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Pharmacokinetics of levofloxacin after single intravenous, oral and subcutaneous administration to dogs

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Abstract

The pharmacokinetic properties of the fluoroquinolone levofloxacin (LFX) were investigated in six dogs after single intravenous, oral and subcutaneous administration at a dose of 2.5, 5 and 5 mg/kg, respectively. After intravenous administration, distribution was rapid ($T_{½dist}$ 0.127 ± 0.055 hr) and wide as reflected by the volume of distribution of 1.20 ± 0.13 L/kg. Drug elimination was relatively slow with a total body clearance of 0.11 ± 0.03 L kg^{-1} hr^{-1} and a $T_{½}$ for this process of 7.85 ± 2.30 hr. After oral and subcutaneous administration, absorption half-life and T_{max} were 0.35 and 0.80 hr and 1.82 and 2.82 hr, respectively. The bioavailability was significantly higher ($p < 0.05$) after subcutaneous than oral administration (79.90 vs. 60.94%). No statistically significant differences were observed between other pharmacokinetic parameters. Considering the $AUC_{24\ hr}$/MIC and C_{max}/MIC ratios obtained, it can be concluded that LFX administered intravenously (2.5 mg/kg), subcutaneously (5 mg/kg) or orally (5 mg/kg) is efficacious against Gram-negative bacteria with MIC values of 0.1 μg/ml. For Gram-positive bacteria with MIC values of 0.5 μg/kg, only SC and PO administration at a dosage of 5 mg/kg showed to be efficacious. MIC-based PK/PD analysis by Monte Carlo simulation indicates that the proposed dose regimens of LFX, 5 and 7.5 mg/kg/24 hr by SC route and 10 mg/kg/24 hr by oral route, in dogs may be adequate to recommend as an empirical therapy against *S. aureus* strains with MIC ≤ 0.5 μg/ml and *E. coli* strains with MIC values ≤0.125 μg/ml.

KEYWORDS
dog, fluoroquinolones, levofloxacin, pharmacokinetics

1 | INTRODUCTION

Levofloxacin (LFX) is the L-isomer of the fluoroquinolone antibacterial agent ofloxacin. It has been widely used and studied in human medicine (Chow et al., 2001; Pea, Di Qual et al., 2003; Pea, Pavan et al., 2003; Bellmann et al., 2004). Although LFX is not registered in veterinary medicine, its pharmacokinetics has been reported in several species, such as cats, horses, camels, calves, goats, quails and poultry (Aboubakr, 2012; Albarellos, Ambros, & Landoni, 2005; Dumka & Srivastava, 2007; Goudah, 2009; Goudah & Abo-El-Sooud, 2009; Goudah, Abo-El-Sooud, Shim, Shin, & Abd El-Aty, 2008; Lee et al., 2017).

Levofloxacin bactericidal effects are caused by the inhibition of both bacterial DNA gyrase (a type-II topoisomerase) and topoisomerase IV. It has broader antibacterial spectrum than the older fluoroquinolones norfloxacin or ciprofloxacin. Its spectrum includes many Gram-negative (most Enterobacteriaceae) and Gram-positive bacteria (methicillin-susceptible strains of Staphylococcus spp. and Streptococcus spp.), atypical and intracellular bacteria (*Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*) (Langtry & Lamb, 1998). Its activity against anaerobic microorganisms is moderate (Ross, Wright, Hovde, Peterson, & Rotschafer, 2001).

Fluoroquinolones exhibit concentration-dependent killing kinetic; therefore, the best predictors of therapeutic outcome are

area under the concentration–time curve ($AUC_{24\ hr}$) MIC ratio, and peak serum concentration (C_{max}) MIC ratio (Toutain, Del Castillo, & Bousquet-Melou, 2002; Walker, 2000; Wright, Brown, Peterson, & Rotschafer, 2000).

In human beings, it is administered orally once a day and its bioavailability is around 100% (not affected by meals). Therefore, both parenteral and oral administration routes are interchangeable. It exhibits a rapid and wide tissue distribution including lung, skin, urinary tract, prostate and other soft tissues and body fluids. Though, it has a relatively poor penetration into the central nervous system. The drug undergoes a limited metabolism and is primarily excreted by kidney mainly as active drug. Inactive metabolites (N-oxide and demethyl metabolites) represent less than 5% of the total dose (Hurst, Lamb, Scott, & Figgitt, 2002; Langtry & Lamb, 1998).

Few side effects have been reported after fluoroquinolones administration in people and animals; these included gastrointestinal disorders, central nervous system stimulation, cartilage damage and, for enrofloxacin in cats, blindness (Brown, 1996; Stahlmann & Lode, 1999).

As other fluoroquinolones, when administered to young dogs (aged less than 8 months) LFX can induce tendinopathy, tendonitis, spontaneous tendon rupture and cartilage damage (Martinez, McDermott, & Walker, 2006).

To our knowledge, there is only a single report of the pharmacokinetics of LFX after oral administration in dogs at supratherapeutic dose (Yin et al., 2011); therefore, the aims of this study were to describe LFX pharmacokinetics in dogs after single 2.5 mg/kg intravenous and 5 mg/kg subcutaneous and oral administration and, considering that dose proportionality has been reported for LFX in dogs (FDA, 1996, Yin et al., 2011), to assess and foresee by applying Monte Carlo simulation the probability of a favourable outcome in a large population of two oral (5 and 10 mg/kg) and two SC (5 and 7.5 mg/kg) dosage regimens.

2 | MATERIALS AND METHODS

2.1 | Experimental animals

Experimental animals were six adult Beagle dogs, three males and three females, 4.22 ± 2.2 years old, weighing 13.6 ± 1.6 kg (15.5–11.5 kg). All dogs were healthy as determined by clinical examination, complete blood and serum biochemical analysis and urinalysis. Animals were housed in the Faculty of Veterinary Medicine UBA installations and allowed to acclimatize for 2 months before the experiment.

Dogs were dewormed with fenbendazole 50 mg/kg, pyrantel 5 mg/kg, and praziquantel 5 mg/kg (Total Full_ Holliday-Scott, Argentina). Animals were fed with standard commercial dry food (ProPlan® Ralston Purina, Argentina) and water ad libitum.

All animal procedures were approved by the Institutional Animal Care and Use Committee, School of Veterinary, University of Buenos Aires, Argentina.

2.2 | Dosage forms

For intravenous dose, a 0.5% hemihydrate premix levofloxacin human designed formulation (Levaquin, Laboratorio Jansen-Cilag, Argentina) was used. The SC formulation was a 5% aqueous solution (Floxaday 5%, Laboratorio Holliday-Scott, Argentina) and the oral a 100 mg anhydrous LFX tablet (Floxaday 100 mg, Laboratorio Holliday-Scott, Argentina).

2.3 | Experimental design

A three-period, three-treatment crossover design was used in which dogs received three treatments, levofloxacin intravenously (IV), orally (PO) and subcutaneously (SC) at a dosage of 2.5, 5 and 5 mg/kg, respectively. On each experimental day, two animals received each treatment. Two-week intervals were allowed between each period.

For LFX IV administration, the dose was given via bolus (over a minute period) through a catheter placed in the cephalic vein. For the SC administration, the dose was injected into the loose skin over the shoulders. For the oral administration, all dogs were fasted for 6 hr and remained unfed for at least 4 hr after application. Administrationconsisted of entire and split 100 mg tablets (mean dose 4.94 ± 0.19 mg/kg) followed by an oral flush with 12 ml of tap water to ensure the tablet was swallowed.

2.4 | Blood sampling

For sample collection, a cephalic vein was catheterized prior to each study. Blood samples (2.5 ml) were withdrawn, through the cephalic catheter, at the following times: For the IV dose: 0, 0.083, 0.16, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hr post-administration. For the PO and SC administration, blood samples were withdrawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hr.

Blood samples were taken with heparinized syringes, placed into tubes, mixed and kept on ice until plasma separation. Plasma was separated after centrifugation (15 min at 1,500 g) and stored at −20°C until analysis. All samples were assayed not later than 3 weeks from collection (Gao, Yao, Guo, An, & Guo, 2007).

2.5 | Levofloxacin determination

Levofloxacin levels in plasma were determined using the HPLC method described by Gao et al. (2007). Briefly, a 0.5 ml aliquot of plasma was deproteinized by adding 100 μl perchloric acid (0.6 M), vortexed and centrifuged at 10,000 g for 5 min. The supernatant was filtered through Millipore 0.22 μm filter and injected into the HPLC system. Chromatographic separation was performed on a Kromasil C18 column with the mobile phase consisting of acetonitrile, water, phosphoric acid and triethylamine (14:86:0.6:0.3, v/v/v/v), and flow rate was 1.0 ml/min. The method used ultraviolet detection set at a wavelength of 294 nm.

Standard curve was linear between 0.025 and 5 μg/ml, and the low limit of quantification (LLOQ) was set in 0.05 μg/ml. Intraday and interday LLOQ coefficient of variation were 4.87% and 9.39%, respectively.

2.6 | Pharmacokinetic analysis

Pharmacokinetic analyses were performed with computer software (PCNonlin, SCI Software, 4th Edition, 1992, Lexington, USA). Initial estimates were determined using the residual method (Gibaldi & Perrier, 1982) and refitted by non-linear regression.

The number of exponents needed for IV, PO and SC administration data were determined by applying the Schwartz (Schwartz, 1978) and Akaike criterions (Yamaoka, Nakagawa, & Uno, 1978), and the residual distribution around the estimated concentrations.

Pharmacokinetic parameters were calculated using classic equations associated with compartmental analysis, except C_{max} and T_{max} that were determined by visual inspection of plasma concentration–time curves (Gibaldi & Perrier, 1982).

Main parameters for each animal were statistically compared for the three assayed administration routes applying Kruskall–Wallis test. The level of significance was set in 0.05 ($p<0.05$).

2.7 | Monte Carlo Simulation (MCS)

A 500-patient Monte Carlo simulation was implemented in Microsoft Excel using the PK/PD equation $AUC_{24\,hr}$/MIC for two levels of dose (5 and 10 mg/kg PO and 5 and 7.5 mg/kg SC). All the PK parameters were assumed to be normally distributed in the form of mean values and confidence intervals. MIC distribution data were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC distribution website (www.eucast.org/mic_distribution).

The endpoints of PK/PD parameters were determined from bibliographic cut-off values for Gram-positive and Gram-negative pathogens, f $AUC_{24\,hr}$/MIC of 50 (*Staphylococcus aureus*) or 125 (*Escherichia coli*), were included in the analysis (Papich, 2014). Free-drug $AUC_{24\,hr}$ was calculated assuming that protein binding of LFX was 30% (Papich & Riviere, 2009).

The probability of target attainment (PTA), defined as the probability of the dose regimen to achieve a determined PK/PD endpoint for each MIC value, and the cumulative fraction of response (CFR), defined as the probability of the dose regimen to achieve a determined PK/PD endpoint taking into account the total MIC distribution of the bacterial population, were calculated.

3 | RESULTS

No adverse effects were observed in any of the experimental animals. In addition, no pain was observed at the LFX SC administration site, either vomit after the PO administration.

Levofloxacin plasma concentration vs. time curves after IV administration were best described by an open biexponential model in all the dogs (Figure 1). Table 1 shows main pharmacokinetic parameters.

After IV administration LFX was rapidly and extensively distributed as reflected by the short half-life of the process ($T_{½dist}$ 0.127 ± 0.055 hr) and large volume of distribution (1.204 ± 0.130 L/kg). Elimination was relatively slow with a low body clearance (0.113 ± 0.026 L kg^{-1} hr^{-1}) and long elimination half-life (7.84 ± 2.29 hr).

Levofloxacin plasma disposition curves after PO and SC administration (Figure 1) were best described by a biexponential equation explained by an open monocompartmental model with first-order

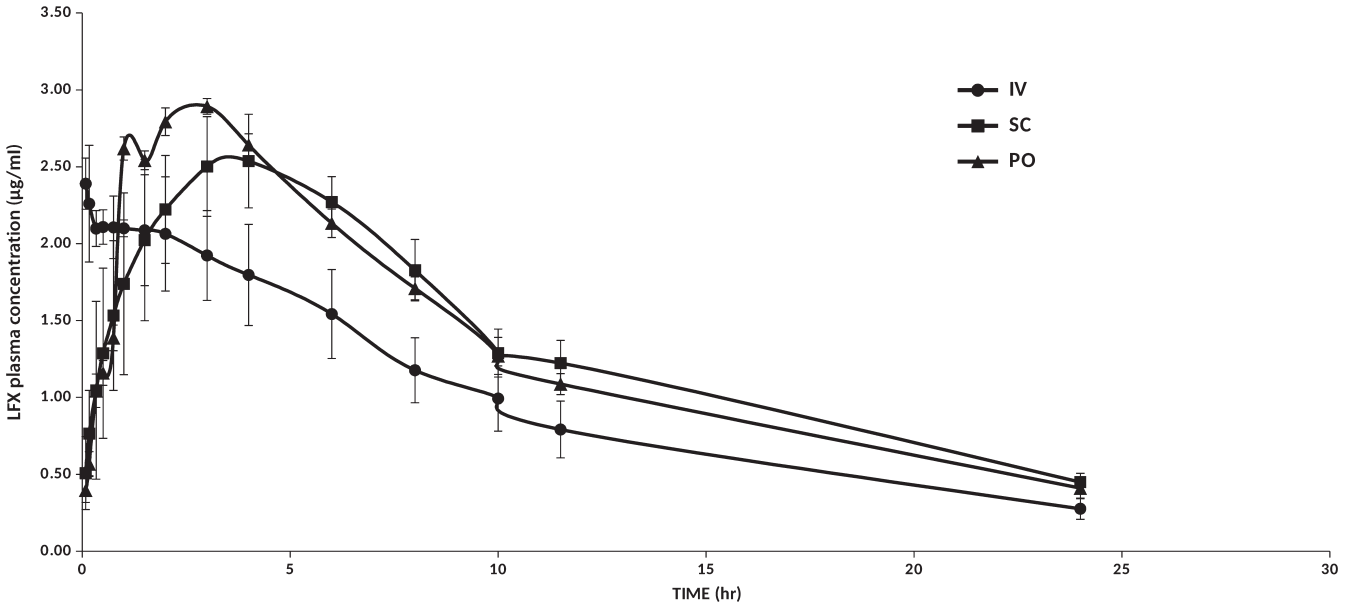

FIGURE 1 Mean (±*SD*) plasma concentration of levofloxacin vs. time after single intravenous (2.5 mg/kg) oral (5 mg/kg) and subcutaneous (5 mg/kg) administration to dogs (n = 6)

TABLE 1 Mean pharmacokinetic parameters for LFX after intravenous (2.5 mg/kg), subcutaneous (5 mg/kg) and oral (5 mg/kg) administration to dogs (n = 6)

	Intravenous		Subcutaneous		Oral	
Parameter	**Mean**	***SD***	**Mean**	***SD***	**Mean**	***SD***
Actual Dose	2.50	0.00	5.00	0.00	5.59	0.65
A (μg/ml)	0.863	0.456	NC	NC	NC	NC
B (μg/ml)	2.068	0.222	NC	NC	NC	NC
K_{dist} (1/hr)	6.059	1.713	NC	NC	NC	NC
K_{elim} (1/hr)	0.095	0.030	0.092	0.020	0.1213	0.0330
K_{abs} (1/hr)	NC	NC	1.008	0.470	3.772	3.117
AUC (hr*μg/ml)	23.179	5.860	36.447	6.065	32.919	9.846
$T_{½dist}$ (hr)	0.127	0.055	NC	NC	NC	NC
$T_{½elim}$ (hr)	7.848	2.297	7.784	1.547	6.009	1.316
$T_{½abs}$ (hr)	NC	NC	0.802	0.318	0.349	0.329
C_{max} (μg/ml)	2.931	0.670	2.506	0.136	3.201	0.693
T_{max} (hr)	NC	NC	2.817	0.640	1.818	0.968
F (%)	100	100	79.894	8.175	60.94*	14.989
ClB (L kg^{-1} hr^{-1})	0.113	0.026	0.140	0.021	0.185	0.068
V_d (L/kg)	1.204	0.130	1.540	0.190	1.542	0.467
$AUC_{24\ hr}$/MIC						
0.05	463.579	117.201	728.944	121.290	658.389	196.918
0.1	231.789	58.600	364.472	60.645	329.195	98.459
0.5	46.358	11.720	72.894	12.129	65.839	19.692
C_{max}/MIC						
0.05	58.618	13.401	50.129	2.730	64.029	13.854
0.1	29.309	6.701	25.064	1.365	32.014	6.927
0.5	5.862	1.340	5.013	0.273	6.403	1.385

Notes. *A* and *B*: *Y*-axis intercept terms; AUC: area under the plasma concentration vs. time curve from 0 to ∞; $AUC_{24\ hr}$: area under the plasma concentration vs. time curve from 0 to 24 hr; ClB: body clearance; K_{abs}: absorption rate constant; K_{dist}: distribution rate constant; K_{elim}: elimination rate constant; NC: not calculated; $T_{½abs}$: absorption half-life; $T_{½dist}$: distribution half-life; $T_{½elim}$: elimination half-life; V_d:volume of distribution.
*p < 0.05.

absorption in all dogs. Pharmacokinetic parameters for both administration routes are shown in Table 1.

Oral absorption was rapid, as reflected by the $T_{½abs}$ (0.349 ± 0.329 hr) and T_{max} (1.81 ± 0.968), although bioavailability (*F*) was relatively low (60.94 ± 14.98%). Elimination half-life was shorter than after IV administration (6.01 ± 1.319), although this difference is not statistically significant. Volume of distribution as well as clearance (both corrected by *F*) was similar to those estimated after IV administration.

Levofloxacin absorption after SC administration was, as reflected by $T_{½abs}$ (0.802 ± 0.318), T_{max} (2.817 ± 0.640 hr), *F* (79.89 ± 8.17%) and C_{max} (2.51 ± 0.136 μg/ml), rapid and almost complete. Distribution and elimination were similar to the observed after IV and PO administration; V_d above 1 L/kg and ClB and $T_{½elim}$ of 0.140 ± 0.021 L kg^{-1} hr^{-1} and 7.78 ± 1.54 hr, respectively.

The probability of target attainment (PTA) of the simulated population taking into account a threshold value of $AUC_{24\ hr}$/MIC > 50 (*Staphylococcus aureus*) and 125 (*Escherichia coli*) for a MIC range from 0.003 to 8 μg/ml is shown in Figure 2.

In the case of *Staphylococcus aureus* (Figure 2 panel a), the PTA for a MIC lower than 0.125 μg/ml is 100% for both administration routes at both studied doses. This value is 0%, except for the highest doses, for MIC values higher than 1 μg/ml.

In the case of *Escherichia coli* (Figure 2 panel b), there was a clear difference between administration routes; probably reflecting the lower bioavailability of the oral route. After SC administration, the PTA is 100% for both doses for a MIC value lower than 0.125 μg/ml and 0% for MIC values higher than 0.5 μg/ml. For the oral route, for a 5 mg/kg dose the PTA value decreases from 100% to a value of 0% at MIC values of 0.5 μg/ml. The same holds true for a dose of 10 mg/kg at MIC values of 1 μg/ml.

4 | DISCUSSION

An important point to discuss is the rationale for the doses used in the present study. As previously mentioned in the introduction

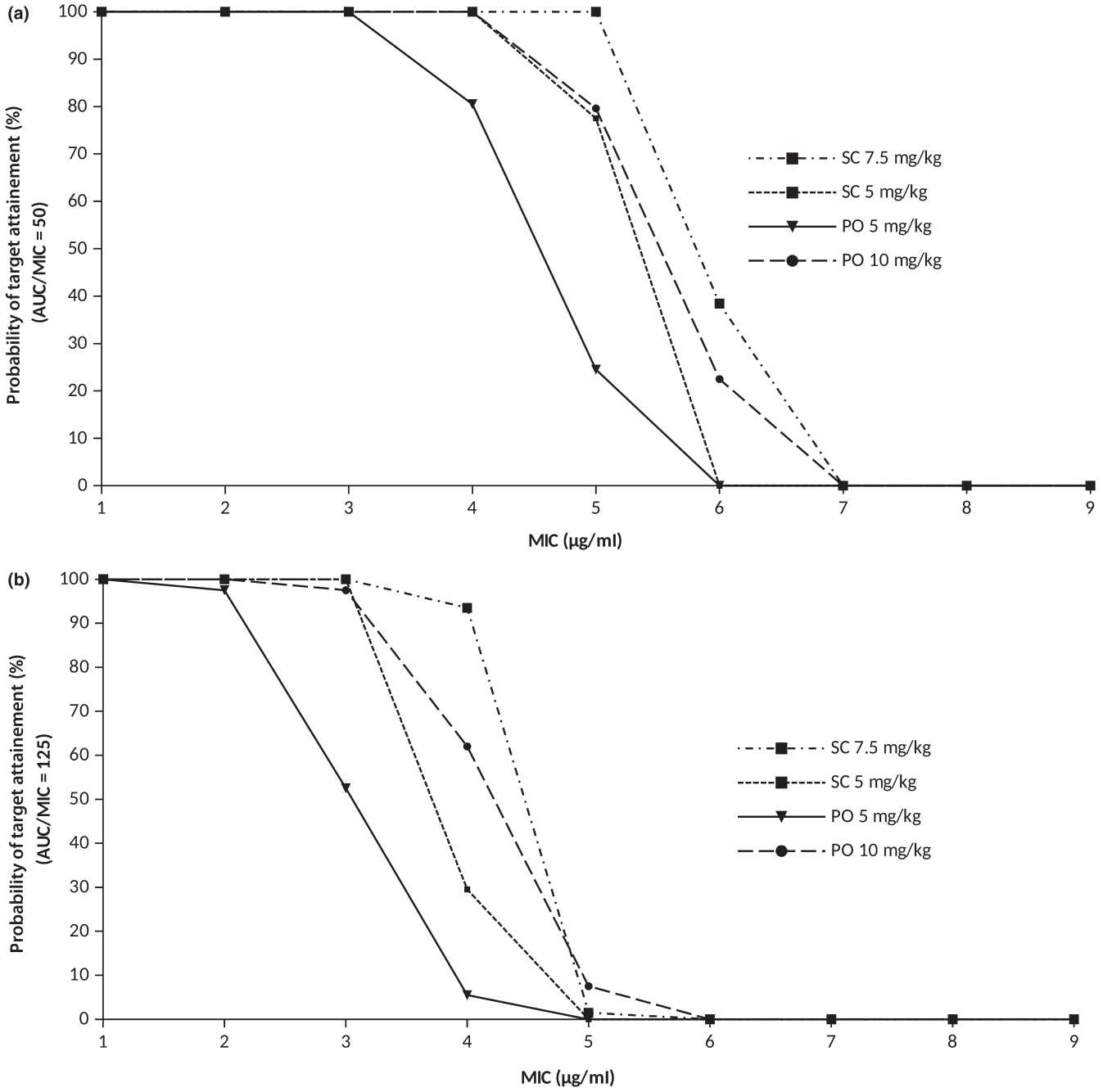

FIGURE 2 (a) Probability of target attainment (PTA) of the threshold value of AUC_{24}/MIC ≥ 50 (*Staphylococcus aureus*) for dogs in the four dosage regimens: PO 5 and 10 mg/kg and SC 5 and 7.5 mg/kg. (b) Probability of target attainment (PTA) of the threshold value AUC_{24}/MIC ≥ 125 (*Escherichia coli*) for dogs in the four dosage regimens: PO 5 and 10 mg/kg and SC 5 and 7.5 mg/kg

section studies of LFX in dogs are scarce; therefore, the actual effective dose of LFX in dogs is unknown.

In the introduction, it was mentioned that fluoroquinolones are classified as concentration-dependent antimicrobials; therefore, $AUC_{24\ hr}$/MIC and C_{max}/MIC are considered efficacy surrogates. Based on Jacobs (2001) and Andes and Craig (2003), for immunocompetent patients an $AUC_{24\ hr}$/MIC value higher than 80–125, for Gram-negative bacteria and 25–50 for Gram-positive bacteria predicts efficacy.

Considering that LFX represents the 50% of any dose of ofloxacin and the lack of enantioselectivity in all pharmacokinetic processes (Okazaki, Kurata, Hakusui, & Tachizawa, 1992; Yabe et al., 2001), the total value of dose-dependent pharmacokinetic parameters of ofloxacin represents twice the correspondent value of LFX. Therefore, a 5 mg/kg dose of ofloxacin corresponds to a 2.5 mg/kg dose of LFX; if, for this dose the AUC of ofloxacin is 34.7 µg hr/ml (Yabe et al., 2001), half of it (17.35 µg hr/ml) corresponds to a 2.5 mg/kg dose of LFX. The same holds true for 10 and 20 mg/kg doses.

In this manner, it was possible to indirectly estimate the AUC values for LFX doses of 2.5, 5 and 10 mg/kg in dogs.

Using these AUC values and MIC values reported for LFX in a number of bacterial isolated from humans (Fu et al., 1992; Takahashi, Masuda, Otsuki, Miki, & Nishino, 1997; Une, Fujimoto, Sato, & Osada, 1988) and for *E. coli* in dogs (Liu, Boothe, Jin, & Thungrat, 2013) a 5 mg/kg dose was selected as the lower theoretical clinically effective dose. For the intravenous administration, a dose of 2.5 mg/kg was preferred to avoid any acute adverse reaction.

Plasma LFX disposition curves after intravenous administration were best fit to an open bicompartmental model in all the animals; which is in accordance with many of the reports for human beings (Chow et al., 2001; Pea, Di Qual et al., 2003; Pea, Pavan et al., 2003) rabbits (Destache, Pakiz, Larsen, Owens, & Dash, 2001) and cats (Albarellos et al., 2005).

The distribution process was fast, reflected by a short distribution half-life, and comparable to that reported for cats (Albarellos et al., 2005). Volume of distribution was above a litre per kilogram, similar to that reported for other fluoroquinolones in this species such as, orbifloxacin (1.2 L/kg) (USP Veterinary Pharmaceutical information, 2003), enrofloxacin (2.45 L/kg) (Cester & Toutain, 1997) and marbofloxacin (1.9 L/kg) (Schneider, Thomas, & Boisrame, 1996).

Elimination half-life was in the range of values reported for cats, humans and rabbits (between 5.2 and 10 hr) (Albarellos et al., 2005; Bellmann et al., 2004; Destache et al., 2001; Pea, Di Qual et al., 2003; Pea, Pavan et al., 2003). It was longer than that reported for enrofloxacin and orbifloxacin in dogs and similar to that reported for marbofloxacin. LFX clearance, 0.113 L kg^{-1} hr^{-1}, is somewhat lower than the normal glomerular filtration rate for this species (0.18 L/hr kg) (Goy-Thollot, Chafotte, Besse, Garnier, & Barthez,2006); this could be reflecting, as reported for cats (Albarellos et al., 2005), that another mechanism such as tubular re-absorption is involved.

After oral and SC administration plasma disposition curves were best described by an open monocompartmental model for all the animals, similar to that reported for PO administration in cats (Albarellos et al., 2005).

The absorption process after PO administration was relatively slow as reflected by the absorption rate constant, absorption half-life and T_{max}. It is important to highlight that for marbofloxacin administered at a dosage of 1 mg/kg a similar absorption half-life has been reported (Schneider et al., 1996). A faster and less variable absorption process was observed after SC administration; however, statistical differences between routes in absorption half-life and T_{max} were not significant. Bioavailability was high for both administration routes; being significantly higher ($p < 0.05$) after SC administration.

Elimination half-life for both administration routes was equally long and similar to that reported in cats after oral administration (Albarellos et al., 2005).

Compared to other fluoroquinolones in dogs, it was similar to that reported for orally administered pradofloxacin (5.6–7.2 hr) (Lees, 2013), shorter than that reported for marbofloxacin (14.7 and 11 hr for PO and SC administration, respectively) (Schneider et al., 1996) and longer than that reported for enrofloxacin (3 and 2.25 hr for PO and SC administration, respectively) (Bidgood & Papich, 2005; Heinen, 2002).

It has been established that for concentration-dependent antibacterial agents such as fluoroquinolones, the $AUC_{24\,hr}$/MIC ratio is the most important efficacy predictor; the rate of clinical cure being greater than 80% when this ratio is higher than 50 for Gram-positive bacteria and 125 for Gram-negative bacteria (Papich, 2014). A second predictor of efficacy for concentration-dependent antibiotic is the ratio C_{max}/MIC, considering that values above 8–10 would lead to better clinical results (Dudley, 1991). It is now accepted that high C_{max}/MIC values are necessary to avoid bacterial resistance emergence (Dudley, 1991; Madaras-Kelly, Ostergaard, Baeker Hovde, & Rotschafer, 1996; Walker, 2000).

The $AUC_{24\,hr}$/MIC and C_{max}/MIC ratios obtained in the present study suggest that levofloxacin administered intravenously, subcutaneously or orally in the dosing schedule applied is efficacious against Gram-negative bacteria with MIC values of 0.1 μg/ml. For Gram-positive bacteria with MIC values of 0.5 μg/ml, only SC and PO administration at a dosage of 5 mg/kg showed to be efficacious.

The use of Monte Carlo simulation (MCS) takes into account the variability of the drug PK and the probability distribution of the bacterial MIC to make predictions of the likely result of different therapeutic approaches, using different antimicrobial dosage regimens. Therefore, it is a useful tool to provide assistance in the optimization of empirical antimicrobial therapy (Asín-Prieto, Rodríguez-Gascón, & Isla, 2015). As most fluoroquinolones, LFX in dog shows dose proportionality (FDA, 1996) allowing Monte Carlo simulations of a range of doses. The reported MIC-based PK/PD analysis by Monte Carlo simulation allows to conclude that the proposed dose regimens of LFX in dogs, 5 and 7.5 mg/kg/24 hr by SC route and 10 mg/kg/24 hr PO may be adequate to recommend as an empirical therapy against *S. aureus* strains with MIC values ≤0.5 μg/ml and *E. coli* strains with MIC values ≤0.125 μg/ml.

CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTION

M.F.L and G.A. carried out the experiment and wrote the manuscript. Both authors have read and approved the manuscript.

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