

*Original Research***Disposition Kinetics of Sparfloxacin in Goats**

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Abstract

The present study was conducted to investigate the distribution, kinetic parameters and dosage regimen of Sparfloxacin in goats after the approval of IAEC as per guideline of CPCSEA. Concentrations of sparfloxacin were estimated by highly sensitive analytical equipment's. High Performance Liquid Chromatography (HPLC) in six healthy goats @ 5 mg.kg⁻¹ intravenous administration in biological fluids i.e plasma and urine at different time interval. From log plasma concentrations versus time, kinetics parameters were calculated. Based on kinetic parameters, loading (D*) and maintenance (D₀) doses were calculated for maintaining C_P[∞] min (MIC) of 0.5 µg/ml at the dosage interval (γ) of 12 h. The mean peak plasma concentration of 59.76 ± 1.91 µg.ml⁻¹ and mean peak urine concentration of 63.16 ± 2.13 µg.ml⁻¹ were found at 0.042 h and 0.333 h, respectively. The study obtained distribution (t_{1/2 α}) and elimination (t_{1/2 β}) half-life, volume distribution, and total body clearance (Cl_B) of 0.43 ± 0.01 h, 8.56 ± 0.25 h, 2.89 ± 0.043 L.kg⁻¹ and 0.233 ± 0.04 ml.kg⁻¹.min⁻¹. D* and D₀ of 3.82 ± 0.06 and 2.38 ± 0.07 mg.kg⁻¹ were calculated to maintain C_P[∞] min of 0.5 µg/ml at γ of 12 h.

Key words: Disposition, Goats, Plasma, Sparfloxacin, Urine

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Introduction

Sparfloxacin is potent, long acting third generation bactericidal fluoroquinolone derivatives (Bhar *et al.*, 2009). The drugs has shown potent antimicrobial activity against wide range of gram negative and gram positive bacteria including glucose non-fermentors and anaerobes, *Legionella*, *Mycoplasma*, *Chlamydia* and *Mycobacterium* spp. Methicillin resistant *Staphylococcus aureus* is also susceptible to Sparfloxacin (Shimada J, *et. al* 1993). The major indication of this drug is in respiratory tract infections which include pneumonia, exacerbation, chronic bronchitis and sinusitis (Tripathi, K. D., 2006). The sporadic disease of pyelonephritis, embolic nephritis and nephrosis in farm animals have been reported which is caused by



different type of bacteria like *Corynebacterium renale*, *Leptospira pomona* and *Leptosira hardjo*, *Pseudomonas* spp, *Streptococcus* spp and *Staphylococcus* spp. Sparfloxacin has revealed excellent effect against these microorganism (Amatredjo *et al.*, 1976). Goat is a versatile animal and mainly reared in tropical countries like India. It is mainly reared by poor sections of society and serve as an easy alternative for uplifting the economic conditions of poor farmers because of its versatile traits like greater adaptability, maintenance on low grade ration, least rearing expenses and early economic return. In order to use a drug effectively, it is important to investigate the detailed pharmacokinetics of the drug in the particular species in which the drug is to be used clinically. The present investigation was undertaken to determine dosages regimen from the data generated through disposition kinetics after the approval of IAEC as per guideline of CPCSEA.

Materials and Methods

Experimental Animals and Administration of Drugs

Six clinically healthy goats (1.5-2 years) weighing 25-30 kg, were maintained under standard conditions and feeding schedule with water *ad lib*. The animals were adapted to laboratory conditions for 2 weeks prior to the commencement of experiment. Sparfloxacin powder, obtained from Wockhardt Pharmaceutical Pvt. Ltd., Bombay, India, was dissolved in sterile distilled water to make strength of 10 mg of Sparfloxacin/ml. The drug was injected @ 5 mg/kg body weight by intravenous (i.v.) route in each goat. The experiment was approved by animal ethical committee of the college which was further approved by Rajendra Agricultural University, Bihar, Pusa (Samastipur) – 848125, Bihar State, India.

Collection of Biological Samples

Blood samples were collected from jugular vein into sterilized centrifuge tubes containing approximate amount of sodium oxalate as anticoagulant. Plasma was separated after centrifugation at 2000 rpm for 15 minutes. Urine was collected by introducing a Foley's balloon catheter (No. 12) into the bladder through urethra and holding it in position by inflating balloon by injecting 20 ml. of air. Samples of plasma and urine were collected at 0.042, 0.08, 0.25, 0.50, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 24, but samples of Urine further upto 48 h (at 30, 36 and 48h) post i.v. administration of Sparfloxacin.

Method of Estimation

Estimation of Sparfloxacin in these body fluids were carried out by highly sensitive analytical equipment high performance liquid chromatography (HPLC) with chromatographic condition flow rate 1.2 ml min⁻¹, wavelength 295 nm, loop size 25 µl. The mobile phase comprised of Acetonitrile: 0.1 M phosphate buffer (25: 75). The pH of mobile phase was 2.5 approximately.

Calculation of Kinetic Parameters and Dosage Regimen

The log plasma drug concentration versus time profile showed a biphasic curve and hence, kinetic parameters were obtained from the formulae derived for a 2-compartment open model (Gibaldi *et al.*, 2007). For most of the susceptible bacteria, the mean therapeutic concentration (MIC) of Sparfloxacin is 0.5 µg/ml. In the present study, the dosage regimen of Sparfloxacin was calculated to maintain this MIC in plasma at two time intervals (12 h and 24 h). On the basis of various kinetic parameters, the loading or priming dose (D^*) and maintenance dose (D_0) were calculated (Notari, 1980).

Results and Discussion

The concentrations of Sparfloxacin in various biological fluids post i.v. administrations (5 mg/kg^1) in goats. The drug achieved peak concentration in plasma ($C_p \text{ max}$) and urine ($C_u \text{ max}$), of $59.76 \pm 1.91 \text{ µg/ml}$ and $63.16 \pm 2.13 \text{ µg/ml}$, respectively, at 0.042 h, and 0.33 h in goats. The drug was detectable in plasma upto 12 h in all the animals with the mean of $0.37 \pm 0.01 \text{ µg.ml}^{-1}$ and in urine upto 36 h with a mean of $0.18 \pm 0.05 \text{ µg.ml}^{-1}$ plasma drug concentration *versus* time profile has confirmed a two-compartment open model for sparfloxacin. Table 1 shows the values of different kinetic parameters calculated by the above noted compartment model.

Table 1: Kinetic parameters of sparfloxacin in goats after single intravenous administration @ 5 mg/kg.

Pharmacokinetics Parameters	Mean \pm S.E
A (mg/ml)	12.54 ± 0.08
B (mg/ml)	1.08 ± 0.02
C_p^0 (µg/ml)	13.63 ± 0.09
α (η^{-1})	1.57 ± 0.03
$T_{1/2 \alpha}$ (h)	0.43 ± 0.01
β (η^{-1})	0.081 ± 0.002
$T_{1/2 \beta}$ (h)	8.56 ± 0.25
AUC ($\text{mg.L}^{-1}.\text{h}$)	21.37 ± 0.37
AUMC ($\text{mg.L}^{-1}.\text{h}^2$)	171.16 ± 7.74
MRT (h)	7.98 ± 0.22
K_{12} (h^{-1})	0.816 ± 0.019
K_{21} (h^{-1})	0.199 ± 0.005
Kel (h^{-1})	0.639 ± 0.014
Fc	0.126 ± 0.001
$T \approx P$	6.92 ± 0.09
Vdc (L.kg^{-1})	0.366 ± 0.003
Vd _B (L.kg^{-1})	4.61 ± 0.089
Vd _{area} (L.kg^{-1})	2.89 ± 0.043
Vd _{ss} (L.kg^{-1})	5.08 ± 0.038
Cl _B ($\text{ml.kg}^{-1}.\text{min}^{-1}$)	0.23 ± 0.004

Table 2 shows the loading (D^*) and maintenance (D_o) doses or maintaining therapeutic concentration (MIC) of $0.5 \mu\text{g.ml}^{-1}$ at selected dosage interval (γ) of 12 and 24 h.

Table 2: Dosage regimen of Sparfloxacin following intravenous administration in goats

$C_p^\infty \text{ min } (\square \text{g.ml}^{-1})$	g (h)	Dose (mg.kg^{-1})	
0.125	12	D^*	0.956 ± 0.015
		D_o	0.595 ± 0.018
	24	D^*	2.540 ± 0.088
		D_o	2.178 ± 0.091
0.25	12	D^*	1.912 ± 0.030
		D_o	1.19 ± 0.035
	24	D^*	5.080 ± 0.177
		D_o	4.358 ± 0.083
0.5	12	D^*	3.826 ± 0.061
		D_o	2.381 ± 0.072
	24	D^*	10.162 ± 0.354
		D_o	8.716 ± 0.367

D^* = Priming or loading dose; D_o = Maintenance dose; \square = Dosage interval; $C_p^\infty \text{ min}$ = Minimum therapeutic concentration in plasma (MIC)

In the present study mean therapeutic concentration ($\geq 0.125 \mu\text{g.ml}^{-1}$) was maintained from 0.042 h to 12 h in plasma. Distribution rate constant (α) of $1.57 \pm 0.03 \text{ h}^{-1}$ and distribution half-life ($t_{1/2} \alpha$) of $0.43 \pm 0.01 \text{ h}$ obtained in the study denotes quicker distribution of sparfloxacin in different body fluids and tissues of goats. Elimination rate constant of (β) of $0.081 \pm 0.002 \text{ h}^{-1}$ and elimination half-life ($t_{1/2} \beta$) of $8.56 \pm 0.25 \text{ h}$ indicates comparatively slow elimination of sparfloxacin as compare to many fluoroquinolones. The values of $t_{1/2} \beta$ were noted to be $2.956 \pm 0.304 \text{ h}$ for norfloxacin (Nitesh, 2005), $2.32 \pm 0.70 \text{ h}$ for ciprofloxacin (Singh *et al.*, 2001), $3.53 \pm 2.26 \text{ h}$ for pefloxacin (Ansari *et al.*, 2000) and $2.92 \pm 0.41 \text{ h}$ for enrofloxacin (Nitesh Kumar *et al.*, 2003) in goat after parental administration. More or less similar elimination half-life of $8.40 \pm 0.74 \text{ h}$ in goat was observed by Kujur (2005) after oral administration (20 mg.kg^{-1}). Higher $t_{1/2} \beta$ of 17.6 h, 15 – 20 h and 20 ± 4 in man were noted by Johnson *et al.* (1992), Seth (1999), Zix *et al.* (1997), respectively. However, a lower $t_{1/2} \beta$ of 5.94 in broiler chicken (Mathuram *et al.*, 2005), 4 h in rat (Furukowa *et al.*, 1991) were noted. Very low $t_{1/2} \beta$ $2.39 \pm 0.29 \text{ h}$ was observed after i.v. administration of sparfloxacin @ 40 mg.kg^{-1} in rabbit. A higher $t_{1/2} \beta$ of 8.56 ± 0.25 obtained in present study denotes slower elimination of the drug from the body of the goat which is further supported by higher mean residential time (MRT) of $7.98 \pm 0.22 \text{ h}$ and lower elimination rate constant of drug from central compartment (K_{el}) of $0.639 \pm 0.014 \text{ h}^{-1}$ and total body clearance of $0.233 \pm 0.004 \text{ ml.kg}^{-1}.\text{min}^{-1}$.

Notari (1980) stated that for a two-compartment open model, the value of $Vd_B > Vd_{area} > Vd_{ss}$ and Vd_c . He further mentioned that among these value of volume of distribution only Vd_{area} correctly predicts the amount of drug in the body during elimination phase whereas Vd_B over estimate and Vd_{ss} and Vd_c under estimate the amount of drug in the body. Similarly, the value of Vd_{ss} obtained by non-compartment model. Correctly predict the amount of drug and / or its metabolite in the body during elimination phase (Singh and Ahuja, 1999). Vd_{area} of $2.89 \pm 0.043 \text{ L.kg}^{-1}$ and Vd_{ss} of $5.08 \pm 0.038 \text{ L.kg}^{-1}$ were obtained for sparfloxacin in the present study in goat after its i.v. administration. This denotes the drug is expected to be distributed in higher amount in body fluids and tissues of goat which is further supported by tissue to plasma concentration ratio (T \approx P) of 6.92 ± 0.09 . Kujur (2005) showed a lower Vd_{area} of 0.97 ± 0.09 in goat. However, Mathuram *et al.* (2005) showed higher volume distribution of 2.4 L.kg^{-1} in chicken. In the present study total body clearance (Cl_B) of $0.233 \pm 0.004 \text{ ml.kg}^{-1}.\text{min}^{-1}$ was obtained which shows that the drug is removed at a slower rate from the body. However, a higher Cl_B of $1.33 \pm 0.4 \text{ ml.kg}^{-1}.\text{min}^{-1}$ in goat (Kujur, 2005) and $4.55 \text{ ml.kg}^{-1}.\text{min}^{-1}$ in broiler chicken (Mathuram *et al.*, 2005) were obtained.

The main purpose of conducting kinetic study is to compute rational dosage regimen for treating various disease states. Generally, plasma is the easily accessible body fluid from which drug enter into the various body fluids and tissue. Therefore, in the present study, dosage regimen for various therapeutic concentrations ($C_p^\infty \text{ Min} = \text{MIC}$) of 0.125, 0.25 and $0.50 \mu\text{g.ml}^{-1}$ were taken for calculating dosage regimen.

Generally for fluoroquinolones the minimum inhibitory concentration for majority of the organism ranged from 0.1 to $0.5 \mu\text{g.ml}^{-1}$ (Trautman *et al.*, 1996; Kraiczky *et al.*, 2001; Kaku *et al.*, 1994) for treating of mild infection and highly susceptible bacteria.

Conclusion

In the present study drug was detectable up to 12h in plasma and 36 h in urine of goats. Hence, it is conclude that meat of such animals should not be used for human consumption from the public health point of view upto 48 hr after the administration of last therapeutic doses. In case of systemic infections, sparfloxacin is indicated @ 5mg/kg i.v. at a dosage interval of 24 h. Variations among species, sex and age may contribute to the wide discrepancies as noted by various workers (Jayachandran C *et al.*, 1990; Baggot, J. D., 2001).

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