

## Disposition kinetics and urinary excretion of ciprofloxacin in goats following single intravenous administration

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We evaluated the pharmacokinetics of ciprofloxacin in serum (n = 6) and urine (n = 4) in goats following a single intravenous administration of 4 mg/kg body weight. The serum concentration-time curves of ciprofloxacin were best fitted by a two-compartment open model. The drug was detected in goat serum up to 12 h. The elimination rate constant ( $\beta$ ) and elimination half-life ( $t_{1/2\beta}$ ) were  $0.446 \pm 0.04 \text{ h}^{-1}$  and  $1.630 \pm 0.17 \text{ h}$ , respectively. The apparent volume of distribution at steady state ( $V_{d_{ss}}$ ) was  $2.012 \pm 0.37 \text{ l/kg}$  and the total body clearance ( $Cl_B$ ) was  $16.27 \pm 1.87 \text{ ml/min/kg}$ . Urinary recovery of ciprofloxacin was  $29.70\% \pm 10.34\%$  of the administered dose within 36 h post administration. *In vitro* serum protein binding was  $41\% \pm 13.10\%$ . Thus, a single daily intravenous dose of 4 mg/kg is sufficient to maintain effective levels in serum and for 36 h in urine, allowing treatment of systemic, Gram-negative bacterial infections and urinary tract infections by most pathogens.

**Keywords:** ciprofloxacin, disposition kinetics, goat, urinary excretion

### Introduction

Ciprofloxacin is a fluoroquinolone derivative in veterinary medicine with outstanding antibacterial activity primarily against Gram-negative pathogens, but also Gram-positive bacteria and some *Chlamydia*, *Mycoplasma*, and many *Mycobacterium* species [12,23,24]. The pharmacokinetics of ciprofloxacin has been investigated in dogs, rats and monkeys, rabbits, ponies, goats, cow calves, and buffalo calves [4,8,29,30,33,34,37]. Because of the lack of sufficient pharmacokinetic studies in goats and potential

species differences, we evaluated the pharmacokinetics of ciprofloxacin after intravenous administration in goats.

### Materials and Methods

#### Experimental animals

Ten clinically healthy goats (15–20 kg) were procured from a local breeding farm in Jammu, India, and housed in a well-ventilated house. All de-wormed animals were housed in hygienic departmental shed for 20 d prior to experiments for acclimatization, and allowed free access to pasture, *ad libitum* water, and received once daily concentrated feed ration. No treatments were performed for two weeks before study initiation. One day prior to the experiment, the goats underwent thorough physical and clinical examinations.

#### Experimental design

The study was performed in two phases. In phase I, six goats were used for evaluating the disposition kinetics of ciprofloxacin. A single intravenous dose of 4 mg/kg body weight of ciprofloxacin hydrochloride monohydrate in sterile distilled water (Cadilla Labs Private, India) was administered into the jugular vein of the six goats. Blood samples of 6–7 ml were obtained directly from the jugular vein using disposable needles. The blood samples were collected in un-heparinized test tubes just prior to and at 2.5, 5, 10, 20, 30, 45, 60 and 90 min and 2, 3, 4, 6, 9 and 12 h after drug administration. Blood samples were allowed to clot at ambient temperature for the collection of serum. The separated serum was then centrifuged for 15 min at 3,000 g to obtain clear supernatant fluid and stored at  $-20^\circ\text{C}$  until analysis, usually within 2–3 days.

In phase II, the urinary excretion of ciprofloxacin was investigated in four goats. The dose and route of administration were the same as in phase I. The animals were placed into metabolic stalls prior to start of the experiment and total urine was collected. The urine samples were collected at 0–3, 3–6, 6–9, 9–12, 12–24, 24–36,

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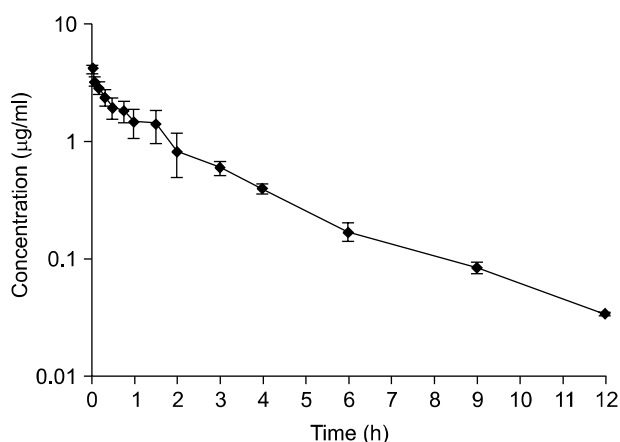
and 36–48 h after drug administration. The whole volume of urine was measured and 10 ml urine samples were taken for analysis.

Ciprofloxacin concentrations in serum and urine were determined using the agar well diffusion assay [5], using *E. coli* ATCC-25922 as test organisms grown on Mueller Hinton agar. This method correlates well with HPLC studies [16]. Standard concentrations (0.015 to 4 mg/ml) were prepared in pooled untreated goat serum and urine, and showed a mean correlation coefficient ( $r$ ) > 0.99% for both serum and urine. The serum concentration time profile showed a correlation coefficient ( $r^2$ ) value of  $0.982 \pm 0.009$ . The intra-assay and inter-assay precision variability were < 10% for standard concentrations in both serum and urine. The lower limit of quantification of the ciprofloxacin assay was 0.015  $\mu\text{g/ml}$ .

The extent of protein binding was determined *in vitro* using an equilibrium dialyzing technique as described by Kunin [18]. To estimate the protein binding of ciprofloxacin, the drug was dissolved in 0.06 M phosphate buffer (pH 7.0) and antibiotic-free healthy goat serum at 0.5, 0.75, 1.0, 1.5, and 2.0  $\mu\text{g/ml}$ . The differences in the diameters of the inhibition zone between the solution of the drugs in the buffer and serum were calculated.

### Pharmacokinetics analysis

The compartment pharmacokinetics of serum concentration-time curves after single intravenous injection were analyzed for each goat by Top-Fit v. 2.0 [13]. The best-fit model was selected based on Akaike's Information Criterion and the Schwartz test [31,40]. Model-dependent pharmacokinetic parameters were obtained as described by Baggot [3] and Gibaldi and Perrier [11]. The two compartment open model was the best fit for intravenous injection of ciprofloxacin. Statistical moments were also



**Fig. 1.** Semi-logarithmic graph depicting the serum concentration-time profile of ciprofloxacin in goat following single intravenous dose of 4 mg/kg body weight ( $n = 6$ ).

used to compute the non-compartmental pharmacokinetic analysis [11,40]. The non-compartment model was used to determine the area under concentration-time curve (AUC), and area under the first moment curve (AUMC), using the linear trapezoidal rule with extrapolation to time infinity. Mean residence time (MRT) and systemic clearance ( $Cl_B$ ) were calculated as  $MRT = AUMC/AUC$  and  $Cl_B = \text{Dose}/AUC$ , respectively. The apparent volumes of distribution at steady state were calculated as  $Vd_{SS} = (\text{Dose} \times AUMC)/AUC^2$ .

### Results

Mean serum ciprofloxacin concentrations following a single intravenous administration of 4 mg/kg body weight

**Table 1.** Pharmacokinetic parameters of ciprofloxacin in goat ( $n = 6$ ) following a single intravenous administration with 4 mg/kg body weight

Parameters	Units	Mean $\pm$ SD
Compartmental analysis		
$C_p^0$	$\mu\text{g/ml}$	$4.470 \pm 0.33$
$\alpha$	$\text{h}^{-1}$	$8.224 \pm 1.99$
$\beta$	$\text{h}^{-1}$	$0.446 \pm 0.04$
$K_{12}$	$\text{h}^{-1}$	$3.826 \pm 0.89$
$K_{21}$	$\text{h}^{-1}$	$3.814 \pm 1.22$
$K_{12}/K_{21}$	Ratio	$1.162 \pm 0.21$
$K_{el}$	$\text{h}^{-1}$	$0.926 \pm 0.13$
$t_{1/2\alpha}$	h	$0.108 \pm 0.03$
$t_{1/2\beta}$	h	$1.630 \pm 0.17$
$V_c$	l/kg	$0.918 \pm 0.06$
$Cl_B$	ml/min/kg	$16.27 \pm 1.87$
Non-compartmental analysis		
$AUC_{0 \rightarrow 12}$	$\mu\text{g.h/ml}$	$5.580 \pm 0.93$
$AUC_{0 \rightarrow \infty}$	$\mu\text{g.h/ml}$	$5.750 \pm 0.92$
MRT	h	$2.510 \pm 0.18$
AUMC	$\mu\text{g.h}^2/\text{ml}$	$14.310 \pm 2.27$
$Vd_{SS}$	l/kg	$2.012 \pm 0.37$
$r^2$	—	$0.982 \pm 0.009$

$C_p^0$ -Serum drug concentration at  $t=0$ ;  $\alpha$  and  $\beta$ -hybrid rate constants represent the slopes of distribution and elimination phases, respectively;  $t_{1/2\alpha}$ -distribution half-lives;  $t_{1/2\beta}$ -elimination half-lives;  $k_{el}$ -first order elimination rate constant;  $V_c$ -volume of distribution from central compartment;  $Vd_{SS}$ -volume of distribution at steady-state;  $K_{12}$ -rate constant of transfer of drug from central compartment into the tissue compartment;  $K_{21}$ -rate constant of transfer of drug from tissue compartment into the central compartment;  $AUC_{0 \rightarrow 12}$ -Area under the serum concentration vs. time curve from 0 to 12 h;  $AUC_{0 \rightarrow \infty}$ -Area under the serum concentration vs. time curve from 0 to  $\infty$ ; AUMC area under the first moment curve; MRT-mean residence time;  $Cl_B$ -total body clearance;  $r^2$ -Correlation coefficient fit curve of serum concentration vs time profile.

are presented in Fig. 1. The drug was detected in goat serum up to 12 h. Following intravenous administration, the elimination half-life ( $t_{1/2\beta}$ ), volume of distribution at steady state ( $V_{d_{ss}}$ ), total body clearance ( $Cl_B$ ), and area under curve from  $0 \rightarrow \infty$  ( $AUC_{0 \rightarrow \infty}$ ) were estimated to be  $1.63 \pm 0.17$  h,  $2.012 \pm 0.37$  l/kg,  $16.27 \pm 1.87$  ml/min/kg, and  $5.75 \pm 0.92$   $\mu\text{g}\cdot\text{h}/\text{ml}$ , respectively (Table 1). The efficacy predictors,  $C_p^0/\text{MIC}$  minimum inhibitory concentration (MIC) and  $AUC_{0-24}/\text{MIC}$  can predict antimicrobial efficacy of fluoroquinolones and to reduce selection for resistance [36]. Efficacy predictors for Gram-negative bacteria at  $\text{MIC}=0.06$   $\mu\text{g}/\text{ml}$  and gram-positive bacteria at  $\text{MIC} = 0.5$   $\mu\text{g}/\text{ml}$  were  $C_p^0/\text{MIC} = 74.53 \pm 14.12$ ,  $AUC_{0-24}/\text{MIC} = 186.11 \pm 75.91$  and  $C_p^0/\text{MIC} = 17.89 \pm 1.69$ ,  $AUC_{0-24}/\text{MIC} = 22.33 \pm 9.11$ , respectively (Table 3).

Ciprofloxacin concentrations in urine were much higher than in serum (Table 2, Fig. 1). Urinary recovery of ciprofloxacin was  $29.70 \pm 10.34\%$  of the administered dose within 36 h post administration (Table 2). The *in vitro* protein percentage of ciprofloxacin at different concentration (0.5, 0.75, 1. 1.5, 2  $\mu\text{g}/\text{ml}$ ) was 20.5, 35.2, 49.3, 51.0, and 49.0, respectively with the mean value  $41.0 \pm 13.1\%$ . The *in vitro* protein binding of ciprofloxacin to serum protein

was  $41.0 \pm 13.10\%$ , and increased with increasing doses.

## Discussion

Following intravenous administration of ciprofloxacin (4 mg/kg), no adverse effect or toxic manifestation was observed. Ciprofloxacin concentration versus time data is best described by a biphasic curve and was similar to the disposition in pre-ruminant calves and piglets, goats, dogs, ponies, sheep, buffalo calves and cats [1,2,8,22,25,29,30]. The distribution of the ciprofloxacin appeared to be quite rapid, as indicated by short distribution half-life ( $0.108 \pm 0.03$  h) and 2.11 fold reduction in the serum drug concentration within 30 min of its administration. The distribution half-life ( $t_{1/2\alpha}$ ) in goats was similar to murrh buffalo calves [29]. However, the values were lower than the observed distribution half-life in pre-ruminant calves [25], cats [2], and cow calves [17].

The elimination half-life was similar to that in rabbits [4] and goats [28]. Higher values were reported in cats [2], horses [26], cow calves [34], buffalo calves [30], and men [6]. Ciprofloxacin showed a  $V_{d_{ss}}$  ( $2.012 \pm 0.37$  l/kg) that indicates the drug is well distributed to extra-vascular tissue, as a volume of distribution of one indicates good extra-vascular tissue distribution [3]. This is supported by the high  $K_{12}/K_{21}$  ratio, which indicates that the drug moves freely between the body compartments, as reported in cats [2]. The  $V_{d_{ss}}$  values were similar in rabbits [9] and horses [26], but lower than in cats [2] and ponies [8]. Ciprofloxacin clearance in goats was similar to dogs [1], calves [25] and pigs [10]. This value in goats was higher than reported in men [6], buffalo calves [30], and cat [2] but lower than in lactating cow [15], and cow calves [34].

Ciprofloxacin was detected in urine following intravenous administration, with a mean of  $29.70\% \pm 10.34\%$  of the total administered dose of ciprofloxacin recovered in urine within 36 h. Urine concentrations up to 36 h were above  $\text{MIC}_{90}$  for both Gram-positive and Gram-negative pathogens responsible for urinary tract infections, suggesting that ciprofloxacin could be used to treat goats with urinary tract infections caused by bacterial strains resistant to other commonly used antimicrobials.

**Table 2.** Urinary excretion of ciprofloxacin and fraction of the dose (%) excreted in aliquots in goats following a single intravenous injection of 4 mg/kg body weight (n = 4)

Time of sampling (h)	Urine concentration ( $\mu\text{g}/\text{ml}$ )	Fraction of the total dose excreted (%)	% Recovery of total dose in urine
0-3	$402.50 \pm 149.75$	$14.50 \pm 3.64$	$14.50 \pm 3.64$
3-6	$151.60 \pm 28.14$	$10.60 \pm 3.60$	$25.10 \pm 7.24$
6-9	$37.35 \pm 28.01$	$2.76 \pm 2.02$	$27.86 \pm 9.26$
9-12	$10.27 \pm 5.25$	$0.88 \pm 0.52$	$28.74 \pm 9.78$
12-24	$2.36 \pm 1.45$	$0.44 \pm 0.22$	$29.18 \pm 10.00$
24-36	$2.15 \pm 2.31$	$0.26 \pm 0.20$	$29.44 \pm 10.20$
36-48	$1.57 \pm 1.08$	$0.26 \pm 0.14$	$29.70 \pm 10.34$

All data are mean  $\pm$  SD.

**Table 3.** Efficacy predictors ( $C_p^0/\text{MIC}$  and  $AUC_{0-24}/\text{MIC}$ ) estimated for ciprofloxacin against Gram-negative and Gram-positive bacteria

	Gram-negative bacteria		Gram-positive bacteria	
	$\text{MIC} = 0.015$ ( $\mu\text{g}/\text{ml}$ )	$\text{MIC} = 0.06$ ( $\mu\text{g}/\text{ml}$ )	$\text{MIC} = 0.25$ ( $\mu\text{g}/\text{ml}$ )	$\text{MIC} = 0.5$ ( $\mu\text{g}/\text{ml}$ )
$C_p^0/\text{MIC}$	$298.11 \pm 56.49$	$74.53 \pm 14.12$	$17.89 \pm 3.39$	$17.89 \pm 1.69$
$AUC_{0-24}/\text{MIC}$	$744.44 \pm 303.63$	$186.11 \pm 75.91$	$44.67 \pm 18.22$	$22.33 \pm 9.11$

For calculations the applied values were:  $C_p^0 = 4.47$   $\mu\text{g}/\text{ml}$ .  $AUC_{0-24} = 11.16$   $\mu\text{g}\cdot\text{h}/\text{ml}$ . This value is obtained after doubling the value of  $AUC_{0-12}$ .

Ciprofloxacin (0.5 to 2.0 µg/ml) protein binding averaged 41.0%, comparable with Joos *et al.* [16] and Hoffken *et al.* [14] who reported serum binding between 21.9% and 39.6% in human.

An optimum dosage is derived by correlating the important pharmacodynamic variables like *in vitro* MIC data with pharmacokinetic variables. The antibacterial activity of the fluoroquinolones is dependent on the drug concentration and the MIC of the micro-organisms [38]. Antimicrobial drugs that act predominantly by concentration-dependent mechanisms generally exert significant post-antibiotic, sub-minimum inhibitory concentration effects. Such drugs continue to inhibit bacterial growth for a period of hours after they have been completely removed from the system. Optimal outcomes with this type of bactericide require high concentrations, with therapeutic success correlating with the AUC/MIC ratio, while prevention of the development of resistance correlating with the  $C_p^0$ /MIC ratio [32]. Accordingly, the  $C_p^0$ /MIC<sub>90</sub> and AUC<sub>24</sub>/MIC<sub>90</sub> are the best parameters for predicting the antimicrobial effects of fluoroquinolones [21]. For fluoroquinolones, a  $C_p^0$ /MIC<sub>90</sub> higher than 3 produced 99% reduction in bacterial count, and a  $C_p^0$ /MIC<sub>90</sub> of 8 or higher prevented the emergence of resistant organisms [7]. In addition, an AUC<sub>24</sub>/MIC<sub>90</sub> higher than 100 should give maximum clinical and bacteriology efficacy [36]. The numerical values of  $C_p^0$ /MIC<sub>90</sub> and AUC<sub>24</sub>/MIC<sub>90</sub> are substitute markers for predicting optimal dosage [35]. The AUC/MIC for cattle, sheep, goats, and camels were lower than 100-125 [19].

Lower and upper MIC<sub>90</sub> values were used for the calculation of dosage regimen [39]. MIC<sub>90</sub> values of 0.015 and 0.06 µg/ml were used for Gram-negative bacteria (*E. coli*, *Pasteurella* spp., *Salmonella* spp., *Klebsiella pneumoniae*, *Proteus mirabilis*, *Bordetella bronchiseptica*, and *Haemophilus* spp.). However, values for Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus intermedius*, *Staphylococcus* spp.) were 0.25 and 0.5 µg/ml [2]. MIC<sub>90</sub> values of 0.007 and 1 µg/ml were used for selected veterinary bacterial pathogens [27].

The efficacy predictors, AUC<sub>0-24</sub>/MIC and  $C_p^0$ /MIC ratios (Table 3) are lower for Gram-negative than Gram-positive bacteria. However, for treatment of gram-positive bacteria with greater MIC, the predicted efficacy is lower. The minimum therapeutic concentration of fluoroquinolones is 0.02-0.5 µg/ml [20]. Here, ciprofloxacin concentration in serum was MIC < 1 µg/ml [28] up to 12 h, a level suitable for Gram-negative bacteria, and levels in urine up to 36 h were sufficient for treating both Gram-negative and Gram-positive microorganisms. Ciprofloxacin also shows post-antibiotic effects (PAE) that persist for 4 to 8 h. We therefore recommend once daily, intravenous ciprofloxacin at 4 mg/kg to maintain effective levels in serum or 36 h intervals for treating urinary tract infections in goats.

In conclusion, ciprofloxacin showed high efficacy

predictors against Gram-negative bacteria with PAE. In addition, the high concentration of ciprofloxacin excreted in urine up to 36 h makes it a better therapeutic option for treating systemic infections, especially of Gram-negative bacterial origin, as well as acute urinary tract infections of resistant strains.

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