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Comparison of the Effects of Food on the Pharmacokinetics of Cefprozil and Cefaclor

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The objective of this study was to assess the effects of food on the pharmacokinetics of cefprozil and cefaclor. A group of 12 healthy male volunteers received a single 250-mg dose of cefprozil or cefaclor under fasting conditions as well as after the intake of food. There was a 1-week washout period between each treatment. Serial blood samples were collected and assayed for cefprozil or cefaclor by specific high-pressure liquid chromatographic methods. The mean ± standard deviation peak concentration (C_{max}) of cefprozil in plasma was 6.13 ± 1.22 μg/ml under the fasting condition and 5.27 ± 1.06 μg/ml after breakfast, and these values were not significantly different from each other. The corresponding median time to reach C_{max} was prolonged after food intake, but this difference was not significant. The mean C_{max} values of cefaclor decreased significantly from 8.70 ± 2.72 μg/ml under the fasting condition to 4.29 ± 1.52 μg/ml after breakfast, and the corresponding median times to reach C_{max} were significantly prolonged. The mean half-lives of cefprozil and cefaclor were nearly identical for the two treatments, suggesting that the elimination kinetics of these cephalosporins remained unaltered when the drugs were administered with food. The area under the plasma-concentration-versus-time curves for fasted and fed conditions were not significantly different for both drugs. The results of this study indicate that the extent of absorption and rate of elimination of both cephalosporins remain unaltered in the presence of food. However, the absorption rate of cefaclor is significantly reduced in the presence of food, while that of cefprozil remains unaltered. As a result, the C_{max} of cefaclor is significantly reduced in the presence of food, whereas that of cefprozil is not significantly affected. Cefprozil can be administered with a meal without markedly affecting levels in blood.

Cefprozil is an oral cephalosporin with an antibacterial spectrum that includes important gram-positive and gram-negative organisms (11). It is more active than either cephalexin or cefaclor against *Staphylococcus aureus*, streptococci, *Haemophilus influenzae*, and *Clostridium difficile* (5, 11). Cefprozil is also more stable than cefaclor against hydrolysis of β-lactamases (4).

The bioavailability of a drug is usually estimated in a fasting state to avoid the complicated interference with food. However, it is important to investigate the effects of food on the bioavailability, as drugs are often administered after food intake, and alteration of the bioavailability caused by food, if it occurs, may cause significant changes in clinical response. There is considerable evidence to suggest that the absorption of various antimicrobial agents, including oral cephalosporins, is influenced by the presence of food in the gastrointestinal tract (7–9, 13, 18). The present study was designed to compare the effect of a standard meal on the absorption of cefprozil and cefaclor.

MATERIALS AND METHODS

Antibiotics. Cefprozil capsules (lot no. 20754) were supplied by the Pharmaceutical Product Development Department, Bristol-Myers Squibb Co. Cefaclor (Distaclor; lot no. S85MO17) was purchased commercially.

Subjects. Twelve healthy male subjects (aged range, 20 to 40 years) participated in the study after signing an informed consent form. The volunteers had a mean ± standard deviation age of 30 ± 6.0 years (range, 20 to 36 years), a mean body weight of 72 ± 9.4 kg (range, 59.4 to 90 kg), and an average height of 176 ± 7.1 cm (range, 165 to 190 cm). The subject exclusion criteria included the presence of drug allergies or intolerance and a history of a drug or alcohol abuse. Subjects with renal or hepatic impairments 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.

Study design. This study was an open, four-way crossover design balanced for treatment and sequence in an order determined from the rows of a 4 by 4 Latin square. The study was completed with 12 healthy male volunteers who met the eligibility criteria and successfully passed the criteria for exclusion. There was a 7-day interval between successive treatments. The subjects received either a 250-mg dose of cefprozil or a 250-mg dose of cefaclor under fasting conditions or after a standard breakfast consisting of two eggs, one slice of toast, butter and jelly, two links of sausage, and 200 ml of orange juice.

Drug administration. The subjects were administered one capsule (250 mg) of either cefprozil or cefaclor with 150 ml of water. Subjects who received cefprozil or cefaclor with food were served breakfast 30 min prior to dosing. The subjects were asked to finish the breakfast in 15 min.

Collection of blood samples. Approximately 5 ml of venous blood was collected in prelabeled VACUTAINERS (7 ml; no. 6480; Becton Dickinson Vacutainer Systems, Rutherford, N.J.) which contained heparin as the anticoagulant. Blood samples were collected from each subject by the following sampling schedules: for cefprozil, at predose and at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, and 8.0 h after drug administration; for cefaclor, at predose and at 0.10, 0.20, 0.30, 0.40, 0.50, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, and 5.0 h after drug administration. The

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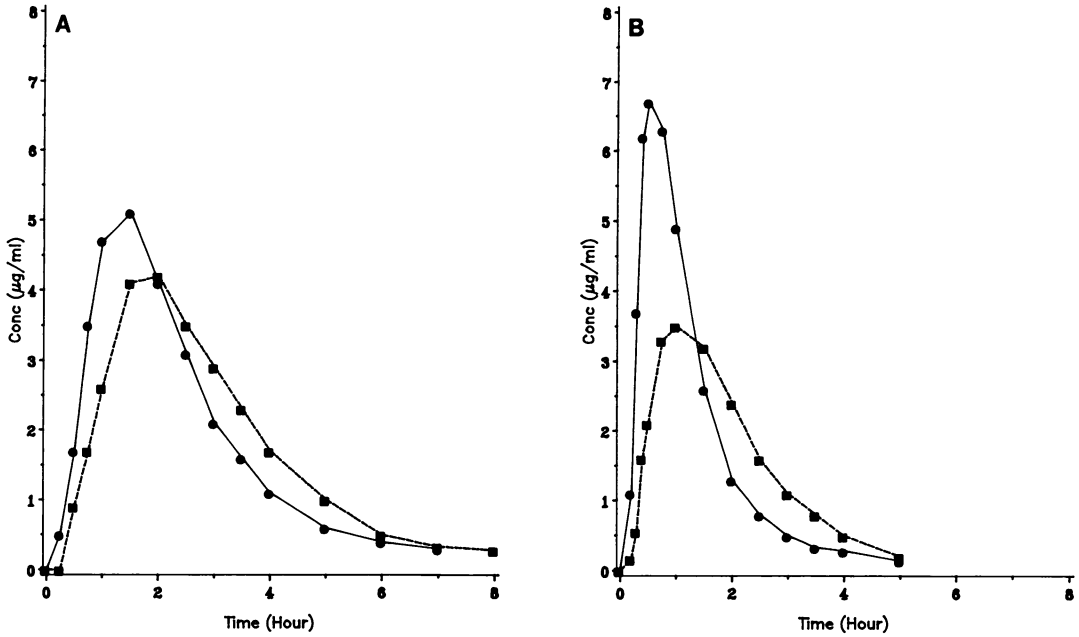

FIG. 1. Mean plasma-concentration-versus-time profiles of cefprozil (A) and cefaclor (B) under fed (■) and fasting (●) conditions.

blood sampling schedules in subjects who received cefprozil were different from those in subjects who received cefaclor, because of the different absorption characteristics of the two cephalosporins. The blood samples were centrifuged within 30 min of collection, and the plasma was separated. The plasma samples were then flash-frozen in a solid CO_2-methanol bath and stored at or below −70°C, with quality-control samples prepared prior to dose administration for each treatment.

Plasma assays. Plasma samples were analyzed for cefprozil or cefaclor by validated high-pressure liquid chromatographic methods (2, 14). The standard curves for the plasma assays of cefprozil and cefaclor were linear in the range of 0.2 to 20 and 0.1 to 22 μg/ml, respectively. The quality-control samples, which were prepared for each drug at the start of the clinical study, were assayed during each analytical run. The accuracy and precision of the determinations of plasma quality-control samples, which were prepared at 1.94 and 20 μg/ml for cefprozil and 1.89 and 20.0 μg/ml for cefaclor, were generally within 2.57 and 12% during the course of the analyses of study samples containing cefprozil and cefaclor, respectively.

Pharmacokinetic analyses. The following noncompartmental pharmacokinetic parameters were calculated by standard techniques (6, 15): 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 ($AUC_{0-\infty}$), elimination half-life ($t_{1/2}$), and mean residence time (MRT). Terminal elimination rate constants (β) were estimated for all plasma-level-versus-time profiles by performing standard unweighted 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 AUC from time zero to time m, the portion prior to the log-linear phase, was calculated by 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 (6).

Statistical analyses. The noncompartmental pharmacokinetic parameters C_{max}, T_{max}, MRT, $t_{1/2}$, and $AUC_{0-\infty}$ under fasted and fed conditions were analyzed to evaluate the effects of food on the kinetics of each drug (cefprozil and cefaclor). Analyses were carried out in the context of a split-plot analysis of variance model. The Bonferroni procedure was used for comparisons among four treatments. Hypotheses were tested at the 5% significance level.

RESULTS

The mean plasma-concentration-versus-time profiles for cefprozil and cefaclor under fed and fasting conditions are shown in Fig. 1. The mean pharmacokinetic parameters listed in Table 1 indicate that the C_{max} levels of cefprozil after food intake were slightly lower relative to those in the fasting condition; however, the levels were not significantly different from each other. The corresponding values for T_{max} were also not significantly different. The $AUC_{0-\infty}$s for cefprozil were 15.0 ± 2.81 μg · h/ml under the fasting condition and 14.9 ± 1.98 μg · h/ml after breakfast; these values were not significantly different. The mean MRT of cefprozil increased significantly from 2.45 ± 0.29 h under the fasting condition to 2.99 ± 0.44 h after food intake. The $t_{1/2}$ of 1.17 ± 0.15 h under the fasting condition and 1.16 ± 0.19 h after breakfast were virtually identical for the two cefprozil treatments.

The mean C_{max} of cefaclor decreased significantly from 8.70 ± 2.72 μg/ml under the fasting condition to 4.29 ± 1.52 μg/ml after breakfast. The corresponding values for T_{max} increased significantly from 0.6 to 1.3 h. The mean cefaclor $AUC_{0-\infty}$s were 8.60 ± 1.43 μg · h/ml under the fasting condition and 7.57 ± 1.20 μg · h/ml after breakfast, and these values were not significantly different from each other. The mean MRT under the corresponding conditions increased significantly from 1.28 ± 0.22 h to 2.06 ± 0.49 h.

DISCUSSION

There is considerable evidence to indicate that the absorption of various antimicrobial agents, including oral cephalo-

TABLE 1. Pharmacokinetic parameters for cefprozil and cefaclor[a]

Treatment	C_{max} (μg/ml)	T_{max} (h)[b]	$t_{1/2}$ (h)	MRT (h)	$AUC_{0-\infty}$ (μg · h/ml)
Cefprozil, fasting	6.13 ± 1.22	1.2 (1.0,2.0)	1.17 ± 0.15	2.45 ± 0.29	15.0 ± 2.81
Cefaclor, fasting	8.70 ± 2.72	0.6 (0.4,1.0)	0.83 ± 0.21	1.28 ± 0.22	8.60 ± 1.43
Cefprozil, with food	5.27 ± 1.06	2.0 (1.5,3.5)	1.16 ± 0.19	2.99 ± 0.44	14.9 ± 1.98
Cefaclor, with food	4.29 ± 1.52	1.3 (0.5,1.5)	0.86 ± 0.17	2.06 ± 0.49	7.57 ± 1.20
Statistical comparisons[c]					
B (fasting vs fed)	ND	ND	ND	Fed > fast	ND
C (fasting vs fed)	Fast > fed	Fed > fast	ND	Fed > fast	ND
Fasting (B vs C)	C > B	B > C	B > C	B > C	B > C
Fed (B vs C)	ND	B > C	B > C	B > C	B > C

[a] Values are means ± standard deviations. Doses of 250 mg of both drugs were administered.
[b] Median values are reported, with minimum and maximum values given in parentheses.
[c] Cefprozil (B) and cefaclor (C) were compared for statistical significance (ND, no difference). Each comparison was made at the $\alpha = 0.05/4 = 0.0125$ significance level.

sporins, is influenced by the presence of food in the gastrointestinal tract (18). Solid food has been shown to decrease the stomach emptying rate, but gastrointestinal motility increases in the presence of food. Because most drugs are absorbed from the small intestine, delayed stomach emptying may delay the onset and reduce the rate of absorption. Food may reduce the extent of absorption of drugs that are unstable at low pH. On the other hand, prolonged retention in the stomach may increase the percentage of an administered drug that is in solution when it eventually passes into the small intestine and may thereby increase the extent of absorption. For drugs that are absorbed by active and saturable processes, slow stomach emptying may increase the extent of absorption because of the nonsaturation of carrier mechanisms. Increased intestinal motility in the presence of food may promote drug absorption because of the faster dissolution and greater exposure of drug molecules to the intestinal epithelium, but it may also reduce absorption because of an increased drug transit rate through the intestine.

Several studies have defined the pharmacokinetics of cefprozil (1–3) and cefaclor (10, 12, 16, 17) under fasting conditions. The results from the present study on the pharmacokinetic parameters of these cephalosporins under fasting conditions are in close agreement with previously published data. The presence of food did not significantly alter the $AUC_{0-\infty}$ of either drug, although a slight decrease with food was observed for cefaclor. When compared with values in a fasting condition, mean C_{max} values of cefprozil decreased slightly and T_{max} values increased in the presence of food, but these differences were not significant. However, in the case of cefaclor, mean C_{max} values decreased significantly and T_{max} also increased significantly in the presence of food. A similar finding has been reported previously for cefaclor (7, 13). Because cefaclor is absorbed much more rapidly than cefprozil is under a fasting condition (2, 3), slight perturbations in gastric emptying and gastrointestinal motility by the presence of food are more likely to affect the absorption rate of cefaclor than that of cefprozil. The reduced C_{max} and increase T_{max} values indicate that the onset of absorption of cefaclor is not only delayed but the rate of absorption is also reduced significantly in the presence of food. The increased T_{max} of cefprozil indicated a delayed onset of absorption, but the rate of absorption was unaltered in the presence of food, as indicated by no difference in C_{max} values.

Cefadroxil and cephalexin are two other oral cephalosporins with antimicrobial spectra somewhat inferior to those of cefprozil and cefaclor. Investigation of the effects of food on the pharmacokinetic behavior of cefadroxil indicates that the rate and extent of absorption of cefadroxil remain unaltered after food intake relative to those in a fasting condition (12). The C_{max} of cephalexin was significantly reduced under the fed condition relative to that in a fasting state. However, the extent of absorption of cephalexin, indicated by the AUC, remains unchanged under the fed condition relative to that in a fasting state (12). Thus, it appears that the absorption characteristics of cefprozil are similar to those of cefadroxil, while the absorption characteristics of cefaclor are similar to those of cephalexin. This can possibly be attributed to the identical phenylglycine side chains of cefprozil and cefadroxil; similarly, the side chains of cefaclor and cephalexin are identical. Therefore, it appears that the presence of a hydroxyl group on the side chains of cefprozil and cefadroxil results in slower absorption of these two drugs compared with the absorption of cefaclor and cephalexin, which lack the hydroxyl group.

In summary, the rate of cefprozil absorption remains unchanged in the presence of food relative to that in the fasted state, whereas that of cefaclor is significantly decreased. The extent of absorption of each drug is not affected by food. The cefprozil $t_{1/2}$ and AUC are significantly greater than those of cefaclor under fasted as well as fed conditions. Although the C_{max} of cefprozil is significantly lower than that of cefaclor under a fasting condition, there is no difference in the C_{max} values of these cephalosporins when they are administered with food. Cefprozil can be given with a meal without markedly affecting levels in blood.

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