

Pharmacokinetic-pharmacodynamic integration of moxifloxacin in rabbits after intravenous, intramuscular and oral administration

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The pharmacokinetics of moxifloxacin was studied following intravenous (i.v.), intramuscular (i.m.) and oral dose of 5 mg/kg to healthy white New Zealand rabbits ($n = 6$). Moxifloxacin concentrations were determined by HPLC assay with fluorescence detection. The moxifloxacin plasma concentration vs. time data after i.v. administration could best be described by a two-compartment open model. The disposition of i.m. and orally administered moxifloxacin was best described by a one-compartment model. The plasma moxifloxacin clearance (Cl) for the i.v. route was (mean \pm SD) 0.80 ± 0.02 L/h·kg. The steady-state volume of distribution (V_{ss}) was 1.95 ± 0.18 L/kg. The terminal half-life ($t_{1/2\lambda z}$) was (mean \pm SD) 1.84 ± 0.12 , 2.09 ± 0.05 and 2.15 ± 0.07 h after i.v., i.m. and oral, respectively. Minimal inhibitory concentration (MIC) assays of moxifloxacin against different strains of *S. aureus* were performed in order to compute pharmacodynamic surrogate markers. From these data, it is concluded that a 5 mg/kg dose moxifloxacin would be effective by i.m. and oral routes in rabbits against bacterial isolates with $MIC \leq 0.06$ $\mu\text{g/mL}$ and possibly for $MIC \leq 0.12$ $\mu\text{g/mL}$, but in the latter case a higher dose would be required.

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INTRODUCTION

Moxifloxacin is a new 8-methoxy-quinolone with a broad spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria, anaerobes and atypical organisms such as *Mycoplasma* and *Chlamydia* spp.

Fluoroquinolones are considered to have a concentration-dependent effect, although a time-dependent bactericidal effect against some Gram-positive bacteria has also been described (Spreng *et al.*, 1995; Cester *et al.*, 1996). They also have some characteristics such as a wide spectrum of bactericidal activity, a large volume of distribution, low plasma protein binding and relatively low MICs against susceptible target microorganisms (Spreng *et al.*, 1995; Brown, 1996). In recent years many pharmacokinetic studies of fluoroquinolones have been carried out in several species (Marangos *et al.*, 1997; Aliabadi & Lees, 2001; Abd El-Aty *et al.*, 2005; Gaur *et al.*, 2004; Seguin *et al.*, 2004). Recent studies in humans demonstrate excellent

clinical efficacy of moxifloxacin, showing high systemic bioavailability, extensive distribution to pulmonary tissues and fluids, and a low incidence of gastrointestinal side effects (Stass & Kubitzka, 1999; Stass, 1999; Ball, 2000; Blondeau & Hansen, 2001).

In vivo, moxifloxacin is effective in mouse models of typical and atypical respiratory tract infections and in guinea pigs infected with *Mycoplasma pneumoniae* (Stass *et al.*, 1998). In recent years, consideration of rabbits has passed from being an animal production field to small animal practice as a companion animal which makes it necessary to reconsider strategies in the treatment of infectious diseases in this species.

There are few published data on the pharmacokinetics of moxifloxacin in animals. Gardner *et al.* (2004) reported pharmacokinetics of moxifloxacin after oral administration to horses. The present study was designed to determine the plasma pharmacokinetics of moxifloxacin following intravenous (i.v.), i.m. and oral administration to rabbits and to compute the main

surrogate efficacy markers using MICs against *S. aureus* strains from rabbits.

MATERIALS AND METHODS

Animals

Six New Zealand white rabbits of both sexes weighing between 3.2 and 3.8 kg were collected from the Laboratory Animal Farm of the University of Murcia. The rabbits were determined to be clinically healthy before the study, based on physical and blood analytical examination. The animals were housed individually in cages under a 12-hour light/dark cycle and were fed pelleted feed concentrate with free access to food and water. They did not receive any drug treatment before the study. The study was approved by the bioethics committee of the University of Murcia.

Experimental design

A crossover design was used in three phases ($2 \times 2 \times 2$), with two washout periods of 15 days. Aqueous solutions of moxifloxacin (2%) were administered by i.v., intramuscular (i.m.) and oral route at single doses of 5 mg/kg bodyweight (Bayer AG, Wuppertal, Germany). Before i.v. administration each animal was placed in a restraining device. One ear was used for injecting into the marginal ear vein, and the opposite ear was used to obtain blood samples. Intramuscular administration was performed in the semimembranous muscle and oral administration by nasogastric tube. Blood samples were collected at 0, 5, 10, 15, 30, 45 min and 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 32 and 48 h following i.v. drug dose and at 0, 10, 15, 30, 45 min and 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 32, 48 and 72 h following i.m. and oral administration. Blood samples (1 mL) were collected by inserting a 20-gauge needle into the marginal ear vein, and allowing the blood drip into a 2 mL heparinized syringe following, which it was placed in a tube. Samples were centrifuged at 1500 g for 15 min within 30 min after collection. Plasma was immediately removed and stored at -45°C until assayed.

Analytical method

Plasma concentrations of moxifloxacin were measured using a modified HPLC method previously reported by Siefert *et al.* (1999a). The HPLC system was equipped with a model LC-10Asvp pump, a RF-10Axl Fluorescence Detector and a model SIL-10Advp autoinjector (Shimadzu, Kyoto, Japan). The above-mentioned system was connected to a computer with a Shimadzu Class-VPTM Chromatography Data System Programme (Shimadzu, Columbia, MD, USA).

Moxifloxacin pure substance was supplied by Bayer AG (Wuppertal, Germany). Ciprofloxacin (Vita Farma, Madrid, Spain) was used as internal standard. After addition of 10 μL of the internal standard to 200 μL plasma, 200 μL acetonitrile was added. Plasma proteins were precipitated by shaking in an ultrasonic bath followed by centrifugation for 10 min at

1600 g. The supernatant was diluted fourfold with 0.067 M disodium hydrogen phosphate buffer pH = 7.5 and transferred to HPLC autosampler vials. The HPLC separation was performed using a reverse-phase Discovery C₁₈ column, 250 \times 4 mm, 5 μm particle size (Supelco, Bellefonte, PA, USA) with an injection volume of 50 μL . Autosampler vials and column temperature was set at 5 $^{\circ}\text{C}$. The mobile phase consisted of acetonitrile (20%) and tetrabutylammonium hydrogensulphate solution (10 g/L) (80%) using an isocratic form with a flow rate of 1.0 mL/min. Moxifloxacin eluted at approximately 11.3 min. The fluorescence detection was performed at an excitation wavelength of 296 nm and an emission wavelength of 504 nm.

Method validation

The calibration curve was prepared with seven concentrations between 10 and 1000 $\mu\text{g/L}$ using blank rabbit plasma.

Standard curves were collected by unweighted linear regression of the moxifloxacin peak areas vs. known concentrations. Each point was established from an average of six determinations. Correlation coefficients (r) were >0.98 for calibration curves.

Working standard solutions were prepared from moxifloxacin stock solutions by serial dilution with phosphate buffer to yield final concentrations of 10, 25, 50, 100, 250, 500 and 1000 $\mu\text{g/L}$. Quality controls were prepared from a pool of blank rabbit plasma spiked with known amounts of moxifloxacin to reach similar concentrations. Plasma aliquots were stored at -45°C until assay.

Aliquots of standards, quality controls and plasma samples were extracted as above and 50 μL was injected into the chromatographic system.

The percentage recoveries were determined by comparing the peak areas of plasma blank samples spiked with different amounts of drug and treated as any sample, with the peak areas of the same standards prepared in phosphate buffer. Each point was established from an average of six determinations. The average ($\pm\text{SE}$) recoveries between and within batch were 98.7 ± 0.18 and 99.6 ± 0.12 . The assay precision (RSD) was assessed by expressing the standard deviation of repeated measurements as a percentage of the mean value. Intra-day precision was estimated from six replicates of three standard samples used for calibration curves (RSD $< 8\%$). Inter-day precision was estimated from the analysis of standard samples on three separate days (RSD $< 10\%$). The limit of quantification (LOQ) of moxifloxacin in plasma was chosen as the concentrations used for the lowest concentration on the calibration curves and for which the RSD $< 15\%$ (LOQ: 10 $\mu\text{g/L}$).

Bacterial isolates and MIC assays

Sixteen rabbit *S. aureus* strains were tested. Four of these strains were high virulence strains, isolated from commercial rabbitries with chronic problems of staphylococcosis. (Devriese *et al.*, 1996; Hermans *et al.*, 1999). The other strains were low

virulence strains. The strains were isolated in Belgium (12) and France (4).

The MICs were determined using the NCCLS (National Committee for Clinical Laboratory Standards) agar dilution method (NCCLS, 2002). After overnight incubation at 37 °C, the inocula were suspended in 0.9% NaCl solution to a 0.5 McFarland standard. By means of a Steers inoculum applicator, a 1/10 dilution of these suspensions was inoculated on Mueller-Hinton II agar (Beckton Dickinson, Le Pont de Claix, France) containing moxifloxacin concentrations ranging from 0.03 to 128 µg/mL. The plates were incubated at 37 °C and observed after 24 h. The MIC was defined as the lowest concentration producing no visible growth. *S. aureus* ATCC 29213 and *E. coli* ATCC 25922 strains were used as reference strains.

Pharmacokinetic analysis

The concentration-time data collected after each treatment in each individual animal were initially fitted to one-, two-, three- and four-exponential equations by the retroprojection method (Gibaldi & Perrier, 1982) and the PKCALC computer program (Shumaker, 1986) was used to obtain the best estimates of the parameters of these equations. The final curve fitting was carried out using nonlinear regression with the MULTI computer program and Gauss-Newton damping algorithm (Yamaoka *et al.*, 1981). Akaike's Information Criterion (AIC) (Yamaoka *et al.*, 1978) was used to determine the number of compartments used in the pharmacokinetic analysis and the most appropriate weighting for the data. The data points were weighted with the inverse of the squared fitted value. Pharmacokinetic parameters were collected from the individual fitted equations (Gibaldi & Perrier, 1982). The absorption and disposition half-lives were calculated as $t_{1/2a} = \ln 2/k_a$, $t_{1/2\lambda_1} = \ln 2/\lambda_1$ and $t_{1/2\lambda_2} = \ln 2/\lambda_2$, respectively.

A noncompartmental model was used to determine the area under the concentration-time curve (AUC), area under the first moment curve (AUMC), using the linear trapezoidal rule with extrapolation to infinity. Mean residence time was calculated as $MRT = AUMC/AUC$. Mean absorption time was calculated as $MAT = MRT_{i.m.} - MRT_{i.v.}$ and the systemic clearance as $Cl = Dose/AUC$. Bioavailability (*F*) was calculated by the method of corresponding areas:

$$F (\%) = \frac{AUC_{i.m.}/D_{i.m.}}{AUC_{i.v.}/D_{i.v.}} \times 100$$

where *D* is the administered dose.

Statistical analysis

Descriptive statistical parameters as mean, standard deviation and coefficient of variation were calculated. Harmonic means were calculated for the half-lives of elimination and absorption. The Wilcoxon Rank Sum test was used to test parameters for significant differences between i.v. with respect to i.m. and oral administration (Powers, 1990). The Statistical Software used was Statgraphics 7.0 (Manugistic Inc., Rockville, MD, USA).

RESULTS

The mean (±SD) plasma concentration of moxifloxacin following i.v., i.m. and oral administration are shown in Fig. 1 and mean (±SD) values for pharmacokinetic parameters are given in Table 1. No adverse effects were observed in any of the rabbits following i.v., i.m. and oral dose of moxifloxacin at 5 mg/kg.

The moxifloxacin plasma concentration vs. time data after i.v. administration could best be described by a two-compartment open model, for which the general polyexponential equation is:

$$C = \sum_{i=1}^n C_i \cdot e^{-\lambda_i t}$$

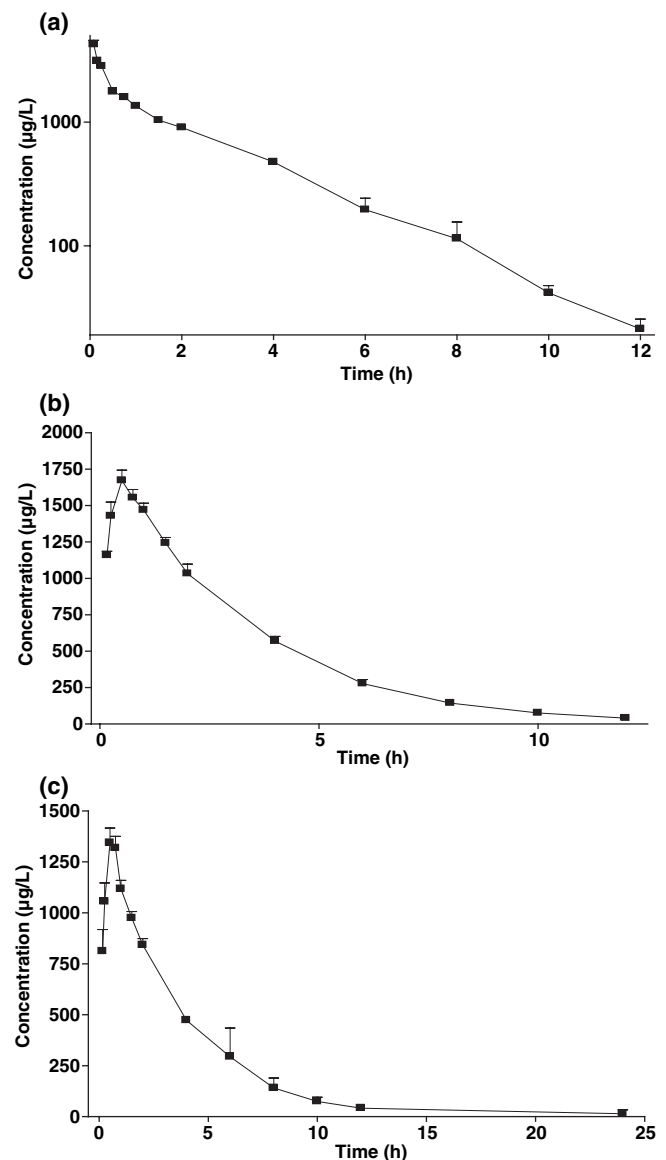


Fig. 1. Experimental plasma concentrations (mean ± SD) of moxifloxacin at a single dose of 5 mg/kg bodyweight (*n* = 6). (a) Semilogarithmic plot after i.v. administration. (b) Arithmetic plot after i.m. administration. (c) Arithmetic plot after oral administration.

Parameters	Units	Intravenous	Intramuscular	Oral
C_1	µg/L	3895.76 ± 472	–	–
C_z	µg/L	2095.11 ± 149	–	–
λ_1	h ⁻¹	5.66 ± 0.46	–	–
λ_z	h ⁻¹	0.38 ± 0.02	0.33 ± 0.01*	0.32 ± 0.02*
$t_{1/2\lambda_1}$	h	0.12 ± 0.01	–	–
$t_{1/2\lambda_z}$	h	1.84 ± 0.12	2.09 ± 0.05*	2.15 ± 0.07*
V_z	L/kg	2.12 ± 0.14	–	–
V_{ss}	L/kg	1.95 ± 0.18	–	–
AUC	mg·h/L	6.28 ± 0.13	5.84 ± 0.26*	4.74 ± 0.071*
$AUMC$	mg·h ² /L	15.34 ± 1.10	18.69 ± 1.29	15.59 ± 0.40
MRT	h	2.44 ± 0.20	3.20 ± 0.08*	3.29 ± 0.05*
Cl	L/h·kg	0.80 ± 0.02	–	–
K_a	h ⁻¹	–	6.51 ± 1.37	6.17 ± 2.03
$t_{1/2k_a}$	h	–	0.11 ± 0.02	0.12 ± 0.03
MAT	h	–	0.76 ± 0.19	0.84 ± 0.23
C_{max}	µg/L	–	1643.51 ± 49	1288.17 ± 43
T_{max}	h	–	0.50 ± 0.05	0.55 ± 0.07
F	%	–	92.96 ± 5.66	75.49 ± 1.50

Table 1. Pharmacokinetic parameters (mean ± SD) of moxifloxacin in rabbits after i.v., i.m. and oral dose of 5 mg/kg bodyweight ($n = 6$)

C_1 , intercept of the ordinate by the fastest disposition slope minus the intercept of the next fastest disposition slope; C_z , intercept of the slowest disposition slope with the ordinate; $t_{1/2\lambda_1}$, the disposition half-life associated with the initial slope (λ_1) of a semilogarithmic concentration–time curve; $t_{1/2\lambda_z}$, the elimination half-life associated with the terminal slope (λ_z) of a semilogarithmic concentration–time curve; V_z , the apparent volume of distribution calculated by the area method; V_{ss} , the apparent volume of distribution at steady-state; Cl , the total body clearance of drug from the plasma; AUC , the area under the plasma concentration–time curve from zero to infinity; $AUMC$, area under the moment curve; MRT , mean residence time; F , the fraction of the administered dose systemically available (bioavailability); T_{max} , the time to reach peak or maximum plasma concentration following i.m. and oral administration; k_a , absorption rate constant (first-order); $t_{1/2a}$, absorption half-life; MAT , mean absorption time; C_{max} , the peak or maximum plasma concentration following i.m. and oral administration. *Significantly different from i.v.

where C is plasma concentration of drug; t is time after drug administration; C_i and λ_i are the intercept and slope, respectively, of the different disposition phases and e is the base of the natural logarithm.

The disposition of i.m. and orally administered moxifloxacin in rabbits was best described by a one-compartment model.

The mean ± SD plasma moxifloxacin clearance (Cl) for the i.v. route was 0.80 ± 0.02 L/h·kg. The steady-state volume of distribution (V_{ss}) was 1.95 ± 0.18 L/kg. The terminal half-life ($t_{1/2\lambda_z}$) was 1.84 ± 0.12 h and the MRT was 2.44 ± 0.20 h.

Moxifloxacin was rapidly absorbed after i.m. administration ($T_{max} = 0.50 \pm 0.04$ h; $MAT = 0.76 \pm 0.19$ h) and after oral administration ($T_{max} = 0.55 \pm 0.07$ h; $MAT = 0.84 \pm 0.23$ h). After i.m. administration, the absolute bioavailability was 92.96 ± 5.66% and the terminal half-life 2.09 ± 0.05 h. The C_{max} was 1.64 ± 0.05 mg/L. After oral administration, the

absolute bioavailability was 75.49 ± 1.50% and the terminal half-life 2.15 ± 0.07 h. The C_{max} was 1.29 ± 0.04 mg/L.

Significant differences were found between i.v. respect to i.m. and i.v. respect to oral administration for λ_z , $t_{1/2\lambda_z}$, AUC and MRT ($P < 0.05$). The $MICs$ values and surrogate markers are shown in Tables 2 and 3.

DISCUSSION

The results collected demonstrate a rapid and wide distribution of moxifloxacin after i.v. administration with a $t_{1/2\lambda_1}$ of 0.12 h and a volume of distribution at steady-state (V_{ss}) of 1.95 L/kg suggesting a wide penetration through biological membranes and a good tissue distribution. The K_{12}/K_{21} ratio of 1.27 corroborate the above statement. The V_{ss} collected is large and in

Table 2. $MICs$ of moxifloxacin on rabbit *Staphylococcus aureus* strains ($n = 16$)

Species	Origin	Number of strains with moxifloxacin MIC (µg/mL) of													
		≤ 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
<i>S. aureus</i>	Rabbit		9	6	1										
<i>S. aureus</i> ATCC 29213	Control			×											
<i>E. coli</i> ATCC 25922	Control		×												

Table 3. Surrogate markers of efficacy from pharmacokinetic parameters collected after i.m. and oral administration of moxifloxacin at a single dose of 5 mg/kg bodyweight ($n = 6$)

	Intramuscular	Oral
$MIC = 0.12 \mu\text{g/mL } S. aureus$		
AUC_{24}/MIC	48.66 h	39.5 h
C_{max}/MIC	13.69	10.73
$MIC = 0.06 \mu\text{g/mL } S. aureus$		
AUC_{24}/MIC	97.33	79
C_{max}/MIC	27.38	21.46

agreement with V_{ss} of other fluorquinolones in the same species. Abd El-Aty *et al.* (2005) reported a V_{ss} of 1.5 L/kg for difloxacin and Broome *et al.* (1991) a V_{ss} of 0.93 L/kg for enrofloxacin, in rabbits.

Elimination half-lives ($t_{1/2\lambda z}$) in this study after i.v., i.m. and oral dosing were 1.84, 2.09 and 2.15 h, respectively. This value are close to those reported in rabbits for enrofloxacin with a $t_{1/2\lambda z}$ after i.v. and oral dosing of 2.5 and 2.41 h, respectively (Broome *et al.*, 1991). The longer half-life after extravascular routes (i.m. and oral) is conditioned by the absorption process, although MAT and MRT do not suggest a flip-flop effect. Data for moxifloxacin have been reported only in horses after oral administration (Gardner *et al.*, 2004) with a half-life of 33.98 h, significantly longer than collected in the present study. Stass and Kubitzka (1999) reported in humans a half-life for moxifloxacin after i.v. and oral dose of 15.4 and 15.6 h, respectively. However, Siefert *et al.* (1999b) collected half-lives in rat and mouse after i.v. and oral dosing ranging from 0.93 to 1.2 h, similar to those in our study.

Moxifloxacin was well absorbed following i.m. and oral administration with an absolute bioavailability (F) of 92.96 and 75.49%, respectively. The absorption process was rapid with a $T_{max \text{ i.m.}}$ = 0.50 h and $T_{max \text{ oral}}$ = 0.55 h and corroborated by the absorption rate constant (K_a) and absorption half-life ($t_{1/2ka}$). Bioavailability results collected show a low variability after both routes of administration, which is an advantage in treatment. Variability in the absolute bioavailability can be associated with two disadvantages: (a) underexposure of animals with low bioavailability which favours the emergence of resistance and (b) overexposure of animal with high bioavailability, with risk of side effects (Bousquet-Melou *et al.*, 2002). This situation has been described for some quinolones such as enrofloxacin (Langston *et al.*, 1996).

Gardner *et al.* (2004) in their study in horses, based on the adverse gastrointestinal effects, could not recommend moxifloxacin (5.8 mg/kg) for treatment of equine bacterial pneumonia. In the present study, the tolerability profile of moxifloxacin in rabbits was very high without evidence of adverse effects.

The specific parameters most commonly correlated with clinical outcome include the ratio of peak to minimum inhibitory concentration (C_{max}/MIC), the ratio of the 24-hour area under the curve to MIC (AUC_{24}/MIC) and the duration of time that serum levels exceed the MIC ($T > MIC$). For a concentration-dependent drug such as moxifloxacin, clinical response usually

correlate with AUC_{24}/MIC and C_{max}/MIC , and high ratios of the latter have also been associated with a lower incidence of resistance development (Drusano *et al.*, 1993; Lode *et al.*, 1998). However, for some Gram-positive bacteria, a time-dependent effect has been associated with fluorquinolones, in this case, time above the MIC ($T > MIC$) would be the PK-PD surrogate marker with the best prediction of success (Andes & Craig, 2002). Animal models with different quinolones showed that an AUC_{24}/MIC ratio of about 100 h or C_{max}/MIC ratio of 10 should be achieved to give maximum clinical and bacteriology efficacy (Turnidge, 1999). However, some authors have pointed out that when surrogate markers are used to predict optimal dosage, the numerical values of AUC_{24}/MIC , C_{max}/MIC and $T > MIC$ have been generated in experimental infections in laboratory animals or in human clinical trials (Lees & Aliabadi, 2002). These numerical values may or may not be applicable to rabbit's infections or in general to animal infections. However, numerical values for AUC_{24}/MIC breakpoint are generally similar across species because they take into account pharmacokinetic interspecies variability (Toutain *et al.*, 2002). Hence, several authors have suggested that lower AUC_{24}/MIC values may be appropriate for immunocompetent animals in veterinary medicine. According to MIC data collected against *S. aureus* strains tested and using the above surrogate markers (Table 3) a single i.m. and oral dose (5 mg/kg) of moxifloxacin in rabbits had an AUC_{24}/MIC ratio of 50 h (i.m.) and 40 h (oral) for a MIC of 0.12 $\mu\text{g/mL}$. For a MIC of 0.06 $\mu\text{g/mL}$ the AUC_{24}/MIC ratio was 97 h (i.m.) and 79 h (oral). The C_{max}/MIC ratio for both routes of administration and for all MIC s values was approximately 10 indicating a high protection against resistance emergence. Therefore, the use of moxifloxacin in rabbits as companion animals should be effective by i.m. and oral route at 5 mg/kg against bacterial isolates with $MIC \leq 0.06 \mu\text{g/mL}$ and possibly for $MIC \leq 0.12 \mu\text{g/mL}$, although in the latter case an increase of dose would be required.

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