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Effect of Standard Breakfast on Drug Absorption and Multiple-Dose Pharmacokinetics of Ciprofloxacin

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Ciprofloxacin was administered to 10 volunteers, who received seven oral doses of 250 mg each at 12-h intervals. Volunteers alternately fasted (F) or received a standard breakfast (B) before the morning dose. Pharmacokinetic parameters were derived from high-pressure liquid chromatography data from samples taken after the first and seventh doses and were analyzed in addition for differences caused by food intake. A significant ($P < 0.05$) influence of the standard breakfast on the time to the peak was observed. Peak levels (± standard deviation) after the first and seventh doses averaged F (fasting): 1.35 ± 0.17, B (breakfast): 1.02 ± 0.28 μg/ml, and F: 1.41 ± 0.32, B: 1.17 ± 0.5 μg/ml, respectively. Mean trough concentrations after the first and seventh doses were F: 0.10 ± 0.03, B: 0.14 ± 0.03 μg/ml, and F: 0.16 ± 0.05, B: 0.14 ± 0.04 μg/ml, respectively. As with the peak, trough concentrations were not affected significantly by food intake or by accumulation over the study period. Breakfast equally did not affect the terminal half-lives, which averaged F: 3.97 ± 0.67, B: 4.35 ± 0.88 h after the first dose and F: 4.64 ± 0.91, B: 3.72 ± 0.84 h after the seventh dose. Twelve-hour urinary recovery measured by high-pressure liquid chromatography averaged F: 31, B: 30% for the first dose and, in spite of a possible carry-over from the sixth dose, decreased to F: 25, B: 28% after the seventh dosing interval. When measured by bioassay, an increase of urinary recovery between the first dose (F: 38, B: 38%) and the seventh dose (F: 45, B: 45%) was observed. These differences suggest induction of drug metabolism with repeated doses. Ciprofloxacin was well tolerated by the volunteers.

Ciprofloxacin is a new quinoline carboxylic acid derivative with high in vitro activity against a broad spectrum of gram-positive and gram-negative organisms (1, 2, 4, 9). Only two pharmacokinetic studies of single oral doses of ciprofloxacin have been published (3) or presented in public (R. Ziegler, K.-H. Graefe, W. Wingender, W. Gau, H.-J. Zeiler, U. Lietz, and P. Schacht, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 23rd, Las Vegas, Nev., abstr. no. 851, 1983). These studies revealed considerable differences in mean levels in serum and in elimination parameters, and it was suggested that they might be due to the influence of food intake.

The present study was performed (i) to evaluate the multiple-dose pharmacokinetics of ciprofloxacin and (ii) to determine the influence of food intake on the various pharmacokinetic parameters.

MATERIALS AND METHODS

Volunteers. Ten healthy volunteers (5 men, 5 women) aged from 22 to 37 years (mean age, 25.7 years) with a mean weight of 63 kg (range, 47.5 to 79 kg) were entered into the study after exclusion of biochemical, urological, or hematological disorders. All underwent a complete physical examination 2 weeks before the study; the results of the examination were normal in all cases. Informed written consent was obtained from each volunteer in accordance with the guidelines of the local ethical committee. Biochemical and hematological profiles were repeated at the conclusion of the study.

Study drug. Tablets of 250 mg (lot Pt 929089) and laboratory reference powder (lot 828269) of ciprofloxacin (Bay o 9867) were obtained from Bayer AG, Wuppertal, Federal Republic of Germany.

Drug assay. Drug concentrations were determined by high-pressure liquid chromatography (HPLC) and a microbiological assay. The methods were previously described in detail (6).

Study design. Seven tablets of 250 mg of ciprofloxacin were given with 150 ml of water at 8 a.m. and 8 p.m. Volunteers, after an overnight fasting period of 8 h, were randomized into two groups which alternately continued fasting (F) for 2 hours or received a standard breakfast (B) immediately before the morning doses (Table 1). The breakfast consisted of 120 g of white bread, 10 g of butter, 10 g of jam and 150 ml of rose hip tea. The protocol specified that the subjects should refrain from taking alcohol and any other drugs for 8 h before the first dose and throughout the entire study period.

Blood and urine samples. Blood samples were taken from an indwelling intravenous cannula at 0, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h after administration of the first and seventh doses. Since the third and fifth doses were also controlled with regard to food intake (F,B), trough levels after administration of these doses were also measured. Urine samples were collected during the three periods from 0 to 4, 4 to 8, and 8 to 12 h after administration of the first and the last doses.

Pharmacokinetic analyses. Fasting and nonfasting pharmacokinetic parameters were derived individually for each volunteer from concentrations in serum and urine, measured by HPLC during the first and last dosing interval. Recovery from urine during the first dosage interval was calculated as a percentage of the administered dose from both HPLC and bioassay data. Arithmetic means ± standard deviations were calculated for peak (C_{max}) and trough (C_{min}) concentrations and from the time to the peak concentration (T_{max}). Areas under the concentration-time curves from 0 to 4, 4 to 8, and 8 to 12 h (AUC_{0-4}, AUC_{4-8}, and AUC_{8-12}) were calculated from the trapezoidal rule, and cumulative amounts of ciprofloxacin excreted in urine within the respective inter-

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TABLE 1. Schedule of multiple-dose study

Group	No. of volunteers		Status of volunteers on day no. (dose no.):			
	Male	Female	1 (1)	2 (3)	3 (5)	4 (7)
I	2	3	F	B	F	B
II	3	2	B	F	B	F

[a] At the beginning, five volunteers were fasting (F) and five volunteers received a standard breakfast (B), whereas the conditions for the last dose on day 4 were reversed.

vals were used to calculate the mean renal clearance (CL_R) (5). The area under the serum concentration curve ($AUC_{0-\infty}$), the terminal half-life ($t_{1/2\beta}$), and the absorption rate constant (K_a) were calculated from polyexponential parameter estimates (8), which were obtained with the program CSTRIP (7). Values for $AUC_{0-\infty}$ were normalized to dose per kilogram of body weight: $AUC_{0-\infty n}$ = (weight/dose) × $AUC_{0-\infty}$ (kg · h/liter).

Statistical analyses. The Welch and Student *t* tests were applied to compare the fasting and nonfasting pharmacokinetic parameters and the differences between the first and seventh dosing intervals. The significance level was $P < 0.05$.

RESULTS

The mean ciprofloxacin concentrations found in serum are shown in Fig. 1. In the nonfasting group (B), peak concentrations in serum are delayed and the standard deviations demonstrate a marked variability of the absorption phase among the subjects within the first 2 h after drug administration. The increase of the trough concentrations between the first and seventh doses was not significant.

The mean values of urinary recovery measured by HPLC and bioassay for the different sampling periods are shown in Fig. 2. They appear to be independent of food intake. The decrease of the 12-h values from the first to the seventh dose, measured by HPLC, is accompanied by an increase in microbiological activity. These changes, although not statistically significant, suggest that less unchanged drug is voided

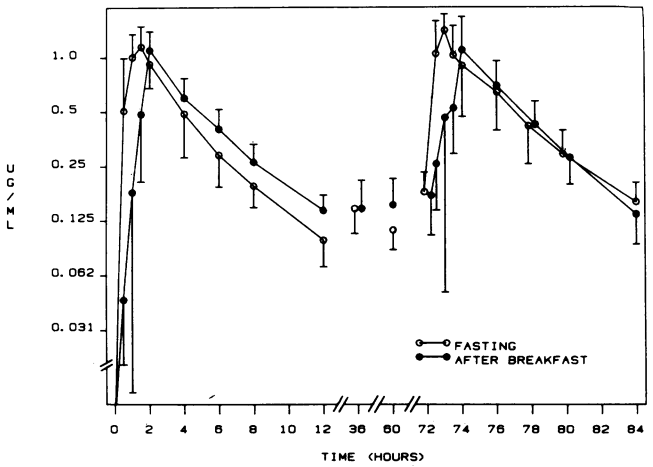

FIG. 1. Mean concentrations of ciprofloxacin in serum after seven oral doses of 250 mg were administered at 12-h intervals to 10 volunteers who either were fasting or had received a standard breakfast. Bars indicate standard deviation.

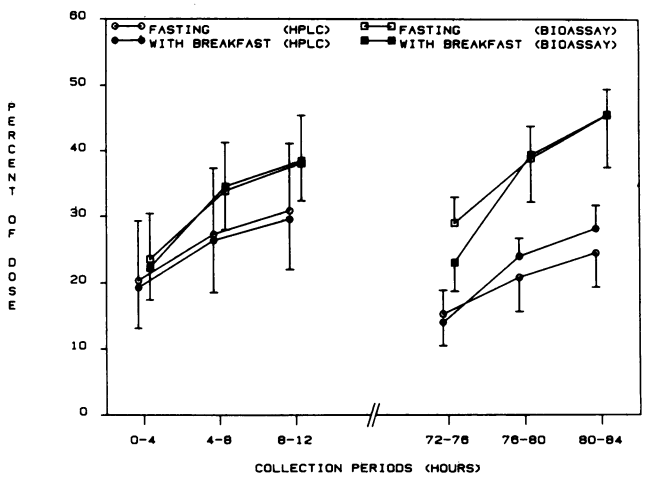

FIG. 2. Mean values of cumulative recovery of ciprofloxacin from urine after the first and seventh oral dose of 250 mg, respectively. Fasting conditions did not significantly influence the extent of renal elimination. Bars indicate standard deviation.

after repeated dosing than after the first dose; this may be due to induction of drug metabolism enzymes.

A summary of pharmacokinetic parameters is shown in Table 2. Food intake had a significant influence on the time to the peak. The terminal half-lives ranged from 3.16 to 6.14 h and were not influenced by the breakfast. Normalization of serum data to body weight did not improve the variability of the pharmacokinetic parameters, and differences between male and female volunteers were not observed.

There were no adverse effects of the drug during this study, and the hematological and biochemical parameters did not change significantly in the pre- and posttreatment period.

DISCUSSION

So far only two pharmacokinetic studies of ciprofloxacin with single oral doses of 250 and 500 mg have been published. No differences are seen for the observed times to the peak concentration and absorption rate constants. Assuming dose-proportional serum levels, the data of Crump et al. (3), who observed peak concentrations of 2.3 μg/ml and a terminal half-life of 3.9 h after a single 500-mg dose, are in agreement with our results. Slightly lower peak values of 0.82 and 1.58 μg/ml, but similar half-lives of 6.55 and 4.54 h after single doses of 250 and 500 mg, respectively, were reported by Ziegler et al. (23rd ICAAC, abstr. no. 851, 1983).

Comparison of microbiological activity and HPLC results for renally excreted ciprofloxacin after the first dose revealed an increasing difference, which was 8% at the end of the first dosing interval. Despite a possible carry-over from the sixth dose, HPLC values for recovery from urine were even lower after the seventh dose, and the difference between HPLC and bioassay increased to 19% at 72 h, which strongly suggests an inducible metabolism of the drug.

This study has shown that (i) multiple doses of ciprofloxacin were well tolerated in healthy volunteers, (ii) no relevant accumulation occurred after seven doses, and (iii) food intake delayed absorption, as shown by an increase in the time to peak concentrations, but did not appear to induce other changes in the pharmacokinetics of ciprofloxacin.

TABLE 2. Pharmacokinetic parameters of ciprofloxacin derived from serum and urine samples of 10 volunteers who alternately were fasting (F) or received a standard breakfast (B) before the first and seventh oral dose of 250 mg

Status of volunteers (dose no.)	C_{max}[a] (μg/ml)	T_{max} (h)	C_{min} (μg/ml)	$t_{1/2\beta}$ (h)	K_a (h^{-1})	$AUC_{0-\infty n}$ (kg · h/liter)	feU (% of dose) by:		CL_R (ml/min per kg)
							HPLC	Bioassay	
F (1)	1.35 ± 0.17	1.30 ± 0.27	0.10 ± 0.03	3.97 ± 0.67	2.46 ± 1.49	1.34 ± 0.24	38.0 ± 10.2	30.8 ± 5.68	4.44 ± 1.96
B (1)	1.02 ± 0.28	1.90 ± 0.22	0.14 ± 0.03	4.35 ± 0.88	1.11 ± 0.34	1.24 ± 0.24	29.6 ± 7.54	38.4 ± 6.82	5.00 ± 1.38
F (7)	1.41 ± 0.32	1.00 ± 0.00	0.16 ± 0.05	4.64 ± 0.91	3.69 ± 3.03	1.77 ± 0.48	24.6 ± 5.20	45.4 ± 7.92	2.90 ± 0.67
B (7)	1.17 ± 0.50	2.20 ± 1.10	0.14 ± 0.04	3.72 ± 0.84	1.04 ± 0.53	1.31 ± 0.26	28.2 ± 3.52	45.5 ± 3.89	3.61 ± 0.40

[a] Abbreviations: C_{max}, maximum concentration in serum; T_{max}, time at which maximum concentration was achieved; C_{min}, trough concentration; $t_{1/2}\beta$, terminal elimination half-life in serum; K_a, absorption rate constant; $AUC_{0-\infty n}$, area under the serum concentration curve normalized to dose per kilogram of body weight (see equation); feU, fraction of dose excreted in urine within 12 h; CL_R renal clearance of ciprofloxacin.

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