STANDARD ARTICLE

Journal of Veterinary Internal Medicine ACVIM

American College of Veterinary Internal Medicine

Pharmacokinetics of isavuconazole in healthy cats after oral and intravenous administration

Dennis J. Woerde[1] | Luke A. Wittenburg[2] | Jonathan D. Dear[3]

[1]William R Pritchard Veterinary Medical Teaching Hospital, University of California-Davis, Davis, California, USA

[2]Department of Veterinary Surgical and Radiological Sciences, University of California-Davis, Davis, California, USA

[3]Department of Veterinary Medicine and Epidemiology, University of California-Davis, Davis, California, USA

Correspondence
Dennis J. Woerde, William R Pritchard Veterinary Medical Teaching Hospital, University of California-Davis, 1 Garrod Drive, Davis, CA 95616, USA.
Email: djwoerde@ucdavis.edu

Abstract

Background: Isavuconazole is a triazole antifungal drug that has shown good efficacy in human patients. Absorption and pharmacokinetics have not been evaluated in cats.

Objectives: To determine the pharmacokinetics of isavuconazole in cats given a single IV or PO dose.

Animals: Eight healthy, adult research cats.

Methods: Four cats received 100 mg capsules of isavuconazole PO. Four cats received 5 mg/kg isavuconazole solution IV. Serum was collected at predetermined intervals for analysis using ultra-high performance liquid chromatography-tandem mass spectrometry. Data were analyzed using a 2-compartment uniform weighting pharmacokinetic analysis with lag time for PO administration and a 2 compartment, $1/y^2$ weighting for IV administration. Predicted 24 and 48-hour dosing intervals of 100 mg isavuconazole administered PO were modeled and in vitro plasma protein binding was assessed.

Results: Both PO and IV drug administration resulted in high serum concentrations. Intravenous and PO formulations of isavuconazole appear to be able to be used interchangeably. Peak serum isavuconazole concentrations occurred 5 ± 3.8 hours after PO administration with an elimination rate half-life of 66.2 ± 55.3 hours. Inter-subject variability was apparent in both the PO and IV groups. Two cats vomited 6 to 8 hours after PO administration. No adverse effects were observed in the IV group. Oral bioavailability was estimated to be approximately 88%. Serum protein binding was calculated to be approximately 99.0% ± 0.03%.

Conclusions and Clinical Importance: Isavuconazole might prove to be useful in cats with fungal disease given its favorable pharmacokinetics. Additional studies on safety, efficacy, and tolerability of long-term isavuconazole use are needed.

KEYWORDS
antifungal, azole, bioavailability, blastomyces, cryptococcus, fungal

---

Abbreviations: AUC, area under the concentration-time curve; C_{max}, peak concentration; SDMA, symmetric dimethylarginine; T_{max}, time to peak concentration; UPLC-MS/MS, ultrahigh performance liquid chromatography-tandem mass spectrometry.

1 | INTRODUCTION

Systemic fungal infections in cats pose therapeutic challenges. Currently, treatment of systemic fungal disease is difficult because of unpredictable pharmacokinetics and variable bioavailability among patients receiving PO triazole antifungal drugs.[1,2] Treatment is further hindered by limited IV options, with nephrotoxicity reported with amphotericin B and IV formulations of triazole antifungal drugs containing beta-cyclodextrin as an excipient.[3,4]

Isavuconazole, a water soluble triazole antifungal drug, has been shown to have excellent in vitro and in vivo activity against both yeast and molds. Of clinical relevance to feline medicine, isavuconazole has documented efficacy against *Cryptococcus neoformans*,[5-7] *Cryptococcus gattii*,[7] *Candida* spp.,[8] *Coccidioides* spp.,[9] *Aspergillus* spp.,[10] *Blastomyces dermatitidis*,[11] and *Histoplasma capsulatum*.[11] Similar to other triazole antifungals, isavuconazole inhibits the cytochrome P450 enzyme lanosterol 14-α-demethylase, disrupting synthesis of ergosterol which maintains fungal cell membrane integrity.[12] Both PO and IV formulations have been developed and are commercially available (Cresemba, Astellas Pharma Co, Northbrook, Illinois).[13]

In pharmacokinetic studies of humans, isavuconazole has an PO bioavailability of 98%, allowing the IV and PO formulations to be used interchangeably.[14] Isavuconazole also has been shown to have excellent distribution and penetration into tissues[15,16] and can safely be administered in human patients with impaired renal function without dose reduction because of its intravascular metabolism and primarily biliary excretion.[15-18]

In contrast to other triazole antifungal drugs, isavuconazole does not require the addition of beta-cyclodextrin to its IV formulation to facilitate solubility, which contributes to a more favorable adverse effect profile.[19] Additionally, no significant food effect has been found with PO administration of isavuconazole.[20] In clinical studies, isavuconazole has been demonstrated to be noninferior and have an improved safety and tolerability profile in human patients when compared with posaconazole[16] and voriconazole.[21]

These clinical and pharmacologic advantages make isavuconazole an attractive choice for treating systemic mycoses in cats. Our goal was to determine the pharmacokinetics of isavuconazole in healthy cats after a single PO or IV dose.

2 | MATERIALS AND METHODS

2.1 | Study population

The research protocol was approved by the University of California Institutional Animal Care and Use Committee. Eight sexually intact female cats from a closed university research colony were included, aged 5 to 8 years (mean, 7.1 years) with body weights between 3.5 and 7.0 kg (mean, 4.5 kg). Complete physical examination and routine laboratory testing including CBC, serum biochemistry panels, and symmetric dimethylarginine (SDMA) concentration were performed on the cats to assess their general health.

2.2 | Experimental protocol

Cats were sedated using a combination of butorphanol (0.2-0.4 mg/kg IM) and alfaxalone (2.5-3.5 mg/kg IM). Triple lumen catheters (MILA International, Inc, Florence, Kentucky; 5.5Fr × 8 cm) were aseptically placed into the jugular vein of each cat and they were given 96 hours to acclimatize before isavuconazole administration. Catheters were maintained for the duration of the study. Cats were randomly allocated into 2 groups, with 1 group receiving PO administration and the other IV administration.

Peripheral cephalic vein IV catheters were placed in cats receiving the IV formulation 3 to 6 hours before administration. Butorphanol (0.2 mg/kg IV) was given via the jugular catheter to facilitate peripheral IV catheter placement. Food was not withheld before administration[22] and food was available throughout the experiment. Cats were not fed explicitly at the same time as capsule administration. Water was available ad libitum.

Four cats received 100 mg isavuconazole capsules (Cresemba, 186.3 mg isavuconazonium capsules, equivalent to 100 mg isavuconazole, Astellas Pharma Co) PO (14-28 mg/kg) followed by 2 to 3 mL of tap water to ensure the capsule was swallowed. Four cats received 5 mg/kg isavuconazole IV (Cresemba, lyophilized powder for IV infusion, containing 372.6 mg isavuconazonium, equivalent to 200 mg isavuconazole, Astellas Pharma Co) via a peripheral cephalic catheter. The IV dose was prepared according to the manufacturer's label instructions by diluting isavuconazole solution (40 mg/mL) in 0.9% NaCl to a 0.8 mg/mL solution (Isavuconazole, Cresemba [package insert], Astellas Pharma Co). The drug was administered over 1 hour through a 0.2 μm in-line filter (Ambler Surgical LLC, Exton, Pennsylvania) according to the manufacturer's instructions (Isavuconazole, Cresemba [package insert], Astellas Pharma Co).

2.3 | Blood collection

Blood (0.5-1 mL) was collected from the jugular catheter at predetermined intervals for assessment of isavuconazole concentrations after PO and IV administration (0, 0.17, 0.33, 0.67, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 30, 36, and 48 hours). For cats receiving IV medication, additional samples of blood were collected at 20 and 55 minutes during the infusion (before time 0). Samples were transferred into plain tubes, immediately placed on ice and subsequently centrifuged in batches within 20 minutes of collection. Serum was separated and stored in plastic cryovials at −80°C.

2.4 | Isavuconazole assay

Serum samples were analyzed by use of an ultrahigh performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) assay technique. Analysis was performed in accordance with a previously described modified method used for analysis of concentrations in human serum.[14] Voriconazole was simultaneously analyzed as an internal standard.

The analytical system consisted of a Sciex 6500+ QTRAP triple quadrupole mass spectrometer with a turbo ionspray source coupled to the Sciex Exion UPLC system with cooled autosampler (Applied Biosystems, Inc, Foster City, California). Samples were chromatographed on a Kinetex C18, 2.6 μm, 2.1 × 50 mm reverse-phase chromatography column protected with a C18 filter frit guard cartridge (Phenomenex, Torrance, California). A liquid chromatography gradient was employed with mobile phase A consisting of 2 mM ammonium acetate in water with 0.1% formic acid and mobile phase B consisting of 2 mM ammonium acetate in methanol with 0.1% formic acid at 500 μL/minute. Chromatographic separation was achieved by holding mobile phase B steady at 5% from 0 to 0.2 minutes, increasing linearly from 55% to 65% between 0.2 and 0.5 minutes, increasing linearly from 65% to 100% between 0.5 and 3.75 minutes, holding steady at 100% until 4.25 minutes, decreasing linearly from 100% to 5% between 4.25 and 5.0 minutes and equilibrating at 5% until 5.5 minutes. The sample injection volume was 1 μL and analysis run time was 5.5 minutes. Retention times for isavuconazole and voriconazole were 1.8 and 1.5 minutes, respectively. The mass spectrometer settings were optimized as follows: turbo ion spray temperature, 300°C; ion spray voltage, 2500; source gas 1 and 2, 30 and 35 units, respectively; curtain gas, 30 units; collision gas, medium. Compound parameters for isavuconazole were optimized as follows: declustering potential (DP), 52V; entrance potential (EP), 4V; collision energy (CE), 30 and 73V; and collision cell exit potential (CXP), 12V. Sample concentrations of isavuconazole were quantified by the internal standard reference method in the multiple reaction monitoring mode with 2 ion transitions for isavuconazole at m/z 438.1 → 224.1 and 438.1 → 127.0 and a single ion transition for the internal standard, voriconazole, at m/z 350.2 → 127.0. Scan times were 75 mseconds, and Q1 and Q3 were both operated in unit resolution mode.

Analytical standards of isavuconazole and voriconazole (Sigma-Aldrich, Inc, St. Louis, Missouri) were obtained for generation of calibration curves in blank feline serum obtained and pooled from 8 individual healthy cats. Analytical standards ranging from 25 to 5000 ng/mL (8 nonzero concentrations), quality controls (4 each at 50, 250, and 2500 ng/mL) and unknown serum samples were prepared by protein precipitation with acetonitrile. For extraction, 45 μL of standard, quality control or unknown serum sample was added to 1.5 mL polypropylene tubes containing 5 μL of a 1 μg/mL solution of internal standard (voriconazole) followed by 500 μL of acetonitrile. Samples were then vortex mixed for 1 minute, centrifuged at 4°C for 10 minutes at 10 000g, and 150 μL of supernatant was transferred to a fresh 1.5 mL polypropylene tube containing 850 μL mobile phase A. Samples were then vortex mixed briefly and transferred to glass autosampler vials for injection onto the UPLC system.

The assay was evaluated for accuracy and precision of calibration curves, interday and intraday coefficient of variation of calibrators and quality control samples, stability for 24 hours in the cooled autosampler (15°C) and 2 freeze-thaw cycles.

2.5 | Serum protein binding

The proportion of isavuconazole bound to feline serum proteins was determined in vitro using pooled serum of 8 separate healthy cats. Briefly, blank feline serum was fortified with isavuconazole at 1000 ng/mL (in triplicate) and incubated at 37°C for 30 minutes. Serum then was added to a Centrifree ultrafiltration device (Millipore, Burlington, Massachusetts) that was equilibrated to 37°C and samples were centrifuged at 37°C for 15 minutes at 2000g. After centrifugation, equal volumes of serum and ultrafiltrate were removed and, after sample preparation as described above, injected onto the UPLC-MSMS analysis system. The percentage of drug bound to the plasma proteins was determined using the following equation:

$$\text{Bound \%} = 100\% - \left(\left[\frac{\text{Concentration of ultrafiltrate}}{\text{Concentration of serum}} \right] \times 100\% \right).$$

Concentration of the ultrafiltrate was determined from a calibration curve generated in blank ultrafiltrate.

2.6 | Pharmacokinetic analysis

Serum drug concentrations were plotted on semilogarithmic graphs for analysis and to allow visual assessment of the best model for pharmacokinetic analysis. Analysis of the curves and pharmacokinetic models then was performed by use of a commercial pharmacokinetic program (Phoenix WinNonlin software, version 8.3.3, Certara Co, Princeton, New Jersey). Analysis was performed by both noncompartmental and compartmental methods. Compartmental models were evaluated for best fit based on visual analysis of goodness-of-fit, visual inspection of residual plots and comparison of Akaike information criteria (AIC) values.

Dose normalization of both PO and IV administration subsequently was performed by dividing serum concentrations at each time point by the dose administered, allowing better visualization of route comparisons.

2.7 | Bioavailability

Bioavailability of the PO formulation was calculated using data obtained from noncompartmental analysis by use of the following equation[23]:
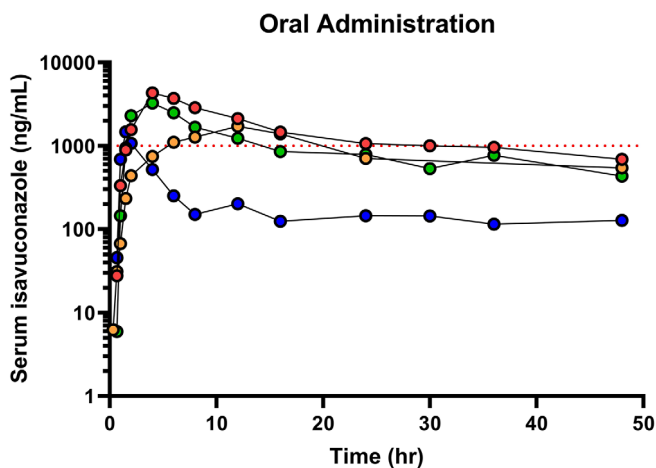
Bioavailability:

$$F = \left(\left[\frac{\text{AUC}\infty\,(\text{oral}) \times \text{dose}\,(\text{IV}) \times T\frac{1}{2}\,(\text{IV})}{\text{AUC}\infty\,(\text{IV}) \times \text{dose}\,(\text{oral}) \times T\frac{1}{2}\,(\text{oral})} \right] \times 100 \right),$$

where AUC is area under the curve.

2.8 | Prediction of concentration-time curves after multiple dosing

Prediction of serum isavuconazole concentration-time graphs after either daily dosing or every-other-day dosing of 100 mg PO capsules

Oral Administration

FIGURE 1 Isavuconazole serum concentrations (circles) in cats (n = 4) after 100 mg PO capsule (14-28 mg/kg) administration. Time 0 = time of administration. Dotted red line = serum trough concentration goal of isavuconazole in human patients (1000 ng/mL)[28]

was performed using nonparametric superposition of the noncompartmental data and were graphed as the predicted mean with upper and lower bounds of the predicted standard deviation (SD).

2.9 | Statistical analysis

Pharmacokinetic parameters were reported as mean ± SD, with the exception of rate constants and half-lives, which were reported as harmonic mean with pseudo SD.

3 | RESULTS
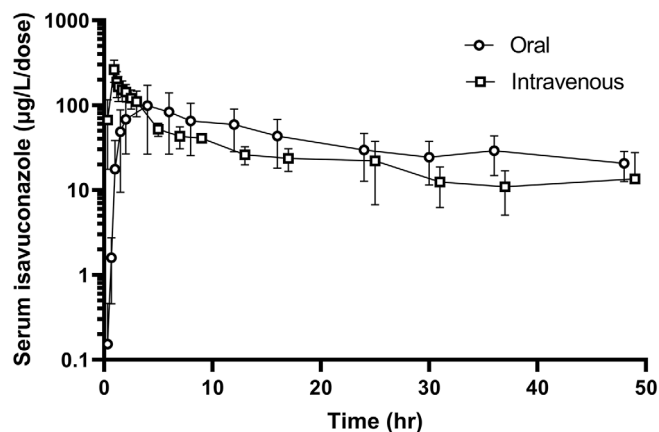
3.1 | Drug administration

The PO isavuconazole capsule was consumed by all cats in the PO group. Two cats in the PO group vomited once 6 to 8 hours post-capsule administration. The capsule was not visible in the vomitus and both cats continued to eat well with no further vomiting. No other adverse effects were noted in the PO administration group and no adverse effects were noted in the IV administration group.

3.2 | Isavuconazole assay performance

The accuracy and precision of the calibration curves was within 15% and 10%, respectively. Curves were linear (r > 0.99) between 25 and 5000 ng/mL and intraday coefficient of variation (CV%) for calibration curves was 5.6%. Interday and intraday coefficients of variation for the quality control samples were 4.0% and 4.5%, respectively. Concentrations calculated in the 24-hour stability and freeze-thaw stability were all within 10% of nominal. The lower limit of detection

Intravenous Infusion
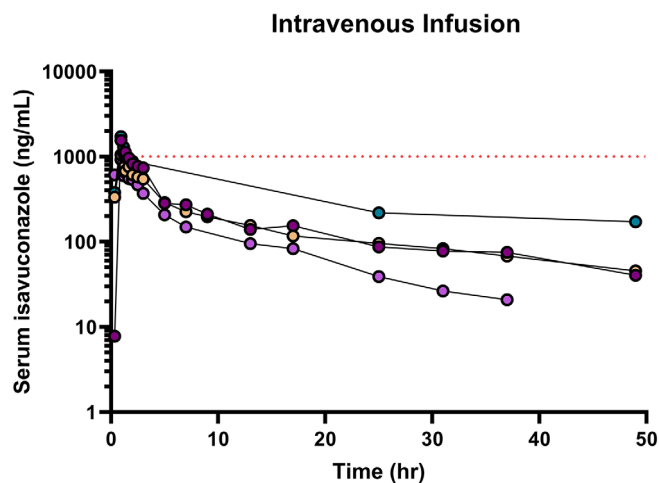
FIGURE 2 Isavuconazole serum concentrations (circles) in cats (n = 4) after 5 mg/kg IV administration. Time 0 = beginning of infusion. Dotted red line = serum trough concentration goal of isavuconazole in human patients (1000 ng/mL)[28]

FIGURE 3 Dose normalized data for PO (open circle) n = 4 and IV (open square) n = 4 administration of isavuconazole. Time 0 = time of administration for PO dosing and beginning of infusion for IV dosing. Values reported are mean ± SD concentration

(LOD) and lower limit of quantitation (LOQ) were 0.5 ng/mL and 1.25 ng/mL, respectively, and were calculated as the concentrations giving a signal to noise ratio (S/N) of >3 for LOD and >10 for LOQ.

3.3 | Pharmacokinetic analysis

Blood samples were obtained at most timepoints for all cats in both the PO and IV groups. For 1 cat in the IV group, samples could only be obtained during the infusion and then 24 and 48 hours after completion of the infusion.

Serum concentrations of cats that received the PO and IV doses were calculated and plotted over time (Figures 1 and 2). Variability in serum isavuconazole concentrations was seen between cats in both the PO and IV groups. One cat in the PO group had markedly disparate serum isavuconazole concentrations compared with the other

TABLE 1 Pharmacokinetic parameters from compartmental analysis of isavuconazole in cats (n = 4) after PO administration of 100 mg capsule (14-28 mg/kg)

Parameter	Units	Mean	SD
C_{max}	ng/mL	2442	1357
T_{max}	h	5.1	3.8
AUC	h*ng/mL	1 895097	3647699
A	ng/mL	135194	881055
α	1/h	0.26	0.3
$\alpha\, T_{1/2}$	h	1.6	1.9
B	ng/mL	809	621
β	1/h	0.01	0.009
$\beta\, T_{1/2}$	h	66.2	55.3
$K_{01}\, T_{1/2}$	h	1.2	0.9

Abbreviations: C_{max}, peak concentration; T_{max}, time to peak concentration; AUC, area under the concentration time curve; A, intercepts for distribution phase; α, distribution rate; $\alpha\, T_{1/2}$, distribution rate half-life; B, intercepts for elimination phase; β, elimination rate constant; $\beta\, T_{1/2}$, elimination rate half-life; $K_{01}\, T_{1/2}$, absorption rate half-life; SD, standard deviation.

TABLE 2 Pharmacokinetic parameters from compartmental analysis of isavuconazole in cats (n = 3) after a 60-minute IV infusion of 5 mg/kg

| Parameter	Units	Mean	SD
C_{max}[a]	ng/mL	1164	240
AUC	(h*ng/mL)	7932	2870
A	ng/mL	1097	194
α	1/h	0.53	0.26
$\alpha\, T_{1/2}$	h	0.99	0.99
B	ng/mL	241	55
β	1/h	0.04	0.02
$\beta\, T_{1/2}$	h	14	12.3
CL	L/h/kg	0.71	0.25
V_{SS}	L/kg	11.9	1.7
V2	L/kg	8.1	1.1
$K_{10}\, T_{1/2}$	h	3.6	2.6
MRT	h	19.3	8.6

[a]C_{max} calculated from n = 4 cats.
Abbreviations: C_{max}, peak concentration; AUC, area under the concentration time curve; A, intercepts for distribution phase; α, distribution rate; $\alpha\, T_{1/2}$, distribution rate half-life; B, intercepts for elimination phase; β, elimination rate constant; $\beta\, T_{1/2}$, elimination rate half-life; CL, drug clearance; V2, volume of peripheral compartment; $K_{10}\, T_{1/2}$ terminal rate half-life; MRT, mean residence time; V_{SS}, steady state volume of distribution; SD, standard deviation.

3 cats (Figure 1). Given the difference in dose between the 2 groups, dose normalized data was calculated and graphed to compare the routes of administration (Figure 3).

After PO dosing, a 2-compartment model with first-order input, first-order output, lag time and microconstant parameterization best fit the data with the corresponding equation:
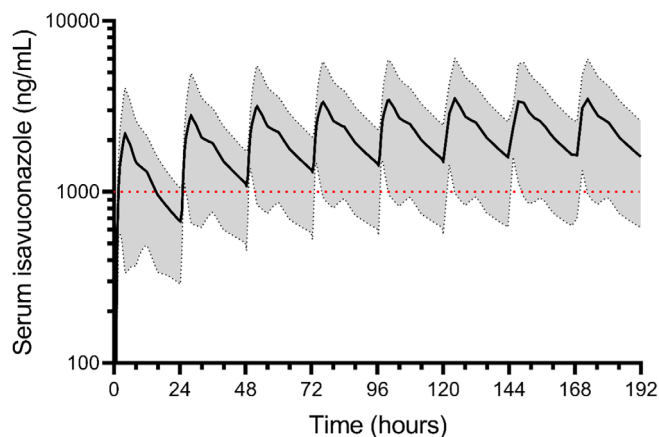
FIGURE 4 Predicted isavuconazole serum concentrations (black line) and SD (gray shading) with 24 hour dosing interval of 100 mg PO. Dotted red line = serum trough level concentration of isavuconazole in human patients (1000 ng/mL)[28]
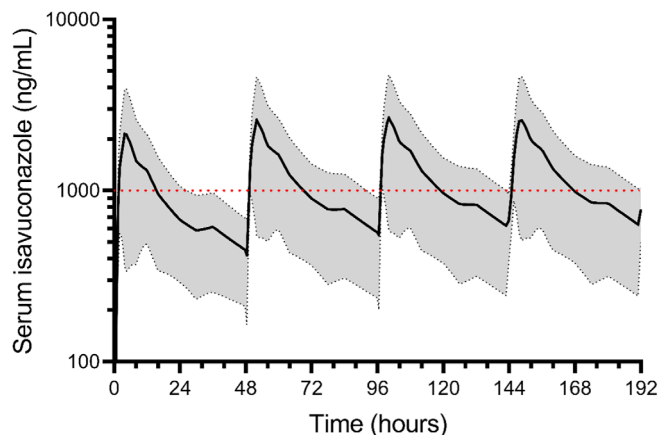
FIGURE 5 Predicted isavuconazole serum concentrations (black line) and SD (gray shading) with 48 hour dosing interval of 100 mg PO. Dotted red line = serum trough concentration goal of isavuconazole in human patients (1000 ng/mL)[28]

$$C(t) = Ae^{-\alpha(t-T\text{lag})} + Be^{-\beta(t-T\text{lag})} + Ce^{-K01(t-T\text{lag})},$$

where $C(t)$ is the concentration at time t, Tlag is the lag time, and $K01$ is the absorption rate.

After IV infusion, a 2-compartment model with constant IV input (infusion) and first-order output with microconstant parameterization best fit the data with the corresponding equation,

$$C(t) = \frac{A}{T\text{inf}(\alpha)}\left[e^{(-\alpha t*)} - e^{(-\alpha t)}\right] + \frac{B}{T\text{inf}(\beta)}\left[e^{(-\beta t*)} - e^{(-\beta t)}\right],$$

where $C(t)$ is the concentration at time t, Tinf is the length of infusion, and $t*$ is equal to (t-Tinf) for any time point greater than the length of infusion and equal to 0 for any time point less than the length of infusion.

Compartmental pharmacokinetic parameters after PO and IV administration are expressed in Tables 1 and 2, respectively. Serum protein binding was calculated to be 99.0% ± 0.03%. Bioavailability was estimated to be approximately 88% based on the data from 4 cats in the PO group and 3 cats in the IV group. Predicted 24- and 48-hour dosing intervals of 100 mg isavuconazole PO were modeled (Figures 4 and 5, respectively). Predicted 24-hour dosing attained mean serum isavuconazole trough concentrations >1000 ng/mL consistently, whereas 48-hour dosing attained trough concentrations on average < 1000 ng/mL.

4 | DISCUSSION

Both PO and IV drug administration achieved high serum concentrations and were generally well tolerated. Peak serum isavuconazole concentrations occurred 5 ± 3.8 hours after PO administration compared with 18.70 ± 7.32 hours after PO posaconazole suspension[24] and 1 ± 0.52 hours after PO voriconazole suspension administration.[25] Elimination rate half-life was 66.2 ± 55.3 hours and PO bioavailability was estimated at 88%. Two cats vomited during PO administration, 6 to 8 hours post-capsule administration, closely corresponding to T_{max}. No adverse effects were observed in the IV group. Given that butorphanol was used to facilitate peripheral IV catheter placement, the antiemetic effects of butorphanol[26] may have masked any nausea in this group.

Whereas on initial assessment IV administration of isavuconazole appeared to achieve a lower mean C_{max} compared with PO administration (1164.2 and 2442.3 ng/mL, respectively), the IV dose administered was 2.8 to 5.6 times less than that of the PO drug administration. When plotted as dose normalized data (Figure 3), both IV and PO formulations of isavuconazole appeared to have similar pharmacokinetics. Intersubject variability was apparent in both the PO and IV groups, which is a consistent feature of other azoles in cats.[24,25] Given the closeness of age among cats and the fact all were intact females, age and sex are not likely to be the cause of the variability. Some of the variability seen in the PO group (Figure 1) may be a consequence of 1 of the cats in this group vomiting (blue dots), with this cat having the more variable serum concentration curve compared with the other 3 cats. The other cat that vomited received a PO dose of isavuconazole but was not included in the study because of jugular catheter sampling issues. Food was not withheld during the study because absorption is not impacted by food intake or gastric acid suppressant medications in human patients.[22] The impact of food is not known in cats, and this factor may have affected some pharmacokinetic parameters. Gastrointestinal transit time of drugs can be affected by whether cats are fed or food is withheld,[27] with differences in subject eating habits potentially causing some variation in the measured pharmacokinetic parameters.

Therapeutic plasma drug concentrations and optimal serum concentrations of isavuconazole have yet to be determined in cats. As with other triazole medications, feline-specific fungal isolate susceptibility to isavuconazole has not been performed. Serum isavuconazole trough concentrations in human patients >1000 ng/mL have been used in therapeutic drug monitoring to ensure efficacy.[28] Based on predicted modeling

(Figure 4), PO administration of a 100 mg isavuconazole capsule every 24 hours would attain serum trough concentrations >1000 ng/mL consistently. Every other day 100 mg isavuconazole capsule administration (Figure 5) modeling suggests serum trough isavuconazole concentrations on average below 1000 ng/mL. In human medicine, a loading dose either PO or IV q8h for 48 hours is recommended, which then is followed by once daily dosing.[13] A loading PO or IV dose followed by 100 mg PO q48h may result in serum trough concentrations in cats >1000 ng/mL over time and may limit the adverse effects of the drug. Every other day dosing may further increase owner compliance in cats. Clinical studies are required to determine whether this therapeutic target would be reasonable in cats.

Serial monitoring in human patients receiving prolonged isavuconazole treatment suggests a gradual, near-linear accumulation of the drug over many weeks,[29] and therefore the tolerability of this dose over time should be assessed. The most common adverse effects of isavuconazole in human patients include nausea, vomiting, and diarrhea.[14] As with other triazole antifungal drugs, drug-related hepatotoxicity is a possibility, although in the SECURE trial,[21] there was a lower frequency of drug-related hepatotoxicity in the isavuconazole group compared to the voriconazole group. Studies involving repeated doses in cats will be necessary to assess effects of long-term administration of this medication in cats.

When reconstituted, the manufacturer recommends that the IV solution be discarded after 6 hours if stored at room temperature and after 24 hours if stored between 2°C and 8°C (Isavuconazole, Cresemba [package insert], Astellas Pharma Co). Given the cost of the IV solution, daily or every other day administration may not be economically feasible in cats. Alternatively, IV isavuconazole formulation may play a role in administration of a loading dose, during the initial treatment period of severely affected cats in which PO administration might be challenging or in cats in which intestinal absorption is suspected to be impaired.

Our study had some limitations. In many veterinary pharmacokinetic studies, 6 subjects are allocated per group and this number was not achieved in our study. We aimed to include 6 cats per group but because of jugular catheter sampling issues and the temperament of the subjects, only 4 cats could be allocated to each group. This sample size might limit the generalizability of our data. Additionally, we encountered challenges with the jugular catheter of 1 cat in the IV group and were only able to obtain 24- and 48-hour samples after completion of the infusion, and thus data from this cat was used only for the calculation of average C_{max}, because estimates of total AUC, rate constants and half-lives would have been inaccurate given the lack of sample time points.

A crossover study is ideal for assessing bioavailability in order to limit interindividual variability. We used a parallel study design which is not the preferred method, given the feasibility and cost of completing a crossover study of a drug with presumed prolonged elimination. Because our study only involved a single administration of isavuconazole in healthy cats, potential adverse effects from repeated administration of isavuconazole as well as safety and efficacy of the drug in cats with fungal disease require further study. Because our study evaluated single dosing, systemic health assessment was not performed after drug

administration. In human medicine, increased liver enzyme activities and hypokalemia occurred in 16% and 14%, respectively, of patients with adverse reactions to isavuconazole.[28] Our goal was to establish the pharmacokinetics of this drug in healthy cats, and thus our data might not be representative of cats with fungal infection because they might have altered absorption or elimination of the drug.

Overall, isavuconazole may be a useful drug in feline medicine. Both IV and PO forms may be able to be used interchangeably. Additional studies on safety and tolerability of long-term isavuconazole use are needed. After such studies, a dosing regimen based on the pharmacokinetic data obtained in our study can be constructed.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

This study investigated the pharmacokinetics of isavuconazole in cats, which constitutes an off-label usage of an antimicrobial drug.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the IACUC of the University of California, Davis, protocol # 22331.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Dennis J. Woerde https://orcid.org/0000-0003-1511-8231
Jonathan D. Dear https://orcid.org/0000-0002-7166-1442

REFERENCES

1. Mawby DI, Whittemore JC, Genger S, Papich MG. Bioequivalence of orally administered generic, compounded, and innovator-formulated itraconazole in healthy dogs. _J Vet Intern Med_. 2014; 28(1):72-77.
2. Kendall J, Papich MG. Posaconazole pharmacokinetics after administration of an intravenous solution, oral suspension, and delayed-release tablet to dogs. _Am J Vet Res_. 2015;76(5):454-459.
3. Wilby KJ. A review of the clinical pharmacokinetics and pharmacodynamics of isavuconazole. _Eur J Drug Metab Pharmacokinet_. 2018;43(3): 281-290.
4. Luke DR, Tomaszewski K, Damle B, Schlamm HT. Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). _J Pharm Sci_. 2010;99(8):3291-3301.
5. Pfaller MA, Messer SA, Rhomberg PR, Jones RN, Castanheira M. In vitro activities of isavuconazole and comparator antifungal agents tested against a global collection of opportunistic yeasts and molds. _J Clin Microbiol_. 2013;51(8):2608-2616.
6. Illnait-Zaragozi MT, Martínez GF, Curfs-Breuker I, et al. In vitro activity of the new azole isavuconazole (BAL4815) compared with six other antifungal agents against 162 cryptococcus neoformans isolates from Cuba. _Antimicrob Agents Chemother_. 2008;52(4):1580-1582.
7. Espinel-Ingroff A, Chowdhary A, Gonzalez GM, et al. Multicenter study of isavuconazole MIC distributions and epidemiological cutoff values for the cryptococcus neoformans-cryptococcus gattii species complex using the CLSI M27-A3 broth microdilution method. _Antimicrob Agents Chemother_. 2015;59(1):666-668.
8. Seifert H, Aurbach U, Stefanik D, Cornely O. In vitro activities of isavuconazole and other antifungal agents against Candida bloodstream isolates. _Antimicrob Agents Chemother_. 2007;51(5):1818-1821.
9. Heidari A, Quinlan M, Benjamin DJ, et al. Isavuconazole in the treatment of coccidioidal meningitis. _Antimicrob Agents Chemother_. 2019; 63(3):e02232-18.
10. Warn PA, Sharp A, Denning DW. In vitro activity of a new triazole BAL4815, the active component of BAL8557 (the water-soluble prodrug), against _Aspergillus_ spp. _J Antimicrob Chemother_. 2006;57(1): 135-138.
11. González GM. In vitro activities of isavuconazole against opportunistic filamentous and dimorphic fungi. _Med Mycol_. 2009;47(1):71-76.
12. Shirley M, Scott LJ. Isavuconazole: a review in invasive _Aspergillosis_ and _Mucormycosis_. _Drugs_. 2016;76(17):1647-1657.
13. Astellas Pharma US Prescribing Information for Isavuconazonium Sulfate. https://www.astellas.us/docs/cresemba.pdf. Accessed 1 September 2020.
14. Schmitt-Hoffmann A, Roos B, Heep M, et al. Single-ascending-dose pharmacokinetics and safety of the novel broad-spectrum antifungal triazole BAL4815 after intravenous infusions (50, 100, and 200 milligrams) and oral administrations (100, 200, and 400 milligrams) of its prodrug, BAL8557, in healthy volunteers. _Antimicrob Agents Chemother_. 2006;50(1):279-285.
15. Jenks JD, Salzer HJ, Prattes J, et al. Spotlight on isavuconazole in the treatment of invasive _Aspergillosis_ and _Mucormycosis_: design, development, and place in therapy. _Drug des Devel Ther_. 2018;12:1033-1044.
16. Ledoux MP, Denis J, Nivoix Y, Herbrecht R. Isavuconazole: a new broad-spectrum azole. Part 2: pharmacokinetics and clinical activity. _J Mycol Med_. 2018;28(1):15-22.
17. Miceli MH, Kauffman CA. Isavuconazole: a new broad-spectrum triazole antifungal agent. _Clin Infect Dis_. 2015;61(10):1558-1565.
18. Kovanda LL, Desai AV, Lu Q, et al. Isavuconazole population pharmacokinetic analysis using nonparametric estimation in patients with invasive fungal disease (results from the VITAL study). _Antimicrob Agents Chemother_. 2016;60(8):4568-4576.
19. Wilson DT, Dimondi VP, Johnson SW, Jones T, Drew R. Role of isavuconazole in the treatment of invasive fungal infections. _Ther Clin Risk Manag_. 2016;12:1197-1206.
20. McCarthy MW, Moriyama B, Petraitiene R, et al. Clinical pharmacokinetics and pharmacodynamics of isavuconazole. _Clin Pharmacokinet_. 2018;57(12):1483-1491.
21. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by _Aspergillus_ and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. _Lancet_. 2016;387(10020):760-769.
22. Schmitt-Hoffmann A, Desai A, Kowalski D, Pearlman H, Yamazaki T, Townsend R. Isavuconazole absorption following oral administration in healthy subjects is comparable to intravenous dosing, and is not affected by food, or drugs that alter stomach pH. _Int J Clin Pharmacol Ther_. 2016;54(8):572-580.
23. Riviere JE. Compartmental models. _Comparative Pharmacokinetics: Principles, Techniques, and Applications_. 2nd ed. Oxford, UK: Wiley-Blackwell; 2011.
24. Mawby DI, Whittemore JC, Fowler LE, Papich MG. Posaconazole pharmacokinetics in healthy cats after oral and intravenous administration. _J Vet Intern Med_. 2016;30(5):1703-1707.

25. Vishkautsan P, Papich MG, Thompson GR 3rd, et al. Pharmacokinetics of voriconazole after intravenous and oral administration to healthy cats. *Am J Vet Res.* 2016;77(9):931-939.

26. Papastefanou AK, Galatos AD, Pappa E, Lymperis AG, Kostoulas P. The effect of butorphanol on the incidence of dexmedetomidine-induced emesis in cats. *Vet Anaesth Analg.* 2015;42(6):608-613.

27. Sutton SC. Companion animal physiology and dosage form performance. *Adv Drug Deliv Rev.* 2004;56(10):1383-1398.

28. Kosmidis C, Otu A, Moore CB, Richardson MD, Rautemaa-Richardson R. Isavuconazole therapeutic drug monitoring during long-term treatment for chronic pulmonary *Aspergillosis. Antimicrob Agents Chemother.* 2020; 65(1):e01511-20.

29. Borman AM, Hughes JM, Oliver D, et al. Lessons from isavuconazole therapeutic drug monitoring at a United Kingdom Reference Center. *Med Mycol.* 2020;58(7):996-999.