Pharmacokinetics and adverse effects of voriconazole administered orally q72 hours in healthy cats

by

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Abstract

Objective: Some cats with systemic fungal disease fail to respond to itraconazole and fluconazole, thus this study aimed to investigate pharmacokinetics and adverse effects of voriconazole in cats with an extended dosing protocol.

Methods: Nine healthy cats were administered voriconazole at a loading dose of 25 mg/cat PO followed by 12.5 mg/cat PO every 72 hours for 16 days. Plasma voriconazole concentration was measured: 4, 8, and 12 hours after voriconazole administration on days 0 and 15; on days 3, 6, 9, 12, and 15 before drug administration; and every 48 hours for 6 days after the last dose. Pre- and post-treatment physical examination, electroretinography (ERG), electrocardiography (ECG), complete blood count, serum chemistry, and urinalysis were performed.

Results: Plasma trough concentration 72 hours after the first dose was 1.80 ± 0.48 μg/mL, increasing to 4.53 ±1.05 μg/mL immediately prior to the last dose ($P < .001$). Half-life also significantly increased from day 0 (5.5 ± 1.4 days) to day 15 (11.9 ± 5.2 days) ($P = .001$). Adverse effects included weight loss (mean = 0.24 kg in 8/9 cats), vomiting (4/9), and sporadic miosis (3/9). The mean ERG b-wave amplitude decreased from 317 to 213 μV with treatment ($P < .001$). No clinical vision deficits were appreciated.

Conclusions: Voriconazole had a long half-life and continued accumulation in cats when administered orally at 72-hour intervals. Further research is needed to determine the optimum dosage and whether decreased ERG b-wave amplitude is a clinically significant effect.

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Acknowledgements

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Background

Fungal infections in animals may be localized to one part of the body or disseminated to multiple organs and body cavities. Fungal infections reported in cats include cryptococcosis, histoplasmosis, blastomycosis, coccidioidomycosis, aspergillosis, candidiasis, sporotrichosis, dermatophytosis, mucormycosis, phaeohyphomycosis, rhinosporidiosis, and mycetomas.[1-3] These infections can cause significant morbidity and mortality. Antifungal drugs may be effective for treatment, but efficacy is variable among pathogens, treatment periods are prolonged, and treatment can be costly. Generally, itraconazole or fluconazole, sometimes in combination with amphotericin B, is the treatment of choice for cats with systemic fungal infections.[4] Histoplasmosis in cats is treated for a median of 6 months, and 6-month survival rates have been reported to be 60 to 70%, with 40% experiencing relapse after initial treatment.[5,6] Poor response to therapy may be due to side effects of the medications or fungal organism resistance. Resistance to itraconazole and fluconazole is rarely documented in some fungal organisms isolated from cats[7-10] and other species,[11-16] so there is a need for alternative antifungal therapies in some patients who fail first line therapies.

Voriconazole is a synthetic triazole antifungal medication used to treat fungal infections. This medication works by inhibiting fungal 14-alpha-sterol-demethylase (a CYP-dependent enzyme) which disrupts the fungal cell membrane and halts fungal growth. Voriconazole, under the brand name VFEND®, was approved by the United States Food and Drug Administration (FDA) for oral use in humans in May 2002. In humans, voriconazole is considered a first-line treatment for invasive nasal aspergillosis and has been successfully used in other invasive fungal infections such as candidiasis, fusariosis and scedosporiosis.[17] Voriconazole is also used in some veterinary

species.[18-20] *In vitro* experiments have determined that fungal isolates obtained from cats (i.e., *Cryptococcus* spp., *Candida* spp., and *Aspergillus fumigatus*) are susceptible to voriconazole;[10,21] therefore, voriconazole is a promising antifungal option for cats with these species of infections and potentially for cats with other species of infections (histoplasmosis, blastomycosis, etc.) that do not respond to traditional azole therapy.

Few studies report outcomes of cats treated with voriconazole, and the optimal dosage for cats has not been determined. When a dosage similar to what is used to treat humans and dogs (10 mg/kg/day per os (PO)) was administered to cats with naturally occurring fungal infections, severe adverse events were reported.[10,18,19,22] Signs of toxicosis in cats included vision abnormalities, mydriasis, ataxia, hypokalemia, and arrhythmias. All adverse effects improved, and in many cases resolved, after the drug was discontinued.[10,18,19] Plasma concentrations of voriconazole were not measured in these studies. Since these cats had naturally occurring fungal infections, it is possible that some adverse effects were due to progression of disease rather than true side effects of voriconazole. However, similar side effects have been reported in humans with high blood concentrations of voriconazole.[17]

The most frequent adverse effects reported in humans taking voriconazole include neurological effects such as hallucinations, abnormal dreams, confusion, hypoesthesia, neuropathy, and paresthesia; hepatic toxicity; nausea and vomiting; QT interval prolongation; and vision disturbances.[17] One study reported at least one vision adverse event (enhanced visual perceptions, blurred vision, color vision changes or photophobia) in 83.3% of volunteers treated with voriconazole.[23] That same study found nonprogressive, reversible changes in

electroretinogram (ERG) that may indicate voriconazole causes the retina to be in a more light-adapted state and leads to increased relative contrast sensitivity.[23] A pivotal investigation of voriconazole drug monitoring in humans with invasive fungal diseases found that treatment outcome was associated with drug concentration.[24] Complete resolution of invasive fungal disease was observed in all cases with blood concentrations above 1 µg/mL, and neurological adverse effects only occurred when blood concentrations exceeded 5.5 µg/mL indicating a narrow therapeutic range.[24]

Pharmacokinetics (PK) of voriconazole have been studied in rodents, guinea pigs, rabbits, dogs,[25,26] horses,[27,28] alpaca,[29] rattlesnakes,[30] and several avian species.[31-36] Additionally, one study has investigated the PK of voriconazole administration in healthy cats.[37] This study found that voriconazole had an excellent oral bioavailability and long half-life in cats. When a loading dose of 25 mg/cat (4.1 to 5.4 mg/kg) PO was administered followed by 12.5 mg/cat (2.05 to 2.7 mg/kg) PO every 48 hours for 14 days, plasma concentrations were within the target range (1 to 5 µg/mL) and increased over time, suggesting drug accumulation.[37] The half-life after oral administration (>43 hours) was much longer than the half-life after intravenous administration (12 hours).[37] Based on these results, the investigators concluded that oral administration of 12.5 mg/cat every 72 hours may be more appropriate. Adverse effects observed in this study included hypersalivation (after administration of oral suspension only) and miosis in some cats.

The voriconazole dosage regimen of 12.5 mg/cat PO every 72 hours was recently investigated in a retrospective study.[20] Six cats with disseminated histoplasmosis were treated with oral voriconazole at a median starting dose of 3.51 mg/kg PO every 72 hours (the dosing interval was

later extended to 96 hours in two cats).[20] Cats in this study were treated with voriconazole for one to two months after testing negative for *Histoplasma* using a urine antigen test, which occurred at a median of 256 days after initiation of voriconazole therapy. This study reported infrequent mild adverse effects (hyporexia in two cats, weight loss in three cats, elevated alanine aminotransferase in one cat, and subdued behavior in one cat) and a favorable outcome for all cats, but therapeutic drug monitoring was not performed. No ocular adverse effects were reported, but complete ophthalmic exams were not performed on all cats in this study.

The PK of voriconazole administered at a dose of 12.5 mg/cat PO every 72 hours has not been formally investigated, which was the primary goal of the present study. We hypothesized that a loading dose of voriconazole 25 mg/cat PO followed by 12.5 mg/cat PO every 72 hours over a 2-week period would result in plasma voriconazole concentrations reaching a steady state within the target range (1 to 5 µg/mL). Additionally, we aimed to investigate adverse effects of this dosing strategy of voriconazole in healthy cats by monitoring physical examination findings, horizontal pupil diameter, electroretinography (ERG), electrocardiography (ECG), and clinicopathologic tests.

Methodology

Animals

Nine healthy adult cats greater than one year old weighing between 4 kg and 9 kg were included in the study. Cats receiving any oral medications were excluded. Prior to the start of the study, cats were assessed as healthy based on history provided by the owner, physical examination conducted by a veterinarian (AB), and clinicopathologic results (complete blood count, serum biochemical analysis, and urinalysis) within respective reference ranges. Cats were owned by faculty, staff, or students at Kansas State University. Cats lived at home and were fed their typical diet throughout the study period. Cats were brought to the Kansas State University Veterinary Health Center for sample collection. The study was approved by the Institutional Animal Care and Use Committee at Kansas State University (IACUC-4905).

Study Design

The day prior to the start of the study, approximately 4 ml of blood was collected for baseline plasma voriconazole level, complete blood count (CBC), and serum biochemical analysis. Urine was collected via cystocentesis for urinalysis. An electrocardiogram (ECG; Datex-Ohmeda Cardiocap/5) was assessed on each cat by a board-certified anesthesiologist. A physical examination and complete ophthalmic examination including topical fluorescein staining (BioGlo, HUB Pharmaceuticals), rebound tonometry (Tonovet, icare), slit lamp biomicroscopy (Kowa SL-17), and indirect ophthalmoscopy (Keeler Vantage Plus Binocular indirect; Volk 28 diopter condensing lens), was performed by the primary investigator (AB). Horizontal pupil diameter (HPD) was measured using Jameson calipers held approximately 2 mm from the cornea, and both eyes were photographed for reference. Pupils were assessed in the same room

with consistent lighting (measured with Light Meter LM-3000 app on iPhone 13) throughout the study. Both eyes were dilated with tropicamide 1% ophthalmic solution and then dark adapted for at least 20 minutes prior to performing an ERG (An-vision RETIport). A pre-programed short scotopic protocol ("Scot. ERG – LED") was used, which involves flashes of light starting at -20 decibels increasing to 0 decibels. Electroretinography of the right eye was performed first, followed by the left eye. After application of proparacaine 0.5% ophthalmic solution (Bausch + Lomb), a contact lens electrode (An-vision ERG jet) was placed on the eye with a lubricant eye gel (Alcon Systane Lubricant Eye Gel) and reference electrodes (An-vision 13 mm subdermal electrodes) placed subcutaneously approximately 2.5 cm from the lateral canthus over the zygomatic arch near the eye being tested, and a ground electrode at the occiput. Light was provided by an LED flash/Koijman combination electrode (An-vision) held in front of the jet electrode during the examination.

Cats were fasted for at least eight hours prior to each dose of voriconazole (Solco Healthcare). Cats received a loading dose of voriconazole 25 mg/cat PO followed by 12.5 mg/cat PO every 72 hours over a course of 16 days (doses were administered on days 0, 3, 6, 9, 12, and 15). All doses were tablet formulation (½ tablet for the loading dose, and ¼ tablet for subsequent doses) administered by one investigator (AB) in the morning. Tablets were not scored but divided into halves or quarters as equally as possible using a commercial pill cutter. Cats were offered a liquid treat (Inaba Churu or Hartz Delectables Squeeze Up) to take the dose or were manually pilled if not willing to ingest on their own. Each dose was followed by additional liquid treat or 2 to 3 mL of water via oral syringe to ensure the tablet was swallowed. Food was offered two or more hours after drug administration.

Blood, approximately 1 ml per timepoint, was collected at various timepoints including: 4, 8, and 12 hours after voriconazole administration on day 0 (first dose) and day 15 (last dose); within 1 hour prior to voriconazole administration (to assess trough levels) on days 3, 6, 9, 12, and 15; and every 48 hours after the last dose through day 21 (end of the study). Blood was drawn from the cephalic or medial saphenous veins.

On days 3, 6, 9, 12, 15, 17, 19, and 21 just prior to venipuncture, a brief ophthalmic exam was performed including slit lamp biomicroscopy and indirect ophthalmoscopy without dilation, measurement of HPD, and photographs. Cats were also weighed on each study day.

Owners were provided with an instruction sheet (Appendix A Table A.1) to monitor daily for adverse effects including changes in pupil size, vision, activity level, appetite, vomiting, diarrhea, or abnormal behavior. Photographs were provided to each owner of the cat's baseline pupil size at the beginning of the study. On day 15 (last day receiving voriconazole), physical examination, complete ophthalmic examination, CBC, serum biochemistry, urinalysis, ECG, and ERG were repeated as described previously. ERG was repeated again approximately one month after the study period in seven cats.

Determination of voriconazole plasma concentration

All blood samples were collected into a tube containing lithium heparin, gently inverted, then placed on ice until centrifugation for 10 min at 3200×g. Plasma was then separated and stored at −80°C until analysis.

Plasma concentrations of voriconazole were measured using ultra-high pressure liquid chromatography (UPLC H-class, Waters Corp) with triple quadrupole mass spectrometry (Xevo TQD, Waters Corp). Voriconazole (TCI America) reference standard was used to fortify the feline plasma standards and quality control samples in feline plasma and voriconazole d3 (MedChemExpress) was used for the internal standard. Plasma standards, quality controls and samples were processed identically. Plasma (0.050 mL) was treated with 0.2 mL internal standard solution (voriconazole d3, 500 ng/mL in acetonitrile with 0.1% formic acid) in a phospholipid removal device (Ostro 96-well plates, Waters Corp). The mixture was mixed by aspiration, then positive pressure was applied and the supernatant collected in clean 96-well plates. The injection volume was 0.01 mL. The mobile phase consisted of A (deionized water with 0.1% formic) and B (acetonitrile with 0.1% formic acid) at a flow rate of 0.6 mL/min. The mobile phase gradient started at 80%A until 0.3 min, then a linear gradient to 40% A at 1 minute which was held until 1.8 minutes, then a linear gradient to 80% A at 2 minutes with a total run time of 3 minutes. Separation was achieved with a column (Acquity HSS T3, 1.8 micrometer, 2.1x50mm, Waters Corp) maintained at 50 °C. The retention time was 1.6 minutes. The parent ions (m/z) for voriconazole and voriconazole d3 were 350.1 and 353.13, respectively. The product ions (m/z) for voriconazole and voriconazole d3 were 127.05 and 130.05, respectively. The cone voltage was 26 and 34 V for voriconazole and voriconazole d3, respectively. The collision voltage was 32 and 24 V for voriconazole and voriconazole d3, respectively. The desolvation temperature was 500 °C, the desolvation gas flow rate was 800 L/hr and the cone gas flow rate was 25 L/hr. Plasma curves were made daily from 0.01 to 50 mcg/mL and were accepted if the measured concentrations were within 15% of the actual concentration and the r^2

was at least 0.99. The analytical runs were accepted if at least 4/6 quality controls were within 15% of their actual concentration. The accuracy of 5 QC samples at each of the following concentrations at 0.01, 1 and 10 mcg/mL were 105%, 103% and 104%, respectively. The coefficients of variation for the QC samples were 7%, 1% and 3%, respectively.

Pharmacokinetic and statistical analysis

Due to lack of normal distribution or uniform variance, plasma concentrations were log-transformed prior to statistical analyses of the trough concentrations. The log-transformed plasma trough concentrations were compared for differences to the trough from the first dose to assess for potential accumulation using a one-way ANOVA with the Holm-Sidak method for comparison to control. The half-lives determined by noncompartmental methods from the first dose were compared to the last dose using a Mann-Whitney rank sum test. A two-compartment pharmacokinetic model using microconstants and 1/Y2 weighting was chosen for the multiple dose pharmacokinetic model based on the ability of the model to fit all cats, visual inspection of the residuals and goodness of fit.

Pre- and post-treatment data were compared for each cat, including changes in weight, clinicopathologic parameters, HPD, ECG findings, and ERG values. Normality of weight, intraocular pressure, HPD, and ERG data were assessed using Q-Q plots and histograms and determined to be normally distributed. Data for the right and left eye were analyzed using a paired t-test and determined not to be statistically different, so right and left eye were averaged for further analysis. Repeated measures analysis of variance (ANOVA) and paired t-tests were used to compare data at various timepoints using Microsoft Excel Analysis ToolPak. For all

statistics, $P < .05$ was considered significant. The client monitoring sheet was used to report any subjective changes throughout the treatment period.

Results

Nine cats met the inclusion criteria and were enrolled in the study on a rolling basis from January 2024 to June 2024. Signalment, baseline weight, and body condition score (BCS) of each cat are summarized in **Table 1**.

Table 1. Signalment, baseline weight, and body condition score (BCS) of 9 healthy cats enrolled in a study to assess pharmacokinetics and adverse effects of oral voriconazole.

Cat	Age (years)	Sex	Breed	Weight (kg)	BCS (range 1 to 9)
Cat 1	8	MC	DSH	8.60	9
Cat 2	14	MC	DSH	5.69	5
Cat 3	7	MC	Siamese mix	5.32	6
Cat 4	10	MC	DSH	5.55	7
Cat 5	1.5	FS	DMH	4.20	5
Cat 6	1.5	MC	DSH	5.20	5
Cat 7	3.5	FS	DSH	4.95	6
Cat 8	4	FS	DSH	5.24	7
Cat 9	9	MC	DLH	5.24	6

Abbreviations: MC = male castrated; FS = female spayed; DSH = domestic short hair; DMH = domestic medium hair; DLH = domestic long hair

The mean age was 6.5 years (range: 1.5 to 14 years) and mean baseline weight 5.55 kg (range: 4.2 to 8.6 kg). Cat 1 was previously diagnosed with feline immunodeficiency virus and feline asthma but remained asymptomatic during the study period. Cat 2 was also previously diagnosed with feline asthma but remained asymptomatic during the study period. Cat 1 and Cat 2 were

both treated with a corticosteroid inhaler (fluticasone propionate 110 mcg/puff) one puff once daily at night throughout the study period. All the other cats were historically healthy and did not receive any medication according to owners. Investigators administered gabapentin 100 mg PO to one cat (Cat 6) on day 15 approximately 5 hours after voriconazole administration to decrease stress because the cat was becoming resistant to venipuncture.

Physical and ophthalmic examination

Rectal temperature, heart rate, and respiratory rate were within normal limits pre- and post-treatment with voriconazole for all but one cat that had an increased respiratory rate attributed to stress. General physical examination was unremarkable in all cats besides mild dental disease noted in five cats. No new abnormalities developed after treatment with voriconazole. The median body condition score (BCS) was 6 out of 9 (range: 5 to 9).

On initial ophthalmic examination, all cats had normal vision as determined by a positive menace response in both eyes. Palpebral and pupillary light reflexes were normal in all cats. Minor ocular abnormalities included multifocal iris hyperpigmentation in both eyes of one cat, an irregular third eyelid margin (presumed due to prior traumatic injury) in the right eye of one cat, mild iris atrophy in both eyes of one cat, nuclear sclerosis in both eyes of the two oldest cats, iris-to-iris persistent pupillary membranes in three eyes of two cats, and incipient cataract in both eyes of one cat. Cat 3 also had an intermittent horizontal nystagmus and convergent strabismus which are common inherited disorders in the Siamese breed.[38] These abnormalities did not affect pupil size or ability to constrict, did not impair vision, and were not expected to progress, and therefore were not considered exclusion criteria. Ocular fundic examination was normal in all

cats. There was no significant difference in mean intraocular pressure at baseline examination compared to day 15 (18.5 mmHg and 16.7 mmHg, respectively; $P > .05$).

Cat 3 developed faint, pinpoint superficial corneal opacities and very mild chemosis of the left eye on day 12 that resolved by day 17. This was suspected to be associated with feline herpesvirus recrudescence due to stress from multiple hospital visits, rather than an adverse effect of voriconazole. Cat 4 developed mild blepharospasm and mucoid discharge of the left eye on day 15 after ERG was performed. This was suspected to be due to irritation from the ERG corneal probe, and symptoms resolved within 24 hours. Fluorescein staining was performed in both cats when symptoms were observed, and no corneal ulcers were detected in either cat. All eyes in all cats were fluorescein negative on baseline examination and day 15. No other changes in ophthalmic examination were observed after treatment with voriconazole. All cats maintained a positive menace response throughout the study, and signs of vision impairment were not observed by any owners at home.

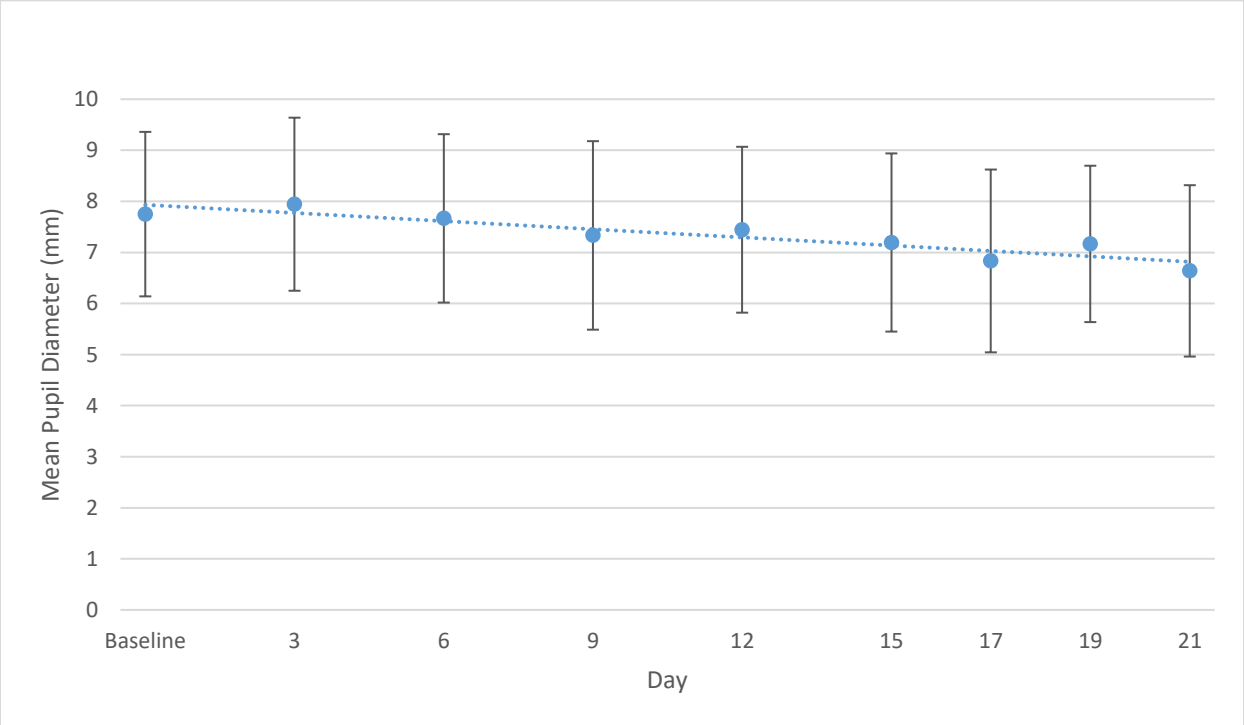
There was a significant decrease in mean weight from baseline to day 21 ($P = .003$). Eight of nine cats (89%) lost weight throughout the study period. Mean weight loss was 0.24 kg in those eight cats. Only one owner (Cat 5) reported a decreased appetite on days 0, 1, and 17. However, most cats lived in a multi-cat household, and individual food intake was not strictly monitored. Investigators observed Cat 4 vomit twice on day 15 at least five hours after voriconazole administration. In total, the owners of five cats found vomitus at home throughout the study period. It could not always be determined which cat vomited as they lived in a multi-cat household. Four cats were confirmed to have vomited at least once during the study period.

Other concerns reported by owners on the client monitoring sheet included more "needy" behavior in one cat.

Pupil diameter

Mean HPD measured each study day is displayed in **Figure 1**. There was no significant difference in mean HPD between any timepoint (P >.05). However, there was a slight trend toward decreasing HPD diameter over time with a mean ± standard deviation (SD) of 7.75 ± 1.61 mm at baseline and 6.64 ± 1.68 mm on day 21 (P =.05).

Figure 1. Mean horizontal pupil diameter (average of left and right eye) of 9 healthy cats treated with oral voriconazole measured every 48 to 72 hours (after baseline measurement) throughout the study period with added trendline. Error bars represent standard deviation for each timepoint. Pupil diameter was measured prior to voriconazole administration on days 3, 6, 9, 12, and 15.



Two cats (Cat 5 and Cat 6) had bilateral, symmetrical miosis observed by the investigators after voriconazole administration on day 0 after the first dose of voriconazole. Pupil diameter (average of right and left eye) of Cat 5 was 7.25 mm at baseline and decreased to 2.75 mm approximately one hour after voriconazole administration, as shown in **Figure 2**. Pupil diameter (average of right and left eye) of Cat 6 was 7 mm at baseline and decreased to 4.24 mm approximately one hour after voriconazole administration. The miosis was transient, resolving within 3 hours for Cat 6 and 12 hours for Cat 5, and was not noticed again on any other study day. There were no other changes on ophthalmic examination when the pupils of these eyes were observed to be miotic. The owner of these two cats did not report miosis at home. One other cat (Cat 9) had miosis reported by the owner at home on days 4 and 6 but was not observed to exhibit miosis by the investigators at any point.

Figure 2. Photographs displaying baseline pupil size (A) and miosis (B) within one hour after administration of the first dose of voriconazole in a 1.5-year-old female spayed domestic medium hair cat.

Exams were performed in the same room at every timepoint for each cat throughout the study. Light intensity at the time of HPD measurement for each individual cat varied by a median of 80 lux between days.

Clinicopathologic results

No clinically significant abnormalities were found on baseline CBC, serum biochemistry, or urinalysis in any cat. Four cats were borderline or mildly azotemic on baseline bloodwork, attributed to mild dehydration rather than renal dysfunction based on urine specific gravity greater than 1.040 in all cats. Treatment with voriconazole did not induce any changes. No cats had progression of azotemia post-treatment. No cats had elevation of liver enzyme activity post-treatment.

ECG & ERG

No abnormalities were noted on ECG for any cat at baseline or day 15.

All cats had a baseline ERG and post-treatment ERG performed on day 15. Seven cats had a recovery ERG performed at a median of 29 days (range: 28 to 33 days) after the study period ended. All ERG examinations produced a normal appearance waveform. Electroretinogram findings are summarized in **Table 2**.

Table 2. Summary of electroretinography findings expressed as mean ± standard deviation (average of left and right eye) for 9 cats treated with oral voriconazole every 72 hours for 6 doses. Electroretinography was performed prior to voriconazole (baseline), post-treatment (day 15), and in recovery (median 29 days later).

	Baseline (n=9)	**Post-treatment (n=9)**	**Recovery (n=7)**
A-wave implicit time (ms)	11.05 ± 1.82	10.76 ± 1.42	10.72 ± 1.58
B-wave implicit time (ms)	29.86 ± 4.21	27.93 ± 4.15	28.29 ± 3.90
A-wave amplitude (μV)	76.97 ± 37.50	74.43 ± 32.84	89.54 ± 40.80
B-wave amplitude (μV)	317.33 ± 67.24	213.00 ± 46.02	323.14 ± 31.65

Only the seven cats with ERG performed at all three timepoints were used for further analysis. There was no significant difference in A-wave amplitude or A-wave implicit time between baseline, post-treatment and recovery ERG. B-wave implicit time at baseline (30.89 ± 4.18 ms) was significantly higher than recovery (28.29 ± 3.90 ms; P =.016), but no statistical difference was found between baseline and post-treatment (28.31 ± 4.72 ms; P >.05) or post-treatment and recovery B-wave implicit time. B-wave amplitude post-treatment (221.29 ± 49.62 μV) was significantly lower than baseline (325.64 ± 54.88 μV; P <.001) and recovery (323.14 ± 31.65 μV; P =.002). There was no statistical difference between baseline and recovery B-wave amplitude.

Pharmacokinetics

Voriconazole was not detected in the plasma of any cats at baseline. Voriconazole plasma concentrations progressively increased in all cats throughout the treatment period, as shown in **Figure 3** and **Figure 4** indicating steady state plasma concentrations were not achieved.

Figure 3. Plasma voriconazole concentrations in 9 healthy adult cats, 6 males (red) and 3 females (black) treated with voriconazole (25 mg/cat loading dose, followed by 12.5 mg/cat) by mouth every 72 hours for 6 doses starting at time 0 with final dose on day 15.

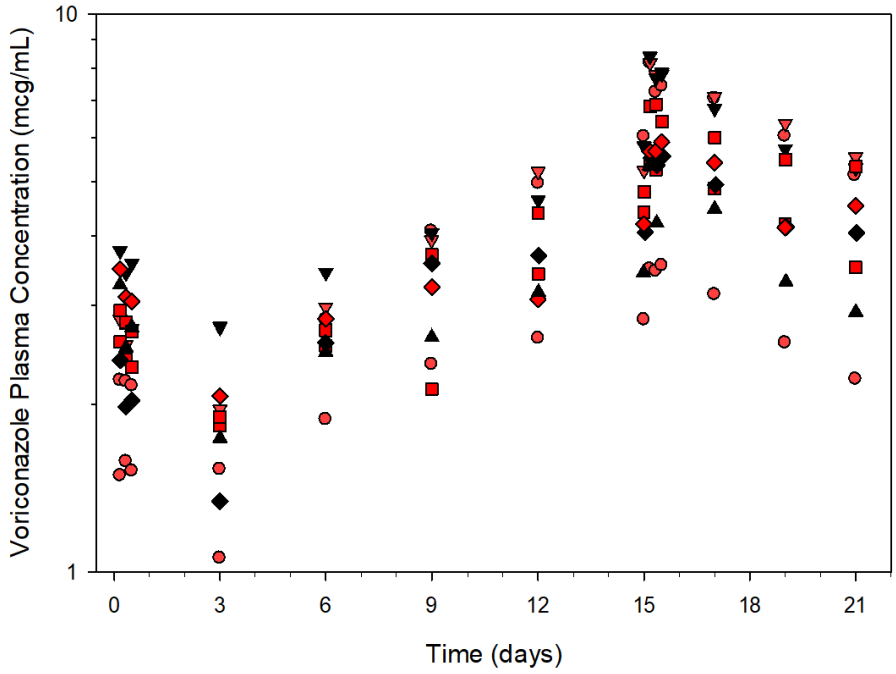
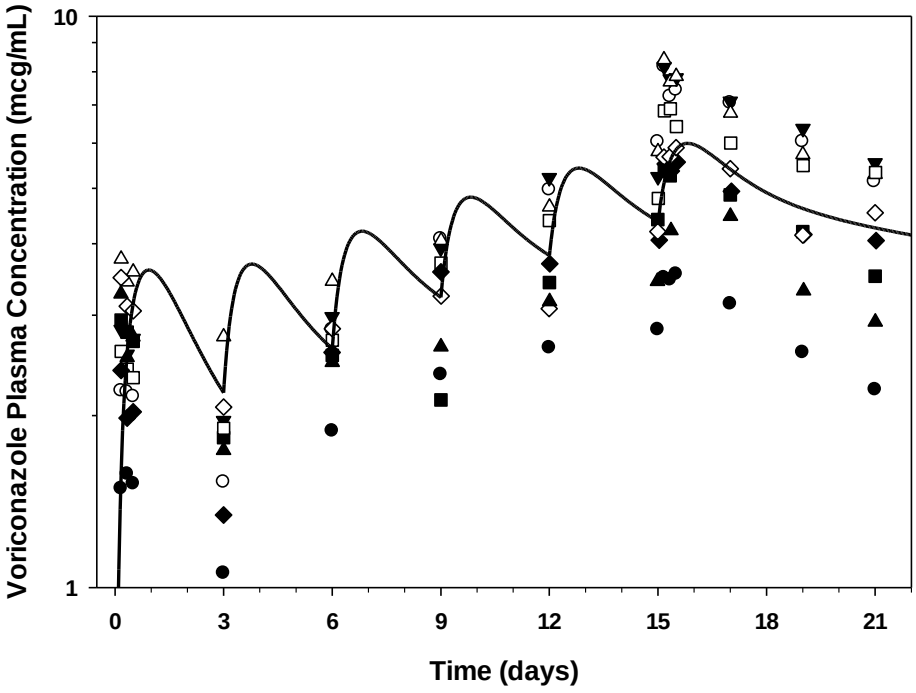


Figure 4. Plasma concentrations of individual cats (symbols) and mean two-compartment pharmacokinetic model predicted fit (line) after voriconazole administered by mouth to 9 healthy cats as a 25 mg/cat loading dose followed by 12.5 mg/cat every 72 hours.



Mean ± SD plasma trough concentration 72 hours after the first dose was 1.80 ± 0.48 μg/mL, increasing to 4.53 ± 1.05 μg/mL immediately prior to the last dose ($P < .001$). The noncompartmental calculated half-life also significantly increased from day 0 (5.5 ± 1.4 days) to day 15 (11.9 ± 5.2 days) ($P = .001$). The mean peak voriconazole plasma concentration on day 15 was 6.3 ± 1.6 μg/mL. A blood sample was unable to be obtained from two cats (Cat 6 and Cat 8) on day 15 at the 12-hour timepoint after voriconazole administration. A two-compartment model using microconstants best fits the plasma concentrations for all nine cats (**Table 3**).

Table 3. Two-compartment pharmacokinetic parameters for voriconazole administered to 9 healthy cats as a 25 mg/cat loading dose followed by 12.5 mg/cat every 72 hours.

Parameter	Units	Mean	Min	Max
K01	1/day	0.752	0.507	0.933
K10	1/day	0.210	0.031	0.438
K12	1/day	1.647	1.647	1.647
K21	1/day	0.235	0.170	0.305
V1_F	mL/kg	300.0	300.0	300.0
Alpha	1/day	2.067	1.893	2.305
Alpha T ½	day	0.337	0.301	0.366
Beta	1/day	0.0240	0.0036	0.0516
Beta T ½	day	56.3	13.4	192.0

Abbreviations: K01 = first order absorption rate constant; K10 = first order elimination rate constant from the central compartment; K12 = first order transfer rate constant from the central compartment to the peripheral compartment; K21 = first order transfer rate constant from the peripheral compartment to the central compartment; V1_F = volume of distribution (per fraction of the dose absorbed) for the central compartment; Alpha = distribution rate constant; Alpha T ½ = distribution half-life; Beta = elimination rate constant; Beta T ½ = elimination half-life

Discussion

This study investigating the pharmacokinetics of voriconazole administered to healthy cats found a much longer half-life (11.9 ± 5.2 days) compared to a prior study (43 ± 9 hours, 1.8 ± 0.4 days) by Vishkautsan et al.[37] The dosing regimen and study design for the present study was based on results of that prior study, and such a difference in half-life was not anticipated. Half-life calculations for the present study may not be robust because sampling ended before the true half-life was achieved. An ideal study would sample for three times the duration of the half-life and in this case would be 169 days to most robustly describe the half-life. This may also explain the difference between the noncompartmental terminal half-life (11.9 days) and the half-life determined by the compartmental modeling (56.3 days). Regardless, the half-life in this study was much longer than previously reported in cats. The difference in half-life between studies could be due to variability between cat populations. The prior study used healthy 1-year-old, specific pathogen-free, sexually intact domestic shorthair cats weighing 4.6 to 6.0 kg. This study included a variety of breeds and ages, as well as a wider range of weights. Cats owned by students, staff, or faculty were selected rather than research-bred cats as they are generally more amenable to handling, preventing the need for sedation that could interfere with voriconazole metabolism. Only clinically healthy cats not receiving other oral medications were chosen to help minimize factors that could influence voriconazole metabolism. Cats were fasted prior to voriconazole administration to minimize variation in drug absorption due to stomach contents. Prolonged half-life can be due to organ (liver or kidney) dysfunction, but no evidence of organ dysfunction was detected on clinicopathological testing in this study. The investigators speculate

that voriconazole may inhibit its own metabolism, leading to the accumulation observed, but further studies are necessary to confirm this theory.

Several factors may explain the wide variability between cats. Voriconazole tablets, rather than compounded oral suspension, was used because hypersalivation has been previously reported as an adverse effect of voriconazole oral suspension administered to cats.[37] Therefore, voriconazole was dosed based on tablet/cat rather than an exact mg/kg basis. The range of mg/kg dosing would be expected to affect the plasma concentrations but would unlikely affect the half-life. Commercially available voriconazole tablets are formulated in 200-mg or 50-mg tablets. The 50-mg tablets are not scored, and it is uncertain if the drug is uniformly distributed throughout the tablet. A commercial pill cutter was used to divide the tablets into halves and quarters as equally as possible, but investigators noted some challenge due to the small size of tablets. It would not be practical to split the tablets any smaller than quarters. The exact dose administered in this study ranged from 2.9 to 6 mg/kg loading dose followed by 1.5 to 3 mg/kg for subsequent doses. This is similar to the median starting dose of 3.51 mg/kg (range: 2.68 to 5.10 mg/kg) reported in the retrospective study by Easterwood et al. evaluating cats with naturally occurring histoplasmosis treated with voriconazole PO every 72 hours.[20] The cat with the heaviest weight (Cat 1) in this study consistently had the lower voriconazole plasma concentrations across most timepoints, which was expected. This cat also had the highest BCS (9/9). Voriconazole is a lipophilic drug, so there may be more distribution into fat in animals with higher BCS.

No severe adverse effects were noted during the study period. Adverse effects included weight loss (mean 0.24 kg, 8/9 cats), vomiting (4/9 cats), and sporadic miosis (3/9 cats). The most

logical explanation for weight loss would be decreased food intake. Only one owner reported their cat had a decreased appetite. However, many cats lived in a multi-cat household and food intake was not strictly monitored for each individual cat. The periodic fasting prior to voriconazole administration is unlikely to contribute to weight loss as cats were provided food within two hours after voriconazole administration and drug administration only occurred every three days. The owner of one cat (Cat 8) was intentionally regulating its intake to promote weight loss. That cat was fed a consistent amount yet lost more weight than intended (0.22 kg) during the study period. The cat that lost the most weight (Cat 3, 0.4 kg) was subsequently diagnosed with inflammatory bowel disease based on lymphoplasmacytic inflammation found on gastrointestinal biopsy samples obtained via endoscopy approximately one month after the end of the study. This cat did not have any clinical signs, physical exam abnormalities, or bloodwork abnormalities consistent with inflammatory bowel disease during the study period. It is uncertain whether the development of inflammatory bowel disease was spontaneous or a drug effect. These two cats may have biased the degree of weight loss in the population. Weight loss was also reported as an adverse effect by Easterwood et al. in 3 out of 5 cats, with one cat losing a substantial amount of weight (1.14 kg) despite a good appetite.[20] Naturally occurring fungal infection may have contributed to weight loss in that population, but results of this study suggest that weight loss can be an adverse effect of voriconazole. Weight loss has also been reported with oral ketoconazole treatment in cats.[39] Decreased appetite, but not specifically weight loss, is a reported adverse effect of oral itraconazole in cats.[40] Vomiting as an adverse effect may be overreported in this study, as some cats historically vomited at home occasionally.

Sporadic miosis occurred in three cats. Miosis was observed by investigators only on day 0 after voriconazole administration in two cats. The other cat had miosis reported by the owner on two separate days. The miosis was transient, and timing did not correlate with peak voriconazole plasma concentration. This is consistent with the study by Vishkautsan et al. that reported transient miosis in 4 out of 6 cats most pronounced during the first three days after initiating treatment with voriconazole.[37] In the present study, resting pupil size prior to voriconazole administration tended to decrease over time but was not statistically significant. This is most likely explained by cats becoming more accustomed to study procedures and reduced sympathetic tone. Assessing pharmacokinetics was the primary goal of this study and determining effects on pupil size were a secondary goal. Cats' stress was minimized by allowing them to return home immediately after voriconazole administration on most days or providing a break after morning procedures on days 0 and 15, so pupil size was not strictly monitored. There were no other abnormalities on ophthalmic examination, and not all cats developed miosis, so this seems to be a benign, idiosyncratic adverse effect. Further studies are necessary to determine the underlying mechanisms of miosis associated with voriconazole in cats.

Voriconazole treatment resulted in a significant decrease in mean ERG B-wave amplitude from 317 μV baseline to 213 μV post-treatment. The mean B-wave amplitude rebounded to 323 μV (in seven cats) approximately one month after the end of the study. Voriconazole plasma concentration was not measured when recovery ERGs were performed. Based on the calculated half-life of voriconazole, the drug may not have been completely eliminated by that time, but plasma concentrations would have been decreasing. This suggests that the decrease in B-wave amplitude post-treatment was truly an adverse drug effect and reversible after the medication

was discontinued. It is unclear if prolonged administration of voriconazole would still produce a reversible effect or if it could become irreversible. B-waves are driven by retinal bipolar cells, whereas A-waves are driven by photoreceptors. Voriconazole seems to affect retinal bipolar cells and not photoreceptors, although the exact mechanism of action remains to be elucidated. Visual disturbances and electroretinogram abnormalities have been reported in humans treated with voriconazole in a study by Zrenner et al.[23] This human study used much more complex ERG testing protocols than were used in the present study. A short ERG protocol was chosen because cats were examined awake. The primary goal of this study was to evaluate pharmacokinetics, so sedatives and anesthetics were avoided as they may interfere with drug metabolism. Variability may have been introduced by movement artifact because the cats were not sedated or anesthetized. The clinical significance of the decrease in B-wave amplitude is unclear. The ERG equipment in this study is generally used to assess dogs prior to cataract surgery, and a B-wave amplitude greater than 100 μV is considered normal in those dogs. Normal ERG values have not been validated for cats using this equipment. Future studies using more complex ERG protocols in sedated or anesthetized cats including a control group would be necessary to help determine the clinical significance of the decreased B-wave amplitude after treatment with voriconazole found in this study. None of the cats displayed evidence of vision deficits on ophthalmic examination or owner monitoring, but subtle vision disturbances may not have been detected because it is challenging to assess visual acuity in cats.

Based on the results of this study, the investigators do not recommend voriconazole as a first-line treatment for fungal infections in cats. Voriconazole plasma concentration continued to accumulate during the study period, and half-life largely varied between cats making it difficult

to predict. The pharmacokinetics of itraconazole and fluconazole in cats have been well studied and found to be more predictable.[40-45] If voriconazole is used, it is recommended to perform therapeutic drug monitoring starting two weeks after initiating therapy to determine an individual cat's dosage. Dosing interval, rather than dose, should be adjusted depending on plasma concentration with the goal of maintaining between 1 and 5 μg/mL. Although voriconazole seems generally well tolerated in cats, there is concern that adverse effects may become more severe over time if drug concentrations continue to accumulate. There is also a concern that inappropriate dosing of voriconazole may contribute to the development of drug resistance in fungal organisms.[46] With appropriate therapeutic drug monitoring, voriconazole seems to be a reasonable alternative for patients that are unresponsive to fluconazole or itraconazole, and the less frequent dosing interval is appealing to cat owners.

This study had several limitations. The timing of blood sample collection was not always exact, as investigators did not have direct vascular access (i.e., intravenous catheters) to sample cats, and their behavior sometimes made venipuncture challenging. However, the exact times when blood was drawn were used for the determination of the drug pharmacokinetics. A blood sample was not able to be obtained for two cats on day 15 at the 12-hour timepoint after voriconazole administration. Half-life calculations may not be robust due to these missing data and limited duration of sampling after the last dose. As previously noted, an extended sampling time after the last dose may be needed (up to 169 days after the last dose). Future studies should treat cats for a longer period to see if a steady state is reached and collect blood samples for a much longer period after the last dose. Adverse effects may not have been accurate due to the study's reliance on owner reports, although all owners had veterinary training. Our study population was diverse,

but sample size was too small to make conclusions about effect of sex, age, body weight, or body condition on voriconazole metabolism. The cats in this study were clinically healthy, and pharmacokinetics may differ in cats with systemic fungal infections.

Conclusion

In conclusion, voriconazole has a long half-life and continued accumulation in cats when administered orally every 72 hours over 16 days. Adverse effects include weight loss, vomiting, sporadic miosis, and decreased B-wave amplitude on ERG. Voriconazole is not recommended as a first-line antifungal drug in cats due to the large variability in half-life and unpredictable plasma drug concentrations. Therapeutic drug monitoring is recommended if voriconazole is used in cats. Additional research is needed to determine pharmacokinetics with longer duration of oral voriconazole therapy in healthy cats and cats with naturally occurring fungal infections.

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Appendix A - Home Monitoring Sheet

Appendix A Table A.1: Home monitoring sheet provided to study participants

Voriconazole Home Monitoring Sheet
Cat Name ___________________

Please monitor for the following side effects and make notes on the table each day.

<u>Side effects</u> Write "none" if not observed. Describe in as much detail as possible.
Change in pupil size (i.e., constricted or dilated pupil size compared to baseline photo)
Change in vision (i.e., bumping into things, decreased play with toys)
Activity level (i.e., normal activity level, lethargic, hyperactive)
Change in appetite (i.e., increased appetite, decreased appetite and give approximate % change)
Vomiting (i.e., vomited once with 3-inch circle of yellow fluid with no food)
Please record the <u>time</u> of vomiting and whether you notice <u>pills</u> in the vomitus
Diarrhea (i.e., number of diarrhea episodes, color, consistency of feces)
Change in behavior (i.e., any changes in behavior from normal)

Date	Side Effects Observed
	Change in pupil size: **Change in vision:** **Activity level:** **Change in appetite:** **Vomiting:** **Diarrhea:** **Change in behavior:**
	Change in pupil size: **Change in vision:** **Activity level:** **Change in appetite:** **Vomiting:** **Diarrhea:** **Change in behavior:**
	Change in pupil size: **Change in vision:** **Activity level:** **Change in appetite:** **Vomiting:** **Diarrhea:** **Change in behavior:**
	Change in pupil size: **Change in vision:** **Activity level:** **Change in appetite:** **Vomiting:** **Diarrhea:** **Change in behavior:**
	Change in pupil size: **Change in vision:** **Activity level:** **Change in appetite:** **Vomiting:** **Diarrhea:** **Change in behavior:**

Use back of page if you need more space to describe any signs noted. Thanks!