Pharmacokinetics of cetirizine in healthy cats

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Objective—To develop a high-performance liquid chromatography (HPLC) assay for cetirizine in feline plasma and determine the pharmacokinetics of cetirizine in healthy cats after oral administration of a single dose (5 mg) of cetirizine dihydrochloride.

Animals—9 healthy cats.

Procedures—Heparinized blood samples were collected prior to and 0.5, 1, 2, 4, 6, 8, 10, and 24 hours after oral administration of 5 mg of cetirizine dihydrochloride to each cat (dosage range, 0.6 to 1.4 mg/kg). Plasma was harvested and analyzed by reverse-phase HPLC. Plasma concentrations of cetirizine were analyzed with a compartmental pharmacokinetic model. Protein binding was measured by ultrafiltration with a microcentrifugation system.

Results—No adverse effects were detected after drug administration in the cats. Mean ± SD terminal half-life was 10.06 ± 4.06 hours, and mean peak plasma concentration was 3.3 ± 1.55 µg/mL. Mean volume of distribution and clearance (per fraction absorbed) were 0.24 ± 0.09 L/kg and 0.30 ± 0.09 mL/kg/min, respectively. Mean plasma concentrations were approximately 2.0 µg/mL or higher for 10 hours and were maintained at >0.72 µg/mL for 24 hours. Protein binding was approximately 88%.

Conclusions and Clinical Relevance—A single dose of cetirizine dihydrochloride (approx 1 mg/kg, which corresponded to approximately 0.87 mg of cetirizine base/kg) was administered orally to cats. It was tolerated well and maintained plasma concentrations higher than those considered effective in humans for 24 hours after dosing. The half-life of cetirizine in cats is compatible with once-daily dosing, and the extent of protein binding is high. (Am J Vet Res 2008;69:670–674)

Cats commonly develop allergies affecting the skin, respiratory system, and gastrointestinal tract. Clinical signs of allergic disease can range from mild and irritating (eg, pruritus in atopic dermatitis) to severe and life-threatening (eg, bronchoconstriction in asthma). Although glucocorticoids are effective for the treatment of animals with allergic disease, high-dose or long-term administration has been associated with adverse drug events. Additionally, glucocorticoids may be relatively contraindicated in cats with diabetes mellitus, infectious disease, and certain types of heart disease; therefore, alternative treatments should be explored. In humans, second-generation antihistamines, such as cetirizine, have provided relief to patients that had various allergic symptoms with fewer adverse effects, compared with results for patients administered first-generation antihistamines.1

Cetirizine, the active metabolite of hydroxyzine, is a potent second-generation H1 receptor antagonist.2,3 It is considered a second-generation antihistamine because, in contrast to earlier antihistamines, it does not cause sedation in people. Hydroxyzine, the parent drug of cetirizine, results in considerably more sedative effects. In dogs, practically all of an administered dose of hydroxyzine is converted to the active drug cetirizine after IV or oral administration.4 In those same dogs, the pharmacodynamic effects (suppression of histamine) were attributed to cetirizine concentrations, rather than to the effects of hydroxyzine.4 Even though cetirizine

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and hydroxyzine have similar structural and H1 receptor binding characteristics, concentrations in the brain differ. Because cetirizine is a substrate for the efflux protein (ie, p-glycoprotein), it does not accumulate in the CNS to cause sedation. Even though histamine is only one of many components in the allergic cascade, antihistamine block of the H1 receptor has been used successfully to minimize the clinical signs of many allergic diseases. After histamine is released, it binds to the H1 receptor, inflammatory cells are recruited, vascular permeability and plasma extravasation increase, and smooth muscle constricts, which ultimately lead to clinical signs of an allergy.

Instead of blocking histamine receptors, antihistamines act as inverse agonists, which stabilize the inactive form of the H1 receptor and shift activity toward an inactive state. Antihistamines have been advocated for use in humans with urticaria, atopic dermatitis, allergic rhinitis, and mild asthma. The improvement in clinical signs can be attributed to antihistamine effects and anti-inflammatory effects independent of blocking of the H1 receptor. Additional anti-inflammatory effects may include attenuation of inflammatory cell migration, inhibition of inflammatory mediator release, and inhibition of expression of adhesion molecules. Because of the success of this drug in human medicine, cetirizine may be a viable alternative to glucocorticoid use in cats with allergic disease.

Although there is anecdotal information about the use of cetirizine in cats, the authors are not aware of published pharmacokinetic studies of this drug in cats, and an appropriate dose for oral administration has not been established by the use of scientific methods. Before clinical studies can be evaluated in cats, the pharmacokinetics (particularly characteristics of oral absorption) require investigation. There is no formulation available for IV administration; therefore, the study reported here was limited to oral administration. Several methods have been developed for detection of cetirizine in human plasma, including gas chromatography, thin-layer chromatography with radiolabeled methods, and HPLC with UV and mass spectrometric detection.

The HPLC method is rapid, allows multiple samples to be assayed in a short amount of time, uses an extraction technique that can be performed in most laboratory settings, and allows detection of low concentrations of cetirizine in plasma. The objective of the study reported here was to develop and validate an HPLC method of measuring cetirizine in feline plasma and to characterize the pharmacokinetic characteristics of cetirizine in cats after oral administration of a single dose. Plasma protein binding is high (93%) in humans, and only the unbound fraction is active. Therefore, an additional objective was to determine the protein binding of cetirizine in feline plasma. We hypothesized that in healthy cats, a dose of 5 mg of cetirizine administered orally once daily would yield effective therapeutic plasma concentrations (ie, concentrations in a range reported to be effective for humans).

Materials and Methods

Animals—Nine privately owned, healthy cats were enrolled in the study at the University of Missouri.

Breed included domestic shorthair and Siamese. Three cats were castrated males, 5 cats were spayed females, and 1 cat was a sexually intact male. Mean ± SD age was 6.6 ± 2.8 years (range, 3 to 12 years), and mean body weight was 5.3 ± 1.4 kg (range, 3.7 to 8.5 kg). All owners signed a consent form prior to enrolling their cat in the study. A complete physical examination was performed, and a CBC, serum biochemical analysis, and urinalysis were performed to rule out concurrent disease.

Drug administration—Each cat was orally administered a single tablet (5 mg) of cetirizine dihydrochloride. Cats were monitored for adverse drug reactions during the 24 hours of the study period.

Sample collection—Blood samples (minimum of 1.5 mL) were obtained by jugular venipuncture and added to heparinized tubes, which were immediately placed on ice. Blood samples were collected before (baseline; time 0) and 0.5, 1, 2, 4, 6, 8, 10, and 24 hours after oral administration of cetirizine dihydrochloride. Samples were centrifuged (1,730 × g for 20 minutes) within 1 hour after collection, and plasma was harvested and stored at −20°C until HPLC analysis. Samples were shipped on ice to the Clinical Pharmacology Laboratory at the College of Veterinary Medicine, North Carolina State University.

Drug analysis—Plasma samples were analyzed with HPLC by use of a method developed by the laboratory group of one of the investigators (MGP). A reference standard of cetirizine dihydrochloride was obtained from the drug sponsor. Cetirizine dihydrochloride was dissolved in methanol to create a stock solution (1 mg/mL) of cetirizine base. The stock solution was kept in a tightly sealed vial and protected from light in a refrigerator. The stock solution was further diluted by the addition of distilled water to prepare cetirizine fortifying solutions.

Blank (control) plasma was used to create calibration standards. Cetirizine fortifying solutions were added to blank plasma to generate 9 calibration standards (including a 0 standard) that ranged in concentration from 0.05 to 10 μg/mL. These were used as the calibration standards for the assay. Concentrations were adjusted to account for differences in the molecular weight of cetirizine dihydrochloride (461.8 daltons) and cetirizine base (388.9 daltons). Only cetirizine concentrations were recorded. Blank plasma was analyzed with the calibration standards for the purpose of determining the amount of background noise and to ensure that there were no interfering peaks eluting during the same time as cetirizine.

Mobile phase for the HPLC analysis consisted of distilled water (55%) and acetonitrile (45%). Trifluoroacetic acid (500 μL) was added to each liter of mobile phase to improve shape of the elution peaks. Fresh mobile phase was prepared and degassed for assays on each day.

The HPLC system consisted of a quaternary solvent delivery system (flow rate of 1 mL/min), autosampler, and UV detector at a wavelength of 210 nm. Chromatograms were integrated by use of a computer program. The analytic column was a reverse-phase, 4.6 × 150-
mm C8 column maintained at a constant temperature of 40°C.

All collected plasma samples, calibration samples, and blank (control) plasma samples were prepared in an identical manner: Solid-phase extraction cartridges were conditioned with 1 mL of methanol followed by 1 mL of distilled water. Each plasma sample (500 µL) was added to a conditioned cartridge, followed by a wash step of 1 mL of a solution of distilled water and methanol (95:5). The drug was eluted with 1 mL of 100% methanol and collected in clean glass tubes. Tubes were evaporated under a flow of air at 40°C for 15 minutes to yield a dry residue. Each tube was then reconstituted by the addition of 200 µL of mobile phase, vortexed briefly, and transferred to an HPLC injection vial. Fifty microliters of each sample was then injected into the HPLC system.

Retention time for the peak of interest was 3.5 to 4 minutes. Calibration and blank samples were prepared for assays on each day. All calibration curves were linear with an r² ≥ 0.99. Limit of quantification for cetirizine in feline plasma was 0.05 µg/mL, which was determined from the lowest point on a linear calibration curve that yielded acceptable precision and accuracy. Quality control samples were analyzed concurrently with the incurred and calibration samples. Laboratory procedures were conducted in accordance with guidelines published by the United States Pharmacopeia.

**Pharmacokinetic analysis**—Plasma drug concentrations were plotted on linear and semilogarithmic graphs for visual analysis. Analysis of curves and pharmacokinetic modeling was conducted by use of a commercial pharmacokinetic program. Data for each cat were analyzed with a compartmental model. A weighting factor of 1/(predicted Y)² was used for pharmacokinetic analysis, where Y is the plasma concentration.

Two models (1-compartment vs 2-compartment model) were tested for best fit on the basis of a smaller value for the Akaike's information criterion and visual examination of observed versus predicted concentrations. Examination of the plasma concentration-versus-time curves and goodness-of-fit analyses indicated that the best pharmacokinetic model was a 1-compartment model with first-order input (absorption) and first-order elimination. A lag-time effect was added to account for tablet dissolution and stomach emptying. The general equation for the best-fit 1-compartment model was as follows:

\[
C_t = \frac{(D \times F \times k_{oi})/(Vd \times (k_{oi} - k_{o1})) \times \exp[-k_{o1} \times T] - \exp[-k_{o1} \times T]}{\exp[-k_{o1} \times T]}
\]

where \(C_t\) is the plasma concentration at time T, D is the dose, F is the fraction absorbed for a dose administered by other than the IV route, Vd is the apparent volume of distribution, \(k_{o1}\) is the first-order rate constant for oral absorption, \(k_{oi}\) is the first-order rate constant for drug elimination, and T is time (hours). In this model, it was assumed that \(k_{o1}\) was much greater than \(k_{oi}\) (i.e., there was no first-order effect caused by slow absorption after oral administration). Without an accompanying dose administered IV, this assumption was only speculative. However, because this was an immediate-release formulation, we believed that this assumption was appropriate. Secondary variables were calculated. For example, the AUC from time 0 to infinity was calculated by use of the equation AUC = Dose/(Vd × \(k_{o1}\)).

**Protein binding study**—Pooled plasma from 3 healthy cats was harvested for use in an in vitro protein binding study. Aliquots of plasma were fortified to achieve concentrations of 2 and 4 µg/mL. Three replicates of fortified samples for each concentration were added to a microcentrifugation system. Replicates of 3 spiked samples at each concentration were incubated in a water bath at 37°C for 30 minutes. After adding 1.0 mL of spiked plasma to the microcentrifugation system, the sample tube was centrifuged at 1,000 × g for 10 minutes. A protein-free ultrafiltrate was obtained in the reservoir of the system. The recovered ultrafiltrate was extracted and then analyzed by use of HPLC. Protein binding of each drug was determined in accordance with the following equation:

\[
\text{Percentage of protein binding} = \frac{\text{[total} - \text{unbound}] \times 100}{\text{[total]}}
\]

where total is the concentration of bound and unbound cetirizine in plasma, and unbound is the concentration of free (protein unbound) cetirizine in plasma.

**Results**

No adverse drug effects were detected in any cat after administration of cetirizine or as a result of the blood collections. Each cat received a single dose (5-mg tablet) of cetirizine dihydrochloride. Mean ± SD dosage of cetirizine dihydrochloride was 1.03 ± 0.24 mg/kg, which corresponded to 0.87 ± 0.20 mg of cetirizine base/kg. Cetirizine pharmacokinetics were derived by use of a compartmental analysis with first-order input and 1-compartment distribution.

A 1-compartment model with first-order input and a lag time was fit to the data for all cats, except for 1 cat. For that cat, the first plasma concentration (30 minutes) represented the \(T_{\text{MAX}}\) value, and a simple 1-compartment model with immediate bolus input was used. A value for \(k_{oi}\) or lag time could not be calculated for that cat.

Results were calculated and reported (Table 1; Figure 1). Mean ± SD terminal half-life was 10.06 ± 4.05 hours, and mean \(C_{\text{MAX}}\) was 3.30 ± 1.35 µg/mL. Mean systemic clearance (mL/kg/h)* was 244.80 ± 91.07 mL/h, mean \(k_{o1}\) was 3.58 ± 4.02 h⁻¹, mean \(k_{oi}\) was 0.08 ± 0.03 h⁻¹, mean half-life was 0.83 ± 1.24 h, mean AUC was 50.12 ± 13.04 µg×h/mL, mean \(Vd/F\) was 29.09 ± 26.03 L, mean \(k_{\text{half-life}}\) was 0.77 ± 0.87 h⁻¹, mean \(k_{\text{half-life}}\) was 10.06 ± 4.05 h⁻¹, mean \(T_{\text{MAX}}\) was 3.14 ± 3.33 h, mean \(V_{\text{MAX}}\) was 3.30 ± 1.55 µg/mL.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>CV (%)</th>
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<tr>
<td>Vd/F (mL)</td>
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<td>37.20</td>
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<tr>
<td>(k_{oi}) (h⁻¹)</td>
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<td>(k_{o1}) (h⁻¹)</td>
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<td>Lag time (h)</td>
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<td>AUC (µg×h/mL)</td>
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<tr>
<td>(k_{\text{half-life}}) (h⁻¹)</td>
<td>0.77 ± 0.87</td>
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<tr>
<td>(k_{\text{half-life}}) (h⁻¹)</td>
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<td>Systemic clearance (mL/kg/h)*</td>
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</tr>
<tr>
<td>(T_{\text{MAX}}) (h)</td>
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<td>106.20</td>
</tr>
<tr>
<td>(V_{\text{MAX}}) (µg/mL)</td>
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Mean ± SD dosage for each cat was 0.87 ± 0.20 mg of cetirizine base/kg. Cetirizine pharmacokinetics were derived by use of a compartmental analysis with first-order input and 1-compartment distribution.

*Calculated as drug clearance/F.
Cats had free drug concentrations during the study reported here revealed that in clinically healthy cats, a single orally administered dose (5 mg) of cetirizine dihydrochloride, which is equivalent to a mean ± SD dosage for each cat of 0.87 ± 0.20 mg of cetirizine base/kg. Mean ± SE values are reported for total drug concentrations (bound plus unbound [black circles]), and mean values are reported for the free drug (protein unbound [white circles]) concentrations. There are no error bars for the free drug concentration because these values were calculated from the mean.

Plasma concentrations were approximately 2.0 µg/mL at 10 hours and remained > 0.72 µg/mL for 24 hours. Mean plasma protein binding was 88.6 ± 1.48% at 2 µg/mL and 87.8 ± 1.14% at 4 µg/mL.

**Discussion**

Analysis of results of the study reported here revealed that in clinically healthy cats, a single orally administered dose of 5 mg of cetirizine dihydrochloride (approx 0.87 mg of cetirizine base/kg) was associated with plasma concentrations higher than those considered effective in humans. Because only the free (protein unbound) drug is considered active, protein binding of cetirizine was measured in this study to enable us to calculate free drug concentrations from the total drug concentrations measured by HPLC. Protein binding was approximately 88% and did not differ substantially between the 2 concentrations tested. This amount of protein binding is slightly less than that listed for humans (96%). Cats had free drug concentrations during a 24-hour period that exceeded the effective free drug concentrations after administration of effective doses to humans (19.5 to 27.3 ng/mL). Thus, even with the high degree of protein binding, free drug concentrations remained higher than the range considered therapeutic in humans. To our knowledge, pharmacodynamic studies have not been conducted in cats to determine the minimum effective concentration; therefore, effectiveness of these concentrations in cats should be interpreted cautiously.

Other pharmacokinetic variables measured in the cats of our study were similar to those in reports for humans. The half-life of 10.06 hours in cats is similar to the half-life in humans, which is approximately 11 hours. The T_{MAX} was slightly longer in cats (3.14 hours), compared with the value in humans (1 hour). In humans, the onset of effect is within 20 minutes after dosing in 50% of subjects and within 1 hour after dosing in 95% of subjects. However, the T_{MAX} was highly variable among cats (CV > 100%) and was < 1 hour in 3 cats of our study. A lag time was used in the pharmacokinetic analysis, which had a mean value of 54 minutes; however, this also was highly variable among cats (CV > 130%). These ranges may have reflected variation in dissolution of the tablet in cats, stomach emptying, or both. Rate of absorption (ie, k_{a}) was also variable, with a half-life of 46 minutes and CV > 100%. Delayed dissolution or stomach emptying in some cats may have caused a double peak, with the second peak evident at 4 hours after administration. Collection of samples prior to 30 minutes after administration (Figure 1) and more frequent collection of samples during the first 6 hours after dosing would have allowed us to better characterize absorption patterns.

Mean ± SD values for Vd and clearance (both determined per fraction absorbed) were 0.26 ± 0.09 L/kg and 0.30 ± 0.09 mL/kg/min, respectively, which suggested a small Vd and low clearance when absorption was assumed to be complete (ie, F is approx 1). Without an accompanying IV-administered dose, we could not assess the extent of oral absorption in this study. There is no IV formulation currently available; therefore, such a crossover study was not performed. The only systemic absorption data available for small animals revealed that oral absorption of hydroxyzine (the parent drug of cetirizine) in dogs is 100%, and it is almost completely converted to cetirizine. Cetirizine administered orally to humans is highly absorbed. The peak concentration in cats of the study reported here was nearly 10 times as high as the peak value for humans (3.30 µg/mL vs 0.36 µg/mL, respectively). This difference is understandable because the dosage of cetirizine dihydrochloride used in these cats was approximately 1.0 mg/kg, whereas the dosage used in humans is typically 10 mg/person. Our study did not address pharmacodynamics of cetirizine, and additional studies would be needed to determine the optimum plasma concentration and dose to achieve the desired clinical effects.

Despite total drug concentrations in these cats that were higher than those reported for humans, none of the cats had any adverse effects, including sedation, after oral administration of cetirizine. Although second-generation antihistamines have substantially fewer sedative effects than first-generation antihistamines, cetirizine in humans has a higher incidence of sedation than for the other antihistamines in its class. Limitations to the study reported here included the relatively small number of cats that may not necessarily have been representative of the treatment population. This design also failed to evaluate special populations (ie, cats receiving other medications for allergic diseases, kittens, and geriatric cats). Although cetirizine

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Figure 1—Plasma concentrations of cetirizine on a linear scale (A) and a semilogarithmic scale (B) for 9 cats orally administered a single dose (5 mg) of cetirizine dihydrochloride, which is equivalent to a mean ± SD dosage for each cat of 0.87 ± 0.20 mg of cetirizine base/kg. Mean ± SE values are reported for total drug concentrations (bound plus unbound [black circles]), and mean values are reported for the free drug (protein unbound [white circles]) concentrations. There are no error bars for the free drug concentration because these values were calculated from the mean.
is safe for use in human pediatric and elderly populations, additional studies should be conducted in cats to determine the safety, especially for administration of multiple doses.

To our knowledge, this is the first study in cats that has reported plasma concentrations after an orally administered dose of cetirizine. We also measured protein binding and determined that the free (protein unbound) drug concentrations were higher than those considered effective in humans. Cetirizine has been advocated for use in cats with allergic disease, with anecdotal information indicating doses ranging from 2.5 mg/cat once daily to 10 mg/cat every 12 hours, despite the fact that a dose in adult humans is much lower (10 mg/d). Our study also revealed a long half-life in cats, which is compatible with once-daily dosing. In humans, a similar half-life has been detected, and the therapeutic effects persist for at least 24 hours after dosing. A once-daily regimen for cats may improve owner compliance, compared with compliance for drugs that must be administered more frequently. The low clearance of cetirizine (0.30 ± 0.09 mL/kg/min) likely contributes to the long half-life. The long half-life is probably not caused by a high volume of distribution because the Vd per fraction absorbed (ie, Vd/F) was small (0.24 ± 0.09 L/kg) in the cats of this study.

Cats orally administered a single dose of approximately 1 mg of cetirizine hydrochloride/kg (0.87 mg of cetirizine base/kg) had high plasma concentrations compared with those reported in humans, a long half-life, and lack of detectable adverse effects. Rate of oral absorption was variable among cats. Plasma protein binding was high, but drug concentrations of free (protein unbound) drug were maintained for 24 hours at values higher than those reported to be effective in humans. Although studies evaluating the therapeutic efficacy of this drug in cats with allergic disease need to be performed, as well as multiple-dose pharmacokinetic and safety studies, results of the study reported here revealed that cetirizine may hold promise as a useful alternative to glucocorticoids in cats.

References