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Full Length Research Paper

Gender independent pharmacokinetics of levofloxacin in healthy black African subjects

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The pharmacokinetic profile of levofloxacin in healthy black African subjects as well as the influence of gender on its pharmacokinetic parameters was investigated. Sixteen healthy adult volunteers (8 males and 8 females) enrolled in the study and took single oral dose of 500 mg levofloxacin (Levoflox®) after informed consent. The blood of the volunteers was withdrawn from their antecubital vein at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 36 h post dosing and analysed for levofloxacin concentration. The results of this study revealed that levofloxacin was well tolerated and detectable in the plasma seventeen min after dosing being faster in female than male. Bioavailability was not affected by gender and T_{max} showed no significant difference between the genders (p 0.05). The C_{max} and AUC_{0-} were higher in the female than in the male subjects, plasma clearance (CL) was lower in female than in the male thus explaining the differences in the total systemic exposure of the drug. The volume of distribution (V_d) was significantly reduced in female compared to the male. When pharmacokinetics parameters were expressed relative to mg drug/total body weight or renal function, gender-related differences were attenuated. This result indicates that subject body weight or renal function may be involved in the pharmacokinetic differences of the subjects, thus drug administration based on sex is not relevant.

Key words: Pharmacokinetics, gender, levofloxacin, bioavailability, volume of distribution.

INTRODUCTION

Levofloxacin, a chiral fluorinated carboxyquinolone, is a synthetic broad spectrum antibacterial agent for oral and intravenous administration. It exhibits in vitro spectrum of activity against aerobic gram-negative and gram-positive bacteria, as well as certain other pathogens such as Myoplasma, Chlamydis, Legionella and Myobacteria species (Fish and Chow, 1997; Thornsberry et al., 1999; Soussy et al., 1999). Levofloxacin is the optically active L-isomer of ofloxacin, significantly more active against bacterial pathogens than R-(+)-ofloxacin but differs from ofloxacin in that its pharmacokinetic profile supports once dosing as opposed to ofloxacin, which is given twice daily (Davis and Bryson, 1994; Fish and Chow, 1997).

Levofloxacin exerts its antibacterial activity by penetrating the bacterial cell inhibiting DNA gyrase (topoisomerase II), an enzyme which is involved in the maintaining of the super helical twist of the genetic material, thus inhibiting bacterial DNA replication, transcription, repair and recombination (Davis and Bryson, 1994; Chambers, 1995; Schaeffer, 2002). Levofloxacin is rapidly and completely absorbed after oral administration (Rubinstein, 2001), undergoes limited metabolism and is excreted (80 – 86%) primarily as unchanged drug in the urine (Traunmüller et al., 2001) . It is about 24 to 38 % bound to plasma protein which is independent of the drug concentration (Rubinstein, 2001). When administered with food, the peak plasma concentration and time to peak plasma concentration decreases, therefore, it can be administered without food

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Table 1. The anthropometric, haematological and urinary parameters of the volunteer subjects.

Subjects	Parameters					
	Age yrs	Height m	Weight kg	Hb g/dl	Serum creatinine mg/dl	Creatinine clearance
Male	23.17 ± 3.31	1.67 ± 0.05	66.00 ± 3.42	13.94 ± 0.74	1.08 ± 0.20	94.77 ± 3.46
(8)	(19 – 29)	(1.62 -1.73)	(62.00 -73.00)	(12.83 -14.81)	(0.81 -1.12)	(90.23 - 99.74)
Female	24.33 ± 3.08	1.65 ± 0.06	62.63 ± 6.23	13.92 ± 0.44	0.97 ± 0.18	89.65 ± 4.63
(8)	(21 – 29)	(1.56 –1.72)	(55.00 -72.00)	(13.42 -14.67)	(0.63 -1.05)	(83.23 - 94.33)
Total	23.75 ± 3.11	1.66 ± 0.05	64.31 ± 5.16	13.93 ± 0.58	1.03 ± 0.23	92.21 ± 4.76
(16)	(19 – 29)	(1.56 –1.73)	(55.00 73.00)	(12.83 -14.81)	(0.63 -1.12)	(83.23 - 99.74)

Values in parentheses are ranges
Values are expressed as Mean ± SD.

(Stein, 1996). It volume of distribution is very large and is widely distributed into many tissues and body fluid (Rubinstein, 2001).

Ethnic differences in drug metabolism are well established (Kalow, 1982). Many reports of the pharmacokinetic profile of levofloxacin exist amongst the white Caucasians, but data is sparse, even non-existent in the black African subjects. We therefore determine the pharmacokinetic profile of an orally administered levofloxacin, which is presently available in Nigeria. Furthermore, we determined the influence of male or female gender on its pharmacokinetic profile.

MATERIALS AND METHODS

With informed consent and careful explanation of the objectives and procedures of the study, sixteen healthy black African adults (8 males, 8 females) aged, 23.75 ± 3.11 y (19 – 29 y), height, 1.66 ± 0.05 m (1.56 – 1.73 m) and weight, 64.31 ± 5.16 kg (55 – 73 kg) volunteered to participate in the study. This study was approved in June 2006 by the Research and Ethics Committee of the Lagos University Teaching Hospital, Lagos, Nigeria (Ref. No. ADM/DCST/221/Vol.10). The volunteers were judged healthy on the basis of clinical examination, normal haematological and biochemical parameters (Table 1). Each subject's creatinine clearance which indicated renal effectiveness was predicted from their serum creatinine (Cockcroft and Gault, 1976). All were non-smokers, non-alcoholics and had not taken any quinolone or medications capable of interfering with the absorption, metabolism or excretion of the study drug in 4 months preceding and during the study period. Any volunteer with history of chronic drug use or hypersensitivity to the study drug or had donated blood in 6 months prior to the study, pregnant and nursing mothers, obese or underweight individuals were excluded from the study. Volunteers were prevented from taking beverage containing xanthine derivatives (tea, coffee, caffeine) within 48 h prior to the study and throughout the study period.

Sample collection

After an overnight fast of 12 h, at 0700 h, each of the volunteers received a single oral dose of 500 mg levofloxacin (Levoflox®, Corriander Resources, Nigeria). The drug was ingested with 200 ml of water. Subjects were not allowed food for 3 h post dose. Five ml of whole blood was withdrawn from antecubital vein of each subject before and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 36 h after drug dosing into heparinized bottles and centrifuged immediately at 2,000 g within 15 min. The plasma was separated using Pasteur pipette and stored frozen at -20 °C until analyzed.

Chemicals

All chemicals were of analytical reagent grade, unless indicated otherwise. Tetrabutylammonium bromide (Aldrich Chemical Co. England), phosphoric acid (BDH, England), acetonitrile and methanol (Reidel-de Haen chromasol ®, V. Germany) were HPLC grade. Tablets and reference standard of levofloxacin were kindly supplied by Corriander Resources, Lagos, Nigeria. Sparfloxacin (internal standard, I.S.) was a generous gift from SAM pharmaceutical, Lagos Nigeria.

Standard stock solutions

Levofloxacin and sparfloxacin (Figure 1), were made up as 0.2 mg/ml stock solutions in distilled water or methanol and distilled water (3:7 v\v) respectively. Sparfloxacin (I.S.) was diluted with distilled water to obtain a single internal standard stock solution of 100 μg/ml.

Assay validation

Calibration procedure

The calibration points were obtained by spiking drug-free plasma with levofloxacin working standards solution to obtain concentrations of 5 to 25 μg/ml of levofloxacin. The peak area ratio of levofloxacin to I.S. was plotted against the corresponding concentration. A linear regression was performed in order to obtain the linearity, slope, intercept and correlation coefficients.

Recovery, precision and accuracy

Recovery was determined by comparing the peak area ratio of the spiked drug-free plasma with the peak area ratio obtained by direct injection of the standard solutions of the same concentration. The intra-day calibration curves were obtained in seven replicate assays

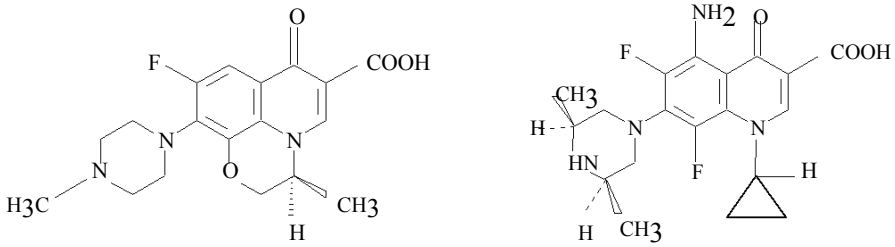

Figure 1. Molecular structure of levofloxacin and sparfloxacin.

at five different concentrations. The inter-day calibration curves were carried out in one-week at five different concentrations. Working standards were made fresh each day of the assay. The relative standard deviation (RSD) or coefficient of variation of the estimated concentrations were determined and used for the assessment of precision.

Assay stability of levofloxacin

The stability of levofloxacin in distilled water or spiked plasma was determined in four weeks. The drug solution (n = 5, 20 μ g/ml) in distilled water prepared on the first day was stored in the dark at room temperature and assayed once each week. The concentration of levofloxacin in spiked plasma (n = 5, 20 μg/ml) was determined on the day of preparation and the remainder of the plasma was stored frozen at -20°C. On each week of the experiment, the plasma was thawed, re-assayed and refrozen over a period of four weeks. In each experiment, concentrations of levofloxacin were extrapolated from a calibration curve obtained from freshly prepared standard stock solution.

Apparatus and chromatographic condition

The High-pressure liquid chromatography analyses were performed using Agilent 1100 series pump (Serial No. DE 43630403, Product No. G1311A; Hewlett-Packard, Germany) equipped with Rheodyne 7725i injector (USA) coupled to UV detector (Serial No. JP 43826101, Product No. G1314A; Japan). The degasser (Serial No. JP40720373, Product No. G1379A; Japan) was used to remove possible gas in the mobile phase. The Chromatographic responses were recorded by Agilent ChemStation software (Agilent technologies, USA) running on Compaq compatible personal computer (Hewlett-Packard) with an Intel Pentium processor operating at 2799 MHz under Microsoft® Window operating environment. The ChemStation also consist of an interface bus for data acquisition and a pinwriter hp DeskJet 5652 printer.

The chromatographic separation was performed at column temperature of 25^{O}C on an inert silica C_{18} hypersil ODS column, 5 m particle size, 250 mm x 4.6 mm i.d. protected by a Lichrospher^{R} Si 60 guard column, 30 mm x 4.6 mm i.d., which was placed between the injector and the analytical column. The component samples were eluted with mobile phase of 0.05 M tetrabutylammonium bromide: methanol (80: 20, v/v) distributed by the gradient pump a flow rate of 1.5 ml/min. The mobile phase was adjusted to pH of 2.0 with phosphoric acid using Thermo Orion pH meter (model 420A) . The injection volume was 20 l, and the effluent was monitored by ultraviolet detector at 278 nm.

Drug analysis

The concentration of levofloxacin in the plasma was determined by a validated HPLC method involving protein precipitation [9] with slight modification. Briefly, to 1 ml aliquot of plasma was added 500 μl of 100 μg/ml I.S. and 2 ml of acetonitrile and precipitated proteins were centrifuged at 2,000 g within 15 min. The acetonitrile phase was concentrated to dryness under reduced pressure and the residue reconstituted in 100 μl methanol. Twenty μl of the reconstituted residue was injected into the HPLC system for chromatographic separation.

Pharmacokinetic analysis of data

The plasma levofloxacin concentration-time data was obtained by a two-compartmental open pharmacokinetic model. The pharmacokinetic parameters characterizing absorption (time to peak plasma concentration [T_{max}], peak plasma concentration [C_{max}]), distribution (V_d), elimination (half-life elimination [$t_{½}$], clearance [CL]) were estimated using standard formulae (Gibaldi, 1982). The total systemic exposure (area under the plasma concentration-time curve [AUC]) was estimated by the trapezoidal rule method for observed values and was extrapolated to infinity [AUC_{0-}] . Pharmacokinetic parameters normalized to body weight were also estimated.

Statistical analysis

Data are expressed as mean ± SD (standard deviation). The significance of gender effect on the pharmacokinetics profile of levofloxacin was compared by variance analysis. The pharmacokinetic parameters analysed were C_{max}, T_{max}, $t_{½}$, CL/F, V_d/F and AUC_{0-} . Since most pharmacokinetic parameters are dependent on dose/ total body weight, normalization of these parameters to dose/ total body weight was examined. Correlation (r) between some pharmacokinetic parameters and subject's creatinine clearance (CLcr) was also examined. Statistical analyses were performed with Student's t- test using SPSS 11 statistical package. The gender group effect was tested at the 5 % level of significance.

RESULT

Anthropometric measurements

The enrolment characteristics of the volunteer subjects are shown in (Table 1). The subjects were reasonably

Table 2. Intra-day and Inter-day precision and accuracy of levofloxacin determination in plasma.

Nominal concentration (μg/ml)	Concentration found [a] (μg/ml)	R.S.D. (%) [b]	Accuracy [c] (%)	Recovery [a] %
Intra-day (n = 7)				
5	4.83 ± 0.11	2.30	-3.40	90.01 ± 0.15
10	9.84 ± 0.14	0.89	-1.60	91.53 ± 0.59
15	15 02 ± 0.42	0.63	0.13	91.03 ± 0.61
20	19.84 ± 0.50	0.49	-0.80	90. 67 ± 0.25
25	25.11 ± 0.44	0.51	0.44	91.63 ± 0.74
Inter-day (n = 7)				
5	5.10 ± 0.23	4.53	2.06	90.47 ± 0.31
10	9.79 ± 0.47	4.81	-2.09	90.83 ± 0.24
15	14.74 ± 0.56	3.80	-1.76	91.37 ± 0.34
20	19.57 ± 0.81	4.14	-2.17	90.98 ± 0.17
25	24.84 ± 0.75	3.01	-0.64	91.42 ± 0.32

[a] mean ±SD
[b] coefficient of variation
[c] % bias = (conc. found – nominal conc.)/nominal conc. x 100

well matched for age and height. All the sixteen subjects who enrolled successfully completed the study without any clinical adverse effects and data from all subjects are included in the pharmacokinetic analysis. All the subjects were healthy as revealed by their biochemical parameters.

Assay validation

The calibration curve yielded a good linearity, with a correlation coefficients (r) of 0.9993 (n = 5); the calibretion function was y = 0.252 x + 0.061; where x = concentration of levofloxacin and y = drug/I.S. peak area ratio. The plasma concentrations of levofloxacin in the volunteer subjects were interpolated from the generated calibration curve. Precision was expressed as the coefficient of variation (CV) of the mean. The intra-day (n = 7) or inter-day (n = 7) coefficient of variation were less than 5 % in each concentration studied (Table 2). These values demonstrate that the precision of the method is good over the range of the concentration studied.

Accuracy expressed as percentage bias were -1.60 % or -2.10 % for intra or inter-day assays respectively (10 μg/ml; n = 7). Accuracy was also assessed from analyticcal recovery of levofloxacin that was added to the plasma. The mean recovery for intra-day assay were 90.01 ± 0.15 % and 91.63 ± 0.74 % for 5 and 25 μg/ml respecttively. Chromatograms of standard solution of levofloxacin or plasma spiked with the same concentration are shown in [Figures 2 a-b]. Levofloxacin in distilled water or spiked plasma stored frozen at -20^{O}C was stable during the four week experimental period. The daily concentrations of levofloxacin in the assay were found to be less than 5 %. No change in concentration within the study periods was noted. This result also indicates that repeated freezing and thawing of the plasma did not alter the concentration of the drug.

Pharmacokinetic results

The mobile phase used in this study provided a good resolution for levofloxacin and I.S. and no endogenous serum components interference were noted. The time course of levofloxacin concentrations (mean ± S.D.) in the plasma of the male or female subjects are shown in (Figure 3). The pharmacokinetic parameters obtained from this investigation are listed in (Table 3). Levofloxacin was rapidly absorbed from the gastrointestinal tract and was detectable in the plasma within 17 min after administration being faster in female (0.29 ± 0.08 h) than male (0.31 ± 0.09 h). In all, the concentration of levofloxacin in the plasma increased rapidly reaching a maximum in 1.39 ± 0.31 h. From the peak plasma (C_{max}) of 5.89 ± 1.07 μg/ml, the concentration fell gradually and was still detectable in the plasma at 36 h after dosing. The elimination half-life ($t_{½}$) varied from 5.81 to 9.11 h (7.45 ± 1.07 h); the plasma clearance (CL) and volume of distribution (V_d) parameters were 115.69 ± 15.59 ml/min and 73.93 ± 13.40 l respectively. The area under the plasma curve (AUC_{0-}) was 70.38 ± 9.04 μg/ml/hr. There was significant difference in C_{max}, $t_{½}$, CL, V_d and AUC_{0-} between the male and female subjects (p 0.05). However, T_{max} showed no significant difference (p 0.05). When dose/body weights of the subjects were considered in the analysis, the statistical significance observed in the pharmacokinetic parameters were eliminated (Table 4).

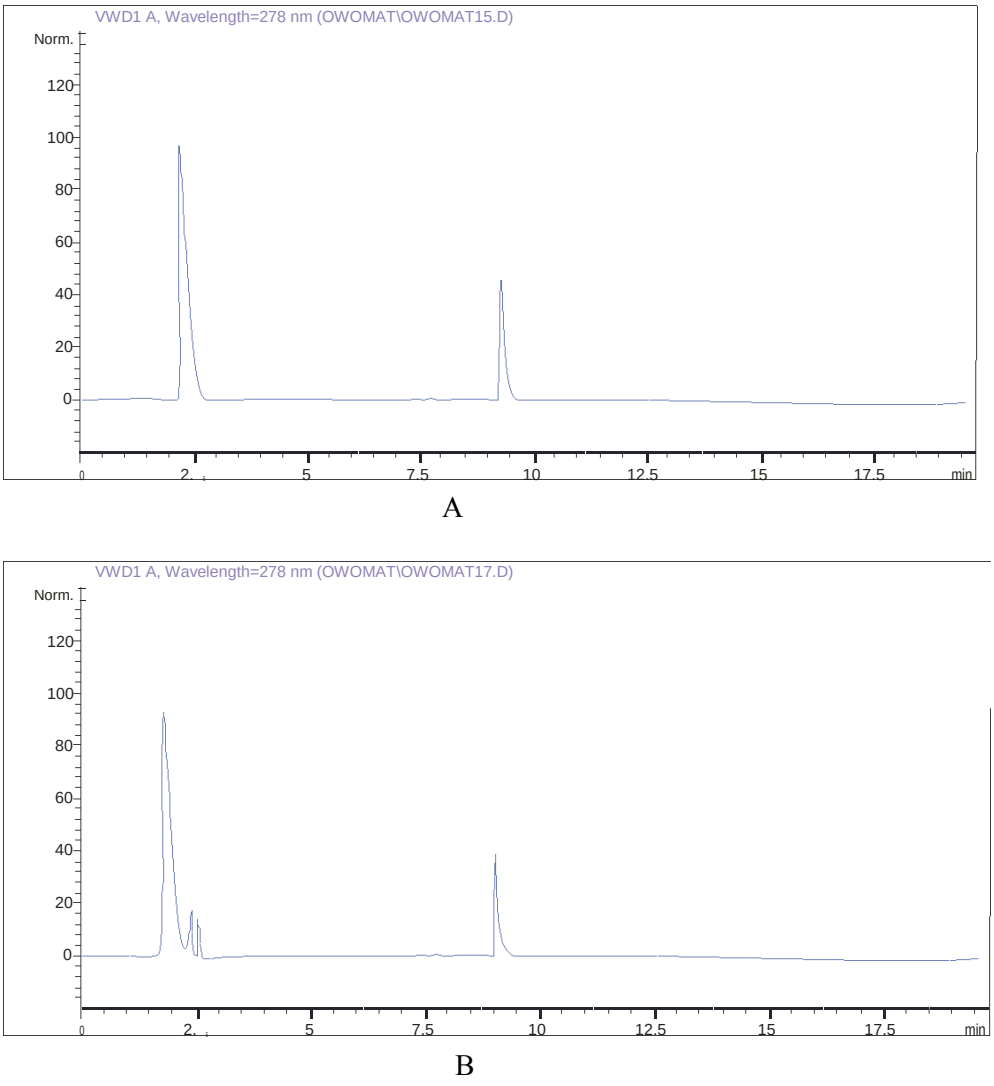

Figure 2. Representative chromatograms of standard solution of levofloxacin (a) or plasma spiked with the same concentration of levofloxacin (b).

This result indicates that subject body weight may be involved in the pharmacokinetic differences of the subjects. There was positive correlation between creatinine clearance (CLcr) and C_{max}, CL, AUC_{0-}, V_d (0.691, 0.813, 0.721 and 0.734) respectively with no statistical signify-cant difference between the genders.

DISCUSSION

Like other quinolones, levofloxacin chelate cations such as aluminum, magnesium, calcium, iron, and zinc when administered concurrently with significant decrease in their absorption and bioavailability, resulting in lower serum drug concentrations and less target-tissue penetration (Fish and Chow, 1997; Sakai et al., 1999; Oliphant and Green, 2002). These findings informed our recruiting volunteers who have not taken food or any form of medication 12 h before and 3 h after drug administration. The pharmacokinetic parameters for the female and male in our study showed that bioavailability was not affected by gender as shown by the consistency in T_{max} in the different groups. The C_{max} was higher in the female than in the male subjects; however C_{max} when normalized to dose (mg drug/ kg body weight) showed no difference between the genders. The goal of normalization is to correct for differences in parameters that are due solely to differences in body size. The AUC_{0-} value for female subjects was significantly different being about 16% higher than those for the male subjects. This result indicates that fixed doses given regardless of body weight may result in higher drug exposure in tissues of women

Table 3. Pharmacokinetic parameters of the volunteers following a single 500 mg oral dose of levofloxacin.

Subject	C_{max} (µg/ml)	T_{max} (hr)	Elimination half-life $t_{½}$ (hr)	AUC_{0-} (µg/ml/hr)	V_d (liter)	CL (ml/min)
Male	5.34 ± 1.09 [a]	1.43 ± 0.34 [b]	7.71 ± 1.06 [b]	64.24 ± 8.40 [a]	81.73 ± 14.29 [a]	122.81 ± 16.63 [a]
Female	6.43 ± 0.76 [a]	1.36 ± 0.29 [b]	7.18 ± 1.08 [b]	74.38 ± 7.32 [a]	66.13 ± 6.44 [a]	108.57 ± 11.34 [a]
Total	5.89 ± 1.07	1.39 ± 0.31	7.45 ± 1.07	69.31 ± 9.24	73.93 ± 13.40	115.69 ± 15.59

Values are expressed as Mean ± SD.

[a] *P* 0.05 when male and female were compared. [b] *P* 0.05 when male and female were compared.

Table 4. Adjusted pharmacokinetic parameters of 500 mg oral levofloxacin for volunteers.

Subject	C_{max} (µg/ml/dose)	AUC_{0-} (µg/ml/hr/dose)	V_d/F (liter/kg)	CL/F (ml/min/kg)
Male	0.70 ± 0.11 [a]	8.45 ± 0.82 [a]	1.23 ± 0.18 [a]	1.86 ± 0.19 [a]
Female	0.81 ± 0.14 [a]	9.25 ± 0.48 [a]	1.07 ± 0.16 [a]	1.73 ± 0.08 [a]
Total	0.75 ± 0.14	8.85 ± 0.77	1.15 ± 0.18	1.80 ± 0.15

Values are expressed as Mean ± SD.

[a] *P* 0.05 when male and female were compared for all parameters

who generally are lower weight than men thus resulting in females showing improved efficacy. However, when normalized to dose, the values for the male and female subjects were not significantly different.

The plasma clearance (CL) was lower in female than in the male thus explaining the differences in the total systemic exposure (AUC_{0-}) of the drug in the female and the male subjects. When CL values were normalized to total body weight, the differences were no longer evident. The decrease in lean body mass is associated with a corresponding increase in body fat; reduction in the proportion of lean body mass per total body weight has been shown to alter the volumes of distribution of several drugs (Crowley et al., 1990; Shah et al., 1995). The apparent volume of distribution (V_d) in our study was signify-cantly reduced in female subjects compared to the male subjects, however, when normalized to total body weight, the difference was minimized. This finding could be explained from the fact that females have higher percentage of their weight as fat than the males with resultant lower lean body mass.

Our study agrees with the works of Chien et al., (1997) and Overholser et al., (2005) who reported on the gender characteristic in the pharmacokinetics of levofloxacin among the African-Americans or Caucasians following oral and intravenous administrations respectively. The study of Chien et al., (1997) reported significant difference in C_{max}, AUC_{0-} , V_d, CL and $t_{½}$ between the males and females, however, when subjects' renal function (creatinine clearance) and total body weight were considered, the differences between males and females were not evident. The gender difference in T_{max}, observed by Chien et al., (1997) was attributed to an artifact of the collection time.

In the study of Overholser et al., (2005), after 60 minutes intravenous administration of 500 mg levofloxacin to male and female subjects, a 16 % increase in the C_{max}, and a significantly larger AUC_{0-} were seen in women compared to the men.

Half-life elimination ($t_{1/2}$) was not significantly different between sexes. Also signi-ficant decrease in CL and V_d in the female subjects compared with the male subjects was observed. Overholser et al., (2005) attributed the difference in the parameters to lower body weight in the women compared to the men; however, when results were adjusted to lean and total body weight, the difference in CL was ate-nuated but V_d remained signify-cantly smaller in women compared to that in men, suggesting that a gender differences may exist in V_d after intravenous admini-stration of levofloxacin.

The validation experiment of levofloxacin showed good accuracy and precision and the mobile phase gave a good resolution of the study drug and I.S. The results of this study demonstrates that pharmacokinetic parameters C_{max}, AUC_{0-} , CL, and V_d normalized the body weight were similar for males and females, indicating that the pharmacokinetic differences between males and females were largely due to differences in body weight. There was positive correlation between creatinine clearance and some pharmacokinetic parameters with no significant difference between the sexes. Therefore we conclude that no sex-related difference was seen between male fe-

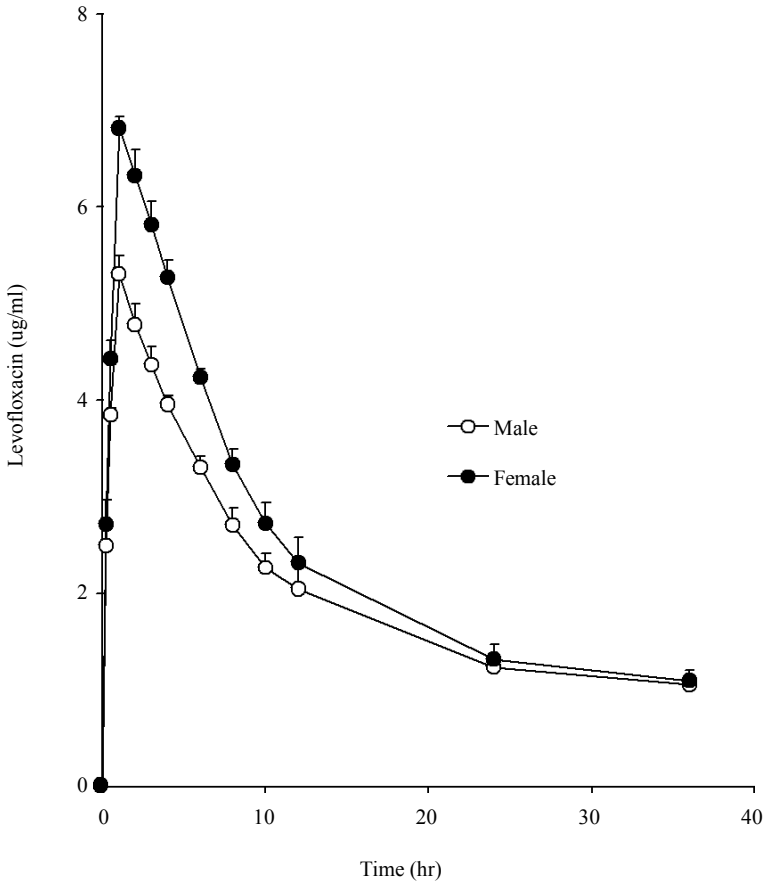

Figure 3. Mean plasma concentration-time plot of oral levofloxacin (500 mg) in male (○) and female ( ) volunteer black African subjects.

male subjects.

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