

## Effect of Food on Absorption of Cefpodoxime Proxetil Oral Suspension in Adults

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Received 6 June 1994/Returned for modification 30 July 1994/Accepted 24 October 1994

**The effect of a high-fat meal on absorption of a 200-mg dose of cefpodoxime proxetil oral suspension was evaluated in 20 healthy, male volunteers in a randomized, two-way crossover study. The concentrations of cefpodoxime in plasma and in urine were determined by sensitive and specific high-performance liquid chromatography methods. The area under the plasma drug concentration-time curve, time to peak concentration, and urinary excretion of cefpodoxime were significantly greater ( $P \leq 0.05$ ) after administration of cefpodoxime proxetil oral suspension with food than under fasting conditions. However, the difference in the areas under the curve between fed and fasted treatments was only 11%, and application of the two one-sided tests procedure showed bioequivalence between treatments for this parameter. The slight increase in the extent of drug absorption and the slower rate of absorption which results when cefpodoxime proxetil is given with food are unlikely to be of clinical importance.**

Cefpodoxime proxetil, a broad-spectrum, oral cephalosporin, is an ester prodrug that is believed to be cleaved in the intestinal epithelium by nonspecific esterases to yield the active metabolite cefpodoxime (11). Cefpodoxime exerts its activity by binding to penicillin-binding proteins, thereby interfering with bacterial wall synthesis (18). Its antibacterial spectrum includes staphylococci, streptococci, and gram-negative species (*Citrobacter*, *Enterobacter*, *Haemophilus*, *Klebsiella*, and *Proteus* spp). In infants and children, a cefpodoxime proxetil oral suspension is effective for the treatment of urinary tract infections, otitis media, and pharyngitis/tonsillitis.

Cefpodoxime proxetil is not completely absorbed after oral administration; the absolute bioavailability of cefpodoxime after a 100-mg dose of cefpodoxime proxetil tablets is approximately 50% (16). Food has been shown to alter cefpodoxime bioavailability from tablets by increasing the extent of absorption of cefpodoxime proxetil (2, 8). This food effect was not associated with meal composition because the increases in cefpodoxime bioavailability were similar in five equicaloric test meals which varied with respect to fat and protein content (8). Administration of a cefpodoxime proxetil oral solution with food had no effect on the extent of drug absorption, suggesting that food may improve drug solubility from the tablet dosage form by facilitating drug dissolution and/or by retaining the tablet in the acidic environment of the stomach, where cefpodoxime proxetil is more soluble and stable (3).

The effect of food on absorption of cefpodoxime proxetil oral suspension has not been studied with either adults or children. A few reports from the Japanese literature suggested that food had no effect on drug absorption after administration of a cefpodoxime proxetil dry syrup to children (6, 9). However, because of different diets in Japan and the United States, as well as formulation differences, these data may not be relevant to the oral suspension formulation marketed in the United States. The present study was conducted with adults given a high-calorie meal to represent the extreme effect of food on absorption of the cefpodoxime proxetil oral suspension.

(This material was presented in part at the American Association of Pharmaceutical Scientists Eighth Annual Meeting, Lake Buena Vista, Fla., November 1993.)

Twenty male volunteers ranging in age from 20 to 48 years (mean, 29 years) and ranging in body weight from 62.1 to 89.8 kg (mean, 76.3 kg) were enrolled in the study after giving written informed consent and a medical history. All subjects had normal physical examinations and electrocardiograms and acceptable clinical laboratory test values. Excluded from the study were subjects with a history of drug addiction, chronic alcoholism, hypersensitivity to penicillin or cephalosporins, use of antibiotics within 10 days of the study, or use of any prescription or nonprescription medication within 7 days of the study. Subjects took single, oral 200-mg doses of cefpodoxime proxetil (expressed in cefpodoxime equivalents) on two occasions, separated by a 5-day washout period, according to an open-label, randomized, crossover design. Treatments consisted of a 10-ml cefpodoxime proxetil oral suspension (100 mg/5 ml) (Upjohn lot no. 36,118; Kalamazoo, Mich.) given after an overnight fast and with a high-fat meal. Both treatments were taken with 180 ml of water. The high-fat meal administered as part of the nonfasting treatment was a breakfast consisting of two slices of toasted white bread with four pats of butter, two eggs, two slices of bacon, 3 oz (~85 g) of hash-browned potatoes, and 8 oz (~227 g) of whole milk. For both treatments, subjects had lunch 4 h after dosing. Except for the high-fat breakfast given with the oral suspension, the nutritional and caloric contents of all other meals served in the clinic were similar.

Blood samples were collected in tubes containing EDTA anticoagulant at zero hour (prior to drug administration) and at 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h after dosing. Samples were immediately refrigerated and then were centrifuged at  $2,060 \times g$  for 6 min at 4°C. Harvested plasma was immediately frozen and stored at  $-20^{\circ}\text{C}$  until assayed for cefpodoxime concentration. Urine was collected before dosing (–12 h to zero hour) and during the following collection intervals: zero hour to 4 h, 4 to 8 h, 8 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h. After each collection interval, the time of collection and urine weight were recorded. A 12-ml aliquot of each collection was frozen and stored at  $-20^{\circ}\text{C}$  until assayed.

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Concentrations of cefpodoxime in plasma and in urine samples were determined by reversed-phase high-performance liquid chromatography methods (1, 14). Standard curves were linear from 0.010 to 5.0  $\mu\text{g/ml}$  for the plasma method and from 0.50 to 50  $\mu\text{g/ml}$  for the urine assay, with correlation coefficients greater than 0.998. Between-day coefficients of variation for back-calculated concentrations of calibration standards ranged from 0.8 to 6.1% in plasma and from 0.6 to 4.3% in urine. Assay precision levels, expressed as coefficients of variation of estimated concentrations of quality control samples, were less than 9%. Assay accuracy, expressed as the ratio of estimated to theoretical quality control concentrations, averaged from 96 to 102%.

Pharmacokinetic parameters were determined by noncompartmental methods (7). Elimination rate constants ( $k_{el}$ ) were estimated by least-squares regression of values in the terminal log-linear region of the plasma cefpodoxime concentration-time curves. Half-life ( $t_{1/2}$ ) was calculated as  $0.693/k_{el}$ . Areas under the plasma drug concentration-time curve and under the first-moment curve from time zero to the time ( $T$ ) of the last detectable concentration ( $\text{AUC}_{0-T}$  and  $\text{AUMC}_{0-T}$ , respectively) were calculated by using the trapezoidal rule and were extrapolated to infinity ( $\text{AUC}_{0-\infty}$  and  $\text{AUMC}_{0-\infty}$ ) by adding the expressions  $C_T/k_{el}$  and  $[(T \times C_T/k_{el}) + C_T/k_{el}^2]$ , respectively, to  $\text{AUC}_{0-T}$  and  $\text{AUMC}_{0-T}$ , where  $C_T$  is the last detectable plasma drug concentration. Mean residence time was determined as  $\text{AUMC}_{0-\infty}/\text{AUC}_{0-\infty}$ . Peak plasma drug concentration ( $C_{max}$ ) and time to peak concentration ( $T_{max}$ ) were determined by inspection of individual subject concentration-time curves. Fractional drug absorption was calculated by the Wagner-Nelson method, which assumes a one-compartment model (4, 17). The fraction absorbed data for each subject and treatment were fitted to the equation  $F_a = 1 - e^{-k_a(t - T_{lag})}$  for estimation of the apparent absorption rate constant,  $k_a$ , and the lag time for absorption,  $T_{lag}$ , by using nonlinear least-squares regression (NLIN procedure of SAS, version 5; SAS Institute, Inc., Cary, N.C.). Urinary excretion of cefpodoxime was determined by multiplying urine concentrations by the corresponding urine volume values. Cumulative urinary excretion ( $A_e$ ) was calculated by summing the amounts of drug excreted at each of the collection intervals. Recovery was complete, as indicated by undetectable concentrations of cefpodoxime in virtually all urine samples from the last collection interval (36 to 48 h). The fraction of the administered dose excreted in the urine,  $f_e$ , was determined as  $A_e$  divided by the dose. Renal clearance ( $\text{CL}_R$ ) was calculated as  $A_e$  divided by  $\text{AUC}_{0-\infty}$ .

Pharmacokinetic parameters and plasma concentrations at each sampling time were compared by using a mixed-effects analysis of variance model, with group, period, and treatment as fixed effects and subjects within the group as a random effect. Statistical significance was defined as  $P \leq 0.05$ . Bioequivalence between fed and fasted treatments was assessed by the two one-sided tests procedure for  $\text{AUC}_{0-\infty}$  and  $C_{max}$  (13). All statistical evaluations were conducted with SAS, version 5, software.

Mean plasma drug concentration-time data for each treatment are shown in Fig. 1. Plasma cefpodoxime concentrations were normalized to correspond to a 200-mg dose, on the basis of the actual dose of oral suspension each subject received in each study period. At the early time points ( $<2.5$  h), cefpodoxime concentrations were significantly lower for the fed treatment than for the fasted treatment, whereas the opposite was true at times greater than 3 h. Mean pharmacokinetic parameters and results of the analysis of variance are provided in Table 1.  $\text{AUC}_{0-\infty}$  and cumulative urinary excretion of cef-

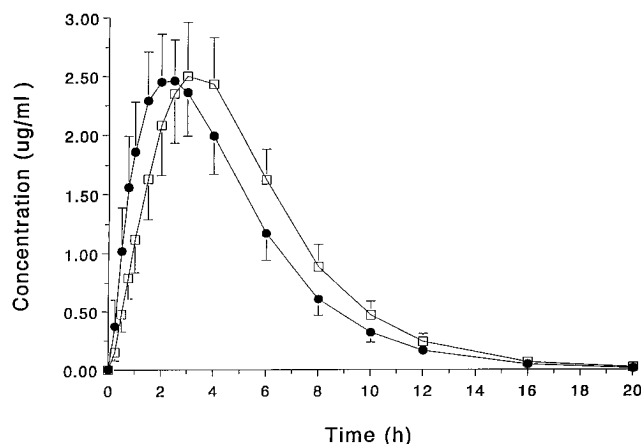


FIG. 1. Mean ( $\pm$  standard deviation) plasma cefpodoxime concentrations after a 200-mg dose of cefpodoxime proxetil oral suspension taken while fasting ( $\bullet$ ) and with a high-fat meal ( $\square$ ).

podoxime were significantly higher (11 and 14%, respectively) when the cefpodoxime proxetil oral suspension was taken with the high-fat meal than for dosing under fasted conditions.  $C_{max}$ , however, was unchanged. The 90% confidence intervals for between-treatment differences in  $\text{AUC}_{0-\infty}$  and  $C_{max}$  were 106 to 116% and 93 to 107%, respectively, indicating an equivalent extent of absorption for the fed treatment relative to the fasted treatment. The rate of drug absorption, as assessed by  $T_{max}$  and  $k_a$ , was significantly slower and the lag time for onset of absorption was significantly longer for the fed than the fasted treatment. No significant difference between treatments was observed for  $k_{el}$ , but mean residence time was significantly higher for the oral suspension taken with food than under fasted conditions, reflecting the difference in rate of absorption between these treatments.  $\text{CL}_R$  did not differ significantly between treatments.

The results of this study are consistent with previous findings for a 200-mg dose of cefpodoxime proxetil tablets in demonstrating that dosing with food results in a greater extent of drug absorption (8). However, the magnitude of the observed increase in AUC with the oral suspension is much lower than that observed with tablets (11% versus 21 to 33%). Also, unlike what is seen with the tablets,  $C_{max}$  for the oral suspension is not affected by food. Administration of the oral suspension with a high-fat meal also results in a slower rate of drug absorption and a prolonged lag time relative to dosing in the fasted state. These effects are not of clinical importance, because a decrease in rate and delay in onset of absorption primarily affect initial drug levels after the first dose, not subsequent doses, of a therapeutic regimen. A decrease in absorption rate when cefpodoxime proxetil was administered with food was also seen with the oral solution (3). Slower gastric emptying due to the high-fat content of the meal may account for delayed drug absorption. Improved drug solubility with the oral suspension relative to a solid tablet may account for the difference in rate of drug absorption under fed conditions. The role of food in solubilizing drug is likely greater with the solid dosage form.

The increase in extent of cefpodoxime proxetil absorption with food is greatest for the tablet (and within tablet doses is higher for a higher dose), followed by the suspension and then the solution. Conversely, the decrease in rate of drug absorption is more pronounced for the solution and suspension relative to the tablet. Similar findings have been reported for syrup and tablet formulations of cefetamet pivoxil, a prodrug

TABLE 1. Cefpodoxime pharmacokinetic parameters after a 200-mg dose of cefpodoxime proxetil oral suspension<sup>a</sup>

Treatment	AUC <sub>0-∞</sub> (μg · h/ml)	C <sub>max</sub> (μg/ml)	T <sub>max</sub> (h)	k <sub>a</sub> (h <sup>-1</sup> )	T <sub>lag</sub> (h)	Mean residence time (h)	t <sub>1/2</sub> (h)	f <sub>e</sub> (%)	CL <sub>R</sub> (ml/min)
Fasted	14.7 (2.0)	2.56 (0.37)	2.25 (0.50)	0.751 (0.15)	0.072 (0.060)	4.48 (0.40)	2.21 (0.19)	41.8 (5.0)	97.1 (13)
Fed	16.4 (2.3)	2.57 (0.46)	3.32 (0.59)	0.477 (0.080)	0.184 (0.075)	5.20 (0.41)	2.28 (0.34)	47.8 (6.5)	98.4 (17)
P	0.0015	>0.05	0.0001	0.0001	0.0001	0.0001	>0.05	0.0179	>0.05

<sup>a</sup> Values are means, with standard deviations given in parentheses.

ester. When cefetamet pivoxil is taken with a meal, bioavailability is increased by 25 to 30% for tablets and by only 12% for the syrup (5, 12, 15). However, as was observed for the cefpodoxime proxetil oral suspension, food delayed absorption of cefetamet pivoxil syrup to a greater extent than that of the tablet (5). For a prodrug, it is difficult to interpret and explain data from food effect studies. Differences in absorption processes due to reduced gastric emptying rate when drugs are taken with food may be confounded with ester hydrolysis processes pre- and postabsorption.

The relevance of the data from this study to the target population for the cefpodoxime proxetil oral suspension, pediatric patients, can be postulated on the basis of differences in diet and similarities in fasted-state pharmacokinetics (10). Because a high-calorie meal is likely to represent the most extreme effect on absorption, a typical child's meal may have only a minimal effect on the extent of drug absorption, but a delay in achieving peak levels is possible. A decrease in the rate and/or onset of absorption is not of clinical importance for a beta-lactam antibiotic such as cefpodoxime proxetil, because drug levels exceeding the MIC at which 90% of the isolates are inhibited are still achieved within the dosing interval.

We thank Gary Peters and Esther Wyman for technical assistance in conducting this study.

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