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Pharmacokinetics of Enoxacin and Its Oxometabolite following Intravenous Administration to Patients with Different Degrees of Renal Impairment

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Enoxacin is a fluorinated quinolone with potential clinical use in the treatment of serious infections. Twenty-three patients (age, 19 to 87 years) with different degrees of renal function, including a group undergoing chronic hemodialysis, received enoxacin (400 mg) by intravenous infusion (1 h). Blood samples were collected before infusion; at the end of infusion; and at 5, 10, 20, 30, 45, 60, 90, and 120 min and 3, 4, 6, 12, 18, 24, 48, and 72 h after infusion. Enoxacin and oxoenoxacin concentrations were measured by high-pressure liquid chromatography. Pharmacokinetic parameters (mean ± standard deviation) were calculated by using a noncompartmental PK model according to creatinine clearances (in milliliters per minute). Total clearance of enoxacin decreased from 4.95 ± 1.16 ml/min per kg in the group with normal creatinine clearance to 0.76 ± 0.21 ml/min per kg in the patients with severe renal failure (creatinine clearance, <15 ml/min), whereas the elimination half-life increased from 4.5 ± 1.0 to 20 ± 5 h, respectively. The elimination of oxoenoxacin (the main metabolite of enoxacin) in urine was markedly decreased when creatinine clearance was <15 ml/min. Hemodialysis removed an insignificant amount of enoxacin and oxoenoxacin. These data indicate that as creatinine clearance falls below 30 ml/min, the daily enoxacin dose should be reduced by half. During prolonged administration of enoxacin to patients with creatinine clearances of <30 ml/min, the accumulation of oxoenoxacin might lead to unexpected side effects.

The family of DNA gyrase inhibitors comprises two types of molecules: those which inhibit subunit A (quinolones) and those which inhibit subunit B (coumermycin, novobiocin, chlorobiocin).

The "first generation" of quinolones comprise nalidixic acid, cinoxacin, pipemidic acid, oxolinic acid, flumequine, and acrosoxacin and are indicated primarily for the treatment of urinary tract infections. The "second generation" comprises recently developed molecules of clinical interest in the treatment of systemic infections (pefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, fleroxacin, lomefloxacin). These agents are characterized by their enhanced in vitro activities against gram-negative aerobes and improved intestinal absorptions.

Enoxacin is a new fluorinated quinolone with high in vitro activity. Available studies indicate that it is effective in the management of infections caused by susceptible organisms (4, 9).

The influence of renal failure on the pharmacokinetics of enoxacin given orally has been studied previously (1, 7), but not following intravenous (i.v.) administration. Furthermore, the disposition of the major metabolite of enoxacin, oxoenoxacin, in patients with renal impairment has not been described.

The purpose of this study was to evaluate the pharmacokinetics of i.v. administered enoxacin and its oxometabolite in patients with different degrees of renal impairment.

MATERIALS AND METHODS

The protocol for this study followed the guidelines of the Declaration of Helsinki and was reviewed by the local ethical committee. Each patient gave informed consent.

Patients. Twenty-three patients (age, 19 to 87 years) with various degrees of renal impairment were enrolled in this study. Patients were categorized prior to the administration of enoxacin into five classes according to the measured creatinine clearances, which were based on 24-h urine collections. The following classes were defined (number of patients): 1, patients on chronic hemodialysis (four patients); 2, creatinine clearance, <15 ml/min (four patients); 3, creatinine clearance, 15 to 30 ml/min (six patients); 4, creatinine clearance, 30 to 60 ml/min (four patients); 5, creatinine clearance, >60 ml/min (five patients).

The exclusion criteria were pregnant or lactating women; hepatic enzymes twice the upper limit of normal or serum bilirubin levels of >1 mg/dl; patients with an allergy to any quinolone agent; patients who were on concomitant antibacterial therapy or who received any antibiotic during the previous week; and patients who weighed less than 40 kg.

Experimental design. Patients received a single 400-mg dose of enoxacin (supplied as 200-mg/ml ampoules [batch RM 830567] by Parke Davis & Co., Warner-Lambert, Detroit, Mich.) diluted in 100 ml of 5% glucose in water. The dose was given as a constant-rate infusion over 1 h through the antecubital vein by using an infusion pump. All four patients in the dialysis group were studied twice while they were off dialysis; three of these patients were also studied during dialysis. The interval between studies done while

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TABLE 1. Demographic characteristics of patients examined in study

Group (no. of patients)	Median age (yr [range])	No. of men, no. of women	Median wt (kg [range])	Median creatinine clearance (ml/min [range])
1 (4)	56 (19–83)	1, 4	60.5 (52.5–80.8)	5 (0–10)
2 (4)	50 (36–79)	1, 3	76.1 (63–146)	9 (9–14.9)
3 (6)	66 (57–87)	5, 1	65 (58.8–104)	23.2 (18–27)
4 (4)	79 (66–83)	2, 2	73.1 (68.7–88)	41 (34–61)
5 (5)	54 (26–68)	1, 4	73.7 (48–132)	82.8 (67–146)

patients were on and off dialysis was at least 24 h. Dialysis was initiated 3 h after drug administration.

Clinical and laboratory data. Base-line clinical and laboratory data were taken within 24 h prior to the start of the study and again on completion of the study. The following data were obtained: patient medical history and physical examination; β_2-microglobulin (serum and urine); complete blood count with differential; serum urea and creatinine; serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, total bilirubin, and alkaline phosphatase; total serum protein or serum albumin; erythrocyte sedimentation rate; serum electrolytes; and creatinine clearance.

Blood sampling times. Blood samples were obtained before drug administration and at 5, 10, 30, 45, 60, 90, and 120 min and 3, 4, 6, 12, 18, 24, 48, and 72 h after drug administration. After clotting, the blood samples were centrifuged and the serum was stored at −20°C.

Urine sampling times. Urine was collected from each patient (excluding dialysis patients) beginning at the time of dosing. The collections were taken at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 h postdosing. The volume of urine from each collection period was noted, and a 50-ml portion was stored at −20°C until the quinolone concentration in the sample was analyzed.

Dialysate sampling times. Portions of the dialysate were obtained at time zero and at 30, 60, 90, 120, 150, 180, 210, and 240 min after the beginning of hemodialysis.

Assay. The concentrations of enoxacin and oxoenoxacin were measured by high-pressure liquid chromatography. Standards (enoxacin [potency, 918 mg/g] and oxoenoxacin [potency, 1,000 mg/g], 5, 2, 1, 0.5, 0.25, and 0.12 mg/liter) and controls (enoxacin, 8 and 0.8 mg/liter; oxoenoxacin, 4 and 0.4 mg/liter) were prepared in a fashion similar to that described above for test samples, from pooled sera (serum assay), and in phosphate buffer (urine and dialysis fluid assays). An external serum control sample was obtained from Warner-Lambert.

All chemicals used in this study were of analytical high-pressure liquid chromatography grade. Enoxacin, oxoenoxacin, and norfloxacin (internal standard) reference powders were obtained from Warner-Lambert. Water was passed through a water purification system (Millipore Corp.). Phos-

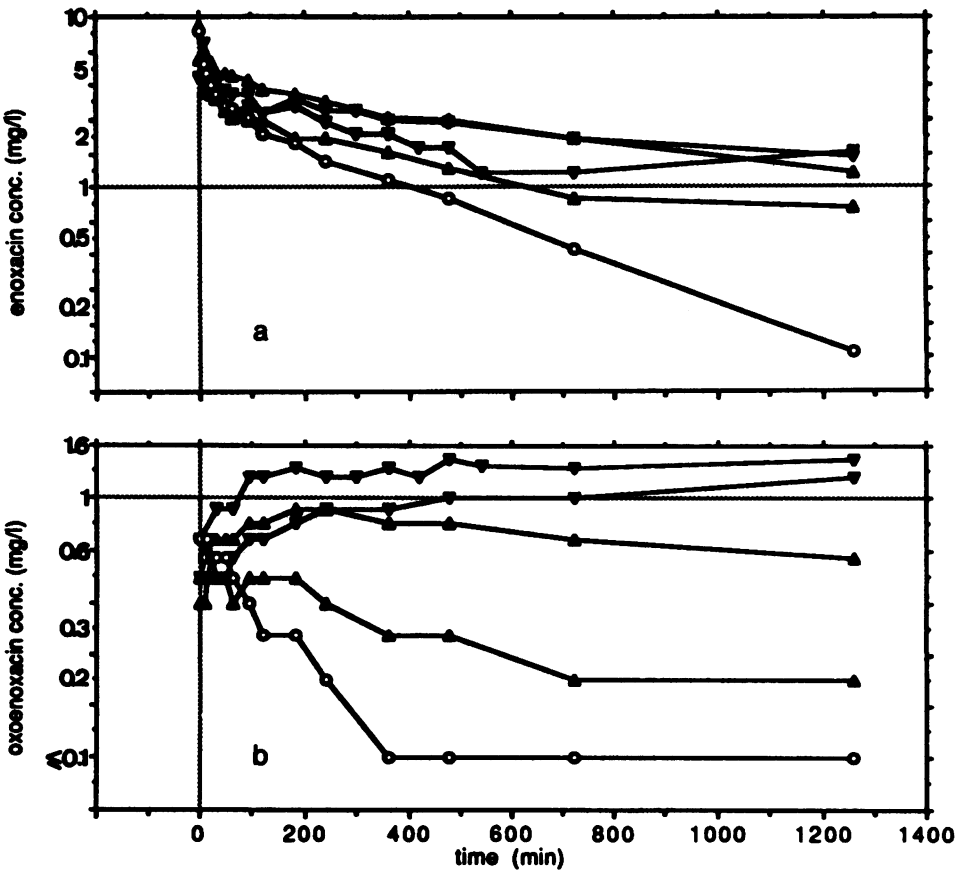

FIG. 1. Mean concentrations of enoxacin (a) and oxoenoxacin (b) in serum following the i.v. administration of enoxacin (40 mg) in the five groups of patients investigated. Symbols: ▽, group 1 (off dialysis); ▼, group 2; △, group 3; ▲, group 4; ○, group 5.

TABLE 2. Enoxacin pharmacokinetic parameters according to degree of renal impairment[a]

Pharmacokinetic parameter[b]	Group 1 (<15 ml/min,[c] hemodialysis)	Group 2 (<15 ml/min)	Group 3 (15–30 ml/min)	Group 4 (30–60 ml/min)	Group 5 (>60 ml/min)
CL_T (ml/min per kg)	1.72 ± 0.58 (0.92–2.19)[d,e]	0.99 ± 0.21 (0.76–1.26)[d,f,g]	1.32 ± 0.36 (0.91–4.68)[h]	3.98 ± 2.90 (1.12–7.41)	4.95 ± 1.16 (3.70–6.36)
CL_R (ml/min per kg)	ND[i]	0.16 ± 0.006 (0.10–0.16)[d]	0.47 ± 0.17 (0.31–0.76)[d]	1.00 ± 1.00 (0.40–2.16)[j]	2.22 ± 0.57 (1.57–2.93)[k]
CL_{NR} (ml/min per kg)	ND	0.84 ± 0.16 (0.64–1.02)[d]	0.90 ± 0.33 (0.54–3.92)[l]	2.55 ± 2.39 (0.72–5.25)[j]	3.00 ± 0.93 (2.13–4.33)[k]
V_{ss} (liters/kg)	2.68 ± 1.53 (1.36–4.74)	1.78 ± 0.68 (1.15–2.71)	1.66 ± 0.53 (1.18–2.60)	2.34 ± 1.50 (1.46–4.59)	1.59 ± 0.41 (1.14–2.13)
$t_{1/2\lambda_z}$ (h)	19.86 ± 14.16 (9.8–36.5)[d]	19.77 ± 5.50 (13.33–26.65)	12.98 ± 4.33 (6.60–16.12)[d]	8.40 ± 4.03 (4.75–13.86)	4.47 ± 0.96 (3.57–5.92)
C_{max} (mg/liter)	5.66 ± 1.92 (3.82–7.77)	5.04 ± 1.41 (2.99–6.13)	7.13 ± 2.34 (4.28–9.94)	4.76 ± 1.61 (3.06–6.45)	6.97 ± 1.75 (4.0–8.16)
C_{12} (mg/liter)	0.90 ± 0.18 (0.78–1.03)	1.60 ± 0.62 (1.07–2.31)[d]	1.86 ± 0.50 (1.31–2.60)[d,g]	0.76 ± 0.65 (0.24–1.65)	0.68 ± 0.20 (0.40–0.94)

[a] Values are means ± standard deviations; ranges are given in parentheses.
[b] Abbreviations: CL_T, total clearance; CL_R, renal clearance; CL_{NR}, nonrenal clearance; V_{ss}, volume of distribution at steady state; $t_{1/2\lambda_z}$, half-life at the terminal elimination phase; C_{max}, maximum concentration of exoxacin in serum; C_{12}, concentration of exoxacin in serum at 12 h.
[c] Values are creatinine clearance.
[d] Significantly different ($P < 0.05$) from group 5.
[e] Not significantly different from group 5 if data for patient 11 in group 3 are excluded from the statistical computations.
[f] Significantly different ($P < 0.05$) from group 5 if data for patient 11 in group 3 are excluded from the statistical computations.
[g] Significantly different ($P < 0.05$) from group 5.
[h] Data for patient 11 in group 3 were excluded from statistical computations ($P < 0.05$ versus group 5).
[i] ND, Not detectable.
[j] Urine collections were adequate to estimate this parameter in only three patients in this group.
[k] Urine collections were adequate to estimate this parameter in only four patients in this group.
[l] Data for patient 11 in group were excluded from statistical computations.

phate buffer (0.2 M; pH 7.4) was prepared from monobasic and dibasic sodium phosphate (E. Merck AG, Darmstadt, Federal Republic of Germany). Other chemicals included citric acid (Merck), ammonium perchlorate (99.8%; Ega-Chemie, Steinheim, Federal Republic of Germany), tetrabutylammonium hydroxyde (20% in water; Merck), acetonitrile (70 to 72%; Merck), and perchloric acid (D = 1.67, 70%; Merck). The chromatographic system (Waters Associates, Inc., Milford, Mass.) used in this study consisted of a model 510 pump, a model 710B WISP autosampler, a Lambda-Max-481 variable-wavelength detector set at 340 nm, a data module recorder integrator, and a programmable system controller. The column (12.5 cm by 4.6 mm) was packed with C_{18} reversed-phase (LiChrospher, 100RP-18e, 5 μm; Merck). The mobile phase was 0.1 M citric acid–acetonitrile (86:14) with 1.3 ml of tetrabutylammonium hydroxide and 0.9 g of NH_4ClO_4 at a flow rate of 1 ml/min at room temperature.

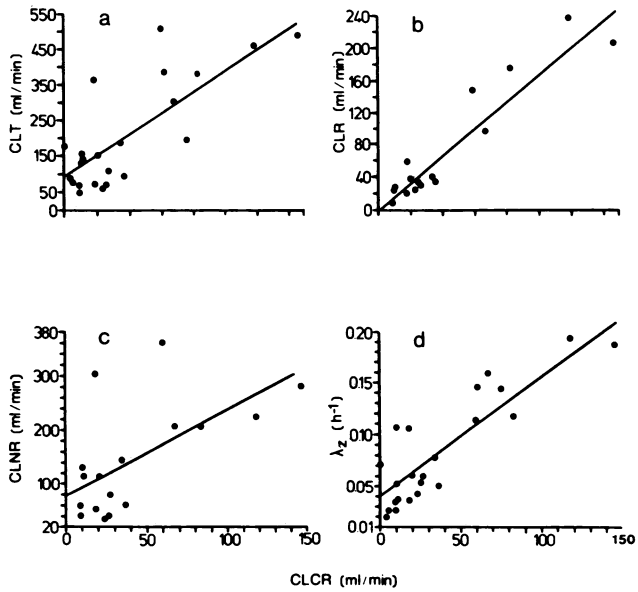

FIG. 2. Relation between creatinine clearance (CL_{CR}) and enoxacin total clearance (CL_T) [$CL_T = (3.1 \times CL_{CR}) + 88.0$; $P < 0.05$] (a), renal clearance (CL_R) ($CL_R = 1.7 \times CL_{CR}$; $P < 0.05$) (b), nonrenal clearance (CL_{NR}) [$CL_{NR} = (1.54 \times CL_{CR}) + 79.8$; $P < 0.05$] (c), and slope of the terminal elimination phase (λ_z) [$\lambda_z = (0.0012 \times CL_{CR}) + 0.04$; $P < 0.05$] (d).

(i) Serum assay. A total of 20 μl of internal standard (100 mg/liter in 0.2 M phosphate buffer) was added to 0.2 ml of serum and vortexed. A total of 50 μl of perchloric acid-acetonitrile (1:4; vol:vol) was added, vortexed, and centrifuged for 2 min at 10,000 × g. Duplicate portions of 20 to 30 μl of the clear supernatant were injected onto the column.

(ii) Urine assay. Portions of urine were diluted 50 times in the mobile phase, after centrifugation at 10,000 × g for 2 min, and duplicate portions of 30 μl of the clear supernatant were injected onto the column.

(iii) Dialysis fluid assay. A total of 30 μl of dialysis fluid was injected onto the column. Standards and controls were tested in duplicate (two different extractions or preparations) during each assay run. Patient samples, standards, and controls were placed at random order into the autosampler (WISP; Waters Associates).

Performance of the assays. The assays described here were linear to at least 10 mg/liter for both enoxacin and oxoenoxacin. The sensitivities were 0.05 mg/liter for both enoxacin and oxoenoxacin. For the three fluids assayed, interday assay variabilities ranged from 4 to 10% for enoxacin and 2 to 4% for oxoenoxacin, depending on the concentration

TABLE 3. Urinary recoveries of enoxacin and oxoenoxacin

Drug and group (no. of patients)	Period (h) considered	Recovery[a]		Concn (mg/liter)	
		Mean	Range	Mean	Range
Enoxacin					
2 (4)	0–4	2.6	1.5–3.6	21.8	17.3–26.5
	4–8	2.0	1.5–2.7	17.8	14–23.9
	8–12	1.4	0.8–2.3	15.9	12.5–18.7
	12–24	3.5	2.4–4.3	11.1	10.2–11.6
	24–48	3.7	3.1–4.2	8.7	7.1–10.5
	48–72	4.2	4.2–4.2	6.8	5.6–8.5
	0–72	12.5	6.7–18.6		
3 (6)	0–4	6.4	3.5–11.5	77.0	21.5–139.5
	4–8	3.6	2.5–6.1	57.8	14.6–116.7
	8–12	6.2	1.6–19.1	62.1	11.9–130.0
	12–24	5.3	2.5–7.0	48.4	11.9–72.5
	24–48	5.2	1.7–10.3	22.2	6.7–51.7
	48–72	2.2	0.2–3.5	9.1	1.1–19.2
	0–72	28.9	22.6–39.7		
4 (3)	0–4	9.2	2.5–15.3	108.0	38.8–245.1
	4–8	4.1	1.9–8.5	70.3	31.6–136.8
	8–12	3.3	1.7–5.3	33.2	21.3–39.7
	12–24	4.2	2.3–5.4	15.7	7.1–25.2
	24–48	4.1	2.5–5.6	20.4	6.7–33.5
	48–72	NA[b]		NA	
	0–48	23.6	17.7–34.7		
5 (4)	0–4	23.1	19.2–31.7	246.0	64.3–330.0
	4–8	10.6	5.9–15.1	153.1	42.0–301.7
	8–12	7.4	4.8–10.2	67.1	28.5–161.1
	12–24	6.4	4.7–8.5	43.6	24.0–96.8
	24–48	1.7	0.8–2.6	8.4	1.1–21.1
	48–72	1.1	0.6–1.8	3.3	1.5–4.3
	0–72	48.1	36.2–56.1		
Oxoenoxacin					
2 (4)	0–4	1.3	0–3.5	2.9	0–7.0
	4–8	1.0	0–1.7	2.6	0–7.0
	8–12	0.7	0–0.8	2.6	0–7.0
	12–24	0.1	0–0.4	0.1	0–0.3
	24–48	0.1	0–0.3	0.1	0–0.2
	48–72	0.1	0–0.6	0.4	0–0.9
	0–72	3.5	0–5.5		
3 (6)	0–4	6.1	0.4–5.7	18.5	0.5–57.0
	4–8	8.3	1.4–4.1	16.6	7.1–39.0
	8–12	7.9	0–28.9	22.7	0–47.4
	12–24	19.3	0–14.0	20.1	0–35.0
	24–48	0.7	0–29.4	11.6	0–28.0
	48–72	0.6	0–13.5	5.5	0–14.2
	0–72	40.1	0–71.2		
4 (5)	0–4	8.5	3.5–22.0	28.8	6.2–88.1
	4–8	6.7	6.1–10.1	26.3	10.0–59.8
	8–12	5.1	5.1–6.3	17.5	8.2–28.9
	12–24	5.9	0.4–8.8	10.5	0.3–20.1
	24–48	5.2	0.3–13.7	7.6	0.3–13.3
	48–72	4.4	0–14.8	5.0	0–7.1
	0–72	37.5	20.7–62.3		
5 (4)	0–4	21.1	17.1–27.6	48.4	17.6–68.3
	4–8	9.0	6.6–19.8	36.3	8.2–98.8
	8–12	7.4	0–12.4	17.7	0–58.9
	12–24	7.3	0–12.0	16.5	0–37.2
	24–48	1.8	0–4.7	3.2	0–9.4
	48–72	0.3	0–0.8	0.1	0–0.3
	0–72	46.8	24.8–62.7		

[a] Recovery of enoxacin is expressed as percentage of dose. Recovery of oxoenoxacin is expressed in milligrams.
[b] NA, Not available.

tested. Mean analytical recoveries were 89% for enoxacin and 80% for oxoenoxacin.

Pharmacokinetics and statistical analysis. Serum concentration-time data were analyzed by using noncompartmental pharmacokinetic methods (2). The areas under the zero and first moment of the serum concentration-time curves (AUCs) were calculated by the linear trapezoidal rule method. The terminal slope was determined by fitting an open two-compartment body model to data for serum by using extended least-squares regression, with the variance modeled as Y^{PWR}, where Y is the predicted drug concentration, and PWR is a fitted parameter constrained to be between 1 and 3 (MK model; Elsevier Biosoft, Cambridge, United Kingdom). Residual areas were calculated by dividing the last measurable concentration of enoxacin or oxoenoxacin by the respective terminal slope. Major pharmacokinetic parameters were calculated by using standard equations corrected for an i.v. infusion (2). Enoxacin and oxoenoxacin renal clearances were calculated as follows Ae_{0-24}/AUC_{0-24}, where Ae_{0-24} is the amount of drug or metabolite excreted unchanged in the urine for the collection period from 0 to 24 h and AUC_{0-24} is the area under the serum enoxacin or oxoenoxacin concentration-time curve from 0 to 24 h. Nonrenal clearance of enoxacin was calculated as the difference between total and renal clearances.

The pharmacokinetic parameters obtained in each group were compared by the Peritz F test (3). Correlations were performed by using unweighted least-squares regression analysis. The intercept was forced through zero for correlations between creatinine and enoxacin or oxoenoxacin renal clearance.

RESULTS

Enoxacin pharmacokinetics. Table 1 summarizes the demographic characteristics of the patients examined in this study. None of the patients experienced side effects or toxicity which could be attributed to enoxacin. Figure 1 depicts mean serum concentration-time curves for enoxacin for each of the five patient groups studied. Overall, reduced renal function was associated with higher and more prolonged enoxacin concentrations.

Table 2 summarizes the pharmacokinetics of enoxacin in each of the five patient groups. Average peak concentrations in each group ranged between 4.7 and 7.1 mg/liter; there was no statistically significant difference between groups. At 12 h, enoxacin concentrations in serum were significantly higher in groups 2 and 3 than those observed in group 5. Figure 2 depicts the linear correlation between creatinine clearance and total, renal, and nonrenal enoxacin clearances and the slope of the terminal elimination phase (λ_z). Patient groups with creatinine clearances lower than 30 ml/min had mean values for total enoxacin clearance approximately one-third or less of those observed in group 5 patients (creatinine clearance, >60 ml/min); the total enoxacin clearance in groups 1 to 3 was significantly less than that observed in group 5 patients (Table 2; $P < 0.05$). The reduction in total clearance in these groups was largely due to reduced renal enoxacin clearance; however, nonrenal enoxacin clearance in patients with a creatinine clearance of less than 15 ml/min (group 2) was significantly less than that observed in group 5 patients (Table 2; $P < 0.05$). Interpatient variability was notably large in some patient groups; one patient in group 3 had total and nonrenal enoxacin clearances larger than the calculated mean value plus six times the standard deviation for group 3 without this patient.

Changes in enoxacin clearance were reflected in changes

TABLE 4. Oxoenoxacin pharmacokinetic parameters according to renal impairment[a]

Pharmacokinetic parameter[b]	Group 1	Group 2	Group 3	Group 4	Group 5
C_{max} (mg/liter)	1.78 ± 0.63 (1.18–2.52) (n = 4)[c]	1.24 ± 0.52 (0.78–1.81) (n = 3)	0.95 ± 0.27 (0.5–1.17) (n = 6)	0.54 ± 0.17 (0.36–0.74) (n = 4)	0.71 ± 0.37 (0.36–1.31) (n = 5)
C_{12} (mg/liter)	1.20 ± 0.09 (1.13–1.26) (n = 2)[c]	1.02 ± 0.28 (0.74–1.41) (n = 4)[d]	0.69 ± 0.40 (0.20–1.17) (n = 6)[d]	0.31 ± 0.16 (0.13–0.41) (n = 3)[d]	ND[e]
AUC_{0-24} (mg · h/liter)	44.06 ± 31.0 (22.30–79.53)[d]	24.11 ± 7.85 (17.07–35.35)[c]	17.23 ± 7.62 (6.64–26.59)[d]	7.83 ± 3.29 (4.08–10.23)[d]	2.81 ± 1.16 (1.20–4.24)
CL_R (ml/min per kg)		0.11 ± 0.09 (0.03–0.22)[d]	0.45 ± 0.35 (0.09–1.12)[d]	1.39 ± 1.51 (0.51–3.13)	4.00 ± 3.36 (2.0–9.02)[f]

[a] Values are means ± standard deviations; values in parentheses are ranges.
[b] Abbreviations: C_{max}, maximum concentration of oxoenoxacin in serum; C_{12}, concentration of enoxacin in serum at 12 h; AUC_{0-24}, AUC from 0 to 24 h; CL_R, renal clearance.
[c] Significantly different from groups 4 and 5.
[d] Significantly different from group 5.
[e] ND, Not detectable.
[f] Data for patient 21 in group 5 were excluded from the statistical computations.

in the half-life of the terminal elimination phase (λ_z). The terminal half-life was statistically significantly prolonged in groups 1 to 3 (mean values, 13.0 to 19.9 h) compared with that in group 5 (4.5 h) ($P < 0.05$); interpatient variability was considerably large and did not appear to be related to the degree of decrement in renal function. The steady-state volume of distribution was not different between groups (Table 2). Table 3 shows the urinary excretion of enoxacin. Average urinary recovery in each group ranged from 12.5 to 48.1% of the dose and decreased with worsening renal dysfunction.

Oxoenoxacin pharmacokinetics. Table 4 summarizes the pharmacokinetics of oxoenoxacin in each patient group. Renal dysfunction was associated with higher concentrations of oxoenoxacin in serum. The AUC_{0-24} for oxoenoxacin in groups 1 to 4 differed significantly from those observed in patients with normal renal function; the higher AUCs in each patient group reflect changes in both metabolite formation as well as elimination. Plots of the ratio of oxoenoxacin: enoxacin concentration versus time were convex for all patients, indicating that the rate of metabolite formation was rate limiting in patients with normal as well as decreased renal functions (5).

Figure 3 depicts the linear relationship between creatinine clearance and renal oxoenoxacin clearance. As with enoxacin, oxoenoxacin renal clearance in groups 2 and 3 (creatinine clearance, less than 30 ml/min) was significantly less than that observed in patients with creatinine clearances exceeding 60 ml/min (Table 4).

Table 3 shows the urinary excretion of oxoenoxacin. The urinary recovery of oxoenoxacin was significantly lower in group 1 patients than in the other patients.

Hemodialysis. Figure 4 depicts enoxacin and oxoenoxacin concentrations in serum in a patient who was on and off hemodialysis. Comparison of the respective AUC_{0-24} values for three patients who were on and off dialysis demonstrated that little enoxacin or oxoenoxacin was removed (Table 5); this was confirmed, in that low concentrations of enoxacin (≤0.09 mg/liter) and oxoenoxacin (≤0.28 mg/liter at 30 min to ≤0.09 mg/liter at 240 min) were measured in the dialysate collected over the dialysis period. An increase in oxoenoxacin concentrations (redistribution) was observed following dialysis in all three patients.

DISCUSSION

Studies in normal healthy volunteers demonstrated that enoxacin excretion is balanced between the renal and nonrenal routes. Following a single oral dose of 600 mg orally and an i.v. infusion of 400 mg, 61 and 46% of the doses, respectively, were recovered unchanged in urine (11). Other studies have reported urinary recovery to be between 44 and 60% (1, 2, 10; M. N. Dudley, Postgrad. Med., in press).

Metabolism of enoxacin occurs on the piperazine ring to form oxo, amino, formyl, and acetyl derivatives; the major metabolite is 4-oxoenoxacin (4 to 15% of the dose excreted in urine (11, 12; Dudley, in press). Oxoenoxacin has antimicrobial activity that is 10 to 15 times less than that of the parent drug (8).

The balance in elimination of enoxacin between the renal and nonrenal routes results in the lack of significant changes in enoxacin pharmacokinetics in patients with creatinine clearances exceeding 30 ml/min. However, in patients with creatinine clearances below 30 ml/min (i.e., groups 1 to 3), the group mean values for the total clearance and half-life of

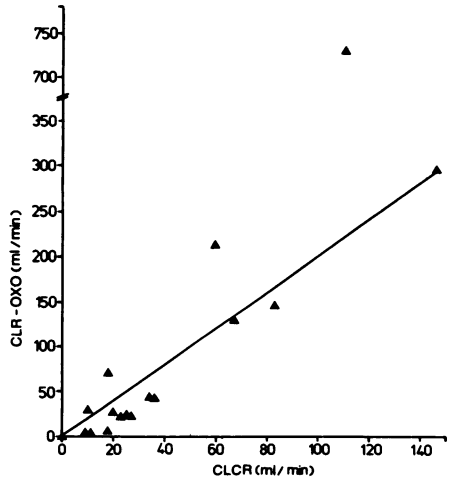

FIG. 3. Relation between creatinine clearance (CL_{CR}) and oxoenoxacin renal clearance (CL_R^{oxo}; $CL_R^{oxo} = 2.02 \times CL_{CR}$; $P < 0.05$). A point (118, 730.8) was not included in the regression.

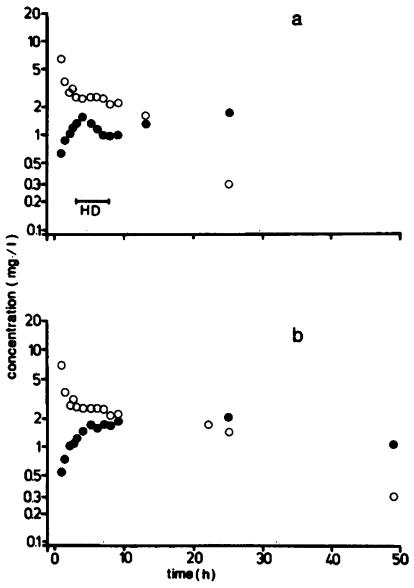

FIG. 4. Enoxacin (○) and oxoenoxacin (●) concentrations in serum in patient 2 after administration of 400 mg of enoxacin i.v. on the day of hemodialysis (HD) (a) and on the day off hemodialysis (b).

enoxacin were significantly prolonged compared with those of patients with creatinine clearances exceeding 60 ml/min. Both renal and, notably, nonrenal enoxacin clearances were significantly correlated with creatinine clearances. The reduction in nonrenal enoxacin clearance with reduced renal function was unexpected, but was consistent with the finding that the formation of the major metabolite oxoenoxacin remained rate limiting for all patients. Our data are in general agreement with those of previous studies of i.v. and oral enoxacin administration in elderly patients (6) and patients with renal dysfunction given a single oral dose (7). Even in the presence of severe renal dysfunction, urinary concentrations of enoxacin exceeded the MICs for most susceptible pathogens, even up to 72 h after administration of a single dose.

In contrast to enoxacin, oxoenoxacin elimination was variably but, on average, lower in patients with milder degrees of renal dysfunction, with marked changes in renal clearance being present as the creatinine clearance fell below 30 ml/min; this is consistent with the fact that renal excretion is the major route of elimination of the metabolite.

In limited studies of three patients undergoing hemodialysis, minimal amounts of enoxacin and oxoenoxacin were found in dialysates; intrapatient comparisons of the serum AUC_{0-24} values confirmed this low extraction. Although clearance of drug by hemodialysis could not be calculated, the low levels of the drug with expected flow rates of between 300 and 500 ml/h suggest a maximum removal of only 10 to 20 mg of drug. The low extraction of enoxacin (and other fluoroquinolones) is consistent with the finding that most of the drug is distributed to extravascular sites in the body and, thus, is not available for extraction during dialysis (4; Dudley, in press). Comparison of group mean values indicated that as the creatinine clearance falls below 30 ml/min, the daily enoxacin dose should be reduced by half; since high peak concentrations of fluoroquinolones may be linked to improved antibacterial effects and reduced selection of resistant bacteria (Dudley, in press), it is recommended that the usual dose be administered once daily (Table 6). With a further decrement in renal function (creatinine clearance, less than 10 to 15 ml/min), half of the usual dose should be given once daily. It should be noted, however, that accumulation of oxoenoxacin will likely occur even with these dosage alterations. The clinical consequences of oxoenoxacin accumulation are unknown.

TABLE 5. AUC_{0-24} for enoxacin or oxoenoxacin for three group 1 patients on and off hemodialysis

Patient no.	AUC_{0-24} (mg · h/liter)			
	Enoxacin		Oxoenoxacin	
	On dialysis	Off dialysis	On dialysis	Off dialysis
2	44.2	55.14	32.5	41.6
3	22.7	31.6	33.4	29.8
4	27.1	34.3	21.2	22.3

TABLE 6. Recommended alterations in enoxacin dosage according to degree of renal impairment

CL_{CR} (ml/min)[a]	Dosage regimen	C_{avg} (mg/liter [95% CI])[b]
80	400 mg every 12 h	1.65 (1.4–2.0)
50	400 mg every 12 h	2.28 (1.9–2.8)
30	400 mg every 12 h	3.04 (2.4–4.0)
30	400 mg every 24 h	1.57 (1.2–2.0)
10	200 mg every 24 h	1.17 (0.8–2.0)

[a] CL_{CR}, Creatinine clearance.
[b] Calculated as C_{avg} (average concentration) = (dose/dosing interval)/[(3.1 × CL_{CR}) + 88]; the 95% confidence intervals (CI) in parentheses are population values.

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