

Original Research Article

<https://doi.org/10.20546/ijcmas.2019.806.183>

Pharmacokinetics of Marbofloxacin after Single Intravenous Administration in Calves

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ABSTRACT

Marbofloxacin is a third generation quinolone developed exclusively for veterinary use. The disposition kinetic profile of marbofloxacin was generated after a single intravenous bolus injection in male *Sahiwal* calves (n = 5) at the dose level of 2 mg.kg⁻¹ body weight. Marbofloxacin concentrations in plasma were determined by microbiological assay using *Escherichia coli* MTCC 443 as the test organism. The plasma concentration–time profile following intravenous administration was best described by a two-compartment open model. The plasma drug concentration $\geq 0.12 \mu\text{g.ml}^{-1}$ was detected at 24 h. The distribution ($t_{1/2\alpha}$) and elimination ($t_{1/2\beta}$) half-lives were 0.12 ± 0.01 h and 5.73 ± 0.15 h, respectively. Area under plasma drug concentration-time curve (AUC), mean residence time (MRT), apparent volume of distribution ($V_{d\text{area}}$) and total body clearance (Cl_B) were $16.49 \pm 0.58 \mu\text{g.ml}^{-1}\cdot\text{h}$, 8.00 ± 0.19 h, $1.01 \pm 0.03 \text{ L.kg}^{-1}$ and $0.12 \pm 0.00 \text{ L.kg}^{-1}\cdot\text{h}^{-1}$, respectively. Marbofloxacin at the dose rate of 2 mg.kg⁻¹ body weight once daily by intravenous route is sufficient in calves for treatment of susceptible bacterial infections.

Keywords

Calves,
marbofloxacin,
pharmacokinetics

Article Info

Accepted:

12 May 2019

Available Online:

10 June 2019

Introduction

Marbofloxacin is a fluoroquinolone systemic antimicrobial agent specifically developed for veterinary use (Garcia-Montijano *et al.*, 2006; Ismail and El-Kattan, 2007; Pallo-Zimmerman *et al.*, 2010; Sidhu *et al.*, 2010a; Pillet *et al.*, 2013 and Cao *et al.*, 2015).

Marbofloxacin has a larger volume of distribution, longer elimination half-life, virtually complete bioavailability after parenteral administration (Altan *et al.*, 2018) and longer post antibiotic effect (Carbone *et*

al., 2001). It, being a fluoroquinolone, shows concentration-dependent bactericidal activity (Pellet *et al.*, 2006 and Celani *et al.*, 2017). It distributes extensively to most tissues including the lung, at higher concentrations than in serum/plasma (Dorey *et al.*, 2017).

Materials and Methods

Drug

For intravenous administration, marbofloxacin injection of a reputed multinational commercial brand was

purchased from local market. One ml of the injection contains 100 mg marbofloxacin.

Animals for experiment

The pharmacokinetic study was done on five clinically healthy male *Sahiwal* calves (A to E) maintained at livestock research station (LRS Kodamdesar) of Rajasthan University of Veterinary and Animal Sciences, Bikaner (India). The calves were regularly dewormed, aging 4-6 months and weighing between 40-60 kg. The study was done after communication of approval from the Institutional Animal Ethics committee of Rajasthan University of Veterinary and Animal Sciences, Bikaner. The animals were kept and maintained in the farm under standard management conditions, were given standard ration and had free access to roughage and water.

Experimental design

Marbofloxacin injection at the dose rate of 2.0 mg.kg⁻¹ body weight was administered in the jugular vein and blood samples were collected in test tubes containing anticoagulant, immediately before administration of marbofloxacin (0 h) and at 0.04, 0.08, 0.17, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 10, 12, 24, 36 and 48 h after administration of the drug. Plasma samples were harvested from the blood samples centrifuged at 3000 rpm for 15 min. Plasma samples were stored at -20°C until analysis.

Drug assay

Concentration of marbofloxacin in plasma samples was determined by microbiological assay method (Arret *et al.*, 1971) using *Escherichia coli* MTCC 443 (ATCC 25922) as test organism (Haritova *et al.*, 2006; Tohamy and El-Gendy, 2013 and Aboubakr and Abdelazem, 2015). Six equidistant wells

of 6 mm diameter were made in standard petri-dishes containing 25 ml of seeded agar. The wells were filled with 100 microlitres of either the test samples or marbofloxacin standard concentrations. The plates were incubated at 37°C for 24 h. The inhibition zone diameters were measured and the marbofloxacin concentrations in the test samples were extrapolated from the standard curve. The lowest detection limit of the assay was 0.1µg.ml⁻¹. Standard curve were prepared using antibacterial-free pooled plasma collected from the animals prior to the experiment. Standard marbofloxacin solutions having its concentrations of 0.098, 0.195, 0.391, 0.78, 1.56, 3.125, 6.25, 12.5 and 25 µg.ml⁻¹ were prepared *in vitro*. Semi-logarithmic plot of the zones of inhibition versus standard drug concentrations gave a linear plot having correlation coefficient of 0.980.

Pharmacokinetic analysis

The plasma marbofloxacin concentration time profile of each animal following intravenous injection of marbofloxacin was used to determine the pharmacokinetic variables describing the distribution and elimination characteristics of marbofloxacin in calves. To determine the different disposition kinetic variables, plasma drug concentration-time data were analyzed by employing the compartmental pharmacokinetic models (Baggot, 2001; Gibaldi and Perrier, 2007).

The plasma concentration versus time data following a single bolus dose of marbofloxacin were best fitted to a two-compartment open model using the bi-exponential equation:

$$C_p = A e^{-\alpha t} + B e^{-\beta t}, \text{ (Riviere, 2016)}$$

Where 'Cp' is the plasma concentration at time 't'; 'α' and 'β' are the distribution and

the elimination rate constants; 'A' and B are the zero time intercepts of distribution and elimination phases, respectively; and 'e' is the base of natural logarithm.

The pharmacokinetic analysis providing the above rate constants, so derived by linear regression and method of residuals, were used to calculate the respective half-life values. Other pharmacokinetic parameters were computed according to the standard formulae (Baggot, 2001; Gibaldi and Perrier, 2007). Values of all the pharmacokinetic parameters have been expressed as the mean \pm SE (n=5).

Results and Discussion

Plasma marbofloxacin concentration versus time data is plotted on a semi logarithmic graph shown in Figure 1. Following intravenous administration of marbofloxacin, the drug concentration of $4.70 \pm 0.07 \mu\text{g.ml}^{-1}$ was observed at 0.04 h which rapidly declined to $2.65 \pm 0.06 \mu\text{g.ml}^{-1}$ at 0.25 h and then gradually decreased to $0.12 \pm 0.00 \mu\text{g.ml}^{-1}$ at 24 h. Concentrations above the minimum inhibitory concentration (MIC) level of $\geq 0.10 \mu\text{g.ml}^{-1}$ were maintained up to 24 h.

The plasma concentration versus time profile following single intravenous dose of marbofloxacin was best described by a two - compartment open model which is similar to that described in dogs (Bidgood and Papich, 2005), cats (Albarellos *et al.*, 2005), healthy and *Mannheimia haemolytica* infected calves (Ismail and El-Kattan, 2007), sheep (Sidhu *et al.*, 2010_b), llamas (Rubio-Langre *et al.*, 2012), foals (Tohamy and El-Gendy, 2013), Japanese quails (Aboubakr and Abdelazem, 2015) and lactating buffaloes (Elzoghby and Aboubakr, 2015).

Different disposition kinetic parameters have been summarized in Table 1. The distribution half-life ($t_{1/2\alpha}$) was found to be 0.12 ± 0.01 h

which is suggestive of its rapid distribution into different body tissues and fluids of calves. Comparable value of $t_{1/2\alpha}$ (0.13 ± 0.02 h) is found in calves by Ismail and El-Kattan (2007) and similar value in dogs (0.12 ± 0.04 h) has been reported by Bidgood and Papich (2005) at the same dose rate.

The concentration dependent bactericidal effect together with short distribution half-life of marbofloxacin suggest it as useful in acute systemic infections where the therapeutic concentrations of antimicrobial agent are required to be achieved within very short period.

The elimination half-life ($t_{1/2\beta}$) was found to be 5.73 ± 0.15 h in the present study. It reflects the advantage of this drug in maintaining effective concentration in the body thereby allowing longer time for drug-pathogen interaction. This finding is comparable to almost similar observation of 5.26 h in broiler chicken (Anadon *et al.*, 2002). Longer elimination half-life ($t_{1/2\beta}$) values of marbofloxacin have been observed in cats (Albarellos *et al.*, 2005), dogs (Bidgood and Papich, 2005), turkeys (Haritova *et al.*, 2006), donkeys (Gonzalez *et al.*, 2007), vultures (Garcia-Montijano *et al.*, 2011), llamas (Rubio-Langre *et al.*, 2012), foals (Tohamy and El-Gendy, 2013) and chicken (Pizarro *et al.*, 2017) with the corresponding values of 7.98 ± 0.57 h, 8.30 ± 2.61 h, 9.01 ± 3.14 h, 8.88 ± 2.20 h, 12.51 ± 2.52 h, 8.26 ± 1.55 h, 6.40 ± 0.08 h and 6.50 ± 0.40 h, respectively.

The average value of AUC was $16.49 \pm 0.58 \mu\text{g.ml}^{-1}.\text{h}$, which is comparable to $16.30 \pm 1.80 \mu\text{g.ml}^{-1}.\text{h}$ in donkeys (Gonzalez *et al.*, 2007). Lower AUC values of marbofloxacin have been observed in dogs (Bidgood and Papich, 2005), turkeys (Haritova *et al.*, 2006), buffalo calves (Baroni *et al.*, 2007), calves (Ismail and El-kattan, 2007), cattle (Belew *et al.*, 2015) and lactating buffaloes (Elzoghby

and Aboubakr, 2015) with the corresponding values of $6.53 \pm 1.11 \mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$, $13.41 \pm 2.64 \mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$, $8.42 \pm 3.71 \mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$, 11.70 ± 1.34

$\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$, $6.87 \pm 0.52 \mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$ and $10.51 \pm 0.44 \mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$, respectively when given at the same dose rate of $2 \text{ mg}\cdot\text{kg}^{-1}$ body weight.

Fig.1

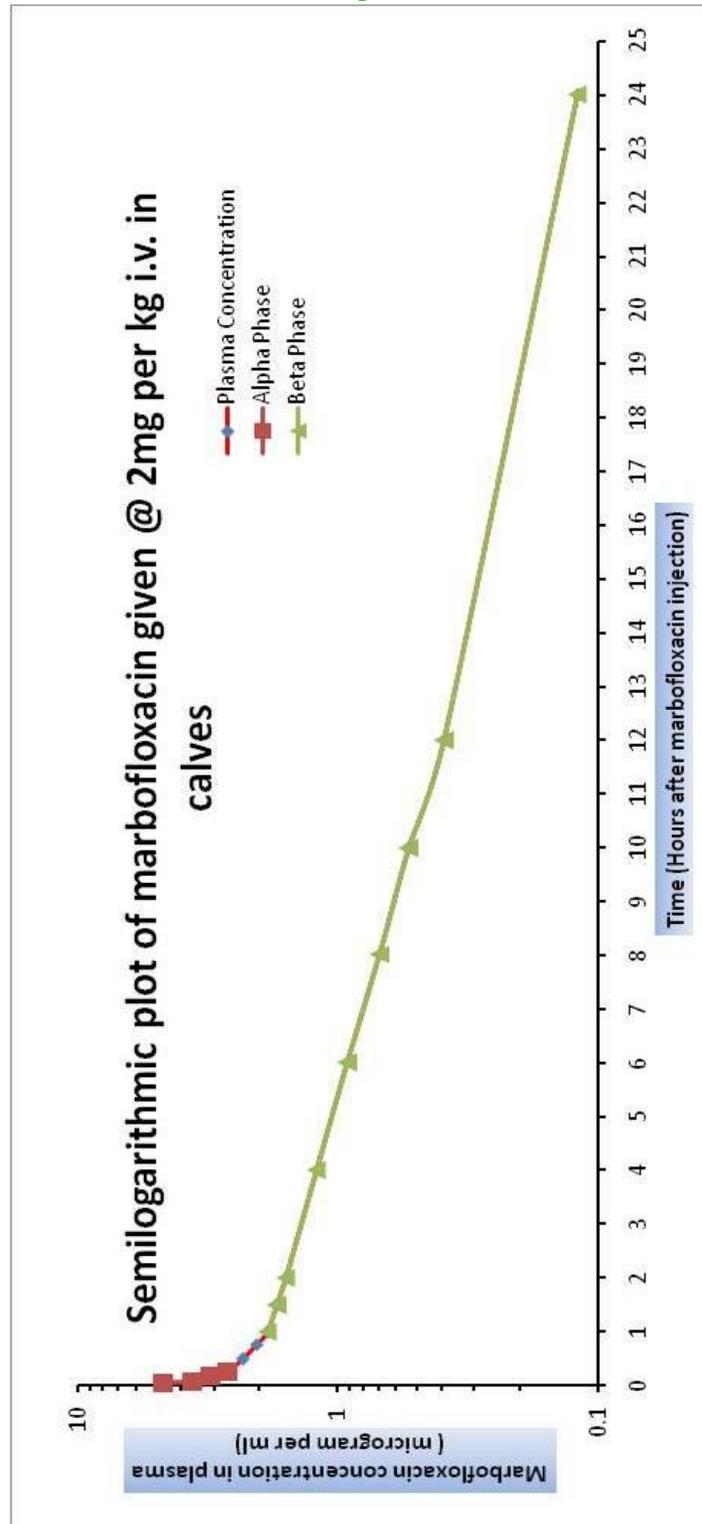


Table.1 Pharmacokinetic determinants of marbofloxacin in calves following a single intravenous dose of 2 mg.kg⁻¹ body weight employing compartmental model

Parameter	Unit	Mean ± S.E.
A	µg.ml ⁻¹	3.11 ± 0.14
α	h ⁻¹	5.76 ± 0.50
t_{½α}	h	0.12 ± 0.01
B	µg.ml ⁻¹	1.92 ± 0.07
β	h ⁻¹	0.12 ± 0.00
t_{½β}	h	5.73 ± 0.15
Cp^o	µg.ml ⁻¹	5.04 ± 0.13
AUC	µg.ml ⁻¹ .h	16.49 ± 0.58
AUMC	µg.ml ⁻¹ .h ²	132.25 ± 6.58
MRT	h	8.00 ± 0.19
Kel	h ⁻¹	0.30 ± 0.01
K₁₂/K₂₁	ratio	1.46 ± 0.09
V_c	L.kg ⁻¹	0.39 ± 0.01
Vd_{area}	L.kg ⁻¹	1.01 ± 0.03
Vd_B	L.kg ⁻¹	1.04 ± 0.04
Vd_{ss}	L.kg ⁻¹	0.97 ± 0.03
Cl_B	L.kg ⁻¹ .h ⁻¹	0.12 ± 0.00
fc	ratio	0.39 ± 0.01

The mean value of apparent volume of distribution (Vd_{area}) recorded in this study was more than one following intravenous injection in calves (1.01 ± 0.03 L.kg⁻¹), indicated wide distribution of marbofloxacin to extra-vascular tissues suggesting, that marbofloxacin can be employed in the treatment of different systemic infections including deep seated infections.

The value of Vd_{area} in the present study is comparable to 1.54 ± 0.39 L.kg⁻¹ in dogs (Bidgood and Papich, 2005) and 1.75 ± 0.25 L.kg⁻¹ in turkeys (Haritova *et al.*, 2006). Higher values of Vd_{area} have been observed 2.83 ± 0.75 L.kg⁻¹ in horses (Bousquet-Melou *et al.*, 2002) and 3.70 ± 0.30 L.kg⁻¹ in chicken (Pizzaro *et al.*, 2017). Wide distribution and penetration of marbofloxacin in body tissues and fluids of calves is further supported by K₁₂/K₂₁ ratio (1.46 ± 0.09) and T/P ratio (1.53 ± 0.10) of more than 1.

Clearance (Cl_B) in the present study was found to be 0.12 ± 0.00 L.kg⁻¹.h⁻¹. This finding is comparable to horses (Carretero *et al.*, 2002), turkeys (Haritova *et al.*, 2006), donkeys (Gonzalez *et al.*, 2007) and vultures (Garcia-Montijano *et al.*, 2011) with the corresponding values of 0.19 ± 0.04 L.kg⁻¹.h⁻¹, 0.11 ± 0.04 L.kg⁻¹.h⁻¹, 0.10 ± 0.02 L.kg⁻¹.h⁻¹ and 0.10 ± 0.02 L.kg⁻¹.h⁻¹, respectively

In conclusion, as marbofloxacin is a fluoroquinolone antimicrobial exerting concentration dependent killing of bacteria (Sidhu *et al.*, 2011), the most appropriate PK/PD parameters to describe drug efficacy is the C_{max}: MIC ratio and AUC: MIC ratio (Craig, 2001). It is recommended that AUC: MIC ratio should be ≥ 125 to optimize efficacy (Toutain *et al.*, 2002) and C_{max}: MIC (inhibitory ratio) should be >10 (McKeller *et al.*, 2004). In the present study with single dose intravenous administration of

marbofloxacin in calves at the dose rate of 2 mg.kg⁻¹, the C_{max}: MIC ratio was found 50.4 and similarly AUC: MIC ratio was found to 164.90, considering the MIC value to be 0.10 µg.ml⁻¹. These values are well above the recommended values of C_{max}: MIC ratio ≥ 10 and AUC:MIC ratio of ≥ 125 thus suggest that marbofloxacin at the dose rate of 2 mg.kg⁻¹ body weight and at 24 h dosing interval by intravenous is likely to be sufficient to treat bacterial infections requiring marbofloxacin concentration up to 0.10 µg.ml⁻¹.

Acknowledgement

The authors thankfully acknowledge the facilities, financial help and animal provided by the Principal Investigator of CEVPAM, Dean CVAS Bikaner and officer in-charge, LRS Kodamdesar, RAJUVAS, Bikaner.

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How to cite this article:

Neelam Dinodia, Pratihtha Sharma, Ashok Gaur and Mamta Meena. 2019. Pharmacokinetics of Marbofloxacin after Single Intravenous Administration in Calves. *Int.J.Curr.Microbiol.App.Sci.* 8(06): 1521-1528. doi: <https://doi.org/10.20546/ijcmas.2019.806.183>