Pharmacokinetic Interactions of Cefprozil With Food, Propantheline, Metoclopramide, and Probenecid in Healthy Volunteers

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Cefprozil, a new oral cephalosporin antibiotic, is composed of cis and trans isomers in an approximate 90:10 ratio. The objectives of this study were: (1) to assess the effects of alterations in gastrointestinal motility by metoclopramide and propantheline on the pharmacokinetics of cis and trans isomers of cefprozil, and to compare them with the effects of food on the pharmacokinetics of cefprozil; (2) to assess the effects of inhibition of renal tubular secretion by probenecid on the pharmacokinetics of cefprozil isomers. In this four-way crossover study, 15 healthy male volunteers received a 1000-mg dose of cefprozil after fasting, pretreatment with metoclopramide or propantheline, after breakfast, or after probenecid in an incomplete, balanced block design. There was a 1-week washout period between each treatment. Blood and urine samples collected over a 24-hour period were assayed for the cis and trans isomers. The concentrations of the trans isomers were generally 1/10 of the cis isomer. The means and variances of the pharmacokinetic parameters of the cis and trans isomers of cefprozil were similar in fasting subjects and were affected in a parallel manner by food, metoclopramide, propantheline, and probenecid. The pharmacokinetics of the cis isomer under the fasting condition were as follows: maximum peak plasma concentration (Cmax), 14.0 ± 2.7 μg/mL; median time to reach Cmax (tmax), 1.5 (range, 1.0–3.5) hours; half-life (t½), 1.24 ± 0.27 hours; area under the concentration (AUC<sub>0</sub>–∞), 47.3 ± 7.7 μg·hour/mL; mean residence time after oral administration (MRT<sub>1</sub>), 2.9 ± 0.4 hours; CL<sub>1</sub>, 219 ± 60 mL/minute; and X<sub>1</sub> (percent cumulative urinary excretion in 0–24 hours), 68.1 ± 12.5. Propantheline delayed the tmax and significantly increased the MRT<sub>1</sub> of the cefprozil isomers, relative to the fasting state, but other pharmacokinetic parameters were not significantly altered. Metoclopramide reduced the tmax and significantly decreased the MRT<sub>1</sub> of both isomers of cefprozil, but other pharmacokinetic parameters were not significantly altered. Food slightly delayed the tmax but did not have a significant effect on other pharmacokinetic parameters of either isomer. Pretreatment with probenecid resulted in a significant increase in the t½, Cmax, AUC<sub>0</sub>–∞, and MRT<sub>1</sub> and in a significant decrease in the CL<sub>1</sub> of each isomer, indicating that probenecid competitively inhibits renal tubular secretion of cefprozil. In summary, the extent of absorption of cefprozil was not affected by drugs that change gastric motility nor by concurrent administration of food. Probenecid significantly decreased the renal clearance and prolonged the t½ of cefprozil, indicating that renal tubular secretion is a significant pathway in elimination of cefprozil.

Cefprozil, a new oral cephalosporin antibiotic, is composed of cis and trans isomers in an approximate 90:10 ratio. It has a broad antibacterial spectrum that includes both gram-positive and gram-negative organisms. The pharmacokinetic properties of cefprozil are typical of those of other oral cephalosporins, but its half-life (t½) is significantly longer than that of cefaclor. The urinary recovery of cefprozil accounts for 60 to 70% of the administered dose. Oral cephalosporins with a phenylglycine side chain generally are completely absorbed and are excreted unchanged in urine. Lack of complete urinary recovery of cefprozil suggests incomplete absorption or significant nonrenal clearance.

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An increase in gastrointestinal motility has been reported to decrease the extent of absorption of some drugs.\textsuperscript{11,12} In contrast, a decrease in gastrointestinal motility has been reported to increase the extent of absorption of poorly soluble and actively transported drugs.\textsuperscript{12-14} Food intake also may affect the absorption of some antimicrobial drugs.\textsuperscript{15} A study of the effects of food on the pharmacokinetics of cefprozil in healthy volunteers indicated that administration of the drug after a meal resulted in a slight increase in the area under the plasma concentration-time curve in some subjects.\textsuperscript{8}

Cefprozil, like many other antibiotics, is an organic anion, and is eliminated unchanged from the body by renal excretion. Its renal clearance is much higher than the glomerular filtration rate, suggesting that renal tubular secretion is an important clearance mechanism.\textsuperscript{5,8} Weak organic acids such as probenecid inhibit the secretion of organic anions in the kidney tubules and thus increase the half-life of drugs undergoing renal tubular secretion.\textsuperscript{16,17} Therefore, probenecid has a potential to prolong the half-life of cefprozil.

The objectives of this study were: (1) to assess the effects of alterations in gastrointestinal motility by metoclopramide and propantheline on the pharmacokinetics of cis and trans isomers of cefprozil, and to compare these effects with the effects of food; (2) to assess the effects of inhibition of renal tubular secretion by probenecid on the pharmacokinetics of cefprozil isomers.

\textbf{METHODS}

\textbf{Study Design}

The study was designed as an open, four-way incomplete block, balanced for treatment in an order determined from the rows of a Youdon Square. Each of the 15 subjects was randomly assigned to receive four of the five treatments in an order established by one of the five sequence groups as shown in Table I. The five treatments consisted of a 1000-mg dose of cefprozil administered under varying conditions: fasting subjects (Trt A); 0.5 hours after a standard breakfast (Trt B), 0.5 hours after a 30-mg dose of metoclopramide (Trt C); 0.5 hours after a 30-mg dose of propantheline (Trt D); and 0.5 hours after the third 1-g dose of probenecid administered at 8-hour intervals. The standard breakfast consisted of two eggs, two slices of toast, butter and jelly, sausage, and 200 mL of orange juice. The subjects consumed breakfast over a 15-minute period. There was a 7-day washout period between each treatment.

\textbf{Subjects}

Fifteen healthy male subjects between the ages of 19 and 47 years (mean, 30 ± 6 years), who were within ±15% of Metropolitan height and weight tables, and gave written informed consent, completed the study. Subjects were excluded if they had a history of disease of a major organ system, drug or alcohol abuse, drug hypersensitivity or intolerance, a medical condition requiring regular drug treatment, or use of any drug within 1 week or of alcohol within 24 hours before study initiation. Concomitant drugs, including alcohol and caffeine, were not allowed during the study.

\textbf{Drug Formulations}

The test drug, cefprozil, was supplied by the Pharmaceutical Product Development Department, Bristol-Myers Squibb Co., Syracuse, New York, as No. 1

\begin{table}
\centering
\caption{Treatment Schedule for Subjects in the Study}
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Sequence Group} & \textbf{Subject No.} & \textbf{Period 1} & \textbf{Period 2} & \textbf{Period 3} & \textbf{Period 4} \\
\hline
I & 1, 8, 13 & A & C & D & E \\
II & 3, 9, 12 & C & D & E & B \\
III & 5, 7, 11 & D & E & B & A \\
IV & 2, 10, 14 & E & B & A & C \\
V & 4, 6, 15 & B & A & C & D \\
\hline
\end{tabular}
\end{table}

where: Trt A = 4 × 250 mg cefprozil capsules under fasting condition
Trt B = 4 × 250 mg cefprozil capsules 0.5 hr after a standard breakfast
Trt C = 4 × 250 mg cefprozil capsules 0.5 hr after 30 mg metoclopramide dose
Trt D = 4 × 250 mg cefprozil capsules 0.5 hr after 30 mg propantheline dose
Trt E = 4 × 250 mg cefprozil capsules 0.5 hr after the third 1 g dose of probenecid given at 8 hr intervals.

opaque white capsules containing 250 mg of cefprozil. The assay of capsule contents indicated 221.5 mg cis isomer and 22.4 mg trans isomer per capsule. Thus each subject received 886.0 mg of the cis isomer and 89.6 mg of the trans isomer. Metoclopramide (Reglan®, A. H. Robins Co., Richmond, VA), propantheline (Pro-banthine®, G. D. Searle and Co., Chicago, IL), and probenecid (Benemid®, Merck, Sharp and Dohme Inc., West Point, PA) were purchased commercially.

Drug Administration

Subjects were confined to the test facility from the evening before each dosing session, and fasted for 12 hours. The subjects received 4 × 250 mg capsules of cefprozil with 200 mL water. Metoclopramide (30 mg), propantheline (30 mg) probenecid (1 g) doses were administered 0.5 hour before the cefprozil dose with 200 mL water. The standard breakfast was also consumed 0.5 hour before the cefprozil dose.

Blood Collection and Processing

Serial blood samples were collected in 5-mL heparinized vacutainers at predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, and 12 hours after drug administration. Plasma was separated by centrifugation, frozen in a carbon dioxide/methanol bath, and stored at or below −20°C. Quality control samples were prepared before administration of the first dose of each treatment session and were stored frozen, along with study samples.

Urine Collection and Processing

The total urine output for each subject was collected at predose and 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 16, and 16 to 24 hour intervals after drug administration. A 5-mL aliquot from each sampling interval was diluted with 5 mL of 0.01 M sodium acetate buffer (pH 3.5) and stored or below −20°C. Quality control samples were prepared before administration of the first dose of each treatment session and were stored frozen along with study samples.

Plasma and Urine Assays

Plasma and urine samples were assayed by validated high-pressure liquid chromatography methods for the cis and trans isomers of cefprozil.18 No interference was observed with metoclopramide, propantheline, or probenecid in the plasma and urine assays for either isomer of cefprozil. The observed concentrations of the cis and trans isomers in the quality control samples were within 10% of the nominal concentrations, indicating the assays were precise and accurate and cefprozil was stable in the study samples during the storage and shipping from clinical site to the analytical site.

Pharmacokinetic Analyses

Pharmacokinetic parameters for each isomer of cefprozil were calculated using noncompartmental methods.$^{16}$ The parameters determined included the maximum plasma concentration (Cmax), the time at which the maximum plasma concentration occurred (tmax), the elimination half-life ($t\frac{1}{2}$), the area under the plasma concentration–time curve from zero to infinity ($AUC_{\infty}$), the mean residence time in the body after an oral dose ($\text{MRT}_{\infty}$), and the total urine recovery from 0 to 24 hours ($X_u$), expressed as a percentage of the administered dose ($X_u\%$). The $t\frac{1}{2}$ was calculated from the slope of the best fit terminal log-linear portion of the plasma concentration–time curve. The $AUC_{\infty}$ was calculated using a combination of the linear and log trapezoidal rules$^{20}$ and was extrapolated to infinity. The renal clearance of each isomer (CL$_R$) was calculated as CL$_R = X_u / AUC_{\infty}$, where $X_u$ is the cumulative amount excreted unchanged in 0 to 24 hours.

Statistical Analysis

An analysis of variance model for balanced incomplete block designs was used to evaluate differences among treatments for the noncompartmental pharmacokinetic parameters Cmax, $t\frac{1}{2}$, AUC$_{\infty}$, MRT$_{\text{pe}}$, CL$_R$, and $\%X_u$. Analyses were carried out to assess differences in the parameters in the fasted state with those observed after pretreatment with either metoclopramide or propantheline, or after breakfast or probenecid.

Differences in the parameter values among the five treatments were assessed by computing the mean values adjusted for block differences (least squares means). The adjusted means of the parameters measured under the fasting conditions were compared with each of the other treatments by computing t-statistics using the estimate of mean square error, and the Bonferroni procedure at the 5% significance level.$^{22}$ Evaluations were carried out separately for the cis and trans isomers of cefprozil.

RESULTS

Pharmacokinetics of the cis Isomer Under Fasting Condition

The mean (± standard deviation) pharmacokinetic parameters of the cis isomer for each treatment are
summarized in Table II. The observed Cmax under the fasting condition was 14.0 μg·hour/mL, median Tmax was 1.5 hours, AUC0-∞ was 47.3 μg·hour/mL, MRTpo was 2.91 hours, t1/2 was 1.24 hours, CLR was 219.5 mL/minute, and Xw was 68.1%.

**Pharmacokinetics of the Trans Isomer Under Fasting Condition**

The mean (± standard deviation) pharmacokinetic parameters of the trans isomer for each treatment are summarized in Table III. The observed Cmax under the fasting condition was 1.5 μg·hour/mL, median Tmax was 1.5 hours, AUC0-∞ was 4.9 μg·hour/mL, MRTpo was 2.97 hours, t1/2 was 1.24 hours, CLR was 164 mL/minute, and Xw was 53.0%.

**Effect of Food, Metoclopramide, and Propantheline**

Mean plasma concentration profiles for the cis and trans isomers after breakfast are compared with those under fasting condition in Figures 1a and 1b, respectively. Administration of cefprozil after breakfast delayed the median Tmax of the cis and trans isomers by 0.5 and 0.75 hours, respectively, but did not have a significant effect on any other pharmacokinetic parameters as compared with the fasting state (Tables II and III).

The profiles for the cis and trans isomers, after metoclopramide and propantheline pretreatments, are compared with the fasting condition in Figures 2a and 2b, respectively. Pretreatment with metoclopramide resulted in a significant reduction in the MRTpo
of the cis and trans isomers (about 0.4–0.6 hours), but did not have a significant effect on any other pharmacokinetic parameter (Tables II and III). Pretreatment with propantheline resulted in a significant increase (about 1 hour) in the MRT_{po} of the cis and trans isomers (Tables II and III). The median t_{max} was also delayed. A small but significant reduction in C_{max} (20%) after pretreatment with propantheline was noted for both isomers, but other pharmacokinetic parameters were not significantly altered.

**Effect of Probenecid**

Mean plasma concentration profiles for the cis and trans isomers after probenecid pretreatment are compared with that observed for the fasting treatment in Figures 3a and 3b, respectively. Pretreatment with probenecid resulted in a significant increase in C_{max}, median t_{max}, AUC_{0-\infty}, MRT_{po} and t\frac{1}{2} of both isomers (Tables II and III). A significant reduction of about 60% in CL_{R} of both isomers was observed after pretreatment with probenecid, but X_{0} (%) was not significantly different (Tables II and III).

**DISCUSSION**

The effects of alterations in gastric emptying and gastrointestinal motility by food, metoclopramide, and propantheline on the pharmacokinetics of cefprozil were evaluated in this study. The effect of probenecid on the elimination of cefprozil also was evaluated. Cefprozil consists of a mixture of cis and trans isomers in approximately 90:10 proportion. The antimicrobial activities of both isomers are similar. Because the isomers of many drugs have been shown to exhibit different pharmacokinetic properties, one of the objectives of the present study was to compare the pharmacokinetics of the trans isomer with those of the cis isomer. The results from this study showed that the pharmacokinetics of the trans isomer of cefprozil corresponded to those of the cis isomer, and were affected by food, metoclopramide, propantheline, and probenecid in a manner similar to that of the cis isomer. Although the physicochemical properties of these isomers are expected to be different, these differences appear to be of insufficient magnitude to elicit significant differences in the pharmacokinetic parameters of these isomers.

Food delayed the time to reach C_{max} but did not have a significant effect on other pharmacokinetic parameters of the cis and trans isomers of cefprozil. Food has been reported to generally delay the rate of absorption and may increase, decrease, or not change the extent of absorption of antimicrobial agents. In this study, food slightly delayed absorption of cefprozil, but the C_{max}, AUC_{0-\infty}, t\frac{1}{2}, and CL_{R} of the cefprozil isomers were comparable to those in the fasted stated. The slight delay in t_{max} is probably a result of an increase in gastric emptying time. Food also has been reported to modify the bioavailability of drugs subjected to extensive presystemic metabolism. Because cefprozil is not subjected to exten-
sive metabolism, however, as evidenced by 60 to 70% of the administered dose of cefprozil being excreted unchanged in the urine, changes in relative bioavailability of cefprozil as a result of coadministration with food are unlikely.

Metoclopramide, which increases gastrointestinal motility, propantheline, and propantheline, which decreases the motility, have been used as probes to assess saturable or site-specific absorption of drugs that are poorly water soluble, such as griseofulvin and digoxin. Serum levels of digoxin were decreased by metoclopramide pretreatment and increased by propantheline pretreatment. It was postulated that the reduced gastric emptying time and increased motility after metoclopramide treatment shortened the effective absorption time of digoxin, lowering its serum levels and bioavailability, whereas propantheline, by increasing gastric emptying time and decreasing gastrointestinal motility, prolonged absorption time and increased serum levels and the bioavailability of digoxin. Using urinary recovery as an indicator, the relative bioavailability of chlorothiazide was increased by propantheline and decreased by metoclopramide. In this study, the effective absorption time as indicated by MRT_{\text{g1}} of cefprozil was decreased by pretreatment with metoclopramide, compared with that for the fasted state. In contrast, propantheline pretreatment increased the residence time of cefprozil in the gastrointestinal tract and thus permitted longer effective absorption time for cefprozil compared with the fasted state. In addition, the C_{\text{max}} was decreased and delayed after the pretreatment with propantheline, but there were no differences in AUC_{0-\infty} and t/2 of cefprozil compared with the fasting condition. These findings suggest that cefprozil is absorbed from a long segment of the gastrointestinal tract and that changes in motility of the gastrointestinal tract do not alter the bioavailability of cefprozil, relative to the fasting condition. Probenecid competitively inhibits the renal tubular secretion of many weak organic acids, including penicillin and cephalosporin antibiotics, resulting in decreased renal clearance, longer half-life, and higher plasma levels of the organic acids. In addition, a change in volume of distribution of the organic acids when coadministered with probenecid has been postulated as a contributing mechanism. After probenecid pretreatment, the AUC_{0-\infty} for cefprozil was significantly increased due to a significant decrease in CL_{\text{R}}. This resulted in a longer mean residence time of cefprozil isomers. The magnitude of decrease in CL_{\text{R}} accounts for most of the increase in AUC_{0-\infty}.

In conclusion, the pharmacokinetic parameters of cefprozil, observed under fasting condition, in the present study, are in agreement with those reported previously. These results also confirm previously reported findings that the cis and trans isomers exhibit similar pharmacokinetic properties. The extent of absorption of cefprozil was not affected by changes in gastric motility and concurrent administration of food.-Probenecid significantly decreased the renal clearance and prolonged the t/2 of cefprozil, indicating that renal tubular secretion is a significant pathway in elimination of cefprozil.

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