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## Pharmacokinetics and Bioavailability of Intravenous-to-Oral Enoxacin in Elderly Patients with Complicated Urinary Tract Infections

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The pharmacokinetics of oral fluoroquinolone antibiotics in normal volunteers have been studied extensively; however, limited patient data exist. Enoxacin steady-state pharmacokinetics and bioavailability were determined following repeated 400-mg intravenous (i.v.) and oral dosing by using compartmental and noncompartmental methods in 10 elderly (mean age, 73.8 years) men with complicated urinary tract infections. Average peak enoxacin concentrations following i.v. and oral dosing were 8.15 and 5.45 mg/liter, respectively. Mean values for major pharmacokinetic parameters (noncompartmental) were similar following i.v. and oral administration, respectively: area under the concentration-time curve from 0 to 12 h, 47.6 and 41.0 mg · h/liter; volume of distribution or volume of distribution/bioavailability, 1.61 and 1.99 liters/kg; total body clearance or total body clearance/bioavailability, 2.58 and 3.01 ml/min per kg; and half-life, 8.2 and 9.1 h. Parameters from analysis of enoxacin plasma concentration data by using a two-compartment pharmacokinetic model also revealed marked similarities between the two administration routes. Enoxacin was highly bioavailable (mean, 86.97%) following oral administration.

Enoxacin is a new naphthyridine fluoroquinolone antibiotic with potent activity *in vitro* against many gram-positive and gram-negative bacteria (10, 18). Studies in normal volunteers have demonstrated that the bioavailabilities of several newer fluoroquinolones, including enoxacin, exceed 70% (12, 16, 22); however, the pharmacokinetics and bioavailabilities of many of these agents in elderly infected patients are not known. This study examined the pharmacokinetics of enoxacin in a group of elderly patients with complicated urinary tract infections (UTIs) who received enoxacin as an intravenous (i.v.)-to-oral regimen.

### MATERIALS AND METHODS

**Patients.** The patient population comprised elderly men with complicated UTIs enrolled in a clinical trial evaluating the efficacy of enoxacin. A complicated UTI was defined by the presence of one or more of the following: urinary tract obstruction, urologic malignancy, neurogenic urologic disease, or recent instrumentation of the genitourinary tract. Patients excluded from the study included those with terminal illnesses or concomitant infections potentially precluding evaluation of response, liver function tests or a serum creatinine greater than twice the upper limit of normal, inability to accept orally administered medications, chronic antacid therapy, and a known or suspected allergy to quinolones.

**Drug administration.** Patients were initially treated with 400 mg of enoxacin i.v. every 12 h. The drug was diluted in 250 ml of 5% glucose in water and infused into a peripheral vein over 1 h by using a constant-rate infusion pump. The

i.v. tubing was flushed with an additional 20 ml of 5% glucose in water at the end of the infusions to ensure complete delivery of the dose. After at least 72 h of parenteral therapy, patients were changed to oral therapy with 400-mg enoxacin tablets every 12 h. The total duration of therapy was 10 to 14 days.

**Timing of pharmacokinetic studies.** Pharmacokinetic studies were performed after patients had received five or more doses by the i.v. and oral routes to assess steady-state pharmacokinetic conditions. Trough blood samples for enoxacin were obtained from all patients prior to the administration of the two doses preceding the study dose to confirm steady-state pharmacokinetic conditions. On days of pharmacokinetic study, patients were fasted overnight and for at least 2 h after administration of study doses.

**Sample collection.** Following the i.v. doses, blood samples were obtained from an indwelling intravenous cannula (heparin lock) at the following times: predose; 30 min (midinfusion); 1.0 h (end of infusion); and 1.08, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after the start of the infusion. After oral doses, samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after administration. Samples were centrifuged for 20 min; and the plasma was removed, divided into portions in small polypropylene tubes, and frozen at -20°C until it was assayed. For both i.v. and oral study doses, urine was collected and pooled over the following intervals: 0 to 4, 4 to 8, and 8 to 12 h after the start of the i.v. infusion or administration of the oral dose, respectively. Urine volumes were recorded, and portions were frozen at -20°C until the time of assay.

**Drug assay.** The enoxacin concentrations in plasma and urine were determined by high-performance liquid chromatography (HPLC). The mobile phase consisted of a mixture

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of HPLC-grade acetonitrile (Aldrich Chemical Co., Inc., Milwaukee, Wis.) with an ion-pair reagent (16:84 [vol/vol]). The ion-pair reagent was prepared by combining 21 g of citric acid monohydrate (Fisher Scientific Co., Fairlawn, N.J.) and 1 g of ammonium perchlorate (Aldrich) in a 1-liter flask. To this dry fraction, 1.15 ml of tetrabutylammonium hydroxide (Aldrich) in 100 ml of HPLC-grade water was added and further diluted to 1 liter with water. This mixture was then degassed by filtering it twice through 0.2- $\mu$ m-pore-size Nylon-66 filters (Rainin Instrument Co., Woburn, Mass.) under vacuum.

A reversed-phase, 25-cm, partisl 5 ODS-3 analytical column (Whatman International Ltd., Maidstone, England) was used. The mobile phase was passed through the column at a flow rate of 1.0 ml/min. A hand-packed guard column of C-18 pellicular material (Whatman), which was repacked with fresh material every 2 to 3 assay days, was also used. The UV  $A_{340}$  was detected (model 481 LC spectrophotometer; Waters Associates, Inc., Milford, Mass.). Enoxacin standards in plasma or urine were prepared fresh each assay day. Standard concentrations in plasma ranged from 0.2 to 5.0 mg/liter, while standard concentrations in urine ranged from 10 to 300 mg/liter. Norfloxacin (Merck Sharp & Dohme, West Point, Pa.) stock solutions of 30 and 100 mg/liter were used as internal standards in the plasma and urine assays, respectively.

Plasma standards and samples were prepared by pipetting 0.4 ml of plasma, 0.1 ml of water, and 0.02 ml of internal standard into a 2-ml polypropylene centrifuge tube. Protein precipitation with 0.1 ml of acetonitrile-perchloric acid (4:1 [vol/vol]) was followed by a 10-min centrifugation at  $700 \times g$  (IEC, Needham Heights, Mass.) at 25°C. The supernatant was used for assay. Urine standards and samples were prepared by adding 0.1 ml of urine to 0.8 ml of HPLC-grade water and 0.1 ml of internal standard.

Column retention times for norfloxacin and enoxacin were 7.5 and 9.0 min, respectively. Enoxacin and norfloxacin peak heights were calculated and recorded by using an electronic integrator (LCI 100; The Perkin-Elmer Corp., Norwalk, Conn.). Peak height ratios (enoxacin to norfloxacin) were calculated and regressed against concentrations of known standards by least-squares linear regression.

The within- and between-day coefficients of variation for assay precision of three plasma controls containing 0.25, 1.0, and 3.0 mg of enoxacin per liter were 7.93, 3.63, and 4.54%, respectively (triplicate injections on three separate days for nine injections per control sample). The accuracies of these same controls during assay of patient samples averaged 4.8, 2.6, and 3.4% (range, -4.0 to 8.0%) variations from target values, respectively. Similarly, for three urine controls containing 20, 50, and 200 mg of enoxacin per liter, the within- and between-day coefficients of variation were 3.84, 4.94, and 2.74%, respectively (triplicate injections on three separate days for nine injections per control sample). Mean accuracies of urine controls over 5 assay days averaged 3.8, 3.2, and 1.6% (range, 5.2 to 8.5%) variations from target values, respectively.

**Pharmacokinetic analysis.** Enoxacin plasma concentration data were analyzed by using both noncompartmental and compartmental methods. The areas under the zero and first moments of the enoxacin plasma concentration-time curve were calculated by using the linear trapezoidal rule method. The linear portion of the terminal phase of individual log-linear concentration-time plots was determined by visual inspection. The terminal slope ( $\lambda_z$ ) was then calculated by using unweighted, linear least-squares regression analysis.

Total body clearance (CL) and steady-state volume of distribution were calculated by using standard pharmacokinetic equations (7, 20). Renal clearance ( $CL_R$ ) was determined by dividing the amount of unchanged drug excreted in the urine during the collection interval by the corresponding area under the plasma concentration-time curve (AUC). Nonrenal clearance was calculated by subtracting  $CL_R$  from CL. Bioavailability (F) was calculated by dividing the AUC following oral administration by the AUC following the i.v. dose. To correct for potential intrasubject variability in drug clearance following i.v. and oral dosings, a corrected bioavailability was also calculated by multiplying F by the ratio of the half-lives ( $t_{1/2}$ ) (i.v.:oral) (7).

Enoxacin plasma concentration data were also analyzed by using an open, two-compartment pharmacokinetic model by using extended least-squares regression with the computer program MKMODEL (11). The decision to use a two-compartment model over a more simple model was based on comparisons of the Schwartz criterion for the fitted data (11, 19). The variance [ $\text{var}(Y)$ ] in the predicted drug concentration was given by  $SD^2 \times (V_0 + Y^{PWR})$ , where SD is a standard deviation scale factor calculated by the program,  $Y$  is the structural model prediction,  $V_0$  is the variance independent of  $Y$  (i.e., "background noise") fixed at a very small value, and PWR is the power parameter (constrained between 0 and 3). Standard equations were used to correct for infusion time and to calculate microscopic rate constants.

In fitting plasma concentration data following oral doses, unrealistic estimates of the volume of the central compartment ( $V_1$ ) were often generated. This was due to problems with parameter identifiability; computer-generated estimates for  $V_1$ , the absorption rate constant, and the distribution rate constant were highly correlated with one another and had large confidence intervals. To overcome this parameter identifiability problem, Bayesian constraints were applied to  $V_1$  when individual oral data sets were fitted based on a priori estimates of  $V_1$  from the i.v. dose for that patient. The constraint was applied by using a penalty to the objective function if values for this parameter exceeded the initial estimate by more than 20% (11).

Creatinine clearance ( $CL_{CR}$ ) was calculated for each patient by the method of Cockcroft and Gault (4). Unweighted, linear least-squares regression analysis was used to correlate  $CL_{CR}$  with enoxacin CL and  $CL_R$ , and the statistical significance of the regression coefficients was determined. The regression line for the correlation of  $CL_{CR}$  with enoxacin  $CL_R$  was forced through the origin.

**Response to therapy.** Clinical and microbiological responses in patients were assessed 1 week after the completion of therapy. Clinical effectiveness was assessed as follows: cure, disappearance of base-line signs and symptoms relative to the acute episode; improvement, remission but not complete disappearance of base-line signs and symptoms; and failure, no significant change in base-line signs or symptoms. Microbiological response was assessed as follows: cure, negative urine culture for the original infecting organism; failure, positive culture for the original infecting organism; and superinfection, eradication of the initial infecting pathogen but a positive culture for a different pathogen.

This protocol was approved by human research review committees at the participating institutions, and informed consent was obtained from the patients according to established guidelines.

TABLE 1. Characteristics of study patients

Patient no.	Age (yr)	Wt (kg)	Calculated $CL_{CR}$ (ml/min)	Urologic complication
1	65	51.1	53	Chronic Foley catheter
2	75	54.2	18	Prostate cancer
3	70	58.2	56	Prostate resection
4	64	61.0	64	Prostatic hypertrophy
5	87	59.1	43	Prostate cancer
6	88	56.8	27	Prostatic hypertrophy
7	63	77.3	74	Prostatic hypertrophy
8	92	61.4	34	Prostatic hypertrophy
9	57	72.7	84	Neurogenic bladder
10	77	81.8	45	Prostate cancer
Mean $\pm$ SD	73.8 $\pm$ 12.0	63.4 $\pm$ 10.3	49.8 $\pm$ 20.7	

## RESULTS

Demographic data for the 10 patients who completed the study are given in Table 1. The patients were elderly men (mean age, 73.8 years) who had renal functions consistent with their advanced age (mean calculated  $CL_{CR}$ , 49.8 ml/min) at the time of entry into the trial. Based on height measurements, all patients were within 20% of their ideal body weight.

Figure 1 depicts enoxacin concentrations in plasma of the 10 patients following i.v. and oral administration. Mean trough concentrations at 24 and 12 h prior to administration of the study doses confirmed that steady-state pharmacokinetic conditions were obtained. Enoxacin concentrations in plasma and calculated pharmacokinetic parameters in patient 2 varied substantially (often, greater than 3 standard deviations) from values obtained in the other nine patients studied. Patient 2 had relatively poor renal function on entry into the trial (Table 1) and experienced acute, unexplained increases in his blood urea nitrogen and serum creatinine along with electrolyte abnormalities during the study that were not thought to be related to enoxacin. Because this patient was thought to be an outlier, parameter values for this patient were excluded when means for the study population were calculated. Parameter values for patient 2 are included in the reported ranges in Table 2.

When data for patient 2 were excluded from the group analysis, mean (range) peak and trough enoxacin concentrations in plasma following i.v. and oral dosing were 8.15

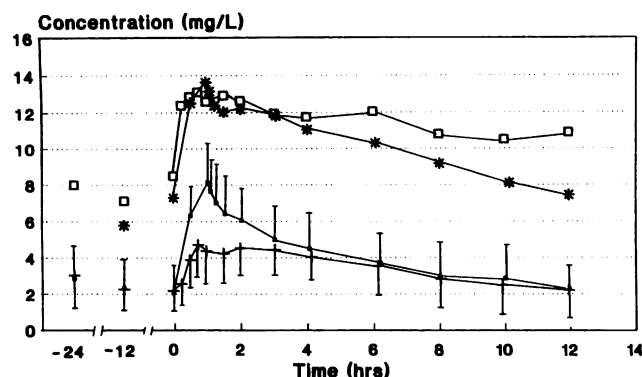


FIG. 1. Enoxacin concentrations (mean  $\pm$  standard deviation) in plasma at steady state in nine patients following 400-mg i.v. (■) and oral (+) doses. The i.v. (\*) and oral (□) data for patient 2 are depicted separately.

mg/liter (range, 5.5 to 11.1 mg/liter) and 2.31 mg/liter (range, 0.4 to 4.7 mg/liter) and 5.45 mg/liter (range, 2.3 to 6.6 mg/liter) and 2.19 mg/liter (range, 0.5 to 4.7 mg/liter), respectively, in the nine patients. The mean time to reach peak concentrations following oral dosing was 2 h, but it varied between 0.5 and 6 h. This variability in time to reach peak concentrations accounts for an artifactual "second peak" in the mean plasma enoxacin concentration-time curve following oral dosing (Fig. 1); a second peak was not observed in individual curves.

The oral F of enoxacin in these patients ranged between 66.5 and 113.1%, with an average of about 87% (Table 2). Application of a correction factor to the AUC ratios for slight changes in noncompartmental elimination  $t_{1/2}$  ( $t_{1/2\lambda_z}$ ) between the i.v. and oral phases had little impact on the calculated bioavailability. The mean fractions of the administered dose excreted unchanged in the urine in six patients with complete 12-h urine collections were 50.6 and 50.0% following i.v. and oral dosing, respectively, when corrected for F.

**Noncompartmental pharmacokinetic analysis.** Noncompartmental pharmacokinetic data were analyzed following i.v. and oral administration, and the results are given in Table 2. Enoxacin disposition was consistent within each patient, as evidenced by marked similarities in major pharmacokinetic parameters following parenteral and oral administration. The apparent volumes of distribution ( $V_{area}$  or  $V_{area}/F$ ) averaged 1.6 liters/kg (range, 1.0 to 2.4 liters/kg) and 2.0 liters/kg (range, 1.4 to 3.2 liters/kg) following i.v. and oral administration, respectively. The mean  $t_{1/2\lambda_z}$  was approximately 8 to 9 h following the two administration routes. The estimated  $t_{1/2\lambda_z}$ s in patient 2 were 14.9 and greater than 38 h following i.v. and oral dosing, respectively.

High concentrations of enoxacin were present in urine following i.v. and oral administration. Mean  $\pm$  standard deviation concentrations of enoxacin in urine over the intervals of 0 to 4, 4 to 8, and 8 to 12 h following the i.v. dose were 446  $\pm$  309, 359  $\pm$  106, and 322  $\pm$  172 mg/liter, respectively. Following oral dosing, concentrations of enoxacin in urine were 376  $\pm$  214, 442  $\pm$  286, and 264  $\pm$  124 mg/liter, respectively, over the same collection intervals.

In the nine patients included in the group analysis, enoxacin CL (or CL/F following oral dosing) averaged 2.58 ml/min per kg (range, 1.0 to 4.84 ml/min per kg) and 3.01 ml/min per kg (range, 1.50 to 6.07 ml/min per kg) following i.v. and oral dosing, respectively. The enoxacin  $CL_R$  was approximately 1.4 ml/min per kg by either route of administration and explained approximately half of the CL. The

TABLE 2. Parameters from noncompartmental pharmacokinetic analysis of enoxacin under steady-state conditions following i.v. and oral administration<sup>a</sup>

Dose	AUC <sub>0-12</sub> (mg · h/liter)	V <sub>area</sub> (liters/kg)	V <sub>ss</sub> (liters/kg)	CL (ml/min per kg)	CL <sub>R</sub> (ml/min per kg)	CL <sub>NR</sub> (ml/min per kg)	f <sub>e</sub> (%)(0-12 h)	t <sub>1/2z</sub> (h)	F (%)	F <sub>corr</sub> (%)
i.v.	47.59 ± 18.40 (18.94-121.1)	1.61 ± 0.49 (0.96-2.41)	1.52 ± 0.52 (0.90-2.50)	2.58 ± 1.11 (1.00-4.84)	1.41 ± 0.66 (0.19-2.41)	1.17 ± 0.90 (0.11-3.04)	50.6 ± 18.90 (33.8-78.0)	8.19 ± 3.56 (4.43-14.87)		
Oral <sup>c</sup>	41.02 ± 15.34 (15.12-138.3)	1.99 ± 0.67 (1.39-3.25)		3.01 ± 1.39 (0.89-6.07)	1.46 ± 0.77 (0.10-2.68)	1.55 ± 0.87 (0.65-3.38)	42.2 ± 19.80 (10.5-69.0)	9.13 ± 5.39 (3.47-38.72)	86.97 ± 16.38 (66.45-114.3)	83.24 ± 19.65 (43.89-115.7)

<sup>a</sup> Values are means ± standard deviations; ranges are given in parentheses and include data for patient 2. Abbreviations: AUC<sub>0-12</sub>, area under the concentration-time curve from 0 to 12 h; V<sub>area</sub>, volume of distribution calculated from the terminal slope and AUC; V<sub>ss</sub>, volume of distribution at steady state; CL, total body clearance; CL<sub>R</sub>, renal clearance; CL<sub>NR</sub>, nonrenal clearance; f<sub>e</sub> (0-12 h), fraction of the administered dose excreted unchanged in urine; t<sub>1/2z</sub>, noncompartmental elimination half-life; F, bioavailability; F<sub>corr</sub>, corrected bioavailability. Median values for selected parameters, including those for patient 2, are as follows: for i.v. dose, AUC<sub>0-12</sub>, 50.21 mg · h/liter; V<sub>area</sub>, 1.49 liters/kg; CL, 2.24 ml/min per kg; t<sub>1/2z</sub>, 8.18 h; for oral dose, AUC<sub>0-12</sub>, 43.32 mg · h/liter; V<sub>area</sub>, 1.79 liters/kg; CL/F, 2.69 ml/min per kg; t<sub>1/2z</sub>, 8.04 h.

<sup>b</sup> Based on complete 12-h urine collections in six patients.

<sup>c</sup> Values for V<sub>area</sub>, CL, and nonrenal clearance represent the value divided by F.

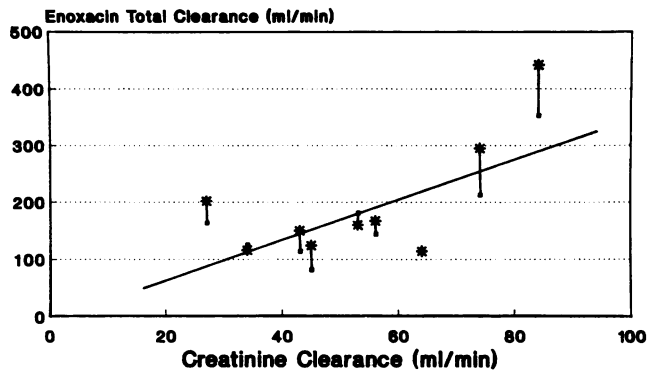


FIG. 2. Correlation of CL<sub>CR</sub> with enoxacin CL following i.v. and oral dosings in nine patients. Connected points indicate values from an individual patient for their i.v. (■) and oral (\*) doses. (CL [ml/min] = 3.53 × CL<sub>CR</sub> [ml/min] - 8.12) (r<sup>2</sup> = 0.46; P < 0.005).

mean enoxacin CL<sub>R</sub> in these patients was approximately 1.8 times greater than the mean calculated CL<sub>CR</sub>. Enoxacin CL and CL<sub>R</sub> in patient 2 were 1.02 and 0.19 ml/min per kg, respectively. Figures 2 and 3 depict the inpatient variability in enoxacin CL and CL<sub>R</sub> and their relation with CL<sub>CR</sub>, respectively. In both cases, statistically significant correlations were found.

**Compartmental pharmacokinetic analysis.** Results of the analysis of pharmacokinetic data by using a two-compartment body model are given in Table 3. Values for major pharmacokinetic parameters derived from compartmental analysis, including CL, volume of distribution at steady state, and compartmental elimination t<sub>1/2</sub> (t<sub>1/2β</sub>) were similar to those obtained by noncompartmental methods. V<sub>1</sub> was found to be about 0.5 liter/kg; a large extravascular compartment of between 0.89 and 1.26 liters/kg was also noted.

**Clinical response.** The infecting organisms and clinical response to enoxacin therapy in the 10 study patients are shown in Table 4. Patient 2 died prior to the assessment of response. All nine evaluable patients had a favorable clinical response; eight were cured and one was classified as improved at the evaluation on day 7. Microbiologically, the original pathogen(s) was eradicated from five of the nine evaluable patients; three patients were found to be superinfected (two with yeasts and one with *Serratia marcescens*) 7 days after enoxacin treatment. Enoxacin failed to eradicate any initial pathogens from one patient with a chronic,

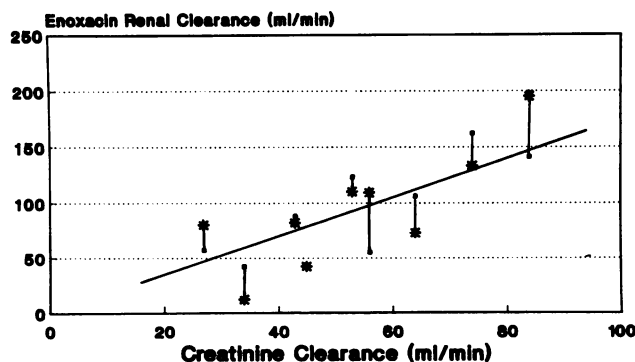


FIG. 3. Correlation of CL<sub>CR</sub> with enoxacin CL<sub>R</sub> following i.v. and oral dosings in nine patients. Connected points indicate values from an individual patient for their i.v. (■) and oral (\*) doses (CL<sub>R</sub> [ml/min] = 1.74 × CL<sub>CR</sub> [ml/min]) (r<sup>2</sup> = 0.60; P < 0.005).

TABLE 3. Parameters from compartmental pharmacokinetic analysis of enoxacin under steady-state conditions following i.v. and oral administration<sup>a</sup>

Dose	V <sub>1</sub> (liter/kg)	CL (ml/min per kg)	α (h <sup>-1</sup> )	β (h <sup>-1</sup> )	t <sub>1/2β</sub> (h)
i.v. <sup>b</sup>	0.47 ± 0.15 (0.21–0.71)	2.68 ± 1.15 (1.12–4.68)	4.64 ± 3.52 (1.14–11.55)	0.11 ± 0.04 (0.06–0.16)	7.42 ± 3.44 (4.36–12.60)
Oral <sup>c</sup>	0.56 ± 0.17 (0.33–0.78)	3.16 ± 1.73 (1.18–6.98)	6.99 ± 3.57 (1.93–12.50)	0.10 ± 0.05 (0.04–0.20)	8.42 ± 4.51 (3.46–15.75)

<sup>a</sup> Values are means ± standard deviations; ranges are included in parentheses. Abbreviations: V<sub>1</sub>, volume of the central compartment; CL, total body clearance; α, distribution rate constant; β, elimination rate constant; t<sub>1/2β</sub>, compartmental elimination half-life; k<sub>10</sub>, k<sub>12</sub>, and k<sub>21</sub>, elimination rate constants from central compartment, from central to peripheral compartment, and from peripheral to central compartment, respectively; V<sub>ss</sub>, volume of distribution at steady state; V<sub>T</sub>, volume of the extravascular compartment. For oral doses, values for V<sub>1</sub>, CL, volume of distribution at steady state, and volume of the extravascular compartment represent the value divided by F.

<sup>b</sup> Patients 2 and 8 were excluded from group analysis (concentration-versus-time data were not described by the two-compartment model).

<sup>c</sup> Patients 2 and 6 were excluded from group analysis (concentration-versus-time data were not described by the two-compartment model).

indwelling urinary catheter, despite mean enoxacin concentrations in urine of 250 to 350 mg/liter following i.v. and oral dosings, respectively. No pharmacokinetic variables appeared to be associated with the clinical or microbiological response in these patients.

### DISCUSSION

Increased emphasis has been placed on the evaluation of pharmacokinetic and pharmacodynamic characteristics of newer antimicrobial agents in populations likely to receive treatment with the agent (21). The pharmacokinetics of the fluoroquinolones have been extensively studied in young, normal volunteers or young patients; however, relatively few studies have characterized the disposition of these compounds in elderly patients receiving therapy with these drugs. Issues such as the reliability of oral absorption and the absence of drug accumulation are important considerations for the use of these drugs in this patient population.

In this study, high enoxacin bioavailability was demonstrated in elderly infected patients. Following the distribution and absorption phases after i.v. and oral administration, respectively, enoxacin plasma concentration-versus-time curves were practically superimposable. The amount of drug excreted in urine, another marker of drug absorption for agents excreted by the renal route, further demonstrated excellent bioavailability following oral dosing. Marked variability in the time to reach maximum concentration in plasma following oral dosing was observed; however, the variation in absorption time did not appear to affect the overall extent of enoxacin absorption within each patient.

These results are comparable to those of other investigations of enoxacin pharmacokinetics in elderly patients. In a group of 19 patients (ages, 61 to 84 years) with complicated UTIs, Naber and colleagues (15) reported a mean peak concentration in plasma of 3.55 mg/liter with a mean t<sub>1/2β</sub> of 7.3 h (range, 3.7 to 38.5 h) following a single 400-mg oral dose. Wise et al. (24) reported steady-state peak concentrations of enoxacin of 2.80 mg/liter and a mean t<sub>1/2β</sub> of 6.7 h after repeated oral dosing of 200 mg twice daily in a group of 23 patients greater than 70 years of age with UTIs.

In evaluating the pharmacokinetics of enoxacin in our elderly patients, a smaller V and decreased CL<sub>R</sub> were noted with the values reported in younger subjects. These pharmacokinetic differences are likely due to the well-described changes in physiology associated with advancing age, particularly decreases in total body water and lean body mass and, perhaps most importantly, a decline in renal function (9,

14). These changes result in higher peak drug concentrations, larger AUCs, and prolonged t<sub>1/2s</sub> of certain drugs in this patient population (9, 14). The change in enoxacin CL<sub>R</sub> with CL<sub>CR</sub> in our patients was similar to that observed by others studies in which elderly patients as well as younger patients with renal impairment were evaluated (3, 17, 23). The relation between decreased enoxacin clearance with declining renal function was vividly demonstrated in patient 2 in this study, highlighting the importance of dosage alterations in similar patients.

A few studies have directly compared fluoroquinolone pharmacokinetics in young and elderly subjects. For a single 600-mg oral dose of enoxacin, Dobbs et al. (5) found that maximum concentrations in plasma and AUCs were statistically higher in a group of elderly subjects compared with a group of younger controls; however, enoxacin t<sub>1/2s</sub> were not different between the groups (7.34 and 6.75 h for the young and elderly subjects, respectively). Other investigations of ofloxacin (8) and pefloxacin (6) (fluoroquinolones with markedly different mechanisms of elimination [17]) revealed significant pharmacokinetic differences between young and elderly subjects. Substantially higher peak drug concentrations and prolonged drug elimination were found in the elderly subjects in both studies.

Comparative pharmacokinetic studies of ciprofloxacin (an agent similar to enoxacin in that excretion is balanced

TABLE 4. Clinical and microbiological responses to enoxacin<sup>a</sup>

Patient no.	Infecting organism(s)	Clinical response	Microbiological response
1	<i>Enterobacter cloacae</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i>	Cure	Failure
2	<i>Pseudomonas aeruginosa</i> , <i>Enterococcus</i> sp.	Unevaluable	Unevaluable
3	<i>Proteus vulgaris</i>	Cure	Cure
4	<i>Escherichia coli</i>	Cure	Cure
5	<i>Klebsiella pneumoniae</i>	Cure	Superinfection <sup>b</sup>
6	<i>Escherichia coli</i>	Cure	Cure
7	<i>Escherichia coli</i>	Cure	Cure
8	<i>Proteus mirabilis</i>	Improvement	Superinfection <sup>c</sup>
9	<i>Pseudomonas aeruginosa</i>	Cure	Cure
10	<i>Providencia rettgeri</i> , <i>Proteus mirabilis</i>	Cure	Superinfection <sup>c</sup>

<sup>a</sup> Response evaluations were made 5 to 9 days after the completion of therapy.

<sup>b</sup> Superinfection was due to *Serratia marcescens*.

<sup>c</sup> Superinfections were due to yeasts.

TABLE 3—Continued

$k_{10}$ ( $h^{-1}$ )	$k_{12}$ ( $h^{-1}$ )	$k_{21}$ ( $h^{-1}$ )	$V_{ss}$ (liters/kg)	$V_T$ (liters/kg)
$0.40 \pm 0.24$ (0.13–0.84)	$3.07 \pm 2.74$ (0.57–8.68)	$1.28 \pm 0.69$ (0.49–2.19)	$1.36 \pm 0.28$ (1.02–1.73)	$0.89 \pm 0.21$ (0.64–1.24)
$0.39 \pm 0.29$ (0.11–0.97)	$4.61 \pm 2.56$ (1.02–7.69)	$2.09 \pm 1.47$ (0.74–5.49)	$1.81 \pm 0.67$ (1.33–3.41)	$1.26 \pm 0.65$ (0.72–2.71)

between renal and nonrenal mechanisms) in young and elderly subjects also indicate age-related differences. Ball and co-workers (1) found significantly greater maximum concentrations in serum and AUCs in an elderly group of patients following single 100-mg oral doses. LeBel et al. (13) studied ciprofloxacin pharmacokinetics in young and elderly (age, 70 to 86 years) subjects following single 500-mg oral doses. Mean peak concentrations in serum 8 h after dosing and mean AUCs were found to be significantly higher in the elderly subjects. The  $t_{1/2}$  was approximately double in the elderly patient group (6.8 h) compared with that in the young volunteers (3.7 h). These differences were explained by significantly smaller volumes of distribution at steady state and reduced clearances (both  $CL_R$  and nonrenal clearance) in the elderly patient group compared with those in the younger subjects.

The clinical significance of these pharmacokinetic differences between young and elderly individuals may be realized only through integration with the dose- or concentration-related adverse effects and pharmacodynamic characteristics of the fluoroquinolones. Correlations between fluoroquinolone concentrations and adverse effects, such as those of the central nervous system, remain poorly defined. Wolf et al. (25) noted that higher doses of enoxacin (1,600 mg), which resulted in peak concentrations in serum of 7 to 8 mg/liter, were associated with adverse central nervous system effects (dizziness) in several volunteers more frequently than lower doses were. Further studies are needed to better define the possible relations between concentrations of drug in serum and adverse effects.

In vitro and animal studies evaluating the pharmacokinetics of the antibacterial activities of fluoroquinolones suggest that dosing regimens that produce high peak concentrations may be optimal. This suggestion is based on a number of characteristics of the fluoroquinolones, including concentration-dependent killing and the observation of a significant postantibiotic effect in vitro and in vivo against a number of bacteria (M. N. Dudley, Postgrad. Med., in press). In addition, high peak concentrations have been shown to reduce the emergence of resistant subpopulations in an in vitro model of infection (2). To take advantage of these pharmacokinetic and pharmacodynamic characteristics, particularly in elderly patients, the optimal dosing strategy for these antibiotics may be through administration of usual doses less frequently (i.e., once daily), since a given dose in elderly patients produces a higher peak concentration (compared with that in a young individual) and elimination of the drug is prolonged.

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#### LITERATURE CITED

- Ball, A. P., C. Fox, M. E. Ball, I. R. F. Brown, and J. V. Willis. 1986. Pharmacokinetics of oral ciprofloxacin, 100 mg single dose, in volunteers and elderly patients. *J. Antimicrob. Chemother.* 17:629–635.
- Blaser, J., B. B. Stone, M. C. Groner, and S. H. Zinner. 1987. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine the importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. *Antimicrob. Agents Chemother.* 31:1054–1060.
- Bury, R. W., G. J. Becker, P. S. Kincaid-Smith, R. F. W. Moulds, and J. A. Whitworth. 1987. Elimination of enoxacin in renal disease. *Clin. Pharmacol. Ther.* 41:434–438.
- Cockcroft, D. W., and M. H. Gault. 1976. Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41.
- Dobbs, B. R., L. R. Gazeley, A. J. Campbell, and I. R. Edwards. 1987. The effect of age on the pharmacokinetics of enoxacin. *Eur. J. Clin. Pharmacol.* 33:101–104.
- Dow, J., A. M. Frydman, F. Djebbar, and J. Gaillot. 1988. Single- and multiple-dose pharmacokinetics of pefloxacin in elderly patients. *Rev. Infect. Dis.* 10(Suppl. 1):S107.
- Gibaldi, M., and D. Perrier (ed.). 1982. *Pharmacokinetics*, 2nd ed. Marcel Dekker, Inc., New York.
- Graber, H., E. Ludwig, M. Arr, and P. Lanyi. 1988. Pharmacokinetics of ofloxacin in young and elderly patients. *Rev. Infect. Dis.* 10(Suppl. 1):S106.
- Greenblatt, D. J., E. M. Sellers, and R. I. Shader. 1982. Drug disposition in old age. *N. Engl. J. Med.* 306:1081–1088.
- Henwood, J. M., and J. P. Monk. 1988. Enoxacin: a review of its antibacterial activity pharmacokinetic properties and therapeutic use. *Drugs* 36:32–66.
- Holford, N. MKMODEL manual. 1988. Biosoft, Inc., Cambridge.
- LeBel, M. 1988. Pharmacokinetics of oral fluoroquinolones, p. 196–201. *ISI atlas of science: pharmacology*. ISI, Philadelphia.
- LeBel, M., G. Barbeau, M. G. Bergeron, D. Roy, and Francois Vallee. 1986. Pharmacokinetics of ciprofloxacin in elderly subjects. *Pharmacotherapy* 6:87–91.
- Ljungberg, B., and I. Nilsson-Ehle. 1987. Pharmacokinetics of antimicrobial agents in the elderly. *Rev. Infect. Dis.* 9:250–264.
- Naber, K. G., F. Sorgel, F. Gutzler, and B. Bartosik-Wich. 1985. In vitro activity, pharmacokinetics, clinical safety and therapeutic efficacy of enoxacin in the treatment of patients with complicated urinary tract infections. *Infection* 13:219–224.
- Neuman, M. 1988. Clinical pharmacokinetics of newer antibacterial 4-quinolones. *Clin. Pharmacokinet.* 14:96–121.
- Nix, D. E., R. W. Schultz, R. W. Frost, A. J. Sedman, A. L. Thomas, A. W. Kinkel, and J. J. Schentag. 1988. The effect of renal impairment and hemodialysis on single dose pharmacokinetics of oral enoxacin. *J. Antimicrob. Chemother.* 21(Suppl. B):87–95.
- Reeves, D. S., M. J. Bywater, and H. A. Holt. 1984. The activity of enoxacin against clinical bacterial isolates in comparison with that of five other agents, and factors affecting that activity. *J. Antimicrob. Chemother.* 14(Suppl. C):7–17.
- Schwartz, G. 1978. Estimating the dimension of a model. *Ann. Stat.* 6:461–464.
- Smith, I. L., and J. J. Schentag. 1984. Noncompartmental determination of the steady-state volume of distribution during multiple dosing. *J. Pharm. Sci.* 73:281–282.
- Temple, R. 1987. The clinical investigation of drugs for use by the elderly: food and drug guidelines. *Clin. Pharmacol. Ther.*



- 42:681-685.
22. **Toothaker, R. D.** 1989. Enoxacin absorption and elimination characteristics. *Clin. Pharmacokinet.* **16**(Suppl. 1):52-58.
  23. **Van der Auwera, P., J. C. Stolear, B. George, and M. N. Dudley.** 1990. Pharmacokinetics of enoxacin and its oxometabolite following intravenous administration to patients with different degrees of renal impairment. *Antimicrob. Agents Chemother.* **34**:1491-1497.
  24. **Wise, R., S. L. Baker, M. Misra, and D. Griggs.** 1987. The pharmacokinetics of enoxacin in elderly patients. *J. Antimicrob. Chemother.* **19**:343-350.
  25. **Wolf, R., R. Eberl, A. Dunky, N. Mertz, T. Chang, J. R. Goulet, and J. Latts.** 1984. The clinical pharmacokinetics and tolerance of enoxacin in healthy volunteers. *J. Antimicrob. Chemother.* **14**(Suppl. C):63-69.