Ciprofloxacin pharmacokinetics and oral absorption of generic ciprofloxacin tablets in dogs

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Objective—To determine the pharmacokinetics of ciprofloxacin in dogs, including oral absorption following administration of generic ciprofloxacin tablets.

Animals—6 healthy Beagles.

Procedures—In a crossover study design, ciprofloxacin was administered as a generic tablet (250 mg, PO; mean dose, 23 mg/kg) and solution (10 mg/kg, IV) to 6 dogs. In a separate experiment, 4 of the dogs received ciprofloxacin solution (10 mg/mL) PO via stomach tube (total dose, 250 mg). Blood samples were collected before (time 0) and for 24 hours after each dose. Plasma concentrations were analyzed with high-pressure liquid chromatography. Pharmacokinetic analysis was performed by means of compartmental modeling.

Results—When ciprofloxacin was administered as tablets PO, peak plasma concentration was 4.4 µg/mL (coefficient of variation [CV], 55.9%), terminal half-life ($t_{1/2}$) was 2.6 hours (CV, 10.8%), area under the time-concentration curve was 22.5 µg•h/mL (CV, 62.3%), and systemic absorption was 58.4% (CV, 45.4%). For the dose administered IV, $t_{1/2}$ was 3.7 hours (CV, 52.3%), clearance was 0.588 L/kg/h (CV, 33.9%), and volume of distribution was 2.39 L/kg (CV, 23.7%). After PO administration as a solution versus IV administration, plasma concentrations were more uniform and consistent among dogs, with absorption of 71% (CV, 7.3%), $t_{1/2}$ of 3.1 hours (CV, 18.6%), and peak plasma concentration of 4.67 µg/mL (CV, 17.6%).

Conclusions and Clinical Relevance—Inconsistent oral absorption of ciprofloxacin in some dogs may be formulation dependent and affected by tablet dissolution in the small intestine. Because of the wide range in oral absorption of tablets, the dose needed to reach the pharmacokinetic-pharmacodynamic target concentration in this study ranged from 12 to 52 mg/kg (CV, 102%), with a mean dose of 25 mg/kg, once daily, for bacteria with a minimum inhibitory concentration ≤ 0.25 µg/mL. (*Am J Vet Res* 2012;73:1085–1091)

Four fluoroquinolone antimicrobials have been approved by the US FDA for oral administration in dogs. The drugs have been established as a valuable and effective group of antimicrobials and have been widely prescribed by veterinarians to treat a variety of bacterial infections. However, ciprofloxacin tablets, available in a generic formulation for people, are increasingly being used for treatment of infections in dogs. Veterinarians can legally prescribe drugs labeled for use in humans but not in animals to non–food-producing animals, according to AMDUCA.

Oral absorption of ciprofloxacin in dogs has been evaluated in only a few limited studies. These studies demonstrated more variable and potentially lower oral absorption in dogs than in people. Estimates derived from independent studies[1–3] indicate that oral absorption may approach 74% to 97% in dogs; however, in the only crossover study[4] reported, the oral absorption was only 42%. These absorption values are quite different from the values reported for fluoroquinolones approved for oral use in dogs, which have nearly complete

Abbreviations

AUC	Area under the time-concentration curve
AUC:MIC	Ratio of the area under the time-concentration curve to the minimum inhibitory concentration
BCS	Biopharmaceutics Classification System
Cmax	Maximum (peak) concentration
CV	Coefficient of variation
D_0	Dose number
HPLC	High-pressure liquid chromatography
MIC	Minimum inhibitory concentration
PK-PD	Pharmacokinetic-pharmacodynamic
Tmax	Time to peak concentration
$t_{1/2}$	Terminal half-life (elimination half-life)

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bioavailability.[5] Oral bioavailability of ciprofloxacin in people is approximately 70% but is more variable with larger tablet sizes.[6,7] In 1 study,[6] the investigators attributed this variability in people to the possible influence of gastrointestinal motility or different disintegration or dissolution rates with the larger tablet size.

Oral absorption of ciprofloxacin is also reportedly low in cats and horses.[8,9] When cats receive ciprofloxacin orally, absorption is only 22% to 33%, which would not be effective against many bacteria, even at 10 mg/kg.[8] The author's collaborators previously reported that oral absorption in horses is only 10.5% and that oral administration yielded adverse effects in most of the treated horses.[9]

Because of the potentially low oral availability of ciprofloxacin in dogs, it is possible that doses should be higher than the doses currently used for drugs such as enrofloxacin, marbofloxacin, or orbifloxacin. Dosage recommendations in veterinary drug handbooks for dogs vary from only 5 to 15 mg/kg, PO, every 12 hours[10] to a higher dosage of 20 to 25 mg/kg, PO, every 24 hours.[11] However, there is a possibility that at high doses (ie, > 20 mg/kg/d), oral absorption is compromised because the absorption processes become saturated. The objective of the study reported here was to evaluate oral absorption of ciprofloxacin generic tablets and identify possible factors that may affect oral absorption in dogs.

Materials and Methods

Animals—Six adult Beagles weighing between 8.3 and 14.6 kg (mean, 11.2 kg) were used in the study. Dogs were determined to be healthy on the basis of results of physical examination. They were housed at the North Carolina State University Laboratory Animal Resources facility and fed a maintenance diet. The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee at North Carolina State University.

Study design—The study consisted of 2 experiments. In the first, a 2-period, 2-treatment crossover design was used with at least a 2-day washout period between each treatment. Random number selection was used to assign dogs to the order of treatments. Before each treatment, food was withheld from the dogs for 18 hours. Also 18 hours before treatment, each dog was lightly sedated by the administration of dexmedetomidine hydrochloride[a] (0.02 mg/kg, IV), and a catheter was inserted into a jugular vein. Catheters were flushed with sterile saline (0.9% NaCl) solution to maintain catheter patency.

The orally administered treatment consisted of an intact 250-mg tablet of ciprofloxacin[b] (mean dose, 23 mg/kg), followed by an oral flush with 12 mL of tap water to ensure the tablet was swallowed. The treatment administered IV consisted of ciprofloxacin solution[c] (2 mg/mL) in 5% dextrose that was injected via a cephalic catheter slowly over 5 minutes at a dose of 10 mg/kg (actual mean dose, 9.8 mg/kg).

The second experiment was conducted 1 month after the first. Four dogs were selected for this portion of the study: the 2 with the lowest and the 2 with the highest oral absorption of the ciprofloxacin tablets. Food was withheld from each dog for 18 hours before treatment began, and a jugular catheter was placed as described for the first experiment. For the second experiment, a solution of ciprofloxacin[d] (10 mg/mL) was administered PO to each dog via a stomach tube for a total dose of 250 mg (25 mL)/dog (mean dose, 24 mg/kg). After the solution was administered, 12 mL of tap water was used to flush the residual contents of the tube into the stomach. Food was reintroduced to all dogs 4 hours after each treatment.

Blood collection—The same sample collection protocol was used for each experiment. Blood samples were collected before (time 0) and 0.17, 0.33, 0.67, 1, 1.5, 2, 4, 6, 8, 10, 12, and 24 hours after ciprofloxacin administration and transferred into glass tubes containing lithium heparin (anticoagulant). Blood samples were immediately placed in ice and were later centrifuged at 1,000 × *g* for 10 minutes. Plasma was subsequently separated and stored at –70°C.

HPLC drug analysis—Plasma samples were analyzed via HPLC to determine the concentration of ciprofloxacin by means of a method slightly modified from that reported by the author's research group for enrofloxacin and ciprofloxacin.[12,13] The HPLC system consisted of a quaternary solvent delivery system[e] (flow rate, 1 mL/min), autosampler,[f] and UV detector[g] set at a wavelength of 279 nm. Chromatograms were integrated with a computer program.[h] The analytic column[i] was a reverse-phase C8 column that was maintained at a constant temperature (40°C). The mobile phase consisted of 78% distilled water and 22% acetonitrile. A 0.1% solution of trifluoroacetic acid was added to the mobile phase as a pH modifier.

The reference standard of ciprofloxacin[j] was used to prepare a stock solution, which was used to fortify plasma from untreated dogs (control plasma). Stock solutions were sealed and stored in the dark in a refrigerator. The calibration curve for ciprofloxacin consisted of 8 standard solutions that ranged from 0.05 to 10 µg/mL and included a blank (0 µg/mL) sample. The blank sample was used to detect interfering peaks that eluted into the window of the chromatographic peak of interest and to measure background interference. The calibration curve was accepted if the linear coefficient of determination (R^2) was ≥ 0.99 and if the calibration curve concentrations could be back-calculated to within ≤ 15% of the true concentration of the standard.

All plasma, calibration, quality-control, and blank-plasma samples were prepared in an identical manner. Five hundred microliters of each plasma sample was added to a conditioned solid-phase extraction cartridge.[k] The eluate from the cartridge was collected into a clean glass tube by elution with 1 mL of 100% methanol. The eluted samples were evaporated to yield a dry residue by heating the tubes at 40°C under a flow of air for 20 minutes. The residue in each tube was reconstituted by the addition of 200 µL of the mobile phase; solutions were briefly mixed with a vortex device and transferred to an HPLC injection vial. Forty microliters of each sample was used for injection into the HPLC system.

Retention time for ciprofloxacin was 3.9 to 4.1 minutes. Fresh calibration and blank samples were pre-

pared for analysis each day. The limit of quantification for the drug in canine plasma was 0.05 µg/mL, which was determined from the lowest point on a linear calibration curve that yielded an acceptable accuracy. Laboratory procedures were conducted in accordance with published guidelines.[14]

Pharmacokinetic analysis—Plasma drug concentrations were plotted on linear and semilogarithmic graphs for analysis and visual assessment of the best model for pharmacokinetic analysis. Analysis of curves and pharmacokinetic modeling were then performed with the aid of a commercial pharmacokinetic program.[l] Compartmental analysis was performed with a weighting factor of 1/(predicted Y)^2, where Y is the plasma concentration. The specific model (eg, 1, 2, or more compartments) was determined for best fit on the basis of a smaller value for the Akaike information criterion[15] and visual inspection of residual plots. The general form for the equation for the compartment analysis was as follows:

$$C = A_n e^{-\lambda nt}$$

where C is the plasma concentration, A_n is the y-axis intercept, e is the base of the natural logarithm, n is the number of compartments, t is time after dose administration, and λn is the rate constant. For the 2-compartment, biexponential analysis used for the data on IV administration, the corresponding equation was as follows:

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where C is the plasma drug concentration at time t, A and B are the y-axis intercepts for the distribution and elimination phases of the curve, respectively, and α and β are the slopes of the distribution and elimination phases of the curve, respectively. The $t_{1/2}$ was estimated from the following relationship: $t_{1/2}$ = ln 0.5/ β. Other compartmental pharmacokinetic parameters were calculated according to formulae described elsewhere.[16]

For the data on oral administration, parameters were calculated by means of the following formula:

$$C = (k_{01} \bullet F \bullet D/V[k_{01} - K_{10}]) \times (e^{-k_{10}t} - e^{-k_{01}t})$$

where C is the plasma concentration; t is time; k_{01} is the non-IV absorption rate, assuming first-order absorption; k_{10} 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. In this model, it is assumed that k_{01} is much greater than k_{10} or that there is no flip-flop effect caused by slow absorption from the gastrointestinal tract. A lag time was added to the model to account for dissolution of the tablet and stomach emptying (mean lag time, 0.33 hours). Secondary parameters from the model included the Cmax, time to Cmax, AUC, and the respective absorption and $t_{1/2}$. Systemic availability from a non-IV dose was calculated from the following formula:

$$F = (AUC_{ORAL}/AUC_{IV}) \times (DOSE_{IV}/DOSE_{ORAL}) \times 100$$

where F is systemic availability, AUC_{ORAL} is the AUC for the dose administered PO, AUC_{IV} is AUC for dose administered IV, $DOSE_{IV}$ is the dose administered IV, and $DOSE_{ORAL}$ is the dose administered PO.

Deconvolution analysis[l,m] was used to evaluate the in vivo drug release and delivery from the input obtained from the pharmacokinetic analysis. A unit impulse response function was first obtained from the initial pharmacokinetic analysis. The unit impulse response function provides exact linkage between drug concentration response (plasma concentration) and the input rate function. The drug appearance from each of the orally administered doses was evaluated to obtain input response rates. Pharmacokinetic data are reported here as geometric mean and corresponding CV.

Results

Animals—The orally administered ciprofloxacin dose was well tolerated by all dogs. In contrast, the dose administered IV resulted in transient vomiting and signs of depression in some dogs.

Pharmacokinetics—Plasma concentrations of ciprofloxacin for all 6 dogs that received the ciprofloxacin tablet and IV solution were graphically displayed (**Figure 1**). After oral administration of the intact tablet, the Cmax was 4.4 µg/mL (CV, 55.9%), terminal $t_{1/2}$ was 2.6 hours (CV, 10.8%), AUC was 22.5 µg•h/mL (CV, 62.3%), and systemic absorption was 58.4% (CV, 45.4%; **Table 1**). After IV administration, the elimination $t_{1/2}$ was 3.7 hours (CV, 52.3%), systemic clearance was 0.587 L/kg/h (CV, 33.9%), and apparent volume of distribution at steady state was 2.39 L/kg (CV, 23.7%).

After the pharmacokinetic results from the orally administered dose were examined, it was apparent that following oral administration, ciprofloxacin was absorbed well (approx 80%) in some dogs but poorly (approx 32%) in others (**Table 2; Figure 2**). To explore the factors that may have affected oral absorption, 2 high-absorber dogs and 2 low-absorber dogs were administered an additional dose as a 10 mg/mL solution (total dose, 250 mg) via gastric tube. After oral administration of the solution, plasma concentrations were more uniform and consistent among dogs (**Figure 3; Table 3**). The Tmax was faster after solution administration,

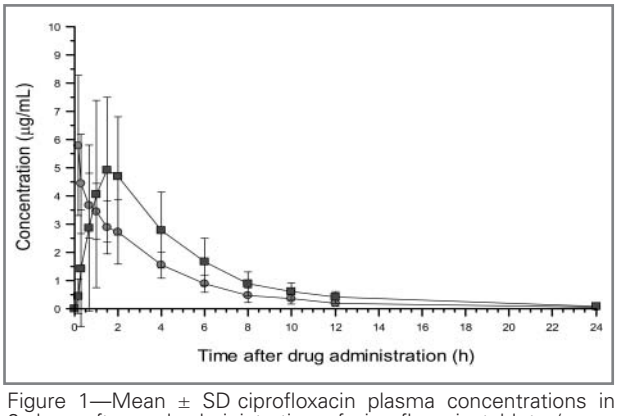

Figure 1—Mean ± SD ciprofloxacin plasma concentrations in 6 dogs after oral administration of ciprofloxacin tablets (mean dose, 23 mg/kg; squares) or IV administration of ciprofloxacin solution (10 mg/kg; circles).

compared with the Tmax for tablet administration, indicating that there was a lag time needed for dissolution of tablets. Absorption of the ciprofloxacin solution was

Table 1—Pharmacokinetic values for ciprofloxacin after IV administration at 10 mg/kg to 6 dogs.

Parameter	Geometric mean	CV (%)
A (μg/mL)	4.61	34.23
α (1/h)	0.77	129.35
α $t_{1/2}$ (h)	0.90	129.35
AUC (h•μg/mL)	16.67	35.87
B (μg/mL)	0.82	495.24
β (1/h)	0.19	52.33
β $t_{1/2}$ (h)	3.72	52.33
CL (mL/h/kg)	587.60	33.88
K_{10} (1/h)	0.33	32.13
K_{12} (1/h)	0.20	343.49
K_{21} (1/h)	0.19	574.08
Mean residence time (h)	7.93	214.70
V_{SS} (mL/kg)	2,389.76	23.67

A = Distribution intercept. α = Distribution rate constant. B = Elimination phase intercept. β = Elimination rate constant. CL = Systemic drug clearance. k_{10}, k_{12}, and k_{21} = Microdistribution rate constants. V_{SS} = Apparent volume of distribution at steady state.

Table 2—Pharmacokinetic values for ciprofloxacin after oral administration of a 250-mg tablet (mean dose, 23 mg/kg) to 6 dogs and of a solution (250 mg; mean dose, 24 mg/kg) to 4 dogs.

	Tablet		Solution	
Parameter	Geometric mean	CV (%)	Geometric mean	CV (%)
AUC (h•μg/mL)	22.50	62.28	24.76	19.78
Cmax (μg/mL)	4.44	55.92	4.67	17.60
k_{01} (1/h)	2.25	63.59	4.14	56.61
k_{01} $t_{1/2}$ (h)	0.31	63.59	0.17	56.61
k_{10} (1/h)	0.27	10.78	0.23	18.61
k_{10} $t_{1/2}$ (h)	2.59	10.78	3.06	18.61
t_{LAG} (h)	0.33	103.64	0.05	39.55
Tmax (h)	1.46	41.00	0.80	28.27
F (%)	58.36	45.36	70.68	7.31

F = Fraction of dose absorbed systemically. k_{01} = Absorption rate. k_{10} = Elimination rate. t_{LAG} = Lag time for tablet dissolution and stomach emptying.

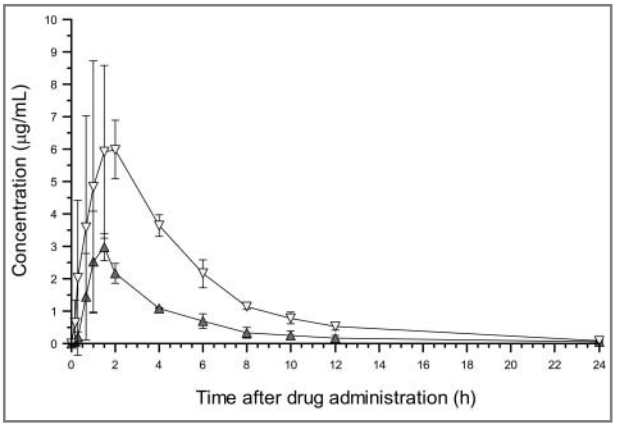

Figure 2—Mean ± SD plasma ciprofloxacin plasma concentrations after oral administration of ciprofloxacin tablets (mean dose, 23 mg/kg) in 4 dogs with a mean percentage absorption of 83% (downward triangles) and in 2 dogs with a mean percentage absorption of 31% (upward triangles).

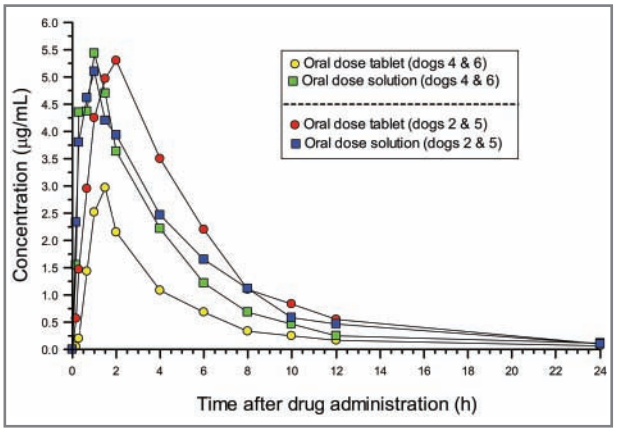

Figure 3—Mean plasma ciprofloxacin concentrations in dogs after a repeated study. Two dogs were high absorbers when orally administered tablets. The other 2 dogs were low absorbers when orally administered tablets. In each dog, oral administration of an identical dose of solution was then repeated.

71% (CV, 7.3%), with a $t_{1/2}$ of 3.1 (CV, 18.6%) hours and Cmax of 4.67 μg/mL (CV, 17.6%).

Deconvolution analysis of both orally administered dose formulations (tablet and solution) showed a variable input response rate among dogs, ranging from 3.5 to 16 mg/kg/h. The fitted curves (not shown) revealed almost exact fits of observed versus predicted absorption profiles for each dog via deconvolution analysis. However, the highest rate of drug absorption (input) occurred primarily within the first 1 to 1.5 hours after each orally administered dose. Regardless of the formulation (solution or tablet), little drug absorption occurred > 2 hours after administration.

Discussion

The results of the present study indicated that among a small group of Beagles, inconsistent oral absorption of ciprofloxacin may be formulation dependent and affected by tablet dissolution in the small intestine. The oral absorption of generic ciprofloxacin tablets in these dogs ranged from 29% to 98%, and even at a high oral dose of 20 to 30 mg/kg, the AUC was insufficient to meet PK-PD targets for bacteria that are considered susceptible according to Clinical and Laboratory Standards Institute interpretive criteria. The failure to reach therapeutic PK-PD targets (defined by the AUC:MIC for fluoroquinolones) may result in therapeutic failure and increased selection for resistant bacteria, particularly when low doses are recommended.[10] High variability in oral absorption of ciprofloxacin may be responsible for the discordant results achieved in previous studies.[1–4]

Recent evidence suggests the emergence of multidrug resistance, including fluoroquinolone resistance, in bacteria isolated from dogs.[17] Although it cannot be established with certainty that this emergence was caused by increased availability and use of inexpensive ciprofloxacin in dogs, that possibility exists. In human medicine, there is evidence that after the introduction of generic ciprofloxacin to the market, a significant increase in the total oral consumption ciprofloxacin was observed in some countries.[18] The increase in consumption was significantly correlated with ciprofloxa-

cin resistance in *Escherichia coli* isolated from people with urinary tract infections.

The dose used for oral administration in the present study was well tolerated by the dogs, but the dose administered IV resulted in transient vomiting and signs of depression in some dogs. The dose administered IV was given more rapidly (over 5 minutes) than is recommended for humans (60-minute infusion). It is not known whether the adverse effects were caused by the medication or other ingredients in the infusion. The solution contains ciprofloxacin (2 mg/mL), 5% dextrose, lactic acid added as a solubilizing agent, and hydrochloric acid for pH adjustment (to a range of 3.5 to 4.6).

An additional experiment that included oral administration of a ciprofloxacin solution was not in the original study plan. However, when the pharmacokinetic results from the orally administered ciprofloxacin tablet were examined, it was apparent that ciprofloxacin was absorbed well orally (approx 80%) in some dogs but poorly (approx 32%) in others. Because all dogs in the study were Beagles of uniform weight that had identical diet and housing conditions, the reasons for the observed variability are unknown. Food ingestion was ruled out because food was withheld from all dogs for at least 18 hours prior to the study. Eighteen hours should have been enough time for stomach emptying of a meal.[19] Although the 2 dogs with poorest absorption rates were female dogs and the other dogs were male, sex is unlikely to have affected oral absorption. Oral administration of ciprofloxacin in people reportedly results in higher drug concentrations in females than in males,[20] not lower concentrations as observed in the present study.

After oral administration of the solution, the plasma ciprofloxacin concentrations were more uniform and consistent among dogs. Oral absorption of the ciprofloxacin solution was 71%, with little variation among dogs (CV, 7%). The Cmax was also more uniform (mean, 4.67 µg/mL [CV, 17.6%]). Therefore, it appears that inconsistent oral absorption of ciprofloxacin in some dogs may be formulation dependent and affected by tablet dissolution in the canine small intestine.

The dose that was administered orally as a solution plus a 12-mL flush (total, 37 mL) resulted in more total volume of liquid administered in this portion of the study, compared with the tablet, with which only 12 mL of water was administered. Ciprofloxacin is classified as a highly soluble drug according to BCS criteria.[21] However, this is on the basis of solubility in humans, in which tablet solubility is calculated from a volume of 250 mL of fluid. Solubility of ciprofloxacin is approximately 10 mg/mL. For even the largest sized tablet in humans (750 mg), this still amounts to a D_0 of 0.3.[21] A $D_0 < 1.0$ is considered highly soluble.[21]

Clearly, a different situation exists in dogs because 250 mL of fluid is not present in the stomach of small Beagles. With a water volume of 12 mL used for oral flushing of the tablet, the calculated D_0 for ciprofloxacin in dogs of the present study is 2.08 (much larger than the value for people), which would deem ciprofloxacin tablets in dogs as poorly soluble.[21] However, when the ciprofloxacin solution was administered orally, it was dissolved in a much larger volume of water (37 mL). The D_0 calculated for this volume was 0.68, which would deem the ciprofloxacin solution as highly soluble in dogs. The solution (obtained from a vial typically used for IV use) also has excipients that maximize the solubility, in addition to the added volume administered. Although the additional volume may have changed the drug solubility, it should not have changed the stomach emptying rate because the drug was dissolved in solution and there was no solid material present in the stomach to slow stomach emptying.[19] The stomach emptying rate in the study dogs that received the solution was obviously more rapid, compared with that when dogs received the tablet, as observed with the earlier Tmax for the ciprofloxacin solution.

The volume of 12 mL was used as a flush to mimic protocols for drug administration in other experimental studies (12 mL is a standard plastic syringe size). However, compared with the situation when pets are given tablets orally at home, this volume is probably the best-case scenario. Realistically, the volume of water given with tablets by pet owners at home is likely to be lower, leading to even poorer solubility and higher variability than observed in the present experiment.

A potential saturation of oral absorption with increasing ciprofloxacin doses was observed in a previous study.[22] When dogs in that study received ciprofloxacin doses of 200 or 30 mg/kg, PO, there was only a 1.9- (day 1) or 1.5-fold (day 5) increase in plasma concentrations, despite a 6.67-fold increase in dose. Although ciprofloxacin is classified by the BCS as a class III drug (highly soluble but poorly permeable),[21] it is possible for a drug with poor permeability to have high bioavailability if it relies on uptake transporters for intestinal absorption.[23] This seems likely, considering that ciprofloxacin is less lipophilic than other fluoroquinolones.[24]

Ciprofloxacin is also classified as a class IV drug according to a modification of the BCS called the biopharmaceutics drug disposition classification system described by Wu and Benet,[25] which means that intestinal absorption is likely to be aided by an intestinal uptake transporter. Such a specific uptake transporter has not been identified in dogs, but the existence of intestinal transporters for ciprofloxacin in laboratory animals[26] raises this possibility. If such transporters are needed for uptake of orally administered drugs in the intestine of dogs, then they would likely be present in the proximal portion of the small intestine. Therefore, if a tablet does not dissolve completely after leaving the stomach in dogs, it is possible to bypass this region, which may result in low oral absorption. Dissolution of the ciprofloxacin formulation as a factor determining oral absorption was explored in this investigation by repeating the experiment in some of these dogs with a solution administered orally. This resulted in consistent absorption among dogs and almost 2-fold higher absorption rates in the dogs that originally had the lowest tablet absorption rates.

Results of deconvolution analysis in the present study support the possibility of early absorption of ciprofloxacin in the proximal portion of the small intestine in dogs. Deconvolution analysis can be used to evaluate drug release and drug absorption from orally admin-

istered drug formulations. The unit impulse response function obtained from results of IV ciprofloxacin administration was used to determine the input response rates from oral administration. This function showed that the highest absorption rates occurred early after oral administration of both the tablet and solution, primarily occurring within the first hour. Two hours after oral drug administration, the input rate was low or negligible. This supports the concept that if the oral tablet does not undergo dissolution soon after oral administration, then systemic absorption can be low because of the small extent of absorption that occurs in the distal portions of the intestine.

The availability of inexpensive generic ciprofloxacin tablets formulated for use in humans combined with the poor oral systemic availability increases the risk that animals given these tablets may receive inadequate antimicrobial exposure, which may increase the emergence of bacterial resistance. The variable oral absorption in the dogs in the present study illustrates the difficulty of determining an effective dose for oral administration of ciprofloxacin tablets. In the present study, an AUC:MIC of 100 was used as the PK-PD target, which is in the range that has been advocated by others for fluoroquinolone administration.[27–30] Because of the variability in oral tablet absorption, achievement of a target AUC:MIC of 100 (MIC ≤ 0.25 μg/mL) would require that dogs be given a dose between 12 and 52 mg/kg (CV, 102%), with a mean dose of 25 mg/kg once daily. Obviously, some dogs may achieve an AUC:MIC lower than the therapeutic target, and other dogs may achieve a higher AUC:MIC when this mean dose is used in clinical situations. In addition, some bacteria may have a higher MIC because the Clinical and Laboratory Standards Institute breakpoint for susceptible bacteria is ≤ 1 μg/mL, which would require administration of an even higher dose to achieve inhibition. These observations assume a PK-PD target of an AUC:MIC of 100. There is also support for even higher ciprofloxacin AUC:MIC for the treatment of some infections.[31] Clearly, a clinical PK-PD study including a larger portion of dogs of both sexes and of various breeds, sizes, and ages is needed.

a. Dexdomitor, 0.5 mg/mL, Pfizer Animal Health, New York, NY.
b. Ciprofloxacin, 250-mg generic tablets, UDL Laboratories Inc, Rockford, Ill.
c. Ciprofloxacin injection, 2 mg/mL in 5% dextrose, Sagent Pharmaceuticals Inc, Schaumburg, Ill.
d. Ciprofloxacin injection, 10 mg/mL, Hospira Inc, Lake Forest, Ill.
e. Agilent 1100 Series solvent delivery system, Agilent Technologies Inc, Wilmington, Del.
f. Agilent 1100 Series autosampler, Agilent Technologies, Wilmington, Del.
g. Agilent 1100 Series Variable Wavelength Detector, Agilent Technologies Inc, Wilmington, Del.
h. Agilent 1100 Series Chemstation 2D software, Agilent Technologies Inc, Wilmington, Del.
i. Agilent Zorbax Rx C8 column, Agilent Technologies Inc, Wilmington, Del.
j. Ciprofloxacin analytic reference standard, United States Pharmacopeial Convention, Rockville, Md.
k. Solid-phase extraction cartridges, Oasis HLB (1 mL), Waters Corp, Milford, Mass.
l. Phoenix software, version 6.0, Pharsight Corp, Mountain View, Calif.
m. QWERT: a convolution/deconvolution software package for the personal computer, 1994 version, SI-Computing, Uppsala, Sweden.

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Correction: Detection of heartworm infection in dogs via PCR amplification and electrospray ionization mass spectrometry of nucleic acid extracts from whole blood samples

In the report "Detection of heartworm infection in dogs via PCR amplification and electrospray ionization mass spectrometry of nucleic acid extracts from whole blood samples" (*Am J Vet Res* 2012;73:854–859), Ranga Sampath's correct name is Rangarajan Sampath; the correct address for Biosciences Incorporated is 2251 Faraday Ave, Ste 150, Carlsbad, CA 92008; and the correct name for Ibis Biosciences Inc in footnote b is Ibis Biosciences Inc, an Abbott Co.

In the Materials and Methods section, the sentence "Because all reactions for a sample were run in the same 96-well RT-PCR plate, cycling conditions were used for both the RT-PCR and PCR procedures as previously described.[14]" should read "Because RT-PCR and PCR reactions were run in the same 96-well plate, RT-PCR cycling conditions were used for all reactions as previously described.[14]"