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Comparative pharmacokinetics of Ofloxacin following single intravenous and oral administration in goat

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Abstract
Pharmacokinetic (PK) behaviour of ofloxacin following single intravenous (iv) and oral administration in goat was evaluated. Ofloxacin was administered @ 5 mg/kg body weight by iv and oral route. Plasma concentration of ofloxacin at pre-scheduled times were processed and estimated by using HPLC. The PK parameters were determined by non-compartmental open model. The therapeutic concentration was achieved in 2.5 min and 45 min and maintained up to 36 h and 8 h following iv and oral administration respectively. The mean AUC, AUMC, $t^{1/2}$, MRT, Cl and V_d are 58.94 ± 19.43 µg h/ml, 1539.57 ± 724.69 µg h^2/ml, 15.58 ± 1.87 h, 22.46 ± 2.71 h, 135.60 ± 31.12 ml/h/kg and 2.85 ± 0.74 L/kg respectively following iv administration. The calculated AUC, AUMC, $t^{1/2}{}_{ka}$, MRT after oral administration was 11.41 ± 1.13 µ/h/ml, 221.11 ± 38.44 µg/h/ml, 5.404 ± 0.78 h, 16.04 ± 1.19 h. The kinetic behaviour following iv administration is suggestive of entero-hepatic recycling with a secondary peak at 24 h. Following oral administration, ofloxacin showed poor absorption and slow elimination with mean bioavailability of 24.14 ± 1.70 % and t_{max} of 5.16 ± 0.72 h.

Keywords: Ofloxacin, pharmacokinetics, intravenous, oral, goat

Introduction
The increasing trend of development of antimicrobial resistance in bacterial pathogens and emergence of new resistant strains has been one of the alarming developments in the field of antimicrobial therapy over the past several decades. Although many novel moieties have been developed, fluoroquinolones have still remained as a trustworthy class of antimicrobial agents against some troublesome resistant pathogens. Ofloxacin has broad spectrum of activity against variety of gram positive and gram negative bacteria and some anaerobes (Monk *et al*., 1987) [12]. Pharmacokinetic studies of ofloxacin have been reported in dog (Yoshida *et al*., 1998) [17], rabbit (Marangos *et al*., 1997) [11], mice (Fu *et al*., 1990) [5], rat (Katagiri *et al*., 1998) [6], chicken (Liu *et al*., 1997) [8], and human (Kawakami *et al*., 1994) [7]. There is lack of detailed PK data of this antimicrobial against goat. Therefore, the objective of the present study was to investigate the pharmacokinetic pattern of the drug following single iv and oral administration in goat. The pharmacokinetic data obtained was applied for computing optimal dosage regimen, comparative study for rational use of the drug in this species, while reducing the risk of drug related toxicity.

Materials and Methods
a) Animals
The study was conducted on six clinically healthy male goats (*Capra hircus*) of Assam of age between 8-12 months old and weighing 10-16 kg. The animals were kept for 2 weeks before initiation of the experiment for acclimatization. During the experimental period, the animals were maintained on concentrate feed and free grazing. Water was provided *ad libitum*.

b) Drugs
The pure standard of ofloxacin and injectable commercial preparation, Zanocin infusion (200 mg/100 ml of distilled water) was from Ranbaxy Laboratories Ltd., India. The drug was administered 5 mg/kg by iv and oral route respectively.

c) Sample collection

Blood samples (3 ml) were collected into heparinized test tubes from jugular vein. The samples prior to and after iv administration of the drugs were collected at 0, 2.5, 5, 10, 20, 30, 45, 60 (1 h), 90 (1.5 h), 120 (2 h), 180 (3 h), 240 (4 h), 360 (6 h), 480 (8 h), 600 (10 h), 720 (12 h), 1440 (24h), 2160 (36 h), 2880 (48 h), 4320 (72 h) and 5760 (96 h) min and following oral administration samples were collected at the same interval except 2.5, 10 and 20 min. Plasma was harvested by centrifugation at 3000 rpm for 15 min and stored at -20ºC until assayed for ofloxacin.

d) Analytical method

For quantitative determination of ofloxacin in plasma, the HPLC method of Teja-Isavadharm *et al.* (1991) [15] was followed with some modification. The analysis for ofloxacin in plasma was performed on a HPLC system (Perkin Elmer, USA) consisting of a binary LC pump, a diode array detector, a LC-100 laboratory computing integrator and a μ Bondapac C_{18} column (Waters, USA, 30 mm x 3.9 mm ID and 10 μm particle size). The mobile phase consists of 0.1M phosphoric acid (adjusted to pH 2.5 with a solution of 45% potassium hydroxide) and acetonitrile mixed in a ratio of 75:25 (v/v). The flow rate of mobile phase was 1.2 ml/min and the eluent was monitored in diode array detector. The chromatograms were integrated on the LC-100 laboratory computing integrator.

Plasma samples were subjected to liquid phase extraction. To 1 ml of plasma, 1 ml of methanol was added and mixed by vortexing for 20 seconds and then placed on ice for 15 min to enhance precipitation. It was centrifuged at 15,600 g for 10 min and the supernatant (750 μl) was transferred to another tube. Dichloromethane (6 ml) was added and the content were mixed by vortexing for 20 seconds followed by centrifugation at 1000 g for 10 min. The organic and aqueous phases formed were separated by using phase separator filter paper. After discarding the aqueous phase, the organic phase was transferred to a clean siliconized tube and evaporated to dryness at 40ºC. The residue was then reconstituted in mobile phase (500 μl) (0.1M phosphoric acid and acetonitrile mixed in a ratio of 75: 25 (v/v)) and was injected into column. The plasma concentrations of ofloxacin in the samples were determined by comparing the detector response for the drug in the sample with the corresponding standards. Extraction recovery was determined by comparing the peak area of an extracted spiked sample with the peak area of direct injection of the mobile phase containing same concentration of pure drug. The extraction recovery and limit of quantification of ofloxacin in plasma was found to be 99.2% and 0.01 mg/L respectively.

Pharmacokinetic analysis

The concentration of ofloxacin in plasma were presented in tabular form against different time intervals and plotted on a semi-logarithmic scale as a function of time (not shown) and the pharmacokinetic parameters were calculated by using statistical moments approach (Mallik 1999). The dosage regimen was computed by the method of Wartak (1983) [16] and Benet *et al*. (1996) [3].

Results and Discussion

Plasma concentration of ofloxacin, parameters at various time intervals following single intravenous and oral administration (5 mg/kg) are given in Table 1 and various kinetic variables are listed in Table 2 for intravenous and oral route respectively.

Table 1: Plasma concentration (μg /ml) of ofloxacin and its mean ± SE in goat following single iv and oral dose of 5 mg /kg body weight (n=6)

Time (min)	Single IV (μg /ml)	Oral (μg /ml)
2.5	14.76 ± 0.47	NC
5	10.30 ± 0.05	0.006 ± 0.01
10	9.03 ± 0.42	NC
15	NC	0.020 ± 0.01
20	7.48 ± 0.34	NC
30	6.56 ± 0.28	0.044 ± 0.01
45	4.79 ± 0.30	0.512 ± 0.15
60 (1.0 h)	5.32 ± 0.26	0.590 ± 0.24
90 (1.5 h)	4.95 ± 0.28	0.718 ± 0.18
120 (2.0 h)	3.94 ± 0.25	0.655 ± 0.18
180 (3.0 h)	2.92 ± 0.42	0.333 ± 0.09
240 (4.0 h)	1.71 ± 0.24	0.193 ± 0.05
360 (6.0 h)	0.94 ± 0.17	0.490 ± 0.21
480 (8.0 h)	0.87 ± 0.15	0.497 ± 0.14
600 (10.0 h)	0.62 ± 0.14	0.392 ± 0.15
720 (12.0 h)	0.53 ± 0.13	0.433 ± 0.22
1440 (24.0 h)	0.64 ± 0.15	0.197 ± 0.09
2160 (36.0 h)	0.62 ± 0.14	0.160 ± 0.08
2880 (48.0 h)	0.44 ± 0.07	0.047 ± 0.02
4320 (72.0 h)	0.35 ± 0.03	0.034 ± 0.01
5760 (96.0 h)	0.05 ±0.03	0.013 ± 0.01

NC: not collected (Not considered during calculation)

Table 2: Pharmacokinetic determinants of ofloxacin in goats following single iv and oral dose of 5 mg/kg body weight (n = 6)

Pharmacokinetic determinants	Unit	Mean ± SE (iv)	Mean ±SE (Oral)
AUC	μg.h/ml	58.94 ± 19.43	11.41 ± 1.13
AUMC	μg.h^2/ml	1539.57 ± 724.69	221.11 ± 38.44
MRT	h	22.46 ± 2.71	16.04 ± 1.19
$t_{1/2}$	h	15.58 ± 1.87	5.40 ± 0.78
K	h^{-1}	0.05 ± 0.01	0.21 ± 0.08
Cl	ml/h/kg	135.60 ± 31.12	164.15 ± 48.98
V_d	L/kg	2.85 ± 0.74	--
V_{dss}	L/kg	2.83 ± 0.74	--
C_{max}	μg /ml	--	1.16 ± 0.07
t_{max}	h	--	5.16 ± 0.72
F	%	--	24.14 ± 1.70
MAT_0	h	--	7.79 ± 1.13

Ofloxacin was detected in plasma up to 96 h following single iv and oral administration, while following oral administration of ofloxacin (5 mg/kg) the minimum inhibitory concentration (MIC≥0.5 μg/mL) was observed at 45 min and maintained up to 8 h. A secondary peak shown in the mean plasma ofloxacin concentration (iv) time profile (0.64 ± 0.15 μg/ml) at 24 h. The appearance of the secondary peak seems to be due to enterohepatic circulation of the drug. The enterohepatic circulation of the drug that is extensively cleared into the bile may produce secondary peak in plasma level time profile (Baggot, 1980) [1]. Enterohepatic recycling is often associated with multiple peaks and a longer apparent half-life in a plasma concentration-time profile (Robert *et al.*, 2002) [13]. Similar time course of ofloxacin (5 mg/kg) was reported in sheep (Takawale *et al*., 2000) [14].

The therapeutic concentration of ofloxacin (MIC ≥ 0.5 μg/ml) was maintained up to 36 h following iv administration, which is reflected by larger values of elimination half-life (15.58 ±1.87 h) and its analogous parameter, MRT (22.46 ± 2.71 h).

A relatively shorter half-life has been reported in man (5.4 h) (Farinotti *et al.*, 1998) [4], rabbit (1.5-1.9 h) (Marangos *et al.*, 1997) [11] and in chicken (4.82 h) (Liu *et al*., 1997) [8]. The longer residence of the drug in the body was further supported by high value of AUC (58.94 ±19.43 µg h/ml) and low clearance rate Cl (135.60 ±31.12 ml/h/kg). The reported AUC of ofloxacin in rabbit (Marangos *et al*., 1997) [11], human (Farinotti *et al.*, 1998) [4], sheep (Takawale *et al*., 2000) [14] and in chicken (Liu *et al.*, 1997) [8] have been 37.09, 14.0, 418.40 and 47.08 µg.h/ml respectively. The Vd of ofloxacin in the present study was found to be 2.85 ±0.74 L/kg indicating wide tissue distribution after iv administration. The reported values of Vd in man (Lode *et al*., 1986) [9] and in sheep (Takawale *et al*., 2000) [14] have been 2.4 L/kg and 1.61 L/kg respectively.

Beermann *et al.* (1984) reported that ofloxacin (200 mg, single oral dose) produced higher serum concentration (2.3 µg/ml vs 1.1 µg/ml with ciprofloxacin and 0.8 µg/ml with norfloxacin) in human. Low C_{max} value observed might be due to the low bioavailability of the drug in goat as compared to man. The absorption half life ($t_{1/2\ ka}$) and mean absorption time (MAT_0) indicated slow absorption rate of the drug, while a higher value of mean residence time (MRT) of 16.05 ± 1.13 h in this study suggested slow elimination rate of the drug. The reported absorption half-life ($t_{1/2ka}$) in human after a single oral dose of 200 mg was in the range of 5.7-7.0 h and MRT, an analogous term for elimination half-life was in the range of 5-7.5 h (Monk *et al*., 1987) [12]. Lie *et al*., (1997) reported the elimination half-life of ofloxacin (10 mg/kg) in chicken was 4.82 h following single oral dose.

The value of AUC in goat after a single oral administration (5 mg/kg) was 11.41± 1.13 µg/h/mL. Liu *et al*., (1997) [8] reported AUC value in chicken 60.92 µg. h/ml after an oral dose of 10 mg/kg ofloxacin. The lower value of AUC might be due to the low bioavailability of the drug in goat. Beermann *et al.* (1984) observed higher AUC values of ofloxacin (15.86 µg.h /mL) than ciprofloxacin (3.57 µg/h/ml) and norfloxacin (3.28 µg.h/mL) in human beings after a single oral dose of 200 mg of each drug.

The bioavailability (F) of ofloxacin in systemic circulation following oral administration (5 mg/kg) in goat was found to be 24.14 ± 1.70 % as compared to 85-95% in human beings (Monk *et al*., 1987) [12]. Baggot (1980) [1] found that biotransformation by enzyme in the gut mucosa or in the liver or both may significantly reduce bio-availability of orally administered drugs. MIC level maintains up to 36 h after iv administration suggestive that comparatively in case of goat, intravenous administration of ofloxacin is better than that of oral administration.

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