Pharmacokinetics of Intravenously Administered Levofloxacin in Men and Women

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Study Objective. To characterize and compare the pharmacokinetics of levofloxacin in men and women after systemic administration.

Design. Prospective, open-label, parallel group pharmacokinetic study.

Setting. University research center.

Subjects. Eleven healthy men and nine healthy women stratified by body mass index.

Intervention. Subjects received levofloxacin as a single 500-mg intravenous dose. Serum and urine were collected over 36 hours.

Measurements and Main Results. Levofloxacin concentrations were determined by high-performance liquid chromatography with ultraviolet detection. Pharmacokinetic analysis was performed with ADAPT II software (University of Southern California, Los Angeles, CA). Median (range) body mass index was 23.2 kg/m^2 (19.9–28.3 kg/m^2) for men and 23.6 kg/m^2 (16.0–32.4 kg/m^2) for women (p=0.67). A two-compartment model best fit the pharmacokinetic data: median (range) R^2 was 0.996 (0.990–0.999). Women had a 24% greater exposure to levofloxacin, with a significantly smaller steady-state volume of distribution (p<0.01) and a slower clearance (p<0.01).

Conclusions. Differences exist in the disposition of levofloxacin between healthy men and women after systemic administration. Fixed intravenous doses of levofloxacin will lead to greater drug exposure in women. Thus, women may have more of an increased risk of fluoroquinolone toxicity than men, and men may need higher doses to achieve similar drug efficacy than women. Levofloxacin dosage adjustments based on sex should be considered on an individual basis.

Key Words: levofloxacin, pharmacokinetics, sex-based differences.

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Fluoroquinolones are broad-spectrum antibiotics commonly used in the treatment of community-acquired pneumonia, among several other infections. They are generally well tolerated, although central nervous system and gastrointestinal adverse effects are common.[1, 2] Observational data suggest that women may have a greater frequency of these adverse effects with certain fluoroquinolone antibiotics than do men.[3, 4] This increased toxicity in women may be attributed to an underlying disposition or response difference to fluoroquinolones between the sexes.

Previous reports indicate that women have increased maximum serum concentrations (C_{max}) and a greater exposure to several fluoroquinolones.[5–10] In most of these studies, the estimated volume of distribution of the compound of interest was found to be smaller in women compared with that in men but was attenuated when normalized to body weight. Other studies report an absence of a sex-related effect on fluoroquinolone disposition when pharmacokinetic parameters are normalized to

total body weight, although none of the studies reported pharmacokinetic parameters unadjusted for weight.[2, 11, 12] Thus, available data suggest that because of smaller body weights, women may be exposed to higher plasma fluoroquinolone concentrations than are men when equal doses are administered. Despite body composition differences, however, to our knowledge, relationships between fluoroquinolone pharmacokinetics and total body weight have not been investigated in men and women to justify weight normalization of pharmacokinetic parameters between the sexes.

We previously published the sex-related effects on the pharmacokinetics of ofloxacin administered as a single 400-mg oral dose in male and female volunteers.[10] Consistent with previous fluoroquinolone studies, the apparent steady-state volume of distribution (V_{ss}) was significantly lower in women than in men, and after weight adjustment the difference was attenuated and no longer statistically significant. Of particular interest, data from that study suggest that differences may exist in the relationship between the apparent V_{ss} of ofloxacin and total body weight in men and women. In men, a strong positive relationship between total body weight and the apparent V_{ss} was observed. In the women, however, no apparent relationship was noted between V_{ss} and total body weight. If a

distinct relationship exists between the sexes, pharmacokinetic parameter normalization to total body weight may be inappropriate for ofloxacin. Since that study was performed after administration of an oral dose, differences in the clearance and V_{ss} could not be distinguished from potential differences in oral bioavailability.

Levofloxacin, the pharmacologically active S-enantiomer of racemic ofloxacin, is frequently used in clinical practice, but potential sex-based disposition differences after intravenous administration have not been established.[2] Based on observations from the ofloxacin study, we hypothesized that sex-based differences exist in the pharmacokinetics of levofloxacin after systemic administration. Therefore, we sought to investigate the pharmacokinetics of intravenous levofloxacin in a group of men and women stratified by body mass index. An additional aim was to justify a weight-based normalization of pharmacokinetic parameter estimates by assessing the relationships between body weight and composition with systemic clearance (Cl_s) and apparent V_{ss} in men and women.

Methods

Study Subjects

Men were enrolled without restriction into one of three groups stratified by body mass index: less than 20 kg/m^2, 20–25 kg/m^2, and greater than 25 kg/m^2. Women were matched to the men based on the stratified groups to ensure similar numbers of men and women in each group. The stratification procedure was implemented to ensure similar body mass indexes were observed between male and female study subjects at study completion. Healthy, nonsmoking male and female volunteers aged 18–40 years were recruited for study participation.

An initial interview was conducted to ascertain information regarding the subject's medical history, current use of drugs, and history of allergies. Subjects were excluded if they were taking any drugs, including over-the-counter drugs within 24 hours before the study visit. Premenopausal women with a history of a regular menstrual cycle and not using any hormone-containing contraceptive methods were eligible for study participation. Women were instructed to use abstinence or effective barrier contraceptive methods from the initial screening until a minimum of 1 week after the study period. Two urine pregnancy tests were obtained for each woman, one during screening and one before

drug administration. Subjects were excluded from participating in the study if they were allergic to fluoroquinolone antibiotics or heparin or if women were breast-feeding, pregnant, or intending to become pregnant within 30 days of the study period. All subjects underwent a screening evaluation based on medical history, physical examination, routine serum chemistry, and urinalysis. Clinically significant abnormalities in any of these tests were criteria for exclusion from study participation.

All subjects provided written informed consent before enrollment, and the study was approved by the Institutional Review Board at Indiana University–Purdue University Indianapolis, Indianapolis, Indiana.

Size Descriptors

Male and female volunteers were stratified by an estimated body mass index (BMI [kg/m^2]) calculation (Equation 1).[13] In addition, ideal body weight (IBW [kg]), lean body weight (LBW [kg]), and body surface area (BSA [m^2]) were estimated for all study subjects by using Equations 2–4.[14–16] Weight is in kilograms and height is in meters, unless otherwise indicated.

(Eq. 1) $BMI = weight/height^2$

(Eq. 2) $IBW_{men} = 50 + 2.3(height - 60)$, and
$IBW_{women} = 45.5 + 2.3(height - 60)$,
where height is in inches

(Eq. 3) $LBW_{men} = (1.10 \cdot weight) - 128[weight^2/(100 \cdot height)^2]$
$LBW_{women} = (1.07 \cdot weight) - 148[weight^2/(100 \cdot height)^2]$

(Eq. 4) $BSA = weight^{0.425} \cdot height^{0.725} \cdot 0.20247$

Study Protocol

Subjects were instructed to avoid alcohol, caffeine, fruit, and fruit juices 24 hours before and during the entire study period. On the morning of the study, after an 8-hour fast, subjects reported to the Indiana University General Clinical Research Center (GCRC), where on arrival a venous catheter was inserted into a forearm vein of each arm. Each subject received levofloxacin (Levaquin; Ortho-McNeil Pharmaceutical, Inc., South Raritan, NJ) as a single 500-mg dose administered with an intravenous infusion pump over 60 minutes. Subjects continued to fast for an additional 4 hours after the end of the infusion. Venous blood samples (10 ml) were obtained from the

indwelling catheter contralateral to the infusion arm, into evacuated blood collection tubes that contained no anticoagulant, immediately before and at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, and 36 hours after the infusion. The venous catheter was removed at 24 hours, and blood samples obtained at 36 hours after the infusion were obtained by a separate venipuncture. Blood was allowed to clot; serum was separated by centrifugation and stored at -70°C until analysis. Subjects were instructed to void before drug administration, and urine was collected for the entire 36-hour study period: between 0 and 24 hours in the GCRC and between 24 and 36 hours as an outpatient. The volume was determined, and an aliquot was stored at -70°C until analysis.

Sample Analysis

Levofloxacin concentrations in serum and urine were determined by a modified reverse-phase high-performance liquid chromatography method with ultraviolet detection, as previously described for the quantification of levofloxacin in serum.[17] Serum samples were thawed at room temperature and vortexed for 30 seconds, and a 50-µl aliquot was collected. After addition of a displacing reagent (acetonitrile-water [20:80, volume:volume ratio, v:v] containing 0.5% sodium dodecyl sulfate [SDS] and 0.075 mol/L phosphate) containing the internal standard (ciprofloxacin; Bayer, West Haven, CT), serum samples were ultrafiltered with an Amicon Centrifree apparatus (Amicon Division, W.R. Grace & Co., Beverly, MA). The ultrafiltrates were then injected onto an Adsorbosphere HS C_{18} column (particle size 5 µm, 4.6 x 250 mm; Alltech Associates, Deerfield, IL) with ultraviolet detection (280 nm). The mobile phase consisted of acetonitrile-water (40:60 v:v) containing 0.01 mol/L SDS, 0.01 mol/L tetrabutylammonium acetate, and 0.025 mol/L citric acid. The serum standard curves were linear over the calibration range of 0.1–10 mg/L with a lower limit of detection of 0.375 mg/L. Serum samples greater than 10 mg/L were diluted 2-fold and reanalyzed. At quality control serum concentrations of 0.375, 1.50, and 6.00 mg/L, interday and intraday coefficients of variation were 7% or less.

The equipment and conditions for the urine levofloxacin assay were identical to those described for the serum assay. Urine samples were thawed and vortexed for 30 seconds, and a 50-µl aliquot was diluted with 1000 µl of mobile phase. Fifty microliters of internal standard

(ciprofloxacin 30 μg/ml) were added to the diluted sample and vortexed for an additional 30 seconds before being transferred to a vial and directly injected onto the column for analysis. The urine calibration curve was linear from 1–500 mg/L with a lower limit of detection of 3.75 mg/L. At urine quality control concentrations of 3.75, 37.5, and 375 mg/L, interday and intraday coefficients of variation were 12% and 9% or less, respectively.

Serum and urine creatinine concentrations were determined by a colorimetric method using a COBAS-Mira spectrophotometer (Roche, Basel, Switzerland) in the Indiana University GCRC core analytical laboratory. Interday and intraday coefficients of variation were 5% or less. The 24-hour creatinine clearance (Cl_{cr}) values were calculated from the urine collection by standard methods.

Pharmacokinetic Analysis

Pharmacokinetic parameters were estimated by fitting pharmacokinetic models to the levofloxacin serum concentration-time data by using maximum likelihood estimation in ADAPT II, release 4.[18] The variance model assumed that the standard deviation of the residuals was linear with increasing concentrations using Equation 5:

(Eq. 5) $\quad f(V) = [y_{int} + m(y)]^2$

where y_{int} is the y intercept of the residual plot and m is the slope of the line. The y intercept was initially fixed at one half of the lower limit of detection for the levofloxacin serum assay and estimated with the combined residuals from all subjects from the final two-compartment model. The slopes were initially set at 10% and estimated in each individual subject.

Model discrimination was accomplished by visual inspection of the distribution of the weighted residuals, Akaike information criteria,[19] sums of the squared weighted residuals, and visual inspection of the predicted versus measured data. The pharmacokinetic model that was best fit to the serum concentration-time data was a two-compartment model with first-order elimination from the central compartment. The model was parameterized by using apparent volume of distribution of the central compartment (V_c), apparent volume of distribution of the peripheral compartment (V_p), Cl_s, and distribution clearance between the central and peripheral compartments (Cl_d).

Secondary pharmacokinetic parameters derived from model estimates including terminal elimination half-life ($t_{1/2}$) were calculated by standard methods.[20] Apparent V_{ss} and renal clearance (Cl_r) were calculated with Equations 6 and 7, respectively:

(Eq. 6) $\quad V_{ss} = V_c + V_p$

(Eq. 7) $\quad Cl_r = Ae_{0-36}/AUC_{0-36}$

where Ae_{0-36} is the amount of levofloxacin excreted in the urine from 0–36 hours after administration and AUC_{0-36} is the area under the concentration-time curve from 0–36 hours. The area under the levofloxacin concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) and AUC_{0-36} were calculated by the integration of the model-derived concentration-time curves. The levofloxacin C_{max} was obtained by visual inspection of each subject's model-derived concentration-time profile.

Statistical Analysis

Statistical analyses were performed by using SigmaStat for Windows, version 2.03 (SPSS Inc., Chicago, IL). Statistical comparisons of pharmacokinetic parameter estimates between men and women were performed with the Wilcoxon rank sum test. Univariate least squares linear regression was used to examine the relationship between Cl_s and V_{ss} of levofloxacin with Cl_{cr}, body mass index, ideal body weight, lean body weight, body surface area, and total body weight in men and women. Overall differences were considered statistically significant at a p value less than 0.05.

Results

The study group was composed of 20 healthy volunteers: 11 men aged 19–39 years (median 27 yrs) and 9 women aged 19–37 years (median 31 yrs). All 20 participants successfully completed the study without any clinically significant adverse effects and were included in the data analysis. Eight subjects were self-reported Caucasian (six men, two women), three African-American (two men, one woman), seven Asian (two men, five women), and two Hispanic (one man, one woman). Individual body mass indexes and total body weights in men and women are depicted in Figure 1. Subject demographics including body surface area, ideal body weight, and lean body weight in the study groups are displayed in Table 1. The mean ± SD 24-hour Cl_{cr} values for men and women were

Table 1. Demographics of the Study Subjects

	Men (n=11)	Women (n=9)	p Value
Body mass index (kg/m^2)	23.2 (19.9–28.3)	23.6 (16.0–32.4)	0.67
Total body weight (kg)	74.8 (57.1–92.3)	64.1 (51.2–79.9)	0.03
Height (cm)	177 (154–198)	168 (157–180)	0.03
Body surface area (m^2)	1.93 (1.54–2.24)	1.67 (1.53–1.85)	0.02
Ideal body weight (kg)	72.0 (51.0–91.0)	60.0 (50.0–70.0)	<0.01
Lean body weight (kg)	60.0 (45.0–72.0)	45.0 (40.0–51.0)	<0.01

Data are median (range).

105.7 ± 33.6 and 97.0 ± 37.5 ml/minute, respectively (p=0.59).

The final pharmacokinetic model fit to the data was a two-compartment open model with first-order elimination from the central compartment. The median (range) R^2 for individual fits with the final model was 0.996 (0.990–0.999). Levofloxacin serum concentration versus time data obtained from a representative male subject and female subject with the fitted serum concentration-time curve are shown in Figure 2. The representative subjects had similar estimated pharmacokinetic parameters to those of the medians obtained from each study group.

Model-estimated pharmacokinetic parameters after intravenous levofloxacin administration are presented in Table 2. The Cl_s of levofloxacin was significantly (p<0.01) slower in women compared with that in men. Similarly, women had a 40% slower Cl_r of levofloxacin despite a comparable (p=0.61) 24-hour Cl_{cr}. The nonrenal clearance (i.e., $Cl_s - Cl_r$) was not significantly different between men and women of this study (p=0.72, data not shown). The V_{ss} and V_c of

levofloxacin were significantly (p<0.01) smaller in women, in concert with a significant 25% increase in the median levofloxacin C_{max}. Women had a 24% increase in the total exposure to levofloxacin as determined by a significantly larger $AUC_{0-\infty}$. The Cl_d and $t_{1/2}$ for levofloxacin were not significantly different between sexes (p=0.56 and 0.06, respectively).

The individual pharmacokinetic parameter estimates were used to simulate the predicted steady-state levofloxacin serum concentrations in each subject. The mean ± SD steady-state levofloxacin concentrations were estimated by the predicted steady-state concentrations in men and women separately. Figure 3 displays the mean ± SD predicted steady-state levofloxacin concentrations after a 5-day regimen of intravenous levofloxacin 500 mg administered by a 60-minute infusion every 24 hours.
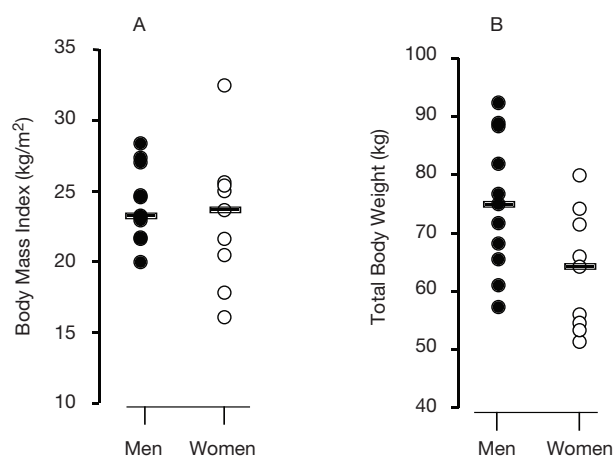
Figure 1. Body mass index (A) and total body weight (B) of the study participants. The medians are identified by (−).

Figure 2. Levofloxacin concentration-time profiles after a 60-minute intravenous infusion of levofloxacin 500 mg, in a representative male (●) and female (○) subject. Symbols represent observed concentration values, with a fitted line depicting the serum levofloxacin concentrations predicted from the pharmacokinetic model. Insert displays the concentration-time curve on a log-linear scale.

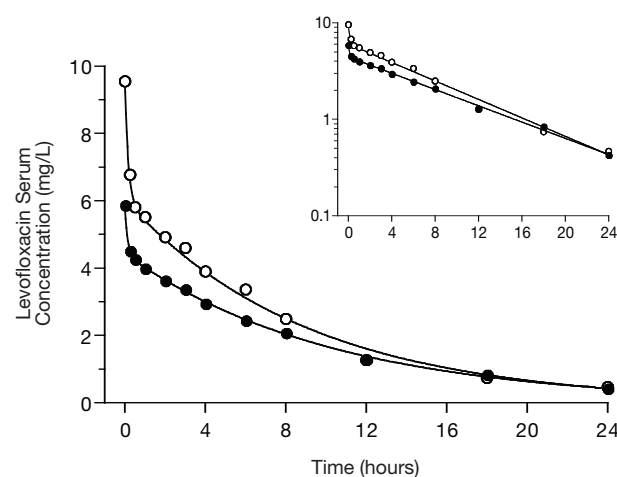**Table 2. Pharmacokinetic Parameter Estimates for Levofloxacin in Men and Women**

Parameter	Men (n=11)	Women (n=9)	p Value
Cl_s (L/hr)	11.0 (9.33–16.5)	8.87 (7.90–10.7)	<0.01
Cl_r (L/hr)	10.4 (7.65–13.5)	6.31 (4.52–9.33)	<0.01
V_c (L)	58.4 (25.5–84.7)	22.0 (7.34–74.6)	<0.01
V_{ss} (L)	117 (93.3–152)	81.0 (59.7–105)	<0.01
Cl_d (L/hr)	73.9 (7.57–560)	75.5 (1.99–399)	0.56
$t_{1/2}$ (hr)	7.3 (6.4–9.4)	6.4 (5.4–13)	0.06
C_{max} (mg/L)	5.4 (4.7–6.2)	6.7 (5.9–13)	<0.01
$AUC_{0-\infty}$ (mg•hr/L)	45.5 (30.3–53.6)	56.4 (46.8–63.3)	<0.01

Data are median (range).
Cl_s = systemic clearance; Cl_r = renal clearance; V_c = central compartment volume of distribution; V_{ss} = steady-state volume of distribution; Cl_d = intercompartmental distribution clearance; $t_{1/2}$ = terminal elimination half-life; C_{max} = maximum serum concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity.

Table 3. Body Weight–Adjusted Pharmacokinetic Parameter Estimates for Levofloxacin

Parameter	Men (n=11)	Women (n=9)	p Value
Normalized for total body weight			
Cl_s (L/hr/kg)	0.16 (0.12–0.19)	0.15 (0.10–0.17)	0.36
V_{ss} (L/kg)	1.62 (1.33–1.72)	1.31 (1.01–1.47)	<0.01
Normalized for lean body weight			
Cl_s (L/hr/kg)	0.20 (0.16–0.24)	0.20 (0.17–0.21)	0.88
V_{ss} (L/kg)	2.00 (1.75–2.20)	1.74 (1.39–2.10)	<0.01

Data are median (range).
Cl_s = systemic clearance; V_{ss} = steady-state volume of distribution.
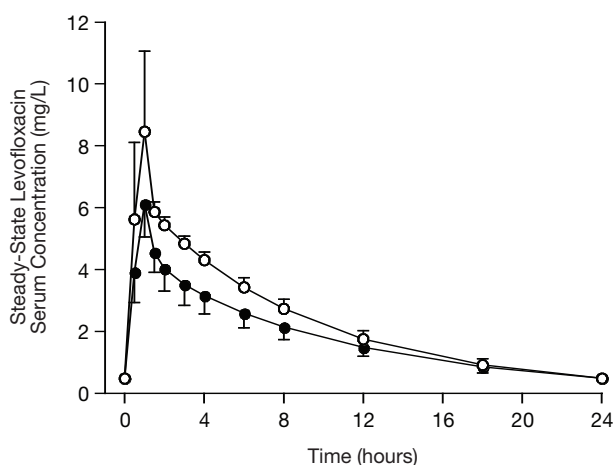

Figure 3. Predicted mean ± SD steady-state serum levofloxacin concentration versus time curve generated from individual simulations of the pharmacokinetic parameter estimates in all study subjects. The symbols represent the predicted mean ± SD levofloxacin serum concentrations in men (●) and women (○) at the predetermined blood sampling times, with a smooth curve though each of the mean values.

The univariate linear regression analysis revealed a positive relationship between total body weight and V_{ss} of levofloxacin in the combined sexes (R^2=0.67, 20 subjects, p<0.05), in men (R^2=0.79, 11 subjects, p<0.05), and in women (R^2=0.46, 9 subjects, p<0.05) alone. Figure 4A shows the relationship between V_{ss} and total body weight in men and women, separately. For any given body weight of men in this study, women of the same weight had a smaller V_{ss} for levofloxacin. Furthermore, the univariate regression analyses of V_{ss} displayed positive relationships versus body mass index (men R^2=0.18, women R^2=0.31), lean body weight (men R^2=0.77, women R^2=0.55), body surface area (men R^2=0.77, women R^2=0.42), and ideal body weight (men R^2=0.52, women R^2=0.06). Lean body weight had the strongest relationship with V_{ss} in men, women, and the combined sexes (R^2=0.87, 20 subjects, p<0.05; Figure 4B).

Systemic clearance and total body weight also displayed a positive relationship in the combined sexes ($R^2=0.53$, 20 subjects, p<0.01). However, as depicted in Figure 4C, differences in total body weight accounted for only 19% of the total variation of the Cl_s in women and 52% in men. The Cl_s of levofloxacin also displayed a positive relationship with measures of body mass index (men $R^2=0.23$, women $R^2=0.04$), lean body weight (men $R^2=0.44$, women $R^2=0.61$), body surface area (men $R^2=0.42$, women $R^2=0.40$), and ideal body weight (men $R^2=0.20$, women $R^2=0.05$). As seen with the relationship with V_{ss}, lean body weight had the strongest relationship with Cl_s in men, women, and the combined sexes ($R^2=0.66$, 20 subjects, p<0.05; Figure 4D).

Primary pharmacokinetic parameter estimates were normalized to total body weight and lean body weight, which displayed the strongest relationship with both Cl_s and V_{ss}. Table 3 displays the lean and total body weight-adjusted Cl_s and V_{ss} for men and women. Sex-based differences in levofloxacin Cl_s and Cl_r were attenuated and no longer statistically significant when adjusted for total body weight (p=0.36 and 0.50, respectively) or lean body weight (p=0.88 and 0.91, respectively). However, V_{ss} normalized to lean or total body weight remained significantly smaller (p<0.01) in women compared with that in men, suggesting that sex-based differences in V_{ss} may exist.

Discussion

Before this investigation, to our knowledge, the sex-based pharmacokinetics of levofloxacin after intravenous administration had not been characterized. In this study, we examined the disposition of systemically administered levofloxacin in a population of men and women who were stratified by body mass index. Results
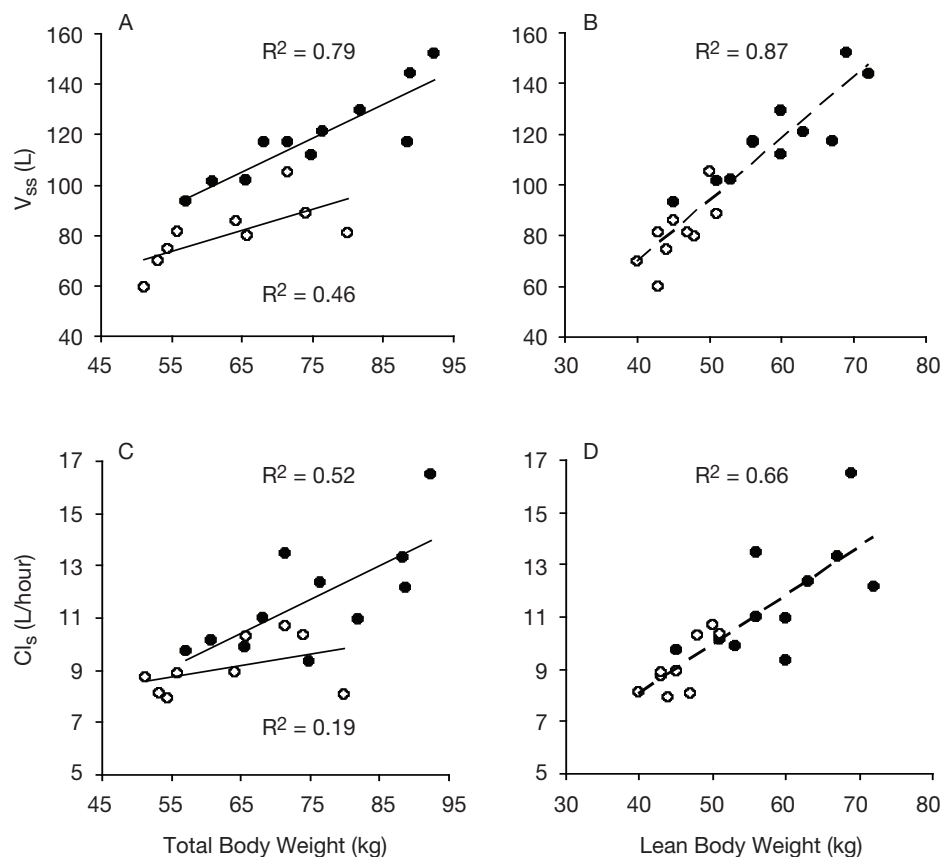

Figure 4. Relationship between levofloxacin steady-state volume of distribution (V_{ss}) and total body weight (A), and V_{ss} and lean body weight (B) in men (●) and women (○). Relationship between levofloxacin systemic clearance (Cl_s) and total body weight (C), and Cl_s and lean body weight (D) in men and women. Solid lines represent the univariate linear regression least squares fit for men and women separately and dashed lines represent the linear regression analyses for the combined study groups, with the corresponding coefficients of determination.

indicated that, after intravenous administration, levofloxacin C_{max} is considerably higher in women than in men of a similar body mass index. In addition, women displayed a greater exposure to levofloxacin due to a slower Cl_s which corresponded to a median $AUC_{0-\infty}$ that was 24% higher than that of men.

The significantly slower Cl_s of levofloxacin in women can predominantly be attributed to a slower Cl_r of similar magnitude. However, the 24-hour Cl_{cr} was not statistically significantly different between men and women in this study. In addition, Cl_{cr} was not a strong predictor of the Cl_r of levofloxacin (R^2=0.17, data not shown). Therefore, it is likely that the disparities in Cl_r are due to differences in the tubular secretion and/or reabsorption of levofloxacin between the sexes, since it is not highly protein bound. Potential differences in tubular secretion and reabsorption have not been well studied between the sexes despite reports that suggest differing renal handling of certain drugs between men and women.[21] Levofloxacin, however, has been shown to be a substrate for drug transporters in vitro, which have known activity in renal tubules.[22] There is no evidence of sex-related differences in active transport proteins such as the multidrug-resistant–associated protein or the organic anion transporters in humans, but differences have been reported in animal models and may have contributed to the findings of this study.[23]

The higher levofloxacin C_{max} observed in women can be attributed to a significantly smaller median V_c. Specifically, the pharmacokinetic analysis revealed that women have both smaller V_c and V_{ss} of levofloxacin, despite an average body mass index similar to that of the male study group. On average, women did weigh less than the men in this investigation, regardless of similar body mass indexes. Nonetheless, the total body weight–adjusted V_{ss} was significantly smaller (p<0.01) in women. However, the V_{ss} normalized to total body weight should be cautiously interpreted since a distinct relationship between V_{ss} and total body weight was observed in men versus women (Figure 4A). Total body weight, therefore, was not found to be the best size descriptor for normalization of levofloxacin V_{ss} between the sexes. Furthermore, normalization of levofloxacin V_{ss} to total body weight may have biased the conclusions of previous pharmacokinetic investigations of levofloxacin.[2, 24]

The estimate of lean body weight was the strongest predictor of V_{ss} in men and women combined. Furthermore, a similar relationship between lean body weight and V_{ss} was observed in men and women separately. Lean body weight differs from ideal body weight and is an estimation of bone, organ, and muscle tissue mass. Theoretically, ideal body weight can approach but never reach lean body weight in any given individual. It is not surprising that lean body weight was found to be a strong predictor of V_{ss} in men, women, and the combined sexes since fluoroquinolones distribute more rapidly and to a greater extent into lean muscle as opposed to adipose tissue.[2, 25–28] In fact, this property may in part explain the smaller V_c and subsequent larger C_{max} after levofloxacin administration in women compared with these parameters in men. Men on average have an increased amount of body water and an increased muscle mass:body fat ratio compared with women.[21] It would therefore be expected that men would have a greater tissue distribution of levofloxacin and subsequent lower serum concentrations than women, as observed in our study. These observations coupled with the differential predictive power of total body weight in men versus women lend strong support for a lean body weight normalization of levofloxacin V_{ss} for comparison between the sexes.

Women appear to be more susceptible to fluoroquinolone toxicity than are men, especially in the central nervous system.[3, 6, 29] Levofloxacin, however, is a fairly well tolerated fluoroquinolone with a low rate of adverse effects that occur in a concentration-dependent manner. Although increased serum levofloxacin concentrations may result in an increased rate of toxicity in women, fluoroquinolones are concentration-dependent bactericidal agents. Therefore, lower average serum concentrations and decreased levofloxacin exposure in men could result in inadequate antimicrobial activity against bacterial strains moderately susceptible to levofloxacin. This supports the performance of clinical investigations into the efficacy of levofloxacin in men versus women in a large population of patients.

Conclusion

Compared with men of a similar body mass index, women have a slower Cl_s and smaller V_{ss} of levofloxacin after intravenous administration. These differences lead to a greater drug exposure and higher C_{max}, respectively, in women. Lean

body weight had the strongest relationship with both Cl_s and V_{ss} in our study. Nevertheless, after normalization to lean body weight, V_{ss} remained significantly smaller in women, suggesting a difference in the pharmacokinetics. Therefore, fixed intravenous doses of levofloxacin will lead to higher C_{max} in women than in men. This may place women at an increased risk of fluoro-quinolone toxicity compared with men but also may necessitate larger doses in men to observe similar antimicrobial efficacy. Therefore, levofloxacin dosage adjustments based on sex or lean body weight should be considered on an individual basis depending on location of infection, susceptibility of the causative microorganism, patient's renal function, and risk for the development of fluoroquinolone toxicity.

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