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Ciprofloxacin Pharmacokinetics in Clinical Canine Patients

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Background: Ciprofloxacin generic tablets approved for human use frequently are administered to dogs for treatment of bacterial infections because they are inexpensive and readily available. However, previous work indicated low and variable oral absorption in healthy research dogs.

Objective: To examine orally administered ciprofloxacin in a group of clinical canine patients using population pharmacokinetics in order to identify minimum inhibitory concentrations (MIC) that potentially could be achieved with orally administered ciprofloxacin in dogs.

Animals: Thirty-four clinical canine patients; mean weight, 22.95 kg (range, 4.6–57 kg).

Methods: Ciprofloxacin generic tablets intended for human use were administered to dogs in a prospective study (mean dose, 23.5 mg/kg). Sparse blood sampling was used to obtain population pharmacokinetic results with nonlinear mixed-effects modeling. These data were used to estimate a breakpoint for susceptible bacteria. Monte Carlo simulations were used to determine the probability of target attainment (PTA) for an area under the curve (AUC)/MIC ratio of ≥100, the pharmacokinetic-pharmacodynamic target for fluoroquinolones.

Results: The values for volume of distribution, peak concentration, and half-life were 10.7 L/kg (11.7%), 1.9 μg/mL (11.66%), and 4.35 hours (7.62%), respectively (mean, % coefficient of variation [CV]). The size of the dog was an important covariate with larger dogs achieving lower plasma drug concentrations than smaller dogs, despite a similar mg/kg dose. Ninety percent PTA was obtained for a MIC ≤ 0.06 μg/mL.

Conclusions and Clinical Importance: A breakpoint (susceptible) of ≤0.06 μg/mL should be considered when ciprofloxacin tablets are administered to dogs at a dose of 25 mg/kg once daily, which is much lower than the breakpoint of ≤1 μg/mL in humans.

Key words: Antibiotic; Canine; Fluoroquinolone; Nonlinear mixed-effects modeling.

Despite the availability of safe and effective veterinary-labeled fluoroquinolones for dogs (enrofloxacin, marbofloxacin, orbifloxacin), ciprofloxacin oral tablets, available in a generic formulation for people, are increasingly being used for treatment of bacterial infections in dogs. Veterinarians can legally prescribe human-label drugs to nonfood producing animals according to the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994. There is a concern that the frequent use of inexpensive generic ciprofloxacin tablets has been linked to increased antimicrobial resistance.[1] The oral absorption of ciprofloxacin, according to published studies, is variable, inconsistent, and lower in some dogs than in humans. Oral absorption of ciprofloxacin in dogs may approach 74–97%, but has been as low as 42%.[2–5] In a more recent study,[6] the mean oral absorption was 58.4%, but with high variability (coefficient of variation, CV, 45.4%) and a range of oral absorption from 30 to 98%. The variable oral absorption appeared to be caused by incomplete and inconsistent dissolution of the generic oral tablet formulated for use in humans. However, the latter study[6] was conducted in experimental Beagle dogs under controlled conditions. Studies are needed in a larger population of clinical canine patients of various sizes and breeds to derive values for population parameters. The objective of our study was to assess the current ciprofloxacin dosing regimens for likelihood of achieving recommended pharmacokinetic-pharmacodynamic (PK/PD) targets using population pharmacokinetic parameters for generic ciprofloxacin when administered PO to clinical canine patients treated at the veterinary hospital at North Carolina State University.

Abbreviations:

AUC	area under the curve for the plasma drug concentration versus time profile (μg·h/mL)
CL	clearance (L/kg/h)
CLSI	Clinical and Laboratory Standards Institute
C_{MAX}	peak (maximum) plasma drug concentration (μg/mL)
CSC	Clinical Studies Core
CV	coefficient of variation (%)
F	fraction of oral dose absorbed systemically
MCS	Monte Carlo simulations
MIC	minimal inhibitory concentration (μg/mL)
NLME	nonlinear mixed-effects modeling
PK/PD	pharmacokinetic-pharmacodynamic
PTA	probability of target attainment
$T_{1/2}$	half-life (hours)
V	apparent volume of distribution (L/kg)
VPC	visual predictive check

Materials and Methods

Patient Population and Blood Sampling

A prospective population pharmacokinetic study was conducted using nonlinear mixed-effects modeling (NLME). Ciprofloxacin

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intact generic tablets (250, 500, or 750 mg) labeled for use in humans were administered to client-owned clinical canine patients at the North Carolina State University Veterinary Hospital. At the outset, the goal was to recruit from 30 to 50 clinical patients. A recruitment flyer was distributed to the hospital clinical staff to recruit patients. Owners completed a Client Consent Form to allow their dogs to participate in the study. The study protocol was approved by the university's Institutional Animal Care and Use Committee (IACUC) and approved by the hospital. Patients enrolled were those already scheduled to receive ciprofloxacin PO as a component of treatment. Blood samples for ciprofloxacin measurement were collected after the dog had received ciprofloxacin PO for at least 1 day (to ensure that concentrations were at steady state). Patients were excluded if they had intestinal disease that could potentially affect oral absorption or known bleeding disorders. As a requirement of enrollment, ciprofloxacin was administered PO as an intact tablet (without crushing or mixing with food or other vehicles). If dogs vomited after PO administration of the tablet, they were ineligible for further participation in the study.

Sparse sampling was designed so that each dog was scheduled for 4 sample times. Some dogs had only 3 samples if they were discharged from the hospital sooner than anticipated. The sample schedule was designed to optimize time points according to a previously published plasma concentration versus time profile in research dogs.[6] Each dog was assigned a study number, and sampling was conducted according to a schedule that corresponded to the dog's study number. The PO dose was intended to be approximately 25 mg/kg once daily according to our estimates from an earlier study.[6] Because the tablets were to be administered intact, and tablet sizes for humans are limited to 250, 500, or 750 mg, we approximated this dose as close as possible for each dog. The sampling schedule and client contact were conducted by the College of Veterinary Medicine's Clinical Studies Core (CSC) trained personnel. A questionnaire checklist was completed for each patient by the CSC staff. Data recorded and maintained by the CSC staff for each patient included breed, age, sex, condition treated, body condition score, feeding schedule, physical examination findings, and any adverse event associated with drug administration. The clinicopathologic data recorded included a packed cell volume (PCV), and total solids if possible.

Blood samples were collected by venipuncture into heparinized tubes, centrifuged, and processed according to a previous protocol.[6] Samples were stored at −70°C until the drug assay could be performed. The plasma samples were analyzed using high-pressure liquid chromatography (HPLC) using a validated assay from a previous study in our laboratory.[6]

Pharmacokinetic Analysis

Initial pharmacokinetic estimates were obtained using naïve pooled modeling. The initial estimates were entered into a population pharmacokinetic analysis with NLME.[a]

For the PO dose, parameters were calculated using the following formula:

$$C = \frac{K_a \cdot F \cdot D}{V \cdot (K_a - K_e)} \times [e^{-K_e \cdot t} - e^{-K_a \cdot t}]. \quad (1)$$

where C is the plasma concentration, t is time, K_a is the non-IV absorption rate, assuming first-order absorption, K_e is the elimination rate constant, V is the apparent volume of distribution, F is the fraction of drug absorbed, and D is the non-IV dose. Because the extent of oral absorption (F) is not known, the volume of distribution parameter (V) is actually V/F, volume of distribution per fraction absorbed. In this model, it is assumed that $K_a \ggg K_e$ or that there is no "flip-flop" effect caused by slow absorption from the gastrointestinal tract.

Various models and different error structures were tested to determine the best fit base model. The models were parameterized by first-order input (K_a) and elimination (K_e). The model was run with the first-order conditional estimation—extended least squares (FOCE ELS) engine. Final model selection was based on goodness of fit plots, statistical significance between models using twice the negative log likelihood (−2LL), Akaike information criterion (AIC)[7]—a goodness of fit measure based on the log likelihood adjusted for the number of parameters and degrees of freedom in the model, obtained in Phoenix NLME, and CV (CV%) of parameter estimates. Secondary parameter estimates were obtained using standard compartmental equations.[8]

Interindividual (between-subject) variability (variance of a parameter among different subjects) was expressed using an exponential error model according to the equation:

$$P_i = P_{pop} \times \exp^{(\eta iP)}, \quad (2)$$

where P is the parameter of interest for the individual i, P pop is θ (theta), the typical value for the population estimate of the parameter of interest, and ηiP is the η (eta) for the individual and parameter of interest. The η values were assumed to be independent and have a normal distribution with a mean of 0 and variance of ω^2. A multiplicative model was chosen (among additive, log-additive, power, and mixed error models) to describe the residual random variability (ε) of the data for once daily dosing, where ε is the residual intrasubject (within subject) variability with a mean of 0 and a variance of σ^2, according to the equation:

$$Cobs_{ij} = Cpred_{ij} \times (1 + \varepsilon_{ij}) \quad (3)$$

where $Cobs_{ij}$ is the observed concentration for subject i at time j for the individual and $Cpred_{ij}$ is the model predicted concentration for subject i at time j plus the error value (ε_{ij}) adjustment for subject i at time t_j (multiplicative residual error).

Once the final model was obtained for the population, an examination of covariates was performed to determine whether there were factors that may explain the variability in the primary parameters (K_a, K_e, and V/F). The covariates examined were dog weight, dose (mg), and age. Examination of covariate plots indicated that the effect of weight on volume of distribution (V/F) was the most likely of these factors contributing to between-subject variation in the population (Fig 1). The covariate of weight was tested in a simple stepwise approach with forward inclusion and backward elimination. The effects of the covariate on the parameter were evaluated based on improvement in the −2LL (equivalent to the objective function value [OFV] in NONMEM). Results were considered statistically significant if the decrease was significant with a P-value < 0.01. A backward elimination step was used to assess the significance of the covariate, and an increase in the −2LL with a P-value < 0.001. After this covariate was considered significant, the covariate remained in the final model. The predictive accuracy of the final model was tested using the visual predictive check (VPC). The VPC was examined to compare observed quantiles with quantiles predicted by the model.

Pharmacokinetic-Pharmacodynamic Modeling and Monte Carlo Simulation

Clinical antibacterial efficacy of fluoroquinolones is based on the PK-PD parameter of area under the curve/minimum inhibitory concentration (AUC/MIC).[9–11] The AUC is derived from the free (protein unbound) plasma drug concentration versus time profile for a 24-hour interval and expressed as $f\text{AUC}_{24}$/MIC. The protein

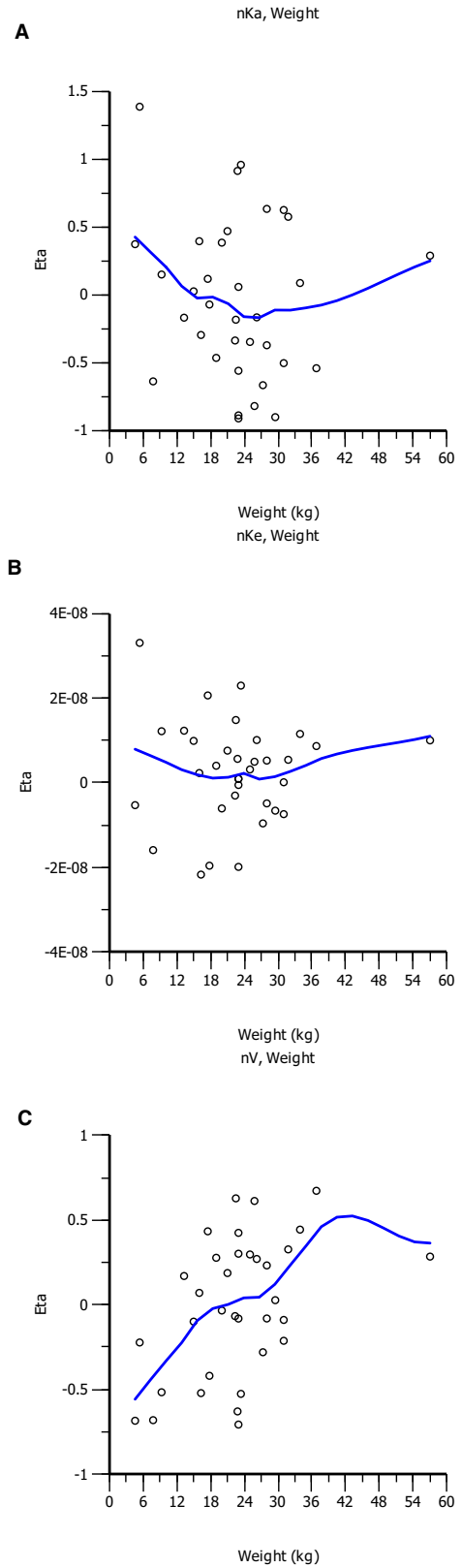

Fig 1. The effect of the covariate (weight) on the intersubject (between-subject) variability. The variability (eta) is shown on the *y*-axis and weight (kg) on the *x*-axis. Effect on rate of absorption (K_a) shown in **A**, effect on elimination rate (K_e) shown in **B**, and effect on volume of distribution (V) shown in **C**.

binding was obtained from an earlier study. Plasma protein binding of ciprofloxacin in dogs has been shown to be 18.48 ± 2.98%.[12] The target of *f*AUC/MIC for fluoroquinolone efficacy is approximately 100, but has ranged from lower values of 72 to as high as 250.[9–11] For this analysis, an AUC/MIC target of 100 was used.

We employed Monte Carlo simulations (MCS) using data from this study to obtain the probability of target attainment (PTA), with the target being *f*AUC/MIC ≥ 100. The values obtained from the population pharmacokinetic analysis, and the target of *f*AUC/MIC > 100 were entered into a forecasting program.[b] Monte Carlo simulations were generated for 1,000 trials. Data entered for forecasting were the values for MIC, clearance (CL)/*F*, dose interval, and dose, as well as protein binding and the variability of the data (standard deviations of the parameters) and were allowed to vary independently in the simulations assuming a log-normal distribution. The MIC values ranged from 0.03 to 16 μg/mL. The ciprofloxacin doses examined were 10, 25, and 50 mg/kg per day PO. A PTA (% certainty) of ≥90% is considered optimal for clinical efficacy.[13]

Results

Thirty-four patients met eligibility criteria for the study. Patient characteristics are shown in Table 1. The pharmacokinetic values obtained for each parameter are shown in Table 2. The population estimate for elimination $T_{1/2}$, AUC, and peak concentration (C_{MAX}) were 4.35 hours, 13.82 μg·h/mL, and 1.19 μg/mL, respectively. The analysis of covariates in the NLME model indicated that body weight (kg) was a significant source of variation in the model that affected the V/F. Other covariates tested were not significant. In the final model, the volume of distribution was a product of 3 factors modified from Equation 2:

$$V/F = \theta V \times (\text{weight}/\text{mean weight})^{\text{dVdWeight}} \times \exp^{(\eta V)} \quad (4)$$

where θV is the typical value of volume of distribution for the population (fixed effect), the value of weight/mean weight is raised to the exponent determined by dVdWeight, and the η (eta) is the random effect to account for interindividual variation. The value of dVdWeight in the model was 0.55 (Table 2) indicating that larger body weight of the dogs resulted in larger estimates for V/F and lower plasma drug concentrations.

The plasma concentration versus time profiles for the dogs are shown in Figure 2 In Figure 2, the spaghetti plots are shown in the left panel (A) for the model fitted to each individual dog. In the right panel, (B) is the population of dogs with the model fitted to the population, accounting for interindividual (between-subject) variability and the effect of covariate (weight, kg) on the model. As seen in Figure 2, the population model in panel B substantially decreases the variation among the curves to obtain an overall population estimate.

Table 1. Patient and dose characteristics (n = 34).

	Weight (kg)	Dose (mg/kg)	Age (Year)
Mean	22.95	23.46	5.89
Std.dev	10.52	4.75	3.41
Min	4.6	11.57	1.0
Max	57.0	33.33	16.0

Table 2. Ciprofloxacin population pharmacokinetics in dogs (n = 34).

Parameter	Estimate	Units	Std Err	CV%
θ K_a	0.39	1/h	0.08	20.28
θ V/F	10.70	L/kg	1.26	11.72
θ K_e	0.16	1/h	0.01	7.62
dVdWeight	0.55		0.13	23.08
T_{MAX}	3.88	hour	0.39	10.08
AUC	13.82	μg·h/mL	1.24	8.98
C_{MAX}	1.19	μg/mL	0.14	11.66
CL/F	1.71	L/kg/h	0.15	8.98
K_a $T_{1/2}$	1.78	hour	0.36	20.28
K_e $T_{1/2}$	4.35	hour	0.33	7.62

θ K_a is the theta (typical value) for absorption rate; K_a $T_{1/2}$ is the associated half-life; θ K_e is the theta for elimination rate; K_e $T_{1/2}$ is the associated half-life; T_{MAX} is the time to peak concentration; C_{MAX} is the peak concentration; CL/F is the systemic clearance per fraction absorbed; θ V/F is the theta for volume of distribution, per fraction absorbed; AUC, area under the curve for the concentration versus time profile; dVdWeight was the effect of the covariate weight on the value of volume of distribution in the model; Std err, standard error, CV%, percent coefficient of variation.

The PTA is shown in Table 3, with corresponding values for % certainty plotted against bacteria MIC (μg/mL) in Figure 3. The probability recommended for clinical efficacy is ≥90%.[13] Figure 3 and Table 3 show that to achieve 90% PTA for an MIC of 0.06 μg/mL, a PO ciprofloxacin dose of 25 mg/kg daily is needed. A dose of 10 mg/kg did not produce a PTA > 90% for any MIC. To reach a PTA of 90% for an MIC of 0.12 μg/mL, a PO ciprofloxacin dose of 50 mg/kg would be necessary.

Discussion

Population Pharmacokinetics

The population estimates obtained here using 34 clinical canine patients were a $T_{1/2}$ of 4.35 hours, a C_{MAX} of 1.19 μg/mL, and AUC of 13.82 μg·h/mL. In a previous study in 6 Beagle dogs using a similar dose,[6] the oral C_{MAX} was 4.4 μg/mL, $T_{1/2}$ 2.6 hours, and AUC 22.5 μg·h/mL. Systemic absorption (F) in that study was 58.4% (CV, 45.4%). These results identify differences that may be observed between healthy research Beagle dogs and a diverse population of canine clinical patients. Similar differences were observed in population pharmacokinetic studies of clinical human patients.[9] The clinical human patients handled PO fluoroquinolones differently than did populations of healthy volunteers.

In another study,[14] ciprofloxacin tablets were administered PO to 5 dogs at a dose similar to that used in our study. The other dogs all were healthy Greyhound research dogs with body weights of 30.4 to 42 kg. The values reported in our study for AUC, $T_{1/2}$, and C_{MAX} were all within the range listed for the dogs in the previous study.[14]

Dosage recommendations in veterinary drug handbooks for administration of ciprofloxacin to dogs have varied from 5 to 15 mg/kg PO q12h to 20 to 25 mg/kg PO once daily. The most recent study in Beagle research dogs[6] concluded that an average dose of 25 mg/kg per day is needed to meet a PK-PD target for an MIC of 0.25 μg/mL. Our study in clinical patients showed that with a PO ciprofloxacin dose of 25 mg/kg, the PK-PD target can be met for bacteria with MIC ≤ 0.06 μg/mL. By contrast, the Clinical and Laboratory Standards

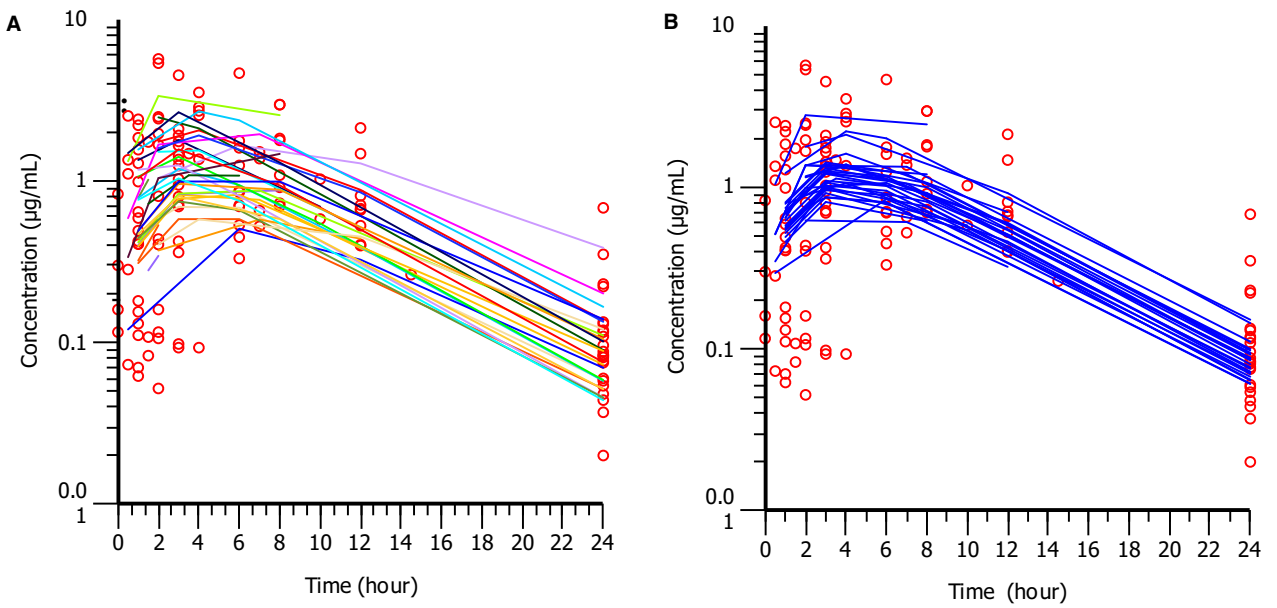

Fig 2. Spaghetti plots for population model fit for ciprofloxacin oral administration in 34 dogs (average dose 23.5 mg/kg). Plot on left (**A**) is individual dogs versus time; plot on right (**B**) is individual dogs fitted to population model to account for individual variation (between-subject) and the covariate of weight. Actual (observed) concentrations are shown with open circles. Each line represents an individual dog. Note the improvement in the model (Panel B) when between-subject variation and covariate are included in the model.

Table 3. Probability of target attainment for ciprofloxacin at an oral dose of 10, 25, and 50 mg/kg administered once daily to dogs. Value in each row is the PTA (% certainty) of attaining a target of AUC/MIC of 100 for the free drug concentration.

Dosage Regimen (Oral)	MIC Values (μg/mL)								
	0.03	0.06	0.12	0.25	0.5	1	2	4	8
10 mg/kg q24h	87.56	47.13	10.16	0	0	0	0	0	0
25 mg/kg q24h	99.54	92.19	63.88	18.09	1.36	0	0	0	0
50 mg/kg q24h	100	99.47	94.24	59.99	16.94	1.54	0	0	0

AUC, area under the curve; MIC, minimum inhibitory concentrations; PTA, probability of target attainment.

Institute (CLSI) susceptible (S) breakpoint for human bacterial isolates is ≤1.0 μg/mL.[15] The CLSI has not established ciprofloxacin interpretive categories (breakpoints) for bacterial isolates from dogs. The CLSI breakpoints are only available for the other FDA-approved fluoroquinolones for dogs.[16]

Based on our results, microbiology laboratories are encouraged *not* to use the ciprofloxacin breakpoint calculated for humans to report susceptibility for bacterial isolates obtained from dogs. The breakpoint of ≤1.0 μg/mL calculated for isolates obtained from humans will greatly overestimate the susceptibility of bacteria isolated from dogs. Based on the data from the MCS presented here, there is essentially a 0% chance that the PK-PD target can be met for bacteria with an MIC of 1.0 μg/mL using a ciprofloxacin dose of 25 mg/kg per day in dogs (Table 3, Fig 3).

The consequence of administering ciprofloxacin PO to dogs is that even high doses of 25 mg/kg (much higher than the dose used in humans on a mg/kg scale) produce high variability and suboptimal antibacterial exposure. As shown by our MCS using the pharmacokinetic data from a population of canine clinical patients, the probability of attaining optimal antibiotic exposure is low, unless the bacteria are highly susceptible with ciprofloxacin MIC ≤ 0.06 μg/mL. Although many bacteria of the Enterobacteriaceae have MICs equal to or below this concentration, the bacteria that cause important resistance problems in dogs such as *Staphylococcus* species and *Pseudomonas aeruginosa* have ciprofloxacin MICs typically >0.06 μg/mL. At a higher MIC of 0.12 μg/mL there is approximately a 64% probability of reaching this target (Table 3). It is possible that suboptimal exposure (i.e., low AUC/MIC ratio) is a contributing factor to the emergence of fluoroquinolone-resistant bacteria isolated from dogs.

The reason for differences between the 34 clinical patients studied in this report and previous studies in dogs is undetermined without further study. The high variation in the clinical patient population in rate and extent of PO absorption contributes to high variability incorporated into the MCS, which greatly decreases the PTA for bacteria with high MICs.

One of the factors (covariates) in the analysis that contributed to variability for the parameter of V/F was the size (weight, kg) of the dogs (Fig 1). Figure 1 shows the relatively normal distribution of weights from dogs in the study. In a previous study,[14] all 5 dogs evaluated were Greyhounds with body weight (30.4–42 kg) at the high end of the range compared to the dogs in our study (Table 1). They did not report F or V/F.

In our final model, the V/F was affected by a factor of (weight/mean weight)$^{0.55}$ (Equation 4, Table 2),

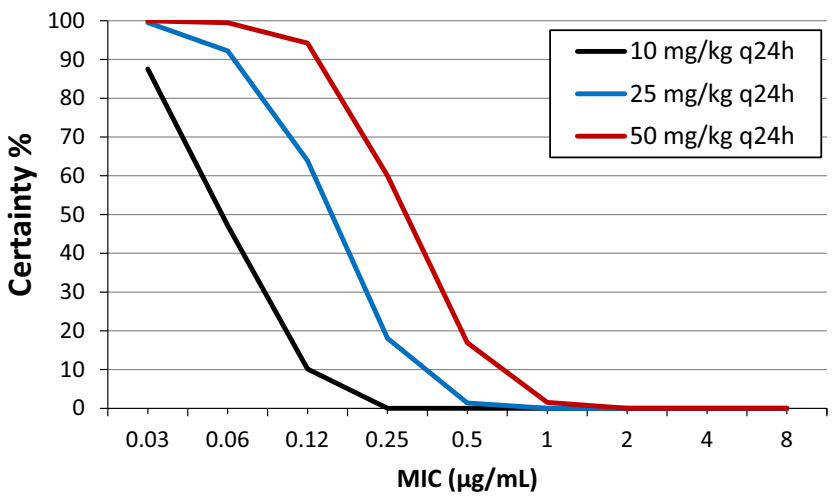

Fig 3. Probability of target attainment (% certainty) based on Monte Carlo simulations of plasma concentration data in dogs for an oral ciprofloxacin dose of 10, 25, and 50 mg/kg administered once daily. MIC are values shown on the *x*-axis. A PTA of at least 90% is associated with clinical efficacy. The target used for this analysis was AUC/MIC of free drug concentration of 100. A dose of 25 mg/kg produces a 90% PTA for a MIC value of 0.06 μg/mL, but a higher dose of 50 mg/kg is needed to attain this PTA for a MIC of 0.12 μg/mL. AUC, area under the curve. MIC, minimum inhibitory concentrations; PTA, probability of target attainment.

indicating that as the body weight for the dogs increased, the V/F increased. Because this is a hybrid parameter, it is not known whether it is F or V that is affected without further study. Regardless of the factor affected, the result of a larger V/F is a correspondingly lower plasma drug concentration. If the average values from an earlier study[14] are used in Equation 4, the value for V/F is indeed higher than the typical value for V/F reported for our study. If larger dogs actually have lower absorption of PO ciprofloxacin tablets compared to lower body weight dogs, this difference may have implications for therapy. One of the reasons why ciprofloxacin frequently is administered to dogs is to decrease the expense of treating large dogs, and larger tablets made for humans can be more convenient than multiple tablets of the veterinary formulations. However, using the tablet formulated for humans may have an unintended consequence of less systemic exposure (AUC) for larger dogs compared to smaller dogs.

Conclusions

A population pharmacokinetic analysis was successfully conducted on 34 client-owned clinical canine patients using NLME. This approach provided population-based estimates that were used for determining the probability of attaining therapeutic targets. Based on our analysis, a 90% PTA for free drug AUC/MIC > 100 was achieved for an MIC ≤0.06 μg/mL after administration of ciprofloxacin tablets in dogs at a dose of 25 mg/kg per day. A lower dose of 10 mg/kg per day did not reach target attainment for any MIC tested.

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Conflict of Interest Declaration: The work from this study has not previously been published. This work was presented at the 2017 ACVIM Forum. The author has no conflicts of interest related to the drug studied in this investigation.

Off-label Antimicrobial Declaration: The antibiotic studied in this investigation was administered in an extra-label manner to dogs.

Footnotes

[a] Phoenix NLME software, Certara, St. Louis, MO.

[b] Crystal Ball software, Oracle, Version 11.1.2.2.000, www.oracle.com/crystalball.

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