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Ofloxacin Pharmacokinetics in Renal Failure

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The pharmacokinetics of ofloxacin were investigated in 12 normal subjects and 21 uremic patients after the administration of a single oral 200-mg dose. An open three-compartment body model was used to calculate ofloxacin pharmacokinetic parameters. In healthy subjects, the peak plasma level averaged 2.24 ± 0.90 μg/ml and was obtained at 0.83 ± 0.31 h. The absorption rate constant was 4.22 ± 1.64 h^{-1}. The terminal half-life was 7.86 ± 1.81 h. The apparent volume of distribution was 2.53 ± 0.78 liters/kg. Total body and renal clearances were 241.4 ± 53.8 and 196.5 ± 42.9 ml/min per 1.73 m^2, respectively. A total of 68.4 ± 11.9% of the dose was recovered unchanged in 24-h urine. In uremic patients, the terminal half-life increased in relation to the degree of renal failure: from 8 h in normal subjects to 37 h in severely uremic patients. Renal insufficiency did not significantly modify the peak plasma level, the apparent volume of distribution, the fractional clearance, or the nonrenal clearance of ofloxacin. However, the time to peak level was delayed in patients with creatinine clearance of <30 ml/min. Linear relationships were found between ofloxacin pharmacokinetic parameters and glomerular filtration rate data. Ofloxacin is only very slightly removed by hemodialysis. Dosage adjustments of ofloxacin in uremic patients are proposed.

Ofloxacin is a new fluoroquinolone oral derivative characterized by a broad spectrum of activity against gram-negative and gram-positive bacteria, including obligate anaerobes. The activity of ofloxacin against *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and *Clostridium perfringens* was roughly comparable to that of norfloxacin and far exceeded that of pipemidic and nalidixic acids. Its activity against gram-positive aerobes was 4 to 16 times greater than that of norfloxacin (1, 6). Ofloxacin was well absorbed after oral administration and was excreted unchanged (70%) in urine.

The purpose of this study was to determine the pharmacokinetic parameters of ofloxacin in normal subjects and in patients with various degrees of chronic renal impairment after the oral administration of a single 200-mg dose.

MATERIALS AND METHODS

Subjects studied. Thirty-three subjects participated in the study, after informed written consent was obtained. Twelve subjects had normal renal function; 21 had chronic renal impairment to various degrees, with 5 patients being on hemodialysis. The 21 patients with chronic renal failure, ranging in age from 29 to 77 years and in weight from 50 to 105 kg, were divided into the four following groups on the basis of glomerular filtration rate, as determined by endogenous creatinine clearance (CL_{CR}): group I, mild renal impairment (n = 4), CL_{CR} > 40 ml/min; group II, moderate renal impairment (n = 7), CL_{CR} 20 to 39 ml/min; group III, severe renal impairment (n = 5), CL_{CR} < 20 ml/min; group IV, hemodialysis patients (n = 5). Characteristics of the subjects are given in Table 1.

Study design. All subjects fasted overnight before the study and for 2 h after ofloxacin administration. They were given a single oral dose of 200 mg of ofloxacin. Two hours after administration, all subjects had breakfast; thereafter, food and drink were ad libitum.

Sampling. In subjects with normal renal function, blood samples were drawn at 0, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after ofloxacin administration. Urine samples were collected during seven periods: from 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, and 36 to 48 h after administration.

In patients with renal impairment, blood samples were taken at 0 and 30 min and 1, 2, 4, 6, 10, 24, 34, and 48 h (for group I), 72 h (for group II), and 82 and 96 h (for group III). Four to six urine samples were collected according to the degree of renal failure: 0 to 6, 6 to 10, 10 to 24, 24 to 48, 48 to 72, and 72 to 82 h.

In the dialysis study, the oral 200-mg dose of ofloxacin was given 6 h before the beginning of hemodialysis. Blood samples were collected at the beginning of dialysis, 30 min, and 1 h and each hour thereafter up to the end of the dialysis session, which lasted 4 to 5 h. Hemodialysis was performed with 2308CF1511 dialyzers. The blood flow rate was 300 ml/min and the dialysate flow rate was 500 ml/min.

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

TABLE 1. Data on volunteers and patients

Renal function (n)	Mean ± SD		
	Age (yr)	Wt (kg)	CL_{CR} (ml/min per 1.73 m^2)
Normal (12)	27.7 ± 3.1	71.0 ± 6.2	119.6 ± 20.8
Mild renal impairment, group I (4)	58.0 ± 11.9	63.6 ± 11.5	45.0 ± 4.8
Moderate renal impairment, group II (7)	63.3 ± 8.2	72.4 ± 12.9	26.2 ± 4.4
Severe renal impairment, group III (5)	63.6 ± 13.3	74.4 ± 20.5	11.5 ± 3.0
Hemodialysis, group IV (5)	52.8 ± 16.6	61.9 ± 12.2	Anuric patients

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TABLE 2. Ofloxacin pharmacokinetic data in subjects with normal and impaired renal function after a single oral dose of 200 mg

Subjects	C_{max} (μg/ml)	T_{max} (h)	AUC (μg · h/ml)[a]	V/F (liters/kg)	k_a (h^{-1})	$t_{1/2}$ (h)	ml/min per 1.73 m^2		Urine, 24 h (%)
							CL/F	CL_R	
Normal	2.24 ± 0.90	0.83 ± 0.31	13.18 ± 3.12	2.53 ± 0.78	4.22 ± 1.64	7.86 ± 1.81	241.4 ± 53.8	196.5 ± 42.9	68.4 ± 11.9
Group I	2.18 ± 0.53	1.75 ± 1.66	32.33 ± 4.18	2.14 ± 0.50	4.13 ± 2.27	15.00 ± 4.40	109.4 ± 18.3	60.6 ± 9.3	37.7 ± 3.5
Group II	1.84 ± 0.32	2.36 ± 1.60	47.48 ± 14.00	2.15 ± 0.31	1.71 ± 1.41	25.37 ± 8.56	70.8 ± 15.9	30.9 ± 7.7	22.7 ± 6.2
Group III	1.71 ± 0.62	1.60 ± 1.34	65.98 ± 15.00	2.02 ± 0.26	2.80 ± 2.03	34.84 ± 15.46	50.6 ± 14.5	13.7 ± 6.2	11.8 ± 6.2
Group IV	1.97 ± 0.56	3.20 ± 2.59	86.05 ± 49.72	2.02 ± 0.37	2.35 ± 2.42	37.16 ± 23.26	49.2 ± 21.6		

[a] AUC, Area under the concentration-time curve.

Assay technique. Ofloxacin concentrations in plasma and urine were measured by microbiological assay, using *Klebsiella pneumonia* ATCC 10031 as the test strain. The lowest limit of sensitivity for the assay was 0.08 μg/ml. Dilutions were made in pooled human serum for plasma samples and in phosphate buffer (pH 6) for urine samples. The intra- and interrun coefficients of variation were 6.6 and 8.8%, respectively.

Pharmacokinetic analysis. Ofloxacin plasma concentration versus time curves were best fitted by using an open three-compartment body model, with first-order absorption. Pharmacokinetic parameters of ofloxacin were calculated by least-squares regression, using the residual values method (Apple IIe with printer Epson FX 80+) (4).

Statistical analysis. Comparison of the pharmacokinetic parameters of ofloxacin obtained after a single oral 200-mg dose in subjects with normal renal function and in the various groups of uremic patients was performed by using analysis of variance. The significance level was $P < 0.05$.

RESULTS

Normal subjects. In subjects with normal renal function, after a single oral dose of 200 mg, the mean peak plasma concentrations of ofloxacin (C_{max}) were 2.24 ± 0.90 μg/ml and were obtained at T_{max} i.e., 0.83 ± 0.31 h after administration. The terminal elimination half-life ($t_{1/2}$) was 7.86 ± 1.81 h. The absorption rate constant (k_a) was 4.22 ± 1.64 per h. The apparent volume of distribution (V/F), calculated from oral data, was inaccurate since ofloxacin bioavailability (F) could not be determined; it was 2.53 ± 0.78 liters/kg (i.e., about 120 liters). The total body clearance (CL/F) was 241.4 ± 53.8 ml/min per 1.73 m^2, and the renal clearance (CL_R) was 196.5 ± 42.9 ml/min per 1.73 m^2. A total of 68.4 ± 11.9%

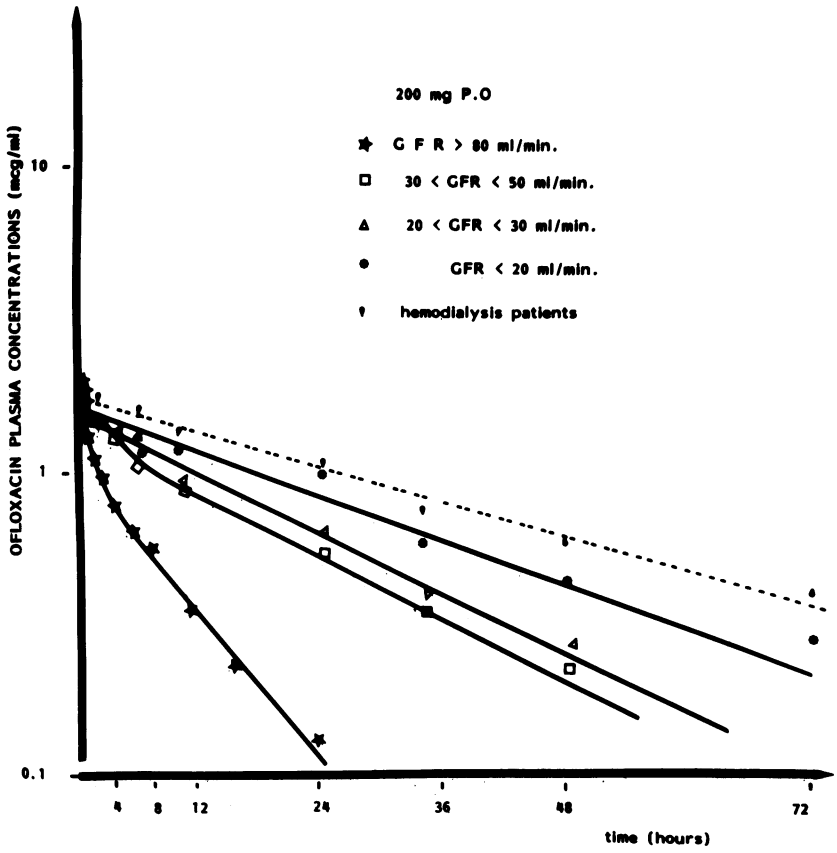

FIG. 1. Mean ofloxacin plasma concentration versus time curves in subjects with normal and impaired renal function. GFR, Glomerular filtration rate.

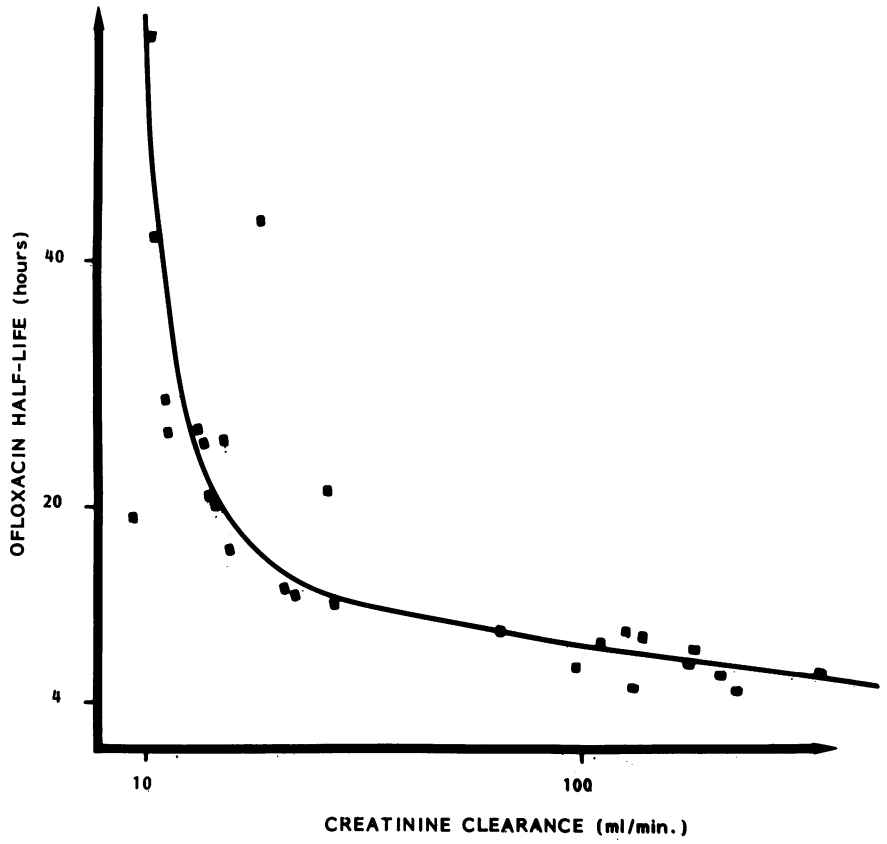

FIG. 2. Relation between ofloxacin half-life and creatinine clearance.

of the dose was recovered, in active form, in 24-h urine samples (Table 2).

Chronic renal impairment patients. Figure 1 shows representative mean graphs of the plasma concentration-time curves after the oral 200-mg dose in subjects with normal renal function and in uremic patients from each group. As renal function decreased, the average apparent elimination half-life of ofloxacin increased to 15.00 ± 4.40, 25.37 ± 8.56, 34.84 ± 15.46, and 37.16 ± 23.26 h in group I, II, III, and IV patients, respectively. After the same oral dose as in normal subjects, the mean peak plasma ofloxacin concentrations were not significantly different in uremic patients: 2.24 ± 0.90 μg/ml in healthy subjects and 2.18 ± 0.53, 1.84 ± 0.32, 1.71 ± 0.62, and 1.97 ± 0.56 μg/ml in groups I, II, III, and IV, respectively ($F_4/28 = 0.75$; $P > 0.10$). The time to peak level was delayed in patients with a glomerular filtration rate of <30 ml/min: 0.83 ± 0.31 h in normal subjects and 3.20 ± 2.59 h in hemodialysis patients ($P < 0.05$).

Renal impairment did not significantly modify the apparent volume of distribution of ofloxacin: 2.53 ± 0.78 liters/kg in healthy subjects and 2.02 ± 0.37 liters/kg in hemodialysis patients ($F_4/28 = 1.25$; $P > 0.10$). The absorption rate constant was not significantly different in normal subjects and uremic patients ($F_4/28 = 2.59$; $P > 0.10$). The total body clearance and the renal clearance of ofloxacin decreased in relation to the degree of renal failure: from 241.4 ± 53.8 to 49.2 ± 21.6 ml/min per 1.73 m^2 for the total body clearance and from 196.5 ± 42.9 to 13.7 ± 6.2 ml/min per 1.73 m^2 for the renal clearance (Table 2). However, the fractional clearance (ratio of renal clearance/creatinine clearance) and the nonrenal clearance were statistically unchanged in subjects with normal and impaired renal functions. The fractional clearance was 1.67 ± 0.38 in normal subjects and 1.35 ± 0.20, 1.21 ± 0.38, and 1.22 ± 0.55 in group I, II, III patients, respectively ($F_3/24 = 2.68$; $P > 0.10$). The extrarenal clearance of ofloxacin was 50.4 ± 16.2 ml/min per 1.73 m^2 in normal subjects and 48.8 ± 9.7, 39.9 ± 14.2, and 36.9 ± 11.2 ml/min per 1.73 m^2 in group I, II, and III patients, respectively ($F_3/24 = 0.86$; $P > 0.10$). Urinary excretion of ofloxacin decreased in patients with renal impairment: from 68.4 + 11.9% of the dose in 24-h urine in normal subjects to 11.8 ± 6.2% of the dose in patients with severe renal insufficiency (Table 2).

Hemodialysis patients. In hemodialysis patients, the same oral dose of 200 mg was given off hemodialysis and 6 h before hemodialysis. During hemodialysis, a slight decrease in ofloxacin plasma concentrations was noted, from 0 to 34.1% depending on the patient (mean ± standard deviation, 14.7 ± 12.8%). As with the other new quinolone derivatives, ofloxacin elimination by hemodialysis is negligible.

DISCUSSION

In healthy subjects, ofloxacin pharmacokinetic data are in good agreement with those reported by Lockley et al. (5): T_{max}, 1.2 ± 0.9 h; $t_{1/2}$, 7.0 ± 0.1 h; k_a, 2.9 ± 1.7 h^{-1}; 72.9% of the dose recovered unchanged in 24-h urine. In a previous study performed in healthy subjects receiving three single doses of 100, 200, and 400 mg, ofloxacin pharmacokinetics were found to be dose independent, and no metabolite was found in plasma and urine by high-pressure liquid chromatography (7; G. Humbert, F. Borsa, W. Couet, J. B. Fourtillan, M. Vincent du Laurier, and A. Bryskier, Proc. 14th Int. Congr. Chemother. S41-3, p. 179, 1985).

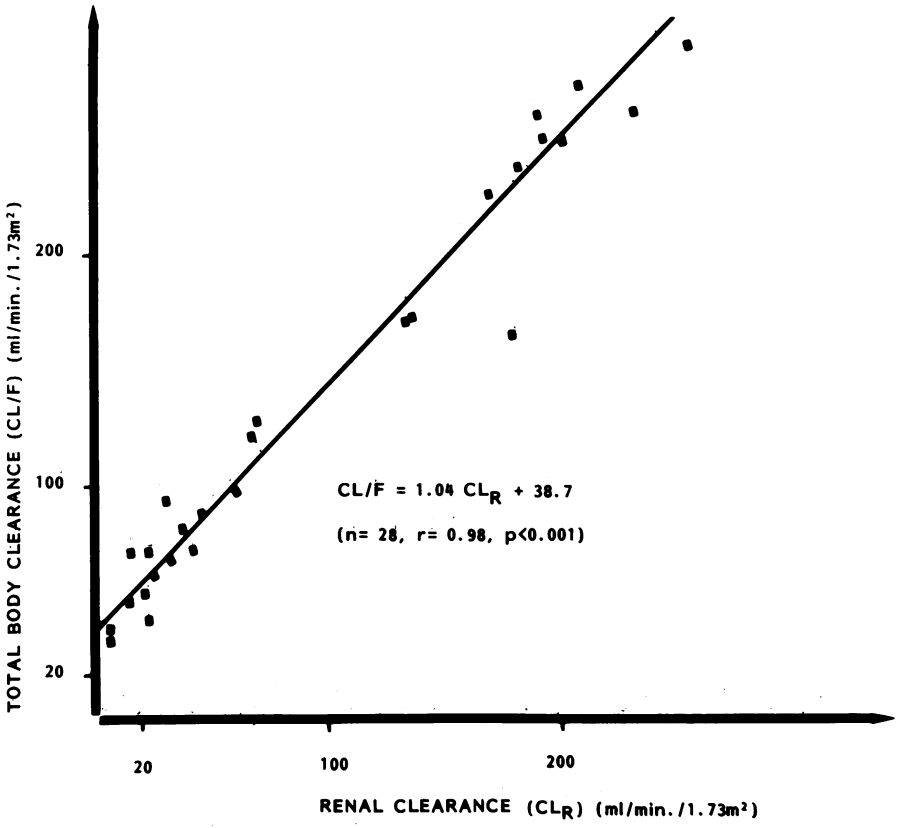

FIG. 3. Relationship between ofloxacin total body clearance and renal clearance.

In uremic patients, the ofloxacin half-life increased in relation to the degree of renal failure in patients with end-stage renal dysfunction, reaching values fivefold higher than those obtained in normal subjects: 37 and 8 h. This increase is particularly pronounced as soon as creatinine clearance falls below 20 ml/min (Fig. 2).

Linear relationships were found between ofloxacin pharmacokinetic parameters and glomeruler filtration rate data: $CL/F = 1.69\ CL_{CR} + 33.56$ ($n = 28$; $r = 0.91$; $P < 0.001$); $CL_R = 1.68\ CL_{CR} - 7.99$ ($n = 28$; $r = 0.95$; $P < 0.001$); $CL/F = 1.04\ CL_R + 38.73$ ($n = 28$; $r = 0.98$; $P < 0.001$). From the last relation (Fig. 3), the nonrenal clearance of ofloxacin could be estimated as 39 ml/min per 1.73 m^2, i.e., about 16% of the total body clearance.

TABLE 3. Simulated ofloxacin concentrations after multiple oral doses of 200 mg

Group[a]	C_{min} (μg/ml)			C_{max} (μg/ml)		
	12 h[b]	24 h	48 h	12 h	24 h	48 h
Normal subjects, GFR > 80 ml/min	0.54			2.60		
Mild renal impairment, 30 < GFR < 80 ml/min	2.33	0.92	0.26	4.02	2.68	2.05
Moderate renal impairment, 20 < GFR < 30 ml/min	2.74	1.13	0.35	4.13	2.59	1.85
Severe renal impairment, GFR < 20 ml/min	4.36	2.05	0.77	5.87	3.70	2.45

[a] GFR, Glomerular filtration rate.
[b] Time interval between doses.

Pharmacokinetic studies were performed for other new quinolone derivatives. Ciprofloxacin kinetics do not appear to be greatly modified by renal impairment; that is explained by the main extrarenal elimination of this drug (E. Singlas, A. M. Taburet, I. Landru, et al., Proc. 14th Int. Congr. Chemother., P37-84, p. 397, 1985). Norfloxacin is excreted both as unchanged drug (30%) and as metabolites. Thus, minor dosage adjustments are required only in severe renal impairment (2, 3).

Based upon pharmacokinetics and antibacterial activity (6), ofloxacin dosage should be adjusted to the degree of renal impairment. Multiple-dose simulated kinetics were performed from results obtained for each group of subjects studied. Minimal (C_{min}) and maximal (C_{max}) ofloxacin plasma concentrations were determined after 10 200-mg doses given every 12, 24, and 48 h (Table 3). The following dosage adjustments are proposed: in normal subjects, oral doses of 200 mg every 12 h should be sufficient to treat the most susceptible bacterial systemic infections, with a 400-mg dose given for less susceptible bacteria; in uremic patients, the same standard dose of 200 mg may be used every 24 h in patients with mild or moderate renal failure ($CL_{CR} > 20$ ml/min) and every 36 to 48 h in cases of severe renal impairment ($CL_{CR} < 20$ ml/min). No supplemental dosage of ofloxacin is necessary after hemodialysis, since ofloxacin elimination by hemodialysis was found to be negligible.

In conclusion, ofloxacin pharmacokinetics are characterized by prolonged plasma levels with a half-life of about 8 h. In healthy subjects, twice-daily administration should provide adequate treatment of most gram-negative and gram-positive bacterial infections. Dosage adjustment is required in patients with renal insufficiency.

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