PHARMACOKINETICS AND DOSAGE REGIMEN OF CIPROFLOXACIN FOLLOWING SINGLE INTRAMUSCULAR ADMINISTRATION IN *TEDDY* GOATS

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ABSTRACT

The objective of this study was to determine the pharmacokinetics and dosage regimen of ciprofloxacin in *Teddy* goats. Ciprofloxacin was administered intramuscularly at 5 mg/kg body weight in each of eight animals. Following drug administration, blood samples were collected at different time intervals and analyzed for ciprofloxacin using HPLC. Pharmacokinetic parameters were calculated using two compartment open model. Peak plasma concentration (C_{max}) of ciprofloxacin, 1.77 ± 0.20 µg/ml was achieved at 0.90 ± 0.04 hours (T_{max}). Values for half-life of absorption ($t_{1/2}$ abs), distribution ($t_{1/2}$ α) and elimination ($t_{1/2}$ ß) were 0.52 ± 0.04, 0.52 ± 0.04 and 2.62 ± 0.39 hours, respectively. The value for apparent volume of distribution (Vd) was 3.76 ± 0.92 l/kg, area-under-the-curve (AUC) 5.89 ± 0.91µg.hr/ml and total body clearance (CL) was 1.09 ± 0.11 l/hr/kg. Based on these results, it was concluded that calculated dose should be higher than the dose recommended by the manufacturer to treat susceptible bacteria in goats.

Keywords: Pharmacokinetics, dosage regimen, ciprofloxacin, HPLC, teddy goats.

INRODUCTION

Fluoroquinolones (FQs) are synthetic antimicrobial agents which are used in the treatment of a variety of bacterial infections. The FQs have been valuable in veterinary medicine and they have extensive application in clinical practices because of favorable bioavailability and pharmacokinetic profile (Vancutsem *et al.*, 1990; Papich and Riviere, 2009). FQs act by concentration dependent killing mechanism, where the optimal effect is attained by administration of high doses over a short period of time (Drusano *et al.,* 1993). This concentration dependent killing profile is associated with a relatively prolonged post antibiotic effect (Aliabadi and Lees, 2001). All FQs are bactericidal and act against the same bacterial target: the bacterial DNA gyrase (type II topoisomerase) and topoisomerase IV. DNA gyrase is the major target in gram-negative bacteria and topoisomerase IV is the major target for gram-positive bacteria (Blondeau *et al.,* 2004). FQs accumulate within bacteria very rapidly, so that a steady-state intrabacterial concentration is obtained within a few minutes (Smith, 1986).

Ciprofloxacin is one of the FQs that has been used to treat various infectious diseases in animals (Stein, 1996). Although the administration of ciprofloxacin to food – producing animals in some countries (e.g., the United States) would be considered extra-label and prohibited, it has been used in food-producing animals in other countries. A search of the literature indicates that disposition of ciprofloxacin has not been studied in local ruminant species. Because there is wide-spread clinical use of ciprofloxacin in local animals, but little information regarding its disposition, the present study was undertaken with the objective to determine the pharmacokinetics and optimal dosage regimen of this drug in *Teddy* goats. It is hoped that the study will help in optimizing the dosage of ciprofloxacin in local goats.

MATERIALS AND METHODS

Experimental animals and drug administration

Pharmacokinetics and dosage regimen of ciprofloxacin were investigated in eight healthy adult goats of *Teddy* breed. The average ± SE weight of the goats was 35 ± 2 kg. All the goats were maintained under similar environmental and managemental conditions at the Experimental Farm, Department of Livestock Management, University of Agriculture, Faisalabad, Pakistan. The animals were fed with the green fodder of the season and had free access to drinking water. Experiments were conducted during the month of December, 2006. The protocol was approved by the Animal Care and Use Committee of the University of Agriculture, Faisalabad, Pakistan, prior to the initiation of the study. A commercial injectable preparation of ciprofloxacin (Han Dong Corporation Ltd., Korea) was injected intramuscularly in the neck region at the dose rate of 5 mg/kg body weight.

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Collection of blood samples

Blood samples were collected in heparinized plastic centrifuge tubes. Prior to drug administration, a control blood sample was collected in each experiment. Following drug administration, the blood samples were drawn at 15 and 30 minutes, then at half-hourly intervals until 3 hours, followed by the samples collected at 4, 6, 8 and 10 hours, after injection. The pH of fresh blood samples was recorded by a pH meter (Beckman HS, Germany) with a glass electrode at 37°C. Blood samples were centrifuged and plasma was separated and stored at - 20°C until analysis.

HPLC analysis

The concentration of ciprofloxacin in plasma was determined by using high-pressure liquid chromatography (HPLC). The HPLC unit consisted of a quaternary pump (Sykam, S-1122) and a UV/Vis detector (Sykam, S-3210). The output of the detector was monitored with computer software (Peak Simple Chromatography Data System, Buck Scientific Inc., East Norwalk). A stainless steel column packed with YMC pack A-312 (Thermo Hypersil-Keystone, BDS-C_{18} with 250 x 4.6mm dimensions and 5µm particle size) was used. The column was protected with a pre-column filled with C_{18} cartridge (Thermo Hypersil, England). Separation of ciprofloxacin was achieved at 37°C, using an isocratic mode. The mobile phase consisted of a mixture of 800 ml of 14 ml/L phosphoric acid and 200 ml of acetonitrile per liter. The UV detector was set at 275 nm and the flow rate was 1 ml/min.

For preparation of plasma samples, in a centrifuge tube 2 ml of acetonitrile was added to 1 ml of incurred plasma, plasma blank or plasma calibrator. The mixture was vortexed for one minute and centrifuged for 30 minutes at 4000 rpm. The supernatant was transferred into a glass tube and the liquid phase was evaporated to dryness in a boiling water bath. The residue was then reconstituted in 10 µl of the internal standard (IS) paracetamol and 1 ml of 14 ml/L phosphoric acid. The final solution was again vortexed for 30 seconds; filtered and 20 µl was injected into the HPLC system.

All drug concentrations were determined from calibration curves made from spiked blank samples of the plasma collected from the experimental animals prior to drug administration. Calibration curves were prepared by fortifying the blank matrix with a reference drug standard of ciprofloxacin and paracetamol as internal standard (IS). This method has already been used (Soback *et al.,* 1994) and was partially modified and validated. The ciprofloxacin recovery was 76 % and coefficient of variation was < 2 % for intra and inter assays differences. The limit of detection was 75 ng/ml while the limit of quantitation was 250 ng/ml.

Pharmacokinetic analysis

The plasma concentration versus time profile of ciprofloxacin after intramuscular administration in each animal was used to establish various pharmacokinetic parameters. A standard two-stage (STS) approach was used in which each animal's data was analyzed separately, then averaged to produce the mean value for the group. A two-compartment open model was fitted to the data with a computer programme, MW/PHARM version 3.02, a MEDIWARE product, Holland (Netherlands). Least Square Regression Analysis was applied to discriminate the best model and correlation coefficient was taken as measure of goodness-of-fit.

Dosage regimen

Based on pharmacokinetic/pharmacodynamic (PK/PD) parameters; optimal dosage regimen of ciprofloxacin to be repeated after 24 hours interval was calculated in adult *Teddy* goats using the following equation:

$$\text{Dose} = \frac{\text{CL} \cdot (\text{AUC/MIC}) \cdot \text{MIC}}{\text{fu} \cdot \text{F} \cdot 24\,\text{hr}}$$

To derive a dose for this study, we used the average clearance value produced by our study (reported as CL/F), an estimated protein fraction unbound from other studies (fu), and MIC values across a range for the pathogens obtained from these animals. The AUC calculated from a compartmental approach is from time zero to infinity. This AUC is used for dose calculations because it is recognized that, at steady-state, AUC_{24} from a dose administered once per day (every 24 hours), the value of 24 in the above equation cancels out.

RESULTS

Pharmacokinetic analysis

The mean ± SE values for plasma concentration of ciprofloxacin after intramuscular injection in 8 *Teddy* goats have been plotted on a semilogarithmic scale against time after injection in fig. The plasma concentration revealed a biphasic decline; a rapid decline in first half hour after administration was followed by a slow decline until 10 hours after injection.

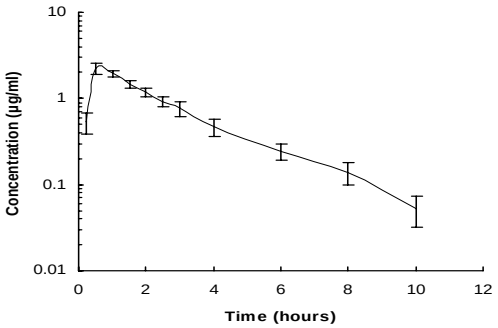

Fig. 1: Mean ± SE plasma concentration of ciprofloxacin on a semilogarithmic scale versus time after single intramuscular administration (5 mg/kg) in 8 *Teddy* goats.

Pharmacokinetic parameters (mean ± SE) of ciprofloxacin in goats are presented in table 1. The time to reach maximum concentration (T_{max}) was observed as 0.90 ± 0.04

hours. The values of C_{max}, A and B were 1.77 ± 0.20, 3.08 ± 0.40 and 1.07 ± 0.24 µg/ml, respectively. The mean ± SE values for half life of absorption ($t_{1/2}$ abs), distribution ($t_{1/2}$ α) and elimination ($t_{1/2}$ ß) were 0.52 ± 0.04, 0.52 ± 0.04 and 2.62 ± 0.39 hours, respectively. Mean ± SE value for volume of distribution (Vd) was 3.76 ± 0.92 l/kg, for AUC was 5.89 ± 0.91 µg. hr/ml and for total body clearance (CL) was 1.09 ± 0.11 l/hr/kg.

Table 1: Mean ± SE values for the disposition kinetics of ciprofloxacin following intramuscular administration of 5 mg/kg body weight in each of the 8 adult *Teddy* goats.

Parameters	Units	Goats (n = 8)
C_{max}	(µg/ml)	1.77 ± 0.20
t_{max}	(hr)	0.90 ± 0.04
K_{abs}	(hr^{-1})	1.38 ± 0.10
$t_{1/2abs}$	(hr)	0.52 ± 0.04
A	(µg/ml)	3.08 ± 0.40
α	(hr^{-1})	1.38 ± 0.10
$t_{1/2}$α	(hr)	0.52 ± 0.04
B	(µg/ml)	1.07 ± 0.24
β	(hr^{-1})	0.29 ± 0.03
$t_{1/2}$β	(hr)	2.62 ± 0.39
V_c	(l/kg)	1.33 ± 0.16
Vd	(l/kg)	3.76 ± 0.92
K_{el}	(hr^{-1})	0.74 ± 0.05
k_{12}	(hr^{-1})	0.32 ± 0.05
k_{21}	(hr^{-1})	0.62 ± 0.14
CL	(l/hr/kg)	1.09 ± 0.11
AUC	(µg . hr/ml)	5.89 ± 0.91

A and *B*, *Y*-axis intercept terms; C_{max}, peak plasma concentration of drug; t_{max}, time to reach peak plasma concentration; K_{abs}, absorption rate constant; α, distribution rate constant; K_{el}, elimination rate constant; β, overall elimination rate constant; $t_{1/2abs}$, absorption half-life; $t_{1/2}\alpha$, distribution half-life; $t_{1/2}\beta$, elimination half-life; k_{12}, rate constant from central to peripheral compartment; k_{21}, rate constant from peripheral to central compartment; *Vc,* volume of distribution in the central compartment; *Vd,* volume of distribution; *AUC,* area under the concentration-versus time curve from time zero to infinity; *CL,* total body clearance.

Dosage regimen

Based on the pharmacokinetic/pharmacodynamic parameters, optimal dosage regimen of ciprofloxacin was calculated in adult *Teddy* goats. The calculations of dose were based on the minimum inhibitory concentration (MIC) of ciprofloxacin in blood, fraction of the drug not bound to plasma proteins (fu) which was taken as 0.70 and ratio of AUC/MIC which was taken as 100. The value of 100 is used in this equation because it represents a conservative consensus as reported in review of the relevant literature by McKellar *et al*. (2004). Occasionally, higher values (e.g., AUC/MIC) of 125 have been cited when protein binding was not factored into the equation. McKellar's review also points out that for some organisms (e.g., gram-positive) lower ratios might be possible, but for this study our desire was to predict a single dose that would encompass both gram-positive and gram-negative bacteria. The MICs of ciprofloxacin 0.02, 0.03, 0.1, 0.2, 0.3, 0.4, 0.5 and 1.0 µg/ml were used in the calculations because they represent the range of values for pathogens that cause infections in goats. The intramuscular dose of ciprofloxacin in mg/kg body weight for 24 hour dosing interval in adult *Teddy* goats is presented in table 2. In *Teddy* goats**,** at MIC 0.1 µg/ml the calculated intramuscular dose is 15.57 mg/kg, to be repeated after 24 hour interval.

Table 2: Intramuscular dosage regimens of ciprofloxacin (mg/kg) to be repeated after 24 hours interval in adult *Teddy* goats in order to produce AUC/MIC value > 100 for the unbound drug (fu).

MIC (µg/ml)	Dose (mg/kg)
0.02	3.11
0.03	4.67
0.05	7.79
0.10	15.57
0.20	31.14
0.30	46.71
0.40	62.28
0.50	77.86
1.00	155.71

DISCUSSION

Pharmacokinetic analysis

Absorption of ciprofloxacin was rapid from the intramuscular injection site and mean absorption half life was 0.52 hours in *Teddy* goats. The values of distribution and elimination half life of ciprofloxacin (0.52 and 2.62 hours, respectively) in the present study were comparable to the results of another study, where elimination half life value (2.73 hours) of ciprofloxacin in goats was almost similar but distribution half life (0.29 hours) was almost half of the respective value established in the present study (Garcia Ovando *et al.,* 2000). Following 5 mg/kg intravenous and intramuscular injections of ciprofloxacin in goats, shorter distribution (0.31 hours) but longer elimination half life (2.78 hours) was reported (El-Banna and Abo El-Sooud, 1998). Appreciably lower elimination half life of ciprofloxacin (1.82 hours) was recorded in goats after intramuscular injection of 5 mg/kg enrofloxacin but when the same drug was concurrently administered with probenecid (40 mg/kg I/V), the elimination half life increased two-folds to 3.85 hours which indicates that ciprofloxacin competes with probenecid for secretion in the renal tubules (Rao *et al.,* 2002). When compared with the present study, different fluoroquinolones depicted different elimination half life

values in goats; danofloxacin 1.35 and 4.54 hours, respectively (Atef *et al.,* 2001; Ismail, 2006), pefloxacin 1.6 and 1.12 hours (Abd El-Aty and Goudah, 2002; Malik *et al.,* 2002), marbofloxacin 7.32 and 7.18 hours (Waxman *et al.,* 2003; Waxman *et al.,* 2004) and ofloxacin 15.58 hours (Baruah *et al.,* 2004). The half life value (2.62 hours) in goats of present study has been found shorter than the most reported values in their foreign counterparts.

In present study volume of distribution (Vd) in goats (3.76 l/kg) was comparable to 3.37 l/kg (Garcia Ovando *et al.,* 2000) while higher than 2.14 l/kg (El-Banna and Abo El-Sooud, 1998), following intravenous injection in lactating goats. Values of Vd of other fluoroquinolones in goats were; 1.29 l/kg for enrofloxacin (Rao *et al.,* 2002), 1.41 l/kg for danofloxacin (Atef *et al.,* 2001) 1.1 l/kg for difloxacin (Atef *et al.,* 2002), 1.08 l/kg for pefloxacin (Malik *et al.,* 2002), 1.19 l/kg for marbofloxacin (Waxman *et al.,* 2003) and 2.85 l/kg for ofloxacin (Baruah *et al.,* 2004). Although there was a large Vd in this study, one cannot infer that this represents extensive distribution to tissues. Because the value reported here was Vd/F, poor absorption would produce a low value of "F" and inflate this value. Because we were unable to measure F in this study because of a lack of an IV dose, we cannot make any conclusions about Vd. Nevertheless, other studies have shown that fluoroquinolone concentrations in most tissues or fluids are generally higher to those observed in the plasma, with exception of a lower penetration observed in the aqueous humor and in the central spinal fluid (Stein, 1996) and that higher Vd reflects intracellular concentrations higher than in plasma.

Total body clearance (CL), 1.09 l/hr/kg, in local goats of present study was slightly lower than 1.18 l/hr/kg (Garcia Ovando *et al.,* 2000) but it was higher than 0.88 l/hr/kg (El-Banna and Abo El-Sooud, 1998). Other fluoroquinolones have lower total body clearance values; danofloxacin 0.59 l/hr/kg (Atef *et al.,* 2001), difloxacin 0.13 l/hr/kg (Atef *et al.,* 2002), pefloxacin 0.82 l/hr/kg (Malik *et al.,* 2002), marbofloxacin 0.24 l/hr/kg (Waxman *et al.,* 2003), ofloxacin 0.14 l/hr/kg (Baruah *et al.,* 2004), as compared to that of ciprofloxacin in the present study.

Although an IV dose was not administered, which would have defined more precisely the pharmacokinetic parameters, these results show that ciprofloxacin in these goats has the general pharmacokinetic characteristics of a typical fluoroquinolone antimicrobial agent. That is, it has distribution, clearance and half-life that are similar to other studies. Also, because the values of Vd/F and CL/F determined from this study are in general agreement with the value obtained from intravenous studies, it may indicate high bioavailability and a value of F that is near 100 % from the IM injection used in this study.

Dosage regimen

Inadequate antibiotic concentrations can be one of the causes of ineffectiveness (Kiss *et al.,* 1976; Nicolau, 2003). Suboptimal concentrations may also contribute to resistance. Also, Peter Lees stated that it was exposure, and especially exposure to sub-optimal drug concentrations that was the most important single factor in resistance emergence and its subsequent spread (Lees *et al.,* 2008). The susceptibility of bacteria to the action of ciprofloxacin varies not only between species but also between strains within the same species resulting in a very wide range of minimum inhibitory concentration (MIC) against the susceptible microbes. For the majority of the organisms that are susceptible to enrofloxacin and ciprofloxacin, the reported MIC values are 0.1 - 1 µg/ml (Bauditz, 1990) and even < 0.5 µg/ml (Giguere *et al.,* 1996). Lower range of MIC of ciprofloxacin for bacteria isolated from buffaloe calves was 0.10 µg/ml (Saini and Srivastava, 2001) and ≥ 0.1 µg/ml (Kaartinen *et al.,* 1997). MIC value of enrofloxacin for susceptible bovine pathogens has also been reported to be 0.06 µg/ml (Davis *et al.,* 2007). The information provided on enrofloxacin's FDA-approved label (Baytril 100) in the United States lists the MIC90 for susceptible pathogens to be 0.03 to 0.06 µg/mL for non-Mycoplasma organisms. An MIC_{90} for ciprofloxacin was reported as 0.015 - 0.06 µg/ml against gram negative while 0.25-0.5 µg/ml against most of the gram positive veterinary pathogens and it was also reported that ciprofloxacin MIC values were similar to MIC values of enrofloxacin for P. multocida and H. somnus and slightly lower for *M. haemolytica* (Prescott and Yielding, 1990). Based on these observations, a range of MIC values of, 0.02-1.0 µg/ml was used to develop a *target attainment table* (table 2) to provide estimated doses needed to attain an AUC/MIC target of 100, for unbound drug. This may be used to determine the optimal dosage regimen suggested in *Teddy* goats (table 2). Based on these calculations, we suggest an optimal dosage regimen of ciprofloxacin in local goats as 15.57 mg/kg to be repeated intramuscularly after 24 hours and will become 16 mg/kg in the field conditions. The dose recommended by the manufacturer of the pharmaceutical preparation of ciprofloxacin (5 mg/kg/24 hours) attained a target of AUC/MIC of 100 for unbound drug (fu) only for bacteria with MIC < 0.03 µg/mL (table 2). Other investigators have recommended higher doses or more frequent intervals. An intravenous dose of 10 mg/kg ciprofloxacin was suggested to be repeated after 12 hours in goats (Garcia Ovando *et al.,* 2000) while intramuscular dose of 5 mg/kg body weight was suggested after every 12 hours in cross-bred cow calves (Singh and Srivastava, 2000). In another study, a dose of 3 mg ciprofloxacin/kg body weight was recommended to be repeated after 12 hours interval in buffalo calves (Saini and Srivastava, 2001).

CONCLUSIONS

Based on the findings of the present study it was concluded that the dosage regimen of ciprofloxacin in local goats recommended by the manufacturers was much lower than the suggested dosage regimen investigated in the present study.

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