Pharmacokinetics of Lomefloxacin in Renally Compromised Patients

ROBERT A. BLUM,1,2* ROBERT W. SCHULTZ,3 AND JEROME J. SCHENTAG1,2

Clinical Pharmacokinetics Laboratory1 and Department of Medicine,2 Millard Fillmore Hospital, Buffalo, New York 14209, and School of Pharmacy, State University of New York at Buffalo, Amherst, New York 14260

Received 8 May 1990/Accepted 9 October 1990

The single-dose pharmacokinetics of orally administered lomefloxacin (400 mg) were studied in normal subjects and in patients with various degrees of renal function. The subjects were classified by creatinine clearance (CLCR) normalized for body surface area: group 1, CLCR of >80 ml/min/1.73 m²; group 2, CLCR of 80 to >40 ml/min/1.73 m²; group 3, CLCR of 40 to >10 ml/min/1.73 m²; and group 4, CLCR of ≤10 ml/min/1.73 m². Each group consisted of eight subjects. The pharmacokinetics of lomefloxacin were significantly influenced by renal function. There were significant differences in the elimination rate constant, half-life, area under the concentration-time curve from 0 h to infinity, apparent total drug clearance, renal clearance, and apparent nonrenal drug clearance between the four renal function groups. Mean half-lives for groups 1, 2, 3, and 4 were 8.09, 9.11, 20.90, and 44.25 h, respectively. There were no significant differences between the renal groups for maximum concentration of the drug in serum and apparent volume of distribution. Age had no apparent effect on lomefloxacin disposition. There was a significant relationship between CLCR and lomefloxacin total body clearance (r = 0.92, P = 0.001) and renal clearance (r = 0.94, P = 0.001). Despite a predominate renal route of elimination, nonrenal lomefloxacin clearance significantly decreased with decreasing renal function (r = 0.72, P = 0.001). Mean lomefloxacin excretion rates over 48 h were 60.7, 56.8, 29.1, and 1.0% of the administered dose for groups 1, 2, 3, and 4, respectively. Mean glucuronide excretion rates over 48 h were 7.8, 6.3, 10.0, and 0.6% of the administered dose for groups 1, 2, 3, and 4, respectively. Hemodialysis had no effect on lomefloxacin concentrations in plasma. In patients with normal to moderate renal function, 400 mg of lomefloxacin per day should provide therapeutic concentrations in blood. The lomefloxacin dose should be reduced to 200 mg/day as the CLCR falls below 30 ml/min/1.73 m². No additional dosage adjustments appear to be necessary for hemodialysis patients.

Lomefloxacin is a difluorinated quinolone antimicrobial agent with a broad spectrum of activity against gram-negative and gram-positive bacteria (1, 9). Its antibacterial activity is similar to those of enoxacin, fleroxacin, norfloxacin, and ofloxacin (1, 10). Pharmacokinetic studies in normal volunteers showed that following oral administration, lomefloxacin is rapidly absorbed into the blood, distributed into peripheral tissues, and primarily excreted unchanged at high concentrations into urine (6, 8). Lomefloxacin has a half-life (t1/2) of approximately 7 to 8 h in normal volunteers (6, 8). Lomefloxacin renal clearance (CLR) has been estimated to be about 76% of total body clearance (6), suggesting that lomefloxacin accumulation may occur when renal excretory mechanisms are impaired. The purposes of this study were to determine the pharmacokinetics of lomefloxacin following a single 400-mg oral dose in patients with various degrees of renal function (ranging from normal to hemodialysis) and to determine whether hemodialysis causes any significant change in lomefloxacin disposition.

MATERIALS AND METHODS

Subjects. The investigation was an open-labeled single-dose study with 32 male and female volunteers. Four groups were used, with eight volunteers in each group. All four groups were predefined by protocol and were selected for groups to be of equal size. Initial creatinine clearance (CLCR) values were estimated by the Cockcroft and Gault equation (2). Body surface area was determined by the method of Dubois and Dubois (3). The four groups were eventually defined by endogenous CLCR normalized for body surface area: group 1, CLCR of >80 ml/min/1.73 m²; group 2, CLCR of 80 to >40 ml/min/1.73 m²; group 3, CLCR of 40 to >10 ml/min/1.73 m²; and group 4, CLCR of ≤10 ml/min/1.73 m². Study volunteers were between 18 and 65 years of age and within 15% of standard weight based on height, according to the Metropolitan Life Tables. Informed consent was obtained in writing prior to the start of the study. Volunteers were entered into the study on the basis of their physical examinations and medical histories, color perception tests, neurologic and ophthalmologic assessments, hematologies, plasma chemistries, urine tests, blood and urine drug screening, and electrocardiograms. Blood and urine tests were performed predose and 96 h postdose. Electrocardiogram, neurologic, and ophthalmologic examinations were obtained at -2 to 0 h predose and 2 to 4, 24 to 26, and 96 h postdose. Standing and supine blood pressure, respiration, and heart rate were obtained predose and at 2, 4, 12, 24, and 48 h postdose.

Drug administration and sampling. All subjects were confined to the Clinical Research Center under continuous supervision from 12 h before drug administration until 48 h after the dose. Subjects fasted for at least 10 h prior to receiving 400 mg of lomefloxacin orally. Blood specimens were collected predose and then at 0.33, 0.67, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48, 72, and 96 h postdose. Plasma, separated by centrifugation, was frozen at -20°C until analyzed. Urine was collected predose (-2 to 0 h) and over the intervals of 0 to 24 and 24 to 48 h postdose. Sample aliquots of the urine collection were frozen at -20°C until analyzed. Fresh urine was examined microscopically for crystals predose, on all voids made during the first 6 h, and 24 h postdose. Subjects were monitored for adverse effects and used diaries to record any subjective effects.

* Corresponding author.
Hemodialysis subjects had additional blood samples drawn at predialysis (48 h), the end of dialysis (52 h), and 4 h postdialysis (56 h). All dialysate fluid was collected, and an aliquot was analyzed for the drug. The dialyzer used was the Travenol 1211 (Baxter) with a surface area of 1.8 m². Blood flow rates ranged from 200 to 300 ml/min. Dialysate flow rate ranged from 500 to 550 ml/min.

Assays. Plasma, urine, and dialysate samples were measured by a sensitive and specific high-performance liquid chromatographic assay (7). All concentration values were reported as the lomefloxacin base. The interday coefficients of variation for lomefloxacin base in plasma, urine, and dialysate ranged from 4.3 to 10.2, 1.8 to 11.2, and 3.1 to 6.5%, respectively. The interday coefficients of variation for lomefloxacin glucuronide in urine ranged from 3.7 to 7.2%.

Pharmacokinetic analysis. Lomefloxacin pharmacokinetics were analyzed by noncompartmental methods (4). The elimination rate constant (kₐ) was determined by nonlinear regression analysis of the terminal elimination phase (4 to 96 h concentration points) with a weighting factor of 1/y². Concentration values during the elimination phase were fitted by a one-compartment model to determine kₐ. The corresponding tₑ/₂ was calculated as ln(2)/kₐ. Area under the concentration-time curve to infinity (AUC₀₋∞) was determined by the trapezoidal rule and by extrapolation of the terminal slope to infinity. Apparent total drug clearance (CL/F) was calculated as dose/AUC₀₋∞. CLₚ was calculated by dividing the amount of lomefloxacin excreted during a specified time by the AUC over the same time interval. Apparent nonrenal drug clearance (CLₚR/F) was determined as CL/F – CLₚ. All clearance values were standardized to 1.73 m². The apparent volume of distribution was determined as dose/(AUC₀₋∞ · kₐ).

Statistical analysis. Mean pharmacokinetic parameters and demographic data for each renal function group were compared by analysis of variance. Tukey's method of post-hoc multiple comparisons was used to compare mean values between two renal function groups. Linear correlations between various pharmacokinetic parameters and renal function effects were evaluated by simple linear regression analysis. Student’s t test was used to evaluate statistical significance. A P value of ≤0.05 was considered statistically significant.

RESULTS

A total of 32 subjects (18 males, 14 females) were enrolled in and completed the study. There were no statistically significant differences in mean age, height, weight, and body surface area between the four renal function groups. The predetermined renal groups 1, 2, 3, and 4 had CL_CR (mean ± standard deviations) of 94.6 ± 7.1, 66.2 ± 8.9, 24.7 ± 7.7, and 1.2 ± 2.3 ml/min/1.73 m², respectively. Serum creatinine values (means ± standard deviations) were 1.15 ± 0.26, 1.21 ± 0.42, 3.11 ± 1.05, and 11.09 ± 3.85 mg/dl, respectively. Mean lomefloxacin plasma concentration-versus-time curves for all four groups are shown in Fig. 1. Mean 24-h lomefloxacin concentrations were 0.23, 0.34, 1.3, and 2.0 μg/ml for groups 1 to 4, respectively.

Mean pharmacokinetic parameters are listed in Table 1. The elimination of lomefloxacin occurred primarily by the renal route. There were significant differences in kₐ, t₁//₂, AUC₀₋∞, CL/F, CLₚ, and CLₚR/F among the four renal function groups. There was a significant relationship between CL_CR and both CL/F and CLₚ (Fig. 2). Despite a predominate renal route of elimination, CLₚR/F significantly decreased with decreasing renal function (r = 0.72, P = 0.001). CLₚR significantly correlated with kₐ (r = 0.88, P = 0.001), t₁//₂ (r = -0.82, P = 0.001), and AUC₀₋∞ (r = -0.78, P = 0.001). There were no significant differences between the renal groups in the maximum concentrations of drug in serum (Cmax) and apparent volumes of distribution. The time to maximum drug concentration in serum increased as renal function decreased and showed borderline significance (P = 0.06). There was also a significant correlation between the time to maximum drug concentration in serum and CL_CR (r = -0.48, P = 0.01). Age had no effect on lomefloxacin disposition. Female subjects had a significantly higher Cmax (5.48 versus 4.28 μg/ml, P = 0.006) and lower volume of distribution (1.71 versus 2.25 liter/kg, P = 0.003) than the males. When Cmax was normalized to body weight, females had a significantly higher Cmax than males.

The mean cumulative urinary excretion of lomefloxacin is listed in Table 2. In renal function groups 1, 2, and 3, urine lomefloxacin concentrations exceeded 18 and 2.5 μg/ml in the 0-to-24-h and 24-to-48-h urine collections, respectively. There was a significant relationship between CL_CR and the amount of lomefloxacin excreted over 48 h (r = 0.92, P = 0.001).

There were no significant hemodialysis effects on lomefloxacin plasma concentrations postdialysis (1.09 ± 0.51 μg/ml) and 4 h postdialysis (1.09 ± 0.53 μg/ml). During each hemodialysis treatment (mean = 3.37 ± 0.38 h), only 1.0 to 5.2% (mean = 2.6% ± 1.4%) of the administered lomefloxacin dose was removed by the hemodialysis treatment. Lomefloxacin was well tolerated by all study subjects. No clinically significant adverse effects were noted, and no alterations of biochemical or hematological parameters were found. No drug crystals were found in the urine samples of any subjects.

DISCUSSION

The results of this study demonstrate that as expected for a drug whose primary route of removal is renal excretion,
Lomefloxacin clearance varies directly with the degree of renal function. The mean $t_{1/2}$ in this study was 8.1 h in normal-renal-function subjects as compared with 7.0 and 7.6 h in two previous reports (6, 8). These slight differences might be attributed to the higher mean age in our study population. In subjects with normal renal function, lomefloxacin has a longer $t_{1/2}$ than ciprofloxacin (9) and norfloxacin (12) and a $t_{1/2}$ similar to those of enoxacin (11) and ofloxacin (5). The lomefloxacin $t_{1/2}$ increased in relation to the degree of renal failure, with the $t_{1/2}$ being about twice the normal value in subjects with CLCR<sub>8</sub> of about 35 to 40 ml/min/1.73 m<sup>2</sup>, approximately 24 h in subjects with CLCR<sub>8</sub> of about 25 to 30 ml/min/1.73 m<sup>2</sup>, and about 2 days in anuric patients.

Lomefloxacin absorption and distribution were not significantly affected by renal function. Lomefloxacin was rapidly absorbed, with peak concentrations occurring between 0.9 and 1.75 h. There was an increase in the time to maximum drug concentration in serum with decreasing renal function. However, this was consistent with a decreased elimination rate for lomefloxacin, since there was no evidence for a decreased absorption rate in these patients. Mean $C_{\text{max}}$<sub>8</sub> ranged from 5.22 µg/ml for group 1 to 4.48 µg/ml for group 4 and were comparable to those obtained previously (6, 8). Mean 24-h lomefloxacin concentrations were 0.23 and 0.34 µg/ml in groups 1 and 2, respectively. In groups 3 and 4, therapeutic concentrations of lomefloxacin were detectable to 96 h, with the mean 24-h concentrations being 1.2 and 2.0 µg/ml, respectively. Since lomefloxacin is only 15% protein bound (10), sufficient free drug is still available at 96 h at concentrations to inhibit 90% of strains for the majority of susceptible members of the family Enterobacteriaceae.

The mean percentage of lomefloxacin recovered in the urine declined with decreasing renal function (Table 2). For subjects with normal renal function, the urinary recovery of parent lomefloxacin was in agreement with results from other investigators (6, 8). Excretion rates from urine and the cumulative amount excreted have been shown to increase in a dose-related fashion from 100- to 400-mg doses, although CL<sub>R</sub> decreased slightly at the 600- and 800-mg doses (6). Urinary recovery of lomefloxacin decreased with decreasing renal function, but concentrations of lomefloxacin in urine for groups 1, 2, and 3 exceeded 18 and 2.5 µg/ml in the 0-to-24-h and 24-to-48-h urine collections, respectively. These concentrations are above the MICs for susceptible strains of Escherichia coli, Morganella morganii, salmonellae, shigellae, Haemophilus influenzae, Neisseria gonorrhoeae, Branhamella catarrhalis, and legionellae (1).

The decrease in CL/F with decreasing renal function can

---

**TABLE 1. Pharmacokinetic parameters<sup>a</sup> of lomefloxacin after a single oral dose of 400 mg**

<table>
<thead>
<tr>
<th>Group</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$k_{d}$ (h&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>$t_{1/2}$ (h)</th>
<th>AUCC&lt;sub&gt;0-24&lt;/sub&gt; (µg·h/ml)</th>
<th>V/F (liters/kg)</th>
<th>CL/F (ml/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>CL&lt;sub&gt;R&lt;/sub&gt; (ml/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>CL&lt;sub&gt;EQ/F&lt;/sub&gt; (ml/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.22 ± 1.18</td>
<td>0.90 ± 0.29</td>
<td>0.091 ± 0.022</td>
<td>8.09 ± 2.20</td>
<td>27.9 ± 6.6</td>
<td>2.25 ± 0.30</td>
<td>229.2 ± 45.3</td>
<td>140.4 ± 35.6</td>
<td>88.7 ± 28.6</td>
<td>NS&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>4.54 ± 1.62</td>
<td>1.31 ± 0.83</td>
<td>0.084 ± 0.026</td>
<td>9.11 ± 3.43</td>
<td>34.3 ± 10.7</td>
<td>2.04 ± 0.57</td>
<td>192.7 ± 53.5</td>
<td>111.2 ± 28.9</td>
<td>81.5 ± 29.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>4.99 ± 0.92</td>
<td>1.36 ± 0.53</td>
<td>0.035 ± 0.008</td>
<td>20.90 ± 4.54</td>
<td>93.9 ± 43.2</td>
<td>1.93 ± 0.62</td>
<td>77.1 ± 25.4</td>
<td>28.4 ± 15.9</td>
<td>48.7 ± 13.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>4.48 ± 1.33</td>
<td>1.75 ± 0.60</td>
<td>0.07 ± 0.005</td>
<td>44.25 ± 14.02</td>
<td>208.6 ± 83.8</td>
<td>1.82 ± 0.58</td>
<td>33.8 ± 10.8</td>
<td>0.6 ± 0.8</td>
<td>33.2 ± 11.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup> $T_{\text{max}}$, Time to maximum concentration of drug in serum; V/F, apparent volume of distribution.

<sup>b</sup> NS, Not significant.
also decreasing renal function

turbation in Group
dosing is the renal excretion of lomefloxacin. For lomefloxacin’s excellent tissue penetration, females have a larger volume of distribution than males. These differences are not independent of renal function, which may account for differences in the volume of distribution.

On the basis of pharmacokinetic and antimicrobial activities, lomefloxacin dosage should be adjusted according to renal function. The volume of distribution of lomefloxacin is independent of renal function; thus, no loading-dose adjustment is required in patients with renal impairment. Proposed adjustments of the maintenance dose are based on multiple-dose simulations of steady-state plasma lomefloxacin concentrations and linear regression analysis of predicted Cmax and average and minimum concentrations values. Predicted steady-state Cmax and minimum concentration values were determined as the product of the observed single-dose value and the accumulation factor [\( R = 1/(1 - e^{-\tau CB}) \) where \( \tau \) was equal to 24 h]. Predicted mean concentrations at steady state were calculated as dose/W CL/F, where CL/F was obtained from the regression of CL/F to CLCR. Acceptable steady-state predictions for Cmax and mean and minimum concentration values were obtained by selecting a dose of 400 mg every 24 h when CLCR was greater than 30 ml/min/1.73 m2 and 200 mg every 24 h when CLCR was less than 30 ml/min/1.73 m2 (Fig. 3). Since the available data suggest good tolerance of lomefloxacin, especially at concentrations in plasma of less than 10 \( \mu \)g/ml (6), dose adjustment is recommended only for patients with severe renal impairment. In patients with a CLCR greater than 30 ml/min/1.73 m2, 400 mg once a day should provide peak concentrations of approximately 4 to 9 \( \mu \)g/ml and trough concentrations of approximately 0.25 to 2 \( \mu \)g/ml. In patients with CLCR below 30 ml/min/1.73 m2 and receiving 200 mg once a day, approximate peak and trough concentrations of 4 to 6 and 1 to 3 \( \mu \)g/ml, respectively, are expected. No additional dosage adjustments are necessary for hemodialysis patients.

In conclusion, lomefloxacin clearance is significantly affected by renal function, with renal excretion being the primary route of removal. In patients with normal to moderate renal function, 400 mg of lomefloxacin per day provides therapeutic and well-tolerated concentrations in plasma. Lomefloxacin doses should be reduced to 200 mg/day in patients with CLCR below 30 ml/min/1.73 m2. No additional dosage adjustments are necessary for hemodialysis patients.

Acknowledgment

This work was supported by a grant from G. D. Searle & Co., Skokie, Ill.

Literature Cited


---

TABLE 2. Cumulative urinary recovery of lomefloxacin and lomefloxacin glucuronide after a single 400-mg dose of oral lomefloxacin

<table>
<thead>
<tr>
<th>Group</th>
<th>Lomefloxacin at:</th>
<th>Lomefloxacin glucuronide at:</th>
<th>Total at 0-48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-24 h</td>
<td>0-48 h</td>
<td>0-24 h</td>
</tr>
<tr>
<td>1</td>
<td>54.1 ± 10.8</td>
<td>60.7 ± 10.8</td>
<td>7.2 ± 2.4</td>
</tr>
<tr>
<td>2</td>
<td>49.5 ± 10.4</td>
<td>56.0 ± 8.3</td>
<td>5.5 ± 1.7</td>
</tr>
<tr>
<td>3</td>
<td>21.0 ± 9.5</td>
<td>29.1 ± 11.5</td>
<td>7.4 ± 3.6</td>
</tr>
<tr>
<td>4</td>
<td>0.5 ± 0.6</td>
<td>1.0 ± 1.5</td>
<td>0.3 ± 0.4</td>
</tr>
</tbody>
</table>

FIG. 3. Simulations of steady-state Cmax (---) and mean (—), and minimum (——) concentration values at 400 mg every 24 h for CLCRs greater than 30 ml/min/1.73 m2 and 200 mg every 24 h for CLCRs less than 30 ml/min/1.73 m2. Micrograms.