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PLASMA PHARMACOKINETICS OF CIPROFLOXACIN IN SHEEP

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ABSTRACT

The study was carried out to determine the biodisposition kinetics of ciprofloxacin in sheep model in Department of Pharmacology, Bangladesh Agricultural University. Healthy sheep of both sexes (n=65) were divided into 13 groups, each consists of five and given a single dose of ciprofloxacin @ 5 mg/kg bwt intramuscularly .Blood sample was collected from each group of sheep at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10 and 12 hours interval respectively. Serum concentration of ciprofloxacin was determined by spectrophotometric method. The pharmacokinetic parameters were measured by single compartment open model and first order kinetics. The peak concentration of ciprofloxacin was 3.56±0.15µg/ ml, absorption half-life and biological half-life were 0.0846±1.79 and 1.75±0.15 h respectively. The apparent volume of distribution was found 35.54 mg/liter. The absorption rate constant was $8.188h^{-1}$, MRT was $2.647h^{-1}$ and total body clearances were found 16.88 h^{-1}. These result suggested that a dose of 5 mg/kg bwt provides maximum plasma concentration and is effective in the control of many infectious diseases of sheep.

Key wards: Plasma pharmacokinetics, ciprofloxacin, sheep

INTRODUCTION

Ciproflocxacin a broad spectrum antibacterial has been shown to be effective in the treatment of a wide variety of infections in man and animals (Moellering, 1996; Hooper, 1998). Ciprofloxacin belongs to a class of antibacterials known as fluroquinolones. It is a synthetic antibacterial that works on bacterial DNA topoisomerase II and IV (Drlica and Zaho, 1997) and is rapidly absorbed from the site of absorption and well distributed into tissues. The fluoroquinolones are currently enjoying extensive clinical application world wide in human because of their good bioavailability and pharmacokinetic profile. Investigations into all aspects of the pharmacokinetic of all clinically relevant quinolones have been carried out notably in Europe, USA and Japan. Metabolic as well as drug-drug and drug-food interactions have also been extensively investigated (Bergan *et al.,* 1987). A great variation in pharmacokinetic parameter in man and animals has been observed by Mattie *et al.* (1987).

Several numbers of investigation and research have already been completed on the pharmacokinetics parameter of Ciprofloxacin in different species (Munoz *et al.*, 1996 and Mengozzi *et al.,* 1996) in abroad. However; the pharmacokinetic parameters may vary across breed and variety (Ahangar *et al.,* 2000). But pharmacokinetic data of Ciprofloxacin in native sheep are scare. Therefore, this study was undertaken to determine the pharmacokinetic parameter of Ciprofloxacin in native sheep along with dose, plasma concentration, half-life, maximum concentration in plasma, time to peak concentration, volume of distribution and therapeutic concentration.

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MATERIALS AND METHODS

Pharmacokinetics of ciprofloxacin was studied in 65 healthy sheep in the experimental pharmacological laboratory, Department of Pharmacology, Bangladesh Agricultural University.

Experimental sheep

The experiment was performed in 65 clinically healthy native sheep. The animal was under the Department of Pharmacology, Bangladesh Agricultural University. The animals was provided with normal feed and water to get acclimatized for 8 weeks before the study to make sure that none of them had received any medication for this period. All sheep were kept in good housing. They were divided into 13 groups (A-M) with five sheep in each group.

Administration of ciprofloxacin and sampling

Ciprofloxacin (Cipryl® 50 ml, 1 ml contain 50 mg ciprofloxacin) was administered intramuscularly at the rate of 5mg/kg body weight with the help of syringe and needle. 5 ml of blood samples were collected from jugular vein of each sheep at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12.0 hour interval strictly under aseptic conditions**.**

Preparation of blood sample

Collected blood sample was transferred into hematocrit tube and it was allowed to stand for 20 minutes and then centrifuged at 4000 rpm for 15 minutes, serum was separated and stored at -20^0C till further analysis.

Analytical procedure

Ciprofloxacin concentration was measured by UV-spectrophotometeric revised method by De *et al.* (1993). The method involves deproteinization of plasma samples by using isopropyl alcohol and measuring the absorbance at 280 nm. Since isopropyl alcohol gave high absorbance of its own in the blank samples therefore the method was modified and improved. Before running the plasma samples standard curve for Ciprofloxacin was made.

Statistical analysis

The data was analyzed statistically by '*t*' test described by Khan (1989).

Kinetic parameters

The plasma concentration versus time was analysed by single compartment open model. Kinetic parameters like maximum concentration of ciprofloxacin (C_{max}), time to peak concentration (T_{max} h), half life of absorption (t½ (α), distribution half life (t½), elimination half life $t_{(\beta)}$½h, area under curve (AUC), volume of distribution V_d (mg/litre), absorption rate constant (Ka), distribution rate constant (K), elimination rate constant K_e (h^{-1}), mean residual time MRT (h), therapeutic concentration of the drug $\{^tc_{p(ther)}\}$body clarence (CL) were determined.

RESULTS AND DISCUSSION

Plasma pharmacokinetics of ciprofloxacin

After administration of a single dose of ciprofloxacin, concentration in the plasma started to rise from 0.5 hour and peaked after 1.61 hours. Then the concentration began to decline with an elimination rate constant of 0.67 hours. The plasma concentration of ciprofloxacin at different time intervals was plotted taking plasma concentration at Y-axis and time interval at X-axis (Fig. 1).

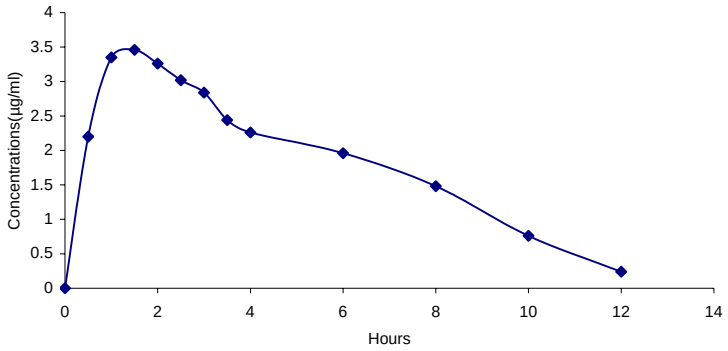

Fig. 1. Mean serum concentrations of ciprofloxacin versus time following a single intramuscular administration of 5 mg/kg body weight in sheep.

Pharmacokinetics parameters

A number of pharmacokinetic parameters were obtained after the single intramuscular dose of ciprofloxacin (Table 1).

Table 1. Pharmacokinetic parameters of ciprofloxacin in native sheep after a single intramuscular dose determined by single compartment open model

S/N	Kinetic parameters	Symbols	Results
1	Maximum drug concentration	C_{max} (µg/ml)	3.56±0.15
2	Time to peak concentration	T_{max} (h)	1.61
3	Absorption half-life	$t_{1/2(\alpha)}$ (h)	0.0846
4	Distribution half-life	$t_{1/2}$ (h)	1.75±0.15
5	Elimination half-life	$t_{1/2(\beta)}$ (h)	1.029
6	Area under curve	(AUC) µg/ml/h	2.28±1.14
7	Volume of distribution	(Vd) mg/litre	35.54
8	Absorption rate constant	Ka (h)	8.188±1.79
9	Distribution rate constant	K (h)	0.3960±0.15
10	Elimination rate constant	Ke (h)	0.6734
11	Mean residual time	MRT (h)	2.647
12	Therapeutic concentration	$^{t}c_{p(ther)}$	7.425
13	Body clearance	CL (h)	14.07±0.15

Ciprofloxacin was routinely prescribed to treat a variety of infections (Moellering, 1996; Hooper, 1998). No literature is available yet in its bioavailability and pharmacokinetics profile in Bangladeshi animal population. To achieve optimum therapeutic benefits of the drug, all factors which influences its pharmacokinetics and effectiveness, need to be determined. However; the pharmacokinetic parameters may vary across breed and variety (Ahangar *et al.*, 2000).

The pharmacokinetics analysis was performed after one compartment model. Following intramuscular administration of Ciprofloxacin in sheep, the peak serum concentration of drug occurred after approximately one and half hour (1.61 hr). The maximum plasma concentration of Ciprofloxacin was found 3.56 µg/ml, which is more or less similar to the literature values of 3.56µg/ml and 3.57µg/ml as reported by Girard *et al.* (1992) and Khurram *et al.*(2003), respectively but it was higher than some other literature value reported by Chkwuani *et al.* (1998) (2.92 µg/ml) and Kung *et al.* (1993) (0.02 µg/ml) and Abadia *et al.* (1995) (3.08 mg/l) and Banna *et al.* (1998) (1.92 mg/l) and Munoz *et al.* (1996) (0.69±0.27mg/l). Maximum plasma concentration of ciprofloxacin (3.56 µg/ml) was the lower than the literature value of Idown and Peggins (2004) (6.14µg/ml). According to Bayer *et al*. (1987), the peak serum concentration was 0.25 to 4.32µg/ml.

Biological elimination half-life was found 1.029h^{-1}, which is very less those values reported by Chkwuani *et al.* (1998), who examined 7.52h. The value was more or less similar to literature values reported by Khurram *et al.* (2003) (1.45h^{-1}) and Rao *et al.* (2002) (1.39h^{-1}) and Munoz *et al.* (1996) (1.12h^{-1}). Elimination half-life is lower than the literature values of Banna *et al.* (1998) (2.78h^{-1}) and Abadia *et al.* (1994) (2.09-3.00h^{-1}) and Nouws *et al* (1988) (2.5h^{-1}) and Girard *et al.* (1992) (7.8h^{-1}). In this study, area under curve (AUC) was found 2.28±1.46µg/ml/h that was lower than literature value of Khurran *et al.* (2003) (18.02µg/ml/h) and Ovando *et al.* (2000) (10.32±5.137 µg/ml/h) and more or less similar to literature value reported by Rao *et al.* (2002) (2.55µg/ml/h). Calculated volume of distribution was found 35.54 mg/l, was higher than the literature value reported by Khurram *et al.* (2003) (28.59 mg/l). This may be reason of high plasma drug concentration. It was reported by Banna *et al.* (1998) (2.14±0.072 l/kg) and Rao *et al.* (2002) (1.52 l/kg) and Ovando *et al.* (2000) (3.373±0.893 l/kg).

Therapeutic concentration of ciprofloxacin was 10 hour in serum and 24 hours in milk (Banna *et al.,* 1998). In this study, therapeutic concentration of ciprofloxacin in plasma was 7.425 hour. Absorption rate constant and absorption half-life was obtained 0.0846h^{-1} and 8.188±1.79 h^{-1} respectively. It was 1.07h^{-1} in case of oral administration which reported by Khurram *et al.* (2003). No data absorption half-life and absorption rate constant were found in case of sheep dog, and other animals. Furthermore, distribution rate constant was obtained 0.396±0.15h^{-1} it was less than the literature value 0.50h^{-1}, reported by Khurram *et al.* (2003). A significant deviation in pharmacokinetic parameters was observed from the literature values with respect to peak plasma concentration, area under curve and volume of distribution. All these factors play important role in the biodisposition of ciprofloxacin. This variation might be due to species difference, breed, variety and environment.

In conclusion, ciprofloxacin @ 5mg/kg body weight intramuscularly gives some variable pharmacokinetics parameters with regard to cited literature in native sheep and further investigation should carry out to find out the cause of variations.

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