

Phase I Study of Multiple-Dose Cefprozil and Comparison with Cefaclor

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The objectives of this study were to assess the safety and tolerance of cefprozil, to characterize the pharmacokinetics of cefprozil after administration of multiple doses of the drug, and to compare these pharmacokinetic parameters with those obtained with cefaclor. The volunteers received 28 doses of 250, 500, or 1,000 mg of cefprozil or 500 mg of cefaclor every 8 h for 10 days. Serial blood samples and the total volume of urine voided by each individual were collected for pharmacokinetic evaluation on days 1, 5, and 10. Both cephalosporins were well tolerated after multiple oral dosing. The peak levels in plasma (C_{max}) of cefprozil ranged from 5.7 to 18.3 $\mu\text{g/ml}$ after oral administration of 250- to 1,000-mg doses. The regression analysis of C_{max} on cefprozil dose showed a dose-linear response. The mean C_{max} of cefaclor ranged from 15.2 to 16.7 $\mu\text{g/ml}$ and did not change significantly on multiple dosing. The overall mean terminal half-life of cefprozil was 1.2 h and was invariant with respect to dose or duration of dosing. The area under the plasma-concentration-versus-time curve from 0 h to infinity ($AUC_{0-\infty}$) of cefprozil increased in a dose-proportional manner with an increase in dose. The overall urinary recovery (61% of dose) and renal clearance values of cefprozil were generally invariant with respect to dose and duration of dosing. While cefprozil was apparently absorbed less rapidly and achieved lower C_{max} values than cefaclor, the $AUC_{0-\infty}$ of cefprozil was nearly twofold greater than that of cefaclor. The half-life of cefprozil was also twofold longer than that observed for cefaclor. Although the urinary recovery of cefaclor (75% of dose) was significantly higher than that of cefprozil (61% of dose), the concentrations of cefprozil in urine remained significantly higher than those of cefaclor from 2 to 8 h postdosing. If the therapeutic concept is maintained that levels of beta-lactam antibiotics in plasma should exceed the MIC for the offending organisms over a period that approximates the dosing interval, then cefprozil would appear to be suitable for twice-daily administration, whereas cefaclor should probably be administered three or even four times a day.

Cefprozil is an oral cephalosporin with an antibacterial spectrum that includes important gram-positive and gram-negative pathogens usually associated with infections of the urinary and respiratory tracts (5, 8, 11, 16). It is structurally similar to other cephalosporins in that it has a phenylglycine side chain. The antimicrobial spectrum of cefprozil is superior to those of cephalixin and cefadroxil and similar to that of cefaclor (5, 8, 11). Studies in animals suggested that cefprozil might offer some pharmacokinetic advantages over cefaclor (11).

The results from a phase I study of single-dose cefprozil indicated that this cephalosporin is well tolerated and exhibits linear pharmacokinetics over a 250- to 1,000-mg dose range (1). One of the objectives of the present study was to assess the safety and tolerance of cefprozil and to characterize the pharmacokinetics in normal volunteers receiving 28 oral doses of 250, 500, or 1,000 mg on a three-times-a-day (t.i.d.) dosing schedule. Another objective was to compare the safety of pharmacokinetic profiles of cefprozil with those of cefaclor after 500-mg t.i.d. dosing for 10 days.

MATERIALS AND METHODS

Antibiotics. Cefprozil capsules (lot no. 20741) were supplied by the Pharmaceutical Product Development Depart-

ment, Bristol-Myers Squibb Co. Cefaclor (Distaclor; lot no. 64137AE) was purchased commercially.

Subjects. A group of 12 subjects was selected randomly to receive the drugs at each dose level. A total of 51 healthy male subjects participated in the study after signing an informed consent form, and 48 completed the study. The subjects had a mean \pm standard deviation age of 26.6 ± 5.6 years, a mean body weight of 71.5 ± 9.0 kg, and a mean height of 174 ± 5.92 cm. The subject exclusion criteria included the presence of drug allergies or intolerance and a history of drug or alcohol abuse. Subjects with renal or hepatic impairment were also excluded from the study. Use of any medications within 2 weeks and use of alcohol within 24 h of induction into the study were not permitted. Use of any drug, including alcohol and caffeine, was forbidden during the course of the study. Confinement to the test facility began the day before the subject received the first dose and continued until the time of release from the study.

Drug administration. The subjects fasted from 10 p.m. of the day before dosing until 4 h after dosing during each session associated with blood and urine sampling. During these sessions, each subject emptied his bladder upon rising in the morning, and approximately 1 h prior to drug administration, each subject drank approximately 360 ml of water. In order to ensure adequate urine flow, subjects drank 100 ml of water every hour for the first 3 h after dosing and as desired thereafter. Twelve subjects were assigned to each of

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the four dose groups. Administration of cefprozil doses proceeded sequentially, with increasing doses given only after the safety and tolerance of the previous dose were determined. The subjects received oral doses of 250, 500, or 1,000 mg of cefprozil or 500 mg of cefaclor every 8 h for 10 days. In all, subjects received 28 doses of either cefprozil or cefaclor. Each dose was given with 300 ml of water.

Sample collection and processing. Serial blood and urine samples were obtained after doses 1 (day 1), 13 (day 5), and 28 (day 10). Approximately 10 ml of blood was drawn immediately before dosing and at 0.25, 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, and 8 h after drug administration on the mornings of dosing days 1, 5, and 10. Single blood samples were drawn for the determination of trough levels (C_{\min}) just prior to administration of the morning dose on each day. Total urine collections were made just prior to dosing and over the intervals of 0 to 2, 2 to 4, 4 to 6, and 6 to 8 h after dosing on the mornings of dosing days 1, 5, and 10.

Immediately after collection, each blood sample was gently inverted a few times for complete mixing with the anticoagulant and then placed in chipped ice. Within 1 h of collection, each blood sample was centrifuged for 15 min at $1,000 \times g$ and 5°C to separate the plasma. The separated plasma was transferred to a screw-cap polypropylene tube, flash-frozen in a solid CO_2 -methanol bath at -70°C , and stored at or below -20°C .

The volume of the urine sample obtained at each collection interval was measured. A 5.00-ml portion of the urine sample was then transferred to a polypropylene tube containing 5.00 ml of sodium acetate buffer (pH 3.57), mixed, and stored at or below -20°C .

Quality-control samples of cefprozil and cefaclor were prepared in drug-free plasma and urine samples on day 1 of dosing. These quality-control samples were stored and assayed together with the study samples.

Assays in biological fluids. For the plasma assay, a solution of cephalixin (150 μl ; internal standard, 300 $\mu\text{g}/\text{ml}$) was added to 100 μl of plasma. The plasma proteins were precipitated by the addition of 20 μl of 5% (wt/vol) trichloroacetic acid and 100 μl of acetonitrile. The mixture was vortexed and centrifuged for 2 min at $13,000 \times g$, and the aqueous phase was transferred to a clean tube containing 40 μl of 5% (wt/vol) trichloroacetic acid and 300 μl of methylene chloride. The mixture was vortexed for 60 s and was centrifuged at $13,000 \times g$ for 3 min. Approximately 150 μl of the upper aqueous layer was transferred to a 330- μl polyethylene vial, and 40 μl was injected onto the high-pressure liquid chromatographic system through a Waters intelligent sample processor (Waters Association, Inc., Milford, Mass.).

For the urine assay, a solution of cephalixin (100 μl ; internal standards, 1,500 $\mu\text{g}/\text{ml}$) was added to 500 μl of buffered urine (each urine sample was buffered with an equal volume of 20 mM sodium acetate buffer [pH 3.8] and 150 μl of 5% [wt/vol] trichloroacetic acid). The mixture was vortexed for 30 s, approximately 200 μl was transferred to a polyethylene vial, and 10 μl was injected onto the high-pressure liquid chromatographic system through a Waters intelligent sample processor.

The high-pressure liquid chromatographic system consisted of a solvent delivery system (590; Waters) and 441 an absorbance detector with a fixed wavelength of 280 nm (model 441; Waters). Chromatographic separation for the plasma and urine assays was accomplished on a reversed-phase C8 Partisil-5-CCS-C8RAC column (0.94 by 10 cm; Whatman Inc., Bridewell, N.J.) and a C18 Partisil-5-ODS-

3RAC column (0.94 by 10 cm; Whatman Inc., Clifton, N.J.), respectively. A precolumn packed with C18 packing material (particle size, 37 μm ; Corasil; Waters Associates) was fitted just before the inlet junction of each analytical column. The eluting solvent mixture for the plasma assay was acetonitrile-0.003 M sodium acetate buffer (pH 3.8; 13:87 [vol/vol]). The mobile phase for the urine assay was prepared by dissolving 1.54 g of sodium acetate trihydrate and 2.67 g of sodium dodecyl sulfate in 1,000 ml of distilled water; adding 5.0 ml of glacial acetic acid, 30 ml of 5% (wt/vol) trichloroacetic acid, 500 ml of acetonitrile, 60 ml of methanol, and 18.5 ml of tetrahydrofuran; and diluting the mixture to 2,000 ml with distilled water. The eluting solvent was delivered at a flow rate of 0.9 ml/min for the plasma assay and 2.0 ml/min for the urine assay.

Levels of cefaclor in plasma and urine were measured by a previously described method (14).

Pharmacokinetic analysis. The following noncompartmental pharmacokinetic parameters were calculated by standard methods (9): maximum concentration in plasma (C_{\max}), time to C_{\max} (T_{\max}), area under the drug-concentration-versus-time curve from 0 h to infinity ($\text{AUC}_{0-\infty}$), mean residence time (MRT), elimination half-life ($t_{1/2}$), renal clearance (CL_R), and percentage of dose excreted in the urine ($\%X_u$). Terminal elimination rate constants (β) were estimated for all plasma level-versus-time profiles by performing linear least-squares regression analysis of the linear segment of the log concentration-versus-time data. The elimination $t_{1/2}$ was estimated by dividing 0.693 by β . The area under the curve (AUC) from time zero to time m , the portion prior to the log-linear phase, was calculated by using the linear trapezoidal rule method, and the AUC from time m to the last measurable time point n was calculated by using the log trapezoidal rule method and was extrapolated to infinity (9). The MRT at steady state was calculated by the method proposed by Pfeffer (15). The accumulation ratios (R) for cefprozil and cefaclor were calculated by the three different methods proposed by Colburn (6). The three methods for the estimation of R are as follows: method 1, $R_1 = \text{AUC}_{(0-T)}\text{ss}/\text{AUC}_{(0-T)}1$; method 2, $R_2 = C_{(\min)\text{ss}}/C_{(\min)}1$; and method 3, $R_3 = 1/(1 - e^{-\beta\tau})$, where $\text{AUC}_{(0-T)}1$ is the AUC during the dosing interval after the first dose, $\text{AUC}_{(0-T)}\text{ss}$ is the AUC during a dosing interval at steady state, $C_{(\min)}1$ is the drug concentration in plasma immediately prior to administration of the second dose, $C_{(\min)\text{ss}}$ is the steady-state concentration of drug in plasma immediately prior to administration of any dose at steady state, β is the elimination rate constant, and τ is the dosing interval.

Statistical analysis. The plasma and urine pharmacokinetic parameters for cefprozil and cefaclor were compared within each dose group across study days 1, 5, and 10 in the context of a repeated-measures analysis of variance (ANOVA) model (18). Comparisons of cefprozil parameters in plasma and urine between dose levels were carried out separately on each day by using a one-way ANOVA model. Both ANOVA models were followed by the Tukey multiple comparison procedure to evaluate mean parameter differences. A weighted (1/variance) linear regression model was used to assess whether $\text{AUC}_{0-\infty}$ and C_{\max} were linear and dose proportional. The pharmacokinetic parameters for cefprozil and cefaclor at the 500-mg dose level in plasma and urine were compared by using a split-plot ANOVA model (18). All hypotheses were tested at the 5% significance level.

RESULTS

Safety. The adverse clinical events (ACEs) which occurred during the study are summarized below by dose level and by the drug received.

Two subjects who received the 250-mg dose had mild intestinal effects which were probably drug related. Four subjects who received 500 mg of cefprozil had mild to moderate intestinal effects which were probably drug related. These were described as loose bowel movements with and without an increased frequency. Two subjects developed itchy red rashes (one on his neck, the other on his arms and legs) which were thought to be contact allergies and which were probably not drug related. One subject developed some symptoms of coryza (normal temperature, normal leukocyte and differential counts). One subject developed a red eye that was not clinically infected, that was thought to be due to accidental trauma, and that was probably not drug related.

In the subjects who received 500 mg of cefaclor, all ACEs were of mild to moderate severity and were probably drug related. Five subjects reported intestinal effects listed as loose bowel movements with no increased frequency. Of these five subjects, one subject also complained of colicky abdominal pain. A sixth subject reported a peculiar sensation in his throat and abdomen.

Seven subjects who received the 1,000-mg dose reported moderate intestinal effects, and four subjects reported mild epigastric symptoms which were probably drug related. One subject vomited before dose 6. This was thought to be gastric intolerance of the previous meal that was not drug related, and he recovered quickly and continued in the study. One subject developed nausea, anorexia, shivering, and aching muscles on day 8; there were no other signs or symptoms and he recovered within 24 h. It was thought to be a mild intercurrent viral illness and was probably not drug related.

There were no significant abnormalities in the hematological values in any of the subjects who received cefprozil (250-, 500-, and 1,000-mg dose groups) or in the subjects who received cefaclor (500 mg).

Of 12 subjects who received 250 mg of cefprozil, 3 subjects had mild elevations of alanine aminotransferase (ALT) which normalized on follow-up. These may have been drug related. Of 12 subjects in the 500-mg cefprozil dose group, 2 subjects had possible drug-related elevations of ALT during dosing. One of these subjects had a marked rise of ALT (three times the upper limit of normal) that coincided with a slight rise of aspartate aminotransferase. Three weeks after dosing, all values were normal for both subjects. In the 500-mg cefaclor dose group, 2 of 12 subjects had slight elevations of ALT during dosing. Both subjects were normal at follow-up, and the elevation may have been drug related in both subjects. Of 12 subjects who received 1,000 mg of cefprozil, 2 subjects had elevations of ALT during dosing. One subject did not return for follow-up, and the other subject was normal 10 days after dosing. There was no other clinically significant biochemical results, and there were no abnormalities in the urinalyses during the study period.

Assays. Typical chromatograms obtained from the human plasma or urine samples containing no drugs and those samples containing cefprozil and cephalixin showed that cefprozil was completely separated from the internal standard and that there was no interference at the retention time of the drug or internal standard from any endogenous substance. The retention times for cefprozil and cephalixin were approximately 10.2 and 12.4 min, respectively, and the

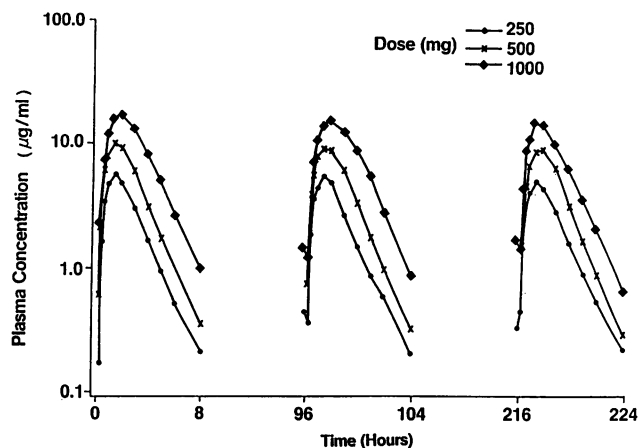


FIG. 1. Mean plasma-concentration-versus-time profiles of cefprozil following 250-, 500-, and 1,000-mg oral doses administered every 8 h.

response curve (concentration-versus-peak-height ratio) was linear in the range of 0.5 to 40 $\mu\text{g/ml}$ for the plasma assay. Standard curves were $y = 0.081x - 0.0005$ ($r = 0.999$). Typical chromatograms obtained from the urine samples showed that there was base-line separation between cefprozil and cephalixin and that there was no interference at the retention time of cefprozil or the internal standard from any endogenous substance in the urine samples. The retention times for cefprozil and cephalixin were approximately 12 and 17 min, respectively. The urine assay was linear in the range of 5 to 500 $\mu\text{g/ml}$. Standard curves obtained from repeated determinations of urine standards were $y = 0.0103x - 0.0036$ ($r = 0.999$). Excellent data for accuracy (deviation from nominal, less than 1.5%) and a coefficient of variation consistently less than 4.2% for the blinded quality-control samples suggest that the assays for cefprozil in plasma and urine were accurate and precise. The between-day coefficients of variation for concentrations of cefprozil in plasma of 3.50 ($n = 15$) and 33.3 ($n = 15$) $\mu\text{g/ml}$ were 6.3 and 4.0%, respectively. The between-day coefficients of variation for concentrations of cefprozil in urine of 27.6 ($n = 15$) and 276 ($n = 15$) $\mu\text{g/ml}$ were 0.86 and 0.84%, respectively.

Cefprozil was stable in human plasma for at least 38 days at -20°C . The stability in diluted buffered urine was established for up to 6 months at -20°C . Both cefprozil and cephalixin were stable for up to 28 h in the injection solvents for the plasma and urine assays.

The results of the analysis of cefprozil and cefaclor quality-control samples, which were prepared prior to the initiation of the study and which were stored with the study samples, were within 8% of the nominal values in each analytical run. These data suggest that the cefprozil and cefaclor assays were accurate and precise during the analysis of the study samples and that each cephalosporin was stable under the storage conditions.

Pharmacokinetics. The mean cefprozil concentrations in plasma for each dose level are plotted in Fig. 1. The data for dosing days 1, 5, and 10 were nearly superimposable at each dose level. The mean plasma-concentration-time profiles of cefprozil and cefaclor after administration of 500-mg t.i.d. doses are compared in Fig. 2. The mean cefprozil pharmacokinetic parameters derived from the noncompartmental analysis of the data are listed in Table 1. The mean C_{max} at each dose level was fairly constant throughout the dosing interval. In the regression assessment of the C_{max} of cef-

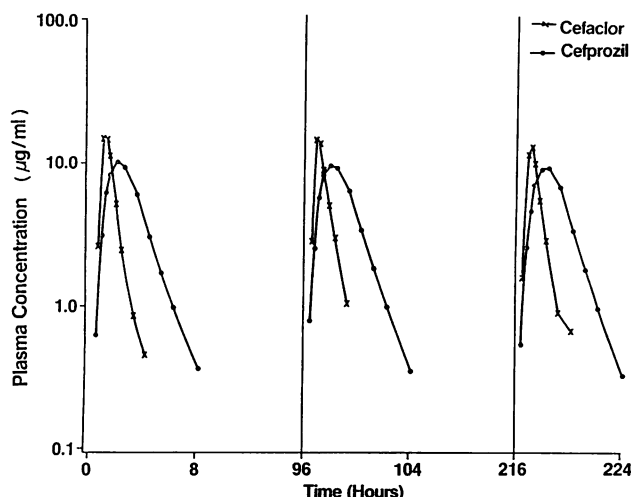


FIG. 2. Mean plasma-concentration-versus-time profiles of cefprozil and cefaclor following 500-mg oral doses administered every 8 h.

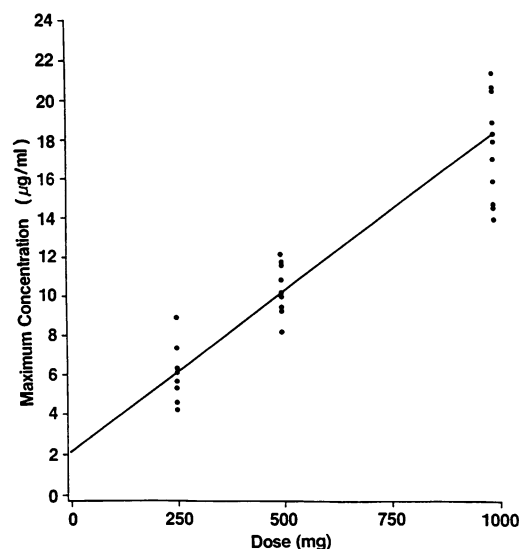


FIG. 3. Linear regression relationship between C_{max} and dose of cefprozil [$r = 0.92$; $C_{max} = 2.15 + (0.016 \times \text{dose})$].

prozil, no deviation from linearity was observed (Fig. 3). The mean $t_{1/2}$ values of cefprozil ranged from 1.13 to 1.29 h and were invariant with respect to both dose and duration of administration. The mean $AUC_{0-\infty}$ data listed in Table 1 for day 1 were not significantly different from mean AUC_{0-T} data for days 5 and 10 for subjects in the 250- and 500-mg dose groups. The AUC_{0-T} versus dose data for day 10 (Fig. 4) are indicative of the dose-proportional increase in AUC with an increase in dose.

The single- and multiple-dose pharmacokinetic parameters of cefaclor and cefprozil at 500-mg t.i.d. doses are summarized in Table 2. The plasma-concentration-versus-time plots showed sharp peaks for cefaclor, suggesting rapid absorption of this drug. The mean values of C_{max} , T_{max} , $t_{1/2}$, MRT, and AUC of cefprozil as well as those of cefaclor were invariant with respect to the dosing day. The overall mean X_u of cefprozil was 61% and remained generally invariant with respect to dose and duration of dosing (Table 1). The mean CL_R of cefprozil ranged from 159 to 185 ml/min. The CL_R values were invariant with respect to the dose and duration of multiple dosing. The overall mean X_u of cefaclor

was about 75% and remained invariant with respect to the duration of dosing. The mean CL_R of cefaclor ranged from 377 to 406 ml/min (Table 2) and remained invariant with respect to the duration of multiple dosing.

Evaluation of accumulation potential. The accumulation ratios for cefprozil and cefaclor, which were calculated by three different methods, are presented in Table 3. All three methods gave nearly identical results, showing no accumulation of either cephalosporin upon t.i.d. dosing after dose 13 on day 5 and dose 28 on day 10.

DISCUSSION

The safety of cefprozil was demonstrated during multiple dosings at several dose levels. There were no clinically significant ACEs. In the subjects who received cefprozil, only the gastrointestinal ACEs were considered to be possibly drug related. These were mild, and no subjects dropped out because of ACEs. In subjects in the 500-mg dose group, in which direct comparison with control subjects was possi-

TABLE 1. Steady-state pharmacokinetic parameters of cefprozil after oral administration

Parameter	Mean \pm SD of the parameters by the following dose level and administration intervals ^a :								
	250 mg			500 mg			1,000 mg		
	Day 1	Day 5	Day 10	Day 1	Day 5	Day 10	Day 1	Day 5	Day 10
C_{max} ($\mu\text{g/ml}$)	6.1 \pm 1.3	6.2 \pm 1.1	5.7 \pm 1.1	10.5 \pm 1.2	10.5 \pm 2.2	10.4 \pm 1.3	18.3 \pm 3.2	17.7 \pm 3.4	17.5 \pm 3.9
T_{max} (h)	1.5 \pm 0.4	1.5 \pm 0.4	1.7 \pm 0.6	1.5 \pm 0.4	1.8 \pm 0.5	1.9 \pm 0.6	2.0 \pm 0.5	2.2 \pm 0.9	1.8 \pm 0.4
$t_{1/2}$ (h)	1.28 \pm 0.34	1.24 \pm 0.24	1.21 \pm 0.24	1.29 \pm 0.14	1.18 \pm 0.14	1.20 \pm 0.20	1.27 \pm 0.12 ^b	1.13 \pm 0.09 ^c	1.25 \pm 0.13 ^b
MRT (h) ^d	2.7 \pm 0.4		2.6 \pm 0.4	2.7 \pm 0.2		2.6 \pm 0.2	3.1 \pm 0.5 ^b		2.7 \pm 0.3 ^c
AUC ($\mu\text{g} \cdot \text{h/ml}$) ^d	16.4 \pm 2.7	16.3 \pm 2.8	16.0 \pm 3.1	31.1 \pm 3.2	30.8 \pm 3.7	30.8 \pm 4.4	61.2 \pm 14.3 ^b	59.8 \pm 14.0 ^b	53.6 \pm 13.9 ^c
CL_R (ml/min)	160 \pm 38.2	185 \pm 51.4	174 \pm 26.9	171 \pm 25.5	166 \pm 42.2	183 \pm 31.0	159 \pm 42.1	175 \pm 63.2	178 \pm 31.1
X_u (%) ^e	60.4 \pm 12.4	70.6 \pm 16.2	65.7 \pm 11.1	61.6 \pm 4.9	60.4 \pm 12.4	66.3 \pm 5.0	54.1 \pm 8.4	58.9 \pm 12.5	55.7 \pm 10.1

^a The 250-, 500-, and 1,000-mg oral doses were administered every 8 h for 10 days. Means across time are not significantly different, unless indicated by the superscripts b and c. Means with the same superscript are not significantly different. Means are not significantly different among doses, unless indicated by the superscript e.

^b See footnote a.

^c See footnote a.

^d Parameters were evaluated to infinity on day 1 and were evaluated from time zero to time t on day 5 and 10.

^e On day 10, percents urinary recovery with the 500- and 250-mg doses were significantly greater than the percent urinary recovery with the 1,000-mg dose.

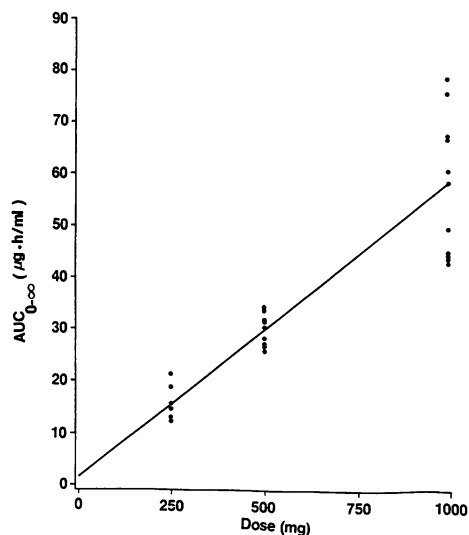


FIG. 4. Linear regression relationship between $AUC_{0-\infty}$ and dose of cefprozil [$r = 0.92$; $AUC_{0-\infty} = 1.60 + (0.058 \times \text{dose})$].

ble, the frequencies of possible drug-related ACEs were similar (4 of 12 subjects who received cefprozil, 6 of 12 subjects who received cefaclor). Cefprozil thus appears to be well tolerated, similar to other oral cephalosporins.

The pharmacokinetic parameters of cefprozil presented in this report are consistent with previously published single-dose data (1-3) and indicate that this cephalosporin is well absorbed after oral administration and is eliminated primarily by the kidneys. In this respect, the pharmacokinetics of cefprozil are typical of those of other oral cephalosporins. The single- and multiple-dose kinetics of cefprozil indicate an average $t_{1/2}$ of about 1.3 h, which is similar to those reported for cephalexin (4, 17), cephadrine (4, 17), and cefadroxil (4, 12); but it is significantly longer than that reported for cefaclor (13, 17).

The pharmacokinetics of cefprozil and cefaclor do not change on multiple dosings. The C_{\max} and $AUC_{0-\infty}$ values for cefprozil showed a dose-proportional increase, whereas $t_{1/2}$ and CL_R remained dose independent. These observations suggest that cefprozil obeys linear pharmacokinetics. This is consistent with earlier reports of the single-dose pharmacokinetics of cefprozil (1, 3). The average CL_R of cefprozil is about 170 ml/min. Because CL_R has a significantly greater than average glomerular filtration rate (about 120 ml/min), a significant portion of the drug must be cleared from the kidneys by tubular secretion.

Profiles of the levels of cefaclor in plasma showed sharper

TABLE 3. Accumulation ratios for cefprozil after multiple dosing to 12 subjects

Dose (mg)	Dose no.	Avg β (h^{-1})	Accumulation ratios of cefprozil calculated by three different methods ^a		
			R_1	R_2	R_3
250	1	0.54			
	13	0.55	1.02	1.00	1.00
	28	0.57	1.00	1.00	1.00
500	1	0.54			
	13	0.59	1.01	0.75	1.00
	28	0.58	1.01	0.75	1.00
1,000	1	0.54			
	13	0.61	1.01	0.90	1.00
	28	0.55	0.90	0.80	1.00

^a Methods R_1 , R_2 , and R_3 are explained in the text.

and higher peaks than those of cefprozil. Although cefprozil C_{\max} values are lower than those of cefaclor, it disappeared from plasma much more slowly than cefaclor did. The elimination of cefprozil (1.3 h) was significantly longer than that of cefaclor (0.6 h). With beta-lactam antibiotics, the pharmacodynamic variable that may correlate with clinical efficacy is the duration over which the concentrations in plasma and tissues remain above the MIC (7). The levels of cefprozil in plasma remained above the MICs for susceptible organisms for significantly longer periods of time than the levels of cefaclor did. Similarly, the levels of cefprozil in tissues, as judged by the skin blister fluid model, also showed higher levels of cefprozil for a prolonged period of time than those of cefaclor did (3).

The primary route of elimination of both cephalosporins is via excretion in the urine. The recovery of cefaclor in urine was about 75% of the dose, while that of cefprozil was about 61% of the dose. The urinary recovery and C_{\max} values for cefaclor in plasma observed in the present study were somewhat higher than those reported in the literature (4, 10, 12, 13, 17). One possible explanation for this observation may be the flash-freezing of plasma and urine samples immediately after collection. This may have prevented in vitro degradation of relatively unstable cefaclor. Because cefaclor is very rapidly absorbed and eliminated from the body, the concentrations of cefaclor in urine in the 0 to 2 h collection interval were significantly higher than those of cefprozil. However, the concentrations of cefprozil in urine remained significantly greater than those of cefaclor for the collection intervals of 2 to 4, 4 to 6, and 6 to 8.

The results from the present study indicate that cefprozil

TABLE 2. Steady-state pharmacokinetic parameters of cefprozil and cefaclor after oral administration^a

Parameter	Cefprozil				Cefaclor				B versus C ^b
	Day 1	Day 5	Day 10	Day P value	Day 1	Day 5	Day 10	Day P value	
C_{\max} ($\mu\text{g}/\text{ml}$)	10.5 \pm 1.2	10.5 \pm 2.2	10.4 \pm 1.3	0.95	16.7 \pm 3.67	16.5 \pm 5.96	15.2 \pm 4.74	0.62	B < C
$t_{1/2}$ (h)	1.29 \pm 0.14	1.18 \pm 0.14	1.20 \pm 0.20	0.06	0.54 \pm 0.10	0.60 \pm 0.21	0.55 \pm 0.14	0.56	B > C
MRT (h)	2.73 \pm 0.20		2.65 \pm 0.20	0.20	1.13 \pm 0.10		1.22 \pm 0.24	0.56	B > C
AUC ($\mu\text{g} \cdot \text{h}/\text{ml}$)	31.1 \pm 3.2	31.3 \pm 3.7	31.2 \pm 4.4	0.95	16.9 \pm 2.5	16.2 \pm 2.4	15.92 \pm 2.2	0.33	B > C
CL_R (ml/min)	171.0 \pm 25.5	166.0 \pm 42.2	183.0 \pm 31.0	0.07	377.0 \pm 61.4	395.0 \pm 62.3	406.00 \pm 79.6	0.56	B < C
$\%X_u$	61.6 \pm 4.9	60.4 \pm 12.4	66.6 \pm 5.0	0.99	72.0 \pm 15.6	75.5 \pm 8.9	77.0 \pm 6.5	0.35	B < C

^a Cefprozil and cefaclor were administered at a dose of 500 mg every 8 h for 10 days. Values are means \pm standard deviations.

^b All comparisons were significantly different at the 0.05 level. Cefprozil (B) and cefaclor (C) were compared for statistical significance.

obeys linear pharmacokinetics and that the levels of this cephalosporin in plasma as well as urine remain above the MICs for susceptible organisms for significantly longer periods of time than do those of cefaclor. If the therapeutic concept is maintained that the levels of beta-lactam antibiotics in plasma should exceed the MIC for the offending organisms over a period that approximates the dosing interval, then cefprozil appears to be suitable for twice-daily administration, whereas cefaclor should probably be administered three or even four times a day.

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