Lomefloxacin Pharmacokinetics in Subjects with Normal and Impaired Renal Function

A. LEROY,[1]* J. P. FILLASTRE,[2] AND G. HUMBERT[3]

Departments of Biochemistry,[1] Nephrology,[2] and Infectious Diseases,[3] University of Rouen, Hôpital Charles Nicolle, 76031 Rouen, France

Lomefloxacin pharmacokinetics were investigated in 6 normal subjects and 24 uremic patients after a single oral dose of 400 mg. In subjects with normal renal function, the peak level in plasma averaged 3.5 ± 0.9 µg/ml (mean ± standard deviation) and was obtained at 1.3 ± 0.9 h. The absorption rate constant was 3.8 ± 1.6 h^{-1}. The terminal half-life was 7.77 ± 0.95 h. The apparent volume of distribution was 2.54 ± 0.66 liters/kg. Total body and renal clearances were 259 ± 83 and 200 ± 55 ml/min per 1.73 m^2, respectively. The percentage of the dose recovered unchanged in 48-h urine was 80.6 ± 2.8. In uremic patients, the terminal half-life increased in relation to the degree of renal failure: from 8 h in normal subjects to 38 h in severely uremic patients (glomerular filtration rate, <10 ml/min). Renal insufficiency did not significantly modify the peak level in plasma, the time to peak, the apparent volume of distribution, or the nonrenal clearance of lomefloxacin. The dialysis clearance of lomefloxacin was 54 ± 13 ml/min. Linear relationships were found between lomefloxacin pharmacokinetic parameters and glomerular filtration rate data. Dosage adjustments are necessary in uremic patients.

Lomefloxacin (SC-47111; NY-198) is a new difluorinated quinolone derivative characterized by a broad antibacterial spectrum. It has been shown to have activity against both gram-negative and gram-positive bacteria, including bacteria resistant to beta-lactam antibiotics and aminoglycosides (5, 9). The activity of lomefloxacin was roughly comparable to the activities of ofloxacin and norfloxacin but far exceeded that of pipemidic acid (5). The purpose of this study was to determine the pharmacokinetic parameters of lomefloxacin in subjects with normal and impaired renal function after a single oral dose of 400 mg.

(A part of this study was presented at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy in Los Angeles, Calif. [A. Leroy, G. Humbert, F. Borsa, and J. P. Fillastre, Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 54, 1988].)

MATERIALS AND METHODS

Subjects. Thirty subjects with no known susceptibility to quinolone derivatives participated in the study after ethical committee approval and written informed consent had been obtained. The characteristics of the subjects are given in Table 1.

Six adult male volunteers, aged from 24 to 33 years and weighing from 67 to 82 kg, were selected for the study. These subjects had no evidence of hepatic, hematological, or renal disease confirmed by physical examination and biological tests. Their renal function was normal, with a mean endogenous creatinine clearance (CL_{CR}) of 135 ml/min.

Twenty-four subjects had chronic renal impairment with stable CL_{CR}s during the previous 6 months. The subjects were divided into four groups on the basis of glomerular filtration rate (GFR), as determined by CL_{CR}: group 1 (mild renal impairment; $n = 6$), 32 to 65 ml/min; group 2 (moderate renal impairment; $n = 6$), 12 to 28 ml/min; group 3 (severe

renal impairment; $n = 6$), 4 to 9 ml/min; and group 4 (hemodialysis patients; $n = 6$).

It is to be noted that the normal volunteers were younger than all the uremic patients and had high CL_{CR}s.

Patients taking barbiturates, phenytoin, rifampin, antacids, and calcium salts were excluded from the study.

Study design. All subjects fasted overnight before the study and for 2 h after lomefloxacin administration. They were given a single oral dose of 400 mg of lomefloxacin. Two hours after dosing, all subjects had breakfast; thereafter, food and drink were available ad libitum.

Sampling. Blood samples were collected into VACUTAINER tubes containing lithium heparinate as anticoagulant.

From healthy subjects, blood samples were drawn at 0 and 30 min and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 32, and 48 h after the dose. Urine samples were collected during five periods: from 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 h after drug administration.

From uremic patients, blood samples were collected according to the degree of renal failure: at 58 and 72 h from group 1 and at 76 and 80 h from groups 2 and 3. Three to four urine samples were collected from 0 to 24, 24 to 48, 48 to 72, and 72 to 80 h.

With hemodialysis patients (group 4), the kinetic study was performed both off and on hemodialysis after a single oral dose of 400 mg of lomefloxacin. Blood samples were taken at 0 and 30 min and 1, 1.5, 2, 3, 4, 6, 8, 10, 24, and 48 h. Hemodialysis sessions started at h 48 and lasted 4 h. During dialysis, additional blood samples were obtained from the venous line of the dialyzer just prior to hemodialysis and 30 min, 1 h, and each hour thereafter to the end of the session. Two hours after the start of hemodialysis, blood samples were taken simultaneously from the arterial and venous lines of the dialyzer to calculate the extraction coefficient and dialysis clearance of the drug (CL_D). At this time, the ultrafiltration rate was noted; the hematocrit of these patients had been measured.

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* Corresponding author.

TABLE 1. Data on volunteers and patients[a]

Group and renal function[b]	Age (yr)	Wt (kg)	CL_{CR} (ml/min per 1.73 m^2)
Normal	28.2 ± 3.5	75.3 ± 4.8	134.6 ± 13.4
1, Mild renal impairment	59.0 ± 9.3	70.3 ± 6.1	47.3 ± 11.8
2, Moderate renal impairment	65.3 ± 8.3	82.2 ± 22.2	21.1 ± 6.5
3, Severe renal impairment	65.3 ± 7.6	67.7 ± 11.7	7.4 ± 1.8
4, Hemodialysis	55.8 ± 4.5	64.6 ± 8.6	—[c]

[a] Values are means ± standard deviations.

[b] There were six patients in each group, including the group with normal renal function.

[c] Anuric patients.

Hemodialysis was performed with a Cuprophanne membrane (1.2 m^2; Travenol CF 1511) with a constant blood flow rate of 300 ml/min and dialysate flow rates of 500 ml/min for four patients and 1,000 ml/min for the two other patients.

Plasma and urine samples were stored frozen at $-80°C$ until assay.

Assay technique. Concentrations of lomefloxacin in plasma and urine were measured by microbiological assay with *Escherichia coli* 1346 as the test strain. The medium used was antibiotic medium number 1 (Difco Laboratories) (pH 6.6). Standards were prepared with pooled human serum for plasma samples and with phosphate buffer (pH 7) for urine samples. No significant difference was observed in the antimicrobial activities of lomefloxacin measured in plasma or serum samples, so a pooled human serum without antibiotic could be used as the diluent of the plasma samples. The plates were incubated overnight at 37°C. The linear regression analysis of the standard calibration lines obtained by plotting the log antibiotic concentrations versus the zone diameters of inhibition indicated excellent linearity of the assay between 0.16 and 5.00 μg/ml. The sensitivity limit of the assay was 0.05 μg/ml. The coefficients of variation of the assay were 8% at 5 μg/ml and 10% at 0.16 μg/ml. CL_{CR} was measured. Blood and urine creatinine concentrations were assayed by the method of Jaffe.

Pharmacokinetic analysis. The pharmacokinetic analysis was performed by analysis of individual data and routine graphical methods (4).

The individual concentrations of lomefloxacin in plasma versus time were best described by a biexponential equation chosen on the basis of visual inspection and the F ratio test (1). The peak concentration in plasma (C_{max}) and the time to peak (T_{max}) reported were the experimental values. The apparent terminal elimination rate constant (k_{el}) was calculated by least-squares regression analysis on the terminal portion of the plasma concentration-time profile. The elimination half-life ($t_{1/2}$) was calculated from k_{el} ($t_{1/2} = \ln 2/k_{el}$).

The absorption phase was estimated by using the unweighted method of residuals, and the apparent absorption
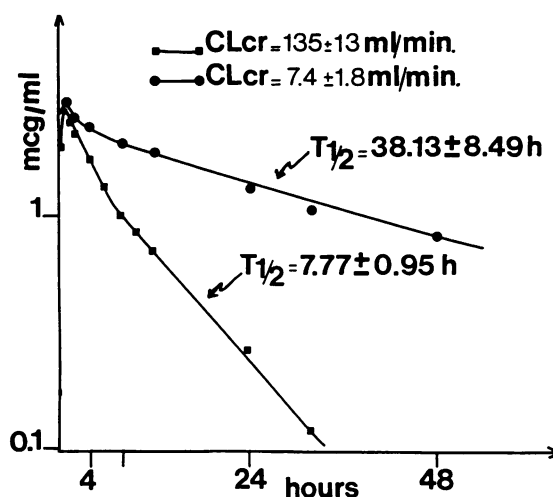

FIG. 1. Lomefloxacin plasma level-versus-time curves in subjects with normal renal function (■) and patients with severe renal impairment (●).

rate constant (k_a) was determined. The area under the plasma curve from 0 h to infinity ($AUC_{0-\infty}$) was calculated with conventional linear trapezoidal and extrapolation methods. Apparent total clearance (CL/F) of lomefloxacin was estimated from the following pharmacokinetic model-independent equation: CL/F = dose/$AUC_{0-\infty}$, where F is the bioavailability of lomefloxacin not determined in this study. Renal clearance (CL_R) was calculated by using the following relationship: $CL_R = X_u^{1-2}/AUC_{t1-t2}$, where X_u^{1-2} is the amount of lomefloxacin excreted in urine from times $t1$ to $t2$.

The apparent volume of distribution (V/F) was calculated by using the following relationship: $V/F = $ dose $/AUC_\infty \cdot k_{el}$.

CL_D was calculated by the method of Gotch (3): $CL_D = [Qp \cdot C_A - (Qp - Quf) \cdot C_V]/C_A$, where C_A and C_V are plasma lomefloxacin concentrations on arterial and venous lines, respectively; Qp is the plasma flow calculated by the relation Qp = Qb (1 − Hte) (Qb is the blood flow, and Hte is the hematocrit); and Quf is the ultrafiltration rate. The extraction ratio by hemodialysis (ERD) was calculated by the relation ERD = $CL_D/[Qp + (Qp - Quf)/2]$.

Statistical analysis. The analysis of variance test was used to determine the statistical significance of the pharmacokinetics in volunteers and in the four groups of uremic patients. A P value of <0.05 was considered to be statistically significant.

RESULTS

Normal subjects. The pharmacokinetic data for six healthy adult male volunteers receiving a single oral dose of 400 mg in the fasting state are shown in Table 2. The nonrenal

TABLE 2. Lomefloxacin pharmacokinetic data for subjects with normal and impaired renal function after a single oral dose of 400 mg[a]

| Subjects	C_{max} (μg/ml)	T_{max} (h)	AUC (μg · h/ml)	V/F (liters/kg)	k_a (h^{-1})	$t_{1/2}$ (h)	ml/min per 1.73 m^2 CL/F	ml/min per 1.73 m^2 CL_R	X_u^{48} (%)
Normal	3.47 ± 0.89	1.33 ± 0.88	25.7 ± 10.5	2.54 ± 0.66	3.78 ± 1.58	7.77 ± 0.95	259.0 ± 83.1	199.5 ± 54.9	80.6 ± 2.8
Group 1	4.71 ± 1.00	1.75 ± 1.21	95.8 ± 24.6	1.85 ± 0.19	3.44 ± 1.86	21.27 ± 4.59	74.6 ± 26.2	36.3 ± 20.8	38.3 ± 16.8
Group 2	3.88 ± 1.22	1.58 ± 0.80	102.0 ± 21.5	2.50 ± 1.05	3.93 ± 3.07	34.28 ± 13.66	60.6 ± 7.5	14.8 ± 8.2	15.7 ± 10.5
Group 3	3.97 ± 1.86	1.75 ± 1.41	114.5 ± 32.9	3.05 ± 0.91	3.99 ± 2.60	38.13 ± 8.49	59.6 ± 15.3	5.1 ± 1.5	5.5 ± 1.8

[a] Values are means ± standard deviations.
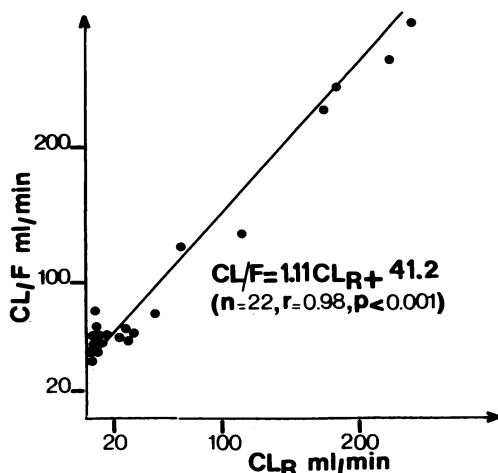
FIG. 2. Regression line between CL/F and CL_R of lomefloxacin after a single oral dose of 400 mg.
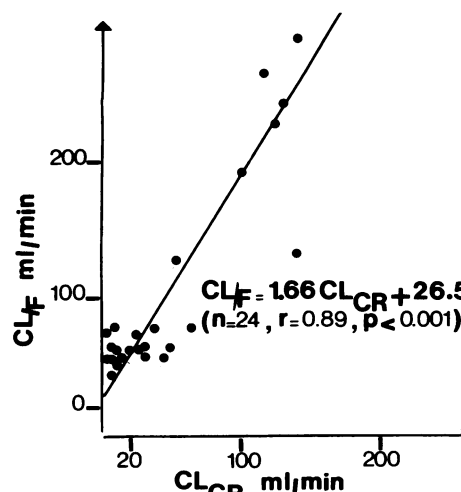

FIG. 3. Regression line between CL/F and CL_{CR} after a single oral dose of 400 mg.

clearance (CL_{NR}) was estimated to be 59.4 ± 33.1 ml/min per 1.73 m^2; i.e., 22 ± 6% of the total clearance.

Uremic patients. As renal function decreased, the apparent $t_{1/2}$ of lomefloxacin increased in groups 1, 2, and 3 (Table 2; Fig. 1). After the same dose as in normal subjects, the lomefloxacin C_{max} and T_{max} were not significantly modified in uremic patients ($P = 0.44$ and $P = 0.84$, respectively).

Renal impairment did not significantly modify the V/F in normal subjects and group 3 patients ($P = 0.10$). The k_as were not statistically different in normal subjects and uremic patients ($P = 0.98$).

The CL/F and CL_R of lomefloxacin decreased in relation to the degree of renal failure. The nonrenal clearance (CL_{NR}) of lomefloxacin (CL/F − CL_R) was statistically unchanged in subjects with normal and impaired renal function. CL_{NR}s were 59.4 ± 33.1 ml/min per 1.73 m^2 in normal subjects and 38.3 ± 15.8, 43.7 ± 4.9, and 51.2 ± 13.2 ml/min per 1.73 m^2 in group 1, 2, and 3 patients, respectively ($P = 0.39$). Urinary excretion of lomefloxacin decreased and was delayed in patients with renal failure.

Hemodialysis patients (group 4). For group 4 patients, the pharmacokinetic data of lomefloxacin were calculated both off and on hemodialysis.

During the first 48 h before hemodialysis, the following kinetic parameters were obtained: C_{max}, 4.10 ± 0.61 μg/ml; T_{max}, 0.75 ± 0.27 h; $t_{1/2}$, 29.71 ± 8.68 h; and CL/F, 64.2 ± 28.3 ml/min per 1.73 m^2.

During hemodialysis, the determination of lomefloxacin levels in both the venous and arterial lines 2 h after the start of dialysis allowed us to calculate the CL_D of lomefloxacin, which was 54.0 ± 13.2 (45 to 70) ml/min, and the extraction ratio by dialysis, which was 0.25 ± 0.06 (0.15 to 0.33).

DISCUSSION

Normal subjects. In normal subjects, the pharmacokinetic parameters of lomefloxacin found in our study are in good agreement with those reported by others (6, 8). In a previous study performed by Morrison et al. (6) with healthy subjects receiving five doses of lomefloxacin (100, 200, 400, 600, and 800 mg), lomefloxacin pharmacokinetics were found to be dose independent. The high urinary recovery of unchanged lomefloxacin suggests that nonrenal mechanisms account for no more than 15 to 25% of its elimination.

Uremic patients. The lomefloxacin $t_{1/2}$ increased in relation to the degree of renal failure, reaching values fivefold higher than those obtained in normal subjects, in patients with end-stage renal dysfunction in 38 and 8 h. However, the C_{max} and T_{max} remained unchanged whatever the degree of renal impairment. Linear relationships were established between lomefloxacin pharmacokinetic parameters and GFR data (Fig. 2 and 3).

From the relation between CL/F and CL_R (Fig. 2), the CL_{NR} of lomefloxacin could be evaluated as 41 ml/min per 1.73 m^2; i.e., about 15% of the CL/F in normal subjects. The present study showed that the concentrations of lomefloxacin measured in plasma after a single 400-mg dose remained above the MIC for most susceptible bacteria, i.e., ≤1 μg/ml, for 8 to 10 h in normal subjects and for 32 to 48 h in group 1, 2, and 3 patients. High concentrations of lomefloxacin found in 24-h urine in both normal subjects and uremic patients suggest that once-daily dosing should be sufficient to treat urinary infections caused by susceptible organisms.

In the treatment of systemic infections, dosage adjustments of lomefloxacin are necessary in relation to the degree

TABLE 3. Simulated lomefloxacin concentrations after multiple oral doses of 400 mg

Group	C_{min}[a] (μg/ml) at:			C_{max} (μg/ml) at:		
	12 h[b]	24 h	48 h	12 h	24 h	48 h
Normal subjects (GFR, >80 ml/min)	1.13			3.91		
Mild renal impairment (30 < GFR < 80 ml/min)	6.59	2.69	0.90	10.42	6.66	4.93
Moderate renal impairment (10 < GFR < 30 ml/min)	6.62	2.82	1.03	9.72	6.05	4.31
Severe renal impairment (GFR, <10 ml/min)	8.10	3.55	1.36	10.82	6.32	4.15

[a] C_{min}, Minimum concentration of drug in plasma.
[b] Time interval between doses.

of renal impairment, but no supplemental dosage seems to be necessary after a hemodialysis session. Multiple-dose simulated kinetics were determined from results obtained for each group of subjects studied. Trough levels and C_{max}s were calculated after 10 days of treatment with 400-mg doses given every 12, 24, or 48 h (Table 3).

In conclusion, lomefloxacin pharmacokinetics are characterized by a rapid absorption, a long $t_{1/2}$ ($\approx$8 h), and a large V/F. Lomefloxacin is almost exclusively excreted unchanged in urine (80 to 85%); thus, metabolism appears to occur to a lesser extent (<20%).

The important increase in $t_{1/2}$ of lomefloxacin observed in patients with chronic renal impairment requires dosage adjustments of lomefloxacin in relation to the degree of renal failure.

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