

Pharmacokinetics of Fleroxacin after Multiple Oral Dosing in Patients Receiving Regular Hemodialysis

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The pharmacokinetic profile of fleroxacin was studied in eight noninfected patients receiving regular hemodialysis (four women and four men; mean age, 63 years; age range, 48 to 73 years). Dialysis clearances (mean \pm standard deviation) calculated from the amount of drug recovered in the dialysate exceeded those calculated from rates of extraction from plasma for fleroxacin (126 ± 29 versus 73 ± 11 ml/min) and its metabolite *N*-demethylfleroxacin (103 ± 31 versus 72 ± 15 ml/min) but not that for the metabolite fleroxacin *N*-oxide (100 ± 26 versus 100 ± 12 ml/min). Data were fitted to a two-compartment model over the total observation period of 8 days (six oral daily doses of 200 mg of fleroxacin on days 1 to 6 and hemodialysis treatments on day 1, 3, and 6) by nonlinear mixed-effects modeling. The random variability of plasma fleroxacin concentrations was 13% about its prediction. The estimated metabolic clearance was 25 ml/min (coefficient of variation, 43%), and the calculated steady-state volume of distribution was 84 liters (coefficient of variation, 16%). The model was expanded for the two major metabolites by the addition of a two-compartment metabolite distribution. Formation clearances of *N*-demethylfleroxacin and fleroxacin *N*-oxide were estimated to be 54 and 33% of fleroxacin's metabolic clearance, respectively. The conclusions were as follows. Because of the slow metabolic clearance and intermittent dialysis treatment, steady-state conditions were not reached after 1 week of oral fleroxacin therapy, and there was relevant accumulation of fleroxacin as well as that of fleroxacin *N*-oxide in our patients with end-stage renal disease. We recommend that infected hemodialysis patients be treated with an initial oral dose of 400 mg of fleroxacin and then daily oral doses of 200 mg. One cannot recommend the treatment of this patient population with fleroxacin over prolonged time periods until more data about the levels of accumulation of fleroxacin and its metabolites in infected patients with renal disease are available.

Fleroxacin is a trifluorinated quinolone derivative with broad antimicrobial activity (18–20, 22, 27). The substance is well absorbed, and its elimination includes both renal and nonrenal pathways (6, 14, 16–22, 24, 25, 27). Two major metabolites of fleroxacin are known: *N*-demethylfleroxacin, which has an antimicrobial activity comparable to that of the mother compound, and fleroxacin *N*-oxide, which has no antimicrobial activity. In patients with normal kidney function, renal clearance is the major elimination pathway, and therefore, a relevant decrease in total body clearance is expected in patients with impaired renal function.

Several studies have investigated the pharmacokinetic profile of fleroxacin in patients with various degrees of renal failure (6, 14, 16, 17, 21, 24). It has been shown that total body clearance of fleroxacin decreases with renal insufficiency and that this decrease is linearly related to the decline in creatinine clearance. Metabolic clearance of fleroxacin is thought to be unaltered in patients with renal failure (17, 21, 24).

Few data exist on the pharmacokinetic profile of fleroxacin in patients with end-stage renal disease (17, 21). One group reported the pharmacokinetics of fleroxacin in six patients on chronic hemodialysis after the administration of a single oral dose of 400 mg of fleroxacin (17). In that study, dialysis clearances of fleroxacin and its major metabolites were calculated from differences in the concentrations in arterial and venous

plasma only, and no dialysate was collected. Since an adequate description of the disposition of fleroxacin requires a two-compartment model (21, 25) and a rebound of plasma fleroxacin concentrations is observed after hemodialysis (17), clearance calculations based solely on rates of extraction from plasma are unlikely to represent true dialysis clearances (7, 9, 10).

The present study was designed to investigate the dialysis clearances of fleroxacin and its metabolites from dialysate collections and multiple blood samples during and after hemodialysis in patients on chronic hemodialyses after 6 days of oral fleroxacin intake. Nonlinear mixed-effects modeling (NONMEM) (2, 3) was used to estimate the pharmacokinetic parameters of fleroxacin in patients on chronic hemodialysis.

MATERIALS AND METHODS

Patients and study design. Renal patients on chronic hemodialysis were studied. All patients had been on a regular dialysis scheme of three dialyses per week for years and gave their written informed consent to participate in the study. The study was approved by the Ethics Committee of the University of Berne, Bern, Switzerland.

Any of the following excluded a patient from the study: allergic, hepatic, gastric, or psychiatric diseases; drug abuse; history of seizures; treatment with theophylline and/or nonsteroidal anti-inflammatory agents; and pregnancy or lactation. None of the patients was infected or had previously been treated with fleroxacin.

The patients received single oral doses of 200 mg of fleroxacin once daily for 6 days. On the basis of an expected nonrenal clearance of slightly less than 50% of the total clearance (17, 21) and additional elimination of fleroxacin and its metabolites by hemodialysis (17), administration of half the recommended dose

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for patients with normal renal function was considered safe for short-term application in our patients with end-stage renal disease.

Floxacin was taken at home with breakfast between 0700 and 0900 h, and the exact intake time was noted by the patient. All patients continued to take their regular medications during the study with the exception of phosphate binders (calcium carbonate, calcium acetate, and/or aluminum hydroxide), which were withheld at breakfast time.

Patients were dialyzed on the first day of feroxacin intake (day 1) as well as on days 3, 6, and 8. Blood samples for determination of the levels of feroxacin and its metabolites in plasma were drawn at the beginning of the last dialysis before drug intake (day -1), at the beginning and end of the dialysis sessions on days 3 and 6, and at the beginning of dialysis on day 8. During dialysis on day 6, blood samples were drawn at 0, 30, 60, 90, 120, 150, 180, and 210 min after the start of dialysis, as well as at 10, 20, 30, 60, and 90 min after the end of dialysis. Additional venous blood samples (collected from the venous blood line immediately after the hemodialysis filter) were drawn at 60, 90, 120, and 210 min.

All dialyses on day 6 were performed on a single dialysis machine (Miroclav; Dialysetechnik, Ettlingen, Germany). This machine was calibrated to an exact blood flow at 300 ml/min and a dialysate flow of 500 ml/min prior to the study, and the flows were controlled for stability at the end of the study. Dialysate collection was done by sampling from the dialysate line immediately after the hemodialysis filter at 30, 60, 90, 120, 150, 180, and 210 min, as well as by collecting the total ultrafiltrate at the outlet of the ultrafiltration pump. Since the ultrafiltration of the machine is volumetrically controlled and all patients were on a constant ultrafiltration rate throughout the dialysis session, the collection of all of the ultrafiltrate provides a representative sample of the total amount of feroxacin and its metabolites removed during the whole dialysis session.

Safety parameters obtained before and after treatment with feroxacin included serum electrolytes, blood urea nitrogen (BUN), creatinine, plasma protein, albumin, liver enzymes, blood counts, and electrocardiogram.

Analytical procedures. Blood samples were drawn into EDTA-containing tubes and centrifuged within 30 min after collection, and the plasma was stored in the dark at -20°C until performance of the assay.

(i) **Sample preparation procedures.** Plasma samples (100 μl) were deproteinized by adding 25 μl of a precipitation reagent (acetonitrile, 70% perchloric acid; 80:20 [vol/vol]) containing an internal standard (pipemidic acid). After vigorous mixing and centrifugation, 5 or 50 μl of the supernatants was injected onto the high-pressure liquid chromatography (HPLC) system.

Dialysate samples (20 μl) were diluted with 980 μl of 0.05 M sodium dihydrogen phosphate buffer containing an internal standard. After thorough mixing, 5 or 10 μl of the dilutions was injected directly onto the HPLC system.

(ii) **HPLC.** Quantification of feroxacin and its metabolites in human plasma and dialysate is based on chromatographic separation on a reversed-phase column (Spherisorb ODS II) with a mixture of 0.1 M citric acid buffer with 5 mM ammonium perchlorate and acetonitrile containing 2 mM tetrabutylammonium hydrogen sulfate (87:13 [vol/vol]) as the mobile phase, with a flow rate of 1.2 ml/min. The pH was adjusted to 2.2. Detection was achieved by fluorescence with an excitation wavelength of 290 nm and an emission wavelength of 460 nm. The retention times of the internal standard (pipemidic acid), *N*-demethylferoxacin, feroxacin, and feroxacin *N*-oxide were 3.2, 5.7, 6.6, and 8.3 min, respectively.

(iii) **Validation data and quality control samples during study sample analysis.** The quantification limits for feroxacin (0.01 $\mu\text{g/ml}$), *N*-demethylferoxacin (0.003 $\mu\text{g/ml}$), and feroxacin *N*-oxide (0.005 $\mu\text{g/ml}$) were identical in plasma and dialysate. In plasma and dialysate the linearity of feroxacin was proven from 0.01 to 10.0 $\mu\text{g/ml}$ ($R^2 \geq 0.999$), that of *N*-demethylferoxacin was proven from 0.003 to 3 $\mu\text{g/ml}$ ($R^2 \geq 0.999$), and that of the *N*-oxide was proven from 0.005 to 4 $\mu\text{g/ml}$ ($R^2 \geq 0.999$). The intra- and interday precisions in plasma and dialysate for all compounds were between 1.1 and 9.9%. The absolute recoveries for feroxacin and its metabolites in plasma and dialysate were between 94.0 and 104.3%.

During analysis of the study samples the interday precisions of the spiked quality control standards in plasma ranged between 2.1 and 5.3%, and the mean accuracy was determined to be between 98.6 and 104.0% for the three compounds. For feroxacin and its metabolites in dialysate, the interday precision and accuracy of the spiked quality control standards ranged from 1.1 to 6.2% and from 100.4 to 105.6% during measurement of the dialysate samples.

Pharmacokinetic and data analysis. Individual dialysis clearances of feroxacin and its metabolites were estimated both from the amount of drug recovered in the dialysate (nonparametric method [9]; see Appendix) as well as from rates of extraction from plasma (9, 10), calculated from the differences in the concentrations measured in arterial and venous plasma before and after the hemodialysis filter (see Appendix). A two-compartment model was used to describe the disposition of feroxacin over the whole treatment cycle of 8 days (see Appendix). With only data for patients receiving the drug orally were available, bioavailability was assumed to be 1 (17, 19, 21, 24, 25) for this model.

The model described above was expanded for each of the two major metabolites, feroxacin *N*-oxide and *N*-demethylferoxacin, to include a two-compartment metabolite disposition (see Appendix). For each of the two metabolites, an unknown fraction of the feroxacin metabolic clearance (nonrenal and nondialysis clearances) serves as input into the metabolite compartment. The model assumes that the metabolites are not metabolized further. For calculations, plasma and dialysate metabolite concentrations were normalized to the molec-

ular weight of feroxacin (molecular weights: feroxacin, 369; feroxacin *N*-oxide, 385; *N*-demethylferoxacin, 355).

The pharmacokinetic models describing drug disposition over the whole treatment cycle of 8 days were calculated with NONMEM (NONMEM Project Group, University of California at San Francisco [2, 3]) on a DEC Alpha 3000-400 computer running OSF/1, version 1.3. The first-order algorithm was used for model building as well as for the final runs. Proportional errors were used for all models. Expanded models were selected over reduced models by using the likelihood ratio test, referred to a chi-square distribution, with the degrees of freedom corresponding to the number of fixed parameters in the reduced model (5). Models with the same number of free (modeled) parameters were discriminated by choosing the model with the better fit (5).

Descriptive statistical analyses were performed with SAS software (release 6.09; SAS Institute Inc., Cary, N.C.) on a DEC VAX computer cluster.

All mathematical formulas are listed in the Appendix.

RESULTS

Eight renal patients (four women and four men; mean age, 63 years; age range, 48 to 73 years) receiving regular hemodialysis were studied. One woman was excluded from analysis for noncompliance with drug intake. Of the seven remaining patients, four patients were anuric and three patients had a minimal residual renal function with a glomerular filtration rate of less than 1 ml/min (range of measured creatinine clearances, 0.1 to 0.5 ml/min). Feroxacin was well tolerated, and none of the safety parameters was significantly altered during the course of feroxacin applications.

The dialysis treatment parameters are listed in Table 1. Dialysis clearances for feroxacin calculated from rates of extraction from plasma (see Appendix) during dialysis on day 6 were lower in all subjects compared with the dialysis clearances derived from drug recovery ($P < 0.001$) (Table 1). A similar difference was observed for the *N*-demethyl metabolite in six of seven patients ($P < 0.05$), whereas both methods yielded similar clearances for feroxacin *N*-oxide (Table 1).

Measured plasma and dialysate feroxacin levels for all patients over the whole observation period of 8 days were combined, and NONMEM was used to fit all data to a basic two-compartment model (see Appendix). The predicted serum and dialysate feroxacin levels are plotted against the corresponding measured values in Fig. 1, and the population means of the pharmacokinetic parameters estimated with this model are given in Table 2. The estimated mean dialysis clearance of feroxacin for the seven patients was 132 ml/min, the estimated mean metabolic clearance was 25 ml/min, and the estimated mean volume of distribution in the central compartment was 14.7 liters. The mean apparent steady-state volume of distribution, calculated from the estimated volume of distribution in the central compartment and the transfer rate constants, was 84 liters. Estimated interindividual variability was 16% (coefficient of variation) for the volume of distribution in the central compartment, 5% for dialysis clearance, and 43% for the metabolic clearance. The estimated intraindividual random variability was 13%.

Analysis of residuals revealed dependencies of the predicted serum feroxacin levels on dialysis treatment parameters (blood flow, ultrafiltration rate, and the theoretically expected filter BUN clearance values), as well as on parameters influencing the drug distribution space (height, body weight, and hematocrit).

The basic model was improved by relating feroxacin's central volume of distribution to the individual total body water calculated from the surface area (see Appendix) (13) and to hematocrit. This expansion of the basic model decreased the minimum value of the objective function from -51 to -79 ($P < 0.001$; likelihood ratio test with two degrees of freedom). Figure 2 shows a plot of the predicted versus the measured feroxacin levels from this model, and the calculated population means are given in Table 2. With a mean total body water

TABLE 1. Dialysis clearances of fleroxacin and its metabolites

Parameter	Mean \pm SD	Patient							
		1	2	3	4	6	7	8	
Dialysis clearance from rate of extraction from plasma (ml/min) ^a									
Fleroxacin									
Mean	73	80	72	74	68	71	57	87	
SD	11	4	2	4	8	9	15	3	
Fleroxacin <i>N</i> -oxide									
Mean	100	102	99	96	88	110	84	119	
SD	12	2	2	4	4	4	5	2	
<i>N</i> -Demethylfleroxacin									
Mean	72	86	64	73	65	68	52	93	
SD	15	17	7	4	10	6	6	15	
Dialysis clearance from drug recovery in dialysate (ml/min) ^b									
Fleroxacin									
Mean	126	145	157	131	82	147	90	129	
SD	29								
Fleroxacin <i>N</i> -oxide									
Mean	100	106	140	85	58	121	88	104	
SD	26								
<i>N</i> -Demethylfleroxacin									
Mean	103	138	131	115	58	120	73	88	
SD	31								
Patient characteristics and dialysis treatment parameters									
Body weight (kg)	60.9	82.5	56.5	52.0	58.0	56.5	56.0	64.5	
Gender ^c		M	M	M	M	F	F	F	
Hematocrit (%)	32	31	33	35	31	34	36	30	
Ultrafiltration (ml/min)	12.9	14.1	8.0	9.8	19.8	9.5	11.9	17.1	
Blood flow (ml/min)	300	350	250	300	300	300	300	300	
Dialysate flow (ml/min)	500	500	500	500	500	500	500	500	
Filter ^d		PS	TA	PS	PS	TA	HF	TA	
Expected BUN filter clearance (ml/min) ^e	219	277	207	195	229	210	191	223	

^a Dialysis clearance was calculated from rates of extraction from plasma (mean of three measurements after 30, 60, and 90 min of dialysis).

^b Dialysis clearance was calculated from the amount of drug recovered in the dialysate.

^c M, male; F, female.

^d Filters: PS, polysulfone (F8; Fresenius); TA, triacetate (CT110; Baxter); HF, hemophane (NT1408H; Sorin).

^e Expected BUN filter clearances were calculated from pre- and postdialysis BUN levels (11).

calculated from the surface area of 35.0 ± 4.8 liters and a mean hematocrit of 0.33 ± 0.02 in our seven patients, the estimated mean volume of distribution in the central compartment was 14.8 liters and the apparent volume of distribution at steady state was 88 liters. The estimate of fleroxacin dialysis clearance was slightly higher, whereas the metabolic clearance was unaffected by using the expanded model (Table 2). The estimated interindividual variability was 4% for dialysis clearance and 28% for metabolic clearance. The intraindividual random variability was 13% with this model.

The inclusion of additional dialysis treatment parameters such as blood flow, ultrafiltration rate, and/or theoretical BUN filter clearances did not improve the model any further.

The basic fleroxacin model was expanded for each of the two major metabolites, *N*-demethylfleroxacin and fleroxacin *N*-oxide, with an unknown fraction of fleroxacin's metabolic clearance serving as the metabolite input function (formation clearance) (see Appendix). For these calculations, metabolite dialysis clearances were fixed to the values calculated from

drug recovery in dialysate (Table 1). Pharmacokinetic population estimates for the two metabolites are given in Table 2. Figures 3 and 4 show plots of the predicted versus the measured values of fleroxacin and metabolites obtained with both metabolite models.

The formation clearance of *N*-demethylfleroxacin was estimated to be 54% of fleroxacin's metabolic clearance, with an interindividual variability of 19%. The estimated interindividual variability of *N*-demethylfleroxacin's formation clearance was 48%, and it was 30% of its dialysis clearance. The random intraindividual variability of fleroxacin and *N*-demethylfleroxacin levels was 14%.

The formation clearance of fleroxacin *N*-oxide was estimated to be 33% of fleroxacin's metabolic clearance, with an interindividual variability of 14%. Estimated interindividual variabilities were 48% for the formation clearance and 26% for fleroxacin *N*-oxide's dialysis clearance. The random intraindividual variability of fleroxacin and fleroxacin *N*-oxide levels was 15%.

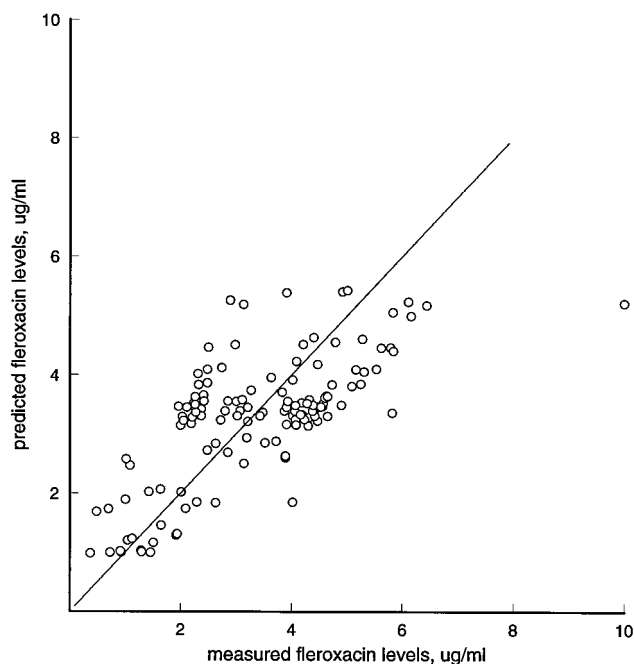


FIG. 1. Relationship between predicted and measured serum and dialysate feroxacin levels assuming a basic two-compartment model. The line represents the identity line.

DISCUSSION

Elimination of feroxacin involves both renal and nonrenal pathways. Since renal clearance accounts for 60 to 70% of total body clearance in healthy subjects, the extent of feroxacin removal during dialysis is relevant in hemodialysis patients with no residual renal function. In the present investigation we calculated a mean dialysis clearance of 73 ± 11 ml/min from individual rates of extraction from plasma in our seven patients. This is in accordance with previously published results (17) when a mean \pm standard error dialysis clearance of 64 ± 1 ml/min was reported after the administration of a single oral dose to six anuric patients who were dialyzed with smaller cuprophane filters (CF 1511; Travenol [Baxter]).

Actual dialysis clearances of feroxacin and its metabolite *N*-demethylferoxacin are significantly higher when they are calculated from drug recovery in dialysate compared with calculations from rates of extraction from plasma. Clearance calculations from rates of extraction from plasma are widely used to describe drug pharmacokinetics during hemodialysis (1, 10). However, these calculations are based on the very specific assumptions of a well-stirred plasma compartment, with extraction occurring only from this compartment and no compartmental shift during passage through the dialysis filter (1, 10), an assumption that holds less and less true with today's dialysis prescriptions of higher blood flows and high-flux dialysis filters. In contrast to feroxacin and *N*-demethylferoxacin, the clearances of which calculated from rates of extraction from plasma accounted only for 58 and 71%, respectively, of those calculated from drug recovery, similar clearance values were estimated by both methods for feroxacin *N*-oxide. The reason why the dialysis clearance of feroxacin *N*-oxide is adequately calculated from rates of extraction from plasma is probably its very slow intercompartmental transfer coefficients (Table 2). The distribution of feroxacin *N*-oxide actually mimics a one-compartment distribution during the short passage of

blood through the dialysis filter. Besides potential uptake and release of drug by erythrocytes (1, 9, 10), protein binding of a drug must also be considered when calculating dialysis clearances from rates of extraction from plasma (1, 9, 10). We did not measure the free drug concentrations in our patients. These have been reported to be in the range of 10 to 25% for healthy subjects and patients with kidney disease (15, 21). Our measured dialysis clearances of feroxacin in the range of 130 ml/min do not allow for substantial protein binding.

We estimated a mean apparent steady-state volume of distribution of 88 liters in our hemodialysis patients. This is well within the range of previously published values for patients with renal impairment (17, 21, 24). The steady-state volume of distribution of feroxacin is thought to be unaltered in patients with kidney failure (17, 21, 24). However, the volume of distribution probably decreases with age (23), and this might be responsible for the observation of values for volumes of distribution of above 100 liters in some kinetic studies with young, healthy volunteers (25, 26).

Modeling of the data for all patients over the whole treatment period by using NONMEM, we observed an unexplained random variability of plasma and dialysate feroxacin and metabolite levels in the range of 13 to 15%. The variation induced by analytical methods accounts only for about 5 to 10% of the total variation. A small error of less than 5% might have been introduced by the simplified dialysate collection method (see Materials and Methods) used for the study. A theoretical sampling time error of 5 min for the dialysate collection would account for less than 3% of the total variation. Our patients had minimal to no residual renal function, and the observed weight changes of 1.7 to 4.3 kg between and during dialysis sessions are likely to influence the distribution volume of

TABLE 2. Estimated population pharmacokinetic parameters

Parameter ^a and compound	Basic model	Expanded model
Fleroxacin		
k_a (min^{-1})	0.0126	0.0138
k_{12} (min^{-1})	0.0369	0.0450
k_{21} (min^{-1})	0.00782	0.00914
V_c (liters) ^b	14.7	
V_{ss} (liters)	84	88
CL_d (ml/min)	132	142
CL_m (ml/min)	25	25
<i>N</i>-Demethylferoxacin		
f (%)	53.6	
CL_{md} (ml/min)	103	
k_{34} (min^{-1})	0.00357	
k_{43} (min^{-1})	0.00028	
Fleroxacin <i>N</i>-oxide		
f (%)	34.3	
CL_{md} (ml/min)	100	
k_{34} (min^{-1})	0.000166	
k_{43} (min^{-1})	0.000009	

^a k_a , absorption coefficient; k_{12} , coefficient of transfer from compartment 1 to compartment 2; k_{21} , coefficient of transfer from compartment 2 to compartment 1; V_c , volume of distribution in the central compartment; V_{ss} , theoretical steady-state volume of distribution (calculated from estimates of the volume of distribution in the central compartment and transfer coefficients); CL_d , dialysis clearance; CL_m , metabolic clearance; VSA, total body water calculated from surface area; Hct, hematocrit; f , fraction of feroxacin's metabolic clearance serving as metabolite formation clearance; CL_{md} , dialysis clearance of metabolites; k_{34} and k_{43} , metabolite transfer coefficients.

^b In the expanded model, $V_c = -35.6 + 0.403 \cdot \text{VSA} + 0.541 \cdot 100 \cdot (1 - \text{Hct})$. The abbreviations are defined in footnote a.

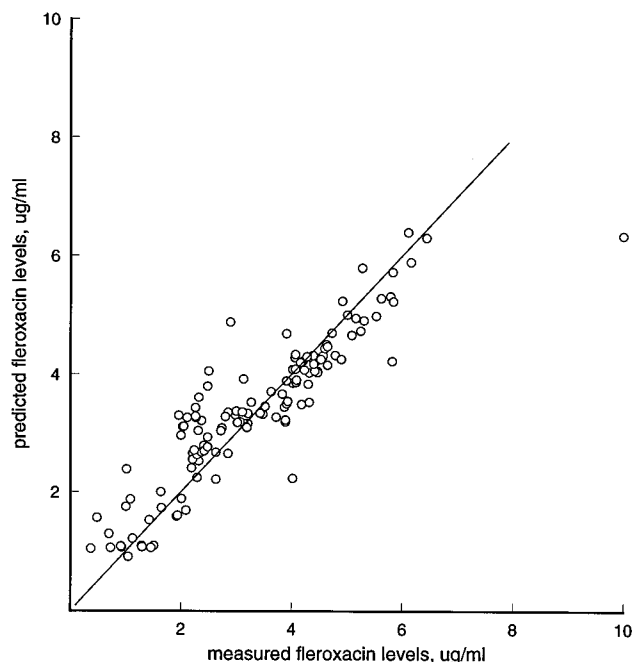


FIG. 2. Relationship between predicted and measured fleroxacin levels after expansion of the basic model (Fig. 1) in relating the volume of distribution to hematocrit and total body water calculated from surface area (see Appendix).

fleroxacin. Our pharmacokinetic models did not account for changes in the volume of distribution, accepting an error that is in the range of the proportion of ultrafiltered volume to apparent steady-state volume of distribution (about 5%). An additional increase in the error is expected when the proportion of the volume of distribution in the central compartment to the total volume of distribution is altered by the hemodialysis treatment. None of our patients showed hypotension or other signs of severe volume dysequilibrium during dialysis sessions. An additional source of variability might be introduced with a significant dialysis fistula recirculation (12). None of our patients had laboratory signs of a clinically relevant fistula recirculation; however, we did not measure fistula recirculation during the study. The major source of unexplained random variation observed in our patients is probably due to the well-known variation of the oral absorption rate constant (21, 26). Our patients were studied after the oral application of fleroxacin only. Reported clearances therefore technically correspond to oral clearances. We assumed a bioavailability of 100% in the study since bioavailabilities of close to 100% have previously been reported for fleroxacin in healthy subjects (19, 21, 25) as well as in patients with renal failure (17, 21, 24). The absolute bioavailability of fleroxacin seems to be affected only minimally, if at all, by food intake (4, 15, 16, 19). Nevertheless, lower peak concentrations in plasma and longer times to peak concentrations in plasma have been reported with fat- and calcium-rich meals (4). As observed with other quinolone antimicrobial agents, fleroxacin absorption is reduced in the presence of high concentrations of metallic ions such as aluminum and magnesium (16). Our patients were not allowed a concomitant intake of phosphate binders during the meals when fleroxacin was administered. Furthermore, none of the patients was taking any additional drugs that might interfere with fleroxacin absorption such as sucralfate or oral iron or zinc preparations (16).

The tendency for the overprediction of plasma fleroxacin

levels with increasing hematocrits by the basic model can be explained either by a decrease in dialysis clearance or by a decrease in the volume of distribution in the central compartment. We improved the basic model by including a linear relationship of the volume of distribution in the central compartment with hematocrit as well as total body water space estimated from surface area (13) (Fig. 2). The model could not be improved any further when including additional treatment parameters, mainly because of the small sample size.

For calculations of metabolite disposition we used a model that assumes no further metabolism of the two major metabolites. Substantial further metabolism of metabolites is not known or expected. Nevertheless, we cannot exclude the possibility that a higher fraction of the fleroxacin metabolic clearance serves as metabolite formation clearance with a corresponding additional metabolism of the metabolites.

We observed the accumulation of both metabolites in our patients, despite intermittent dialysis treatments (Fig. 3 and 4). It has been shown before that the level of accumulation of both major metabolites is high in patients with renal failure during treatment with fleroxacin (17, 21). Toxicological studies in rats showed that the toxicities of *N*-demethylfleroxacin and fleroxacin *N*-oxide are comparable to that of the parent drug (12a). Only fleroxacin *N*-oxide accumulates to relevant levels in plasma during a short treatment period (Fig. 3 and 4). Since dialysis clearance of both metabolites is in the same range, the formation rate of *N*-demethylfleroxacin must be lower in patients on hemodialysis. It has been shown before that the

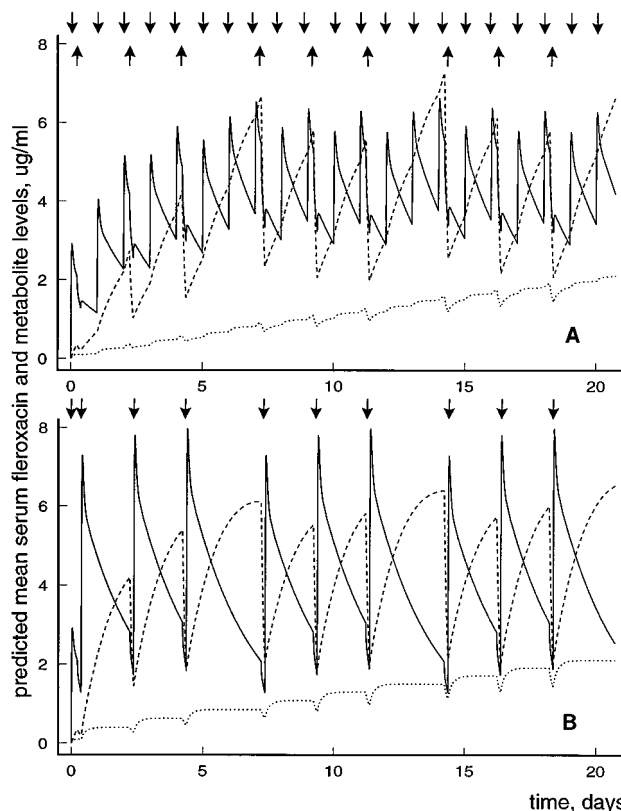


FIG. 3. Predicted mean serum fleroxacin (full line), fleroxacin *N*-oxide (dashed line), and *N*-demethylfleroxacin (dotted line) levels after the administration of an initial oral dose of 400 mg of fleroxacin and then daily doses of 200 mg (A) and after oral doses of 400 mg of fleroxacin administered after each dialysis session (B). ↓, drug intake; ↑, start of dialysis sessions.

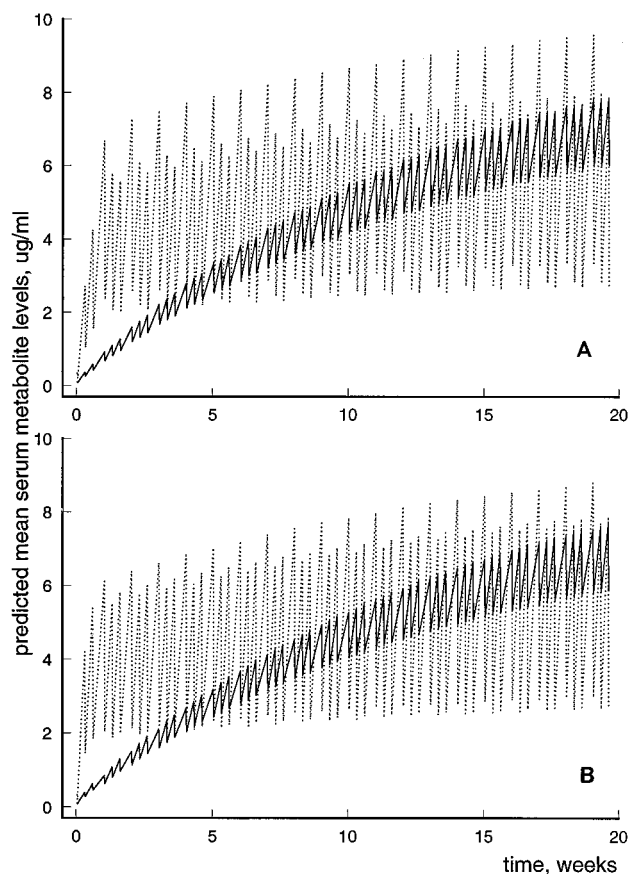


FIG. 4. Predicted mean serum *N*-demethylfloxacin (full line) and floxacin *N*-oxide (dashed line) levels over an observation period of 20 weeks after the administration of an initial oral dose of 400 mg of floxacin and then daily doses of 200 mg (A) and after oral doses of 400 mg of floxacin administered after each dialysis session (B).

formation of floxacin *N*-oxide is not significantly affected by a decrease in renal function, whereas that of *N*-demethylfloxacin declines severalfold in patients with end-stage renal disease (17), and it was therefore speculated that the hepatic enzymes involved in the two metabolic pathways of floxacin are inhibited to different extents in patients with renal failure.

Therapeutic implications. The treatment of hemodialysis patients with floxacin results in significant levels of accumulation of floxacin as well as its two major metabolites, floxacin *N*-oxide and *N*-demethylfloxacin (Fig. 3 and 4). Since the formation rate of *N*-demethylfloxacin is low in patients on hemodialysis, the accumulation of this metabolite becomes of clinical concern only after prolonged use of floxacin in hemodialysis patients (Fig. 4).

We recommend the administration of an initial oral dose of 400 mg of floxacin and then oral daily doses of 200 mg of floxacin for the treatment of infected patients on hemodialysis with no residual renal function (Fig. 3).

As an alternative, oral doses of 400 mg of floxacin can be administered after each dialysis session (Fig. 3 and 4). However, despite the advantage of slower accumulation of floxacin and its metabolites, serum floxacin concentrations show a much larger variation and drop to very low levels by this application scheme.

Until more data on the accumulation of floxacin and its major metabolites over prolonged treatment periods in in-

fectured patients with end-stage renal disease are available, we do not recommend treatment of this patient group for longer than 1 to 2 weeks.

APPENDIX

Dialysis clearance calculated from extraction from plasma.

$$Q_p = (1 - \text{Hct}) \cdot Q_b$$

$$CL_p = [Q_p \cdot C_a - (Q_p - \text{UF}) \cdot C_v] / C_a$$

where Q_p is plasma flow, Q_b is blood flow, Hct is hematocrit, CL_p is dialysis clearance from plasma, C_a is the concentration in arterial plasma (filter inflow), C_v is the concentration in venous plasma (filter outflow), and UF is the ultrafiltration rate.

Dialysis clearance calculated from drug recovery in dialysate.

$$CL_d = A / \text{AUC}$$

where A is the total amount of floxacin recovered in the dialysate and AUC is area under the curve of serum floxacin levels during dialysis (calculated by the standard trapezoidal rule [8] from the concentrations in arterial plasma [filter inflow]).

Two-compartment floxacin disposition over the whole treatment period.

$$dA_1/dt = k_a \cdot A_0 + k_{21} \cdot A_2 - k_{12} \cdot A_1 - k_m \cdot A_1 - k_r \cdot A_1 - l \cdot k_d \cdot A_1$$

$$dA_2/dt = k_{12} \cdot A_1 - k_{21} \cdot A_2$$

where A_0 is the amount of floxacin in the absorption depot, A_1 is the amount of floxacin in the central compartment (compartment 1) at time t , A_2 is the amount of floxacin in the peripheral compartment (compartment 2) at time t , k_a is the absorption rate constant, k_{12} is the transfer rate constant from compartment 1 to compartment 2, k_{21} is the transfer rate constant from compartment 2 to compartment 1, k_r is the residual renal elimination rate constant, k_m is the metabolic elimination rate constant, k_d is the dialysis elimination rate constant, and l is 1 if the patient is on dialysis treatment and 0 otherwise.

Expansion of the model described above by a two-compartment metabolite disposition.

$$dA_3/dt = f \cdot k_m \cdot A_1 - k_{34} \cdot A_3 + k_{43} \cdot A_4 - l \cdot k_{md} \cdot A_3$$

$$dA_4/dt = k_{34} \cdot A_3 - k_{43} \cdot A_4$$

where A_3 is the amount of metabolite in the central metabolite compartment (compartment 3), A_4 is the amount of metabolite in the peripheral metabolite compartment (compartment 4), f is the fraction of the floxacin metabolic elimination rate constant serving as input into the central metabolite compartment, k_{34} is the metabolite transfer rate constant from compartment 3 to compartment 4, k_{43} is the metabolite transfer rate constant from compartment 4 to compartment 3, and k_{md} is the metabolite dialysis elimination rate constant.

Modeled relationship of the volume of distribution of floxacin in the central compartment with the total body water space, calculated from surface area, and with hematocrit.

$$V_c = a + b \cdot \text{VSA} + c \cdot 100 \cdot (1 - \text{Hct})$$

where V_c is the volume of distribution in the central compartment, a , b , and c are regression coefficients, VSA is total body water calculated from surface area (13), and Hct is hematocrit.

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REFERENCES

1. Bass, O., K. D. Nolph, and J. F. Maher. 1974. Dialysance and clearance measurements during clinical dialysis—a plea for standardization. *Lab. Clin. Med.* 86:378–385.
2. Beal, S. L. 1984. Population pharmacokinetic data and parameter estimation

- based on their first two statistical moments. *Drug Metab. Rev.* **15**:173–193.
3. **Beal, S. L., and L. B. Sheiner.** 1980. The NONMEM system. *Am. Stat.* **34**:118–119.
 4. **Bertino, J. S., Jr., A. N. Nafziger, M. Wong, L. Stragand, and C. Puleo.** 1994. Effect of a fat- and calcium-rich breakfast on pharmacokinetics of fleroxacin administered in single and multiple doses. *Antimicrob. Agents Chemother.* **38**:499–503.
 5. **Boeckmann, A. J., L. B. Sheiner, and S. L. Beal.** 1992. NONMEM users guide, part V, p. 41–49. NONMEM Project Group, University of California, San Francisco.
 6. **Fillastre, J. P., A. Leroy, B. Moulin, M. Dhib, F. Borsa Lebas, and G. Humbert.** 1990. Pharmacokinetics of quinolones in renal insufficiency. *J. Antimicrob. Chemother.* **26**(Suppl. B):51–60.
 7. **Frey, F. J., J. G. Gambertoglio, B. M. Frey, L. Z. Benet, and W. J. C. Amend.** 1982. Nonlinear plasma protein binding and hemodialysis clearance of prednisolone. *Eur. J. Clin. Pharmacol.* **23**:65–74.
 8. **Gibaldi, M., and D. Perrier.** 1982. Appendix D, p. 445–449. *In* M. Gibaldi and D. Perrier (ed.), *Pharmacokinetics*. Marcel Dekker, Inc., New York.
 9. **Gibaldi, M., and D. Perrier.** 1982. Clearance concepts, p. 319–353. *In* M. Gibaldi and D. Perrier (ed.), *Pharmacokinetics*. Marcel Dekker, Inc., New York.
 10. **Gibson, T. P., E. Matusik, L. D. Nelson, and M. D. Briggs.** 1977. Artificial kidneys and clearance calculations. *Clin. Pharmacol. Ther.* **20**:720–726.
 11. **Gotch, F. A.** 1995. Kinetic modeling in hemodialysis, p. 156–188. *In* A. R. Nissenson, R. N. Fine, and D. E. Gentile (ed.), *Clinical dialysis*. Appleton & Lange, Norwalk, Conn.
 12. **Greenwood, R. N., C. Aldridge, L. Goldstein, L. R. I. Baker, and W. R. Cattell.** 1985. Assessment of arteriovenous fistulae from pressure and thermal dilution studies: clinical experience in forearm fistulae. *Clin. Nephrol.* **23**:189–197.
 - 12a. **Hoffmann-La Roche.** Data on file.
 13. **Hume, R., and E. Wyers.** 1971. Relationship between total body water and surface area in normal and obese subjects. *J. Clin. Pathol.* **24**:234–238.
 14. **Metz, R., D. Hoffer, F. Soergel, R. Seelmann, and P. Koeppel.** 1989. Pharmacokinetics and metabolism of fleroxacin in patients with renal impairment. *Rev. Infect. Dis.* **11**(Suppl. 5):S1011–S1012.
 15. **Nakashima, M., M. Kanamaru, T. Uematsu, A. Takiguchi, A. Mizuno, T. Itaya, F. Kawahara, T. Oole, S. Saito, and H. Uchida.** 1988. Clinical pharmacokinetics and tolerance of fleroxacin in healthy male volunteers. *J. Antimicrob. Chemother.* **22**(Suppl. D):133–144.
 16. **Nightingale, C. H.** 1993. Overview of the pharmacokinetics of fleroxacin. *Am. J. Med.* **94**:38S–43S.
 17. **Singlas, E., A. Leroy, E. Sultan, M. Godin, B. Moulin, A. M. Taburet, M. Dhib, and J. P. Fillastre.** 1990. Disposition of fleroxacin, a new trifluoroquinolone, and its metabolites. Pharmacokinetics in renal failure and influence of haemodialysis. *Clin. Pharmacokinet.* **19**:67–79.
 18. **Soergel, F., and M. Kinzig.** 1993. Pharmacokinetics of gyrase inhibitors. Part 2. Renal and hepatic elimination pathways and drug interaction. *Am. J. Med.* **94**(Suppl. 3A):56S–69S.
 19. **Soergel, F., and M. Kinzig.** 1993. Pharmacokinetics of gyrase inhibitors. Part 1. Basic chemistry and gastrointestinal disposition. *Am. J. Med.* **94**(Suppl. 3A):44S–55S.
 20. **Soergel, F., R. Metz, K. G. Naber, R. Seelmann, and P. Muth.** 1988. Pharmacokinetics and body fluid penetration of fleroxacin in healthy volunteers. *J. Antimicrob. Chemother.* **22**(Suppl. D):155–167.
 21. **Stuck, A. E., F. J. Frey, P. Heizmann, R. Brandt, and E. Weidekamm.** 1989. Pharmacokinetics and metabolism of intravenous and oral fleroxacin in subjects with normal and impaired renal function and in patients on continuous ambulatory peritoneal dialysis. *Antimicrob. Agents Chemother.* **33**:373–381.
 22. **Stuck, A. E., D. K. Kim, and F. J. Frey.** 1992. Fleroxacin clinical pharmacokinetics. *Clin. Pharmacokinet.* **22**:116–131.
 23. **Taburet, A. M., A. Devillers, P. Thomare, J. P. Fillastre, P. Veyssier, and E. Singlas.** 1990. Disposition of fleroxacin, a new trifluoroquinolone, and its metabolites. Pharmacokinetics in elderly patients. *Clin. Pharmacokinet.* **19**:80–88.
 24. **Weidekamm, E.** 1993. Pharmacokinetics of fleroxacin in renal impairment. *Am. J. Med.* **94**:70S–74S.
 25. **Weidekamm, E., R. Portmann, C. Partos, and D. Dell.** 1988. Single and multiple dose pharmacokinetics of fleroxacin. *J. Antimicrob. Chemother.* **22**(Suppl. D):145–154.
 26. **Weidekamm, E., R. Portmann, K. Suter, C. Partos, D. Dell, and P. W. Lucker.** 1987. Single- and multiple-dose pharmacokinetics of fleroxacin, a trifluorinated quinolone, in humans. *Antimicrob. Agents Chemother.* **31**:1909–1914.
 27. **Wolfson, J. S.** 1993. Quinolone antimicrobial agents. American Society for Microbiology, Washington, D.C.