

Biodisposition Kinetics of Ciprofloxacin in Male Human Volunteers Following Oral Administration

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Abstract: The Biodisposition of Ciprofloxacin was investigated in 10 healthy male volunteers after an oral administration of 250 mg tablet. Antibiotic concentration was measured by UV spectrophotometer. The kinetic parameters were calculated after performing one compartment model analysis. The absorption half-life and biological half-life showed Mean \pm SD values of 1.068 \pm 0.295 and 1.451 \pm 0.516 h the apparent volumes of distribution of Ciprofloxacin were found 28.59 \pm 6.6 liters. The average value of absorption rate constant was 0.625 \pm 0.519 h⁻¹. The mean \pm SD value of MRT was 3.903 \pm 0.802 h total body clearance ranged between 11.13 to 22.48 with mean \pm SD value of 14.33 \pm 3.19 l h⁻¹. These values deviate from the literature values emphasizing that such kind of studies must be conducted in local populations so that an appropriate dosage can be prescribed.

Key words: Biodisposition kinetics, biokinetics, ciprofloxacin, male volunteers, spectrophotometry

Introduction

Human body is constantly exposed to diverse type of pollutants added to the environment. These environmental pollutants may gain access to body directly or indirectly through food chain and may cause a serious human health risk. So to treat various diseases caused by these pollutants it is important to study the disposition of the drugs for the evaluation of their beneficial effect. Drug disposition is a term used to describe the absorption, distribution, and elimination of drug. Distribution kinetic parameters like half-life, distribution and body clearance provide information about accumulation of drug in the blood and tissues and rate of elimination of drug from the body in a specific time period. The distribution is influenced by blood flow to the tissues. The fluoroquinolones are currently enjoying extensive clinical application world wide 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 and described studied in these populations (Bergen *et al.*, 1986). In these studies a great variations in pharmacokinetic parameters in man have been observed (Mattie *et al.*, 1987) since Hameed conducted a study of disposition kinetic of ofloxacin in male volunteers only after administering 200 mg tablet. Similarly, the studies conducted over several years under indigonons conditions have revealed differences between the foreign and local species explained by an original term “geonetics” geographical influences on genetics manifested by dissimilar biochemical, physiological and pharmacological parameters (Nawaz and Shah, 1985, Nawaz *et al.*, 1988 and Nawaz, 1994). Hence it is important that these studies are conducted on any particular drug on the people in the sub region and/or subculture where wide and extensive use of the drug is intended.

Materials and Methods

Biodisposition of Ciprofloxacin was studied in 10 healthy volunteers. Written consent was taken from all volunteers before the start of experiment. Commercial preparation of Ciprofloxacin (Ciprocil-1) 250 mg tablets was administered orally.

Collection of blood samples

Venous blood samples were collected after overnight fasting followed by administration of antibiotic. Then blood samples were drawn after 0.25, 0.75, 1.25, 1.75, 3, 4, 6, 8 and 10 time interval strictly under aseptic conditions. The pH of fresh blood samples was measured by using Beckman pH meter. Plasma was separated after centrifugation at 4000 rpm for 15 min. then samples were stored at -20 °C till further analysis.

Analytical procedure

Ciprofloxacin concentration was measured by UV spectrophotomteric 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.

Concentration of ciprofloxacin in plasma samples was calculated as below:

$$\text{Concentration of ciprofloxacin} = \text{Mean factor} \times \text{absorbance of the sample}$$

Statistical analysis

Statistical calculation was done according to standard method are (Steel and Torrie, 1992).

Kinetic Parameters

The plasma concentration versus time was analyzed by single compartment model. Kinetic parameters like distribution half life ($t_{1/2\beta}$), lag time, time to peak (T_{max}), peak concentration (C_{max}), elimination rate constant (β), area under curve (AUC), volume of distribution (Vd), elimination half life ($t_{1/2\beta}$), mean residence time, distribution rate constant (α), absorption rate constant (K_a), and body clearance (CL_b).

Results

The disposition kinetics of Ciprofloxacin in healthy male volunteers was investigated after oral administration of single dose of 250 mg tablet of Ciprofloxacin. The lag time of Ciprofloxacin in the volunteers was found 0.09 ranging between 0.015 to 0.0169. The plasma concentration of Ciprofloxacin was measured spectrophotometrically. The plasma concentration of Ciprofloxacin at different time intervals was plotted taking plasma concentration at Y-axis, and time intervals at X-axis (Fig. 1). The absorption rate of ciprofloxacin after oral administration ranged between 0.499 to 0.9354 h^{-1} with mean \pm SD of 0.6253 \pm 0.159 h^{-1} . Area under curve ranged between 11.12 to 22.45 $h\ mg\ ml^{-1}$ with mean \pm SD 3.51 $h\ mg\ ml^{-1}$. The mean \pm SD of the half life of ciprofloxacin was 1.45 \pm 0.52 h and ranged between 0.75 to 2.56 h. Absorption half life was 1.07 \pm 0.29 h. Time at which maximum concentration of the drug in plasma was 1.93 \pm 0.30 h. The peak concentration of the drug was found to be 3.57 with a mean value of 0.33 (Table 1).

Table 1: Mean \pm SD values of oral administration of 250 mg Ciprofloxacin tablet

Parameters	Mean	\pm SD
Distribution rate constant (α)	0.50	0.17
Absorption rate constant (K_a) [Lh^{-1}]	0.63	0.16
Area Under Curve (AUC) [$hmg\ l^{-1}$]	18.02	3.52
Auc trapezoidal rule (Auctrp) [$t=24$]	19.81	1.54
Body Clearance (Clb) [$mg\ L^{-1}$]	14.36	3.19
Volume of distribution (Vd) [L]	28.59	6.60
Elimination rate constant (Kel)	0.52	0.18
Elimination half life $t_{1/2\beta}$ [h]	1.45	0.52
Mean Residence Time (MRT) [h]	3.90	0.80
Absorption half life $t_{1/2\beta}$ [h]	1.07	0.30
Time to peak conc. T_{max} [h]	1.93	0.30
Peak concentration (C_{max}) ($mg\ L^{-1}$)	3.57	0.33

Discussion

Ciprofloxacin is routinely prescribed to treat a variety of infections. No literature is available in its bioavailability and pharmacokinetic profile in Pakistani population. To achieve

optimum therapeutic benefits of the drugs, all of the factors, which influence its pharmacokinetics and effectiveness, need to be determined.

Fig. 1 shows a decline in the curve. The first part of the curve shows the absorption phase of ciprofloxacin after oral administration. There is a rapid increase in plasma concentration of drug followed by a distribution phase. After that there is a decline in plasma drug concentration which represents the elimination of drug from the central compartment termed as β or elimination phase. The pharmacokinetic analysis was performed after one compartmental model.

Following an oral administration of ciprofloxacin, the peak serum concentration of drug occurred after approximately 1.5 h. The maximum plasma concentration of ciprofloxacin was found $3.57 \mu\text{g ml}^{-1}$, which is higher than the literature value ($1.2 \mu\text{g ml}^{-1}$) and also reported Chkwani *et al*; 1998 ($2.92 \mu\text{g ml}^{-1}$) and Kung *et al*; 1993 ($0.02 \mu\text{g ml}^{-1}$). According to Bayer *et al*. (1987) the peak serum concentration was 0.25 to $4.32 \mu\text{g ml}^{-1}$. Biological elimination half life was found 1.45 h which is very less than the values reported by Chkwani *et al*. 1998, who examined 7.52 h. Area under curve (AUC) was high during this study, as it was almost double than the literature value.

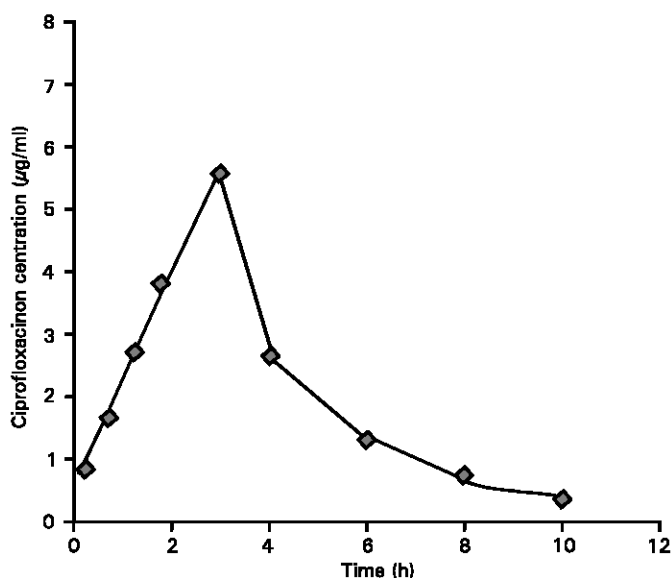


Fig. 1: Plasma concentration of ciprofloxacin with mean \pm SD values versus time after single oral dose of 250 mg

Calculated volume of distribution was found very less, only 28.59 liters. The steady state V_d averaged 178 liters (Lettier *et al.*, 1992). This may be the reason of high plasma drug concentration. Total body clearance for ciprofloxacin was also found to be very less.

A significant deviation was examined 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 any drug. This different trend in the kinetic parameters requires further investigations.

References

- Bayer, A., A.Gajwska, M.Stephens and J. M. Stark, 1987. Pharmacokinetics of Ciprofloxacin in the elderly respiration. J. Pathy., 51: 292-295.
- Bergan, T., S.B.Thorsteinsson and R.Solberg, 1987. Pharmacokinetics of ciprofloxacin intravenous and increasing oral dose. Am. J. Med., 97-102.
- Chkwuani, C.M., H.A.B. Cijer, A.M.J. Oduola, N.D. Ifndn and A. Sowunmi, 1998. Single dose pharmacokinetics study of ciprofloxacin and fleroxacin in healthy male volunteers. Chemotherapy, 44: 369-376.
- De, U.K., K.P. Sinha and N.C. Banerjee, 1993. Biokinetics of ciprofloxacin in non-febrile goats. Ind. J. Ani. Sci., 65: 269-272.
- Hameed, A., 1999. Disposition kinetics ofloxacin in male volunteers following oral administration. M.Sc. Thesis Uni Agri. Faisalabad, Pakistan.
- Kung, K., J.K. Riord and M. Wanner, 1993. Pharmacokinetics of enrofloxacin and its metabolite ciprofloxacin after intravenous and oral administration of enrofloxacin in dogs. J. Vet. Pharmacology and Therapeutics, 16: 462-468.
- Lettier, J.T., M.C. Rogge, L. Kaiser, R.M. Echols and A.H. Heller, 1992. Pharmacokinetics profiles of ciprofloxacin after single intravenous and oral doses. Antimicrob Agents Chemother, 36: 993-996.
- Mattie, H., J.J. Hoogeterp and P.Terporten, 1987. The activity of ciprofloxacin against *Pseudomonas aeruginosa* in normal and granulocytopenic mice. Pharm. Weekbi Sic., 9: 526-529.
- Nawaz, M. and B.H. Shah, 1985. Proc.Int, on policies, management and quality assurance of pharmaceutical 21-25 April. WHO and Ministry of Health, Government of Pakistan.
- Nawaz, M., I. Tahira and N. Rakhshanda, 1988. Geonetical considerations in disposition kinetics evolution of chemotherapeutic agents. Vet. Pharmacol. Toxicol and Therapy in Food Producing animals. Vol 2, P.260. Proceeding of the 4th Cong. Europe Associ. Vet. Pharmacol. and Toxicol., 28th August to 2nd September, Budapest.
- Nawaz, M., 1994. Geonetical factors affecting Biodisposition of drugs. Canadian J. Physio and Pharm. 72 Suppl. Abst. XII. The Int. cong. Pharmacia. Montreal, Canada.
- Steel, R.G.D. and J.H.Torrie, 1992. Principles and procedures of statistics. MC Graw Hill Book Inc, New York.