EFFECT OF ANTIPYRINE ON DISPOSITION KINETICS OF CIPROFLOXACIN IN DOGS

Humaira Akhtar, Faqir Muhammad, Muhammad Salman Akhtar
and Muhammad Shoaib Akhtar

Department of Physiology and Pharmacology
University of Agriculture, Faisalabad 38040 Pakistan.

Summary

Effect of antipyrine on the pharmacokinetic parameters of ciprofloxacin was investigated in clinically healthy dogs. Ciprofloxacin was administered orally as a single dose of 250 mg tablet. After a wash out period of ten days the same dose was repeated along with concurrent administration of antipyrine. Blood samples were collected at proposed time intervals and analyzed for ciprofloxacin with a microbiological assay. Results obtained indicated a significant increase in peak plasma concentration of ciprofloxacin with concurrent administration of antipyrine. The mean ± SEM values of AUC for ciprofloxacin with and without antipyrine were 5.06 ± 0.98 mg-h/l and 2.56 ± 0.65 mg-h/l respectively. The mean ± SEM values for the total body clearance were 4.06 ± 0.62 l/h-kg for ciprofloxacin with antipyrine while this value was 8.3 ± 1.49 l/h-kg when ciprofloxacin was administered alone. Antipyrine significantly ($P \leq 0.05$) reduced the volume of distribution of ciprofloxacin from 28.10 ± 6.6 l/kg to 15.42 ± 2.7 l/kg. The elimination half life was significantly different i.e. 2.71 ± 0.31 hours for ciprofloxacin with antipyrine as compared to 2.09 ± 0.55 hours for ciprofloxacin alone. The time to peak plasma concentration was significantly reduced while maximum peak plasma concentration of ciprofloxacin was increased with concurrent administration of antipyrine. This study indicates that care should be taken when using ciprofloxacin and antipyrine together as the later can significantly modulate the pharmacokinetics of ciprofloxacin in dogs.

Key word: Pharmacokinetics, ciprofloxacin, antipyrine, dogs

Introduction

Investigations dealing with the disposition kinetics of drugs are important to determine rate and extent of drug movement in the body. The influence of biochemical interior milieu of organism on disposition and fate of drug, differences in genetic make up of animals and different environmental conditions has increased the application of pharmacokinetics studies. The fluroquinolone antibacterials are extensively used in clinical practice because of good bioavailability and pharmacokinetic profiles. Ciprofloxacin, a member of fluroquinolones, is rapidly and well absorbed from gastrointestinal tract. This drug is extensively distributed in tissues with an elimination half-life of 3-4 hours (1). Antipyrine, a derivative of pyrazolone has been very successfully used for the treatment of rheumatic fever and for the relief of pain of moderate intensity. This drug is rapidly and evenly distributed throughout the body water and is relatively slowly excreted (2;3).

Combined use of antibacterials and antipyretics is very common in veterinary practice. Pharmacokinetic interactions are often encountered in combination therapy. For example; fluoroquinolones with a bulky substitute at the position 8 are more prone to interact with theophylline than those without substitution at this position. Furthermore, a 4-nitrogen atom in piperazinyl group is essential for interaction, which possibly binds cytochrome P-450 and catalyzes theophylline metabolism (4). Similarly, this is documented in the literature, that ciprofloxacin resulted in a significant decrease in antipyrine elimination by about 35% (5). Ciprofloxacin has also been found to decrease the clearance of theophylline (6) and caffeine (7). Such studies support the idea that ciprofloxacin may inhibit the oxidative metabolic pathways in liver. There is evidence that the elderly and patients with liver disease are particularly susceptible to kinetic interactions with ciprofloxacin (6).

The question arises, what will be the effect of antipyrine on the disposition kinetics of ciprofloxacin that may necessitate the adjustment of dosage regimen, when both drugs are administered concurrently. There is no information available in literature on this issue. Thus, the present study was designed to investigate the effect of antipyrine on the disposition kinetics of ciprofloxacin in dogs.

Materials and Methods

Animals and drug administration

Experiments were performed on six clinically healthy dogs in the month of July and August. The animals were maintained in the dog ward, Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad, Pakistan under similar feeding and manage mental conditions. All the experiments were conducted according to the instructions of animal care committee of the institution. Ciprofloxacin tablet (Ciproxin® 250, Bayer Pakistan) was given orally as a single dose to each dog. A wash out period of 10 days was provided and again ciprofloxacin was administered orally along with intra-muscular injection of antipyrine (Dipyron®, Lawrance Pharma, Pakistan).

Blood sampling

Blood samples were collected from radial vein at 15, 30, 45, 60 minutes and then at 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 hours after drug administration. The blood samples were centrifuged at 4000rpm for 10 minutes. The plasma was separated and stored at -20ºC until analysis. The ciprofloxacin concentration in the plasma samples was determined with microbiological assay according to disc-agar diffusion method as described by Arret et al (8) using *Streptococcus fecalis* as test organism.

Pharmacokinetic and Statistical analysis

The plasma concentration versus time data was analyzed by two compartment open model (9). The pharmacokinetic parameters like Area Under Curve (AUC), Volume of Distribution (Vd), Total body Clearance (Cl), elimination Half-life ($T_{1/2}$), Rate Constants (K10, K12, K21), rate of absorption (α) and rate of elimination (β) etc were calculated according to the standard procedures. The estimated parameters were further subjected to parametric comparison between groups using MS-Excel Statistical tools (descriptive statistical t-test).

Results

Plasma concentration vs. time profiles of ciprofloxacin with and without antipyrine is shown in Fig. 1. A significant increase in peak plasma concentration of ciprofloxacin with concurrent administration of antipyrine was observed (Fig. 1).

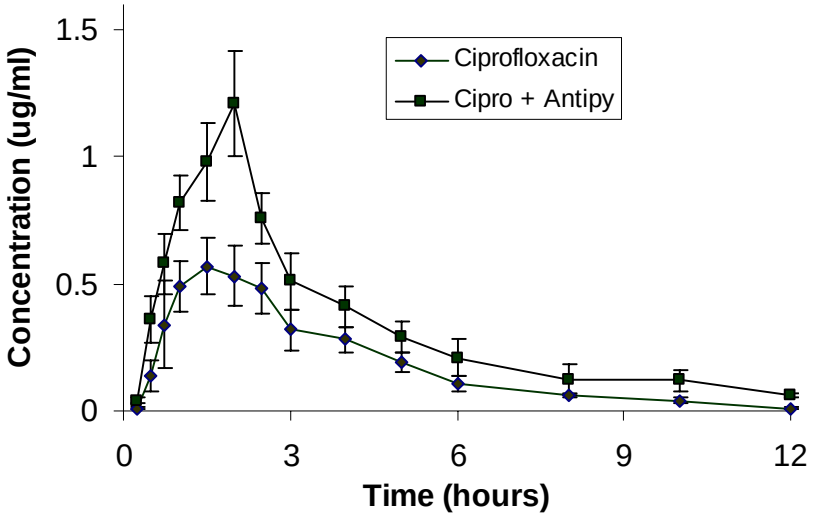

Figure 1. Mean plasma concentrations of ciprofloxacin with and without antipyrine in dogs (n=6).

Mean ± SEM pharmacokinetic parameters of ciprofloxacin with and without antipyrine administration to dogs are presented in Table 1. This is evident from this table that certain pharmacokinetic parameters like AUC, Cl, Vd, $T_{1/2}$, Tmax, and Cmax exhibited significant ($P \leq 0.05$) differences between both drug administration protocols. The mean ± SEM values of AUC for ciprofloxacin with and without antipyrine were 5.06 ± 0.98 mg-h/l and 2.56 ± 0.65 mg-h/l respectively (Table-1). The mean ± SEM values for the total body clearance was 4.06 ± 0.62 l/h-kg for ciprofloxacin with antipyrine while this value was 8.3 ± 1.49 l/h-kg when ciprofloxacin was administered alone. Antipyrine significantly ($P \leq 0.05$) reduces the volume of distribution of ciprofloxacin from 28.10 ± 6.6 l/kg to 15.42 ± 2.7 l/kg (Table-1). Absorption half life of ciprofloxacin was not statistically different while the elimination half life was significantly different i.e. 2.71 ± 0.31 hours for ciprofloxacin with antipyrine as compared to 2.09 ± 0.55 hours for ciprofloxacin alone. Time to peak concentration of ciprofloxacin was significantly reduced with co-administration of antipyrine from 1.70 ± 0.26 hours to 1.40 ± 0.17 hours. While the maximum concentration of ciprofloxacin was significantly increased with concurrent administration of antipyrine form 0.63 ± 0.10 µg/ml to 1.26 ± 0.14 µg/ml (Table-1). Other pharmacokinetic parameters exhibited non-significant differences.

Discussion

Earlier studies have indicated the effect of ciprofloxacin on the elimination of other drugs. For example; ciprofloxacin resulted in a significant decrease in antipyrine elimination in human (5;10), antipyrine elimination in rats (11), theophylline clearance (6), theophylline and caffeine clearance (7). The reason for these interactions may be due to fact that ciprofloxacin inhibits the metabolism of antipyrine, caffeine and theophylline. There is evidence that the elderly and patients with liver disease are particularly susceptible to kinetic interactions with ciprofloxacin (6). The above mentioned studies have demonstrated the effect of ciprofloxacin on the kinetics of antipyrine. No information is available in literature regarding effect of antipyrine administration on the disposition of ciprofloxacin. This scenario is equally important in drug interaction studies.

Present study has demonstrated that antipyrine co-administered with ciprofloxacin significantly ($P \leq 0.05$) increased the peak plasma concentration of ciprofloxacin in dogs (Fig. 1). This finding indicates a synergistic effect of antipyrine on ciprofloxacin. This observation is in accordance to Price (12) who found that cimetidine increases the ciprofloxacin concentration. The minimum inhibitory concentration (MIC) of ciprofloxacin for 90% of the bacterial strains is usually less than 0.2µg/ml (13) and for certain bacteria like Pseudomonas, Enterococci, Pneumococci etc, the values of MIC_{90} range from 0.5-6µg/ml (14). This can be anticipated from Fig.1 that antipyrine favors to maintain the effective ciprofloxacin concentration for prolonged periods as compared to administration of ciprofloxacin with out antipyrine.

Table 1. Mean ± SEM values of pharmacokinetic parameters of ciprofloxacin with and without administration of antipyrine in dogs (n=6)

Parameters	Ciprofloxacin	Ciprofloxacin + Antipyrine
AUC (mg.h/l)	2.56 ± 0.65	5.06 ± 0.98*
Cl (l/h-kg)	8.30 ±1.49	4.06 ± 0.62*
Vdss (l/kg)	19.39 ± 3.24	12.30 ± 1.97*
Vd (l/kg)	28.10 ± 6.60	15.42 ± 2.72*
$T_{1/2}\alpha$ (h)	0.66 ± 0.15	0.63 ± 0.11
$T_{1/2}\beta$ (h)	2.09 ± 0.55	2.71 ± 0.31*
K10 (h^{-1})	0.80 ± 0.15	0.62 ± 0.11
K12 (h^{-1})	0.38 ± 0.14	0.41 ± 0.17
K21 (h^{-1})	0.60 ± 0.14	0.60 ± 0.09
A	1.23 ± 0.29	2.11 ± 0.55
B	0.56 ± 0.22	0.73 ± 0.23
α	1.43 ± 0.35	1.34 ± 0.31
β	0.36 ± 0.08	0.21 ± 0.05*
Tmax (h)	1.70 ± 0.26	1.40 ± 0.17*
Cmax (µg/ml)	0.63 ± 0.10	1.26 ± 0.14*

*means significantly different ($P \leq 0.05$) within the same parameter

Co-administration of antipyrine along with ciprofloxacin significantly ($P \leq 0.05$) increased the AUC which is a measure of the extant of drug absorption. This finding again indicates a synergistic effect of antipyrine on ciprofloxacin disposition. The volume of distribution was significantly increased and body clearance of ciprofloxacin was significantly reduced with concurrent administration of antipyrine (Table-1). This may be due to the fact that antipyrine may involve reduction in intrinsic hepatic clearance as well as reduction in blood flow (15). Similarly, some studies have indicated that cimetidine appears to reduce the metabolism of ciprofloxacin (12). Another study concluded that co-administration of probenecid and ciprofloxacin decreased the renal clearance and hence the plasma concentration of ciprofloxacin was increased (16).

The elimination half life of ciprofloxacin was significantly increased with co-administration of antipyrine (Table-1) in the present study. This increase can be explained on the basis of significant decrease in elimination rate constant (β) of ciprofloxacin after co-administration with antipyrine. The significant changes in important pharmacokinetic parameters of ciprofloxacin by antipyrine suggests that antipyrine may reduce the metabolism/elimination of ciprofloxacin, thus results in increase in plasma concentration and half life. This study concludes that care should be taken when ciprofloxacin is used in combination with antipyrine. Especially, the clinicians should be aware of the adverse effects because of reduced drug clearance when quinolones are used with drugs undergoing hepatic metabolism for their elimination.

References

1. Vance-Bryan K, Guay DR, Rotschafer JC. Clinical pharmacokinetics of ciprofloxacin. Clinic Pharmacok 1990; 19: 434-461.

2. Grossland J. Lewis's Pharmacology, 5th edition, Beccus and London: William Clowes Limited, 1980.

3. Booth NH, McDonald LE. Veterinary Pharmacology and Therapeutics. 5th edition. Ames: The Iowa State University Press, 1982.

4. Marchbank CS. Drug-drug interaction with fluoroquinolones. Pharmacother 1993; 13: 23-28.

5. Ludwig E, Graber H, Szekely E, et al. Metabolic interactions of ciprofloxacin. Diagn Microbiol Infect Dis 1990; 13: 135-141.

6. Davey PG. Overview of drug interactions with the quinolones. J Antimicrob Chemother 1988; 22: 97-107.

7. Edwards DJ, Bowles SK, Svensson CK, et al. Inhibition of drug metabolism by quinolone antibiotics. Clin Pharmacok 1988; 15: 194-204.

8. Arret BD, Johnson D, Amiel K. Outline of details for microbiological assay of antibiotics. J Pharmaceut Sci 1971; 60: 373-378.

9. Riviere JE. Comparative pharmacokinetics: Principles, Techniques and Applications. 1st edition. Ames: Iowa State Press, U.S.A. 1999; 107-147.

10. Tan KK, Allwood MC, Shawket S. Effect of ciprofloxacin on the pharmacokinetics of antipyrine in healthy volunteers. J Clin Pharmacol Therap 1990; 15: 151-154.

11. Anadon A, Martinez-larranaga MR, Fernandiz MJ, et al. Effects of ciprofloxacin on antipyrine pharmacokinetics and metabolism in rats. Antimicrob Agents Chemother 1990; 34: 2148-2151.

12. Price RA. Effect of cimetidine on ciprofloxacin pharmacokinetics. Pharmacother 1990; 10: 234.

13. Norris S, Mondel GL. The quinolones history and overview. In: Andriole VT eds. the Quinolones. Academic Press, Inc., New York, U.S.A. 1988: 1-22.

14. Leysen DC, Maemers A, Pattyn SR. Mycobacteria and the new quinolones. Antimicrob Agents Chemother 1989; 33**:** 1-5.

15. Engelking LR, Blyden GT, Lofstedt J, Breenblatt DT. Pharmacokinetics of antipyrine, acetaminophen and didocaine in fed and fasted horses. J Vet Pharmacol Therapeut 1987; 10: 73-82.

16. Jaechde L, Sorgel F, Reiter A, et al. Effect of probencid on the distribution and elimination of ciprofloxacin in human. Clin Pharmacol Therapeut 1995; 58**:** 532-541.