ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1992, p. 144–149
0066-4804/92/010144-06$02.00/0

Vol. 36, No. 1

Multiple-Dose Pharmacokinetics of Cefprozil and Its Impact on Intestinal Flora of Volunteers

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Received 27 March 1991/Accepted 10 October 1991

The pharmacokinetics of cefprozil were determined with 12 volunteers (8 received cefprozil and 4 received a placebo) after oral administration of 500 mg every 12 h over an 8-day period in a randomized, double-blind, placebo-controlled design. Concentrations in serum and urine were measured by high-pressure liquid chromatography and bioassay. The pharmacokinetic parameters were calculated on the basis of an open one-compartment model. The mean maximum concentration in serum on day 1 was 11.5 ± 2.6 mg/liter, and the time to reach maximum concentration was 122.3 ± 30 min after administration. Bioavailability parameters (area under the concentration-time curve from zero to infinity, maximum concentration of the drug in serum, and urinary recovery) indicated an excellent absorption. No accumulation over the 8-day period was registered. Cefprozil had a short biological elimination half-life of 58 ± 10 min and a renal clearance of 210 ± 51 ml/min, indicating high rates of renal excretion and tubular secretion. Analysis of the fecal flora showed an ecological impact of cefprozil on the intestinal microflora, such as a moderate decrease in enterobacteria and a slight increase in enterococci, staphylococci, and bacteroides during the study. The number of all bacterial species was already normalized 4 days after the administration period. The tolerance of cefprozil proved to be excellent; only a slight and reversible increase of liver enzymes (in two volunteers), mild cephalalgia, tiredness, and soft stool were registered during the 8-day period. Cefprozil had excellent absorption, no accumulation over an 8-day period, and only a limited impact on the intestinal microflora.

Cefprozil (BMY-28100) is a new oral cephalosporin antibiotic with improved antimicrobial activity and efficacy against a broad spectrum of gram-positive and gram-negative pathogens (6, 8, 15, 20, 37). The objectives of our trial were to determine the pharmacokinetic properties of cefprozil after single and multiple dosing, to determine the effect on the intestinal flora in volunteers, and to assess the tolerance of cefprozil over an 8-day application period.

(Part of this paper was presented previously [28a].)

MATERIALS AND METHODS

Study design. The study was based on a randomized, double-blind, placebo-controlled, multiple-dose design. The protocol was approved by the local ethics committee.

Volunteers. Twelve healthy test subjects (six females and six males) participated in the study. Eight of them received cefprozil, and four (two females and two males) took placebos. Mean (± standard deviation) age (24 ± 2 years), body weight (65 ± 9 kg), body surface (1.78 m^2 ± 0.18), and creatinine clearance (108 ± 23 ml/min/1.73 m^2) showed no differences between placebo- and antibiotic-treated volunteers. The volunteers were healthy according to medical histories, physical examinations, hematologic tests, clinical chemistries, and urinalyses. These parameters were examined several times before, during, and after the study and showed no pathological alterations. All subjects had normal and regular bowel habits. The subjects had no known allergy to penicillins or cephalosporins. No medication other than the study drug was allowed 1 week prior to and during the study period; no antibiotics were allowed during the previous 2 months. The females had not taken oral contraceptives within the 2 weeks previous to and during the study; pregnancy was excluded by gravidity testing. No alcohol, coffee, tea, nicotine, or chocolate was allowed during the trial. The volunteers were informed about the background of the study and possible side effects. They all gave written consent to participate.

Cefprozil was administered in the form of capsules (250 mg; lot 20830) provided by Bristol-Myers International Corporation, Brussels, Belgium.

Dosage and administration. The test subjects received 500 mg of cefprozil (two capsules) every 12 h over an 8-day period. On study days 1, 4, and 8, the volunteers fasted for a minimum of 10 h before drug administration; cefprozil was taken with 100 ml of tap water, and drinking was allowed after 2 h and eating was allowed after 4 h. On all other study days, the volunteers had breakfast before drug administration.

Sampling. (i) Blood samples. Blood samples (a total of 13) on day 1 were taken before administration and 15, 30, 45, 60, and 90 min and 2, 3, 4, 5, 6, 8, and 12 h after administration. On days 4 and 8, blood samples (a total of 7) were taken before administration and 1, 2, 4, 6, 8, and 12 h after administration. On all other days, only two samples, before (trough concentrations) and 1 h after intake, were obtained. Approximately 8 ml of venous blood was collected in prelabeled sterile tubes (polypropylene tubes, 17 by 100 mm, 10 ml; Greiner Co., Nürtingen, Germany), stored in ice water, and centrifuged at 5°C within 30 min of collection, and the serum was separated. Serum samples were stored at −80°C until used for assays.

(ii) Urine. Urine samples were taken only on days 1 and 8. On both days, urine samples from three periods, from 0 to 3,

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3 to 6, and 6 to 12 h, were analyzed. On day 8, there was an additional fourth period from 12 to 24 h. Blank urine samples on day 1 before drug administration were free of any antibiotic activity.

(iii) Stool samples. Stool samples were received 9, 2, and 1 days prior to the start of the study; on days 4 and 8 during the study; and 4, 13, 20, and 48 days after the study period. All samples were frozen immediately at −80°C and assayed during the following 4 months.

Methods. The concentrations in serum and urine were determined by bioassay and high-pressure liquid chromatography (HPLC).

(i) Bioassay. The microbiological assay was performed by agar diffusion (cup plate method) as modified by Reeves and Bywater (34). Serum and urine assays were performed with antibiotic medium no. 2 (Difco Laboratories, Detroit, Mich.) with *Bacillus subtilis* ATCC 6633 as the test strain. The details of the bioassay have been described previously (27, 28). Serum and urine samples were assayed in triplicate, and five standard concentrations (in triplicate) were used on each plate. The coefficient of variability (within-batch precision) between concentrations of 1.0 to 20 mg/liter varied between 2.8 and 6.8% (serum and urine, respectively). The lowest detection level of cefprozil in serum and urine was 0.3 mg/liter.

(ii) HPLC. Details of the HPLC method have been described previously (4). Basically, the method consisted of deproteinization of serum followed by separation of the protein-free supernatant by a reversed-phase column (Nucleosil 5C18). The detection limits were 0.2 mg/liter for serum and 0.1 mg/liter for urine. Within-batch precision (coefficient of variation) varied from 3.8% (concentration, 0.4 mg/liter) to 2.1% (concentration, 13.1 mg/liter) for serum. Precision for urine was between 0.4% (concentration, 2.8 mg/liter) and 0.7% (concentration, 300 mg/liter). Since in this study the bioassay determinations were done immediately after the study period and resulted in values 10% higher than the HPLC data, only the bioassay values are referred to in this paper.

(iii) Analysis of the fecal flora. The analysis of the fecal flora was done by the National Bacteriological Laboratory, Stockholm, Sweden. Transport of the deep-frozen specimens from Berlin to Stockholm was done by plane in special, ice-containing packages and took less than 20 h.

The microbiological processing of the specimens was as follows. A 1-g sample of feces was homogenized in 9 ml of prereduced peptone yeast extract medium. Tenfold serial dilutions resulted in a final dilution of 10^{-7}. Each specimen was streaked immediately on two blood agar plates and 10 selective media as described by Heimdahl and Nord (19). All manipulations of the anaerobic bacteria were carried out in an anaerobic chamber (Forma, Philadelphia, Pa.) under 10% (vol/vol) hydrogen in nitrogen. The aerobic agar plates were incubated for 24 h at 37°C, and the anaerobic agar plates were incubated for 48 h at 37°C. The plates were then examined, and different colony types were isolated in pure cultures and identified.

The isolated microorganisms were identified by morphological, biochemical, and immunological tests as described previously (19, 30).

Protein binding. Protein binding in serum was determined at two different concentrations (10 and 25 mg/liter). The measurements were done with a micropartition MPS-1 system for separation of free solute from protein-bound solute (Amicon, Witten, Germany). Separation was done at 22°C, and incubations were done at 37°C. The mean level of protein binding of cefprozil in serum was 42% ± 4.8% (mean ± standard deviation).

Pharmacokinetic calculations. The pharmacokinetic parameters of cefprozil were calculated assuming an open one-compartment model. Following the recommendation of Peck et al. (33), we used the iteratively reweighting least-square method to fit the parameters p_j ($j = 1, \ldots, 4$) of the regression function $C(t)$ to the experimental data of the concentration in serum C_i and t_i:

$$\Sigma\{[C(t_i) - C_i]^2 \cdot w_i\} = \text{minimum with } w_i = 1/[C(t_i)],$$

where $C(t) = p_1\{\exp[-p_2 \cdot (t - p_4)] - \exp[-p_3 \cdot (t - p_4)]\}$, p_1 is the proportionality constant, p_2 is the elimination rate, p_3 is the velocity of absorption, p_4 is lag time, and C_i is the measured concentration at t_i. The calculation of the pharmacokinetic parameters time to maximum concentration (T_{max}), maximum concentration in serum, total area under the concentration-time curve, half-life, and volume of distribution was performed by standard methods as previously described (14, 21, 22, 28, 35). In addition, we calculated the area by a noncompartmental approach, applying the log-trapezoidal rule directly to the data C_i and t_i; the results are included as AUD_{tot} in Table 1. There was an excellent agreement of the total area under the concentration-time curve and AUD_{tot}. Total clearance and renal clearance were calculated from AUD_{tot}, that is, noncompartmentally. Concentration, area, and volume values were normalized to a body weight of 70 kg, and the clearance values were normalized to a body surface of 1.73 m^2.

RESULTS

The individual concentrations in serum and the mean serum line of cefprozil on day 1 are shown in Fig. 1; the pharmacokinetic parameters on days 1 and 8 are given in Table 1.

Figure 1 shows that after slow absorption, a peak level in serum of 11.5 ± 2.2 mg/liter was reached after 122 ± 24 min. The elimination phase was relatively rapid, with a biological half-life of 58 ± 8 min. Elimination was predominantly renal with high urinary recoveries of 70% (day 1, 0 to 12 h) and 79% (day 8, 0 to 24 h) (Fig. 2). Renal clearances (210 ± 42 ml/min on day 1 to 278 ± 59 ml/min on day 8) were significantly above the mean creatinine clearance of our volunteers (108 ± 23 ml/min), indicating additional tubular secretion of this cephalosporin. There is also evidence for some extrarenal elimination of the drug, which is shown by the 11 to 17% extrarenal partition of the total clearance. The predominantly renal elimination of cefprozil resulted in high urinary recoveries and high concentrations in urine (Fig. 2).

No accumulation of cefprozil from day 1 to day 8 could be seen. The accumulation ratio (calculated as $1/[1 - \exp(-k \cdot \text{tau})]$, tau = 12 h) was 1.0003 ± 0.0005 at day 1 and 1.0002 ± 0.0001 at day 8.

Fecal flora. The impact of cefprozil on the fecal flora is demonstrated in Fig. 3, which gives the log numbers of microorganisms per gram of feces for antibiotic- and placebo-treated volunteers. This figure also shows the mean numbers of the different bacterial species 9, 2, and 1 days before the start of the study, on days 4 and 8 during the study, and 4, 13, 20, and 48 days after the study period. The analysis of the fecal flora revealed a moderate decrease of enterobacteria and a slight increase of enterococci, staphylococci, and bacteroides during the study. The numbers of bacteria returned to normal 4 days after the last study day.

TABLE 1. Pharmacokinetic data (bioassay) of eight volunteers after administration of cefprozil[a]

Day	Mean ± CI[b]										
	$UR_{tn} \cdot f$ (% of dose)	$UR_{tot} \cdot f$ (% of dose)	T_{lag} (min)	T_{max} (min)	C_{max} (mg/liter)	$t_{1/2}$ (min)	AUD_{tot} (mg · h liter^{-1})	AUC_{tot} (mg · h liter^{-1})	V/f (1/70 kg)	CL_{tot}/f (ml/min)	CL_R (ml/min)
1	70.58 ± 16.69	84.14 ± 12.68	22.05 ± 5.07[c]	122.25 ± 24.13	11.53 ± 2.17	58.17 ± 8.14	33.11 ± 4.27	33.35 ± 4.37	16.20 ± 4.31[d]	251.88 ± 44.89	209.75 ± 42.41
8	79.05 ± 6.01	90.56 ± 6.50	36.76 ± 13.04[c]	102.24 ± 14.62	9.28 ± 1.49	55.11 ± 5.79	27.54 ± 4.97	27.80 ± 5.02	24.48 ± 3.71[d]	310.25 ± 74.91	277.50 ± 58.81
z[e]	0.53	0.63	2.31	1.37	1.68	0.00	1.89	1.89	2.52	1.26	1.79

[a] Oral administration of 500 mg b.i.d.
[b] CI, confidence interval; UR_{tn}, cumulative amount of excreted drug in % of given dose from 0 to tn (day 1, 0 to 12 h; day 2, 0 to 24 h); f, oral bioavailability; UR_{tot}, cumulative amount of excreted drug in % of given dose from 0 extrapolated to infinity; T_{lag}, time log; T_{max}, time to maximum concentration; C_{max}, maximum concentration; $t_{1/2}$, half-life; AUD_{tot}, area under the data (model-free equivalent to AUC); AUC_{tot}, total area under the concentration-time curve; V/f, rate of metabolism; CL_{tot}/f, total clearance/oral bioavailability; CL_R, renal clearance. P values were not significant except where indicated.
[c] $P < 0.02$, Wilcoxon rank sum test (two-tailed).
[d] $P < 0.01$, Wilcoxon rank sum test (two-tailed).
[e] $z = T - \mu_T/\sigma_T$.

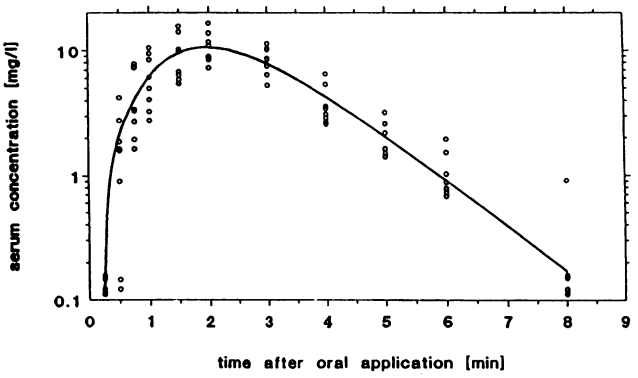

FIG. 1. Serum regression (——) and individual concentrations in serum (○) in eight volunteers after empty intake of 500 mg of cefprozil on day 1.

Clostridium difficile was detected in three volunteers during cefprozil administration, but no *C. difficile* toxins could be identified.

Tolerance. The tolerance of cefprozil seemed to be excellent. Only slight, reversible increases in liver enzymes in two of the volunteers (maximum alanin aminotransferase elevation of twice the normal values), mild cephalalgia and tiredness for 4 h (one volunteer), and soft stool on the second study day (one volunteer) were registered in the antibiotic-treated group. In the placebo-treated group, mild cephalalgia and arthralgia were found in one volunteer on 6 of 8 days during the study period.

DISCUSSION

Cefprozil (BMY-28100) offers in vitro activity superior to those of cephalexin and cefaclor against gram-positive cocci and against β-lactam-producing *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Escherichia coli*, and *Klebsiella* species (6, 8, 20). Many β-lactam antibiotics are poorly

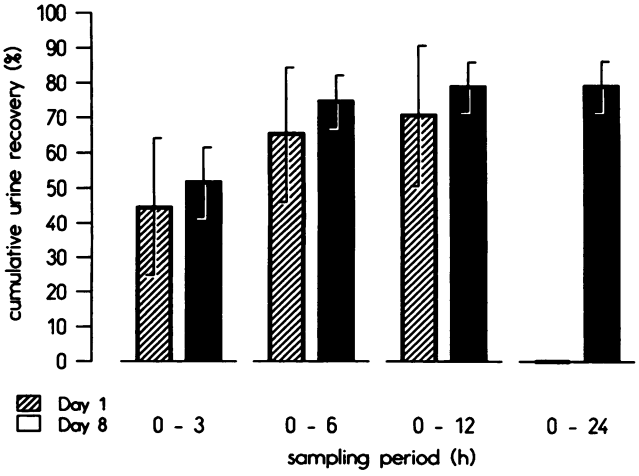

FIG. 2. Cumulative urinary recovery in eight volunteers on day 1 (0 to 12 h) and day 8 (0 to 24 h) after b.i.d. intake of 500 mg of cefprozil orally. Error bars represent sigma values (standard deviations).

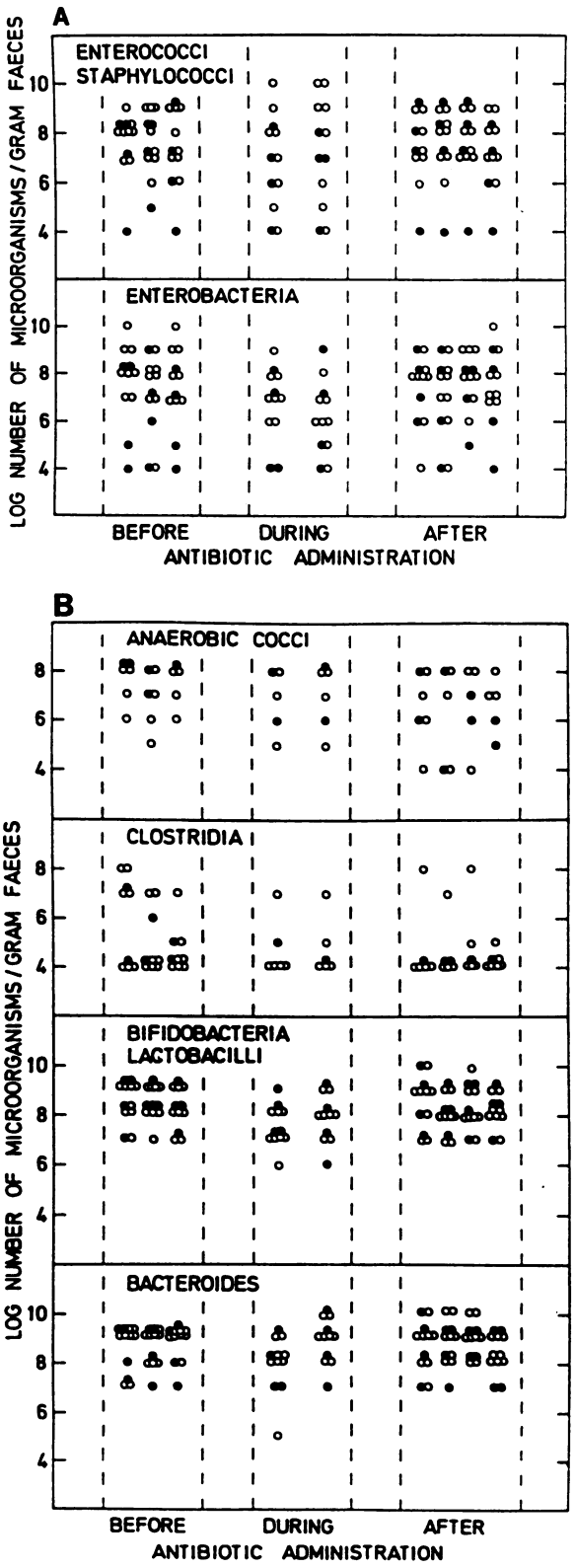

FIG. 3. Analysis of fecal flora in 12 volunteers before, during, and after b.i.d. intake of 500 mg of cefprozil over an 8-day period (○, antibiotic [8 volunteers]; ●, placebo [4 volunteers]).

absorbed from the gastrointestinal tract. Cephalosporins are either inactivated by gastric acid or not significantly absorbed from the intestine, even if deposited directly in the duodenum. Electronegative substitutes improve the acid stability of oral compounds like cephalexin, cefaclor, cephaloglycin, cefadroxil, ceftrizine, cefradine, and cefroxadine (7, 11). After oral administration to mice, 82% of cefprozil was recovered in urine (25). In our study of cefprozil pharmacokinetics in humans, we found nearly the same amount (70.6 to 79%) of the drug in urine after an oral dose of 0.5 g. Cefprozil had a relatively low absorption rate with a mean T_{max} of 122 min, a high maximal mean concentration in serum of 11.5 ± 2.2 mg/liter, and a short half-life of about 1 h. Concentration in serum and pharmacokinetic parameters showed no significant alterations between the first and last administrations of the drug on day 1 and day 8. The volume of distribution in the steady state was calculated to be 35% of the body weight, which is slightly higher than the extracellular volume. High renal and total clearances indicate mainly renal elimination by glomerular filtration and tubular secretion; about 10% of the drug must be eliminated by extrarenal mechanisms. No metabolites were detected in urine by HPLC. Our results are in good agreement with the recently published data on cefprozil in volunteers after single- and multiple-dose applications (1, 2).

In comparison with older orally administered cephalosporins, cefprozil has a position between cefaclor and cefadroxil in terms of its absorption characteristics (7, 15, 24, 29, 38, 42), with a low invasion rate like that of cefadroxil and with a high maximal concentration in serum and fast elimination phase similar to those of cefaclor. With cefadroxil, we found a slight increase in the peak concentrations in serum during an 8-day dosage period with three doses of 1,000 mg per day orally in volunteers, which could not be seen with cefprozil, 500 mg b.i.d. (twice a day) (17, 27).

In comparison with several new compounds of the oral cephalosporin group, distinct differences in the pharmacokinetic parameters of the individual cephalosporins are evident (3, 20). Cefetamet-pivoxil has an absolute bioavailability of 31 to 44%, a low rate of absorption (T_{max} of the drug in plasma, 3.0 to 4.8 h), and low peak concentrations in serum (23). Cefixime is characterized by a low rate of absorption (T_{max}, 3.7 to 4.3 h), a low but prolonged concentration in serum with a long biological half-life of 3.2 to 4.2 h; the absolute bioavailability was calculated at 40 to 52% (5, 9, 10, 16). Cefpodoxime proxetil has nearly the same rate of absorption as cefprozil, low peak concentrations in serum, a biological half-life of about 2 h, and a low renal elimination (urinary recovery, 37.8%) (39). Cefuroxime axetil (13, 18, 43) has a moderate absolute bioavailability of 45 to 60%, a low rate of absorption (T_{max}, 90 to 120 min), low concentrations in serum after 500 mg orally in fasting volunteers (about 3.6 mg/liter), and a plasma half-life of 1.2 to 1.4 h. When the drug was taken after food, serum levels and urinary recoveries increased.

In many countries, investigation of the influence of an antibiotic substance on the fecal flora is currently a prerequisite for a complete evaluation of a new drug (26, 30, 31). Knowledge of the antibiotic impact on the fecal flora is especially helpful in neutropenic and intensive care unit patients, for whom the concept of colonization resistance (12, 26, 40, 41) has become a major issue. In addition, the detection of resistant bacterial strains in fecal flora during or after antibiotic treatment is of great importance. Cefprozil shows high levels of absorption after oral administration, so that the intestinal exposure is relatively low. Therefore, only

a limited decrease in enterobacteria and a slight increase in enterococci, staphylococci, and bacteroides were registered during cefprozil administration, and a rapid normalization was observed after discontinuation of the drug. These results are in good agreement with our own data on parenterally and orally administered cephalosporins as well as reports on the analysis of fecal flora after other cephalosporins (17, 21, 27, 31, 32, 36).

In conclusion, cefprozil is characterized by favorable pharmacokinetic properties after oral administration. We found only a limited impact on fecal flora, and the overall tolerance was excellent.

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