RESEARCH ARTICLE

# Pharmacokinetics of Marbofloxacin following Intramuscular Administration in Rabbits

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## Abstract

Pharmacokinetic study of marbofloxacin was carried out in healthy rabbits following intramuscular administrations @ 2.00 mg/kg body weight once daily for five days. A serial blood samples were collected on 1st and 5th day, *i.e*. at 2.5, 5, 10, 30, 45 min and then at 1, 2, 4, 6, 8, 10, 12 and 24 h after administration of marbofloxacin. Concentrations of the marbofloxacin in blood plasma were estimated by microbiological assay. Kinetic parameters were calculated by using one compartment open model. Apparently higher plasma concentrations of the drug appeared at all intervals from 2.5 min to 24 h on 5th day as compared to 1st day of marbofloxacin administration with significant differences at 10.0 min and 12 h only. The minimum therapeutic concentration (≥ 0.25 µg/mL) of marbofloxacin was maintained up to 12 h and all kinetic parameters differed non-significantly between 1st and 5th day of marbofloxacin administration. On the basis of present findings, a satisfactory dosage regimen of marbofloxacin @ 2.14 mg/kg body weight followed by 2.04 mg/kg body weight intramuscular route at 24 h intervals can be recommended to maintain the minimum therapeutic concentration (≥ 0.25 µg/mL) during the treatment of bacterial infections in rabbit.

**Key words:** Intramuscular, Marbofloxacin, Pharmacokinetic, Rabbits.

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## Introduction

Marbofloxacin is a synthetic, third-generation fluoroquinolone used in veterinary practice. Similar to other fluoroquinolones, marbofloxacin acts by inhibiting the bacterial DNA-gyrase and has high antimicrobial activity against many Gram-negative, some Gram-positive bacteria and *Mycoplasma* spp. (El Garch *et al.*, 2017). Marbofloxacin is safe and efficacious in most of the species. It is administered orally or parenterally for the treatment of gastrointestinal, urinary, reproductive, respiratory tract and soft tissue infections with a high bioavailability (Tohamy and El-Gendy, 2013). Due to its broad spectrum, it is efficient against pathogenic bacteria such as *Streptococcus* spp., *Proteus* spp., *Staphylococcus* spp., and *Escherichia coli*, and is permitted for the treatment of bovine, caprine, wild, pet and laboratory animals (Shan *et al.,* 2014).

Fluoroquinolones share some common pharmacokinetic and pharmacodynamic characteristics such as large volume of distribution, low plasma protein binding and relatively low minimum inhibitory concentrations (MICs) against target microorganisms, however, differences in some pharmacokinetic parameters such as variations in metabolic extent or terminal half-life, have been reported (Waxman *et al.,* 2001), making it necessary to study the pharmacokinetics of individual fluoroquinolone compounds. Moreover, when the drug is given at the same dosage a wide variation in intensity and duration of pharmacological effect are commonly observed among different species of animals. Management of bacterial infections with antimicrobials is a challenging aspect of treatment in rabbits. Therefore, the present study was designed to determine the pharmacokinetics of marbofloxacin in rabbits.

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## Materials and Methods

**Ethical statement:** The experiment was performed, following approval of the protocol by the Institutional Animal Ethics Committee (No-54/IAEC/Vety/Rewa/2021) of the College.

### Experimental Animals

Six clinically healthy New Zealand White rabbits of both sexes (Marin *et al.,* 2013), between 5 to 6 months of age and 2-2.5 kg body weight were included in the present study. The experimental animals were maintained at Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science & Animal Husbandry, Rewa (MP, India), under uniform management conditions and acclimatized prior to commencement of experiment. During the entire period of experimentation, the animals were subjected to regular clinical examination and maintained on dry as well as green fodder every day. Clean drinking water was provided *ad libitum*. All the animals were healthy at the time of experimentation.

### Drugs/Chemicals/Reagents and Test Organism

Injectable commercial preparation containing marbofloxacin equivalent to 100 mg/mL (Zydus AH., Ahmedabad, India) was used in the present investigation. Antibiotic media no. 1 and 11 were procured from Himedia laboratories Pvt. Ltd., Mumbai. *Escherichia coli* (ATCC 25922) as test organism was used for estimation of concentration of the drugs in plasma by microbiological assay technique obtained from the National Collection of Industrial Micro-organism (NCIM), Division of Bio-chemical Sciences, National Chemical Laboratory, Pune.

### Dosage and Administration of Drugs

Marbofloxacin (100 mg/mL) was given to six healthy rabbits @ 2.00 mg/kg body weight once daily through intramuscular (IM) route for five days.

### Estimation of Drug Concentration

Blood samples (approx 0.50 mL) were withdrawn from lateral saphenous vein into heparinized glass centrifuge tubes on days 1 and 5 of treatment at 2.5, 5, 10, 30, 45 min and then at 1, 2, 4, 6, 8, 10, 12 and 24 h after administration of the drug. Plasma was separated and kept at -4°C until analysis.

The concentration of marbofloxacin in plasma was estimated by a rapid, specific microbiological assay technique using *Escherichia coli* as the test organism (Paul *et al*., 1971). The calibration graph was prepared by serially diluting a stock standard solution of 2.0, 1.0, 0.5, 0.25, 0.1, 0.05, and 0.025 micrograms per mL plasma. These standards were used with test samples in assay to measure drug concentration.

### Pharmacokinetic Analysis

The plasma concentration-time profile of marbofloxacin was used to determine the pharmacokinetic profile for each animal. The gathered data was further subjected to appropriate compartment open model and kinetic parameters were calculated on the basis of Gibaldi and Perrier (1982).

For kinetic analysis, data was analyzed using one compartment open model based on kinetic data, the dosage regimen for maintaining minimal therapeutic concentration in plasma at the desired dosage intervals (τ) was calculated using the following equations.

$D^* = C_P^{\infty}$ min. $Vd_{area}$ . $(e^{\beta.\tau})$

$D_0 = C_P^{\infty}$ min. $Vd_{area}$ . $(e^{\beta.\tau} - 1)$

Where,

$D^*$ = Priming or Loading dose

$D_0$ = Maintenance dose

$C_P^{\infty}$ (min) = Desired minimum plasma concentration

τ = Dosage interval

e = Base of natural logarithm

® and $Vd_{area}$ were obtained from kinetic study.

**Statistical analysis**: Concentrations of the drugs in plasma and various kinetic parameters of marbofloxacin on first and last doses were compared by using paired 't' test (Snedecor and Cochran, 1994).

## Results and Discussion

Comparative plasma concentrations of marbofloxacin at various time intervals following IM administration in healthy rabbit are shown in Table 1. The drug was detected from 2.5 min to 24 h with a mean plasma concentration range from 0.19±0.07 to 0.05± 0.01 µg/mL on 1st day and from 0.24±0.06 to 0.06±0.01 µg/mL on 5th day. The minimum therapeutic concentration (≥ 0.25 µg/mL) of marbofloxacin was maintained from 2.5 min to 12 h and mean peak plasma concentration was 2.12±0.10 µg/mL on 1st day and 2.34±0.06 µg/mL on 5th day at 30 min of marbofloxacin administration. Significantly higher plasma concentration of the drug was detected at 10 min and 12 h on 5th day as compared to 1st day of marbofloxacin administration. The plasma concentrations of the drug on other time intervals differed non-significantly between 1st and 5th day of administration. Upadhyay *et al.* (2021) reported a significantly higher plasma concentration of the drug from 5.0 min to 12 h on 5th day as compared to 1st day of amikacin administration in goats.

**Table 1:** Plasma concentrations (Mean ± SE) of marbofloxacin on 1st and 5th day following IM administration in healthy rabbits (n=6)

| Time | Plasma concentration (µg/mL) | |
|---|---|---|
| | 1st Day | 5th Day |
| 2.5 min | 0.19±0.07 | 0.24±0.06 |
| 5.0 min | 0.59±0.05 | 0.72±0.05 |
| 10 min | 1.05±0.05 | 1.19±0.05* |
| 30 min | 2.12±0.10 | 2.34±0.06 |
| 45 min | 1.85±0.11 | 2.05±0.07 |
| 1.0 h | 1.63±0.10 | 1.84±0.06 |
| 2.0 h | 1.32±0.08 | 1.53±0.06 |
| 4.0 h | 0.98±0.06 | 1.16±0.06 |
| 6.0 h | 0.75±0.04 | 0.91±0.04 |
| 8.0 h | 0.57±0.03 | 0.70±0.04 |
| 10 h | 0.45±0.02 | 0.55±0.03 |
| 12 h | 0.35±0.02 | 0.44±0.03* |
| 24h | 0.05±0.01 | 0.06±0.01 |

*Significantly ($p<0.05$) different between days.

The plasma drug concentration of marbofloxacin as a function of time following once daily IM administration on 1st and 5th day of drug administration and the data obtained were adequately described by one compartment open model in the present study. The values of different kinetic parameters in healthy rabbits calculated by PK Solution software are depicted in Table 2. Non-significantly higher values of elimination (B), elimination rate constant (β), absorption rate constant (A'), area under curve (AUC), absorption half-life ($t_{1/2}$Ka), area under first moment curve (AUMC), mean residence time (MRT), maximum plasma concentration ($C_{max}$), time of maximum plasma concentration ($t_{max}$) and elimination half-life ($t_{1/2\beta}$) were observed on 5th day as compared to 1st day of marbofloxacin administration.

**Table 2:** Comparative pharmacokinetic parameters (Mean ± SE) after administration of IM marbofloxacin on 1st and 5th day in healthy rabbits (n=6)

| Parameters | Kinetic parameters of marbofloxacin | |
|---|---|---|
| | 1st day | 5th day |
| B (µg/mL) | 2.47±0.30 | 03.41±0.70 |
| β ($h^{-1}$) | 0.16±0.01 | 00.17±0.02 |
| $t_{1/2}\beta$ (h) | 4.38±0.42 | 04.38±0.49 |
| A' (µg/mL) | 3.15±0.59 | 05.05±1.29 |
| Ka | 2.87±0.54 | 02.57±0.69 |
| $t_{1/2}$ Ka | 0.28±0.04 | 00.42±0.12 |
| C max µg/mL | 2.08±0.10 | 02.30±0.06 |
| $t_{max}$ (h) | 0.50±0.00 | 00.50±0.00 |
| AUC α (µg/mL.h) | 12.92±0.50 | 15.43±0.59 |
| AUMC (µg/mL.$h^2$) | 88.10±6.34 | 108.13±7.26 |
| MRT (h) | 6.82±0.48 | 07.00±0.35 |
| $Vd_{area}$ (L/kg) mL/µg | 0.99±0.11 | 00.83±0.09 |
| $Cl_B$ (mL/kg/h) | 155.80±6.14 | 130.50±5.30 |

None of the parameters differ between days.

The absorption half-life ($t_{1/2}$Ka) of marbofloxacin was 0.28±0.04 h on 1st day & 0.42±0.12 h on 5th day, and the elimination half-life ($t_{1/2\beta}$) of marbofloxacin was 4.38±0.42 h on 1st day & 4.38±0.49 h on 5th day following once daily IM administration. Higher values of elimination half-life ($t_{1/2\beta}$) of marbofloxacin were reported by Yohannes *et al*. (2015) in Beagle dogs (7.51±3.70 h), Hossain *et al*. (2017) in pig (12.80±1.10 h), and Karademir *et al.* (2015) in sheep (9.50±1.86). The species variance in elimination half-life may be attributed to differences in drug metabolism and excretion.

The AUC of marbofloxacin was 12.92±0.50 µg/mL.h on 1st day and 15.43±0.59 µg/mL.h on 5th day following once daily IM administration in rabbits. These findings are in well agreement with the results of Yohannes *et al.* (2015), who reported 11.37±3.07 µg/mL.h (AUC) in Beagle dogs. Similarly, the AUMC value of marbofloxacin was 88.10±6.34 µg/mL.$h^2$ on 1st day and 108.13±7.26 µg/mL.$h^2$ on 5th day following IM administration of marbofloxacin. Lower AUC was reported by Bhardwaj *et al*. (2019) in female goats and Karademir *et al*. (2015) in sheep, whereas higher AUC (25.80±1.40 µg/mL.h) was reported by Hossain *et al*. (2017) in pig. The discrepancy in AUC values may be due to species diversity in physiology and total physiological body space available to medication. AUC is affected by drug absorption patterns, lipid solubility, and tissue barriers (Hossain *et al.,* 2017).

The $Vd_{area}$ of marbofloxacin were 0.99±0.11 L/kg on 1st day and 0.83±0.09 L/kg on 5th day following once daily IM administration. These results are in close agreement with the findings of Yohannes *et al*. (2015) in dogs. The high apparent volume of distribution indicates strong tissue penetration and extensive distribution of marbofloxacin. The $Cl_B$ of marbofloxacin observed was 155.80±6.14 mL/kg/h on 1st day and 130.50±5.30 mL/kg/h on 5th day. These findings are in close agreement with the results of Yohannes *et al*. (2015), who reported 170 mL/kg/h ($Cl_B$) in Beagle dogs. The total body clearance is the sum of clearance of drug from each organ by the elimination processes including hepatic biotransformation and renal excretion. Fluoroquinolones are excreted by renal, biliary, or hepatic metabolic pathways and it varied with species. In general, herbivores species are well-endowed with oxidative enzyme systems like cytochrome P450 group, thus, providing rapid drug elimination by hepatic metabolism. The MRT of marbofloxacin was 6.82±0.48 h on 1st day and 7.00±0.35 h on 5th day following once daily IM administration in rabbits, which is in agreement with the Junjun *et al.* (2010) in rabbit and Karademir *et al*. (2015) in sheep. Similar to half-life, mean residence time was long in this study, indicating good drug persistence in the body for optimal therapeutic effects.

The minimum inhibitory concentration (MIC) of marbofloxacin in different microorganisms ranges from 0.256 to 2.00 µg/mL (Kesteman *et al.,* 2010), 0.05 µg/mL and 0.04 µg/mL for *Pasteurella multocida* and *Escherichia coli,* respectively (Bharadwaj *et al*., 2019) and 0.016 µg/mL and 0.229 µg/mL for *Escherichia coli* and *Staphylococcus aureus,* respectively (Schneider *et al.,* 2004). The ultimate objective of the study of disposition kinetics is to determine an appropriate dosage regimen of marbofloxacin. The dosage regimen for any antimicrobial agent is calculated to maintain the minimum therapeutic concentration (Cp∞min=MIC) throughout the course of infection. Based on these kinetic parameters, the dosage regimen for maintaining minimal therapeutic concentration ($Cp^{\infty}$min) of 0.25, 0.50 and 1.00 µg/mL in plasma at the dosage intervals 24 h have been shown in Table 3. The calculated dosage regimens of marbofloxacin for $C_P{}^{\infty}$min=0.25 µg/mL were 2.14±0.06 mg/kg b.wt. (D*) and 2.04±0.07 mg/kg b.wt. ($D^0$), for $C_P{}^{\infty}$min=0.50 µg/mL 4.26±0.10 mg/kg b.wt. (D*) and 4.14±0.09 mg/kg b.wt. ($D^0$), and for $C_P{}^{\infty}$min=1.00 µg/mL were 8.53±0.18 mg/kg b.wt. (D*) and 8.28±0.17 mg/kg b.wt. ($D^0$), respectively, at 24 h dosage intervals in rabbits. Hossain *et al.* (2017) who reported that marbofloxacin dosage of 2.50 mg/kg of body weight by I/V, I/M and P/O administration with 24 h dosing interval provided effective treatment for the infection of pig by *Actinobacillus pleuropneumoniae.*

**Table 3:** Dosage regimens (Mean ± SE) of marbofloxacin following IM administration in healthy rabbits (n=6)

| $C_P^{\infty}$min (µg/mL) | τ (h) | Dose | mg/kg b.wt. |
|---|---|---|---|
| 0.25 | 24 | D* | 2.14±0.06 |
| | | $D^0$ | 2.04±0.07 |
| 0.50 | 24 | D* | 4.26±0.10 |
| | | $D^0$ | 4.14±0.09 |
| 1.00 | 24 | D* | 8.53±0.18 |
| | | $D^0$ | 8.28±0.17 |

D*=Priming or Loading dose, $D^0$=Maintenance dose, τ=Dosage interval and $C_P^{\infty}$min=Minimum therapeutic concentration in plasma

## Conclusion

The result of the present investigation provided clear evidence that higher plasma concentrations of the marbofloxacin appeared for 10 minutes and 12 hours sample on 5th day as compared to 1st day of drug administration. The minimum therapeutic concentration of marbofloxacin was maintained up to 24 h during 1st to 5th day of drug administration. A satisfactory dosage regimen of marbofloxacin @ 2.14 mg/kg body weight followed by 2.04 mg/kg body weight intramuscular route at 24 h intervals can be recommended to maintain the minimum therapeutic concentration (≥0.25 µg/mL) during the treatment of microbial infections in rabbit.

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