Population pharmacokinetics of marbofloxacin in aqueous humor after intravenous administration in dogs

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Objective—To evaluate, by use of population pharmacokinetics, the disposition of marbofloxacin in the aqueous humor after IV administration in dogs and identify its potential usefulness in the prophylaxis and treatment of intraocular infection.

Animals—63 dogs.

Methods—Dogs received a single dose of marbofloxacin (2 mg • kg^{-1}, IV) at various time intervals before cataract surgery. Aqueous humor and blood samples were collected at the beginning of surgery. Marbofloxacin concentrations were measured by high-pressure liquid chromatography. Data were analyzed with a nonlinear mixed-effect model and, by use of population pharmacokinetic parameters, the time course of aqueous humor concentration was simulated for single doses of 3, 4, and 5.5 mg • kg^{-1}IV. Pharmacodynamic surrogate markers and measured aqueous humor concentrations were used to predict in vivo antimicrobial activity.

Results—A maximum marbofloxacin concentration of 0.41 ± 0.17 µg•mL^{-1} was reached in the aqueous humor 3.5 hours after IV administration. In the postdistributive phase, marbofloxacin disappeared from aqueous humor with a half-life of 780 minutes. The percentage penetration into the aqueous humor was 38%. Predictors of antimicrobial effects of marbofloxacin (2 mg • kg^{-1}, IV) indicated that growth of the enterobacteriaceae and certain staphylococcal species would be inhibited in the aqueous humor. Marbofloxacin administered IV at a dose of 5.5 mg • kg^{-1} would be predicted to inhibit growth of *Pseudomonas aeruginosa* and all strains of staphylococci but would not eradicate streptococcal infections.

Conclusions and Clinical Relevance—Marbofloxacin administered IV can penetrate the aqueous humor of canine eyes and may be suitable for prophylaxis or treatment of certain anterior chamber infections. (*Am J Vet Res* 2003;64:889–893)

Results of several studies indicate that systemic administration of fluoroquinolones, including ciprofloxacin,[1-4] ofloxacin,[3,5,6] pefloxacin,[3,7] and sparfloxacin,[8] achieves therapeutic concentrations in intraocular fluids in humans. In dogs, a few systemic antimicrobials have been evaluated for intraocular penetration[9-12]; however, to our knowledge, no fluorinated quinolone antimicrobials have been tested. Marbofloxacin is a fluoroquinolone antimicrobial developed for veterinary use only. The drug has potent bactericidal activity against a large number of aerobic gram-negative and -positive bacterial strains isolated from dogs,[13] and recent results of susceptibility testing for the most commonly isolated pathogens in dogs indicate that it has better in vitro activity than enrofloxacin.[14] Marbofloxacin has a prolonged half-life of 12.4 hours,[15,16] a low plasma protein binding of 10%, and a large volume of distribution of 1.9 L • kg^{-1}, which are important determinants for intraocular penetration.[16,17]

The purpose of the study reported here was to evaluate, by use of population pharmacokinetics, the disposition of marbofloxacin in aqueous humor after IV administration in dogs. Because only 1 sample is obtained from each dog, data were analyzed by use of a mixed-effect modeling approach to calculate population pharmacokinetic parameters describing aqueous humor exposure to the drug.[4,18] These estimated parameters were also used to calculate the fraction of dogs in the population, for which selected pharmacodynamic and pharmacokinetic surrogate markers were able to predict the efficacy of marbofloxacin as a prophylactic or therapeutic antimicrobial in canine ophthalmology.

Materials and Methods

Dogs and sample collection—Sixty-three dogs admitted for cataract surgery at the eye clinic of the Veterinary School of Toulouse were included in the study. Signs of lens-induced uveitis were controlled with topical and systemic corticosteroids administered for 4 to 6 weeks before cataract extraction. A single standard dose of marbofloxacin[16] (2 mg • kg^{-1}) was administered as an IV bolus to each dog at different time periods before surgery so that the sampling times were scheduled at intervals ranging from 0 to 30 minutes to 721 to 1,080 minutes after drug administration (**Table 1**). At the beginning of the phacoemulsification procedure, 0.2 mL of aqueous humor was withdrawn by use of a 1-mL syringe through a 25-gauge needle after a partial thickness corneal incision had been made and before the anterior chamber had been entered. At the same time, 2 mL of blood was collected, and serum was obtained. The exact interval, in minutes, from marbofloxacin administration to collection of aqueous humor and blood samples was recorded. The specimens of aqueous humor and serum were frozen and stored at –80°C until analyzed.

Analytical methods—The concentration of marbofloxacin in serum was determined by reverse-phase high-performance liquid chromatography.[16] The range of the interassay **coefficient of variation (CV)** for concentrations of

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marbofloxacin in serum was 2.3 to 6.9%, and accuracy of the assay ranged from 97.4 to 104.9%. The concentration of marbofloxacin in the aqueous humor was determined by use of the same method, except the ultraviolet detection was replaced by fluorometric detection with an excitation wavelength of 295 nm and an emission wavelength of 500 nm, and the calibration standard solutions were prepared in phosphate buffer (pH, 7) rather than serum. The range of the interassay CV for concentrations of marbofloxacin in aqueous humor was 1.8 to 5.2%, and accuracy of the assay ranged from 96.7 to 105.8%. The limit of quantification was 0.01 µg • mL^{-1} for both assays.

Table 1—Time intervals from administration of a single dose of marbofloxacin (2 mg • kg^{-1}, IV) to collection of aqueous humor samples in dogs

Time interval (min)	No. of eyes (n = 63)
0 to 30	6
31 to 60	10
61 to 90	9
91 to 120	5
121 to 180	10
181 to 240	6
241 to 360	4
361 to 720	9
721 to 1,080	4

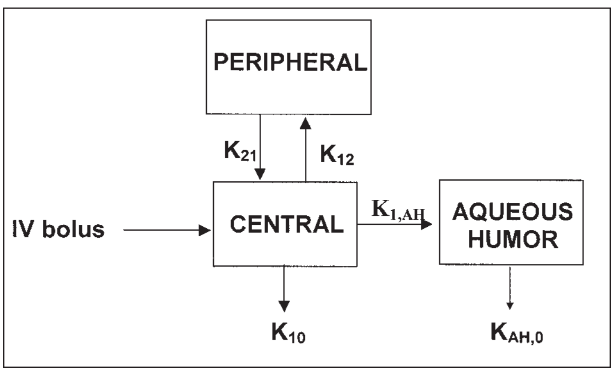

Figure 1—Model of the pharmacokinetic profiles of marbofloxacin in serum and aqueous humor after IV administration in dogs. K_{12} and K_{21} are the first order rate of exchange between central and peripheral marbofloxacin compartments. K_{10} is the elimination rate constant from serum. $K_{1,AH}$ and $K_{AH,0}$ are the rate constants of absorption and elimination for aqueous humor, respectively.

Pharmacokinetic analysis—The serum and aqueous humor data sets were analyzed simultaneously by use of a nonlinear mixed-effects regression model (**Fig 1**) and custom software. The observed concentration of drug in serum and aqueous humor of each dog was described as (**equation [Eq]** 1, 2, and 3):

$$C^1_{i,j} = f^1(\psi_i, t_{i,j}) \bullet (1 + \varepsilon^1_{i,j}),\ i = 1 \text{ to } 63$$
$$C^2_i = f^2(\psi_i, t_i) \bullet (1 + \varepsilon^2_i), \text{ and}$$
$$\psi_i \sim N(\mu; \Omega)$$

where $C^1_{i,j}$ is the drug concentration measured in serum of the i^{th} dog at time $t_{i,j}$, C^2_i is the drug concentration measured in the aqueous humor of the i^{th} dog at time t_i, and f^1 is the function for predicting the mean serum concentration; a biexponential equation of the form (Eq 4) was selected:

$$f^1(\psi_i,t) = \psi_{i,1}\exp(-\psi_{i,2}t) + \psi_{i,3}\exp(-\psi_{i,4}t)$$

where $f^1(\psi_i,t)$ is the actual drug concentration in serum for dog i at time t, $\psi_{i,1}$ and $\psi_{i,3}$ are pre-exponential terms of dog i, and $\psi_{i,2}$ and $\psi_{i,4}$ are exponential terms of dog i (**Table 2**).

Equation 4 was interpreted according to a classical bicompartmental model with elimination from the central compartment, and f^2 is the function for predicting the mean aqueous humor concentration. This function is the solution of a differential equation (Eq 5). In Eq 5, the serum concentration, as obtained by Eq 4 (ie, f^1), was used as an input function to a supplementary compartment to describe the time course of marbofloxacin **concentration in aqueous humor (C_{AH})**:

$$\frac{df^2(\psi_i,t)}{dt} = \psi_{i,5}f^1(\psi_i,t) - \psi_{i,6} \bullet f^2(\psi_i,t)$$

The amounts of marbofloxacin, rather than the concentrations of marbofloxacin, in aqueous humor were considered. The left terms of Eq 5 and $\psi_{i,6}f^2$ were multiplied by the apparent **aqueous humor volume of distribution (V_{AH})**, which includes both anterior and posterior chamber vol-

Table 2—Population pharmacokinetic fixed-effect regression parameters and variability (coefficient of variation [CV%]) after a single dose of marbofloxacin (2 mg • kg^{-1}, IV) in 63 dogs

Parameters	Description (units)	Estimated mean value	CV%
Ψ_1	Serum, intercept, first phase (µg•mL^{-1})	3.53	13.52
Ψ_2	Serum, slope, first phase (min^{-1})	0.0622	42.42
Ψ_3	Serum, intercept, second phase (µg•mL^{-1})	1.49	38.82
Ψ_4	Serum, slope, second (terminal) phase (min^{-1})	0.000985	13.91
Ψ_5	AH, first order rate constant of transfer, ($K_{1,AH}$) from serum to AH (min^{-1})	$4.457 \bullet 10^{-7}$	32.35
Ψ_6	AH, first order rate constant of elimination ($K_{AH,0}$) from AH (min^{-1})	0.008903	20.05
Derived parameters			
Vc	Volume of distribution (central) (L•kg^{-1})	0.398	55.3
Serum clearance	Clearance rate of marbofloaxcin from serum (mL•kg•min^{-1})	1.27	39.8
AUC_{AH}	Area under concentration curve in AH (µg•hr•mL^{-1})	10.07	19.6
AUC_{serum}	Area under concentration curve in serum (µg•hr•mL^{-1})	26.23	39.8
AUC_{AH}:AUC_{serum}	AH to serum concentration ratio	0.38	44.4
Cmax	Peak concentration of marbofloaxcin in AH (µg•mL^{-1})	0.439	20.5
σ_1^2	AH, intra-animal error	0.0598	24.8
σ_2^2	Serum, intra-animal error	0.0598	24.8

Variability is interdog variability for all but σ_1 and σ_2 parameters, which were assumed to be equal. AH = Aqueous humor. Ψ_1 to Ψ_4 = Fixed effect parameters for serum data. Ψ_5, Ψ_6 = Fixed effect parameters for aqueous humor data.

umes, and $\psi_{i,5}f^1$ was multiplied by the **volume of distribution of the central compartment** (V_{Ci}) for the i^{th} dog. The aqueous humor volume of distribution was assumed to be 0.6 mL.[19]

The link model between serum concentration and aqueous humor transfer compartment was described for dog *i* by a first order rate constant $\psi_{i,5}$ (later termed $K_{1,AH}$ for clarity). Because the amount of marbofloxacin transferred to the aqueous humor compartment was considered negligible with respect to the total administered marbofloxacin dose, it was assumed that the transfer of marbofloxacin into aqueous humor was irreversible and described for dog *i* by a first order process $\psi_{i,6}$ (later termed $K_{AH,0}$ for clarity).

In Eq 3, μ is the vector of the mean population parameter (ψ_i), and Ω is the variance-covariance matrix of the individual parameters measuring the dispersion of the individual parameters in the population that were assumed to be mutually independent.

In Eqs 1 and 2, ε^1_j and ε^2_i are independent random variables that measure the intraindividual variability in serum and aqueous humor, respectively. They were assumed to be independent of the ψ_i and mutually independent, with a common distribution N (0; σ^2). Because the model is multiplicative, the SD of the random variables ε^1_j and ε^2_i can be interpreted as the intraindividual CV. For each dog, only 1 drug concentration was measured in aqueous humor; therefore, the SD of $\psi_{i,1}$ is not identifiable. This problem was overcome by assuming that the intraindividual SD (σ^2) was the same for both ε^1_j and ε^2_i. The unknown parameters (μ, Ω, and σ^2) were estimated by use of the first-order conditional estimation method.[20] The **area under the concentration curve (AUC)** from 0 to infinity, the **peak concentration (C_{max})**, and the **peak time (T_{max})** for serum and aqueous humor concentration curves were generated from the estimated distribution of individual parameters (mean, variance). The kinetic parameters also permitted the prediction of the aqueous humor concentrations with marbofloxacin doses of 3, 4, and 5.5 mg • kg^{-1}. The potential efficacy of marbofloxacin was evaluated by use of the **area under the inhibitory curve (AUIC)** and the **C_{max}-to-minimum inhibitory concentration (C_{max}:MIC) ratio**. The AUIC was calculated as the total serum AUC above MIC divided by MIC, as recommended.[21] Breakpoint MICs for target AUICs of 48 hours[22,23] and 125 hours[24-26] and for a C_{max}:MIC ratio of 10 were calculated by use of population cumulative density functions calculated for single marbofloxacin doses of 2, 3, 4, and 5.5 mg • kg^{-1}, IV.[26]

Results

The study population included 30 males and 33 females with a mean ± SD age of 6.5 ± 2.9 years (median, 6 years; range, 2 to 13 years). Twelve breeds of dogs were represented with mixed breed (n = 17), Miniature Poodle (14), and Pyrenees shepherd (7) being the most common.

No adverse reactions developed from the administration of marbofloxacin to the 63 dogs, and no dogs developed endophthalmitis. The serum concentration-time curve had a biexponential decline with mean terminal half-life of 11.73 hours (CV, 13.9%; **Fig 2**). Plasma clearance was 1.27 mL • kg • min^{-1} (CV, 39.8%).

Marbofloxacin was detected in the aqueous humor of all dogs. Mean peak C_{AH} of 0.417 ± 0.173 µg • mL^{-1} was achieved 3.55 hours after IV administration of marbofloxacin. The decline of C_{AH} appeared to be slow, with a mean observed value of 0.290 ± 0.08 µg • mL^{-1} from 721 to 1,080 minutes after administration. Mean population area under the aqueous concentration-time curve (AUC_{AH}; 0 to ∞) was 10.07 µg • hr • mL^{-1}. The calculated mean population **aqueous humor-to-serum concentration ratio (AUC_{AH}:AUC_{serum})** was 0.38. Mean elimination rate constant $K_{1,AH}$ for aqueous humor was 0.0089 • min^{-1}. Mean residence time in aqueous humor (ie, 1/$K_{1,AH}$) and mean half-life for elimination from the aqueous humor were calculated to be 112 and 780 minutes, respectively. Population aqueous humor C_{max} and T_{max} distributions were simulated for single marbofloxacin doses of 3, 4, and 5.5 mg • Kg^{-1}, IV. Corresponding values were 0.622, 0.827, and 1.205 µg • mL^{-1} and 3.60, 3.57, and 3.39 hours for C_{max} and T_{max}, respectively. By use of optimum AUICs of 48 and 125 hours and a C_{max}:MIC ratio of 10, pharmacodynamic MIC critical values were calculated from the distribution of individual parameters (**Table 3**). The per-

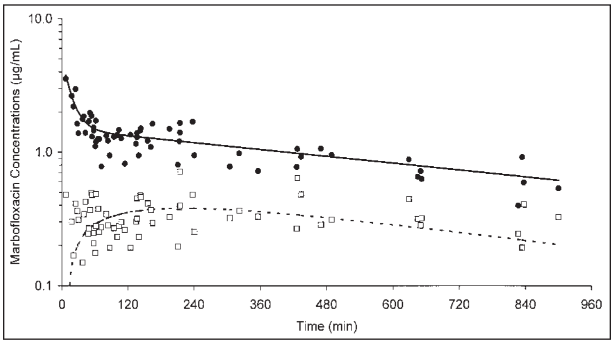

Figure 2—Actual (open squares) and calculated (dashed line) concentrations of marbofloxacin (2 mg • kg^{-1}) in aqueous humor and actual (closed circles) and calculated (solid line) concentrations of marbofloxacin in serum after IV administration in 63 dogs.

Table 3—Pharmacodynamic minimum inhibitory concentration (MIC) critical values (µg • mL^{-1}) calculated for single marbofloxacin doses of 2, 3, 4, and 5.5 mg • g^{-1}, IV, required to achieve a serum area under the inhibitory curve (AUIC) of 48 or 125 hours or a serum peak marbofloxacin concentration-to-MIC(Cmax:MIC) ratio of 10 for 90% of dogs

Marbofloxacin dose (mg • kg^{-1})	Surrogate markers		
	AUIC of 48 h	AUIC of 125 h	Cmax:MIC of 10
2	0.38	0.20	0.31
3	0.56	0.31	0.49
4	0.76	0.42	0.63
5.5	1.05	0.54	0.87

Table 4—Prediction of the percentages of dogs with a serum AUIC ≥ 125 hours for selected targeted MICs (µg • mL^{-1}) after a single marbofloxacin dose of 2, 3, 4, or 5.5 mg·kg^{-1}, IV

Targeted MIC (mg • mL^{-1})	Marbofloxacin dose (mg • kg^{-1})			
	2	3	4	5.5
0.05	99.4	99.5	99.6	99.7
0.10	97.8	98.8	99.2	99.3
0.15	95.2	97.8	98.8	98.9
0.20	89.9	95.8	98.2	98.3
0.25	83.5	94.0	96.8	97.9
0.30	73.8	90.6	95.1	97.3
0.35	61.1	86.3	93.3	96.4
0.40	50.5	79.3	91.5	95.6
0.45	35.7	75.8	86.5	94.0
0.50	24.4	67.7	83.8	92.2

centages of dogs that would have an AUIC of at least 125 hours for certain targeted MICs after IV administration of single marbofloxacin doses of 2, 3, 4, or 5.5 mg • kg^{-1}, were determined (**Table 4**).

Discussion

In clinical practice, it is not possible, for ethical reasons, to obtain serial samples of aqueous humor and, hence, obtain a complete pharmacokinetic characterization of the time course of a drug in the eyes of dogs. The population pharmacokinetic approach allows the determination of pharmacokinetic parameter values from sparse data, even if there is a single observational data for each subject.[27,28] This approach has been used to describe the intraocular disposition kinetics of systemically administered ciprofloxacin in humans[4] and rabbits[28] and of topically administered dorzolamide[18] in humans. This approach also provides a method for determining dosing strategies in a population.

The mean serum marbofloxacin disposition parameters determined in this study are in good agreement with those reported in previous studies[15,16] and by use of conventional kinetic analysis; however, our study also provides an estimate of the interpatient variability in a population. A large interpatient CV (39.8%) was found for the serum clearance of marbofloxacin. Because systemic clearance is the actual kinetic parameter controlling serum concentration, and serum concentration is the driving force controlling drug penetration into aqueous humor, the intersubject variation in serum clearance was reflected in the large CVs of the pharmacokinetic parameters of marbofloxacin in aqueous humor. These CVs are similar to those reported for humans.[4]

Results from our data indicate that penetration of marbofloxacin into aqueous humor, described by the aqueous humor to serum ratio (AUC_{AH}:AUC_{serum}), was 38%. During equilibrium conditions, this ratio is equal to ($K_{1,AH} \times V_C$)/($K_{1,AH} \times V_{AH}$), which was estimated to be 33% from the parameters of the model. Both values are close and compare favorably with the percentage penetrations into the aqueous humor of 23 and 30% that have been reported after IV administration of ciprofloxacin in humans[4] and rabbits, respectively.[29] Our results also indicate that C_{AH} of marbofloxacin peak in canine aqueous humor approximately 3.5 hours after IV administration. Similarly, C_{max} in aqueous humor is reached 4 hours after IV administration of ciprofloxacin and ofloxacin in humans,[3] although the pharmacokinetics of these fluoroquinolones in serum and aqueous humor are different from those of marbofloxacin in dogs. In our study, the time necessary to achieve peak concentration in aqueous humor was because of the long serum half-life of marbofloxacin (11.7 hours) combined with its short rate constant of elimination from aqueous humor (0.008903 min^{-1}), which corresponded to a short intrinsic half-life (1.3 hours) of elimination of marbofloxacin from the aqueous humor. These pharmacokinetic features also explain that in the postdistributive phase, the terminal C_{AH} half-life is controlled by the terminal serum concentration half-life (flip-flop situation), not the intrinsic half-life of elimination for aqueous humor. Consequently, the elimination half-life of marbofloxacin is the same in serum and aqueous humor and, from a clinical standpoint, the recommended 24-hour dosing interval is likely effective in maintaining therapeutic concentrations in aqueous humor for 24 hours. The clearance rate from aqueous humor ($K_{1,AH} \times V_{AH}$), which represents the loss of drug from the biophase, was calculated to be 5 µL • min^{-1} for marbofloxacin. This value is close to that reported for aqueous humor flow rate in dogs[30] and consistent with the fact that elimination of marbofloxacin from the anterior chamber occurs essentially by the bulk flow of aqueous humor.

Bacterial infection of the anterior chamber in dogs can develop as a consequence of intraocular surgery, penetrating corneal laceration, or perforating corneal ulcer and lead to bacterial endophthalmitis, which often results in severe loss of vision. Systemic administration of antimicrobials is indicated whenever there is a high risk or actual contamination or infection of the anterior chamber.[31] Because the plasma kinetics of most antimicrobial agents are representative of what happens in other areas of the body, pharmacodynamic parameters that can predict treatment efficacy at various sites have been evaluated during the last few years.[21-26] The AUIC, which represents the total serum area above a given MIC over 24 hours, and the C_{max}:MIC ratio are considered to be the principal predictors of efficacy of currently available fluoroquinolones against different pathogens.[21] Results of several studies[21,24-26] indicate that an AUIC of approximately 125 hours and a C_{max}:MIC ratio of 10 are the cut-off values that are necessary to optimize bacterial eradication. However, certain investigators[22,23] have suggested that an AUIC of approximately 40 hours would be sufficient to guarantee bacterial eradication in patients with normal host defenses. Because an AUIC threshold value that can predict optimum efficacy of fluoroquinolone treatment of bacterial endophthalmitis has never been proposed, we used both the 48- and 125-hour values to calculate MIC critical values that can predict the antimicrobial effect of marbofloxacin in the aqueous humor of dogs when administered IV. Our results indicate that marbofloxacin (2 mg • kg^{-1}, IV) has a pharmacodynamic profile sufficient for microbiologic effectiveness against bacteria, with MICs ranging from 0.20 to 0.38 µg • mL^{-1} for 90% of dogs. This indicates that only anterior chamber infections with *Enterobacteriaceae* and *Staphylococcus intermedius* would be inhibited.[13] As the bioavailability of marbofloxacin is the same after intravenous or oral administration in the dog,[16] the maximal doses of 4 mg • kg^{-1} and 5.5 mg • kg^{-1} recommended for oral administration of marbofloxacin in Europe[16] and the United States,[32] respectively, were used for simulations. Results of our study indicate that infections caused by bacteria with MIC values of 0.42 to 0.76 µg • mL^{-1} could be effectively treated with the 4 mg • kg^{-1} dose, and those caused by bacteria with MIC values of 0.54 to 1.05 µg • mL^{-1} could be eradicated with the 5.5 mg • kg^{-1} dose. At the marbofloxacin dose of 5.5 mg • kg^{-1}, an AUIC of 125 hours can be predicted in about 90% of dogs for bacteria with MIC values equal to 0.50 µg • mL^{-1}. These findings suggest that at 4 mg • kg^{-1}, marbofloxacin would be effective against all strains of staphylococci but would not prevent pseudomonal or streptococcal infections in the anterior chamber.[13] At the marbofloxacin dose of 5.5 mg • kg^{-1}, results of the simulation study indicate that growth of *Pseudomonas aeruginosa*, but not the other *Pseudomonas* spp or *Streptococcus* spp, would be inhibited. As efficacy indices that consider antimicrobial pharmacokinetics in the biophase have never been defined, the comparison of drug concentrations in ocular fluids with the MIC for likely causative pathogens is used to assess the potential efficacy of systemic fluoroquinolones in the prevention or treatment of intraocular infection.[4,33,34] In our study, the predicted results from the surrogate markers (AUIC and C_{max}:MIC ratio) of antimicrobial efficacy are similar to those obtained by comparing the marbofloxacin C_{AH} to MICs for potential intraocular bacterial pathogens. At the 2 mg • kg^{-1} dose, the marbofloxacin C_{AH} were maintained well above the MIC for *Enterobacteriaceae* and *S intermedius*. Simulations of C_{AH} after IV administration of 3 or 4 mg • kg^{-1} of marbofloxacin suggested that C_{AH} above the MIC for the staphylococci strains would be reached.[13] However, the highest C_{AH} achieved by the 3 and 4 mg • kg^{-1} doses of marbofloxacin would not exceed the concentrations required to inhibit 90% of the *Pseudomonas* and *Streptococcus* spp.[13] In contrast, the 5.5 mg • kg^{-1} dose of marbofloxacin would induce C_{AH} exceeding the MIC for *P aeruginosa.*[13]

Results of our study indicate that IV administration of marbofloxacin may be useful as an antimicrobial agent for prophylaxis or treatment of certain bacterial infections of the anterior chamber in dogs but will not eradicate those caused by *Streptococcus* spp. This agrees with data[4] on the clinical usefulness of ciprofloxacin for prevention of intraocular infection in humans.

[a]Marbocyl FD, 10 mg • mL^{-1}, Vetoquinol Laboratories, Lure, France.

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