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# Effect of Dose on Serum Pharmacokinetics of Intravenous Ciprofloxacin with Identification and Characterization of Extravascular Compartments Using Noncompartmental and Compartmental Pharmacokinetic Models

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The effect of dose on the pharmacokinetics of ciprofloxacin in serum and urine following single intravenous doses of 100, 150, and 200 mg was studied in nine healthy volunteers. Mean peak levels in serum were 1.4, 2.0, and 3.2 mg/liter for the 100-, 150-, and 200-mg doses, respectively. The data on concentrations in serum were best described by a three-compartment pharmacokinetic model. The terminal half-life (from noncompartmental analysis) averaged between 4.2 and 4.6 h. Average urinary recovery ranged between 45.8 and 48.1%. The average renal clearance of ciprofloxacin was 2.9- to 3.4-fold greater than the measured creatinine clearance. Total serum and renal clearances decreased with increasing dose; however, this was not statistically significant ( $P > 0.05$ ; repeated-measures analysis of variance). Ciprofloxacin was well tolerated by all subjects. In this dose range, ciprofloxacin pharmacokinetics are independent of dose.

Ciprofloxacin is a new fluoroquinolone antibiotic with potent activity against many clinically important human pathogens (18). As with several newer agents of this class, ciprofloxacin is well absorbed when administered orally and attains bactericidal concentrations in serum and many body fluids and tissues. The results of clinical trials with the oral formulation have documented the efficacy of this agent (1); studies with the parenteral formulation are in progress.

Nonlinear pharmacokinetic properties are often due to saturation of renal, hepatic, or other excretory pathways. This study was designed to characterize the excretion and distribution of ciprofloxacin following intravenous administration and to assess the effect of dose size on pharmacokinetic parameters. In addition, multicompartmental pharmacokinetic models were used to describe the pharmacokinetics of extravascular distribution of ciprofloxacin.

## MATERIALS AND METHODS

**Volunteers.** Nine healthy men were studied. The mean ( $\pm$  the standard deviation [SD]) age, height, and weight were as follows: 23 ( $\pm 3$ ) years, 70.1 ( $\pm 4.2$ ) in. (1 in. = 2.54 cm), 81.5 ( $\pm 9$ ) kg. All subjects had a normal physical examination (including assessment of visual acuity and color perception), electrocardiogram, blood chemistries, hematology, and urinalysis at screening and before and after each dose. All subjects were in excellent health, had no known medical disorders, and had not ingested any medications for at least 2 weeks before entry into the study. Alcohol-containing beverages were withheld for 72 h before each dose and for the duration of sample collection. Volunteers fasted overnight and for the first 4 h of the study. Informed consent was obtained according to the guidelines of our institution.

**Administration and sample collection.** Each volunteer re-

ceived three single, rising ciprofloxacin doses of 100, 150, and 200 mg at exactly 1-week intervals. Doses were prepared from ampoules containing 100 mg of ciprofloxacin (Miles Pharmaceuticals, West Haven, Conn.), which was diluted in normal saline to make a final volume of 100 ml. Each dose was infused over 30 min into a peripheral vein with a constant-rate infusion pump. Intravenous (i.v.) tubing and catheters were flushed with at least 25 ml of saline at the conclusion of the infusion to ensure complete delivery of the dose.

Blood was collected from a second indwelling intermittent i.v. infusion set (heparin lock) at the following times: predose (time zero) and 15 min (midinfusion), 30 min (end of infusion), 35, 40, and 50 min, and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4.5, 6.5, 8.5, 10.5, 12.5, 16.5, 20.5, and 24.5 h after the start of the infusion. Serum was separated from cells by centrifugation, and aliquots were frozen. Urine samples were collected and pooled during 0 to 1.5, 1.5 to 2.5, 2.5 to 3.5, 3.5 to 4.5, 4.5 to 6.5, 6.5 to 8.5, 8.5 to 10.5, 10.5 to 12.5, 12.5 to 16.5, 16.5 to 20.5, 20.5 to 24.5, 24.5 to 36.5, and 36.5 to 48.5 h after the start of the infusion. All urine and serum samples were stored at  $-90^{\circ}\text{C}$  until assay.

**Drug assay.** Ciprofloxacin concentrations in serum and urine were determined by a new high-pressure liquid chromatography method developed in our laboratory. The mobile phase consisted of acetonitrile-0.025 M phosphoric acid buffer (8:92 [vol/vol]). The phosphate buffer was made with phosphoric acid (high-pressure liquid chromatography grade; Fisher Scientific Co., Medford, Mass.) and adjusted to a pH of 3.0 with 40% tetrabutylammonium hydroxide (Sigma Chemical Co., St. Louis, Mo.). This mixture was prepared fresh daily with acetonitrile (high-pressure liquid chromatography grade; Fisher) buffer, filtered through a 0.22- $\mu\text{m}$  (pore size) membrane filter (GS; Millipore Corp., Bedford, Mass.), and degassed in an ultrasonic water bath. The mobile phase was passed through a 10- $\mu\text{m}$ , 25-cm C<sub>18</sub> reversed-phase column (Versapak; Alltech Associates, Inc.,

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Applied Science Div., State College, Pa.) at a flow rate of 1.5 ml/min. A guard column (Alltech) packed with 10- $\mu$ m (diameter) pellicular C<sub>18</sub> packing was used to maintain analytical-column performance. The guard column was repacked each day by removing the top 1 cm of packing and replacing it with new material. The mobile phase was monitored by a fluorescence detector (GM 770; Schoeffel Instruments, Westwood, N.J.) with an excitation wavelength of 274 nm and an emission wavelength of 418 nm (range,  $R = 0.02$ ). The signal was recorded, and the peak height was determined with an integrator.

Stock solutions of ciprofloxacin (BAY 09867, lot 907337; Miles Pharmaceuticals) at 10  $\mu$ g/ml were prepared fresh daily in distilled water. Pipemidic acid (Sigma) at 100.0 and 5.0  $\mu$ g/ml was prepared fresh daily in 1.0 N HCl and used as an internal standard at these concentrations for assay of urine and serum samples, respectively. Urine and serum standards were prepared fresh daily by using the stock solution of ciprofloxacin.

Standards and unknown serum samples were processed by pipetting 500  $\mu$ l of serum into a 1-ml disposable syringe fitted with a 0.22- $\mu$ m disposable filter (Duropore; Millipore). Fifty microliters of internal standard was added to a syringe, and the mixture was vortexed for 15 s. The filtrate was collected, and 10  $\mu$ l was injected into the instrument. Urine samples were prepared by vortexing thawed samples and diluting an aliquot with an appropriate volume of phosphate buffer to bring the concentration into the range of the standard curve.

The column retention times for pipemidic acid and ciprofloxacin were 3.8 and 5.8 min, respectively. Peak heights were determined by the integrator, and ciprofloxacin peak height-internal standard peak height ratios were calculated; these ratios showed a direct linear correlation with the drug concentrations in known standards. Concentrations of unknown samples were calculated from the serum standard curves by least-squares regression. The sensitivity of the assay in serum was 0.008 mg/liter. Linearity of ciprofloxacin-internal standard peak height ratios was demonstrated with ciprofloxacin concentrations in serum and urine in the range of 0.01 to 1 and 0.1 to 20 mg/liter, respectively. Within-day precision for three serum standards ranging in concentration between 0.05 and 0.5 mg/liter ( $n = 5$ ) was 2.4 to 5.2% (coefficient of variation). The accuracy (calculated as [actual measured]/actual  $\times$  100%) of these standards was  $\pm$ 2.2 to 6.4%. Recovery of ciprofloxacin from serum was 96%. The ciprofloxacin serum standards were shown to be stable for at least 11 days at  $-70^{\circ}\text{C}$  (data not shown).

**Pharmacokinetic and statistical analyses.** Data on concentrations in serum were analyzed by using compartmental and noncompartmental pharmacokinetic models. The areas under the zero and first moments of the concentration-time curves for serum were calculated by using the linear trapezoidal rule. The terminal slope ( $\lambda_z$ ) was identified by visual inspection of plots and calculated by using least-squares regression. Residual areas under the curve were determined by dividing the last detectable concentration in serum by  $\lambda_z$  (6). Total-body clearance, volume of distribution at steady state, mean residence time, and noncompartmental half-life were calculated by using standard equations corrected for an i.v. infusion (6). Renal clearance was calculated as the amount of drug excreted unchanged in urine during the urine collection interval divided by the area under the corresponding concentration-time curve for serum. The net renal secretion clearance of ciprofloxacin was calculated by renal clearance  $-$  (0.573  $\times$  measured creatinine clearance), where

0.573 is the fraction of ciprofloxacin unbound to serum protein measured in a previous study (8).

Data on concentrations in serum were also analyzed by using two- and three-compartment open pharmacokinetic models by extended least-squares regression with an Applesoft version of the computer program MKMODEL (N. Holford, University of Auckland School of Medicine, Auckland, New Zealand, 1985), a variant of the program available on the PROPHET computer network (10, 11). The variance in predicted concentrations was modeled as  $Y^{PWR}$  (power model), where PWR was constrained to be between 0 and 3. Macroscopic pharmacokinetic constants were used in defining pharmacokinetic models; standard equations were applied to correct for infusion time and calculate microscopic pharmacokinetic rate constants (6). The goodness of fit of the two- or three-compartment body model to the data was determined by using the Schwartz criterion, defined as log likelihood  $-$  ( $K/2 \times \ln N$ ), where the log likelihood is computed by using the objective function of the extended least-squares regression and is a measurement of how well the parameters in the model describe the data,  $K$  is the total number of structural and variance model parameters, and  $N$  is the number of observations (13).

The effect of dose on pharmacokinetic parameters was assessed by using analysis of variance for repeated measurements (12).

## RESULTS

Mean concentrations in serum for all dose levels are depicted in Fig. 1. The peak ( $\pm$ SD) concentrations in serum for the 100, 150, and 200-mg doses were 1.4 ( $\pm$ 0.6), 2.0 ( $\pm$ 0.5), and 3.2 ( $\pm$ 0.6) mg/liter, respectively. Concentrations in serum declined rapidly immediately following the infusion, with average concentrations falling below 1 mg/liter within 30 min of completion of the infusion with all doses. Following this rapid-distribution phase, a slow-elimination phase with an average terminal half-life of between 4.2 and 4.6 h was observed.

Noncompartmental pharmacokinetic analysis of data on concentrations in serum is summarized in Table 1. Total-body clearance and its two components, renal and nonrenal clearance, tended to decrease with increasing dose; however, this difference was not statistically significant ( $P > 0.05$ ). The volume of distribution (steady state) of ciprofloxacin was large and averaged between 2.0 and 2.4 liters/kg, with no dose dependence ( $P > 0.05$ ).

Urinary concentrations of ciprofloxacin and the excretion rate are depicted in Table 2 and Fig. 2, respectively. Over 25% of the dose was excreted unchanged during the first 4 h. Concentrations in urine were high, with clinically significant concentrations still present at 48 h after the dose. The average urinary recovery of ciprofloxacin at 48 h ranged between 45.8 and 48.1% and was not dose dependent (Table 1;  $P > 0.05$ ). On average, the renal clearance of ciprofloxacin was 2.9- to 3.4-fold greater than the measured creatinine clearance. The mean ( $\pm$ SD) net renal secretion clearance values were 3.83 ( $\pm$ 1.10), 3.61 ( $\pm$ 1.14), and 3.02 ( $\pm$ 0.92) ml/min per kg for the 100-, 150-, and 200-mg doses, respectively; the differences in these values were not statistically significant ( $P > 0.05$ ).

Analysis of serum data with a three-compartment pharmacokinetic model is depicted in Table 3. On the basis of the Schwartz criterion, most of the data sets were best described by using the three-compartment model; this was particularly true with the 200-mg dose. Two peripheral compartments

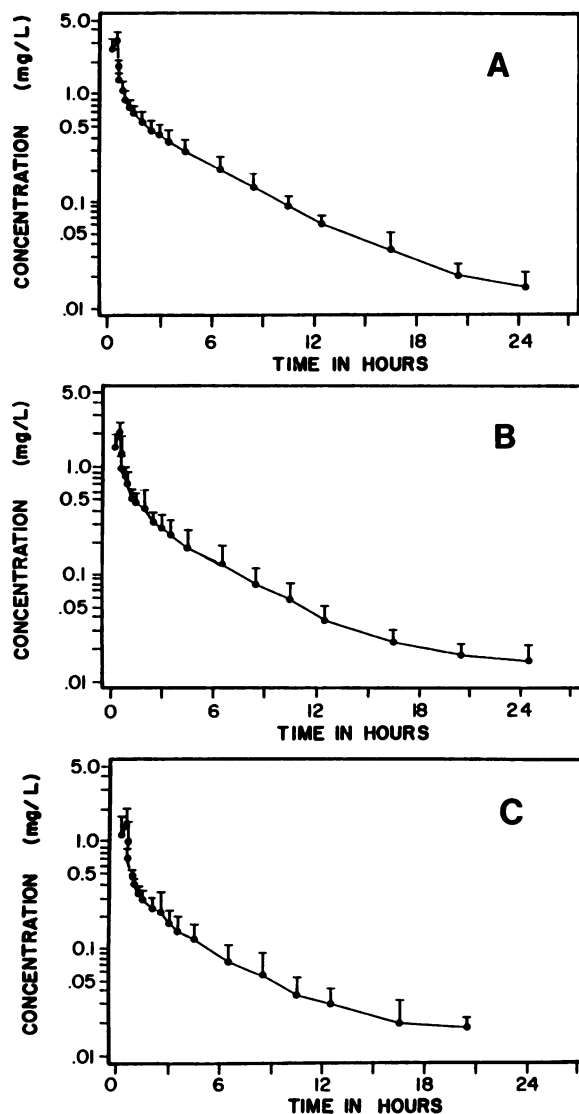


FIG. 1. Mean ( $\pm$ SD) ciprofloxacin concentrations in serum in nine healthy volunteers following a single 30-min i.v. infusion of 200-mg (A), 150-mg (B), and 100-mg (C) doses.

TABLE 1. Noncompartmental pharmacokinetic analysis of ciprofloxacin excretion data for serum and urine

Parameter (unit) <sup>a</sup>	Mean ( $\pm$ SD) value at a dose of:		
	100 mg	150 mg	200 mg
AUC (mg $\cdot$ h/liter)	2.24 (0.54)	3.36 (0.74)	5.17 (0.87)
$V_{ss}$ (liters/kg)	2.17 (0.45)	2.40 (0.61)	2.00 (0.39)
FE (%)	48.1 (5.6)	45.8 (5.9)	46.4 (6.9)
CL (ml/min per kg)	9.60 (2.09)	9.57 (2.02)	8.15 (1.21)
CL <sub>NR</sub> (ml/min per kg)	4.99 (1.18)	5.17 (1.11)	4.34 (0.71)
CL <sub>R</sub> (ml/min per kg)	4.61 (1.14)	4.40 (1.16)	3.80 (0.87)
CL <sub>R-S</sub> (ml/min per kg)	3.83 (1.10)	3.61 (1.14)	3.02 (0.92)
Mean residence time (h)	3.92 (1.81)	4.23 (0.80)	4.10 (0.50)
$t_{1/2\text{eff}}$ (h)	2.72 (0.82)	2.93 (0.56)	2.84 (0.35)
$t_{1/2\lambda z}$ (h)	4.21 (0.89)	4.62 (1.19)	4.22 (0.63)

<sup>a</sup> Abbreviations: AUC, area under the concentration-time curve for serum; FE, fraction of the dose excreted unchanged in urine;  $V_{ss}$ , volume of distribution at steady state; CL, CL<sub>R</sub>, CL<sub>R-S</sub>, and CL<sub>NR</sub>, total serum, total renal, net renal secretion, and nonrenal clearances, respectively;  $t_{1/2\text{eff}}$ , noncompartmental (or effective) half-life; and  $t_{1/2\lambda z}$ , half-life of the terminal slope.

TABLE 2. Mean ( $\pm$ SD) ciprofloxacin concentrations in urine in nine volunteers

Collection interval (h after start of infusion)	Mean ( $\pm$ SD) concn (mg/liter) in urine at a dose of:		
	100 mg	150 mg	200 mg
0-1.5	191.7 $\pm$ 95.9	210.6 $\pm$ 136.8	256.5 $\pm$ 169.6
1.5-2.5	53.8 $\pm$ 49.4	60.8 $\pm$ 33.7	119.0 $\pm$ 82.0
2.5-3.5	41.9 $\pm$ 24.7	59.5 $\pm$ 39.1	81.9 $\pm$ 57.9
3.5-4.5	27.4 $\pm$ 26.4	28.9 $\pm$ 34.4	47.4 $\pm$ 54.1
4.5-6.5	14.4 $\pm$ 8.8	21.0 $\pm$ 17.3	28.1 $\pm$ 28.9
6.5-8.5	10.1 $\pm$ 6.8	13.3 $\pm$ 8.8	26.7 $\pm$ 24.6
8.5-10.5	7.4 $\pm$ 7.5	7.6 $\pm$ 5.5	22.1 $\pm$ 20.2
10.5-12.5	5.1 $\pm$ 4.2	8.6 $\pm$ 6.2	15.4 $\pm$ 11.9
12.5-16.5	5.1 $\pm$ 3.4	4.4 $\pm$ 2.4	11.1 $\pm$ 9.0
16.5-20.5	4.4 $\pm$ 3.6	7.6 $\pm$ 6.5	7.2 $\pm$ 3.4
20.5-24.5	2.6 $\pm$ 3.0	3.9 $\pm$ 2.4	5.3 $\pm$ 3.6
24.5-36.5	0.8 $\pm$ 0.4	1.1 $\pm$ 0.5	1.4 $\pm$ 1.2
36.5-48.5	0.3 $\pm$ 0.1	1.9 $\pm$ 4.2	0.9 $\pm$ 0.8

were identified. A rapidly equilibrating peripheral compartment ( $V_2$ ) accounted for approximately one-fourth to one-third of the total apparent volume of distribution. A deep-tissue compartment ( $V_3$ ) was large and was associated with relatively slow intercompartmental clearance.

Overall, ciprofloxacin was well tolerated by all of the volunteers. There was no laboratory evidence of drug intolerance. Extravasation of infusate containing ciprofloxacin occurred in one subject during the last 5 min of infusion of the 150-mg dose. Slight erythema, induration, and tenderness at the infusion site were observed. Local treatment with warm compresses was applied, and the induration and tenderness subsided within a few hours. No further systemic or local complications were noted in this subject.

## DISCUSSION

Statistical analysis of these data by analysis of variance demonstrated that ciprofloxacin pharmacokinetics are linear and not dose dependent in the narrow dosage range studied, regardless of the type of pharmacokinetic analysis applied; this is similar to the conclusions reached in other studies of i.v. doses in this range (3, 5, 8, 9). The values for total clearance of ciprofloxacin from serum for i.v. doses in the

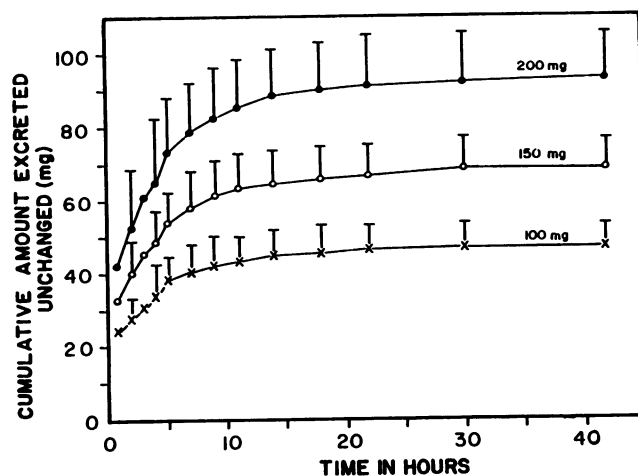


FIG. 2. Cumulative amounts (mean  $\pm$  SD) of ciprofloxacin excreted unchanged in urine for 100-, 150-, and 200-mg doses with time.

TABLE 3. Ciprofloxacin pharmacokinetic parameters with a three-compartment pharmacokinetic model

Parameter (unit) <sup>a</sup>	Mean ( $\pm$ SD) value at a dose of <sup>b</sup> :		
	100 mg	150 mg	200 mg
$k_{10}$ ( $\text{h}^{-1}$ )	2.02 (1.26)	2.20 (1.11)	3.61 (1.99)
$k_{12}$ ( $\text{h}^{-1}$ )	4.48 (4.56)	5.14 (4.08)	8.57 (5.48)
$k_{13}$ ( $\text{h}^{-1}$ )	1.00 (1.12)	1.93 (1.28)	4.31 (3.60)
$k_{21}$ ( $\text{h}^{-1}$ )	1.60 (0.92)	2.44 (1.24)	3.35 (2.74)
$k_{31}$ ( $\text{h}^{-1}$ )	0.19 (0.10)	0.33 (0.25)	0.36 (0.17)
$t_{1/2\lambda_1}$ (h)	0.11 (0.06)	0.08 (0.04)	0.06 (0.04)
$t_{1/2\lambda_2}$ (h)	1.64 (1.18)	0.87 (0.53)	0.92 (0.84)
$t_{1/2\lambda_3}$ (h)	7.40 (3.60)	5.69 (2.24)	4.90 (1.75)
$V_{ss}$ (liters/kg)	2.89 (1.06)	2.53 (0.87)	1.98 (0.39)
$V_1$ (liters/kg)	0.40 (0.56)	0.30 (0.13)	0.20 (0.14)
$V_2$ (liters/kg)	0.91 (0.56)	0.60 (0.36)	0.58 (0.44)
$V_3$ (liters/kg)	1.59 (0.94)	1.63 (0.66)	1.20 (0.47)
$CL_T$ (ml/min per kg)	9.21 (2.46)	9.13 (2.01)	7.96 (1.14)
$CL_{\text{Inter } 1-2}$ (ml/min per kg)	20.67 (15.84)	20.65 (11.60)	20.25 (7.82)
$CL_{\text{Inter } 1-3}$ (ml/min per kg)	4.91 (3.88)	8.62 (6.33)	7.66 (4.94)

<sup>a</sup> There was no effect of dose on any of these parameters ( $P > 0.05$ ; analysis of variance). Abbreviations:  $k_{10}$ ,  $k_{12}$ ,  $k_{13}$ ,  $k_{21}$ , and  $k_{31}$ , intercompartmental transfer rate constants;  $t_{1/2\lambda_i}$ , half-life of the individual slope;  $V_{ss}$ ,  $V_1$ ,  $V_2$ , and  $V_3$ , steady-state volume of distribution and volumes of the central and two peripheral compartments, respectively;  $CL_T$ , total serum clearance;  $CL_{\text{Inter}}$ , intercompartmental clearance.

<sup>b</sup> Data for the 100- and 200-mg doses are for nine volunteers, and those for the 150-mg dose are for eight volunteers, as the data from one subject could not be described by this model.

range reported here are in agreement with those reported by others (3, 7-9, 16, 17) but are higher than those calculated by Drusano et al. (5).

Studies using radiolabeled drug have shown that ciprofloxacin is excreted unchanged in urine and feces and as four metabolites (2). Although not statistically significant, a trend toward decreasing clearance was observed in this study. Both nonrenal and renal ciprofloxacin clearances decreased with higher doses by approximately 15 to 20% with the higher dose. Saturation of nonrenal clearance may occur because of changes in the rate of hepatic biotransformation or decreased excretion into the gastrointestinal tract through biliary or other routes. Dose-ranging studies using large oral doses that might readily saturate hepatic metabolism during the first pass to the liver have not demonstrated changes with increasing dose (9, 15). However, Drusano et al. were able to demonstrate a higher total clearance from serum, particularly of the nonrenal component, with a prolonged infusion of 200 mg over 4 h than with the same dose infused over 30 min (5). Insufficient data exist to determine which of these mechanisms is responsible for the subtle changes in nonrenal clearance observed in these studies.

Renal excretion of ciprofloxacin is predominantly due to net renal tubular secretion of the drug. Although not statistically significant, a trend toward lower renal clearance values with increasing doses was observed in this study as in other studies (8, 9, 15). This may be due to saturable renal tubular secretion of ciprofloxacin, as reflected in decreasing net renal tubular secretion clearance values (Table 1).

Ciprofloxacin distribution to the extravascular space is extensive, as reflected by the large volume of distribution and high concentrations of ciprofloxacin in extravascular fluids and tissues (17, 18). Our analysis with a three-compartmental pharmacokinetic model quantified the approximate sizes and the kinetics of distribution into two peripheral compartments. The rapidly equilibrating compart-

ment ( $V_2$ ) has a high intercompartmental clearance rate; this accounts for the rapid decline in ciprofloxacin concentrations in serum immediately following the conclusion of drug infusion. A third, slowly equilibrating (or deep) tissue compartment with relatively slow intercompartmental clearance contributes to the prolonged terminal half-life (ca. 4 to 5 h) of ciprofloxacin.

Analysis of serum data by different pharmacokinetic methods has resulted in some confusion regarding estimates of some of the pharmacokinetic parameters (e.g., half-life) of the new fluoroquinolones. In contrast to previous studies, we performed our compartmental analysis by using extended least-squares regression, which has been demonstrated to be more precise and less biased in the estimation of pharmacokinetic parameters than other least-squares regression approaches (10, 14). Extended least-squares regression analysis eliminates the necessity of choosing proper weights for analysis of data, which can greatly influence estimates of certain pharmacokinetic parameters (e.g., terminal half-life) whose estimation is largely based on drug concentrations measured in the lower range of assay sensitivity, where precision and accuracy are often poorest. In addition, the value of the terminal half-life may vary according to whether the analysis is conducted with a two- or three-compartment pharmacokinetic model. We used an objective method (the Schwartz criterion) as the basis for determining which model best described the data with the least number of structural-model parameters. This statistic is similar to the Akaike information criterion (19); however, it differs in its use of likelihood ratios rather than the sum of squares. Analysis demonstrated that the three-compartment model was superior to the two-compartment model in most data sets, primarily because of better precision in predicting concentrations in serum during hour 1 following the end of drug infusion. The superiority of the three-compartment model in describing the pharmacokinetics of ciprofloxacin following i.v. infusion has also been noted by others using different criteria (4, 5, 8). However, despite the superiority of the three-compartment model in describing serum data, estimates of the major pharmacokinetic parameters (i.e., clearance, volume of distribution, and half-life) were similar with both methods, perhaps because of frequent sampling in the lower concentration ranges (i.e., the terminal slope).

In summary, we have demonstrated the linearity of ciprofloxacin pharmacokinetics in normal volunteers within the 100- to 200-mg dosage range following i.v. administration. Further studies using higher doses are needed to confirm linear pharmacokinetic properties with larger doses of this drug.

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