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Pharmacokinetics and Biliary Concentrations of Fleroxacin in Cholecystectomized Patients

W. L. HAYTON,[1] V. VLAHOV,[2] N. BACRACHEVA,[2] I. VIACHKI,[3] R. PORTMANN,[4] G. MUIRHEAD,[5] K. STOECKEL,[4] AND E. WEIDEKAMM[4]*

College of Pharmacy, Washington State University, Pullman, Washington 99164-6510[1]; Clinical Pharmacology[2] and Clinic of Urgent Surgery, Center of Urgent Medicine,[3] Medical Academy of Sofia, 1040 Sofia, Bulgaria; Department of Clinical Research, F. Hoffmann-La Roche Ltd., CH-4002 Basel, Switzerland[4]; and Department of Pharmacokinetics and Metabolism, Roche Products Ltd., Welwyn Garden City, Herts AL7 3AY, Great Britain[5]

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Patients with biliary tract infections received 800 mg of fleroxacin orally once daily on five consecutive days; cholecystectomy was on day 3. Starting on the day when dose 5 was administered, serial blood and T-drain bile samples were taken for 72 h and urine was collected for 96 h. The mean (± the standard deviation) peak concentration in plasma was 8.2 ± 4.0 mg/liter at 8.3 h. The harmonic mean elimination half-life was 10.5 h, which is comparable to that reported for healthy volunteers. This increase resulted from reduced renal clearance (mean [± standard deviation], 38 ± 22 ml/min), as the volume of distribution in the patients (1.4 ± 0.7 liter/kg) did not differ from that reported for healthy subjects. Maximum concentrations in T-drain bile were high (median, 22.1 mg/liter) and exceeded those measured in plasma by a factor of 2 to 3; the individual ratios of the area under the curve for bile divided by that for plasma ranged from 1.3 to 9.9. As observed in healthy volunteers, the major pathway for elimination of fleroxacin was via the kidneys. The fraction of dose 5 eliminated in the 0- to 24-h urine was reduced, however, and the fraction of the dose in the urine as the *N*-demethyl and *N*-oxide metabolites was elevated. At the dose regimen used in this study, the MICs for most pathogens that cause biliary tract infections were surpassed in plasma and bile for more than 24 h.

Oral treatment of serious and resistant bacterial infections was considerably improved by introduction of fluorinated 4-quinolones during the past decade (18). These new anti-infective agents provided high in vitro activity against a broad spectrum of gram-positive and gram-negative bacteria, and their clinical efficacy was impressive (3, 11, 14, 15).

A relatively new addition to this group of antibiotics is fleroxacin. In healthy volunteers, fleroxacin was completely absorbed after oral administration (22). The peak concentration in plasma averaged 4.36 mg/liter after a 400-mg dose (n = 12, standard deviation [SD] = 1.15), which surpassed for more than 24 h the MIC for 90% of strains of a broad spectrum of fleroxacin-susceptible pathogens. Within 2 to 3 days, 50 to 60% of the dose was recovered from the urine as unchanged drug; in addition, 10 to 20% was renally excreted as the *N*-demethyl and *N*-oxide metabolites (21). The remaining portion of the dose was found in the feces, almost completely as unchanged drug (23). This fecal fraction was probably excreted via bile and/or gastrointestinal secretion.

In the present study, the plasma and urinary pharmacokinetics of fleroxacin were investigated in cholecystectomized patients at steady state by using a regimen of 800 mg orally once a day. In addition, concentrations of unchanged drug and the two metabolites in T-drain bile were determined. Pharmacokinetic parameters for fleroxacin were changed only slightly compared with those reported for normal subjects. Biliary concentrations exceeded the corresponding concentrations in plasma and were adequate for prophylaxis or treatment of biliary tract infections of fleroxacin-susceptible pathogens.

* Corresponding author.

MATERIALS AND METHODS

Clinical part. Nine subjects undergoing cholecystectomy and fulfilling the criteria for inclusion were consecutively enrolled for pharmacokinetic evaluation and T-drain bile sampling. Patient characteristics, serum chemistry of hepatic and renal functions, diagnoses, and comedications are listed in Table 1. Study approval was obtained from the local institutional ethics committee, and written informed consent was obtained from each participant. Each patient received 800 mg of fleroxacin with 150 ml of tap water on an empty stomach in the morning on five consecutive days; surgery was on day 3. Blood was collected by using glass VACUTAINER containers containing potassium/ammonium-oxalate as an anticoagulant. Samples were taken immediately before and 20 and 40 min and 1, 2, 3, 4, 6, 8, 12, 24, 30, 36, 48, and 72 h after administration of the last dose (dose 5). Plasma was separated by centrifugation at 1,000 × g for 15 min and stored at −20°C until analysis. The complete urine was collected over the intervals 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, and 72 to 96 h after the last dose. In addition, a predose sample was taken. T-drain bile samples were collected at the same intervals for up to 72 h. As fleroxacin is light sensitive, appropriate precautions (use of brown glassware and aluminum foil) were taken during collection, preparation, and measurement of samples.

Assay procedure. The concentrations of fleroxacin and its *N*-demethyl and *N*-oxide metabolites were measured by reverse-phase ion pair high-performance liquid chromatography (7). All three species were determined in urine and bile; in plasma, only fleroxacin was determined. Plasma samples were mixed with trichloroacetic acid, and the precipitated protein was subsequently removed by centrifugation. An aliquot of the supernatant was diluted with the

TABLE 1. Subject characteristics, blood chemistry data, diagnoses, and other medications

Subject no.	Age (yr)	Sex[a]	Wt (kg)	Ht (cm)	Albumin concn (g/liter)		Serum creatinine concn (μM)		Urea concn (mM)		Alanine aminotransferase activity (U/liter)	
					Before treatment	Post-treatment (35–55)[b]	Before treatment	Post-treatment (44–134)	Before treatment	Post-treatment (1.7–8.2)	Before treatment	Post-treatment (12–34)
1	31	M	70	167	41	45	173.3	165.0	6.5	5.8	19	9
2	58	M	78	171	49	44	160.0	182.1	7.2	6.0	10	57
3	62	F	70	164	41	31	258.7	586.1	7.1	5.1	11	13
4	45	F	78	150	39	37	148.8	140.1	5.2	8.9	6	72
5	51	M	79	179	42	44	138.0	195.0	5.3	9.8	29	12
6	42	F	65	156	41	42	168.3	140.0	5.9	5.6	12	11
7	25	F	53	167			108.7	68.0	5.4	5.0	8	3
8	36	M	83	175			108.0	88.4	6.7	9.7	31	86
9	43	F	100	157			74.0		4.5		11	

[a] M, Male; F, female.
[b] Normal ranges are shown in parentheses.

mobile phase and chromatographed. Urine samples to which pipemidic acid was added were mixed with the mobile phase before chromatography. A Toyo Soda ODS-120 T 5-μm column was used, and detection was made by fluorescence measurement (excitation, 290 nm; emission, 450 nm). The mobile phase was a mixture of 5 mM tetrabutylammonium hydrogen sulfate (aqueous solution) and methanol (72:28, vol/vol). Under these conditions, the retention times for the parent drug, the internal standard, the *N*-demethyl metabolite, and the *N*-oxide metabolite were 9.8, 8.0, 11.7, and 14.9 min, respectively. The interassay precisions (relative standard deviations) were 5.6, 1.6, and 1.6% for the parent substance, the *N*-demethyl metabolite, and the *N*-oxide metabolite, respectively. The response was linear within the range of 0.5 to 50 ng of injected material (fluorescence). The limits of quantification were 20 and 500 ng/ml for plasma and urine, respectively. Recovery of fleroxacin from plasma was 81% (range, 0.01 to 5 mg/liter), and from urine it was 86% (range, 10 to 100 mg/liter). Bile samples were diluted 1 in 10 with the mobile phase and then vortexed. The samples were then centrifuged to remove any particulate matter before chromatography. The mobile phase consisted of tetrahydrofuran–0.05 M triethylamine phosphate buffer, pH 2.8 (ratio, 19:81), containing the ion pair agent octanesulfonic acid (0.15%). With a flow rate of 2.3 ml/min, the retention times of the parent drug, the internal standard, and the *N*-demethyl and *N*-oxide metabolites were approximately 7.2, 9.2, 10.6, and 11.6 min, respectively. The standard ranges were 1 to 200 mg/liter for fleroxacin, 0.1 to 20 mg/liter for the *N*-demethyl metabolite, and 0.1 to 20 mg/liter for the *N*-oxide metabolite. For all three substances, the interassay precision was better than 4% over the concentration ranges given.

Pharmacokinetic evaluation. The plasma concentration-versus-time curves for each subject were plotted on semilogarithmic coordinates. The beginning of the terminal elimination phase was determined by eye. The log linear segments were fitted by using nonlinear least squares (ELSFIT) and a weighting function of $1/y$. The elimination rate constant (β) was calculated as $-2.3 \cdot$ slope; the half-life ($t_{1/2}$) was calculated as $\ln 2/\beta$. Peak concentrations (C_{max}) and the times of their occurrence (T_{max}) were estimated from the observed data. The area under the plasma-time profile (AUC) was obtained by the trapezoidal method (8). As sample collection started after dose 5, when steady-state conditions would have been reached (about 8 half-lives), the AUC during one dosing interval (i.e., from 0 to 24 h after dose 5) was used. In principle, this value should be identical to the $AUC_{0-\infty}$ after a single administration of the same dose. The apparent total systemic clearance was calculated as CL_S/F = dose/AUC, where F represents the absolute bioavailability, and total renal clearance was calculated as $CL_R = (CL_S/F)(F \cdot f_e)$, where $F \cdot f_e$ is the fraction of the dose excreted in the urine during the 24 h after the last dose. The apparent volume of distribution (V_β/F) was calculated by the formula $CL_s/F \cdot \beta$. AUC_{bile} was determined by the trapezoidal method after plotting the bile concentration versus the midpoints of the respective sampling intervals. For calculation of the AUC_{bile}/AUC_{plasma} ratio, the corresponding areas for 0 to 36 h were taken. The mean ± the SDs of the pharmacokinetic and bioavailability parameters were calculated, except for the biliary concentrations of fleroxacin and its metabolites. These values were characterized by their median because of the wide range of values observed and their nonnormal distribution.

RESULTS

Adverse events related to the trial drug were reported by 3 of 15 subjects. These three reported nausea and vomiting, fever, and infection at the operation site. A fourth subject experienced tachycardia during surgical intervention; this was considered by the sponsor to be a potentially serious adverse event but unrelated to trial treatment.

The patients generally had normal enzyme activities (except for elevated γ-glutamyltransferase) despite their disease

TABLE 1—*Continued*

Aspartate aminotransferase activity (U/liter)		γ-Glutamyltransferase activity (U/liter)		Total bilirubin concn (μM)		Diagnosis	Other medications
Before treatment	Post-treatment (12–29)	Before treatment	Post-treatment (0–28)	Before treatment	Post-treatment (3.4–21)		
12	7	135	118	13.6	12.3	Cholecystitis chronica calculosa	Alvesin, lidocaine, clemastine, drotaverine, galanthamine, bromhexine
20	76	109	98	26.2	17.1	Cholecystitis chronica calculosa	Alvesin, dipiridamolum, bisacodylum, galanthamine, metamizole
11	13	84	96	10.2	11.6	Echinococces hepatitis, choleystitis chronica calculosa	Cephalexin, metamizole, pethidine
7	39	33	90	13.6	11.4	Cholecystitis chronica calculosa	Dipiridamolum, metamizole, pethidine, bromhexine
20	22	80	160	18.6	34.1	Cholecystitis acuta, empyema vesicae felleae	Alvesin, dipiridamolum, metamizole, aprotinine
10	8	80	73	11.4	10.5	Cholecystitis acuta	Dipiridamolum, bromhexine, pethidine, tinidazole
11	5	17	32	7.0	11.3	Cholecystitis calculosa acuta, biliopancreatitis acuta	Dipiridamolum, alvesin, galanthamine, bromhexine, metamizole, aprotinine
26	22	28	127	18.1	14.7	Cholecystitis acuta calculosa phlegmonosa	Papaverine hydrochloride, alvesin, gentamicin, oxacillin, bromhexine, metamizole, pethidine, scopolamine, butylbromide
8		14		11.4		Cholecystitis chronica calculosa	Acenocoumarol, piritramide

state (cholecystitis); their bilirubin, albumin, and urea concentrations were within the normal range (Table 1). Serum creatinine concentrations were elevated in six of nine patients and were extremely high in patient 3. Several patients were discharged from the hospital after dose 3, as their disease condition was sufficiently improved; they were afebrile, and cholecystectomy was no longer necessary.

Approximately 8 h after the last dose, a mean (± SD) C_{max} of 8.2 ± 4.0 mg/liter was observed (Fig. 1; Table 2). The values of the pharmacokinetic parameters measured are shown in Table 2. Semilogarithmic plots of mean urinary excretion rate versus time were linear and parallel to the mean plasma profile in the postdistributive phase; T-drain biliary excretion rates were more variable but tended to parallel the plasma concentration and urinary excretion rate profiles (Fig. 1).

During the 24 h after the last dose, 33.6 ± 6.8% of the dose was excreted unchanged into the urine (Fig. 2); the corresponding values for the *N*-demethyl and *N*-oxide metabolites were 8.2 ± 2.9 and 6.1 ± 4.7%, respectively. Approximately 3 days passed before urinary excretion of fleroxacin and its metabolites was complete (Fig. 2).

Varying recovery of fleroxacin in T-drain bile was observed during the 24 h after the last dose; these values ranged from a low of 0.06% to a single extreme value of 16.5% of the dose; the mean (±SD) was 2.7 ± 5.0%. The corresponding values were 0.051 ± 0.079 and 0.138 ± 0.167% for the *N*-demethyl and *N*-oxide metabolites, respectively (Fig. 3). In contrast to the urinary elimination, biliary elimination was minimal after about 10 h.

Fleroxacin and its metabolites reached higher concentrations in bile than in plasma. For the unchanged drug, the median maximum concentration was 22.1 mg/liter; for the *N*-demethyl metabolite it was 2.01 mg/liter, and for the *N*-oxide metabolite it was 6.13 mg/liter. In patients 3 and 5, extremely high maximum concentrations in bile were determined: 374 mg/liter during the 2- to 4-h collection interval and 1,110 mg/liter during the 0- to 1-h interval. The AUC_{bile}/

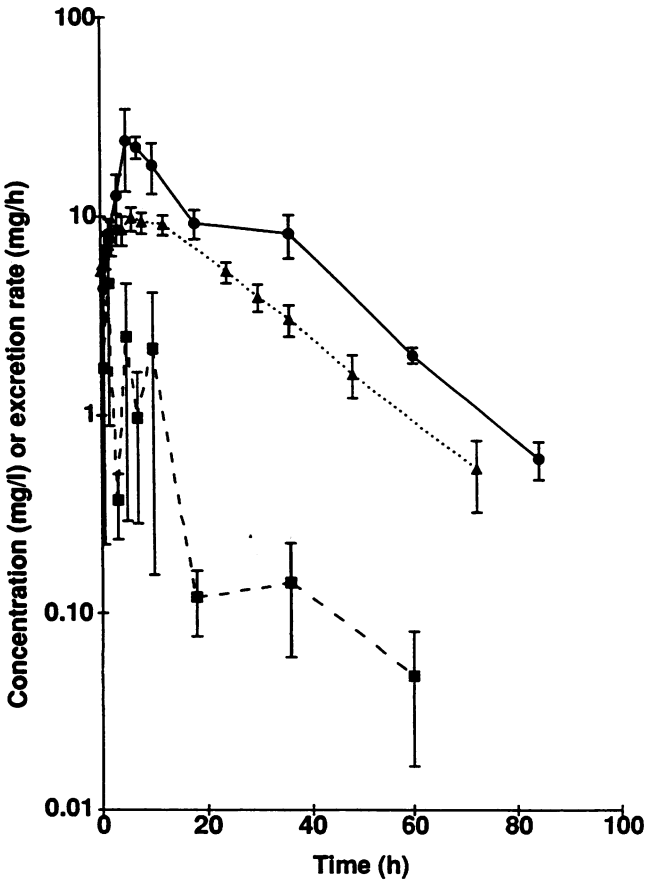

FIG. 1. Mean fleroxacin concentration in plasma (▲), urinary excretion rate (●), and biliary excretion rate (■) versus time after the fifth daily 800-mg oral dose. Each point represents the mean of nine determinations, and the bars show standard errors.

TABLE 2. Pharmacokinetic parameters of fleroxacin after multiple daily doses of 800 mg

Subject no.	C_{max} (mg/liter)	T_{max} (h)	$t_{1/2}$ (h)	AUC (mg · h/liter)	CL_S/F (ml/min)	CL_R (ml/min)	V_β/F (liters/kg)	AUC_{bile}/AUC_{plasma} (0–36 h)
1	14.0	4.0	8.5	229.3	58.2	—[a]	0.73	4.14
2	8.42	12.0	10.3	248.3	53.7	—[a]	0.93	2.61
3	8.13	6.0	13.6	257.7	51.7	20.3	0.83	4.92
4	4.25	12.0	16.9	125.7	106.1	30.0	2.29	1.33
5	3.74	12.0	29.6	217.8	61.2	14.9	1.87	9.85
6	8.53	3.0	11.0	161.1	82.8	25.9	1.57	2.79
7	10.0	12.0	5.6	149.1	89.4	38.0	1.12	1.65
8	13.7	6.0	8.4	230.3	57.9	61.4	0.62	—[b]
9	3.16	8.0	10.8	65.1	204.8	73.1	2.27	3.84
Mean ± SD	8.21 ± 4.0	8.3 ± 3.7	10.5[c]	187.2 ± 65.3	85.1 ± 48.6	37.7 ± 21.7	1.36 ± 0.66	3.89 ± 2.70

[a] —, No urine production.
[b] —, No bile production.
[c] Harmonic mean.

AUC_{plasma} ratio ranged from 1.3 to 9.9, with a mean (±SD) value of 3.89 ± 2.70 (Table 2).

Bile flow was measured over 72 h and showed large inter- and intrasubject variations. In seven subjects, the maximum bile flow did not exceed 40 ml/h; however, subject 3 showed a single peak flow of 90 ml/h, and in subject 5, flow values of 60, 80, and even 210 ml/h were measured 6 to 12 h after the last dose was administered. This flow behavior is typical of bile collection via a T drain, which is incomplete, may vary considerably with time, and may show pronounced fluctuations.

DISCUSSION

In comparison with healthy volunteers (6, 9, 13, 16, 20–22), the patients included in this study revealed reduced values for CL_S and CL_R. This finding may reflect the overall reduction of the patients' physiological condition due to their disease state and the influence of anesthesia and surgery. Nonrenal clearance ($CL_S - CL_R$) was generally unchanged in these patients. Since V_β was similar to that found in healthy volunteers, the reduced CL_R caused the increased $t_{1/2}$ in the patients. The observed decrease in CL_R was comparable to that reported for patients with similar degrees of renal impairment (19). The increased AUC also resulted from impaired renal excretory function in the postoperative period. Despite the increased AUC, the C_{max}s were lower than normal and the time required to reach these maxima was prolonged by a factor of about 7. A probable explanation is a reduced rate of absorption in the patients, perhaps as a result of reduced gastrointestinal motility after abdominal surgery. Because the reduced CL_R accounts for the increased AUC, it appears that the extents of fleroxacin absorption are similar in patients and healthy subjects.

The percentage of the dose recovered from bile as unchanged drug was less than 1% in six patients. In some instances (subjects 2, 3, and 5), a larger fraction of the dose, up to 16.5%, was recovered. The biliary recovery values reported here do not reflect the values found for healthy subjects, as only a fraction of the bile was obtained by the T-drain method and biliary excretion of fleroxacin may have been impaired by the underlying biliary tract disease.

The intersubject variability in the AUC_{bile}/AUC_{plasma} ratio may have been due to physiological variations in the biliary secretion transport process or variations in the bile volume produced or collected. No correlation between bile flow and the AUC_{bile}/AUC_{plasma} ratio was found. The AUC_{bile}/AUC_{plasma} ratio was higher than 1 and reflected the high fleroxacin concentrations in bile, which exceeded by far, under the applied regimen of 800 mg/day orally, the MICs for

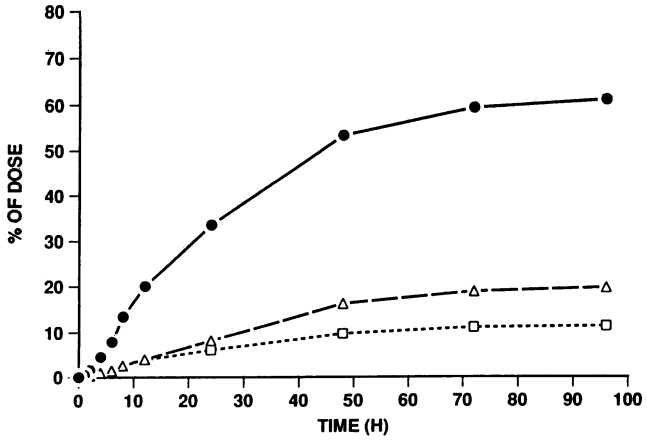

FIG. 2. Mean cumulative urinary excretion of fleroxacin (●), *N*-demethylfleroxacin (△), and the *N*-oxide metabolite (□) versus time after the fifth daily 800-mg oral dose. Each point represents the mean of nine determinations.

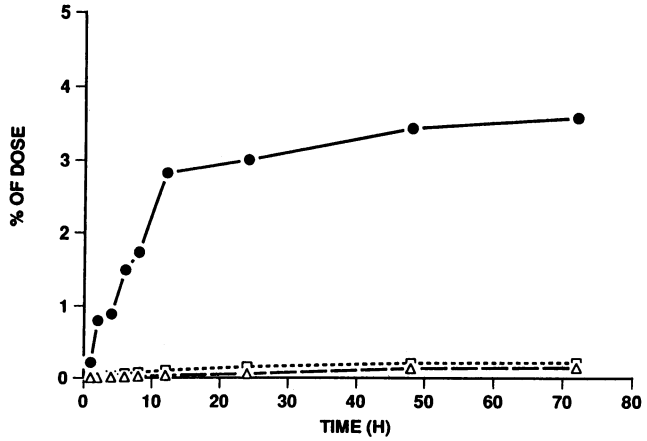

FIG. 3. Mean cumulative biliary excretion of fleroxacin (●), *N*-demethylfleroxacin (△), and the *N*-oxide metabolite (□) versus time after the fifth daily 800-mg oral dose. Each point represents the mean of nine determinations.

TABLE 3. Bile concentration (maximum) and bile/plasma concentration ratios for quinolone antibiotics

Antibiotic	Dose (mg)[a]	No.	Bile source	Bile concn (mg/liter)	Bile/plasma concn ratio	Reference
Ciprofloxacin	500, sd	12	T drain	16	8	2
	750, sd	7	Bladder		49	5
	200, sd	6	Duct	5.7		17
	500, bid	6	Bladder	5.4		17
Enoxacin	400, sd	13	Duct		10.5	Flowerdew et al.[b]
Fleroxacin	800, qd	9	T drain	22.1	3.9	This study
Lomefloxacin	200, sd	3	T drain	9.3		Tanimura et al.[c]
	200, sd	10	Bladder	11–35		Tanimura et al.
Norfloxacin	400, sd	10	Bladder	8.1	7.0	4
Ofloxacin	200, bid	6	T drain	12.0	2.2	10
	200, bid	6	Bladder	24.6	9.5	10
	500, sd	18	T drain	>10		Maruyama et al.[d]
Pefloxacin	800, sd	3	T drain	>20	2–5	12

[a] sd, Single dose; qd, once a day; bid, twice a day.
[b] A. Flowerdew, E. Walker, and S. J. Karran, Proc. 14th Int. Congr. Chemother., p. 1739–1740, 1985.
[c] H. Tanimura, K. Uchiyama, N. Kobayashi, K. Yoshida, and K. Ozawa, Proc. 15th Int. Congr. Chemother., abstr. no. 284, p. 151, 1987.
[d] K. Maruyama, H. Tanimura, N. Kobayashi, S. Mukaihara, and T. Saito, Proc. 14th Int. Congr. Chemother., p. 1811–1812, 1985.

90% of the strains of most pathogens causing biliary tract infections. The mean bile/serum ratio of fleroxacin concentrations and the biliary concentrations of the drug were comparable to the corresponding values of other fluorinated quinolones (1, 14) (Table 3).

In conclusion, effective concentrations of fleroxacin were observed in the bile and plasma of cholecystectomized patients after 800-mg oral doses administered once a day. Compared with normal subjects, the absorption rate of fleroxacin was reduced and the elimination half-life varied between 6 and 30 h. These alterations in fleroxacin pharmacokinetics were not so large as to require alteration of the usual dosage regimen.

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