levels were rated as follows: 1 = minimal, 2 = reduced, 3 = normal, and 4 = excessive. Characteristics of the droppings were rated as follows: 1 = scant quantity, 2 = diarrhea, 3 = normal quantity and quality, 4 = slight polyuria, 5 = moderate polyuria, and 6 = marked polyuria.

**Testing of drug stability—**As described for the multiple-dose trial, a suspension of voriconazole (2.5 mg/mL) was prepared by mixing 1 crushed 200-mg voriconazole tablet with 60 mL of commercial suspending agent2 and 20 mL of deionized water. The mixture was vortex-mixed for 5 minutes and then quickly transferred to capped centrifuge tubes. The mixed suspension was stored at 5°C and protected from light. Two aliquots from each sample were collected immediately after preparation and on days 2, 7, and 17 after preparation. The samples were analyzed via HPLC. Prior to injection of a sample into the HPLC system, 100 µL of the sample was diluted in 900 µL of 100% acetonitrile; this mixture was vortexed for 10 seconds and then sonicated for 5 minutes. A second dilution was performed by adding 100 µL of the previous mixture into 900 µL of mobile phase to achieve a final concentration of 25 µg/mL. Drug concentrations in the samples were determined from a calibration curve prepared in mobile phase. All samples were assayed in duplicate. Drug stability was tested after completion of the experimental portion of the study.

**Measurement of voriconazole concentrations—**Voriconazole concentrations in plasma and compounded drug preparations were determined by use of a method that was previously validated in our laboratory.13 Briefly, drug concentrations were determined by use of HPLC with UV detection at 263 nm. All plasma samples underwent solid-phase extraction by use of cyano-bonded cartridges6 prior to injection into the HPLC system, as previously described.15 Sample volume was 150 to 200 µL, and results were compared with a standard curve for equal volumes. Following extraction, the samples were eluted with 1 mL of methanol, and the eluent was evaporated under compressed air at 40°C for 30 minutes. Samples were reconstituted with 200 µL of mobile phase, which consisted of double-deionized water and HPLC-grade acetonitrile (50:50 [vol/vol]). A reverse-phase C8 column9 was used for separation. The flow rate was 1.0 mL/min, and the sample injection volume was 25 µL.

Prior to each day’s HPLC run, calibration curves were prepared by fortifying a pooled sample of plasma obtained from untreated Timneh African grey parrots with known concentrations of voriconazole reference standard (99% pure). A blank sample was processed and analyzed at the beginning of each assay to check for interfering peaks. Calibration curves were linear between the concentrations of 0.05 and 10 µg/mL (r² > 0.99), and all values were within 15% of the expected range. The lower limit of quantification was defined as the lowest concentration that was consistently linear, as determined on the basis of regression analysis of the calibration curve. For these conditions, the value for voriconazole in plasma was 0.05 µg/mL.

**Pharmacokinetic analysis—**Naïve pooling of datum points was used to generate a mean plasma voriconazole concentration at each time point. Concentrations at or less than the limit of quantification were included as zero. For the 6 mg/kg dose, the 12- and 24-hour time points were excluded from the analysis because of sparse and inconsistent data. For all other doses, the 24-hour time points were excluded for the same reason. A computer program was used to determine pharmacokinetic values. Noncompartmental analysis was performed by use of uniform weighting for all doses except the 18 mg/kg dose, where model fit was improved by weighting the data by use of W = 1/y, where y is the plasma concentration of voriconazole. Terminal half-life (t1/2) was calculated by use of an equation as follows:17

\[ t_{1/2} = 0.693/\lambda_{z} \]

where \( \lambda_{z} \) is the terminal rate constant derived from the terminal slope of the concentration time profile plotted on a semilogarithmic graph. Area under the plasma concentration-versus-time curve was calculated by use of the trapezoidal method. We could not calculate the true oral absorption of voriconazole because there was not an accompanying IV dose in the study design. Therefore, results for volume of distribution and clearance are reported as Vd/F and Cl/F. The linearity of the kinetics was determined by comparing the AUC-to-dose ratio for each dose.

A compartmental model could be fit to data from the 18 mg/kg dose experiment only. On the basis of visual inspection of the plasma concentration-versus-time curve plotted on semilogarithmic paper and by use of the Akaike information criterion,12 the data best fit a 1-compartment open model with first-order input. Fit for the peak and elimination phase concentrations was improved by weighting the data with a factor of 1/y².
and by adding a lag phase. The model was described by an equation as follows:

\[ C = \left( \frac{[D_0] \times F \times D}{Vd} \times [k_{01} - k_{10}] \right) \times \left( e^{-(k_{10} \times t + k_{10} \times t^2)} \right) \]

where C is the plasma concentration, \( k_{01} \) is the absorption rate constant, F is the fraction of drug absorbed, D is the orally administered dose, Vd is the apparent volume of distribution, \( k_{10} \) is the elimination rate constant, t is time, and \( t_{\text{est}} \) is the estimated lag time.

By use of a computer simulation program,1 distribution and elimination rate constants were calculated for the 18 mg/kg dose experiment and used to simulate predicted concentrations after multiple doses of voriconazole.

Table 1—Pharmacokinetic values derived via noncompartmental pharmacokinetic analysis after oral administration of voriconazole (single-dose trials) in 12° Timneh African grey parrots.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Drug dose and vehicle</th>
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<tbody>
<tr>
<td></td>
<td>6 mg/kg in water</td>
</tr>
<tr>
<td></td>
<td>(( \mu )g/mL)</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.54</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2</td>
</tr>
<tr>
<td>AUCmax (( \mu )g h/mL)</td>
<td>2.75</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>1.11</td>
</tr>
<tr>
<td>Vd/F (mL/kg)</td>
<td>3.47</td>
</tr>
<tr>
<td>CI/F (mL/h/kg)</td>
<td>2,184.9</td>
</tr>
<tr>
<td>AUC-to-dose ratio</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Twelve birds in each single-dose trial were assigned to groups of 4; blood samples were collected from birds in group A at 0.5, 4, and 12 hours after drug administration; group B at 1, 6, and 24 hours after drug administration; and group C at 2 and 8 hours after drug administration. Naïve pooling of datum points was used to generate a mean plasma voriconazole concentration at each time point, and these mean values were used for pharmacokinetic analysis. 

Tmax = Time to achieve maximal concentration. AUCmax = Area under the plasma concentration-versus-time curve extrapolated to infinity. T1/2 = Half-life of elimination phase. MRT = Mean residence time.

Statistical analysis—Values are expressed as the mean ± SEM. Plasma concentrations from the 12-hour samples on days 3 and 10 of the multiple-dose trial and 12-hour samples from the 18 mg/kg single-dose trial were compared by use of the Mann-Whitney rank sums test. A value of \( P < 0.05 \) was considered significant.

Results

Single-dose trials—Plasma concentration-versus-time curves were derived from the single-dose trials (Figure 1). For all single-dose trials, pharmacokinetic parameters were calculated by use of noncompartmental methods (Table 1). In the trials in which voriconazole was mixed with water, doubling the dose of voriconazole from 6 to 12 mg/kg resulted in a 370% increase in AUC and a 350% increase in Cmax. In the trials in which voriconazole was mixed with a commercial suspending agent, increasing the dose from 12 to 18 mg/kg resulted in a 200% and 190% increase in AUC and Cmax, respectively. The AUC and Cmax determined for the 12 mg/kg dose of voriconazole compounded in the commercial suspending agent were 1.5 and 1.6 times as great, respectively, as the values determined for that dose of drug mixed with water. The AUC-to-dose ratios differed among doses and between formulations.

Pharmacokinetic parameters were derived from compartmental modeling of the 18 mg/kg dose of voriconazole and used to create a plot of actual and predicted plasma concentration-versus-time (Table 2; Figure 2). Simulated plasma concentrations predicted for an 18 mg/kg dose administered orally given twice daily varied from a trough concentration of approximately 0.35 \( \mu \)g/mL to a peak concentration of approximately 6 \( \mu \)g/mL.

Multiple-dose trial—Trough voriconazole plasma concentrations (assessed 12 hours after drug administration) were greater than the limit of quantitation in 2 of 6 samples (0.075 and 0.57 \( \mu \)g/mL) on day 3 and greater than the limit of quantitation in all 6 samples on day 10 (25% confidence interval, 0.058 \( \mu \)g/mL; 75% confidence interval, 0.063 \( \mu \)g/mL). These concentra-

Figure 1—Mean ± SE plasma concentrations of voriconazole in 12° Timneh African grey parrots after oral administration of a single dose of a suspension that was compounded in water (6 [triangles] and 12 mg/kg [white circles]) and compounded in a commercial suspending agent (12 [black circles] and 18 mg/kg [squares]). Twelve birds in each single-dose trial were assigned to groups of 4; blood samples were collected from birds in group A at 0.5, 4, and 12 hours after drug administration; group B at 1, 6, and 24 hours after drug administration; and group C at 2 and 8 hours after drug administration. Naïve pooling of datum points was used to generate a mean plasma voriconazole concentration at each time point.
Figure 2—Plasma concentrations of voriconazole in 12 Timneh African grey parrots (fitted curve [solid line]; closed circles [individual samples]) after oral administration of a single dose of voriconazole (18 mg/kg) compounded in a commercial suspending agent. See Figure 1 for key.

Figure 3—Percentage of observations (subjectively scored twice daily) of urine that was considered normal (black bar), slightly polyuric (light gray bar), or moderately polyuric (dark gray bar) voided by 6 Timneh African grey parrots that received multiple doses of voriconazole (18 mg/kg, PO, 12 h) and 2 control parrots that received tap water (equivalent volume, PO, 12 h) during a 9-day treatment period. There were 2 birds/cage; control birds were in cage 4.

Table 2—Pharmacokinetic values derived via 1-compartment pharmacokinetic analysis after oral administration of 18 mg of voriconazole/kg (single-dose trial) in 12 Timneh African grey parrots.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>C₀ (µg/mL)</td>
<td>5.85</td>
</tr>
<tr>
<td>t₁/₂ (h)</td>
<td>3.01</td>
</tr>
<tr>
<td>K₀ (1/h)</td>
<td>0.48</td>
</tr>
<tr>
<td>Kₐ (1/h)</td>
<td>0.47</td>
</tr>
<tr>
<td>Kₑ (1/h)</td>
<td>1.44</td>
</tr>
<tr>
<td>Kₐₑ (h)</td>
<td>1.46</td>
</tr>
<tr>
<td>AUC (µg/mL)</td>
<td>33.32</td>
</tr>
<tr>
<td>Cl/F (mL/h/kg)</td>
<td>540.21</td>
</tr>
<tr>
<td>Vd/F (mL/kg)</td>
<td>1,140.47</td>
</tr>
</tbody>
</table>

K₀ = Absorption rate constant, Kₑ = Elimination rate constant, Kₐₑ = Half-life of absorption phase, Kₐ₁/₂ = Half-life of elimination phase.

See Table 1 for remainder of key.

Results of the present study indicated that the terminal half-life of voriconazole in Timneh African grey parrots is short (1.1 to 1.6 hours). This is comparable to the half-life of the drug in chickens receiving 5 to 15 mg of voriconazole/kg (approx 2 hours) and mice receiving 20 mg of voriconazole/kg (1.14 hours) but shorter than the half-life of the drug in rabbits receiving 10 mg of voriconazole/kg (2.5 to 3 hours following multiple doses), guinea pigs receiving 10 mg of voriconazole/kg (5.5 hours following multiple doses), guinea pigs, rabbits, guinea pigs, dogs, and adult humans receiving 3 mg of voriconazole/kg (6 to 8 hours), and horses receiving 4 mg of voriconazole/kg (13 hours).

In the birds of the present study, increases in the dose of voriconazole resulted in supraproportional increases in Cₘₚ and AUC. This, combined with convex shape of the plasma concentration-versus-time curve and non-parallel terminal phases, suggested that voriconazole may have dose-dependent pharmacokinetics in African grey parrots. This was confirmed by calculation of the AUC-to-dose ratio for each dose and formulation used in the present study. For drugs that have linear kinetics, the AUC-to-dose ratio remains constant regardless of the dose administered. Over the range of doses used in the present study, the ratios calculated increased 4-fold. Dose-dependent changes were most marked at lower doses. Dose-dependent pharmacokinetics for voriconazole in mice, rats, rabbits, guinea pigs, dogs, and adult humans have been reported and were presumed to be associated with saturation of metabolic clearance. Be-
cause kinetics are dependent on the administered dose, pharmacokinetic data from one dose cannot be used accurately to predict plasma concentrations achieved with a different dose.

In the multiple-dose trial of the present study, trough plasma voriconazole concentrations measured at 12 hours after drug administration were significantly lower than the 12-hour concentration determined in the 18 mg/kg single-dose trial, and there was no accumulation of drug despite administration of that relatively high dose. This may be a result of the induction of voriconazole metabolism in African grey parrots; errors in drug preparation or administration are less likely possibilities. In some species of mammals, but not others, repeated administration of voriconazole induces the hepatic enzymes responsible for the drug’s metabolism. In rats, mice, and, to a lesser extent, dogs, repeated administration causes autoinduction of hepatic cytochrome P450 metabolizing enzymes. This results in a decrease in AUC and Cmax over time, and escalation of doses may be required to maintain plasma voriconazole concentrations. In contrast, autoinduction of metabolism does not occur in humans, rabbits, or guinea pigs. In humans, steady-state concentrations are reached in approximately 5 days and voriconazole may accumulate in plasma with repeated administration of high doses. However, the drug concentrations determined after multiple doses in the birds of the present study should be interpreted with caution. The birds used in the multiple-dose trial were not those used in the single-dose trials, and it may not be valid to compare the trough plasma concentrations in those birds with concentrations determined in the birds of the 18 mg/kg single-dose trial. Additionally, only trough plasma concentrations were measured on 2 days, and drug was not detected in several of the plasma samples. Further studies regarding the pharmacokinetics of voriconazole after administration of multiple doses are needed to confirm whether voriconazole induces its own metabolism in African grey parrots.

Despite sharing a structural similarity, the pharmacokinetic profile of fluconazole differs markedly from the capacity-limited pharmacokinetic profile of voriconazole. Fluconazole is predominately eliminated unchanged via renal excretion, and its pharmacokinetics are linear in African grey parrots as well as in other species. The elimination half-life of fluconazole in African grey parrots (9 to 10 hours) is much longer than that of voriconazole, and repeated administration of doses of fluconazole did not alter plasma concentrations.

Transient visual disturbances, high serum hepatic enzyme activities, skin rashes, and gastrointestinal tract irritation are the most common adverse effects of voriconazole treatment in humans. The effects are usually mild or transient and seldom lead to discontinuation of drug administration. No visual or dermatologic problems were detected in the treated parrots of the present study; however, it would be difficult to identify mild visual problems in this species. Throughout treatment, the birds’ activity and behavior appeared normal. The mild weight loss and mildly high plasma creatine kinase activity detected in treated and control birds were likely associated with repeated handling and were considered clinically unimportant. The mild, transient increase in plasma aspartate aminotransferase activity detected in 1 treated bird and 1 control bird was also considered clinically unimportant. The only clinically important adverse effect associated with multiple-dose treatment was polyuria (determined via subjective scoring of the droppings during daily observation). In the multiple-dose trial, there was evidence of polyuria in all cages, but the severity was considered greater among treated birds than among control birds. The polyuria resolved 2 days after birds were returned to their home aviary, which was 5 days after treatment ended. Polyuria has many potential causes, including renal dysfunction and stress. The polyuria detected in the birds of the present study could have been an adverse effect of voriconazole treatment but could also have been related to the stress of repeated handling for drug administration. Further studies are needed to determine the clinical importance of the polyuria that developed among the birds of the present study.

Because of limited availability, the number of parrots used in the multiple-dose trial was small and the duration of treatment was 9 days. Treatment of aspergillosis in birds may require a much longer treatment period, and as a result, adverse effects may be encountered that were not evident in the small population used in our short-term study. Of particular concern is the potential for development of severe hepatitis. Hepatitis has been associated with use of other azole drugs, especially itraconazole, in individual African grey parrots and could possibly develop in some individuals treated with voriconazole. Further studies are warranted to assess adverse treatment effects in a larger population of birds, in ill birds, or in birds treated for longer periods.

In the initial single-dose trials, voriconazole was compounded in deionized water at 0.5 to 0.6 mg/mL to avoid potential influence of compounding products on bioavailability. The solubility of voriconazole in water is reportedly 0.7 mg/mL. The final 2 dosing experiments used voriconazole that was compounded at 2.5 mg/mL in an aqueous commercial suspending agent containing methylcellulose and simethicone. Water was added to the suspending agent to thin the mixture, thereby facilitating delivery through the narrow-bore feeding needles. Use of that suspension was successful, and in the 12 mg/kg dose trials, plasma concentrations in birds treated with voriconazole in suspending agent were higher than those achieved after treatment with voriconazole mixed in deionized water. Possible reasons for the higher plasma concentrations associated with administration of the voriconazole-suspending agent formulation include more uniform drug suspension, decreased gastrointestinal tract transit time (allowing more drug absorption), increased solubility of the drug in the vehicle, or experimental variability. On the basis of the limited testing in the present study, the voriconazole-suspending agent formulation was stable for 17 days when refrigerated at 5°C; however, United States Pharmacopeia guidelines recommend discarding aqueous drug suspensions after 14 days to avoid microbial growth.

The use of Timneh African grey parrots in pharmacokinetic studies poses challenges; the birds are expensive to purchase and easily stressed by handling...
for drug administration and blood sample collection. Because of their small size and limited number of veins accessible for venipuncture, repeated blood sample collection is difficult. These factors influenced our study design. A study involving IV administration of voriconazole would have allowed calculation of the drug’s bioavailability, as well as a true volume of distribution and clearance; however, this was not included in the present study because of the difficulty of IV administration and the potential risk of toxicosis and vessel damage in these small, expensive birds. In the single-dose oral administration trials, naive pooling of plasma drug concentrations from multiple birds was used to plot concentration-versus-time curves and calculate pharmacokinetic values. This was necessary because the birds’ small size precluded collection of blood samples at all time points from each bird. It is a limitation that this method does not allow measurement of variability in the calculated pharmacokinetic parameters because the pooled concentrations are analyzed as though they are derived from a single bird. Use of this method limits a description of variability but is unlikely to alter dosage recommendations.

Dosing regimens for antibacterial drugs are often based on pharmacokinetic and pharmacodynamic variables, including the duration of the period in which plasma drug concentrations exceed the MIC, the ratio of AUCl:MIC to MIC, and the ratio of Cmax to MIC for various microbes.34 The relationships of these markers to clinical outcome are less clear for antifungal drugs35 and vary with the type of fungi. For Candida spp, results of in vitro studies34,35,36 suggest voriconazole is fungistatic and maximum activity is attained at 3X to 4X MIC. A free-drug AUCl:MIC ratio of 20 was most closely associated with treatment efficacy in mice with experimentally induced disseminated candidiasis.37 We were unable to find antimycotic drug susceptibility data for yeasts that were isolated from psittacine or other birds; however, the overall MIC reported for 90% of 8,702 Candida spp isolated from humans was 0.25 µg/mL, and 99% of the isolates were inhibited by ≤ 1 µg/mL.38 For Candida isolates with an MIC of 0.25 µg/mL, a dose of 12 mg of voriconazole/kg would achieve a Cmax/MIC ratio of 12 and an AUCl:MIC ratio of approximately 70 and would maintain plasma concentrations greater than the MIC for approximately 11 hours. It is likely that this dose given twice daily would be effective for treating most Candida spp infections in African grey parrots. Although voriconazole is highly active against yeast, fluconazole is currently the drug of choice for treating systemic Candida infections in African grey parrots because it is less costly and can be administered less frequently.39 Voriconazole might be useful if a fluconazole-resistant yeast were encountered. Findings of clinical trials to investigate the efficacy of treatment of gastric yeast infection caused by Macrorhabdus ornithogaster in birds would be of particular interest because the organism is resistant to fluconazole.39

In avian medicine, voriconazole would be most useful for the treatment of aspergillosis. Voriconazole has slow fungicidal activity against Aspergillus spp, with maximal antifungal activity at 2X to 4X MIC.35,40 The MIC of voriconazole for most species of Aspergillus isolated from humans is ≤ 0.5 µg/mL. Similar susceptibility was identified in Aspergillus organisms recovered from the respiratory tract of infected falcons: the MIC for 45 strains was 0.38 µg/mL, and all isolates were inhibited by 1 µg of voriconazole/mL.41 Clinical trial data obtained in a human study42 suggest maintaining concentrations > 0.5 µg/mL improves treatment success. In the single-dose trials of the present study, a dose of 12 mg of voriconazole/kg achieved a mean Cmax of approximately 3 µg/mL and maintained mean plasma concentrations > 0.4 µg/mL for approximately 10.5 hours. For Aspergillus isolates with an MIC of 0.4 µg/mL, this dose would achieve a Cmax/MIC ratio of 7.5 in African grey parrots. Given these values, 12 mg of voriconazole/kg given orally twice daily would be a reasonable starting dose for treatment of aspergillosis in African grey parrots. However, trough concentrations were < 0.4 µg/mL during the multiple-dose trial in which voriconazole was administered at 18 mg/kg; thus, further clinical studies are needed to determine the optimal dosage regimen for chronic treatment of aspergillosis in African grey parrots.

References


