GENDER DIFFERENCES ON BIOAVAILABITY OF OFLOXACIN

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Background: The fluoroquinolones are currently enjoying extensive worldwide clinical applications because of their good bioavailability and pharmacokinetic profile. Investigation into several aspects of the pharmacokinetic of all clinically relevant fluoroquinolones, have been carried out notably in Europe, USA and Japan. In view of the 'geonetical' (geographical influences on genetics-pharmacogenetics) differences, it is important that for the optimal therapeutic outcome, biodisposition studies on drugs are better conducted in the population and environments where wide and extensive use of the drug is anticipated. The Objectives of study were to see the pharmacokinetic parameters in healthy young male and female volunteers. This comparative study was conducted King Edward Medical University, Lahore, Pakistan, from July 2005 to December 2005. **Method:** In Pakistan where the use of antibiotics is more frequent by the general practitioners it is important to elucidate certain dose parameters it is also noticed that side effects are more in females than males so present study is conducted to calculate any differences in bioavailability on the basis of sex**.** The pharmacokinetic parameters of ofloxacin were determined in each of the clinically health eight young girls and boys (mean age 23.9 and 25.1 years, respectively) following a single oral dose of 400 mg tablet. The method adopted was microbiological assay. **Results** The blood samples collected at predetermined time intervals after drug administration revealed almost twice as high concentration of the drug in plasma of the girls than that in the boys. The pharmacokinetic parameters revealed significantly (p<0.01) higher values for area under curve (AUC) and C_{max}, and lower total body clearance (TBC) and volume of distribution in the girls than in the boys. **Conclusion** The gender differences in pharmacokinetic parameters indicate that the dose adjustment should be considered in male and female.

Keywords: Ofloxacin, Pharmacokinetics.

INTRODUCTION

The fluoroquinolones are currently enjoying extensive worldwide clinical applications because of their good bioavailability and pharmacokinetic profile. Investigation into several aspects of the pharmacokinetic of all clinically relevant fluoroquinolones, 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 by Bergon *et al*[1], Forest *et al*[2], Ayo[3] and Nightingale.[4] In these studies considerable variations of the pharmacokinetic parameters in man have been observed by Matter *et al*[5]; and Plaisance *et al*.[6] Thus, underlining the fact that extrapolation and/or extension of data obtained elsewhere to Asians population should be carried out with a great deal of caution and should be avoided if at all population because pharmacogenetics variations may affect the pharmacokinetic profile of drugs that are extensively metabolized.[7] In view of the 'geonetical' (geographical influences on genetics-pharmacogenetics) differences, it is important that for the optimal therapeutic outcome, biodisposition studies on drugs are better conducted in the population and environments where wide and extensive use of the drug is anticipated.[8]

Due to drug regulatory agency guidelines, women of childbearing potential have long been excluded from studies in early drug development and from clinical studies in the United States and Europe. Even with reversal of these guidelines, these policies contribute to the paucity of information regarding pharmacokinetics of drugs in women.[9]

Ofloxacin is a flouroquinolone with broad spectrum activity and is effective after oral and intravenous administration.[10] It is well absorbed after oral administration and is widely distributed to body tissues.[11] Gender-related differences in pharmacokinetics have frequently been considered as potentially important determinants for the clinical effectiveness of drug therapy[12] therefore, future research efforts are needed to assess the full scope and impact of pharmacodynamic gender disparity on applied pharmacotherapy. Ofloxacin is commonly used in clinics but its bioavailability and pharmacokinetic profile needs to be described in local population and environments. This studies deal with the disposition kinetics of ofloxacin in young healthy male and female volunteers.

MATERIALS AND METHODS

Healthy volunteers, girls and boys, of almost the same age and body weight (8 each) participated in the study. Complete medical history, physical examination, vital signs, haemogram and blood chemistry profile was obtained for each subject baseline at the Medical Clinic under the supervision of the medical experts. All volunteers signed 'Informed Consent Form'. The study was approved by the Research Review Board of the King Edward Medical University, Lahore, Pakistan. On the day of study, the subjects came to the clinic after overnight fast. Subjects were orally given ofloxacin 400 mg tablet

each with 240 ml of water. Prior to the oral dose 0 sample was taken. The water intake was restricted for 1 hour before and 2 hours post drug administration and food intake until 4 hours after dosing. No subject was allowed to consume caffeine-containing beverages during the 12 hours period preceding and throughout the study period. During the study period standard meal was served to the volunteers avoiding excessive fatty meal or food containing a lot of plant fibres.

Table-1: Mean±SD values for the demographic data of healthy boys and girls (n=8 each) who participated in biokinetics study of ofloxacin after 400 mg oral dose

Groups	Age (Years)	Weight (kg)	Height (Ft.)	Temp (°F)	BP mmHg	
					Systolic	Diastalic
Girls	23.9 ±3.93	53.36 ±5.16	5.50 ±0.17	98.6 ±0.59	106.0 ±14.07	71.9 ±9.97
Boys	25.1 ±3.84	61.0 ±6.46	5.70 ±0.18	98.1 ±0.58	113.0 ±13.0	67.5 ±8.45

Serial venous blood samples were drawn into heparinised centrifuge tubes at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 12 and 24 hours after the drug administration. The plasma was separated after centrifugation at 3000 RPM for 7–8 minutes and transferred to labelled tubes, frozen at <-20 °C until assayed. Appropriate precaution was taken during blood collection and serum separation to avoid unnecessary exposure to light.

Ofloxacin concentration in the plasma samples was measured by micro-biological assay procedure. The Disc Agar Diffusion Method was standardized and validated for accuracy and precision by using Streptococcus feacalis as test organism by the method of Arret *et al.* [13] From the standard plasma concentration versus zone diameter data, the regression curve for the average values was drawn, regression equation and regression coefficient are shown in Figure-1. The method was reproducible and accurate for plasma concentrations. The microbiological assay procedures measure both the active drug and metabolites accounting for the antibacterial activity of interest during therapy.

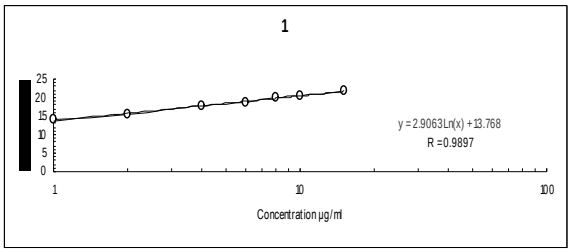

Figure-1: Standard curve of measurement of Ofloxacin in plasma samples

The absorption and elimination kinetics profile of the drug was determined by software APO PC-Computer Program, MWPHARM version Software APO PC-Program, MWPHARM Version 3.02, a MEDIWARE product, Holland. The program determines compartmental and non-compartmental analysis in calculation of the bioavailability and elimination kinetic parameters.

The parameters were estimated by fitting the respective models with different weighing schemes and estimation methods (iterations). The best-fit output was that with the most minimized weighted sum of squares and standard error, with the best randomness of scatter of the graph of weighted residuals and correlation between observed and estimated values. The difference between the pharmacokinetics parameters amongst girls and boys was determined by the Student's *t*-test using Microsoft Excel Software.

RESULTS

The demography of the volunteers has been shown in Table-1. The plasma concentrations of ofloxacin against time in each 8 healthy girls and boys have been shown in Figure-2. The plasma concentration of ofloxacin following similar oral dose of 400 mg showed higher values nearly double in girls than that in boys. The mean values and comparison of pharmacokinetic parameters of ofloxacin following oral dose of 400 mg in girls and boys is presented in Table-2. A highly significant (p<0.01) difference was observed between Area under plasma concentration versus time Curve (AUC) calculated by different methods, while total body clearance was found lower in girls than the respective values in boys.

Table-2: Comparison of Mean±SD values of pharmacokinetic parameters of Ofloxacin after oral dose of 400 mg in each of the 8 girls and boys

Parameters	Girls	Boys	t-test
Area under curve (AUC(h.mg/l)	44.8±39.8	16.9±5.00**	2.2956
AUC polyexponential (t=12)	35.1±37.4	14.8±3.21**	2.1190
AUC trapezoidal rule (t=12)	28.0±3.85	13.9±3.71**	9.4580
Clearance (CL)[l/h]	11.2±4.21	23.6±6.29**	-8.6089
Volume of distribution comp.1 [1]	30.8±17.3	58.3±47.0	-1.3587
Volume of distr. Steady state [1]	54.7±31.9	88.4±52.9	-1.3444
Volume of distribution [1]	68.4±38.3	118±43.9**	-2.3970
Half-life phase 1[h]	0.78±0.71	0.78±0.86	0.0026
Half-life phase 2[h]	4.56±2.62	3.76±2.00	0.7752
Rate constant k10 [l/h]	2.86±6.88	5.88±9.74	-0.6462
Rate constant k12 [l/h]	1.09±1.96	3.30±5.68	-0.9720
Rate constant k21 [l/h]	0.52±0.36	0.52±0.21	0.0037
Mean Residence Time (MRT) [h]	6.18±3.02	6.33±2.00	-0.1183
Absorption Rate Constant (ka) [l/h]	3.08±5.72	6.40±12.1	-0.6839
Absorption Half-life [h]	0.68±0.75	1.15±1.00	-0.7037
Time to peak Tmax [h]	1.43±0.88	1.63±0.97	-0.5525
Peak concentration Cmax[mg/l]	4.86±1.28	2.78±0.85**	3.5720

**Highly significant difference (p<0.01)

The values of elimination half-life of Ofloxacin between girls and boys and the values were 4.56±2.64 and 3.76±2.00 hours, respectively did not show any statistical difference.

The absorption parameter of T_{max} was similar while C_{max} was nearly twice as higher in girls than that in the boys and the difference was highly significant (p<0.01). The values of the volume of distribution in central and peripheral compartments showed wider variations indicating lower values in girls than those in the boys. However, the difference was not statistically significant.

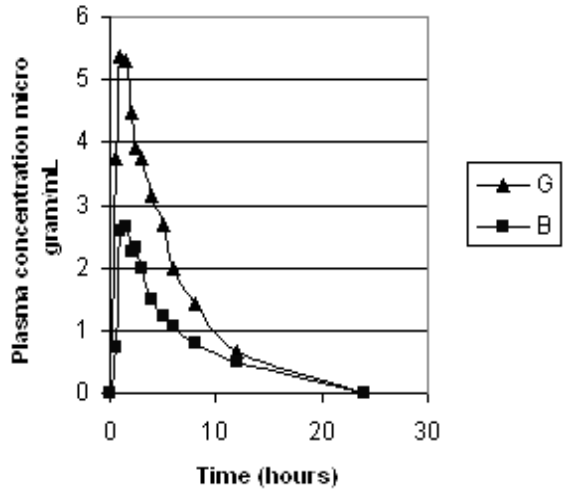

Figure-2: Average±SD (n=8 each) values and ration of the plasma concentrations plotted versus time in girls and boys participated in biokinetics study of ofloxacin 400 mg oral dose.

DISCUSSION

A gender difference showing lower volume of distribution of fluoroquinolones in females than in the males was reported earlier by Kevin *et al*.[14] Hence, clinically, females are likely to experience more side effects of the fluoroquinolones than in the males.[15]

Contrary to the present study showing significant higher C_{max} values in girls, the gender difference in bioavailability parameters amongst females and males was not recorded by Chien *et al*.[16] Gender related differences in pharmacokinetics have frequently been considered as potentially important determinants for the clinical effectiveness of drug therapy.[12]

Of the few studies examining gender related effects on fluoroquinolones pharmacokinetics suggested gender related differences.[17] Sorgel *et al*[18]; reported significantly smaller volume of distribution at steady state (Vss) and lower systemic clearance (Cls) in women than in men. Specifically, Vss was 33% smaller and Cls was 25% lower in women after intravenous administration of levofloxacin. However, when the values were normalized to total body weight, the differences were no longer evident.

Three more recent studies by Shah *et al*[19], Bertino *et al*[20] and Efthymiopoulos *et al*[21] made similar observations regarding gender-related effects on this class of agents. The volume of distribution of steady-state/systemic bio-availability (Vss/F) was smaller after single-dose oral fleroxacin in women than in men[20] and the AUC was greater after a single intravenous dose of ciprofloxacin in young and elderly women than in young and elderly men.[19] Higher AUC (lower clearance) in women suggests that, at the same dosages as in men, women are at risk for higher exposure to the drug and its metabolites accumulated in the body and slow release takes places with are causing potential side effects. A significantly smaller Vss, lower Cls, larger AUC, and higher peak concentrations of grepafloxacin were observed in women compared with men.[21] Such a gender differences suggests that the dosage of the drug needs to be adjusted according to the pharmacokinetics parameters determined in the two sexes of the target population.

CONCLUSION

The gender differences in pharmacokinetic parameters indicate that the dose adjustment should be considered in male and female.

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