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BIOAVAILABILITY AND PHARMACOKINETICS OF NORFLOXACIN AFTER INTRAMUSCULAR ADMINISTRATION IN GOATS

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ABSTRACT

Bioavailability and pharmacokinetics of two commercially available preparations of norfloxacin i.e. A (imported) and B (locally prepared) were determined in six healthy female goats after single intramuscular administration @ 5 mg/kg b.wt following crossover study design. The blood samples collected at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8 and 12 hours postmedication were also analysed for drug concentration by microbiological assay. Results revealed that preparation A showed higher ($p<0.05$) plasma drug levels than the preparation B at 1, 3, 6 and 8 hours after medication. Among bioavailability parameters AUC (μg.h/ml) and relative bioavailability (F%) were higher for preparation A than the preparation B, while other parameters did not differ between the two preparations. Similarly, various pharmacokinetic parameters did not show any statistical difference between preparation A and B. The study revealed comparable elimination kinetics but different bioavailability of two commercial preparations of norfloxacin. It is concluded from the study that for optimal dosage regimen of drugs, the bioequivalence studies and kinetic behavior of the drugs are of paramount importance.

Key words: Bioavailability, pharmacokinetics, norfloxacin, goats.

INTRODUCTION

Bioavailability and pharmacokinetics of drugs influence their therapeutic, clinical and toxic effects. Further, these help in monitoring the course of therapy. The variation in the bioavailability of different formulations of the same drug given at the same strength and in the same dosage form poses a special challenge to health care professionals, making these issues very relevant to pharmacists.

Norfloxacin is a synthetic antibiotic belonging of the flouroquinolones class and is usually prescribed for the treatment of urinary tract infections. Flouro-quinolones are gaining popularity as important antibacterial agents in veterinary practice because of their broad antimicrobial activity (Park *et al*., 1998). Quinolones are active against gram negative and gram-positive bacteria in vitro (Wolfson and Hooper, 1985), as well as trimethoprim/sulfonamide resistant microbes (Perheim *et al.,* 1987). In addition, these antimicrobials are also active against Mycoplasma (Brown, 1996). Moreover, no plasmid resistance has been demonstrated and flouroquinolones have a favorable margin of safety (Bahri and Blouin, 1991).

Norfloxacin is available in the market in different dosage forms and formulations. The method of manufacture and final formulation of the drug can markedly affect its bioavailability and pharmaco-kinetics. Different pharmaceutical companies especially multinational ones claim the superiority of their products with better bioavailability and pharmacokinetics. These claims, as well as increasing use of norfloxacin in the modern human and veterinary practices, necessitate the evaluation of bioavailability and pharmacokinetics of these preparations. Therefore, the present study was designed to investigate the bioavailability and pharmacokinetics of two commercial preparations of norfloxacin.

MATERIALS AND METHODS

Experimental animals and drug

The present study was conducted on six adult healthy female goats maintained under similar managemental conditions at animal shed, Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad, Pakistan. The average body weight of animals was 19 kg (range 15-30 kg). Two commercial injectable preparations of norfloxacin i.e. A (Doctorgin 10% inj., Microbiological Lab., Korea) and B (Norfloxacin-50, 5% inj., Kakhasian Pharmaceutics, Pakistan.) were used. After restraining the animals, a single dose of preparation A (5 mg/kg b.wt) was given intramuscularly. After a wash out period of 7 days, experimental goats were given preparation B at a dose rate of 5mg/kg b.wt I/M following crossover design.

Collection of blood samples

Jugular blood samples were collected from experimental goats in heparinized glass centrifuge tubes before and 0.25, 0.50, 0.75, 1, 2, 3, 4, 6, 8 and 12 hours after medication. Plasma was separated after centrifugation at 3000 rpm for 15 minutes and stored at -4 C° until analysis.

Analytical method

Norfloxacin concentrations in plasma were determined by microbiological assay according to disc agar diffusion method, as described by Arret *et al.* (1971) and Shungu *et al.* (1983), using *Bacillus substilis* as a sensitive organism. Bioavailability and kinetic parameters i.e. area under curve (AUC), absorption rate constant (K_{ab}), absorption half life ($T1/2_{ab}$), peak concentration (C_{max}), time to peak concentration (T_{max}), relative bioavailability (F%), total body clearance (ClB), volume of distribution (V_d), distribution half life ($T_{1/2\alpha}$), elimination half life ($T_{1/2\beta}$), elimination rate constant (K_{el}), drug transfer rate constant (K_{12}) and (K_{21}) and mean residance time (MRT) were calculated by using computer software MW\Pharm Version 3.02.

Statistical analysis

Mean values (± SD) for the concentrations, bioavialability and pharmacokinetics of two preparations of norfloxacine were computed. The data were further subjected to parametric comparison between two groups using Mini-tab computer programme (descriptive statistics t-test).

RESULTS AND DISCUSSION

The mean (± SD) norfloxacin plasma concentrations at various time intervals after intramuscular administration of equal single doses of two commercial norfloxacin preparations A and B are shown in Table 1 and Fig. 1. The values of bioavailability parameters, which describe the rate and extent of absorption of a drug from the site of administration into the blood, are shown in the Table 2. The values of pharmacokinetic parameters which describe disposition of the drug in the body are given in Table 3.

Following an intramuscular administration, the preparation A gave higher drug plasma levels than preparation B. However, these plasma levels were only significantly higher at 1, 3, 6 and 8 hours post medication. The mean (± SD) area under concentration

Table 1: Mean (±SD) plasma concentrations (µg/ml) of two preparations of norfloxacin after I/M administration (5 mg/kg) in goats

Time (hrs)	Preparation A	Preparation B
0.25	1.16 ± 0.47	1.03 ± 0.40 NS
0.50	1.60 ± 0.46	1.60 ± 0.52 NS
0.75	2.70 ± 0.25	2.31 ± 0.83 NS
1.00	2.30 ± 0.60	1.74 ± 0.550*
2.00	1.33 ± 0.28	1.17 ± 0.02 NS
3.00	1.01 ± 0.19	0.55 ± 0.510*
4.00	0.73 ± 0.21	0.35 ± 0.13 NS
6.00	0.49 ± 0.51	0.18 ± 0.08**
8.00	0.33 ± 0.43	0.12 ± 0.05**

NS = Non significant,
* = Significant at P<0.05,
** = Significant at P<0.01.

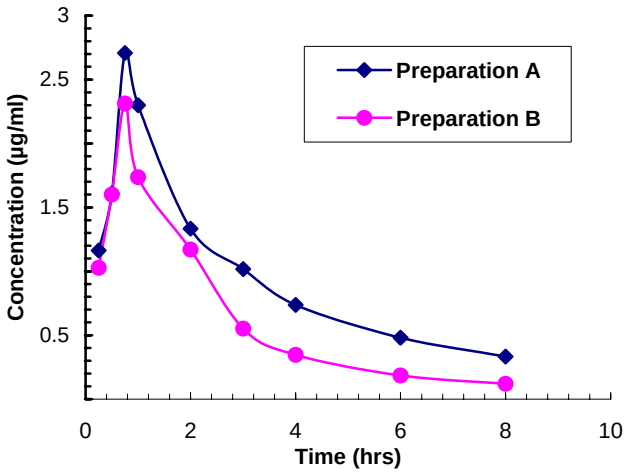

Fig. 1: Mean plasma concentrations of preparations A and B versus time after I/M administrations (5 mg/kg) in goats.

versus time curve (AUC) of preparation A (7.57 ± 1.10 µg.h/ml) was significantly higher (P<0.01) than 5. 05 ± 1.50 µg.h/ml for preparation B. The value of F (%) was also significantly higher (P<0.05) for preparation A than preparation B. However, other parameters of bioavailability did not differ between the two preparations.

It may be revealed from the bioavailability parameters that the rate of absorption of norfloxacin from preparation A was higher than that from preparation B. The preparation A also gave more than 100% relative bioavailability as compared to 66.90% for preparation B. The higher values of relative bioavailability and extent of absorption of the drug indicates that preparation A has different bioavailability from preparations B. Such variations could be attributed to pharmaceutical factors involved during production of the two preparations.

The mean (± SD) values of various pharmacokinetics parameters given in the Table 3 did not differ significantly between two preparations of norfloxacin. The apparent volume of distribution (Vd) relates the drug concentration in plasma to the total amount of drug in the body after the distribution equilibrium has been attained. The mean values for Vd for preparation A and B were 3.37 ± 0.62 and 7.43 ± 4.86 L/kg, respectively.

Body clearance (ClB) represents the sum of metabolic and excretery processes and is the volume of blood completely cleared of a drug in a unit time. The mean ClB values for preparation A and preparation B were 0.55 ± 0.20 and 0.96 ± 0.36 L/h/kg, respectively.

The mean values of elimination half life (T½β) for preparations A and B were 4.60 ± 1.63 and 5.24 ± 1.98 hrs, respectively. However, the half life of the drug recorded in the present study is longer than 3.5 hrs reported in dogs (Brown *et al.*, 1990) and shorter than 9.25 hrs reported in man (Seth *et al.*, 1995)

Table 2: Comparison of bioavailability parameters of two preparations of norfloxacin (5 mg/kg) after I/M administration in goats (Mean ± SD)

Bioavailability parameters	Preparation A	Preparation B
AUC (µg.h/ml)	7.57 ± 1.10	5.05 ± 1.50**
K_{ab} (hr^{-1})	1.55 ± 0.54	1.77 ± 0.91 NS
$T_{1/2abs}$(hr)	0.49 ± 0.13	0.48 ± 0.15 NS
T_{max} (hr)	0.89 ± 0.14	0.77 ± 0.18 NS
C_{max} (µg/ml)	2.06 ± 0.42	1.84 ± 0.50 NS
F%	169.0 ± 2.40	66.90 ± 2.04*

NS = Non significant,
* = Significant at P<0.05,
** = Significant at P<0.01.

Table 3: Comparison of pharmacokinetic parameters after I/M administration of two preparations of norfloxacin in goats (Mean ± SD)

Parameters	Preparation A	Preparation B
ClB (L/kg/h)	0.55 ± 0.20	0.96 ± 0.36 NS
Vd (L/kg)	3.37 ± 0.62	7.43 ± 4.86 NS
$T_{1/2}$-α (hr)	0.51 ± 0.13	0.54 ± 0.05 NS
$T_{1/2}$-β (hr)	4.60 ± 1.63	5.24 ± 1.98 NS
K_{el} (hr^{-1})	0.49 ± 0.18	0.79 ± 0.26 NS
K_{12} (hr^{-1})	0.59 ± 0.21	0.41 ± 0.19 NS
K_{21} (hr^{-1})	0.59 ± 0.42	0.27 ± 0.12 NS
MRT (hr)	5.62 ± 1.75	4.79 ± 2.16 NS
Kab (hr^{-1})	1.55 ± 0.54	1.77 ± 0.91 NS
$T_{1/2abs}$(hr)	0.49 ± 0.13	0.48 ± 0.15 NS

NS = Non-significant.

For optimal therapeutic levels of antibacterial agents in blood, the bioavailability and drug disposition studies play a pivatal role. This study revealed comparable elimination kinetics but different bioavailability of two commercial preparations of norfloxacin in goats. These results signify the importance of the bioequivolence studies of different commercial preparations of the same drug prepared by different companies. Moreover, the pharmacokinetic parameters of norfloxacin determined in goats were different from those found in other animals such as sheep, broilers and dogs (Kivisto *et al.*, 1992; Song and Chen, 1995; Albarellos *et al.*, 1996; Gonzalez *et al.*, 1997).

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