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Pharmacokinetics of Ciprofloxacin after Oral and Parenteral Administration

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In 12 fasting volunteers, the pharmacokinetics of ciprofloxacin (Bay o 9867; 1-cyclopropyl-6-fluor-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carbonic acid) were determined after the administration of 50, 100, and 750 mg orally as well as 50 and 100 mg intravenously over 15 min. Serum and urine concentrations were detected with a bioassay. In addition, urine concentrations after a 50-mg dosing were measured by high-pressure liquid chromatography. The serum course of ciprofloxacin could best be described by an open three-compartment model. High volumes of distribution (exceeding 200 liters/100 kg) suggested effective diffusions in the extravascular space. The terminal half-life of ciprofloxacin ranged between 3 and 4 h. High total and renal clearances suggested additional elimination pathways, such as tubular secretion, metabolism, or biliary excretion. After oral administration, absorption was sufficient, and the absolute bioavailability varied between 0.77 and 0.63. Maximal serum concentrations were attained 0.5 to 1 h after dosing; the higher dosage tended towards a delay in absorption. The proportion of the relative amount of metabolites to the total amount of drug excreted in urine increased from 29.7% after intravenous administration to 42.7% after oral dosing, indicating a first-pass effect of the liver. Ciprofloxacin concentrations with a bioassay were 3 to 27% higher than with high-pressure liquid chromatography, which may indicate the presence of biologically active metabolites. No side effects were recorded.

Ciprofloxacin (Bay o 9867; 1-cyclopropyl-6-fluor-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carbonic acid [CIP]) is a new quinoline carboxylic acid derivative with a broad antibacterial activity against gram-positive and gram-negative bacteria (2, 6, 11, 23). This compound was found to be substantially more active against enterobacteriaceae than were the older drugs of this class, such as nalidixic acid, with MICs ranging from 0.008 to 2.0 mg/liter (2, 10).

The purpose of this study was to investigate the pharmacokinetic properties of this compound after oral and intravenous (i.v.) administration of various dosages to determine the absolute bioavailability and the metabolism of this drug.

(This study was presented in part at the 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., 8 to 10 October 1984.)

MATERIALS AND METHODS

Volunteers. Twelve healthy test subjects (six females and six males) with no known allergies to quinoline derivatives participated in the study. Informed written consent was obtained from all volunteers. None of the females were pregnant, and none of the volunteers took any other antimicrobial agent during the 4 weeks preceding the study or during the study. The mean age was 30.0 years (22 to 34 years), the mean body weight was 67.5 kg (51.0 to 80.5 kg), and the mean body surface was 1.8 m^2 (1.56 to 2.04 m^2). Administration of CIP (LOT-no. 861282 as hydrochloride) was supplied as tablets by Bayer AG, Federal Republic of Germany. For parenteral administration, the lactate was used (Bay q 3939; Lot-no. 250583-100-H).

Dosage. After an overnight fast, the subjects were dosed with 50 and 100 mg of CIP orally as well as i.v. and with 750 mg of CIP orally in a random fashion, with a time interval of 2 weeks between each administration. The fasting state was maintained for an additional hour, followed by a fluid intake of 1,000 ml from h 1 to 6 and breakfast after h 2.

CIP (50 ml of a 0.9% NaCl solution containing 50 or 100 mg of the drug) was constantly infused during a 15-min period with a constant pump (Braun-Melsungen, Federal Republic of Germany) via a peripheral venous access. The amount of drugs infused ranged from 47.7 to 55.8 mg (or from 94.7 to 111.4 mg), as assessed by determination of the antibiotic concentration in the residual volume and by back-calculation to the initial amount of the drug in the solution with a mean value of 51.5 mg (or 102.7 mg). The serum concentrations of each volunteer were corrected according to the actual amount of the drug given.

Sampling. Blood samples (6 to 8 ml each) drawn before the first dose showed no detectable antibiotic activity. Samples for assay of serum antibiotic concentrations were taken from a contralateral vein at 0, 5, 10, 20, 30, 45, 60, 75, 90, and 105 min and at 2, 3, 4, 6, 8, 10, 12, and 24 h after i.v. and oral administration. Blood specimens were centrifuged at 4°C after clotting at room temperature. The samples from 0 to 8 h were assayed immediately, and the remaining samples (10 to 24 h) were frozen at −20°C and assayed during the next 2 days. All samples for high-pressure liquid chromatography (HPLC) were stored at −70°C and analyzed within 3 months. Urine samples were collected before the first dose and from 0 to 3, 3 to 6, 6 to 12, and 12 to 24 h after dosing. After the administration of 750 mg of CIP orally, the urine was collected until h 72 after administration. No antimicrobial activity could be detected in the urines before dosing.

Microbiological assay. The microbiological assay was performed by agar diffusion (cup-plate method) (4) as modified by Reeves and Bywater (18). Serum and urine assays were performed with antibiotic medium no. 2 (pH 7.4) (Difco Laboratories, Detroit, Mich.) with *Klebsiella pneumoniae* ATCC 10031 for low concentrations (below 0.15 mg/liter) and *Bacillus subtilis* ATCC 6633 for high concentrations (above 0.15 mg/liter). Pooled normal human antibiotic-free

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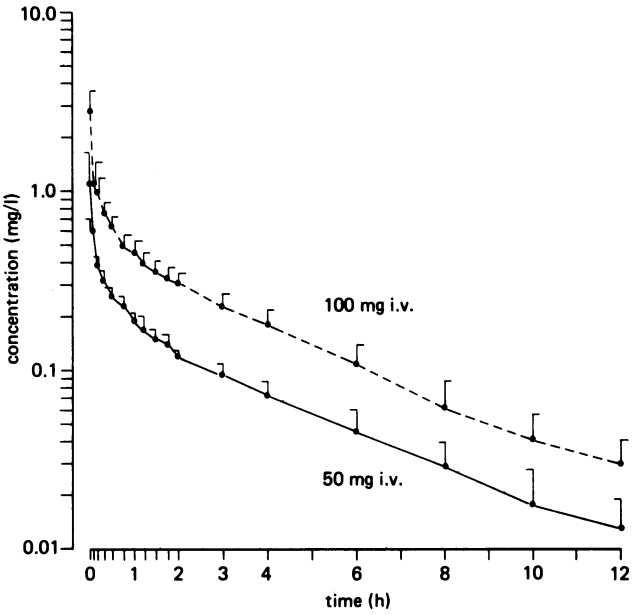

FIG. 1. Serum concentration of CIP (determined by bioassay) after 50- and 100-mg i.v. dosing (15-min infusion) in 12 healthy volunteers (mean body weight, 70.0 kg).

serum (adjusted to pH 7.4) was used as a diluent for serum specimens, and 0.5 M Sörensen phosphate buffer (pH 7.0) was used for urine samples and standards. For laboratory tests, CIP (LOT-no. Pt 828294; activity titer, 845 mg/g) was used. The details of the bioassay have been described previously (4). Serum and urine samples were assayed in triplicate, five standards being used on each plate. Within-batch precision (expressed as coefficient of variation) of the bioassay was 7.2% at 0.1 mg of CIP per liter and 3.8% at 2.0 mg of CIP per liter (n = 12). The detection limits of the bioassay were 0.008 mg/liter with *K. pneumoniae* in serum and buffer (pH 7.4) and 0.15 and 0.07 mg/liter for *B. subtilis* in serum and buffer (pH 7.4), respectively.

Protein binding. Protein binding in serum was determined at different concentrations between 0.1 and 5.0 mg/liter by the micropartition MPS-1 system for separation of free from protein-bound solutes (Amicon GmbH, Witten, Federal Republic of Germany). Separations were done at 22°C, and incubations were done at 37°C.

HPLC. CIP urine concentrations after a 50-mg administration also were determined by HPLC by a modified method (K. Borner, H. Lode, and W. Gau, Abstr. 8th Int. Symp. Column Liquid Chromatogr. 1984, abstr., no. 3a-01; W. Gau, G. Förster, H. J. Ploschke, and H. Schmitz. Abstr. 1st Eur. Congr. Clin. Microbiology. 1983, abstr. no. 348). Basically, the method consisted of the separation of diluted urine by a reversed phase column (Nucleosil 5C18; Macherey & Nagel) at room temperature with the fluorescence detector (FS970; Schoeffel Instruments, Westwood, N.J.; excitation, 275 nm; emission cutoff, >414 nm, sensitivity range, 0.2 μA). An autosampler LC 420 (The Perkin-Elmer Corp., Norwalk, Conn.) was used as the injector, and the flow rate of the pump (model 2/1; The Perkin-Elmer Corp.) was 1.0 ml/min. The retention times for CIP, metabolite 1 (M1), and metabolite 2 (M2) were 3.6, 2.54, and 5.72 min, respectively. The detection limit was 200 μg/liter in urine. Within-batch precision (coefficient of variation) varied from 6.0% (concentration, 0.33 mg/liter to 9.3% (concentration, 2.24 mg/liter); the recovery rate was 99.6%. The calculation of the concentrations of M1 and M2 was based on an assumption of equal fluorescence response of the parent substance.

Biochromatogram. A urine specimen containing high concentrations of CIP and its metabolites was chromatographed at 1 ml/min. The eluate was collected in 1.0-ml fractions, of which UV spectra were recorded. The eluate was diluted with water (1:9), and a microbiological assay was performed with a commercial test strip containing *B. subtilis* ATCC 6051 (5).

Pharmacokinetic analysis. The pharmacokinetic analysis after oral dosing of the substance was based on an open two-compartment model, corresponding to the equation (3, 12, 14): $Cp(t) = Ae^{-\alpha(t - t_0)} + Be^{-\beta(t-t_0)} - Cp_0e^{-k_a(t - t_0)}$, where $Cp(t)$ represents the serum concentration at time t in milligrams per liter, A and B (in milligrams per liter) are the zero intercepts of the tangents α and β with the ordinate, and α and β (per hour) represent the slopes of the rapid initial and the slow terminal distribution and elimination phases, respectively, k_a is the invasion constant, and t_0 is the lag time. After i.v. administration, open two- and three-compartment models were used, following the equations: $Cp(t) = Ae^{-\alpha(t)} + Be^{-\beta(t)}$ (open two-compartment model) and $Cp(t) = Ae^{-\alpha(t)} + Be^{-\beta(t)} + Ce^{-\gamma(t)}$ (open three-compartment model), where $cp(t)$ represents the serum concentration at time t in milligrams per liter; A, B, and C (in milligrams per liter) are the zero intercepts of the tangents α, β, and γ with the ordinate; and α, β, and γ (per hour) represent the slopes of the rapid initial, intermediate, and slow terminal distribution and elimination phase, respectively. The secondary pharmacokinetic parameters were calculated with the aid of these hybrid constants (A, B, and C and α, β, and γ) (14). The least-squares method was used to fit the regression curve to the experimentally obtained values of the serum concentration curve (after normalization of the serum concentrations to a mean body weight of 70.0 kg). A nonlinear least-squares fitting was based as follows on relative errors:

$$\sum_{t=1}^{12} \left(\frac{c_i(t) - \bar{c}(t)}{\bar{c}(t)} \right)^2 = \text{minimum}$$

where c_i stands for the individual serum concentrations of the substance in 12 test subjects at time t, and $\bar{c}(t)$ represents the serum concentration of the regression curve at time t. The pharmacokinetic parameters (for each test subject individually) were calculated by the method of nonlinear regression analysis with a digital computer (IBM 1800 and Control Data Cyber 172) (15). The duration of infusion was considered by the recommendation of Loo and Riegelman (17).

The mathematical calculation of the constants and pharmacokinetic parameters was performed by standard methods as previously described (12, 14, 16). The Wilcoxon test for paired differences was used to distinguish the differences within the pharmacokinetic parameters. Mean geometric regression analyses were done as described previously (1).

Laboratory measurements. Total blood counts, determination of serum creatinine, aminotransferases, alkaline phosphatase, γglutamyl transferase, electrolytes, and bilirubin, Coombs test, and urinalysis were performed before and after the study.

RESULTS

i.v. administration. Mean serum concentrations of CIP after 50- and 100-mg i.v. doses are shown in Fig. 1. The serum concentrations declined from a mean initial value of 1.23 mg/liter (range, 0.7 to 2.2 mg/liter) at the end of the

TABLE 1. Pharmacokinetic parameters[a] (mean ± standard deviation) for CIP in 12 healthy volunteers

Dosage and application	C_{max} (mg/liter)	T_{max} (min)	V_{area} (liters/100 kg)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	$t_{1/2\gamma}$ (min)	AUC_{tot} (mg · h/liter)	f	CL_{tot} (ml/min per 1.73 m^2)	CL_R (ml/min per 1.73 m^2)
50 mg i.v.	–	–	266 ± 40	2.7 ± 0.8	28.6 ± 8.3	180.3 ± 30.1	1.2 ± 0.2	–	687 ± 130	425 ± 116
100 mg i.v.	–	–	210 ± 144	1.7 ± 1.4	20.4 ± 27.7	184.8 ± 113.1	3.0 ± 0.5	–	530 ± 104	335 ± 66
50 mg orally	0.28 ± 0.08	34.9 ± 18.9	304 ± 144	38.3 ± 20.0	206.1 ± 159.3	–	1.0 ± 0.3	0.77 ± 0.16	–	–
100 mg orally	0.49 ± 0.13	49.5 ± 27.0	304 ± 34	41.2 ± 22.9	245.5 ± 25.5	–	1.9 ± 0.6	0.63 ± 0.15	–	–
750 mg orally	2.65 ± 0.48	69.4 ± 17.8	353 ± 57	58.8 ± 22.6	285.1 ± 40.0	–	12.2 ± 2.9	–	–	–

[a] C_{max}, Maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; V_{area}, volume of distribution; $t_{1/2\alpha}$, half-life at α phase; $t_{1/2\beta}$, half-life at β phase; $t_{1/2\gamma}$, elimination half-life; AUC_{tot}, total AUC; f, absolute bioavailability; CL_{tot}, total clearance; CL_R, renal clearance.

50-mg infusion to 0.07 mg/liter (range, 0.05 to 0.11 mg/liter) after 4 h. After 24 h, no serum concentrations could be detected in any of the subjects. After the 100-mg infusion, the mean initial serum level of 2.8 mg/liter (range, 1.9 to 4.4 mg/liter) decreased to 0.18 mg/liter (range, 0.12 to 0.25 mg/liter) after 4 h and to 0.03 mg/liter (range, 0.01 to 0.05 mg/liter) after 12 h. The ranges in serum concentrations indicated considerable interindividual variations. Mean serum concentrations of 0.01 mg/liter could still be measured after 24 h.

The calculation of the pharmacokinetic parameters showed a considerably high volume of distribution with 266 ± 40 liters/100 kg after the 50-mg i.v. infusion and a somewhat smaller volume of distribution of 210 ± 144 liters/100 kg after the 100-mg i.v. infusion (Table 1). Due to the high interindividual variations in the volume of distribution, no statistically significant difference was noted. CIP was eliminated from serum with a terminal elimination half-life, $t_{1/2\gamma}$, of 180 ± 30 min (50 mg i.v.) and 184 ± 113 min (100 mg i.v.).

The total area under the curve accounted for 1.2 ± 0.2 mg · h/liter after the 50-mg infusion and 3.0 ± 0.5 mg · h/liter after the 100-mg CIP infusion. After the 50-mg CIP infusion, a high total clearance of 687 ± 130 ml/min per 1.73 m^2 could be calculated, which exceeded by far the creatinine clearance, indicating additional elimination pathways for the compound. The high renal clearance of 425 ± 116 ml/min per 1.73 m^2 underlined these assumptions. After the 100-mg CIP infusion, the clearance values were smaller; a statistical significance could not be reached due to the considerable interindividual variations (Table 1). These high renal clearances consequently led to high urine drug concentrations, which were 50- to 250-fold higher than concurrent concentrations in serum. The urine concentrations ranged from 172 to 741 mg/liter in the first 3 h and from 15 to 187 mg/liter in the second collection period. Approximately 60 and 62% of each dose were excreted into urine as a biologically active drug during the first 12 and 24 h after administration, respectively (Fig. 2).

Oral administration. Mean serum concentrations of CIP after 50-, 100-, and 750-mg oral doses are depicted in Fig. 3. After a lag time of approximately 10 min (range, 7.4 to 12.3 min), a rapid absorption occurred, leading to maximal peak concentrations between 30 and 70 min after drug administration (Table 1). With increasing doses, a delay in absorption was observed with an increase in the time to maximum concentration of drug in serum from 34.9 min (50 mg) to 69.4 min (750 mg) ($P < 0.05$). The serum concentrations for all dosages offered a rapid distribution and a slow elimination phase (half-life values are shown in Table 1). The terminal elimination half-life could be calculated with 206 ± 159, 246 ± 26, and 285 ± 40 min of 50-, 100-, and 750-mg doses, respectively. Furthermore, the half-life at β phase after the 750-mg oral dosing clearly exceeded that after the i.v. dosing (Table 1) ($P < 0.05$). The quotient oral AUC/i.v. AUC was 77% after 50 mg and 63% after 100 mg of CIP. Progressive reduction of maximal peak concentrations and of AUC after normalization to a reference dose of 0.1 g could be observed as the dose increased (Table 2).

Figure 2 shows the cumulative urine recovery of the three dosages assayed by the agar diffusion test. The highest amount was recovered within the first 3 h for all doses (approximately 18%). After 24 h, 35.6 ± 10.3%, 35.3 ± 8.1%, and 33.0 ± 5.3% were excreted in urine after 50, 100, and 750 mg of CIP, respectively. No relevant additional excretion of the drug could be observed in the 24- to 72-h collecting period after oral administration of 750 mg (0 to 72 h, 33.3 ± 5.8%).

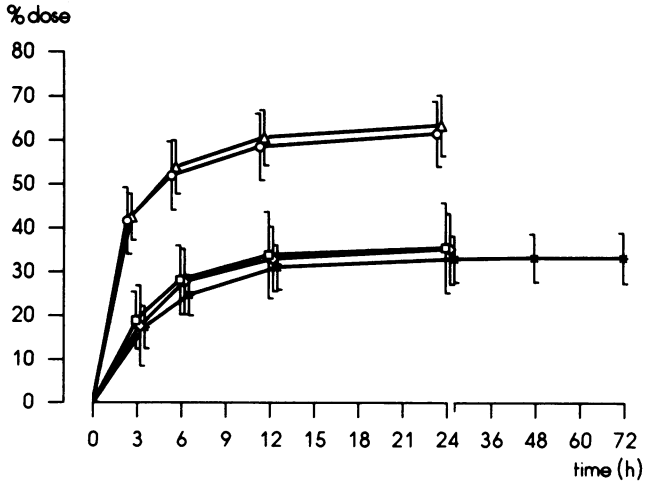

FIG. 2. Cumulative urinary excretion (percentage of dose) of biologically active CIP (determined by bioassay) after various dosages in 12 volunteers. Symbols: ○, 50 mg I.V.; △, 100 mg i.v.; ◇, 50 mg orally; □, 100 mg orally; *, 750 mg orally.

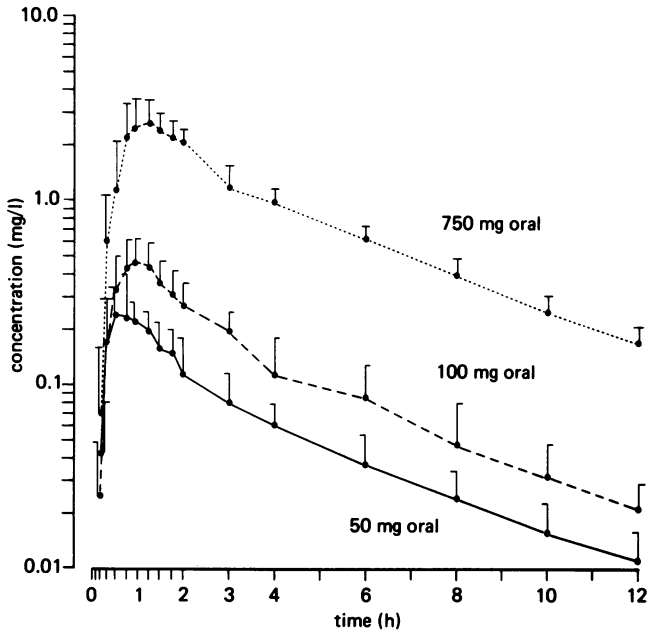

FIG. 3. Serum concentrations of CIP (determined by bioassay) after various oral doses in healthy volunteers (mean body weight, 70.0 kg).

HPLC determination of CIP in urine. After administration of CIP, several fluorescent substances could be detected in urine which were not found in the blanks (chromatogram not shown). Only two major peaks (M1 and M2) were measured in relevant amounts, which did not reveal any antibacterial activity in the biochromatogram against *B. subtilis*. They had the same UV spectrum (240 to 400 nm) as CIP (7). The cumulative excretion in the percentage of dose (mean plus standard deviation) of CIP and M1 and M2 are depicted in Table 3. After an oral dose of 50 mg of CIP, only 29.5% could be recovered as a parent substance; 9.1% appeared as M1, and 12,9% appeared as M2 (amounting to 51% for all three compounds). The cumulative excretion of the parent substance and metabolites after i.v. dosing was considerably different. In the 24-h urine, 57.4% were found as CIP, 10.2% were found as M1, and 14.1% were found as M2, amounting to 81.7% of the dose for all three compounds. The proportion of the relative amount of the metabolites (M1 plus M2) to the total amount of drug (CIP plus M1 plus M2) excreted in the urine increased from 29.7% after i.v. dosing to 42.7% after oral dosing.

Protein binding. The following protein binding values (n = 20) were obtained: 0.5 mg of CIP per liter, 42.7%; 1.0 mg of CIP per liter, 42.7%; 2.0 mg of CIP per liter, 35.8%; and 5.0 mg of CIP per liter, 37.1% with a mean serum protein binding of 39.6% for CIP.

Tolerance. All test subjects were questioned for side effects. There were no complaints. In addition, hematological and chemical parameters remained normal throughout the study.

DISCUSSION

Kinetic model. The decision as to which model best fits the serum concentrations of CIP was based, after calculation of the median values, on both the visual comparison of the regression curve with the measured serum concentrations and on the comparison of the relative squared residuals. The results were confirmed by evaluating the individual data. According to these criteria, after i.v. administration of CIP via a 15-min infusion, the serum time curve could best be described by an open three-compartment model. Furthermore, the goodness of fit and the comparison of the residuals were used for the decision not to use the 24-h values of the serum concentration.

i.v. kinetics. After a 15-min infusion of 100 mg of CIP, it was possible to attain serum concentrations that remained above the mean 90% MIC values for most enterobacteriaceae up to h 3 after administration (2, 6, 11, 23). These concentrations were only attained for the first 15 min after a 50-mg i.v. dose of CIP. CIP was eliminated from the serum with a $t_{1/2\gamma}$ in the same range as that recorded by others (7, 9, 13, 25). The $t_{1/2\gamma}$ in serum for norfloxacin after various oral dosages varied between 5.7 and 7.4 h (22). The total and renal clearances after 50 and 100 mg of CIP were definitely higher than the creatinine clearance, assuming additional elimination pathways, such as tubular secretion, metabolism, or biliary excretion. About 57% of the unchanged substance was recovered in the 24-h urine. The amount of nonrenal elimination of the drug remains open at present, because absolute quantification of the metabolites in urine is not yet possible. Currently, three metabolites of CIP in urine were identified and isolated (H.-J. Zeiler, W. Gau, and U. Petersen, Abstr. 24th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 983, 1984). The amount of renally excreted metabolites of 13.5% reported by these authors roughly equals our own results. The definitive clarification of all metabolites and their quantitative recovery in urine remain to be established.

A noteworthy feature in the kinetics of CIP was the high distribution volume, which far exceeded the extracellular volume (Table 1). Since the determined distribution volume exceeded the volume of the whole body fluid, this could indicate the presence of a deep compartment, e.g., effective diffusion in the extravascular space as shown by Dalhoff and Weidner (9) and Wise et al. (25) in prostate and blister fluids. In view of the serum concentration fluctuations in individual test subjects between h 2 and 4 after dosing, an enterohepatic circulation appears to be theoretically possible (8, 19, 22). Individual patients evidenced serum concentration courses with a hump that was no longer identifiable in the mean value

TABLE 2. Dose dependency of CIP[a]

Oral dosage	C_{max} (mg/liter)	AUC_{tot} (mg · h/liter)
50 mg	0.56	1.80
100 mg	0.49	1.89
750 mg	0.35[b]	1.62[b]

[a] Values are normalized to a 100-mg unit dose. C_{max}, Maximum concentration of drug in serum; ACU_{tot}, total AUC.
[b] $P < 0.05$ for 750 mg orally versus 50 and 100 mg orally.

TABLE 3. Mean excretion of CIP and M1 and M2 in urine as determined by HPLC

Dosage and administration	Mean excretion (% of dose) in urine		Proportion of M1 and M2 on total drug excreted in urine
	CIP	M1 + M2	
50 mg orally	29.5/35.3[a]	22.0	42.7
50 mg i.v.	57.4/61.6[a]	24.3	29.7

[a] Determined by bioassay.

curves obtained by combining the individual curves and superposing the different points of fluctuations.

Oral kinetics. Only limited data exist on the oral pharmacokinetics of CIP in the literature. Comparison of the present results with those published by other authors showed good agreement with respect to the $t_{1/2\gamma}$ and to the time in which the serum concentrations peaked (7, 13, 24, 25). Moreover, the cumulative urine elimination was within the same range (30.6 ± 9.8% of the dose). Wingender and others determined peak serum concentrations after the administration of 250 mg of CIP orally that were nearly identical (0.94 ± 0.28 mg/liter) with the present data when the different dosages were taken into consideration (24). The differences in the terminal half-lives after i.v. and oral administration are difficult to explain (50 and 100 mg versus 750 mg; $P < 0.05$). As identical time periods (approximately 4 to 11 h) in the terminal elimination phase were used for calculation of the $t_{1/2\gamma}$ (i.v. administration) and half-life at β phase (oral administration), these values seem to be independent of the model chosen. The presence of biologically active metabolites or ongoing gastrointestinal absorption might contribute to these differences (25).

Both the urine recovery within 24 h and the absolute bioavailability suggested a sufficient absorption and, to some degree, metabolism of the drug. Furthermore, with increasing doses, a progressive delay in absorption could be detected, evidenced by an increase in the time to maximum concentration of the drug in serum (Table 1). When normalized to a reference unit of 0.1 g of CIP, the maxium concentration of the drug in serum and the total AUC after the 750-mg dosing were smaller than after the 50- or 100-mg oral dosing ($P < 0.05$). Other authors could not detect dose disproportionality of CIP kinetics (13, 20). The different methods used for determination of the serum concentrations (bioassay versus HPLC) might account for these differences.

When the mean recovery rates (percentage of dose) in the 24-h urine as detected by bioassay and by HPLC were compared, a higher amount of drug was recovered by bioassay (50 mg i.v., 61.6 versus 57.4%; 50 mg orally, 35.3 versus 29.5%). As the drug is stable at −20°C, instability might not account for these differences (information from Bayer Co.). Since HPLC is selective for unchanged CIP, this may indicate biologically active metabolites (24). In fact, Wise et al. detected microbiologically active metabolites (25). Additionally, Zeiler et al. reported various antimicrobially active metabolites, one of which showed an activity comparable to that of norfloxacin (Zeiler et al., 24th ICCAC). In this study, the major metabolites M1 plus M2 did not show an antibacterial activity against *B. subtilis* in the biochromatogram.

The increase in the relative amount of M1 and M2 for the total drug excreted in urine after oral dosing may indicate a first-pass effect of the liver. This assumption further underlines the complexity of the pharmacokinetics of CIP. Further studies have to evaluate the specific elimination pathways of this compound.

LITERATURE CITED

1. **Averdunk, R., and K. Borner.** 1970. Korrelation der Thromboplasminzeiten bei Dicumarol-behandelten Patienten unter Verwendung verschiedener Thrombokinase-Präparate. J. Clin. Chem. Biochem. **8**:263–268.
2. **Bauernfeind, A., and C. Petermüller.** 1983. In vitro activity of ciprofloxacin, norfloxacin and nalidixic acid. Eur. J. Clin. Microbiol. **2**:111–115.
3. **Benet, L.** 1978. Effect of route of administration and distribution on drug action. J. Pharmacokinet. Biopharm. **6**:559–585.
4. **Bennet, J. V., J. L. Brodie, E. J. Brenner, and W. M. M. Kirby.** 1966. Simplified accurate method for antibiotic assay of clinical specimens. Applied Microbiology **14**:170–178.
5. **Borner, K., H. Lode, and A. Elvers.** 1982. Determination of apalcillin and its metabolites in human body fluids by high-pressure liquid chromatography. Antimicrob. Agents Chemother. **22**:949–953.
6. **Chin, N. X., and H. C. Neu.** 1984. Ciprofloxacin, a quinoline carboxylic acid compound active against aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. **25**:319–326.
7. **Crump, B., R. Wise, and J. Dent.** 1983. Pharmacokinetics and tissue penetration of ciprofloxacin. Antimicrob. Agents Chemother. **24**:784–786.
8. **Dahlström, B. E., and L. K. Paalzow.** 1978. Pharmacokinetic interpretation of the enterohepatic recirculation and first-pass elimination of morphine in the rat. J. Pharmacokinet. Biopharm. **6**:505–519.
9. **Dalhoff, A., and W. Weidner.** 1984. Diffusion of ciprofloxacin into prostatic fluid. J. Clin. Microbiol. **3**:360–362.
10. **Eliopoulos, G. M., A. Gardella, and R. C. Moellering.** 1984. In vitro activity of ciprofloxacin, a new carboxyquinoline antimicrobial agent. Antimicrob. Agents Chemother. **25**:331–335.
11. **Goodman, L. J., R. M. Fliegelman, G. M. Trenholme, and R. L. Kaplan.** 1984. Comparative in vitro activity of ciprofloxacin against *Campylobacter* spp. and other bacterial enteric pathogens. Antimicrob. Agents Chemother. **25**:504–506.
12. **Greenblatt, D. J., and J. Koch-Weser.** 1975. Clinical pharmacokinetics. N. Engl. J. Med. **193**:702–705, 964–970.
13. **Höffler, D., A. Dalhoff, W. Gau, D. Beermann, and A. Michl.** 1984. Dose- and sex-independent disposition of ciprofloxacin. Eur. J. Clin. Microbiol. **3**:363–366.
14. **Kienel, G.** 1976. Vergleich der Pharmakokinetik von Epicillin und Ampicillin. Drug. Res. **26**:781–789.
15. **Koeppe, P., and C. Hamann.** 1980. A program for nonlinear regression analysis to be used on desk-top computer. Comput. Programs Biomed. **12**:121–128.
16. **Lode, H., R. Stahlmann, and P. Koeppe.** 1979. Comparative pharmacokinetics of cephalexin, cefaclor, cefadroxil, and CGP 9000. Antimicrob. Agents Chemother. **16**:1–6.
17. **Loo, J. C. K., and S. Riegelman.** 1970. Assessment of pharmacokinetic constants from postinfusion blood curves obtained after i.v. infusion. J. Pharm. Sci. **59**:53–57.
18. **Reeves, D. S., and M. J. Bywater.** 1976. Assay of antimicrobial agents, p. 21–78. *In* J. de Lourois (ed.), Selected topics in clinical bacteriology. Balliere Tindall, London.
19. **Ritschel, W. A.** 1980. Handbook of basic pharmacokinetics, 2nd ed. Drug Intelligence Publications, Inc. Hamilton, Ill.
20. **Rogers, J. G.** 1983. Disposition and bioavailability of norfloxacin following oral administration in man, p. 19–23. Proceedings of the 13th International Congress on Chemotherapy, part 38. Verlag-Egermann, Vienna.
21. **Swanson, B. N., V. K. Boppana, P. H. Vlasses, H. R. Rotmensch, and R. K. Ferguson.** 1983. Norfloxacin disposition after sequentially increasing oral doses. Antimicrob. Agents Chemother. **23**:284–288.
22. **Tse, F. L. S., F. Ballard, and J. Skinn.** 1982. Estimating the fraction reabsorbed in drugs undergoing enterohepatic circulation. J. Pharmacokinet. Biopharm. **10**:455–461.
23. **Van Caekenberghe D. L., and S. R. Pattyn.** 1984. In vitro activity of ciprofloxacin compared with those of other new fluorinated piperazinyl-substituted quinoline derivatives. Antimicrob. Agents Chemother. **25**:518–521.
24. **Wingender, W., K.-H. Graefe, W. Gau, D. Förster, D. Beermann, and P. Schacht.** 1984. Pharmacokinetics of ciprofloxacin after oral and intravenous administration in healthy volunteers. Eur. J. Clin. Microbiol. **3**:355–359.
25. **Wise, R., R. M. Lockley, M. Webberly, and J. Dent.** 1984. Pharmacokinetics of intravenously administered ciprofloxacin. Antimicrob. Agents Chemother. **26**:208–210.