

Pharmacokinetics of Orbifloxacin in Mehsana Goats after Intravenous and Intramuscular Administration

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Abstract

Single-dose pharmacokinetics of orbifloxacin (2.5 mg/kg bodyweight) were determined in clinically normal female mehsana goats (n=6) following intravenous and intramuscular administration. Orbifloxacin concentrations were determined by high performance liquid chromatography with ultraviolet detection. The concentration-time data were analyzed by non-compartmental kinetic method. Following a single intravenous injection, an elimination half-life ($t_{1/2\beta}$) of 8.63 ± 0.130 h. Steady-state volume of distribution ($V_{d_{ss}}$) and total body clearance (Cl_b) were 2.99 ± 0.038 L/kg and 0.187 ± 0.002 L/kg/h, respectively. Following intramuscular administration, the elimination rate constant (β), the area under the curve from zero to infinity ($AUC_{0-\infty}$) and the mean absorption time (MAT) were 0.019 ± 0.001 h⁻¹, 19.66 ± 0.216 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 7.618 ± 0.549 h, respectively. The peak plasma concentration (C_{max}) of 1.76 ± 0.010 $\mu\text{g}/\text{mL}$ was achieved at 1.00 ± 0.00 h. The mean residence time (MRT) was 21.07 ± 0.478 h and the absolute bioavailability were $155.5 \pm 2.487\%$, respectively. Orbifloxacin could be useful for the treatment of bacterial infections in goats that are sensitive to this drug.

Keywords: Orbifloxacin; Pharmacokinetics; Goats; High performance liquid chromatography

Introduction

Fluoroquinolones developed over the past few years have greater potency, a broader spectrum of activity, greater in vivo efficacy against resistant organisms and possess a better safety profile than other antimicrobial agents. Orbifloxacin is a third generation synthetic fluoroquinolone, an antimicrobial drug developed extensively for use in veterinary medicine [1,2] and it exhibits high bactericidal activity against Gram-positive, Gram-negative and *Mycoplasma spp.* [3,4] (Table 1). It is commonly used for infections of the skin.

The continuous interest in orbifloxacin has revealed several recent investigations describing their pharmacokinetic studies in pigs [5], cattle calves [2], cats [6], dogs [1,6-8], horses [9,10], goats [11], camels [12], rabbits [13], cattle [14], sheep [15,16] Japanese quail [17], buffalo calves [18] and chickens [19]. These studies have clearly revealed that the pharmacological basis of dosage regimen of orbifloxacin should be determined in the animals in which the drug is to be used clinically. However, no single study is done on the pharmacokinetics of orbifloxacin in goats in India till date. Therefore, we conducted pharmacokinetics of orbifloxacin in goats after intravenous and intramuscular administration.

Materials and Methods

Experimental animals

Twelve healthy adult mehsana goats weighing between 25-35 kg and aged 2-4 years were used in the present study. The animals were procured from Livestock Research Station, Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar, Gujarat, India. Sheep were kept at optimal nutritional conditions and had access to ad libitum water. The animals were kept under observations throughout the study period. The experimental protocol was approved by Institutional Animal Ethics Committee of Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar, Gujarat, India.

Drugs and chemicals

Orbifloxacin was obtained from Intas pharmaceuticals Ltd.,

Ashram road, Ahmedabad. Water, methanol, potassium dihydrogen orthophosphate, acetonitrile, orthophosphoric acid, disodium hydrogen phosphate and triethylamine of HPLC grade were purchased from S. D. Fine Chem. Ltd, Mumbai.

Experimental design and dosing

Twelve animals were divided into two groups - Group I and Group II as 6 animals in each group. Single dose intravenous pharmacokinetics study (Group I) and single dose intramuscular pharmacokinetic study (Group II) of orbifloxacin were performed in mehsana goats. Group I animals were administered with orbifloxacin at 2.5 mg/kg body weight by intravenous route and Group II animals were administered with orbifloxacin at 2.5 mg/kg body weight by intramuscular route.

Sample collection and preparation of plasma samples

Five mL whole blood samples were collected by venipuncture of the jugular vein into 10 mL heparinized tubes at 0 min (pre-administration), 5 min, 10 min, 15 min, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, 48 and 72 h after drug administration. The samples were centrifuged at 1600 rpm for 10 min. The plasma samples were transferred to Cryo-vials (2 mL capacity) and frozen until HPLC analysis.

Analytical method

Plasma samples were analyzed by using HPLC system equipped with G1312A pump, UV detector, SIL6B autoinjector and CTO6A

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Type of bacteria	Activity	Species	References
Gram-positive	in vitro	<i>Enterobacter faecalis</i>	[3,4]
		<i>Staphylococcus epidermidis</i>	
		<i>Staphylococcus intermedius</i>	
		<i>Staphylococcus aureus</i>	
		<i>Streptococcus pyogenes</i>	
Gram-negative	in vitro	<i>Escherichia coli</i>	[4,23]
		<i>Salmonella typhimurium</i>	
		<i>Salmonella typhi</i>	
		<i>Salmonella enteritidis</i>	
		<i>Shigella flexneri</i>	
		<i>Klebsiella pneumoniae</i>	
		<i>Enterobacter aerogenes</i>	
		<i>Pseudomonas aeruginosa</i>	
		<i>Proteus mirabilis</i>	
	in vitro and ex vivo	<i>Mannheimia hemolytica</i>	[14]
Mycoplasma	in vitro	<i>Mycoplasma Spp.</i>	[3,4,24,25]

Table 1: Bactericidal activity of orbifloxacin against different bacteria.

column heater (Agilent 1100 series). Above mentioned system was connected to a computer with Chromeleon Chromatography Data System software.

Plasma proteins were precipitated by adding 1000 µL plasma and 1000 µL acetonitrile. The mixture was vortexed for 10 s and centrifuged at 1600 rpm for 10 min. Then, 250 µL of supernatant was diluted with 750 µL 0.067 M disodium hydrogen phosphate buffer (pH 7.5). Chromatographic separation was performed by using Chromatopak Peerless Basic C₁₈ column (250 × 4.6 mm, 5 µ) at 40°C with an injection volume of 80 µL. The mobile phase (43:57) consisted of 430 volumes of buffer and 570 volumes of methanol with a flow rate of 1.5 mL/min. Buffer was prepared by dissolving 6.8 g of potassium dihydrogen orthophosphate in 1000 mL of water and by adding 3 mL of triethylamine. Then, pH adjusted to 2.5 with orthophosphoric acid. UV detection was performed at a wavelength of 320 nm.

Validation of analytical methods

Blank plasma samples were analyzed to check the absence of interference in the elution position of orbifloxacin. Stock solution of 1 mg/mL orbifloxacin was prepared by dissolving 100 mg powder form of pure drug in 100 mL of HPLC water. Further dilutions of the stock solution were prepared and spiked into blank plasma to produce calibration curves at different concentrations. Linearity was determined by spiking concentrations of orbifloxacin between 0.0625 µg/mL and 20 µg/mL. The mean correlation coefficient (R²) was 0.999. Standard curves were obtained by orbifloxacin peak area and known concentrations. The retention time of orbifloxacin was 2.43 min [20]. The detection limit and quantification limit were determined by analysis of spiked samples at low orbifloxacin concentration.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated from plasma concentration of orbifloxacin by software PK solution (version 2.0), Summit research services, USA. This program uses non-compartmental model of pharmacokinetic analysis of orbifloxacin.

Results

No local or system adverse reaction was observed after intravenous

or intramuscular injection of orbifloxacin. A semi-logarithmic plot of the mean concentration of orbifloxacin in the plasma following intravenous and intramuscular administration of 2.5 mg/kg is shown in Figure 1.

A summary of the pharmacokinetic parameters following intravenous and intramuscular administrations is listed in Table 2. In goats, orbifloxacin showed a range of Vd_{ss} in between 2.85 to 3.09 L/kg and a range of Cl_B in between 0.181 to 0.194 L/kg/h after intravenous administration. Orbifloxacin was absorbed rapidly after intramuscular administration and the C_{max} range was (1.72 to 1.79 µg/mL) attained after 1.00 ± 0.00 h (T_{max}) after injection (Figure 1). The MAT range was 5.21 to 9.13 h. The systemic bioavailability range after intramuscular administration was 147.3 to 165.2%.

Discussion

Orbifloxacin was quickly and widely distributed after intravenous administration with a Vd_{ss} of 2.99 ± 0.038 L/kg, which suggested good

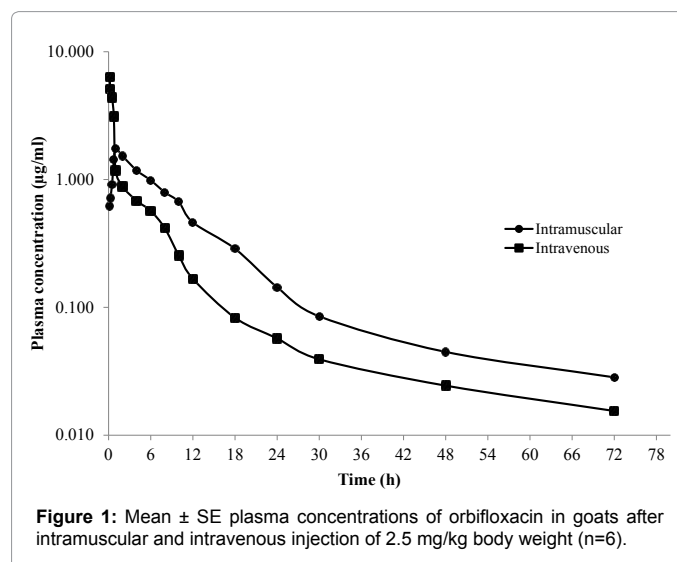


Figure 1: Mean ± SE plasma concentrations of orbifloxacin in goats after intramuscular and intravenous injection of 2.5 mg/kg body weight (n=6).

Pharmacokinetic parameters	Units	Intravenous	Intramuscular
β	/h	0.020 ± 0.001	0.019 ± 0.001
t _{1/2 β}	h	8.63 ± 0.130	17.77 ± 0.058
AUC _{0-∞}	γ·η/µΛ	12.65 ± 0.208	19.66 ± 0.216
AUMC	µγ·η ² /µΛ	207.6 ± 0.50	414.4 ± 12.70
Vd _{area}	L/kg	9.83 ± 0.172	--
Vd _{ss}	L/kg	2.99 ± 0.038	--
Cl _B	L /kg/h	0.187 ± 0.002	--
MRT	h	15.57 ± 0.531	21.07 ± 0.478
MAT	h	--	7.618 ± 0.549
C _{max}	γ/µΛ	--	1.76 ± 0.010
T _{max}	h	--	1.00 ± 0.00
F	%	--	155.5 ± 2.487

Key: β: Elimination rate constant; t_{1/2 β}: Elimination half-life; AUC_{0-∞}: Area under the curve from zero to infinity; AUMC: Area under first of moment curve; Vd_{area}: Apparent volume of distribution; Vd_{ss}: Volume of distribution at steady state; Cl_B: Total body clearance; MRT: Mean residence time; MAT: Mean absorption time; C_{max}: Maximum drug concentration; T_{max}: Time to peak plasma drug concentration; F: Bioavailability.

Table 2: Mean ± SE plasma pharmacokinetic parameters of orbifloxacin in goats (n=6) following intravenous intramuscular administration at a dose rate 2.5 mg/kg body weight.

penetration through biological membranes and was consistent with other species, including horses 4.04 L/kg [9] and 1.58 L/kg [10], goats (1.13 L/kg; [11] and (4.78 L/kg; [21], camels (1.73 L/kg); [12], rabbits (1.71 L/kg); [13], sheep (1.31 L/kg; [15] and 3.09 L/kg); [16], cattle (0.92 L/kg); [14], dogs (1.61 L/kg); [8], buffaloes (1.10 L/kg); [18] and Japanese quail (1.27 L/kg); [17].

The calculated half-life of elimination following intravenous administration in this study was $(8.63 \pm 0.130 \text{ h})$, almost same than in sheep (8.31 h); [16], shorter than in horses (9.06 h); [9] and, longer than that reported in birds (4.92 h); [19], buffalo (4.98 h); [18], horses (5.08 h); [10], camels (5.74 h); [12], dogs (7.1 h); [9] and (4.23 h); [8]. In contrast, a much shorter half-life of elimination of orbifloxacin was recorded in Japanese quail (1.71 h); [17].

The systemic clearance of orbifloxacin after intravenous administration in present study $(0.187 \pm 0.002 \text{ L/kg/h})$ and similar to that reported in buffalo (0.16 L/kg/h); [18] and sheep (0.158 L/kg/h); [16], but slower than that reported in cattle (0.24 L/kg/h); [14], dogs (0.31 L/kg/h); [8], sheep (0.32 L/kg/h); [15], goats (0.40 L/kg/h); [11] and 1.88 L/kg/h); [15], Japanese quail (0.60 L/kg/h); [17] and rabbits (0.91 L/kg/h); [13].

The C_{max} ($1.76 \pm 0.010 \mu\text{g/mL}$) and T_{max} ($1.00 \pm 0.00 \text{ h}$) values after intramuscular administration of orbifloxacin in present study were intermediate between those reported in dogs (1.15 $\mu\text{g/mL}$ and 1.15 h, respectively; [13], cattle (1.21 $\mu\text{g/mL}$ and 1.36 h, respectively); [14], sheep (1.53 $\mu\text{g/mL}$ and 1.25 h, respectively); [15], buffalo (1.6 $\mu\text{g/mL}$ and 1.3 h, respectively); [18], birds (1.63 $\mu\text{g/mL}$ and 1.32 h, respectively); [19] and goats (1.66 $\mu\text{g/mL}$ and 0.87 h, respectively); [11], but much higher to that observed by [15] in goats (0.36 $\mu\text{g/mL}$ and 0.94 h, respectively). In contrast, lower to that reported in camels (1.93 $\mu\text{g/mL}$ and 1.52 h, respectively); [12] and similar to that reported in sheep (1.81 $\mu\text{g/mL}$ and 1.0 h, respectively); [16].

The elimination half-life after intramuscular administration (17.77 h) was much longer than after intravenous administration (8.63 h) and the slower elimination of orbifloxacin from plasma after intramuscular treatment suggested a 'flip-flop' effect [22]. This would mean that the terminal phase of the plasma concentration-time curve was determined by the absorption rate constant and not by the apparent elimination constant.

The systemic bioavailability of orbifloxacin in sheep after intramuscular administration was extensive ($155.5 \pm 2.487\%$) and indicated good absorption from the injection site. It was almost same that have been reported in sheep 150.8%; [16]. Relatively, lower values have been reported in buffalo 91.9%; [18], goats 92.47%; [15] and 105.01%; [11], camels (97.47%) [12], dogs 100.1% [8], cattle 101.4% [14], rabbits (109.87%) [13] and sheep 114.63% [15].

Conclusions

Orbifloxacin showed favorable pharmacokinetic properties, such as a long half-life and high bioavailability, with no obvious adverse reactions. This drug could therefore be an effective treatment in goats for a number of bacterial infections. However, further studies are needed to establish a multiple dosage regimen and clinical efficacy against susceptible organisms that infect goats.

Conflict of Interest Statement

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this paper.

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