Pharmacokinetics of a single dose of voriconazole administered orally with and without food to red-tailed hawks (*Buteo jamaicensus*)

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OBJECTIVE
To determine the pharmacokinetics of voriconazole administered PO with or without food to red-tailed hawks (*Buteo jamaicensus*) and whether any observed variability could be explained by measured covariates to inform dose adjustments.

ANIMALS
7 adult red-tailed hawks.

PROCEDURES
In a crossover study design, hawks were randomly assigned to first receive voriconazole (15 mg/kg, PO) injected into a dead mouse (n = 3; fed birds) or without food (4; unfed birds). Sixteen days later, treatments were reversed. Blood samples were collected at various points to measure plasma voriconazole concentrations by ultraperformance liquid chromatography. Pharmacokinetic data were analyzed by noncompartmental methods and fit to a compartmental model through nonlinear mixed-effects regression, with feeding status and body weight investigated as covariates.

RESULTS
Voriconazole was well absorbed, with quantifiable plasma concentrations up to 24 hours after administration. Mean plasma half-life was approximately 2 hours in fed and unfed birds. Administration of the voriconazole in food delayed absorption, resulting in a significant delay in time to maximum plasma concentration. The final compartmental model included a categorical covariate to account for this lag in absorption as well as body weight as a covariate of total body clearance (relative to unknown bioavailability).

CONCLUSIONS AND CLINICAL RELEVANCE
A single dose of voriconazole (15 mg/kg) administered PO to red-tailed hawks resulted in mean plasma voriconazole concentrations greater than the targeted value (1 μg/mL). Additional studies with larger sample sizes and multidose regimens are required before the model developed here can be applied in clinical settings. (*Am J Vet Res* 2017;78:433–439)

Aspergillosis is a common disease affecting birds in captivity and free-ranging birds managed in rehabilitation settings for other illness.[1] Birds are particularly susceptible to aspergillosis during periods of compromised health or other stressful events, such as recent capture, changing environments, or breeding.[2,3] Aspergillosis is the most common cause of death in recently captured or captive birds of prey.[4,5] Some of the more susceptible species include goshawks, gyrfalcons, and immature red-tailed hawks (*Buteo jamaicensus*),[4,6] and red-tailed hawks are a common species admitted into raptor rehabilitation centers.[a]

Aspergillus fumigatus is the most common cause of aspergillosis in birds, whereas *Aspergillus flavus* and *Aspergillus niger* may also cause disease, but to a lesser extent.[1,7] *Aspergillus* spp have a worldwide distribution, and spores are found throughout soil, moldy feed, hay and straw, and livestock bedding.[2,4,8] *Aspergillus* spp primarily cause disease of the respiratory tract and can involve the pulmonary parenchyma, air sac membranes, and syrinx. Infection may spread from the air sacs to infiltrate adjacent tissues, or systemic infection may develop, involving the gastrointestinal tract, kidneys, liver, and other

ABBREVIATIONS

AIC	Akaike information criterion
AUC	Area under the plasma concentration-versus-time curve
C_{max}	Maximum plasma drug concentration
CL	Total body clearance
F	Bioavailability
k_a	Absorption rate constant
λ_z	Slope of the terminal portion of the concentration-versus-time curve plotted on a semilogarithmic scale
MIC	Minimum inhibitory concentration
MRT	Mean residence time
T_{lag}	Lag time
T_{max}	Time to maximum plasma drug concentration
V	Apparent volume of distribution

tissues.[4] Infection may result in sudden death or become chronic and insidious; successful treatment is challenging.[7]

In birds with aspergillosis, pharmacological interventions have included amphotericin B, triazoles (eg, itraconazole or ketoconazole), and flucytosine.[4,9,10] The drug of choice for severe infection has been amphotericin B, which may be administered IV, intraosseously, intratracheally, via nebulization, or by injection into an air sac. Orally administered itraconazole is most commonly used as a prophylactic or for long-term treatment.[4,10]

Voriconazole is a second-generation triazole drug with broad-spectrum antifungal activity developed for use in immunocompromised humans.[11–13] It can be administered PO or IV, is generally well tolerated,[13] and is absorbed well with high oral F (> 75%) in various mammalian species.[14] In humans, voriconazole has potent in vitro antifungal activity against various clinical isolates of aspergillosis,[11] including strains resistant to amphotericin B and itraconazole.[13] In immunocompromised rats experimentally infected with invasive aspergillosis, voriconazole has good absorption when administered orally and is highly effective in preventing death, compared with itraconazole, which is a first-generation triazole.[11] Voriconazole also has potent in vivo efficacy against experimentally induced invasive pulmonary and systemic aspergillosis in mammals.[11,15–17] Therefore, voriconazole is the drug of choice for treatment of invasive aspergillosis in humans.[11,12]

Pharmacokinetic data for voriconazole have been reported for several laboratory animal species,[14–17] horses,[18,19] and humans,[20] and there is limited evidence of the efficacy of voriconazole in the treatment of birds with aspergillosis. The efficacy of 2 oral administration regimens for the treatment of experimentally infected birds has been evaluated in a small group of racing pigeons (*Columbia livia*).[21] The pharmacokinetics of single and multiple doses have been evaluated in chickens (*Gallus domesticus*),[22] pigeons,[23] ducks (*Anas platyrhynchos*),[24] quail (*Coturnix japonica*),[25] African grey parrots (*Psittacus erithacus timneh*),[26] and Hispaniolan Amazon parrots (*Amazona ventralis*).[27] However, only plasma concentration data (not fitted to a pharmacokinetic model) are available for falcons.[28] The effect of food on the pharmacokinetics of orally administered voriconazole has not been evaluated in birds, but in humans the F of voriconazole is decreased by 22% when administered PO postprandially or simultaneously with food.[29] The objective of the study reported here was to evaluate the pharmacokinetics of a single dose of voriconazole administered PO with (injected into a dead mouse) or without food to red-tailed hawks.

Materials and Methods

Animals

Seven adult captive red-tailed hawks (4 females and 3 males), with body weights ranging from 926 to 1,410 g (mean, 1,199 g), were used in this study. The sex of the birds was determined from their adult body weights; birds weighing > 1,200 were designated as female, and birds weighing < 1,200 g were designated as male. All birds were considered healthy on the basis of results of physical examination, annual evaluation of clinical laboratory variables, and evaluation of body weight history. During the study, all birds were housed in their regular mews at the University of California-Davis Raptor Center and had access to fresh drinking water. Food was withheld 9 hours before voriconazole administration, and birds were not fed until 24 hours after drug administration. All procedures relating to this study were performed in strict accordance with protocols approved by the Institutional Animal Care and Use Committee of the University of California-Davis.

Drug formulation

Voriconazole powder[b] was reconstituted in accordance with the manufacturer's instructions by adding 11.5 mL of deionized ultrafiltered water to 11.295 g of powder to obtain a suspension with a final voriconazole concentration of 40 mg/mL.

Experimental protocol

In a crossover study design, birds were randomly assigned by means of drawing of numbered cards to receive 1 of 2 treatments first. In period 1 of the study, 4 birds received voriconazole PO with food (fed birds), and the other 3 received voriconazole PO without food (unfed birds). The dose was the same for all the birds (one 15 mg/kg dose). When the drug was administered with food, the treatment was prepared by injection of the appropriate dose of voriconazole suspension into the peritoneal cavity of a small mouse (approx 24 g) via a 25-gauge needle to minimize loss of the drug from the injection site. The mouse was then force-fed to the birds. When the drug was administered without food, the treatment was administered via a 1.0-mL syringe inserted into the proximal aspect of the esophagus. A washout period of 16 days was provided, and then period 2 commenced, with the treatments reversed.

Blood samples (1.0 mL/collection point) were collected from a medial metatarsal, jugular, or cutaneous ulnar vein before voriconazole administration (blank sample) and 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after administration. Samples were placed in tubes[c] containing lithium heparin, which were then placed on ice until centrifugation. Within 1 hour of collection, the blood samples were centrifuged at 4,200 × *g* for 10 minutes. Plasma was decanted into freezer vials,[d] which were labeled and frozen at –80°C until assays were performed.

Ultraperformance liquid chromatography

Plasma voriconazole concentrations were measured by means of ultraperformance liquid chromatography coupled with UV detection. Plasma samples (250 µL) were prepared on cyanopropyl solid phase extraction cartridges[e] in accordance with a published protocol.[30] Methanol extracts were dried under nitrogen at 40°C, reconstituted in 250 µL of mobile phase,

and centrifuged at 14,000 X *g* for 5 minutes at 20°C prior to analysis on the ultraperformance liquid chromatography system.[f] The isocratic mobile phase was 0.02% trifluoroacetic acid in a mixture of acetonitrile and water (ratio, 37:63 [vol/vol]), the flow rate was 0.25 mL/min, and the injection volume was 5 µL. Voriconazole was separated from plasma by use of a 2.1 X 50-mm C18 column[g] (1.7-µm particle size) and detected by UV absorption at 263 nm. Calibration standards of voriconazole prepared in mobile phase ranged from 0.02 to 2.0 µg/mL, whereas quality control plasma samples were spiked with voriconazole standard at 0.05, 0.2, and 1.0 µg/mL.

Pharmacokinetic analysis

Noncompartmental analysis of plasma voriconazole concentrations over time was performed by use of statistical software.[h] The parameters calculated by this approach included C_{max}; T_{max}; λ_z; AUC calculated by use of the trapezoidal rule (linear upward portion and logarithmic downward portion) and extrapolated to infinity adding the term $C_{lastobs}/\lambda_z$, where $C_{lastobs}$ is the value of the last observed plasma concentration; area under the first moment curve extrapolated to infinity; and ratio of the AUC extrapolated to infinity to the area under the first moment curve extrapolated to infinity, which equals the MRT. Total body clearance and volume of distribution based on the terminal phase were both normalized to an unknown F. The noncompartmental parameters were compared between fed and unfed birds by means of a linear mixed-effects model that included sequence and period as regressors. Relationships between pharmacokinetic parameters and body weight were also explored. Values of $P < 0.05$ were considered significant for comparisons.

The data were also fit to a compartmental model by means of nonlinear mixed-effects regression by use pharmacokinetic analysis software.[i] Structural models incorporating either 1 or 2 compartments with first-order oral absorption and elimination were explored. An improvement in model fit with the addition of an oral absorption T_{lag} was also evaluated. Choice of the final structural model choice was made on the basis of plots of predicted versus observed plasma concentrations (no systematic bias), values of the AIC (a decrease of 6.635 was considered enough to justify a more complex model), and the precision of the parameter estimates. Proportional, additive, and Poisson residual error models were evaluated. The final residual error model was chosen on the basis of plots of weighted residuals versus observed concentrations (an error model that resulted in a consistent spread of residuals around a mean of 0 was chosen).

The compartmental model was fit to the data from periods 1 and 2 separately. Available clinical data (body weight and fed-unfed status) were explored as possible covariates in the model to explain some of the variability in parameter values. The best model was chosen on the basis of a combination of goodness-of-fit plots and AIC values.

Results

Animals

All 7 red-tailed hawks received both treatments and completed both study periods, yielding a total of 140 blood samples for pharmacokinetic analysis for each study period. No adverse reactions were observed in any bird at the time of voriconazole administration, during blood sample collection, or during a 2-week follow-up period.

Pharmacokinetic analysis

Voriconazole appeared to be well absorbed, with C_{max} values measured between 2 and 8 hours after oral administration ranging from 3.68 to 8.65 µg/mL **(Table 1)**. Mean plasma voriconazole concentrations remained > 1 µg/mL, a concentration to which 100% of *Aspergillus* isolates from falcon species are reportedly susceptible,[31] for 8 hours in unfed birds and 12

Table 1—Values of noncompartmental pharmacokinetic parameters for 7 adult red-tailed hawks (*Buteo jamaicensus*) at various points after receiving a single 15 mg/kg dose of voriconazole PO with (fed) and without (unfed) food.

	Unfed		Fed	
Variable	**Mean ± SD**	**Median (range)**	**Mean ± SD**	**Median (range)**
λ_z (1/h)	0.36 ± 0.09	0.37 (0.21–0.46)	0.36 ± 0.15	0.39 (0.20–0.56)
Plasma half-life (h)	2.04 ± 0.62	1.85 (1.52–3.26)	2.29 ± 1.01	1.76 (1.25–3.44)
T_{max} (h)	2.29 ± 0.76*	2 (2–4)	4.86 ± 1.95*	4 (2–8)
C_{max} (µg/mL)	7.23 ± 1.34	7.08 (4.93–8.65)	6.18 ± 1.59	6.55 (3.68–8.43)
$AUC_{0-\infty}$ (h•µg/mL)	46.01 ± 11.80	45.66 (24.80–64.31)	45.70 ± 20.96	38.24 (20.67–81.53)
V_z/F (mL)	1,180.38 ± 361.81	1,014.75 (860.46–1,793.63)	1,349 ± 406.26	1,237.13 (936.22–2,088.22)
CL/F (mL/h)	430.57 ± 188.36	408.01 (215.99–819.63)	485.16 ± 274.93	457.32 (228.50–1,023.08)
MRT (h)	4.84 ± 0.72*	4.74 (3.95–6.15)	6.57 ± 1.12	6.86 (5.16–7.87)

*Value differs significantly ($P < 0.05$) from that of fed hawks.

$AUC_{0-\infty}$ = AUC extrapolated to infinity. V_z = Terminal volume of distribution.

In a crossover study design, birds were randomly assigned to first treatment (with or without food; period 1). When the drug was administered with food, the treatment was prepared by injection of the appropriate dose of voriconazole suspension into the peritoneal cavity of a small mouse (approx 24 g) via a 25-gauge needle to minimize loss of the drug from the injection site. The mouse was then force-fed to the birds. When the drug was administered without food, the treatment was administered via a 1.0-mL syringe inserted into the proximal aspect of the esophagus. A washout period of 16 days was provided, and then the treatments were reversed (period 2).

hours in fed birds (that consumed the drug injected into a mouse). Visual inspection of the plasma drug concentration-verus-time profiles revealed a slightly lower peak C_{max} at a later time (T_{max}) in fed versus unfed birds, suggesting that administration with food caused a lag in the absorption **(Figure 1)**.

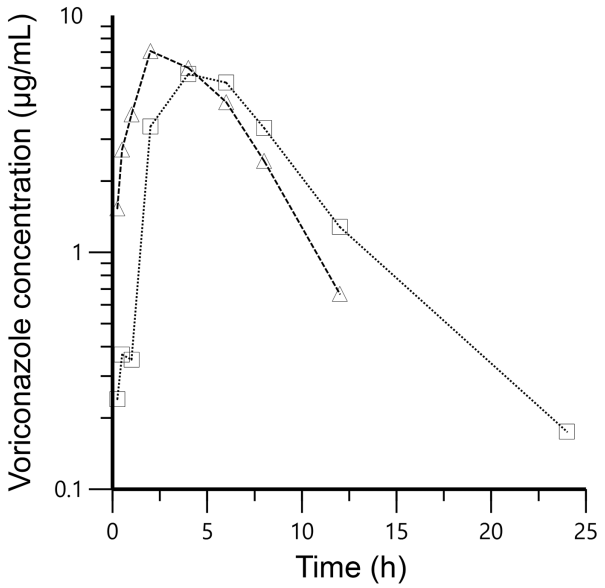

Figure 1—Mean plasma voriconazole concentrations in 7 adult red-tailed hawks (*Buteo jamaicensus*) at various points after receiving one 15 mg/kg dose of voriconazole PO with (squares) and without (triangles) food in a crossover study design. Birds were randomly assigned to first treatment (with or without food; period 1). When the drug was administered with food, the treatment was prepared by injection of the appropriate dose of voriconazole suspension into the peritoneal cavity of a small mouse (approx 24 g) via a 25-gauge needle to minimize loss of the drug from the injection site. The mouse was then force-fed to the birds. When the drug was administered without food, the treatment was administered via a 1.0-mL syringe inserted into the proximal aspect of the esophagus. A washout period of 16 days was provided, and then the treatments were reversed (period 2).

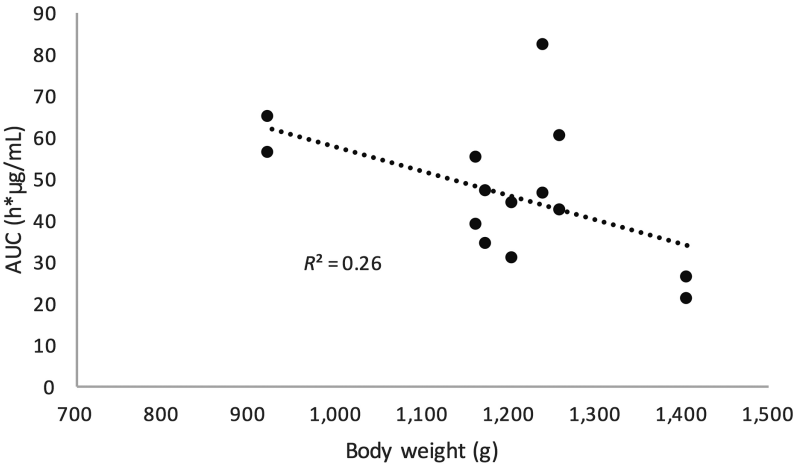

Figure 2—Plot of AUC values for plasma voriconazole concentration versus body weight for the hawks in Figure 1. The relationship between these variables was not significant ($P = 0.08$). ***See*** Figure 1 for remainder of key.

Statistical comparison of the noncompartmental pharmacokinetic parameters revealed that T_{max} was significantly later and MRT was significantly longer in fed versus unfed birds. A negative albeit nonsignificant ($P = 0.08$) association was identified between AUC and body weight **(Figure 2)**. No significant effects of study period or treatment sequence were identified. The plasma half-life of voriconazole was fairly short, ranging from 1.5 to 3.4 hours.

A 1-compartment open model with first-order absorption, a T_{lag}, and first-order elimination was judged to be the best structural model to describe the plasma voriconazole concentrations over time. The equation (equation 1) was as follows:

$$C(t) = ([F \times D]/V) \times (k_a/[k_a - k_e]) \times (e^{-ke \times [t - Tlag]} - e^{-ka \times [t - Tlag]})$$

where C(t) is concentration at time t, D is the administered dose, and k_e is the elimination rate constant. Note that when $t < T_{lag}$, $k_a = 0$.

Additional equations for the full covariate model were explored, relating parameter values for each bird to the typical value (tv) for the population and taking into account possible covariates and residual interindividual variability (η) as follows:

$$k_a = (tvk_a + [\{fed = 0\} \times dk_{a\{unfed\}}]) \times e^{\eta ka} \quad \text{(equation 2)}$$

$$T_{lag} = (tvT_{lag} + [\{fed = 0\} \times dT_{lag\{unfed\}}]) \times e^{\eta Tlag} \quad \text{(equation 3)}$$

$$\Delta V/F = tvV/F \times (weight/mean\ weight)^{d(V/F[weight])} \times e^{\eta V/F} \quad \text{(equation 4)}$$

$$CL/F = tvCL/F \times (weight/mean\ weight)^{d(CL/F[weight])} \times e^{\eta CL/F} \quad \text{(equation 5)}$$

where fed = 0 indicates the categorical covariate set to 0 for fed birds and 1 for unfed birds. In the final model, only the covariate models for T_{lag} and CL/F were included.

Parameter estimates were summarized for the final structural model (equation 1) with the 4 covariate models that were subsequently explored to explain the variability in the pharmacokinetic data **(Table 2)**. The final model, for which the AIC value decreased from 194.96 to 138.79 for period 1 and from 225.31 to 146.33 for period 2, compared with the base model, included fed-unfed status as a covariate of T_{lag} and body weight as a covariate of CL/F. This final model appeared to predict the observed data for both study periods without any systematic bias **(Figure 3)**.

Discussion

The study reported here represented the first in which a nonlinear mixed-effects model was created on the basis of pharmacokinetic data for a single dose of voriconazole administered PO to red-tailed hawks. The data were well described by a 1-compartment model with first-order absorption and elimination. This differs from the

Table 2—Comparison of results of population pharmacokinetic models of plasma voriconazole concentrations in the hawks in Table 1 during both treatment periods.

Parameter, by period	Base model	Alternate model 1	Alternate model 2	Alternate model 3	Alternate model 4	Final model	Final model CV (%)
Period 1							
tvk_a (1/h)	0.45	0.38	0.27	0.27	0.45	0.42	12.92
tvT_{lag} (h)	0.77	1.29	0.13	0.13	1.27	1.24	20.47
tvV/F (mL)	1,031.21	984.33	1,029.77	1,023.51	1,044.96	1,020.46	6.54
tvCL/F (mL/h)	432.10	490.36	374.71	374.28	389.64	389.54	11.35
dk_a (unfed)	NC	0.46	0.16	0.15	–0.03		
dT_{lag} (unfed)	NC	NC	NC	NC	–1.17	–1.12	–22.05
dCL/F (body weight)	NC	NC	2.32	2.34	2.01	2.01	35.20
dV/F (body weight)	NC	NC	NC	–0.15	NC	NC	NC
Residual error	1.032	1.364	0.612	0.612	0.415	0.420	10.35
AIC	194.96	208.02	165.63	167.63	140.70	138.79	NC
Period 2							
tvk_a (1/h)	0.48	0.135	0.59	0.95	0.20	0.31	10.65
tvT_{lag} (h)	0.58	0.62	1.36	1.83	1.49	1.64	8.73
tvV/F (mL)	1,082.95	1,018.29	1,343.3	1,683.33	712.30	808.02	22.00
tvCL/F (mL/h)	540.93	476.29	721.18	730.58	429.63	453.14	7.33
dk_a (unfed)	NC	0.45	0.23	2.73	0.11	NC	NC
dT_{lag} (unfed)	NC	NC	NC	NC	–1.47	–1.63	–10.55
dCL/F (body weight)	NC	NC	0.23	3.39	2.57	2.82	13.58
dV/F (body weight)	NC	NC	NC	2.31	NC	NC	NC
Residual error	1.374	1.271	1.91	1.89	0.47	0.45	11.16
AIC	225.31	221.81	242.07	242.47	147.38	146.33	NA

When preceding parameter names, the "d" indicates that the typical value (tv) for the population of the indicated parameter was modified by the covariate indicated in parentheses. For example, for dCL/F (body weight), the tvCL/F was modified by a value in relation to body weight.

CV = Coefficient of variation. NA = Not applicable. NC = Not calculated.

See Table 1 for remainder of key.

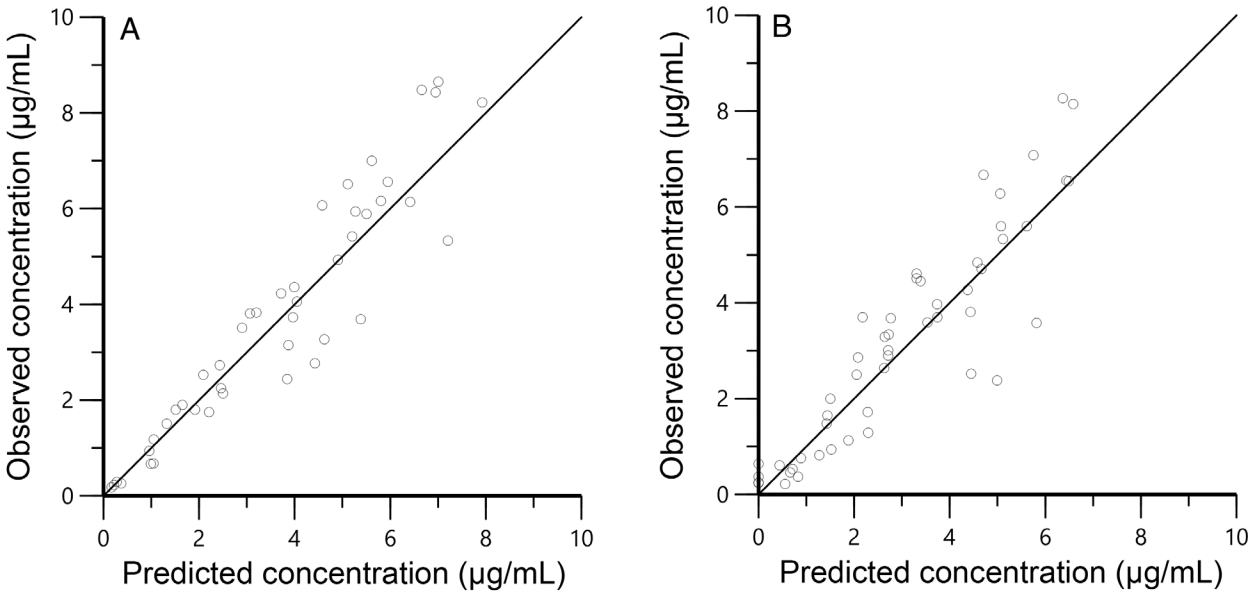

Figure 3—Observed plasma voriconazole concentrations versus concentrations predicted by the final compartmental pharmacokinetic model for the hawks in Figure 1 during periods 1 (A) and 2 (B). ***See*** Figure 1 for remainder of key.

published model for pediatric humans, in which incorporation of saturable elimination was required to obtain the best fit.[30] The reason for this difference was likely that peak plasma voriconazole concentrations never exceeded 10 µg/mL in the red-tailed hawks, and therefore saturated elimination was not observed.

Results of the present study can be used to predict plasma voriconazole concentrations in red-tailed hawks following administration PO at various doses and frequencies and can then be compared with pharmacodynamic data (MICs) to design effective administration regimens. The advantage of a compartmental model is that it can be used to simulate time-

versus-concentration profiles for different dosages, taking into account the covariate values for specific patients and allowing for prediction of whether effective concentrations will be achieved.

In vitro and in vivo studies[32,33] have shown that the inhibitory effect of voriconazole is dependent on time rather than concentration. This means that optimal dosages should maximize total and duration of exposure (AUC and time above the MIC) rather than peak exposure (C_{max}).

Findings suggested that, to ensure adequate exposure, doses of voriconazole administered to red-tailed hawks will need to be adjusted for body weight on the basis of a relationship that is more complex than the simple linear relationship assumed when doses are calculated on a milligram-per-kilogram basis. The relationship between CL and body weight was exponential in the nonlinear mixed-effects pharmacokinetic model that included covariates. Whether this relationship was attributable to differences in the metabolism of voriconazole between the sexes (because females were heavier than males) or in body condition and health status is unknown. The potential for AUC to be negatively associated with body weight ($P = 0.08$) suggests that doses calculated on a milligram-per-kilogram basis may be too low for heavier birds.

Initial analysis of the pharmacokinetic data by use of noncompartmental methods revealed a significant delay in achievement of C_{max} (ie, later T_{max}) when the drug was administered by injecting it into a mouse that was force-fed to hawks, suggesting a lag in absorption (Table 1). This conclusion was further supported by a significantly longer MRT (6.57 vs 4.84 hours). Mean C_{max} was 15% lower in the fed birds, but this difference from unfed birds was not significant. Plasma half-life and AUC were also not significantly different between fed and unfed birds. This food effect would be unlikely to have clinically important consequences given that the effect of voriconazole has not been shown to be dependent on C_{max}.

Effects of voriconazole administration with food differ among species. When voriconazole was administered to falcons in food rather than directly PO in another study,[28] peak plasma concentration of the drug decreased by between 21% and 26%. Similar to in hawks, oral absorption is delayed in fed humans by a mean of 1.1 hours.[29] In contrast, significant increases were observed in AUC and observed maximal concentration when ducks in another study[24] were fed a liquid diet just prior to PO administration of voriconazole. In both the hawks of the present study and ducks,[24] the time above the MIC (conservatively assumed to be 1.0 µg/mL) was increased in fed versus unfed birds. The AUC was also increased in humans, in which the C_{max} was increased by feeding during a multidose study.[29]

The C_{max} of voriconazole in both unfed and fed hawks receiving a 15 mg/kg dose (7.2 and 6.3 µg/mL, respectively) was comparable to that reported for other avian species,[23–27] except for chickens, in which the C_{max} for the same dose is only 0.5 µg/mL.[22] The nonlinear mixed-effects model confirmed that PO administration of voriconazole by force-feeding an injected mouse delayed absorption, given that addition of a T_{lag} variable was needed to prevent overprediction of the time-concentration data during the initial assessment times after administration to fed hawks (Table 2).

No adverse clinical reactions were observed in the hawks of the present study following voriconazole administration with or without food, whether at the time of administration, during blood sample collection, or during a 2-week period following the study. Similarly, no adverse reactions were reported for a single dose of the drug administered PO to African grey parrots,[26] mallard ducks,[24] and pigeons[23] or for multiple doses administered PO to horses, mice, rabbits, and guinea pigs.[14,19] However, clinicians should be aware that reports[12,13,22–24,26,29,34] exist of adverse reactions following administration of multiple doses.

In the present study, several challenges were encountered. The number of available birds was limited, and large intersubject variation in plasma concentrations was evident (coefficients of variation for concentrations measured at each assessment time ranged from 25% to 87%), which was expected on the basis of studies[28,35] involving other species. Voriconazole cannot be presumed to have similar pharmacokinetics across avian species, as suggested by comparisons of C_{max} values for hawks and chickens.[22] Therefore, caution must be exercised with clinical administration. When voriconazole was administered to the study hawks in food, C_{max} was decreased and T_{max} was delayed, but these findings are unlikely to reduce the success of treatment given that the effect of voriconazole is concentration independent and more closely related to total and duration of exposure. More research is needed to investigate how voriconazole clearance is related to body weight or sex in red-tailed hawks, as it appears possible that heavier birds may need to receive the drug more frequently or at higher doses than lighter birds to ensure adequate drug exposure.

Acknowledgments

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Footnotes

a. Bret Stedman, Director, California Raptor Center, University of California-Davis, Davis, Calif: Personal communication, 2015.
b. Vfend, Pfizer Pharmaceuticals, New York, NY.
c. Microtainer tubes, Beckton Dickinson & Co, Franklin Lakes, NJ.
d. Cryovials, Nalge Nunc International Corp, Penfield, NY.
e. Bond-Elut CN-E, 50 mg, 1 mL, Varian Inc, Palo Alto, Calif.
f. ACQUITY UPLC TUV Detector, Waters Corp, Taunton, Mass.
g. BEH C18 column, Waters Corp, Taunton, Mass.
h. StatPlus, AnalystSoft, Walnut, Calif.
i. Phoenix 64, Certara USA Inc, Princeton, NJ.

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