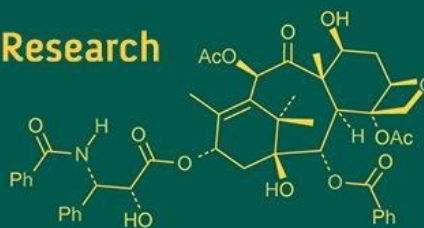


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Pharmacokinetics of marbofloxacin in sheep following intravenous administration

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Abstract

The pharmacokinetics of marbofloxacin were investigated in sheep following single-dose intravenous administration at a dose rate of 2.0 mg/kg. The plasma concentration of marbofloxacin was assayed using an LC-MS/MS method. Following single dose intravenous administration of marbofloxacin at the dose rate of 2.00 mg/kg, the plasma concentrations of marbofloxacin $> 0.04 \mu\text{g mL}^{-1}$ persisted for up to 24 hours post drug administration. The mean values of elimination rate constant, half-life, area under curve, mean residence time, and total body clearance were found to be $0.28 \pm 0.07 \text{ h}^{-1}$, $3.03 \pm 0.51 \text{ h}$, $6.87 \pm 1.08 \mu\text{g}\cdot\text{h/mL}$, $3.30 \pm 0.78 \text{ h}$, and $0.39 \pm 0.04 \text{ L/h/kg}$, respectively. The present study demonstrates that single intravenous administration of marbofloxacin in sheep at the dose rate of 2.0 mg/kg led to persistence of effective therapeutic concentration in sheep for a longer duration of time (up to 24 hours), so it can be effectively employed in the treatment of susceptible bacterial infections.

Keywords: Intravenous administration, LC-MS/MS, marbofloxacin, pharmacokinetics, sheep

Introduction

Marbofloxacin, a fluorinated quinolone, is introduced for exclusive use in veterinary medicine (Brown, 1996; Walker, 2000) [5, 34]. Marbofloxacin exhibits high bactericidal activity against some Gram-positive and most Gram-negative bacteria and *Mycoplasma spp.* (Hannan *et al.*, 1997; Papich and Riviere, 2001) [12, 18]. The drug is approved in many countries for use in cattle, pigs, dogs, horses, and cats for respiratory, urinary tract, soft tissue, and dermatological infections (Cotard *et al.*, 1995; Thomas *et al.*, 1997, 1998^a, 1998^b, 2001) [6, 32, 29-31]. The successful outcome of clinical trials of marbofloxacin in cattle and pigs has been reported for respiratory infections (Thomas *et al.*, 1997, 1998^a, 1998^b, 2001) [32, 29-31]. The same can also be extended to minor species as sheep and goats, which are more prone to bacterial infections, causing morbidity, mortality, and economic loss. However, there is limited published information in sheep on the pharmacokinetics of marbofloxacin, the drug selected for the investigation in the present study. The pharmacokinetics and tissue disposition of marbofloxacin were investigated extensively in different species of domestic animals. *viz.*, in cattle (Aliabadi and Lees, 2002; Schneider *et al.*, 2004; Ismail and El-Kattan, 2007; Sidhu *et al.*, 2011; Valle *et al.*, 2012; Potter *et al.*, 2013) [2, 22, 13, 27, 33, 20], sheep (Sidhu *et al.*, 2010) [24], goats (Waxman *et al.*, 2004; Sidhu *et al.*, 2006; Samanta *et al.*, 2007) [35, 26, 21], horses (Peyrou *et al.*, 2004; Lallemand *et al.*, 2013) [19, 16], poultry (Ding *et al.*, 2013) [7], dog (Korber *et al.*, 2012) [15], cat (Kietzmann *et al.*, 2011) [14] and rabbit (Abo-El-sooud and Goudah, 2010; Marin *et al.*, 2013) [1, 17]. The pharmacokinetics of any new drug is an essential step to predict the possibility of using the drug in the treatment of susceptible bacterial diseases, causing huge economic loss in the form of morbidity and mortality at the global level. It also helps to establish optimum dosage regimens for effective therapeutic concentration to be maintained in blood/plasma/body fluids. Integrating pharmacokinetic data and reported MIC values of known pathogens, the efficacy of marbofloxacin can be predicted. Thus, looking to the current status of pharmacokinetic data and the possibility of marbofloxacin being a potential veterinary drug, the present study on the pharmacokinetics of marbofloxacin in sheep following intravenous administration was conducted to bridge the gap between existing pharmacokinetic data in sheep and its clinical prospects.

Materials and Methods

Experimental animals and location

The study was conducted on six healthy adult male sheep (*Ovis aries*) of the Patanwadi breed with body weights ranging between 30 to 38 kg. The sheep were housed in a loose housing shed with a sandy floor at the Livestock Research Station, Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar, Gujarat (India). The latitude and longitude of the experimental location are: N 24.324309 and E 72.296369, respectively. The animals were maintained as per the Livestock Research Stations' maintenance schedule. Drinking water was made available *ad libitum* and free from any contaminants. An acclimatization period of fifteen days was observed before the beginning of the actual experiment. During this period, all the animals were subjected to clinical examination so as to preclude the possibility of any disease or abnormality among them. Standard management practices were adopted so sheep remained free from stress and diseases. Prior approval for the experiment was obtained from the Institutional Animal Ethics Committee.

Drugs and chemicals

Certified sample of marbofloxacin (assayed between 99.0 to 101%) was procured from Nexia Enterprise, Mumbai, India. The marbofloxacin procured passed all quality control tests as per the European Pharmacopoeia 7.0. Water, Acetonitrile, and methanol of LC/MS grade were procured from J. T. Baker, Boston (USA). Formic acid of HPLC grade was procured from S.D. Fine Chemical Limited, Mumbai.

Drug administration and sample collections

1% solution of marbofloxacin was administered at the dose rate of 2.0 mg/kg via the intravenous route in each of six sheep. Approximately 5.0 mL of blood samples were collected with the help of an intravenous catheter placed in the jugular vein in test tubes containing heparin (as an anticoagulant) at 0 min (pre-administration), 2, 5, 10, 15, 30 minutes, and at 1, 2, 4, 8, 12, 24, and 36 hours after intravenous administration of the drug. Plasma was separated by centrifugation at 1600 RPM for 15 minutes at 4 °C and stored at -20 °C until analysis.

LC-MS/MS assay

Plasma concentration of marbofloxacin was assayed by the LC-MS/MS technique using a Varian 310-MSTQ Mass spectrometer equipped with an auto sampler (Prostar 410) and pump (Prostar series). The data were acquired and integrated by the software 'MS Work Station' version 6.9.2 (Varian Inc). The mobile phase consisted of a mixture of 10 mM formic acid and acetonitrile (90:10). The mobile phase was filtered and degassed properly and pumped at a flow rate of 0.2 mL/min at 40 °C. The separation was carried out using a reverse-phase column C₁₈ (50 mm x 2.2 mm, 2 µm, Varian). The detection was carried out with MRM in positive ionization mode by collision-activated dissociation (CAD) of selected precursor ions in the collision cell of the triple quadrupole and analysed with the second Mass Analyzer of the system. MS/MS fragmentation of the ion m/z 363 of marbofloxacin had typical mass spectra with two product ions, 320 and 345. The needle voltage was set at 5000 volts, and the capillary voltage was kept at 80 v.

Preparation of the calibration curve of marbofloxacin in plasma

The stock solution (1 mg/mL) was diluted using acetonitrile: water (10:90) to prepare different spiking solutions in the range of 0.05 to 500 µg/mL. The spiking solution was added to blank drug-free plasma to obtain 0.001, 0.01, 0.1, 1, 2, 4, 8, 10 µg/mL concentration of spiked plasma. The value of the regression coefficient of standard curve was calculated and found to be greater than 0.99. The assay was found to be linear between a concentration ranges of 0.001 to 10 µg/mL. The range of recovery of marbofloxacin was found to be 74.906 to 78.903%. Based on standard concentrations and intensity of signals (peak area), a standard curve was prepared and used to calculate the plasma concentration of marbofloxacin from the samples collected.

Extraction and sample preparation for marbofloxacin

Exactly 0.2 mL of plasma sample was added to 1.8 mL of 1% acetic acid in acetonitrile in a 2.0 mL capacity Eppendorf tube. This was followed by mixing and vortexing for about 30 seconds. Freshly dried 200 mg of anhydrous sodium sulphate was added to this mixture and again mixed by vortexing. This was followed by centrifugation at 10,000 RPM and 4 °C. The supernatant was transferred to another Eppendorf tube of 1.5 mL capacity and centrifuged at 10,000 RPM and 4 °C. Finally, supernatant was transferred to LC vial for LC-MS/MS analysis.

Pharmacokinetic analysis

The plasma concentration-time curves of individual sheep were analyzed for pharmacokinetic parameters with the 'PK Solver' software (Zhang *et al.*, 2010) [36] using a non-compartmental approach. The peak concentration (C_{max}) and the time to the maximum concentration (T_{max}) were read from the plotted concentration-time curve in each animal. The area under the concentration-time curve (AUC) was calculated by the trapezoidal rule (Gibaldi and Perrier, 1982) [11] and further extrapolated to time infinity by dividing the last experimental concentration with the terminal slope (λ_z). The mean plasma residence time (MRT) of marbofloxacin was calculated using the arithmetic trapezoidal rule (Gibaldi and Perrier, 1982) [11]. Pharmacokinetic values are presented as mean ± standard error (SE).

Table 1: Pharmacokinetic parameters of marbofloxacin (2.0 mg/kg b. wt.) after single dose intravenous administration in sheep

Pharmacokinetic Parameters*	Unit	Mean ±SE
C _{max}	µg/mL	7.31 ± 0.64
T _{max}	h	0.03 ± 0.00
β	h ⁻¹	0.28 ± 0.07
t _{1/2β}	h	3.03 ± 0.51
AUC	µg·h/mL	6.87 ± 1.08
AUMC	µg·h ² /mL	28.20 ± 6.60
MRT	h	3.30 ± 0.78
V _{d(area)}	L/kg	1.67 ± 0.31
V _{d(ss)}	L/kg	1.28 ± 0.35
Cl _B	L/h/kg	0.39 ± 0.04

*The pharmacokinetic parameters as described by Gibaldi and Perrier (1982) [11]. C_{max}: maximum plasma concentration T_{max}: the time to reach maximum plasma concentration, β: elimination rate constant, t_{1/2β}: elimination half-life, AUC: total area under plasma drug concentration-time curve, AUMC: total area under the first

moment plasma drug concentration-time curve, MRT: mean residence time, $V_{d(are)}$: apparent volume of distribution, $V_{d(ss)}$: apparent volume of distribution at steady state, Cl_B : total body clearance

Results

The plasma concentrations (Mean $\pm$ SE) of marbofloxacin in relation to time in healthy sheep after single dose intravenous administration are graphically represented in Fig. 1. The plasma marbofloxacin concentration immediately after drug administration was found to be 7.31 ± 0.64 $\mu\text{g/mL}$ at 2 min and same declined to 5.20 ± 0.37 $\mu\text{g/mL}$ at 5 min. The values of plasma concentration at 10, 15, and 30 min were found to be 3.47 ± 0.29 , 3.16 ± 0.29 , and 2.34 ± 0.19 $\mu\text{g/mL}$, respectively. The same values at 1, 2, 4, 8, 12, and 24 h were found to be 1.37 ± 0.30 , 0.73 ± 0.19 , 0.26 ± 0.04 , 0.16 ± 0.04 , 0.08 ± 0.03 , and 0.04 ± 0.01 $\mu\text{g/mL}$, respectively. The plasma concentration versus time data set was analyzed by a non-compartmental approach to

calculate the pharmacokinetic parameters of marbofloxacin. The pharmacokinetic parameters are presented in Table 1. The mean value of the elimination rate constant (β) varied from 0.17 to 0.54 with a mean value of 0.28 h^{-1} . The mean ($\pm$ SE) of its corresponding half-life was calculated to be 3.03 ± 0.51 with a range of 1.28 to 3.96 h. The average value for the area under the curve (AUC) of plasma marbofloxacin concentration *versus* time was found to be $6.87 \mu\text{g}\cdot\text{h/mL}$, and the mean value for area under the first moment of the plasma drug concentration curve (AUMC) was obtained to be $28.20 \mu\text{g}\cdot\text{h/mL}$. The mean value of mean residence time (MRT) was 3.30 ± 0.78 h. The mean values of apparent volume of distribution ($V_{d(are)}$) and volume of distribution at steady state ($V_{d(ss)}$) were 1.67 ± 0.31 and 1.28 ± 0.35 L/kg, respectively. The value for total body clearance (Cl_B) was found to be 0.39 ± 0.04 L/h/kg (or 6.50 ± 0.66 mL/min/kg).

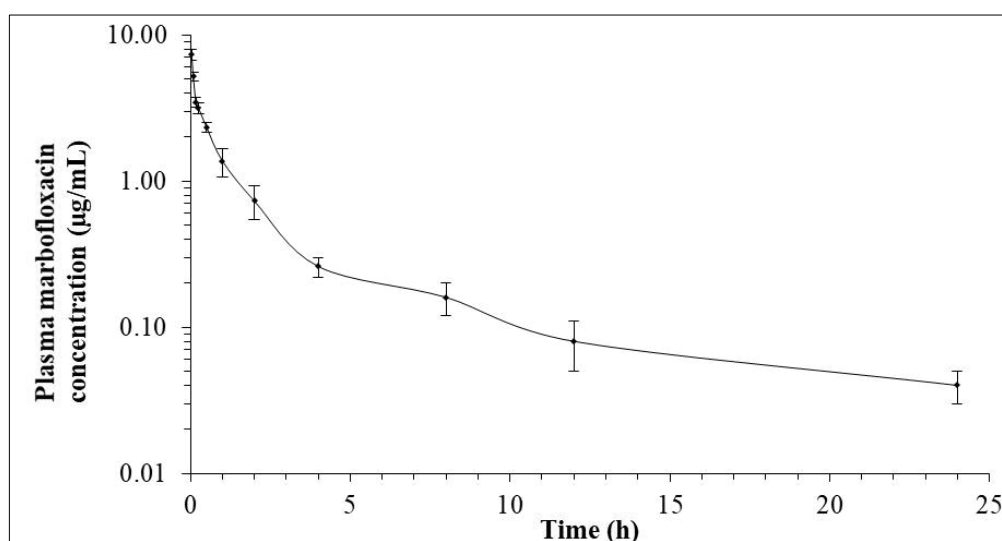


Fig 1: Semi-logarithmic plot of plasma marbofloxacin concentrations *versus* time following single dose intravenous administration (2.0 mg kg^{-1} body weight) in sheep

Discussion

Following single-dose intravenous administration of marbofloxacin at the dose rate of 2.0 mg/kg body weight, the mean peak plasma level was $7.31 \mu\text{g/mL}$ found at 2 min, and the lowest detectable plasma level of the drug was $0.04 \pm 0.01 \mu\text{g/mL}$ observed at 24 h.

The high value of the elimination rate constant in the present study (0.28 h^{-1}) indicates that the drug is excreted rapidly. The similar value of half-life in sheep was reported as 3.96 h by Sidhu *et al.* (2010) [24] following single-dose intravenous administration. Approximately similar value of elimination rate constant ($0.13 \pm 0.02 \text{ h}^{-1}$) was reported by Anadon *et al.* (2002) [3] in broiler chickens. The values of elimination half-life reported in calves (4.23, 4.6 and 4.7 h) by Aliabadi and Lees (2002) [2], Ismail and El-Kattan (2007) [13], and Schneider *et al.* (2004) [22], respectively, are slightly higher than the value of half-life obtained in the present study in sheep following single-dose intravenous administration of marbofloxacin. The mean apparent volume of distribution calculated following single dose intravenous administration of marbofloxacin (2 mg/kg of body weight) was 1.67 L/kg , which is comparable to those of 1.31 L/kg in goats, 1.28 L/kg in calf, $1.78 \pm 0.37 \text{ L/kg}$ in duck and $1.99 \pm 0.27 \text{ L/kg}$ in rabbits as reported by Waxman *et al.* (2004) [35], Aliabadi and Lees (2002) [2], Garcia *et al.* (2012) [9], and Marin *et al.*

(2013) [17], respectively. The observed value of volume of distribution is comparable to that of $1.33 \pm 0.33 \text{ L/kg}$ reported in broiler chickens for marbofloxacin by Anadon *et al.* (2002) [3]. In contrast, a higher value (2.77 L/kg) was reported in sheep by Sidhu *et al.* (2010) [24]. The values of V_d in the present study are indicative of good distribution of the drug in the body of sheep. Marbofloxacin has a large volume of distribution owing to its high lipid solubility and low plasma protein binding property, which results in extensive penetration in tissues, as also seen for other members of fluoroquinolones. In the present study, the mean value of total body clearance (Cl_B) was calculated to be $0.39 \pm 0.04 \text{ L/h/kg}$ (or $6.5 \pm 0.66 \text{ mL/min/kg}$) after intravenous administration of marbofloxacin given at the dose rate of 2.0 mg/kg body weight. Approximately similar values of 0.48 L/h/kg in sheep (Sidhu *et al.*, 2010) [24], 0.42 L/h/kg in rabbits (Marin *et al.*, 2013) [17], and $0.59 \pm 0.08 \text{ L/h/kg}$ in ducks (Garcia *et al.*, 2012) [9] were reported for single-dose intravenous administration of marbofloxacin. Relatively lower values of total body clearance were also reported in goats (0.23 L/h/kg) by Waxman *et al.* (2004) [35] and in cats (0.1 L/h/kg) by Kietzmann *et al.* (2011) [14]. Clearance is a function of both the intrinsic ability of certain organs, such as the kidneys and liver, to excrete or metabolise a drug and the blood flow rate to these organs. The variation in the

values of clearance is always expected due to species and breed-specific metabolic and absorption patterns of drugs (Gibaldi, 2008) ^[10]. The mean value of AUC was found as $6.87 \pm 1.08 \mu\text{g.h/mL}$ after intravenous administration of marbofloxacin (2.0 mg/kg body weight). Anadon *et al.* (2002) ^[3] have reported relatively higher values of AUC ($11.81 \pm 2.21 \mu\text{g.h/mL}$) of marbofloxacin (2.0 mg/kg) in broilers following intravenous administration. Similarly higher value of AUC ($18.60 \pm 4.75 \mu\text{g.h/mL}$) was reported for marbofloxacin in a dog following 2.0 mg/kg intravenous administration (Schneider *et al.*, 1996) ^[23]. Higher value of AUC has also been reported as $8.44 \pm 1.42 \mu\text{g.h/mL}$ in adult goats (Waxman *et al.*, 2004) ^[35] and $9.99 \mu\text{g.h/mL}$ in calves (Aliabadi and Lees, 2002) ^[2] following 2.0 mg/kg intravenous administration of marbofloxacin.

The difference in AUC values might be related to species variation in the physiology of the fluid compartment and the total physiological body space available to the drug. The absorption patterns, lipid solubility of the drug, and specific tissue barriers influence the value of AUC. The MRT (Mean Residence Time) indicates persistence of the drug in the body, and it is virtually similar to the half-life of the drug. The MRT calculated following a single dose intravenous administration of marbofloxacin in sheep was $3.3 \pm 0.78 \text{ h}$. An approximately nearer value of MRT was reported as $2.99 \pm 0.52 \text{ h}$ in ducks by Garcia *et al.* (2012) ^[9]. A slightly higher value of MRT ($4.36 \pm 0.8 \text{ h}$) has been reported by Anadon *et al.* (2002) ^[3] in broiler chickens following 2 mg/kg intravenous administration of marbofloxacin. Schneider *et al.* (1996) ^[23] and Sidhu *et al.* (2010) ^[24] have reported higher values of MRT as 14.5 and 8.6 h in dog and sheep, respectively, following 2.0 mg/kg intravenous marbofloxacin administration. Likewise, Waxman *et al.* (2004) ^[35] have reported slightly higher values of MRT as $5.06 \pm 0.48 \text{ h}$ for marbofloxacin (2.0 mg/kg) in adult goats. This indicates that marbofloxacin remains in the body of sheep for a shorter span of time due to relatively faster elimination of the drug as compared to other species.

The efficacy of antimicrobial therapy can be directly correlated with one or more indices, like AUC/MIC, $C_{\text{max}}/\text{MIC}$, and $T > \text{MIC}$. These three indices have been widely employed to establish dosages regimens having the potential to cure bacterial infections. The breakpoint for AUC/MIC of at least 125 h and $C_{\text{max}}/\text{MIC}$ ratio of 10 or greater has been proposed for fluoroquinolone (Forrest *et al.*, 1993; Sullivan *et al.*, 1993) ^[8, 28]. In the present study, the MIC of marbofloxacin against common veterinary pathogens has not been evaluated. But based on reported values of MIC of marbofloxacin $0.035 \mu\text{g/mL}$ (Sidhu *et al.*, 2010) ^[24] and $0.04 \mu\text{g/mL}$ (Aliabadi and Lees, 2002) ^[2], the respective values of AUC/MIC and $C_{\text{max}}/\text{MIC}$ exceed recommended values for these two indices. The plasma concentrations of marbofloxacin $> 0.04 \mu\text{g/mL}$ persisted for up to 24 h post drug administration. It is concluded that the marbofloxacin treatment at the dose rate of 2.0 mg/kg is effective against bacteria having MIC values equal to or lower than $0.04 \mu\text{g/mL}$. Similar findings were also reported by Bousquet-Melou *et al.* (2002) ^[4].

Conclusions

The present investigation demonstrates that marbofloxacin, when administered intravenously at a dose rate of 2.0 mg/kg body weight in sheep, exhibits rapid systemic distribution, moderate elimination, and sustained plasma concentrations above the reported MIC ($\leq 0.04 \mu\text{g/mL}$) for up to 24 hours. The non-compartmental pharmacokinetic analysis revealed

a relatively large volume of distribution, moderate total body clearance, and a mean residence time consistent with effective tissue penetration and therapeutic persistence. Integration of the obtained pharmacokinetic parameters with previously reported MIC values indicates that the achieved AUC/MIC and $C_{\text{max}}/\text{MIC}$ ratios exceed the recommended pharmacodynamic targets for fluoroquinolones, supporting the clinical efficacy of this dosing regimen. Overall, the findings suggest that a single intravenous dose of marbofloxacin at 2.0 mg/kg is pharmacokinetically adequate for the treatment of susceptible bacterial infections in sheep and provides a rational basis for its therapeutic use in this species.

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