

# Posaconazole pharmacokinetics after administration of an intravenous solution, oral suspension, and delayed-release tablet to dogs

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## OBJECTIVE

To determine pharmacokinetics of posaconazole in dogs given an IV solution, oral suspension, and delayed-release tablet.

## ANIMALS

6 healthy dogs.

## PROCEDURES

Posaconazole was administered IV (3 mg/kg) and as an oral suspension (6 mg/kg) to dogs in a randomized crossover study. Blood samples were collected before (time 0) and for 48 hours after each dose. In an additional experiment, 5 of the dogs received posaconazole delayed-release tablets (mean dose, 6.9 mg/kg); blood samples were collected for 96 hours. Plasma concentrations were analyzed with high-performance liquid chromatography.

## RESULTS

IV solution terminal half-life ( $t_{1/2}$ ) was 29 hours (coefficient of variation [CV], 23%). Clearance and volume of distribution were 78 mL/h/kg (CV, 59%) and 3.3 L/kg (CV, 38%), respectively. Oral suspension  $t_{1/2}$  was 24 hours (CV, 42%). Maximum plasma concentration ( $C_{max}$ ) of 0.42  $\mu$ g/mL (CV, 56%) was obtained at 7.7 hours (CV, 92%). Mean bioavailability was 26% (range, 7.8% to 160%). Delayed-release tablet  $t_{1/2}$  was 42 hours (CV, 25%), with a  $C_{max}$  of 1.8  $\mu$ g/mL (CV, 44%) at 9.5 hours (CV, 85%). Mean bioavailability of tablets was 159% (range, 85% to 500%). Bioavailability of delayed-release tablets was 497% (range, 140% to 1,800%) relative to that of the oral suspension.

## CONCLUSIONS AND CLINICAL RELEVANCE

Absorption of posaconazole oral suspension in dogs was variable. Absorption of the delayed-release tablets was greater than absorption of the oral suspension, with a longer  $t_{1/2}$  that may favor its clinical use in dogs. Administration of delayed-release tablets at a dosage of 5 mg/kg every other day can be considered for future studies. (*Am J Vet Res* 2015;76:454–459)

Oral formulations of triazole antifungal agents are approved by the US FDA for the treatment of fungal infections in humans, but none are approved for administration to dogs in the United States. Veterinarians can legally prescribe human-label drugs for non-food-producing animals in accordance with the Animal Medicinal Drug Use Clarification Act of 1994; thus, various triazole antifungals have been used to treat infections caused by *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides* spp, *Cryptococcus* spp, and *Aspergillus* spp. Azole antifungals commonly used to treat dogs include fluconazole and itraconazole.<sup>1</sup> Recently, voriconazole also has been used in dogs.<sup>1</sup>

## ABBREVIATIONS

|                  |   |
|------------------|---|
| AUC              | Area under the concentration-time curve         |
| $C_{max}$        | Maximum concentration                           |
| F                | Fraction of the drug absorbed                   |
| HPLC             | High-performance liquid chromatography          |
| $t_{1/2}$        | Terminal half-life                              |
| $T_{max}$        | Time to maximum concentration                   |
| V <sub>dss</sub> | Apparent volume of distribution at steady state |

Despite the extralabel use of antifungal drugs, some fungal infections remain difficult to treat. In addition, problems with currently used orally administered azole antifungal drugs in dogs include poor antifungal activity (fluconazole), highly variable absorption after oral administration to dogs (itraconazole), adverse events in dogs (ketoconazole), twice-daily (or more) administration (itraconazole and voriconazole), and high expense (voriconazole and itraconazole). Ketoconazole also has become less available and more expensive.

A new triazole antifungal, posaconazole, has been approved by the FDA for use in humans. Posaconazole has broad-spectrum activity that is superior to that of other antifungals against many clinically important organisms.<sup>2</sup> In 1 study,<sup>3</sup> it was more active than itraconazole and fluconazole against all fungal strains tested and more active than amphotericin B against 95% of strains evaluated. It is active against fluconazole-resistant strains of *Candida* spp dermatophytes and other opportunistic fungi and more potent than fluconazole

or itraconazole against *Aspergillus* spp.<sup>2,3</sup> The spectrum of activity for posaconazole also includes zygomycetes and *Fusarium* spp.<sup>2</sup> Moreover, the drug has a higher safety margin, fewer drug interactions, and a narrower toxicity profile, compared with characteristics of other marketed antifungals.<sup>4</sup>

Despite these potential advantages, there is currently only limited information on the administration of posaconazole to dogs and sparse data on absorption after oral administration that can be used to guide clinical use. Existing pharmacokinetic data from the manufacturer are from preclinical studies. Studies<sup>3,5</sup> for dogs have yielded conflicting or incomplete data. The objective of the study reported here was to determine the pharmacokinetics of posaconazole in dogs, including the extent of absorption after oral administration, and to evaluate the ability to achieve critical pharmacokinetic-pharmacodynamic targets for susceptible organisms. Furthermore, we sought to investigate properties of an extended-release tablet for oral administration to dogs for potential clinical use.

## Materials and Methods

### Animals

Six adult mixed-breed hound dogs that weighed between 20.1 and 38.8 kg (mean, 32.1 kg) were used in the study. Results of physical examination were used to determine that the dogs were healthy prior to enrollment in the study. Dogs were housed at the North Carolina State University Laboratory Animal Resources facility and fed a maintenance diet.<sup>a</sup> The study was reviewed and approved by the Institutional Animal Care and Use Committee at North Carolina State University.

### Study design

An initial experiment that involved a 2-period, 2-treatment crossover design with at least a 4-day washout period between subsequent treatments was used. A coin was flipped to assign dogs to the order of treatments. Food was withheld from all dogs for 12 hours before administration. An IV dose (3 mg/kg) was administered by diluting posaconazole solution<sup>b</sup> (18 mg/mL) in saline (0.9% NaCl) solution to a final volume of 35 mL; the solution was infused over a 5-minute period via a catheter inserted in a cephalic vein. A dose (6 mg/kg) of an oral suspension<sup>c</sup> (40 mg/mL) was administered orally with a syringe. Immediately prior to administration of the oral suspension, each dog was fed one-third can of a maintenance commercial dog food.<sup>d</sup> In addition, 12 mL of tap water was administered to ensure the suspension was swallowed. Food<sup>a</sup> was reintroduced to all dogs within 4 hours after drug administration.

After examining results from the initial experiment, a second experiment was conducted to investigate the potential for obtaining a more favorable plasma concentration profile with a new posaconazole delayed-release tablet<sup>e</sup> (100-mg tablets). The

delayed-release tablet dose (mean dose, 6.9 mg/kg) was administered to 5 dogs used in the initial experiment; there was a period of approximately 3 weeks between the initial experiment and the second experiment. The manufacturer recommended in the product insert that it was important these tablets remain intact to preserve the delayed-release properties. Similar to the initial experiment, food was withheld from dogs for 4 hours before drug administration and each dog was fed one-third can of a maintenance commercial dog food<sup>d</sup> immediately prior to administration of the tablets. In addition, 12 mL of tap water was administered to ensure the tablets were swallowed. Food<sup>a</sup> was reintroduced to all dogs within 4 hours after drug administration.

### Blood collection

Approximately 18 hours before drug administration, each dog was sedated with dexmedetomidine hydrochloride (10 µg/kg, IV) and a catheter was inserted into a jugular vein. Catheters were flushed with sterile saline solution to maintain catheter patency. Blood samples were collected before (time 0) and 0.17, 0.33, 0.67, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 30, 36, and 48 hours after administration of the IV solution and oral suspension of posaconazole. Blood samples were collected before (time 0) and 0.25, 0.50, 1, 1.5, 2, 4, 6, 8, 10, 12, 14, 24, 30, 34, 48, 55, 72, and 96 hours after the administration of the delayed-release tablets. Samples were transferred into glass tubes containing lithium heparin as the anticoagulant. Blood samples were immediately placed on ice and subsequently centrifuged at 2,000 X g for 10 minutes. Plasma was separated and stored at -70°C.

### HPLC analysis

Plasma samples were analyzed by use of HPLC to determine the concentration of posaconazole; analysis was performed in accordance with a modified method used for analysis of concentrations in human and canine plasma.<sup>3,6</sup> The HPLC system consisted of a quaternary solvent delivery system<sup>f</sup> (flow rate, 1 mL/min), autosampler,<sup>g</sup> and UV detector<sup>h</sup> set at a wavelength of 262 nm. Chromatograms were integrated with a computer program.<sup>i</sup> The analytic column<sup>j</sup> was a stable-bond C8 column that was maintained at a constant temperature (40°C). The mobile phase consisted of 52% distilled water and 48% acetonitrile. A 0.02% solution of trifluoroacetic acid was added to the mobile phase to modify pH.

A reference standard of posaconazole<sup>k</sup> (99.9% pure) was dissolved in 100% methanol to prepare a stock solution that was used to fortify blank canine plasma. Stock solutions were placed in glass vials, sealed, and stored in the dark in a refrigerator. The calibration curve for posaconazole consisted of 10 standard solutions that ranged between 0.05 and 5 µg/mL; it also included a blank (0 µg/mL) sample. The blank sample was used to detect interfering peaks that eluted into the chromatographic peak of interest and

to measure background noise for calculation of the signal-to-noise ratio. The calibration curve was accepted when the linear coefficient of determination (ie,  $r^2$ ) was 0.99 and the calibration curve concentrations could be back-calculated to within 15% of the true concentration of the standard. Fresh calibration and blank samples were prepared for analysis each day.

All plasma, calibration, quality control, and blank-plasma samples were prepared in an identical manner. An aliquot (500  $\mu$ L) of each sample was added to a glass tube with 500  $\mu$ L of acetonitrile. The solution was mixed briefly in a vortexer and then centrifuged at 1,200  $\times$  g for 10 minutes. Supernatant was transferred to an HPLC injection vial. Fifty microliters of each sample was injected into the HPLC system for analysis.

Retention time for posaconazole chromatographic peaks was 4.9 to 5.2 minutes. The lowest point on the linear calibration curve (0.05  $\mu$ g/mL) met acceptance criteria for accuracy. The limit of quantification for the drug in canine plasma was 0.04  $\mu$ g/mL, as determined on the basis of a signal-to-noise ratio of 6. Laboratory procedures were conducted in accordance with published guidelines.<sup>7</sup> A previous study<sup>3</sup> revealed that posaconazole is stable in canine serum frozen at  $-20^\circ\text{C}$  for 348 days of storage and after being subjected to 3 freeze-thaw cycles. That study<sup>3</sup> also revealed that processed canine samples are stable at room temperature throughout the assay procedure.

### Pharmacokinetic analysis

Plasma drug concentrations were plotted on linear and semilogarithmic graphs for analysis and to allow visual assessment of the best model for pharmacokinetic analysis. Analysis of the curves and pharmacokinetic models was then performed by use of a commercial pharmacokinetic program.<sup>1</sup> Compartmental analysis of the delayed-release tablet results was performed with a weighting factor of  $1/(\text{predicted plasma concentration})$ .<sup>2</sup> Compartmental analysis of results for both the IV solution and oral suspension was performed by use of uniform weighting. Specific models (eg, 1- or 2-compartment) were determined for best fit on the basis of visual analysis for goodness of fit and by visual inspection of residual plots. The general form of the equation for the compartment analysis was as follows:

$$C = A \cdot e^{-\lambda_n t}$$

where C is the plasma concentration, A is the y-axis intercept, e is the base of the natural logarithm,  $\lambda_n$  is the rate constant for the number (n) of compartments, and t is time after administration. For the 2-compartment model, biexponential analysis was used for the IV administration with a corresponding equation as follows:

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

where A is the y-axis intercept for the distribution phase of the curve,  $\alpha$  is the slope of the distribution phase of the curve, B is the y-axis intercept for the elimination phase of the curve, and  $\beta$  is the slope of the elimination phase of the curve. The value for  $t_{1/2}$  was estimated by use of the following equation:  $t_{1/2} = (\ln 0.5)/\beta$ . Other compartmental pharmacokinetic parameters were calculated in accordance with equations provided elsewhere.<sup>8</sup>

For both oral doses, parameters were calculated by use of the following formula:

$$C = ([k_{01}FD]/[Vd\{k_{01} - k_{10}\}]) \cdot (e^{-k_{10}t} - e^{-k_{01}t})$$

where  $k_{01}$  is the non-IV absorption rate, assuming first-order absorption; D is the non-IV dose; Vd is the apparent volume of distribution; and  $k_{10}$  is the elimination rate constant. Lag time was added to the model to account for dissolution of the oral solution or delayed-release tablet and stomach emptying (mean lag time, 0.25 hours for the oral suspension and 2.3 hours for the delayed-release tablet). Secondary parameters calculated from the model included Cmax, Tmax, AUC, and the respective values for absorption and  $t_{1/2}$ . Systemic availability for a non-IV dose was calculated by use of the following equation:

$$F = (AUC_{\text{ORAL}}/AUC_{\text{IV}}) \times (\text{Dose}_{\text{IV}}/\text{Dose}_{\text{ORAL}}) \times 100\%$$

Relative bioavailability of the 2 oral formulations was calculated in a similar manner by use of the following equation:

$$\text{Relative F} = (AUC_{\text{TABLET}}/AUC_{\text{SUSPENSION}}) \times (\text{Dose}_{\text{SUSPENSION}}/\text{Dose}_{\text{TABLET}}) \times 100\%$$

### Plasma protein binding

In vitro analysis of plasma protein binding was conducted at 2 concentrations to represent the range of plasma concentrations anticipated for the study. Posaconazole plasma protein binding was performed by use of ultrafiltration.<sup>m</sup> Aliquots of pooled canine plasma were spiked with posaconazole to generate concentrations of 1 and 5  $\mu$ g/mL. Each spiked sample was divided into 3 replicates of 1 mL, which were subsequently added to the micropartition system<sup>m</sup> and centrifuged at 1,000  $\times$  g for 30 minutes to obtain a protein-free ultrafiltrate for HPLC analysis. A second set of 3 replicates of plasma spiked at the same concentrations was processed via a normal protein precipitation procedure and analyzed by use of HPLC for comparison. Protein binding was determined by use of the following equation:

$$\text{Protein binding} = ([\text{total concentration} - \{\text{protein-unbound concentration}\}]/\text{total concentration}) \times 100\%$$

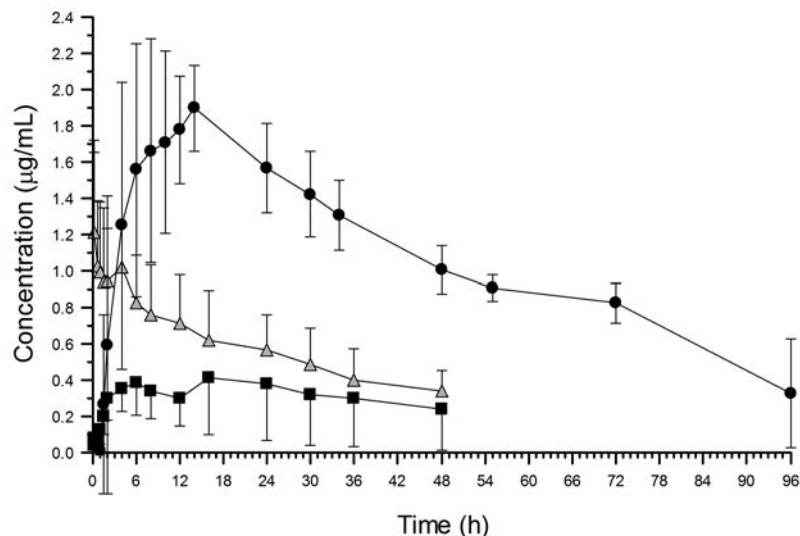
### Statistical analysis

Geometric means and corresponding CVs were calculated with the pharmacokinetic program.<sup>1</sup>

## Results

Posaconazole was well tolerated when administered via the oral and IV routes, and no adverse effects were observed during the course of the study. Geometric mean plasma concentrations for all 6 dogs administered the oral suspension and IV solution as well as for the 5 dogs administered the delayed-release tablet were plotted (**Figure 1**). Plasma protein binding was > 99% at both of the concentrations tested.

Pharmacokinetic parameters were calculated (**Tables 1 and 2**). After administration of the IV solution,



**Figure 1**—Posaconazole plasma concentrations in dogs after administration of an IV solution (3 mg/kg [gray triangles]; n = 6), an oral suspension (6 mg/kg; 6), and delayed-release tablets (mean dose, 6.9 mg/kg; 5). Time 0 = Time of administration. Values reported are mean + SD concentration after administration of the IV solution, mean – SD concentration after administration of the oral suspension, and mean ± SD concentration after oral administration of the delayed-release tablets.

**Table 1**—Pharmacokinetic parameters after administration of an IV solution of posaconazole (3 mg/kg) to 6 dogs.

| Parameter                          | Geometric |              |        |
|------------------------------------|-----------|--------------|--------|
|                                    | mean      | Range        | CV (%) |
| A (µg/mL)                          | 0.37      | 0.22–0.91    | 52.79  |
| $\alpha$ (h <sup>-1</sup> )        | 1.72      | 0.32–11.05   | 167.12 |
| $\alpha$ t <sub>1/2</sub> (h)      | 0.40      | 0.06–2.20    | 167.12 |
| AUC (h•µg/mL)                      | 38.40     | 13.35–63.76  | 59.02  |
| B (µg/mL)                          | 0.90      | 0.46–1.31    | 37.67  |
| $\beta$ (h <sup>-1</sup> )         | 0.02      | 0.02–0.03    | 22.65  |
| $\beta$ t <sub>1/2</sub> (h)       | 29.29     | 19.93–35.71  | 22.65  |
| CL (mL/h/kg)                       | 78.13     | 47.05–224.75 | 59.02  |
| C <sub>max</sub> (µg/mL)           | 1.29      | 0.79–2.23    | 35.39  |
| K <sub>12</sub> (h <sup>-1</sup> ) | 0.46      | 0.07–4.53    | 253.49 |
| K <sub>21</sub> (h <sup>-1</sup> ) | 1.21      | 0.24–6.49    | 145.09 |
| MRT (h)                            | 41.95     | 28.68–51.36  | 22.41  |
| V <sub>dss</sub> (L/kg)            | 3.28      | 2.25–6.45    | 38.21  |

$\alpha$  = Distribution rate constant. A = Distribution intercept. B = Elimination intercept.  $\beta$  = Elimination rate constant. CL = Systemic clearance. K<sub>12</sub> = Microdistribution rate constant for transfer from compartment 1 (central compartment) to compartment 2 (peripheral compartment). K<sub>21</sub> = Microdistribution rate constant for transfer from compartment 2 to compartment 1. MRT = Mean residence time.

t<sub>1/2</sub> was 29.3 hours (CV, 22.7%), systemic clearance was 78.1 mL/h/kg (CV, 59.0%), and V<sub>dss</sub> was 3.2 L/kg (CV, 38.2%). After administration of the oral suspension, C<sub>max</sub> was 0.42 µg/mL (CV, 55.8%), T<sub>max</sub> was 7.7 hours (CV, 92.2%), t<sub>1/2</sub> was 23.9 hours (CV, 42.1%), and systemic absorption was 26% (range, 7.8% to 160%). After administration of the delayed-release tablet, C<sub>max</sub> was 1.8 µg/mL (CV, 44.4%), T<sub>max</sub> was 9.5 hours (CV, 85.1%), t<sub>1/2</sub> was 41.7 hours (CV, 24.5%), and systemic absorption was 159% (85% to 500%). Bioavailability of the delayed-release tablet was 497% (range, 140% to 1,800%) relative to that of the oral suspension.

## Discussion

Analysis of the results of the present study indicated that posaconazole has properties that could be advantageous for treating fungal infections in dogs. Compared with other antifungal drugs currently administered to dogs, posaconazole has better in vitro activity.<sup>2,3</sup> Previously, there was not enough pharmacokinetic data to evaluate the potential for posaconazole as an antifungal treatment in dogs. On the basis of the present study in a small number of dogs, there now are data that can be used to generate dosages for larger studies. The mean t<sub>1/2</sub> for the posaconazole IV solution, oral suspension, and delayed-release tablet was 29 (CV, 23%), 24 (CV, 42%), and 42 (CV, 25%) hours, respectively (Tables 1 and 2). No adverse effects were detected for any of the routes of administration, even though blood concentrations after administration of the delayed-release tablet persisted for > 96 hours.

Values reported for the dogs of the present study were similar to those reported for humans.<sup>9–11</sup> Comparisons with other studies in dogs are not possible. Investigators of 1 study<sup>3</sup> of dogs provided incomplete data. In that study,<sup>3</sup> C<sub>max</sub> after administration (200 mg) of an unspecified tablet to Beagles was 1.5 µg/mL, but other parameters were not listed. Investigators of another study<sup>5</sup> of dogs listed conflicting values for t<sub>1/2</sub> (7 or 15 hours) and bioavailability in 2 dogs with oral formulations that differed from those used in the present study. In that study,<sup>5</sup> bioavailability was improved approximately 4-fold when the medication was administered with food, which is the reason that dogs in the present study were fed immediately before posaconazole administration.

Bioavailability of both the oral suspension and delayed-release tablet was highly variable among the dogs of the present study (Table 2). Analysis of the data revealed that the delayed-release tablet was more bioavailable than was the oral suspension. Although the range of bioavailability was high, it was clearly higher for the delayed-release tablet than for the oral



**Table 2**—Pharmacokinetic parameters after administration of posaconazole formulation as an oral suspension (6 mg/kg) to 6 dogs and as a delayed-release tablet (mean dose, 6.9 mg/kg) to 5 dogs.

| Parameter                            | Oral suspension |             |          | Delayed-release tablet |               |        |
|--------------------------------------|-----------------|-------------|----------|------------------------|---------------|--------|
|                                      | Geometric mean  | Range       | CV (%)   | Geometric mean         | Range         | CV (%) |
| AUC (h•µg/mL)                        | 19.73           | 6.43–75.43  | 119.59   | 130.39                 | 106.81–229.70 | 33.27  |
| C <sub>max</sub> (µg/mL)             | 0.42            | 0.19–0.81   | 55.79    | 1.80                   | 1.15–3.55     | 44.44  |
| K <sub>01</sub> (h <sup>-1</sup> )   | 0.35            | 0.03–0.90   | 205.72   | 0.44                   | 0.07–2.36     | 201.49 |
| K <sub>01</sub> t <sub>1/2</sub> (h) | 1.98            | 0.77–23.16  | 205.72   | 1.57                   | 0.29–9.41     | 201.49 |
| K <sub>10</sub> (h <sup>-1</sup> )   | 0.03            | 0.01–0.05   | 42.13    | 0.02                   | 0.01–0.02     | 24.53  |
| K <sub>10</sub> t <sub>1/2</sub> (h) | 23.92           | 14.18–48.85 | 42.13    | 41.71                  | 31.59–60.54   | 24.53  |
| T <sub>LAG</sub> (h)                 | 0.03            | 0–0.88      | 1,748.99 | 1.80                   | 1.24–2.87     | 33.57  |
| T <sub>max</sub> (h)                 | 7.69            | 4.18–34.28  | 92.17    | 9.48                   | 3.36–25.41    | 85.06  |
| F (%)                                | 26              | 7.8–79.0    | 126      | 159                    | 85–500        | 87     |

K<sub>01</sub> = Absorption rate constant. K<sub>10</sub> = Elimination rate constant. T<sub>LAG</sub> = Lag time for dissolution of oral solution or delayed-release tablets and stomach emptying.

suspension in all dogs (Figure 1). Posaconazole, similar to itraconazole, is extremely insoluble (classified as practically insoluble in water, according to the United States Pharmacopeia definition). High variability in absorption after oral administration is inherent among insoluble medications.

After examination of the pharmacokinetic results for each of the orally administered formulations, it was apparent that better antifungal exposure would be possible with administration of the delayed-release tablets to dogs. On the basis of the mean pharmacokinetic values obtained for the delayed-release tablet, a dosing simulation<sup>1</sup> at 5 mg/kg every other day for 14 days indicated that a trough plasma concentration would be maintained above the suggested<sup>12,13</sup> therapeutic target of 1 µg/mL throughout a course of treatment. Thus, the plasma concentration profile in dogs for delayed-release tablets met pharmacokinetic-pharmacodynamic targets established for humans<sup>12,13</sup> and thus may result in successful therapeutic treatment of susceptible organisms if administered to dogs at a dosage of 5 mg/kg every 48 hours. Most organisms susceptible to posaconazole have a minimum inhibitory concentration at which 90% of organisms are inhibited (ie, MIC<sub>90</sub>) < 1.0 µg/mL<sup>2,14</sup>. Additional studies and clinical trials would be required to determine whether administration at this dosage would result in therapeutic concentrations sufficient to treat fungal infections in dogs. Other studies would also be needed to determine optimal dosage regimens in dogs for the IV solution and oral suspension.

Bioavailability of the delayed-release tablet was > 100% for 4 of 5 dogs. Ordinarily, this is not possible,<sup>15</sup> but it is often observed with slow-release or delayed-release formulations in which the t<sub>1/2</sub> is influenced by the rate of absorption rather than the rate of elimination (flip-flop effect). But the rate of absorption did not differ substantially between the oral suspension and delayed-release tablet (Table 2). Results of a deconvolution analysis<sup>1</sup> (data not shown) also indicated a rapid release of each formulation in the canine intestines,

which rendered a flip-flop effect to be less likely. Calculation of bioavailability assumes equal clearance for the IV and oral formulations. In the present study, the t<sub>1/2</sub> for the delayed-release tablet (42 hours) was much longer than that for the oral suspension (24 hours) or IV solution (21 hours). Half-life is dependent on both clearance and volume of distribution,<sup>16</sup> and either of those parameters (or both) could have differed between the IV solution and delayed-release tablet. If it is assumed that the apparent volume of distribution in a subject is invariant among experiments, then it is possible that differences in clearance between the IV solution and oral delayed-release tablet existed and accounted for the longer t<sub>1/2</sub>. Confirmation of a difference in clearance would require additional studies. Dose-dependent changes in clearance also are possible because the dose for the delayed-release tablet (mean, 6.9 mg/kg) was > 2 times the dose for the IV solution (3 mg/kg).

The present study had some limitations. The dose administration was performed as a crossover experiment involving only 6 dogs. These dogs may not have been representative of the population of dogs treated for fungal infections. Administration of the delayed-release tablet was performed with only 5 of these dogs (1 dog was unavailable), and it was not performed as a crossover experiment with the other 2 treatments. This portion of the study was added later because delayed-release tablets were not available at the time of the initial evaluations of the IV solution and oral suspension. Equal clearance and lack of a period effect were assumed for the delayed-release tablet portion of the study. The dogs were maintained in the same environment and on the same feeding regimen throughout both experiments. The sample collection time was extended for the second experiment on the basis of half-life estimates obtained for the initial crossover experiment. Nevertheless, the assumption of consistent clearance and lack of a period effect may not have been correct.

Another limitation was the duration of sample collection. The study was originally designed with an

assumption that the half-life for the IV solution and oral suspension would be less in dogs than in humans. Thus, the sample collection period for the initial experiment did not provide at least 3 times the estimated half-life, which is the preferred method.<sup>16</sup>

In the present study, pharmacokinetic data were determined after administration of the IV solution, oral suspension, and delayed-release tablet formulations of posaconazole to dogs. Detailed pharmacokinetic data for dogs of previous studies<sup>3,5</sup> have not been published or they are incomplete. Analysis of the results reported here indicated a longer  $t_{1/2}$  than that reported for other oral formulations of azole antifungal drugs in dogs, which may allow for more convenient dosing than previously reported for other orally administered azole antifungal agents.<sup>1</sup> Posaconazole is more active against a broad spectrum of fungi than are other currently available antifungal drugs, which also makes this drug an attractive candidate for further study in dogs. The pharmacokinetic results reported here may allow for the generation of dosage regimens for the IV solution and oral suspension of posaconazole in dogs. Administration of the delayed-release tablet resulted in a longer  $t_{1/2}$  and better oral bioavailability in dogs, compared with results for the oral suspension. To achieve therapeutic pharmacokinetic-pharmacodynamic targets in dogs, administration of the delayed-release tablet at a dosage of 5 mg/kg every 48 hours may be considered for future studies.

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## Footnotes

- a. Iams ProActive Health Adult MiniChunks, Iams Pet Food, Mason, Ohio.
- b. Noxafil injectable (18 mg/mL), Schering-Plough (Brinny) Co, Brinny, Innishannon, County Cork, Ireland.
- c. Noxafil oral suspension (40 mg/mL), Patheon Inc, Whitby, ON, Canada.
- d. Hill's Science Diet, Adult Gourmet Chicken Entrée, Hill's Pet Nutrition Inc, Topeka, Kan.
- e. Noxafil delayed-release tablet, 100 mg, NV Organon, Oss, The Netherlands.
- f. Agilent 1100 series solvent delivery system, Agilent Technologies, Santa Clara, Calif.
- g. Agilent 1100 series autosampler, Agilent Technologies, Santa Clara, Calif.

- h. Agilent 1100 series variable wavelength detector, Agilent Technologies, Santa Clara, Calif.
- i. Agilent OpenLAB software, Agilent Technologies, Santa Clara, Calif.
- j. Zorbax SB C8 column, Agilent Technologies, Santa Clara, Calif.
- k. Posaconazole analytical reference standard, Sigma-Aldrich Corp, St Louis, Mo.
- l. Phoenix software, version 6.3, Pharsight Certara Co, St Louis, Mo.
- m. Centrifree micropartition device, Amicon Millipore, Billerica, Mass.

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