

Biodisposition Kinetics of Ofloxacin in Pakistani Healthy Female Volunteers after Oral Administration

¹Amjad Hameed, ¹Faiz Batool, ¹Tahira Iqbal, ¹Tayyba Tabassum Baig, ²Javed Anver Qureshi
¹Department of Chemistry (Biochemistry), University of Agriculture Faisalabad, Pakistan
²National Institute for Biotechnology and Genetic Engineering (NIBGE),
P.O. Box No 577 Jhang road Faisalabad, Pakistan

Abstract: This study was based on biodisposition kinetics of ofloxacin in Pakistani healthy female volunteers after oral administration. Ten healthy female volunteers were included in this study. The blood samples of each volunteer were collected after oral administration of ofloxacin. The concentration of ofloxacin in blood samples was measured by microbiological assay. The mean (SE) values of time to peak (t_{max}), peak concentration (C_{max}), absorption half life ($t_{1/2\alpha}$), absorption rate constant (k_a), elimination half life ($t_{1/2\beta}$), elimination rate constant ($K_{10\beta}$), were 1.012 ± 0.176 h, $0.907 \pm 0.126 \mu\text{g ml}^{-1}$, 0.516 ± 0.093 h, $13.593 \pm 2.936 \text{ L h}^{-1}$, 2.996 ± 0.567 h and $0.291 \pm 0.693 \text{ L h}^{-1}$ respectively. The mean (SE) values for area under curve (AUC), clearance (CL), volume of distribution (Vd) and mean resident time (MRT) were $4.358 \pm 0.771 \text{ h.mg l}^{-1}\text{liter}$, $53.470 \pm 11.068 \text{ l h}^{-1}$, 214.41 ± 49.127 liter and 5.030 ± 0.705 h respectively. Values of parameters like, volume of distribution, total body clearance and absorption rate constant were higher, while elimination half life, AUC, C_{max} , and t_{max} were lower in local population as compared with foreign studies. There was no influence of body surface area on total body clearance of ofloxacin ($R^2=0.0581$). There was an increase in body clearance of ofloxacin ($R^2=0.2236$) and area under curve (AUC) for ofloxacin ($R^2=0.258$) with increasing body surface area of volunteers. Therefore body surface area of volunteers may slightly influence the total body clearance and area under curve for ofloxacin. These gender-related differences mainly low body weight and surface area in females may warrant dosage adjustments.

Key words: Ofloxacin, biodisposition kinetics, female volunteers, orally

Introduction

Biodisposition kinetics describes the rate and extent of movement of a drug in a biosystem. Disposition kinetics parameters like half-life, distribution and body clearance provide information about the rate of elimination of drug from the body in a specific time period. The distribution is influenced by blood flow to the tissue. This depends on the ionization constant of drugs (Pk values), the biodisposition is determined in different body fluid compartments by the value of pH. Besides the other factors that can affect biodisposition and fate of drug under indigenous conditions include blood proteins, drug metabolism and excretion. The factors that modify the absorption of a drug can change its bioavailability (Bagget., 1977). In view of these differences, it is important that imported drug be evaluated under local environment.

Ofloxacin is a 4-quinolone synthetic fluorinated analog of nalidixic acid. The drug is a broad-spectrum antibacterial agent and inhibits the bacterial topoisomerase II (DNA gyrase) and topoisomerase IV (Katzung, 1998). Fluoroquinolone antibiotics are commonly administered to treat bacterial infections (Sovinski *et al.*, 1999). The efficacy of fluoroquinolones is concentration dependent; specifically, the ratio of the area under the plasma concentration-time curve (AUC) relative to the minimum inhibitory concentration of the organism is suggested to be an important predictor of clinical response. In addition, the frequency of adverse effects increases as dose increases, suggesting a relationship with drug concentration. Thus, thorough understanding of the pharmacokinetics of fluoroquinolones in all patient subgroups (women, men, elderly, etc.) is essential (Sowinski *et al.*, 1999). The drugs used in Pakistan for health programs of man and animals are being imported from abroad either in the raw or finished form. The studies conducted over several years under indigenous conditions have revealed difference between the foreign and local species explained by an original term "geonetics" geographical influence on genetics manifested by dissimilar biochemical, physiological and pharmacological parameters (Nawaz and Shah, 1985; Nawaz *et al.*, 1988; Nawaz, 1994). The present project was therefore planned to study biodisposition kinetics of ofloxacin in female volunteers under local environmental

conditions.

Material and Methods

This project was initiated in August 1999 and was completed in December 2000. This project was designed to find the biodisposition kinetics (pharmacokinetics) of ofloxacin in endogenous conditions. The study includes female volunteers and 200 mg ofloxacin in tabulated form was administered through oral rote. Ofloxacin was manufactured by Hoechst Pakistan Limited and was purchased from local market. A total of ten female volunteers included in this study were university students. The sampling for this study was done in the month of August. Each volunteer was apprised of the design of the study, dosing and sampling protocol. The volunteers who willingly offered to participate were included in the study. The weight and height of the volunteers were recorded and body surface area of each volunteer was calculated in square meters by the formula of Ganong (1995).

Blood sampling: The volunteers were kept fasting for last 12 h and after that normal or blank blood samples were taken. Following this each volunteer was allowed to take the 200 mg-ofloxacin tablet with 250 ml of water.

The blood samples of each volunteer were collected at 0.5, 1, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0 and 12.0 h in heparinized centrifuge tubes and pH of the samples was recorded. The plasma was collected after centrifugation at 4000 rpm. Plasma samples were then kept at -4°C until analysis.

Microbiological assay using disc agar diffusion method: Ofloxacin concentration in plasma samples was determined by microbiological assay using disc agar diffusion method (Arret *et al.*, 1971) using *Streptococcus fecalus* as test organism.

Preparation of microbial suspension: All glass apparatus was sterilized by autoclaving at 121°C for 20 min at 15 lb /inch² pressure and then in oven by maintaining the temperature at $160-170^\circ\text{C}$ for 30 min.

The test organism *Streptococcus fecalus* was maintained on a

Table 1: Zones of inhibition due to standard ofloxacin concentrations

Standard concentrations ($\mu\text{g ml}^{-1}$)	Log Concentrations	Zone Size(mm)
0.5	0.301	13.75
1.0	0.000	16.25
2.0	0.301	18.75
4.0	0.602	21.5
6.0	0.778	23.75
8.0	0.903	26.25
10.0	1.000	27.50
15.0	1.176	28.75

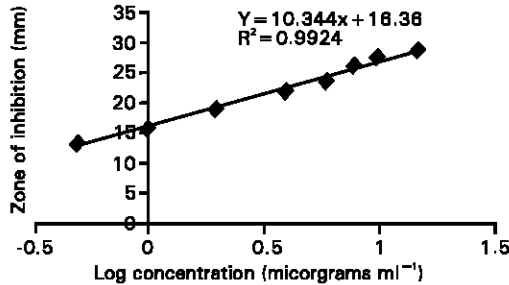


Fig. 1: Standard curve for ofloxacin

slant of nutrient agar medium. The organism was transferred to a fresh slant and incubated at 37°C for 24 h. The resultant growth was washed with 3ml sterilized normal saline poured on Roux flask containing 200 ml of nutrient agar and incubated for 48 h. The resultant growth was washed from the nutrient surface using 100 ml 0.1 M phosphate buffer (22.264 g of mono basic potassium phosphate and 14.052 g of dibasic potassium phosphate dissolved in liter) of pH 7.9. The spore suspension was collected in sterilized conical flask and stored under refrigeration.

Nutrient agar: Media was prepared by using nutrient agar made by Merck Company. Media contained 20 g of nutrient agar and 5 g NaCl dissolved in one liter. Media was sterilized by autoclaving at 121°C for 20 min at 15 lb/inch².

Standard curve of ofloxacin: 0.5 g of ofloxacin was dissolved in 50 ml distilled water to prepare the stock solution. Standard solution of ofloxacin with different concentrations including 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0 and 15.0 $\mu\text{g ml}^{-1}$ were prepared in 10 ml blood plasma by using stock solution.

After autoclaving, the medium was cooled and 50 $\mu\text{l}/100$ ml of spore suspension was added. Fifteen ml of this medium was poured into each petridish. Petridishes were placed on flat surface for solidification. Disc with 1.3 cm diameters were prepared by using Beckman paper wicks (No=319329) and were sterilized by ultra violet radiation. Disks were impregnated with 100 μl of plasma (standard dilutions). Triplicate samples were used for each dilution. These discs were then transferred to the agar plates, which were previously seeded with test organism. Plates were left for diffusion for half an hour and then incubated at 37°C for 18 h. Zones of inhibition due to antimicrobial activity of ofloxacin were seen after 18 h and their diameters were measured with the help of vernier calliper (Table 1).

Zones of inhibition (mm) were plotted against concentration ($\mu\text{g ml}^{-1}$) and a liner curve was obtained (Fig. 1). Simple linear regression equation $Y = a + b(x)$ was fitted by taking concentration as (x) and zone of inhibition as (y) ($R^2 = 0.992$) which is as follow:

$$Y = 10.344 (x) + 16.36$$

Ofloxacin concentration in plasma samples was calculated using this equation from different drug sensitivity zone sizes. The plasma concentration time data was used to determine

pharmacokinetics parameters and was analyzed by single compartment model (Baggat, 1977) using computer program MW/PHARM version 3.02 (Rombout., 1987).

For biodisposition kinetic parameters of ofloxacin, descriptive statistics including mean, median, standard error, minimum, maximum value (range) and sample variance were applied. All descriptive statistical parameters were calculated at 95% confidence level. All these descriptive statistical parameters were calculated using Microsoft Excel 2000.

Results

The plasma concentration of ofloxacin at different time intervals was calculated for female volunteer. The mean was calculated for concentration at different time intervals. The mean representative plot of plasma concentration versus time data for female volunteers is shown in Fig 2. The first part of curve shows a gradual increase in concentration of drug in the plasma and then after there was a decline in drug concentration in plasma.

Biodisposition kinetics of ofloxacin was described by one compartment model that showed its goodness to fit over data. Disposition kinetic parameters including time to maximum concentration (T_{max}), maximum concentration (C_{max}), absorption half life ($t_{1/2 \alpha}$), absorption rate constant (ka), elimination half life ($t_{1/2 \beta}$), elimination rate constant ($k_{10 \beta}$), area under curve (AUC), total body clearance (CL), volume of distribution (V_d) and mean residence time (MRT) were calculated for each volunteer. The mean (SE) values of disposition kinetic parameters are given in Table 2.

Absorption rate constant (ka): The absorption rate constant is the rate constant for the absorption of drug after its oral administration. The mean (SE) absorption rate constant (ka) of ofloxacin was $13.593 \pm 0.928 \text{ L h}^{-1}$ (Table 2). The median absorption rate constant (ka) of ofloxacin was 12.5 L h^{-1} . The sample variance for absorption rate constant (ka) of ofloxacin was 43.101.

Area under curve (AUC): Area under curve is total area under plasma concentration curve from t_0 to t_6 . The mean (SE) area under curve was $4.358 \pm 0.244 \text{ h mg l}^{-1}$ (Table 2). The median value for area under curve of ofloxacin was $4.108 \text{ h mg l}^{-1}$ (Table 2) which is very close to mean value. The sample variance for area under curve of ofloxacin was 2.974.

Total body clearance (CL): Total body clearance is the volume of blood cleared of the drug by various elimination processes like biotransformation and excretion. The mean (SE) value for total body clearance was $53.470 \pm 3.500 \text{ l h}^{-1}$ (Table 2). The median value for total body clearance was 49.48 l h^{-1} (Table 2). The sample variance for total body clearance was very high and was 612.650.

Volume of distribution (Vd): Volume of distribution of drug is that volume of fluid required to contain amount of drug in the body, if it was uniformly distributed at a concentration equal to that in plasma. The assumption is made that the body acts as single homogenous compartment with respect to drug. The apparent volume of distribution does not represent the actual concentration of drug in plasma at any time after distribution equilibrium has been attained to the amount present in the body.

The mean (SE) value for volume of distribution (Vd) was 214.410 ± 15.535 liters (Table 2). The median value for volume of distribution was 160.07 liters. The sample variance regarding volume of distribution of ofloxacin was much higher and was 2942.777.

Elimination half life ($t_{1/2 \beta}$): The biological half-life is the time required for 50% of the drug to be eliminated from the body after distribution equilibrium has been attained. The mean (SE) value of the elimination half-life of ofloxacin in female volunteers was $2.966 \pm 0.179 \text{ h}$. The median value of the elimination half-life of

Table 2: Descriptive statistical analysis of biodisposition kinetic parameters of ofloxacin

Kinetic parameters	Mean ± SE	Median	Sample variance
T _{max} (h)	1.012 ± 0.0556	1.114	0.156
C _{max} (µg ml ⁻¹)	0.907 ± 0.0398	0.941	0.080
t _{1/2 α} (h)	0.156 ± 0.093	0.056	0.044
k _a (l / h)	13.593 ± 0.928	12.5	43.101
t _{1/2 β} (h)	2.996 ± 0.179	3.342	1.613
k _{10 β} (l / h)	0.291 ± 0.219	0.230	0.024
AUC (h.mg l ⁻¹)	4.358 ± 0.244	4.108	2.974
CL (l / h)	53.470 ± 3.500	49.48	612.650
V _d (l)	214.410 ± 15.535	160.07	2942.777
MRT (h)	5.030 ± 0.223	5.299	2.493

All descriptive statistical parameters were calculated at 95% confidence level

T_{max} is time to maximum concentration, C_{max} is maximum concentration, t_{1/2 α} is absorption half life, k_a is absorption rate constant, t_{1/2 β} is elimination half life, k_{10 β} is elimination rate constant, AUC is area under curve, CL is total body clearance, V_d is volume of distribution, and MRT is mean residence time.

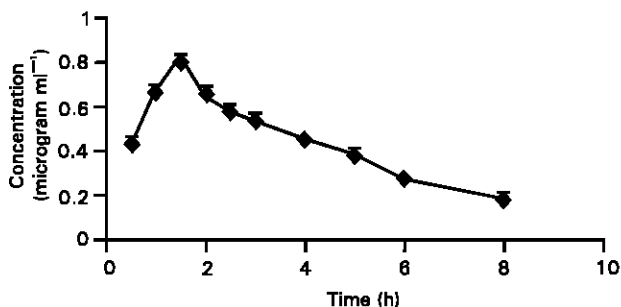


Fig. 2: Mean plasma concentrations of ofloxacin in female volunteers at various time intervals following 200mg oral dose

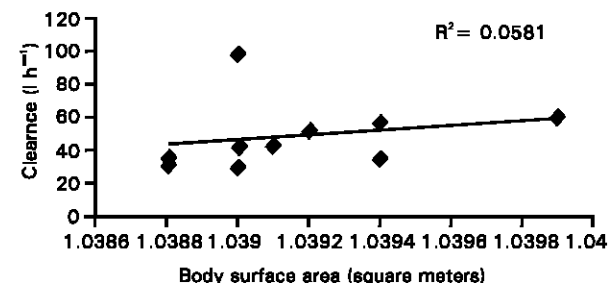


Fig. 3: Influence of body surface area on total body clearance of ofloxacin in female volunteers

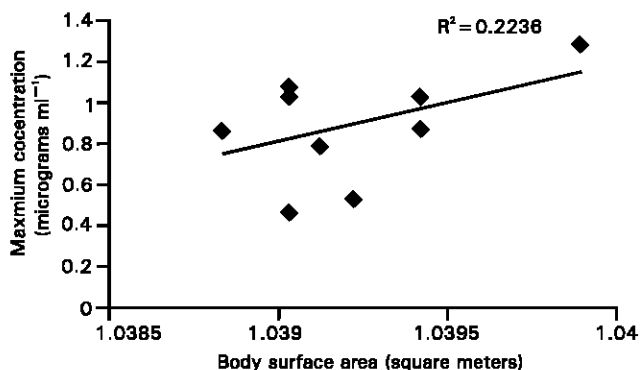


Fig. 4: Influence of body surface area on C_{max} of ofloxacin in female volunteers

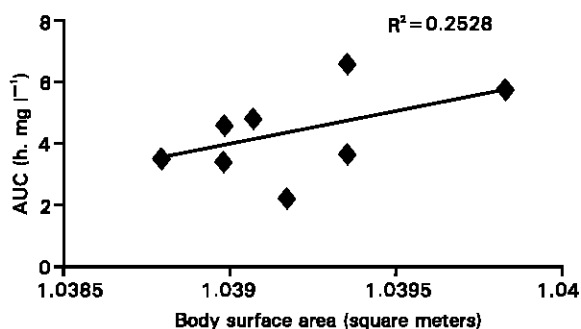


Fig. 5: Influence of body surface area on area under curve (AUC) of ofloxacin in female volunteers

ofloxacin was 3.342 h. The sample variance for elimination half-life of ofloxacin was not much higher and it was 1.613.

Elimination rate constant (k_{10 β}): It is the rate constant for elimination of drug from the body. Mean (SE) value for elimination rate constant (k_{10 β}) of ofloxacin was 0.291 ± 0.219 L h⁻¹ (Table 2). Median value for elimination rate constant (k_{10 β}) of ofloxacin was 0.230 L h⁻¹. As the mean and median values for elimination half life are very close to each other, therefore sample variance for elimination half life was also very small. The value for sample variance regarding elimination rate constant (k_{10 β}) of ofloxacin was 0.024.

Mean resident time (MRT): Mean resident time is the time at which AUC value measured in the plasma is achieved. The mean residence time (MRT) was 5.030 ± 0.223 h (Table 2). Median value for mean residence time of ofloxacin was close to mean value and it was 5.299. This closeness between mean and median values indicates a low sample variance, therefore sample variance concerning mean residence time was 2.493.

Absorption half life (t_{1/2 α}): The mean (SE) value for absorption half-life was 0.156 ± 0.093 h (Table 2). While median value for absorption half-life was 0.056. The sample variance for absorption half-life was 0.044.

Time to maximum concentration (T_{max}): It is the time at which the maximum concentration of the drug is achieved in blood plasma. The mean (SE) value for time to maximum concentration of ofloxacin was 1.012 ± 0.056 h (Table 2). Similarly the median value or time to maximum concentration of ofloxacin was 1.114. The sample variance due to closeness between mean and median was very small and was 0.156.

Maximum concentration (C_{max}): The mean (SE) value for maximum concentration of ofloxacin was 0.907 ± 0.040 µg ml⁻¹ (Table 2). Very close to this, the median value for maximum concentration of ofloxacin was 0.941 µg ml⁻¹ and sample variance was 0.080.

Body surface area and total body clearance: Influence of body surface area on total body clearance of ofloxacin in female volunteers was investigated. For this purpose body surface area of volunteers were plotted against their body clearance (Fig. 3). Regression analysis showed a very small R² value (R²=0.0581) that indicates no regression between these parameters. This means body surface area of volunteers did not influence the total body clearance of ofloxacin.

Body surface area on C_{max}: Influence of body surface area on maximum concentration (C_{max}) of ofloxacin in female volunteers was also studied. Regarding this body surface area of volunteers were plotted against their maximum plasma concentration (C_{max}) of ofloxacin (Fig. 4). Regression analysis between these two parameters showed little positive regression (R²=0.2238)

indicating an increase in body clearance of ofloxacin with increasing body surface area of volunteers. This means body surface area of volunteers may slightly influence the total body clearance of ofloxacin.

Body surface area and area under curve (AUC): The interaction between body surface area and area under curve (AUC) for ofloxacin in female volunteers was also discussed in this study. For this purpose body surface area of volunteers were plotted against their area under curve (AUC) for ofloxacin (Fig. 5). Regression analysis between these two parameters again showed a little positive regression ($R^2=0.2528$) indicating an increase in area under curve (AUC) for ofloxacin with increasing body surface area of volunteers. This means body surface area of volunteers may also influence the area under curve (AUC) for ofloxacin.

Discussion

Most of the developing countries like Pakistan are importing raw or finished drugs for their human or veterinary health programs. In most cases, the genetic make up of man and animals and environmental conditions are different from their foreign counterparts. The studies have shown that amongst the geonetical factors effecting biodisposition and fate of drugs, pH (blood, urine and stomach etc) is an important parameter which differs amongst local and foreign species (Navvaz, 1994). The other factors, which differ and can effect the biodisposition kinetics and fate of drugs under indigenious conditions, include blood protein, drug metabolism and excretion. pH is an important parameter which differs amongst local and foreign species (Navvaz and Shah, 1985; Navvaz *et al.*, 1988; Navvaz, 1994). Such influences have been reported for blood and urine pH, blood proteins, drug metabolism and kidney function in buffaloes, cows, sheep and goats (Navvaz *et al.*, 1988). Therefore it is very important that imported drugs should be evaluated under local environment to determine their dosage regimen.

The mean concentration of drug at various time intervals was lower in as compared with those already reported in Pakistani male volunteers (Hameed *et al.*, 2002). This shows that ofloxacin did not attain as high plasma concentration in female volunteers as in male volunteers. Furthermore in female volunteers ofloxacin was not detectable in plasma after 8 h while in male volunteers reported previously its concentration was detectable even after 12 h post administration (Hameed *et al.*, 2002).

Therefore absorption rate of drug was much faster in female volunteers. The absorption rate constant was much higher (13.593 h^{-1}) in female volunteers as compared with Pakistani male volunteers reported early (7.833) (Hameed *et al.*, 2002). The possible reason may be high sample variance (43.101). As minimum and maximum values (range) of absorption rate constant (k_a) were approximately similar (0.637 to 23.30 hr^{-1}) to those reported previously (1.214 to 23.93 hr^{-1}) in Pakistani male volunteers.

The value for absorption rate constant (13.593 L h^{-1}) was also higher than 2.26 hr^{-1} (Yuen *et al.*, 1992) and $2.668 \pm 1.256 \text{ hr}^{-1}$ (Corvaisier *et al.*, 1999) reported previously in populations other than Pakistan. So absorption rate constant in present study was very high as compare to the values in other studies. This difference may be due to indigenious conditions (Navvaz and Shah, 1985, Navvaz *et al.*, 1988, Navvaz, 1994) but need to be much further investigation by large scale studies.

Area under curve for ofloxacin was less ($4.358 \pm 0.244 \text{ h mg l}^{-1}$) in female volunteers as compared with Pakistani male volunteers ($14.545 \text{ h mg l}^{-1}$) (Hameed *et al.*, 2002). Similarly minimum and maximum values (range) for area under curve were also lower (2.040 to $6.767 \text{ h mg l}^{-1}$) as in Pakistani male (8.744 to $22.93 \text{ h mg l}^{-1}$) volunteers (Hameed *et al.*, 2002).

Mean (SD) area under curve (AUC) was also lower than $15.22 \mu\text{g ml}^{-1} \text{ h}$ (Eboka *et al.*, 1997), 15 (Zhou *et al.*, 1993) and 14.6 h mg l^{-1} (Verho *et al.*, 1996) reported previously in other populations. The total body clearance of ofloxacin was much higher ($53.470 \pm 3.500 \text{ l h}^{-1}$) as in male ($14.953 \pm 1.383 \text{ l h}^{-1}$) volunteers (Hameed *et al.*, 2002). Similarly minimum and maximum values

(range) for clearance were also higher in this study (29.55 to 98.04) as (8.722 to 22.870 l h^{-1}) as compared to those in Pakistani male volunteers (Hameed *et al.*, 2002). This difference may be due to very high sample variance 612.650 . Like wise mean total body clearance was also higher than 15.08 l h^{-1} (Corvaisier *et al.*, 1999), 16.67 l h^{-1} (Guay *et al.*, 1991), 13.98 (Molinaro *et al.*, 1992), 14 (Zhue *et al.*, 1993) and 15.06 l h^{-1} (Stein *et al.*, 1991) reported previously.

The mean (SE) volume of distribution (Vd) was lower in Pakistani male (130.776 ± 8.095) liters) volunteers reported previously (Hameed *et al.*, 2002) as in female volunteers (214.410 ± 15.535) liters) in this study. Minimum and maximum values (range) for volume of distribution were also lower in Pakistani male (82.61 to 168.7 liters) as compared to those in present study (102.5 to 412.6 liters). However mean (SE) volume of distribution (Vd) in Pakistani male (130.776 ± 8.095 liters) volunteers reported previously is within the range in present study. Moreover the median value for volume of distribution was 160.07 liters, which is somewhat close to that in male volunteers (Hameed *et al.*, 2002). Therefore reason for differences seems to be very large sample variance regarding volume of distribution of ofloxacin 2942.777 . The mean volume of distribution of ofloxacin was also higher than 121 to 135 liters after 200 mg intravenous dose (Guay *et al.*, 1991) and $68, 58, 94$ liters (Zhue *et al.*, 1993) which is already reported in other populations.

The elimination rate constant (k_{10}) of ofloxacin was higher ($0.291 \pm 0.219 \text{ L h}^{-1}$) in female volunteers as compared with male volunteers ($0.155 \pm 0.044 \text{ L h}^{-1}$) reported previously (Hameed *et al.*, 2002). Minimum and maximum values (range) of elimination half-life were higher in female volunteers (0.054 to 0.158 L h^{-1}) as in male (0.083 to 0.647 L h^{-1}) volunteers (Hameed *et al.*, 2002) reported early.

The previously reported data (Hameed *et al.*, 2002) shows that mean absorption half-life of ofloxacin was nearly double (0.232 h) in Pakistani male volunteers as in this study (0.156 h). Minimum value of absorption half-life of ofloxacin was similar (0.029 h) to that in male volunteers reported previously (Hameed *et al.*, 2002). On the other hand maximum value of absorption half-life of ofloxacin was lower in Pakistani male volunteers reported early (0.571 h) as compared with present study (1.088 h).

The elimination half-life of ofloxacin was lower ($2.966 \pm 0.179 \text{ h}$) as compared with Pakistani male volunteers ($6.421 \pm 0.559 \text{ h}$) (Hameed *et al.*, 2002). This means that elimination half-life of ofloxacin was approximately twice in male volunteers as in female volunteers. Similarly minimum and maximum values (range) of elimination half-life were higher in Pakistani males (3.918 to 10.710 h) (Hameed *et al.*, 2002) as in female (1.274 to 4.383 h) volunteers in this study.

As the mean elimination half-life of ofloxacin was (2.966 h), this is less than 5.6 (Stein *et al.*, 1991), 5.29 (Guay *et al.*, 1991), 6.2 (Molinaro *et al.*, 1992), 5 (Zhue *et al.*, 1993), 4.98 (Guay *et al.*, 1992) and 4.9 h (Orlando *et al.*, 1992) reported previously after 200 mg intravenous dose. For human beings after 400 mg oral dose elimination half-life of ofloxacin was reported as 6.54 h (Israel *et al.*, 1993) and in some studies ranging from 5 to 8 h (Lamp *et al.*, 1991). After 400 mg intravenous dose, elimination half-life ranged from 5.06 to 6.67 h (Guay *et al.*, 1992). This difference in elimination half-life of ofloxacin may be due to different glomerular filtration rate (GFR) in local population and should be studied.

The mean time to maximum concentration of ofloxacin was little higher ($1.412 \pm 0.176 \text{ h}$) in male volunteers reported previously (Hameed *et al.*, 2002) as compared with female volunteers (1.012 h) in this study. Minimum and maximum values (range) for time to maximum concentration of ofloxacin were not much different (0.405 to 2.641 h) to those reported in male (0.678 to 2.395 h) (Hameed *et al.*, 2002). The mean (SE) values for t_{max} was also less than 1.74 ± 0.57 (Yuk *et al.*, 1991), 1.5 (Stein *et al.*, 1991), 1.7 (Flor *et al.*, 1991) and 2 h (Eboka *et al.*, 1997) reported previously in other populations.

The maximum plasma concentration of ofloxacin was also higher ($1.316 \mu\text{g ml}^{-1}$) in male volunteers reported previously (Hameed *et al.*, 2002) as in female volunteers ($0.907 \mu\text{g ml}^{-1}$) in this study. Similarly minimum and maximum values (range) for maximum

plasma concentration of ofloxacin were higher in male volunteers (1.067 to $2.149 \mu\text{g ml}^{-1}$) (Hameed *et al.*, 2002) compared with female (0.449 to $1.273 \mu\text{g ml}^{-1}$) volunteers in this study. Mean (SE) value for C_{max} in present study was $0.907 \pm 0.126 \mu\text{g ml}^{-1}$ which is less than 3.14 (Yuk *et al.*, 1991), 1.74 (Stein *et al.*, 1991), 1.96 (Eboka *et al.*, 1997), 1.9 (Zhue *et al.*, 1993) 4.4 (Flor *et al.*, 1991), 2 to 3 (Lamp *et al.*, 1991), 6.5 (Israel *et al.*, 1993), 4.44 (Echols *et al.*, 1994) and $1.99 \mu\text{g ml}^{-1}$ (Verho *et al.*, 1996) reported previously. The lower values for C_{max} and t_{max} in indigenous conditions may be due to deferent environmental conditions (Nawaz and Shah, 1985; Nawaz *et al.*, 1988; Nawaz, 1994). Influence of body surface area on total body clearance of ofloxacin in female volunteers was investigated. Regression analysis showed a very small R^2 value ($R^2=0.0581$) that indicates no regression between these parameters. This means body surface area of volunteers did not influence the total body clearance of ofloxacin in female volunteers. While regression analysis between body surface area and maximum concentration (C_{max}) of ofloxacin showed a little positive regression ($R^2=0.2236$) indicating an increase in body clearance of ofloxacin with increasing body surface area of volunteers. This means body surface area of volunteers may slightly influence the total body clearance of ofloxacin. Similarly the interaction between body surface area and area under curve (AUC) for ofloxacin in female volunteers was also discussed in this study. For this purpose body surface area of volunteers were plotted against their area under curve (AUC) for ofloxacin. Regression analysis between body surface area and area under curve (AUC) for ofloxacin again showed a little positive regression ($R^2=0.2528$) indicating an increase in area under curve (AUC) for ofloxacin with increasing body surface area of volunteers. This means body surface area of volunteers may also positively influence the area under curve (AUC) for ofloxacin. Similar to these influences previously the differences in gatifloxacin pharmacokinetics values were largely attributed to differences in body weight (LaCreta *et al.*, 2000). These gender-related differences mainly low body weight and surface area in females may warrant dosage adjustments. In conclusion values of parameters like volume of distribution, Total body clearance and absorption rate constant were higher, while elimination half life, AUC, C_{max} , t_{max} were lower in Pakistani female volunteers as compared with foreign studies. In view of these differences, it is very essential that imported drugs be evaluated under local environment specially in countries like Pakistan in which drugs used for health programs of man and animals are being imported from abroad either in the raw or finished form.

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