Journal of Animal Research: v.13 n.03, p. 411-417. June 2023

DOI: 10.30954/2277-940X.03.2023.16

Pharmacokinetic Evaluation of Marbofloxacin Following Single and Repetitive Intravenous Administration in Rabbits

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Received: 08 April, 2023 **Revised:** 12 May, 2023 **Accepted:** 19 May, 2023

ABSTRACT

Pharmacokinetic study of marbofloxacin was carried out in rabbits following single and repetitive intravenous (IV) administration. Serial blood samples were taken from days 1st and 5th of marbofloxacin administration. Concentrations of the marbofloxacin in blood plasma were estimated by microbiological assay techniques. Various kinetic parameters were calculated by using two compartment open model. Significantly higher plasma concentrations of the drug appeared from 0.5 to 12 hr on 5th day as compared to 1st day of marbofloxacin administration. The minimum therapeutic concentration (≥ 0.25 µg/ml) of marbofloxacin was maintained up to 12 hr in both 1st and 5th day of drug administration. Following multiple once IV dose, significantly higher values of $t_{1/2}\beta$, and AUC were observed in 5th day as compared to 1st day of marbofloxacin administration, whereas significantly lower value of Vd_{area} and Cl_B were observed in 5th day as compared to 1st day of marbofloxacin administration. All the other kinetic parameters differ non-significantly between 1st and 5th day of marbofloxacin administration. On the basis of present findings a satisfactory dosage regimen of marbofloxacin @ 0.91±0.03 mg/kg bwt followed by 0.71±0.03 mg/kg bwt at 12 hr intervals can be recommended to maintain the minimum therapeutic concentration (≥ 0.25 µg/ml)) during the treatment of microbial infections in rabbit.

HIGHLIGHTS

- Significantly higher plasma concentrations of the marbofloxacin appeared from 0.5 to 12 hr on 5th day as compared to 1st day of drug administration.
- The minimum therapeutic concentration of marbofloxacin was maintained up to 12 hr in both 1st and 5th day of drug administration.

Keywords: Pharmacokinetics, marbofloxacin, intravenous, rabbits

Marbofloxacin is a synthetic third-generation fluoroquinolone, developed exclusively for the use in veterinary medicine. It has bactericidal activity against many gram-negative, some gram-positive bacteria and *mycoplasma* (Dorey *et al.*, 2017). Due to its broad spectrum it is efficient against pathogenic bacteria such as *Streptococcus* spp., *Proteus* spp., *Staphylococcus* spp., *Escherichia coli* etc. (Tohamy and El-Gendy, 2013). It is administered orally or parenterally for the treatment of gastrointestinal and respiratory tract, urinary tract infections and neonatal calves with diarrhoea and, for the treatment of skin infections, soft tissue infections in cattle, pigs, dogs, cats and many other species (Shan *et al.,* 2014).

How to cite this article: Mir, A.M., Kumar, N., Shrivastav, A., Ranjan, R., Singh, S.K., Yadav, A., Shrivastava, N. and Sheikh, T.J. (2023). Pharmacokinetic Evaluation of Marbofloxacin Following Single and Repetitive Intravenous Administration in Rabbits. *J. Anim. Res.,* **13**(03): 411-417.

Source of Support: None; **Conflict of Interest:** None

The pharmacokinetics actions of marbofloxacin have been studied in various animals such as cows, goats, sheep, pigs, cats, and dogs. These studies showed that marbofloxacin was widely and rapidly distributed in tissue, with a high bio-distribution in the peripheral tissue and plasma, and showing very high bioavailability (Sun *et al.,* 2015). Marbofloxacin differs in particular from other fluoroquinolones on account of its oxadiazine ring, which is supposed to give the molecule some pharmacokinetic advantages such as a long elimination half-life (Bharadwaj *et al.,* 2018).

Moreover, the wide variations in intensity and duration of pharmacological effect are commonly observed among different species of domestic animals, when the drug is given at the same dose level. Thus, it is important to elucidate the pharmacokinetics of the drugs in each species, in order to minimize dosage errors, which otherwise could lead to therapeutic failures, toxic effects or bacterial resistance (Bharadwaj *et al.,* 2019). Similar to other fluoroquinolones, marbofloxacin has large volume of distribution with good concentrations in tissues and body fluids and activity at extremely low concentrations (Ding *et al.*, 2013). Hence, the present study was undertaken to investigate whether the dosage regimen of marbofloxacin calculated from single Intravenous (IV) administration actually maintains the minimum inhibitory concentration (MIC) at the end of every dosage interval during repetitive administration or not.

MATERIALS AND METHODS

Experimental Animals

The experiment was performed in six clinically healthy domestic rabbits of both sexes, between 5 to 6 months of age and 2 - 4 kg body weight. The experimental animals were maintained at department of veterinary pharmacology and Toxicology, College of Veterinary Science & A.H., Rewa, under uniform managemental 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. All the animals were apparently healthy during the study. The experimental protocol for general procedure and use of animals for conducting the present study has been reviewed and approved by the Institutional Animal Ethics Committee (IAEC), College of Veterinary Science & AH, Rewa, Madhya Pradesh, India,

Drugs /Chemicals /Reagents

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. All other chemical used for analysis were of analytical grade extra pure quality and purchased from reputed companies.

Test Organism

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 Drugs Administration

Marbofloxacin (100 mg/ml) was administered at the dose rate of 2.00 mg/kg body weight as multiple once daily dose IV route for five consecutive days in each of six healthy rabbits (Marin *et al*., 2013).

Collection of Blood Samples

Blood samples approx (0.50 ml) was withdrawn from lateral saphenous vein into heparinized glass centrifuge tubes on days 1 and 5 of treatment: at 0, 5, 10, 30, 45 min and 1, 2, 4, 6, 8, 10, 12 and 24 hr after administration of the drug. Plasma was separated by centrifugation at 3,000 rpm for 15 min at room temperature and kept at -4ºC until analysis, which was usually done within two days of collection of samples.

Estimation of Marbofloxacin in Plasma

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). Punch bioassay technique, which is

the modified method of standard cylinder plate bioassay technique was used to estimate the concentration of marbofloxacin in plasma. In this technique, only a seed layer with bacteria suspension was poured on assay plates and the wells were prepared on assay plates (Arret *et al*., 1971).

Pharmacokinetic Analysis

The plasma concentration-time profile of amikacin 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).

Calculation of Dosage Regimen

For kinetic analysis, data was analyzed using an appropriate 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 (Baggot, 1977):

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

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

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

b and Vd_{area} was obtained from kinetic study.

STATISTICAL ANALYSIS

Comparison of concentrations of the drugs in plasma and various kinetic parameters of marbofloxacin on first and last doses after multiple IV administration in rabbits was compared by using paired '*t*' test (Snedecor and Cochran, 1994).

RESULTS AND DISCUSSION

Intravenous administration of an antibiotic is the most reliable means of managing very ill patients and severe bacterial infections as initially very high antibiotic concentration in central compartment is desired to obtain favorable diffusion gradient from blood to tissues. Pharmacokinetic studies of marbofloxacin have also been conducted following its multiple intravenous administrations at the dose rate of 2.00 mg/kg bwt in goats (Bhardwaj *et al.,* 2018) and 5.00 mg/kg bwt in broiler chickens (Patel *et al.,* 2018). The pharmacokinetic studies of marbofloxacin have also been conducted following its single intravenous administration at the dose rate of 2.00 mg/kg bwt in horses (Peyrou *et al.,* 2004), rabbits (Abo-el-sooud *et al.,* 2010), rabbits (Marin *et al*., 2013), dog (Yohannes *et al.,* 2015) and broiler chicken (El-Komy *et al*., 2016).

Table 1: Comparative plasma concentrations (Mean±SE) of marbofloxacin on 1st and 5th day following IV route of drug administration in healthy rabbits (n=6)

Time (hr)	Plasma Concentration of Marbofloxacin (mg/ml)	
	1st Day	5th Day
0.042	3.44 ± 0.06	3.54 ± 0.06
0.083	3.14 ± 0.06	3.26 ± 0.07
0.166	2.74 ± 0.02	2.94 ± 0.08
0.50	2.12 ± 0.02	2.35 ± 0.06*
0.75	1.83 ± 0.03	2.09 ± 0.04*
1	1.57 ± 0.03	1.90 ± 0.03*
2	1.25 ± 0.03	1.55 ± 0.03*
4	0.99 ± 0.02	1.21 ± 0.03*
6	0.81 ± 0.02	0.99 ± 0.04*
8	0.67 ± 0.03	0.81 ± 0.03*
10	0.56 ± 0.03	0.67 ± 0.03*
12	0.46 ± 0.03	0.57 ± 0.03*
24	0.05 ± 0.01	0.08 ± 0.02

*Significantly ($p<0.05$) different as compared to corresponding values following IV route of drug administration.

Comparative plasma concentrations of marbofloxacin in healthy rabbits after IV have been shown in Table 1 and Fig. 1. The drug was detectable up to 24 hr. The minimum therapeutic concentration (≥ 0.25 µg/ml) of marbofloxacin

was maintained up to 12 hr in both 1st and 5th day of marbofloxacin administration. Significantly higher plasma concentrations of the drug appeared from 0.50, 0.75, 1, 2, 4, 6, 8, 10 and 12 hr to except 0.042, 0.083, 0.166 and 24 hr in 5th day as compared to 1st day marbofloxacin administration in healthy rabbits. The mean peak plasma concentration was 3.44±0.06 µg/ml on 1st day and 3.54±0.06 µg/ml on 5th day at 0.042 hr and marbofloxacin was detected up to 24 hr with a mean plasma concentration of 0.05 ± 0.01 µg/ml on 1st day and 0.08±0.02µg/ml on 5th day.

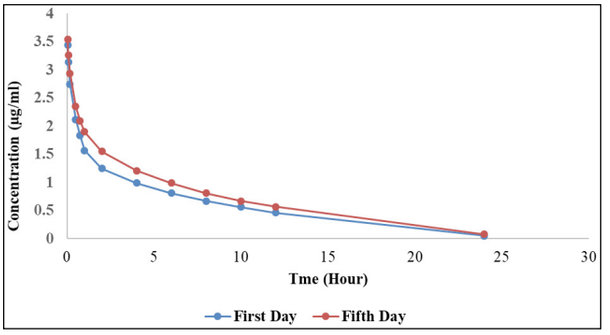

Fig. 1: Comparative plasma concentration of marbofloxacin on 1st and 5th day following IV route of drug administration in healthy rabbits

Based on the plasma levels, the distribution and elimination kinetic parameters for marbofloxacin after its multiple IV administration in healthy rabbits were calculated and are presented in Table 2. In the present study, plasma concentrations of marbofloxacin versus time disposition curves following multiple dose IV administration at the dose rate of 2.00 mg/kg bwt in healthy rabbits were best fitted to a two compartment open model. Similar finding also reported by Junjun *et al*. (2010) after the IV dose of 2.50 mg/kg bwt of marbofloxacin in rabbits, broiler chicken (El-Komy *et al*., 2016), beagle dogs (Yohannes *et al*., 2015) and in foals (Tohamy and El-Gendy, 2013).

Following multiple once daily IV administration, significant higher values of elimination half-life ($t_{1/2}\beta$) and area under curve (AUC), whereas significantly lower values of volume of distribution (Vd_{area}) and total body clearance (Cl_B) are observed on 5th day as compared to 1st day of marbofloxacin administration. All other kinetic parameters differ non-significantly between 1st and 5th day of marbofloxacin administration. The distribution half-life ($t_{1/2}\alpha$) of marbofloxacin in rabbit following multiple once daily IV administration in the present study was 1.08±0.24 hr on 1st day and 1.31±0.36 hr on 5th day. The contrary result (0.25±0.02 hr) was also reported by El-komy *et al. (*2016) in broiler. Upadhyay *et al.* (2020) reported that $t_{1/2}\alpha$ of amikacin in goat following multiple once daily IV administration were 0.40±0.11 h on 1st day and 1.04±0.49 h on 5th day.

Table 2: Comparative pharmacokinetic parameters (Mean±SE) of marbofloxacin on 1st and 5th day following IV route of drug administration in healthy rabbits (n=6)

Kinetic Parameters (Unit)	1st Day	5th Day
A (mg/ml)	0.36 ± 0 .19	0.48 ± 0.08
B (mg/ml)	2.26 ± 0.18	2.64 ± 0.30
C_p^o (mg/ml)	2.61 ± 0.12	3.12 ± 0.32
b (h^{-1})	0.15 ± 0.01	0.15 ± 0.01
a (h^{-1})	0.81 ± 0.15	0.80 ± 0.21
$t_{1/2}$ a (h)	1.08 ± 0.24	1.31 ± 0.36
$t_{1/2}$b (h)	4.60 ± 0.38	4.95 ±0.46*
AUC (mg/ml.h)	14.82 ± 0.49	18.13± 0.57*
AUMC (mg/ml.h^2)	103.12± 7.80	133.35± 9.90
MRT (h)	6.90 ± 0.32	7.33 ± 0.41
K_{12} (h^{-1})	0.12 ± 0.07	0.16 ± 0.04
K_{21} (h^{-1})	0.68 ± 0.11	0.65 ± 0.16
Kel (h^{-1})	0.18 ± 0.002	0.18 ± 0.02
Vd_{area} (L/kg)	0.89 ± 0.06	0.79 ± 0.07*
Cl_B (ml/kg/h)	134.70± 3.88	110.91± 3.67*

Zero-time concentration during distribution phase (A); Zero-time concentration during elimination phases (B); Theoretical zero time concentration (Cpo); Elimination rate constant (β); Distribution rate constant (α); Distribution half-life ($t_{1/2}\alpha$); Elimination half-life ($t_{1/2}\beta$); area under curve (AUC); Area under first moment curve (AUMC); Mean residence time (MRT); Rate of transfer of drug from central to peripheral compartment (K_{12}) and from peripheral compartment to central (K_{21}); Elimination of drug from central compartment (Kel); Volume of distribution (V_d); Total body clearance (Cl_B); *Significantly ($p<0.05$) different as compared to corresponding values following IV route route of drug administration.

The elimination half-life ($t_{1/2}\beta$) provides a good indicator of time which is required to reach steady state after initiation of dosage regimen. It is the time taken for plasma concentration in the body to be reduced by its half (50%). The elimination half-life ($t_{1/2}\beta$) of marbofloxacin in rabbits

following multiple once daily IV administration in the present study was 4.60±0.38 hr on 1st day and 4.95±0.46 hr on 5th day. The present finding was well supported by Bharadwaj *et al*. (2018), who reported the $t_{1/2}\beta$ were 5.11±0.22 hr following single and 4.37±0.18 hr following multiple administration in goats. Whereas, $t_{1/2}\beta$ were 5.55±0.67 and 5.12±0.25 hr following single and repeated intravenous administration in broiler chickens respectively (Patel *et al*., 2018). The lower value of $t_{1/2}\beta$ (1.69±1.09hr) was reported by Junjun *et al*. (2010) in rabbit and higher value of $t_{1/2}\beta$ (8.60±0.30 hr) was reported by Hossain *et al. (*2017) in pigs.

The AUC values of marbofloxacin in rabbit following multiple once daily IV administration in the present study was 14.82±0.49 µg/ml.hr on 1st day and 18.13±0.57 µg/ml.hr on 5th day. While the AUMC values of marbofloxacin in rabbit following multiple once daily IV administration in the present study was 103.12±7.80 µg/ml.hr^2 on 1st day and 133.35±9.90 µg/ml.hr^2 on 5th day. The high values of AUC and AUMC reflect that most of the body area is covered with the drug concentrations. The contrary result reported by Patel *et al*. (2018) after single (26.80 ± 2.08 µg/ml.hr) and repeated (27.60 ± 2.57 µg/ml.hr) drug administration in broiler. The higher values of AUC (24.80±0.90 µg/ml.h) was reported by Hossain *et al.* (2017) in pig, while lower values of AUC (8.47±3.52 µg/ml.hr) was reported by Yohannes *et al*. (2015) in beagle dogs.

The mean residence time (MRT) of marbofloxacin in rabbit following multiple once daily IV administration in the present study was 6.90±0.32 hr on 1st day and 7.33±0.41 hr on 5th day. The present results are in accordance with Rubio-langre *et al*. (2012), who reported 7.30±1.07 hr (MRT) in llamas, while contrary result 1.82±1.15 hr (MRT) reported by Junjun *et al*. (2010). The volume of distribution (Vd_{area}) values of marbofloxacin in rabbit following multiple once daily IV administration in the present study was 0.89±0.06 L/kg on 1st day and 0.79±0.07 L/kg on 5th day. The present results are in accordance with El-komy *et al*. (2016) and Rubio-langre *et al*. (2012), who reported 0.76±0.08 L/Kg in broiler and 0.72±0.22 L/Kg in llamas respectively. While, Patel *et al*. (2018) reported 1.49±0.12 L/Kg (Vd_{area}) and 1.37±0.08 L/Kg (Vd_{area}) of after single and repeated drug administration in broiler.

The total body clearance (Cl_B) values of marbofloxacin in rabbit following multiple once daily IV administration in the present study was 134.70±3.88 ml/kg/hr on 1st day and 110.91±3.67 ml/kg/hr on 5th day. The present result are in accordance with El-komy *et al*., (2016) and Rubio-langre *et al*. (2012), who reported 0.09±0.002L/Kg/hr (Cl_B) in broiler and 0.09±0.02 L/Kg/hr (Cl_B) in llamas respectively. While, contrary result 0.36±0.01 L/Kg/hr (single dose) and 0.29±0.01 L/Kg/hr (multiple dose) was reported by Bharadwaj *et al*. (2018) following marbofloxacin administration in goats. The higher clearance (0.42±0.04 L/Kg/hr) was recorded by Marin *et al.* (2013) in rabbit, 0.71±0.29 L/Kg/hr (Junjun *et al*., 2010) and 0.23±0.06 L/Kg/hr in beagle dogs (Yohannes *et al*., 2015).

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 amikacin. The dosage regimen for any antimicrobial agent is calculated to maintain the minimum therapeutic concentration ($C_p^{\infty}min$ = MIC) throughout the course of infection. Based on these kinetic parameters, the dosage regimen for maintaining minimal therapeutic concentration of 0.25, 0.50 and 1.00 µg/ml in plasma at the dosage intervals 12 hr have been shown in Table 3.

Table 3: Comparative dosage regimens (Mean±SE) of marbofloxacin following IV route of drug administration in healthy rabbits

C_P^{∞}min (µg/ml)	t (hr)	Dose	mg/kg bwt
0.25	12	D*	0.91±0.03
		D^0	0.71±0.03
0.50	12	D*	1.81±0.06
		D^0	1.42±0.07
1.00	12	D*	3.63±0.12
		D^0	2.84±0.13

C_P^{∞}min = Minimum therapeutic concentration in plasma (MIC); τ (h) = Dosage interval; D* = Loading or priming dose; Do = Maintenance dose.

The calculated dosage regimens of marbofloxacin for C_P^{∞} *min* = 0.25 µg/ml were 0.91±0.03 mg/kg bwt (D*) and 0.71±0.03 mg/kg bwt (D_0), for C_P^{∞} *min* = 0.50 µg/ml were 1.81±0.06 mg/kg bwt (D*) and 1.42±0.07mg/kg bwt (D_0) and for C_P^{∞} *min* = 1.00 µg/ml were 3.63±0.12mg/kg bwt (D*) and 2.84±0.13 mg/kg bwt (D_0), respectively at 12 hr dosage intervals (τ) respectively at 12 hr dosage intervals (τ) in rabbits.

ACKNOWLEDGEMENTS

The authors are grateful to College of Veterinary Science & A.H., Rewa (Nanaji Deshmukh Veterinary Science University, Jabalpur, Madhya Pradesh, India) for providing necessary facilities to carry out the present investigation.

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