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Pharmacokinetics of Cefpodoxime Proxetil and Interactions with an Antacid and an H_2 Receptor Antagonist

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Cefpodoxime proxetil is a new oral esterified cephem antibiotic with a broad antibacterial spectrum. The dissolution of cefpodoxime proxetil is pH dependent. The objectives of this study were to characterize the pharmacokinetics of cefpodoxime proxetil in two different oral doses and to examine possible interactions with an antacid, aluminum magnesium hydroxide (Maalox 70), and an H_2 receptor antagonist, famotidine. Two studies involving the same 10 healthy volunteers were performed. In the first study, cefpodoxime proxetil was administered in two doses, 0.1 and 0.2 g. In the second study, two interventions were performed in a randomized crossover design. For one intervention, the volunteers were pretreated with 40 mg of famotidine 1 h before 0.2 g of cefpodoxime proxetil was administered. In the second trial, participants were given 10 ml of Maalox 70 2 h and 10 ml of Maalox 70 15 min before they received 0.2 g of cefpodoxime proxetil. Serum and urine concentrations were determined by high-performance liquid chromatography. For the statistical evaluation, these data were tested by using the pharmacokinetics of 0.2 g of cefpodoxime proxetil from the first study. The maximum concentrations were 1.19 ± 0.32 mg/liter after 0.1 g of cefpodoxime proxetil and 2.54 ± 0.64 mg/liter after 0.2 g of cefpodoxime proxetil. The elimination half-lives were 149 min for 0.1 g and 172 min for 0.2 g of cefpodoxime proxetil. The total increase in the area under the concentration-time curve (AUC) was dose dependent. Combination with Maalox 70 caused a reduction in the AUC from 14.0 ± 3.9 to 8.44 ± 1.85 mg · h/liter. After famotidine, the AUC decreased to 8.36 ± 2.0 mg · h/liter. Corresponding changes were registered for the maximum concentration of drug in serum, 24-h urine recovery, and the time to maximum concentration of drug in serum. Cefpodoxime proxetil was well tolerated without any seriously adverse drug reactions.

Cefpodoxime proxetil is one of several new cephems given orally as inactive esters of the antibiotic cefpodoxime. Cefpodoxime is quickly liberated from its prodrug by esterases of the intestinal wall and is absorbed into the bloodstream as an active substance (7, 21). The prodrug and active metabolite are both shown in Fig. 1. Cefpodoxime shows a broad spectrum of activity that includes many gram-positive and -negative aerobic and anaerobic pathogens. It is stable with a variety of β-lactamases (4, 6, 12, 13, 21).

One factor determining the in vivo efficacy of an antibiotic is its bioavailability. Since dissolution, and hence absorption, can be pH dependent, it seems necessary to investigate whether the bioavailability of a drug is changed by interactions with antacids or H_2 receptor antagonists.

This study was designed to characterize the basic pharmacokinetics of cefpodoxime proxetil and to examine interactions between the esterified cephem and an antacid as well as an H_2 receptor antagonist. Both cause a rise in gastric pH and have been shown to influence the absorption of other antibiotics (5, 8, 9, 16, 21).

MATERIALS AND METHODS

Volunteers. Ten healthy male volunteers, aged 21 to 33 years, provided informed written consent for these studies, which had been approved by the local ethical committee. The mean body weight was 71 ± 7 kg, and the mean body surface was 1.87 ± 0.11 m^2. Renal function was normal in all participants. Creatinine clearance was 107 ± 34 ml/min/1.73 m^2 (mean ± standard deviation [SD]). Two studies involving the same 10 healthy volunteers were performed. In our first study, 0.2 g of cefpodoxime proxetil was administered to all volunteers on day 1 after overnight fasting. After a washout period of 2 weeks, the same 10 subjects were treated with 0.1 g of cefpodoxime proxetil.

The second study was conducted over 2 days in a randomized crossover design. On day 1, five volunteers received 20 ml of Maalox 70 in two doses of 10 ml of Maalox 70 each. The doses were taken 2 h and 15 min before the ingestion of 0.2 g of cefpodoxime proxetil after overnight fasting. The other five volunteers were pretreated with 40 mg of famotidine 1 h before 0.2 g of cefpodoxime was administered after overnight fasting (16). After a washout period of 1 week, both groups of five were treated vice versa.

Before dosing, all participants underwent comprehensive medical assessments, including a medical history, a hematology screening, a chemistry profile, an electrocardiogram, and supine and erect heart rate and blood pressure registration. For safety, the electrocardiogram was repeated 2 and 6 h after drug ingestion on each study day. Heart rate and blood pressure were recorded 2, 6, 12, and 24 h after dosing. The participants had taken no other antimicrobial agents in the 4 weeks prior to the study and took none during the course of the study. To exclude drug abusers, a routine

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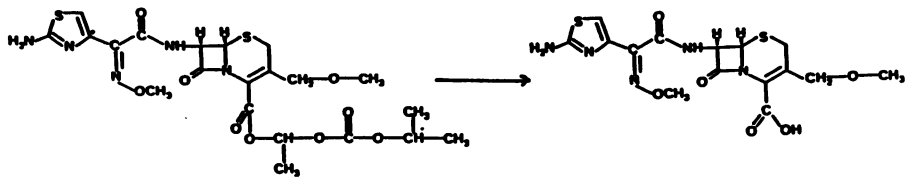

FIG. 1. Chemical structure of cefpodoxime and its oral prodrug, cefpodoxime proxetil.

drug-screening test was performed prior to the study and also on two random study days.

Dosing. Cefpodoxime proxetil (batch RU 51807; Roussel Uclaf, Paris, France) was given as 0.1-mg tablets. A Maalox 70 suspension (batch 842338III; Rorer GmbH, Bielefeld, Germany) was furnished in portioned 10-ml packets consisting of 600 mg of magnesium hydroxide and 900 mg of aluminum hydroxide. Famotidine (batch 87801; Pepdul, Frosst Pharma, Munich, Germany) was administered in the form of a 40-mg tablet. These products were kindly supplied by Sankyo Europe GmbH, Frankfurt, Germany.

The cefpodoxime proxetil tablet was swallowed with 200 ml of tap water. The Maalox 70 suspension was taken directly from the packet, 1 dose 2 h and the other dose 15 min before the administration of cefpodoxime proxetil. When famotidine was given, volunteers took the tablet 1 h before ingesting the antibiotic. Then, liquid was allowed ad libitum, and food was allowed after 3 h.

Sampling. Blood samples were drawn via an indwelling intravenous catheter immediately before and 15, 30, 45, 60, 90, 120, and 150 min and 3, 4, 6, 8, 12, and 24 h after oral administration of cefpodoxime proxetil. After clotting, blood samples were centrifuged at 1,500 × *g* for 10 min. All volunteers provided predose urine samples. After dosing, urine was collected for 24 h during four different periods: 0 to 3, 3 to 6, 6 to 12, and 12 to 24 h. Serum and urine samples were stored at −80°C until analysis.

Detection methods. All samples were assayed for their concentrations of cefpodoxime by high-performance liquid chromatography (HPLC). Proteins in serum were precipitated with acetonitrile. Samples were then centrifuged, and the supernatant was extracted with dichloromethane, whereby acetonitrile was removed from the aqueous phase. After centrifugation again, aqueous supernatant was diluted with sodium acetate buffer (10 mmol/liter, pH 4). Urine was diluted with sodium phosphate buffer (20 mmol/liter, pH 5.5). The analyte was separated by reversed-phase chromatography on a column of Necleosil 5 C 18 (Macherey & Nagel) in isocratic elution mode. The mobile phase consisted of a mixture of 9 volumes of acetonitrile and 91 volumes of sodium acetate buffer (10 mmol/liter, pH 4.0). For detection and quantitation, a UV absorption detector was used at 260 nm.

Chromatographic peaks were verified by complete enzymatic hydrolysis with β-lactamase from *Bacillus subtilis*. The lowest detectable concentration of cefpodoxime in serum was 0.05 mg/liter. The limit of quantitation was 0.16 mg/liter, the linear range was 5.00 mg/liter, and the precision within the batch (coefficient of variation [CV]) was 2.9 to 12.0%. The precision between batches (CV) was 7.0 to 12.5%. The recovery rate from 10 spiked serum samples was 95.8 ± 5.5%. The detection limit for urine was 2 mg/liter. The limit of quantitation was 5 mg/liter, and the linear range was 800 mg/liter. The precision between batches (CV) was 1.8 to 5.2% (3).

Pharmacokinetic analysis. (i) Compartmental approach. The data were fitted according to an open two-compartment model by using our own nonlinear regression program (15). Each observation was weighted according to the equation $W_i = 1/C(t_i)$, where W_i is the "standard weight" (17) and $C(t_i)$ is the computed concentration. The dimensions of the compartmental model were based on the Schwarz criterion (18). The compartmental approach was used to calculate the half-lives, the total area under the curve (AUC_{tot}), the time to maximum concentration of drug in serum (T_{max}), and the maximum concentration of drug in serum (C_{max}) ($C_{max} = C(T_{max})$).

(ii) Model-free approach. Without referring to any mathematical model, the area was calculated directly from the data (area under the data [AUD]) with an additional term for the area between the last measurement and infinity to estimate the total area under the data (AUD_{tot}). As can be seen in Tables 1 and 2, both area values (AUC_{tot} and AUD_{tot}) are very close although they were calculated independently, thus indicating the validity of the model. The mean residence time (MRT) and the distribution volume at steady state (V_{SS}) are also derived from the data by using the usual equations; for an example, see reference 1. Note that the observed MRT, i.e., the time including the MRT at input due to lag time and the time for absorption, is given. All bioavailabilities were calculated individually for each volunteer, and then the mean ± SD was calculated.

Statistical evaluation. Since the individuals in the respective studies were identical, Wilcoxon's rank sum test was applied. P values of <0.05 were considered significant. Note that all dose-dependent parameters are calculated for each dose per 70 kg of body weight.

RESULTS

Safety and tolerance. Cefpodoxime proxetil was well tolerated in these single-drug administration studies. There were no significant changes in the clinical laboratory control parameters during the two study periods. Some symptoms of the gastrointestinal tract, such as stomachaches, loose stools, and flatulence, were observed after each treatment. Seriously adverse drug reactions did not occur.

Pharmacokinetics. The pharmacokinetic parameters of studies 1 and 2 are shown in Tables 1 and 2, respectively.

The regression line is shown in Fig. 2 together with the arithmetic means for serum concentrations and standard deviations following 0.1 and 0.2 g of cefpodoxime proxetil.

After a lag time of approximately 14 ± 6 min, cefpodoxime was absorbed at a rather slow rate, with peak concentrations occurring at a mean of 119 min after 0.1 g of antibiotic and at 135 min after the 0.2-g dose (Table 1). This slight difference

TABLE 1. Pharmacokinetic parameters of 0.1- and 0.2-g oral doses of cefpodoxime proxetil[a]

Parameter (unit)	Value (mean ± SD) for dose of CEPO (g)	
	0.1	0.2
C_{max} (mg/liter)	1.19 ± 0.32[b]	2.54 ± 0.64
T_{max} (min)	119 ± 26	135 ± 22
$t_{1/2}$ (min)	149 ± 37	172 ± 51
MRT (min)	284 ± 44	298 ± 41
AUC_{tot} (mg · h/liter)	6.35 ± 1.30[b]	14.0 ± 3.9
AUD_{tot} (mg · h/liter)	6.57 ± 1.45[b]	14.0 ± 3.9
$V_{SS/f}$ (liters/70 kg)	74.2 ± 27.9	72.5 ± 24.4
Ur_{rec}, 24 h (%)	41.9 ± 11.8	39.7 ± 7.6

[a] All samples were assayed for their concentrations of cefpodoxime by HPLC. C_{max}, AUC_{tot}, and $V_{SS/f}$ were normalized to 70 kg of body weight. Ur_{rec}, recovery in urine; CEPO, cefpodoxime proxetil. Bioavailability is indicated by *f*.

[b] When these values were doubled for 0.1 g, no significant differences from those for 0.2 g were seen ($P > 0.05$).

in T_{max} is not statistically significant ($P > 0.05$). Elimination of cefpodoxime was prolonged, leading to terminal half-lives of 149 and 172 min, with no significant difference. The C_{max} for the 0.1-g dose was 1.2 mg/liter, and it approximately doubled following the 0.2-g dose (2.5 mg/liter). The AUC_{tot} of 6.4 mg · h/liter following 0.1 g of cefpodoxime proxetil increased to 14.0 mg · h/liter when 0.2 g was administered. The C_{max} and the AUC_{tot} were multiplied by two and then statistically evaluated, showing no significant difference ($P > 0.05$). The model-independent parameter AUD_{tot} hardly varied from the AUC_{tot} for both doses (6.6 mg · h/liter for 0.1 g and 14.0 mg · h/liter for 0.2 g), and the MRT showed no difference (284 and 298 min, respectively).

Cumulative recoveries in urine (in percentages of the given dose) were almost the same for both doses: 42% for 0.1 g and 39% for 0.2 g.

After 0.1 g of cefpodoxime proxetil, five participants reported headaches, and one of these also noted loose stools and flatulence. One additional participant complained of a stomachache, and one complained of dizziness. Headaches were reported by two subjects after they took 0.2 g of cefpodoxime proxetil. Another subject had loose stools after the 0.2-g dose.

In the second study, we found several changes in the pharmacokinetic parameters of 0.2 g of cefpodoxime proxetil when it was administered together with Maalox 70 or famotidine. To compare the results of the second treatment period with the pharmacokinetics of 0.2 g of cefpodoxime proxetil in the same subjects after overnight fasting, we derived all of these data from the previous study.

Figure 3 shows the mean concentrations of cefpodoxime in serum resulting from pretreatment with antacid and famotidine. The mean peak level was reduced by 48%, from 2.5 to 1.3 mg/liter, after famotidine. Maalox 70 led to the peak concentration being reduced by 36%, from 2.5 to 1.5 mg/liter.

Peak levels for 0.2 g of cefpodoxime were measured approximately 2 h after administration. When it was given after H_2 blocker, there was a significant change in the T_{max} of 45 min. The delay of 8 min found after pretreatment with the antacid was not significant. There was no significant change in the elimination half-lives following pretreatment. The changes found in the area under the curve (AUC) after both famotidine and Maalox 70 were significant and are concurrent with those in other parameters. The changes in the model-independent parameter AUD after pretreatment with famotidine and Maalox 70 were in agreement with those in AUC. Combination with the H_2 antagonist also resulted in a significant increase in the MRT, from 298 to 380 min ($P < 0.01$). Combination with Maalox 70 caused no change in the MRT. There were also correspondingly significant changes in 24-h urine recoveries, measured in percentages of the given dose. The adverse drug reactions following the combination with famotidine included headaches in six volunteers and a stomachache with flatulence in one. After pretreatment with Maalox 70, one subject reported loose stools and flatulence, and two complained of headaches.

DISCUSSION

Study 1. The pharmacokinetics evaluated for 0.1- and 0.2-g single doses of cefpodoxime proxetil suggest good absorption of the active substance in comparison with that of other cephalosporin esters. The rate of absorption was rather slow, and the elimination was prolonged. Peak levels and the AUC increased in proportion to the two administered doses, indicating linear dose response. The maximum serum concentrations were above most of the MICs for 50% of the

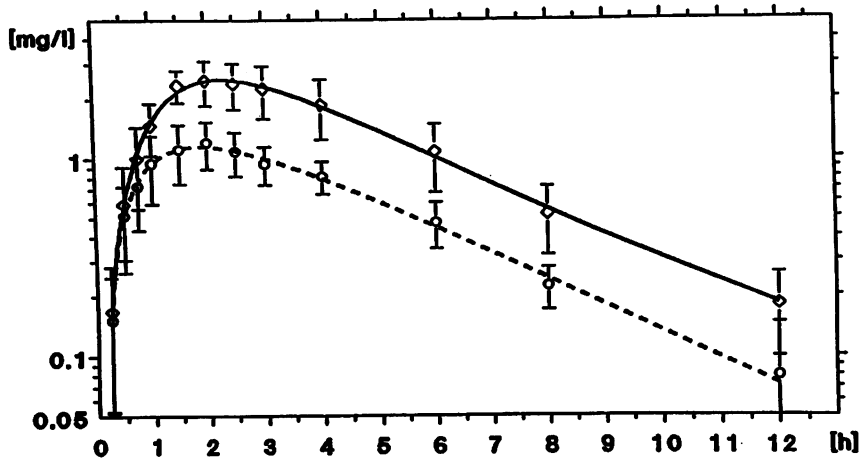

FIG. 2. Regression lines and SD for concentrations of 0.1 (○) and 0.2 (◇) g of cefpodoxime proxetil in serum.

TABLE 2. Pharmacokinetic parameters of cefpodoxime proxetil following concomitant intake with famotidine and Maalox 70[a]

Paramater (unit)	Value (mean ± SD) for dose of CEPO (0.2 g)		
	Alone	Plus 40 mg of FA	Plus 20 ml of MA
C_{max} (mg/liter)	2.54 ± 0.64	1.26 ± 0.43	1.55 ± 0.29[b]
T_{max} (min)	135 ± 22.1	179 ± 39[b]	143 ± 27
$t_{1/2}$ (min)	172 ± 50	238 ± 74	169 ± 37
MRT (min)	298 ± 41	380 ± 73[b]	299 ± 24
AUC_{tot} (mg · h/liter)	14.0 ± 3.9	8.36 ± 2.0[b]	8.44 ± 1.85[b]
AUD_{tot} (mg · h/liter)	14.0 ± 3.9	8.46 ± 2.1[b]	8.27 ± 2.02[b]
$V_{SS/f}$ (liters/70 kg)	72.5 ± 24.4	155 ± 52[b]	122 ± 25[b]
Ur_{rec}, 24 h (%)	39.7 ± 7.6	24.9 ± 4.9[b]	27.0 ± 5.8

[a] CEPO, cefpodoxime proxetil; FA, famotidine; MA, Maalox 70; Ur_{rec}, recovery in urine. Bioavailability is indicated by *f*.
[b] $P > 0.01$; all values not marked are not significant ($P > 0.05$).

strains of the family *Enterobacteriaceae* tested (4, 20). These results are in agreement with the pharmacokinetic parameters evaluated by Borin et al. in an extensive pharmacokinetic study of cefpodoxime proxetil (2). There are some differences in the pharmacokinetics of cefpodoxime proxetil and those of some older cephalosporins, such as cephalexin, which is totally absorbed after oral administration, with peak levels occurring after 1 h and fast elimination (terminal half-life, 1 h) (10). In comparison, cefuroxime axetil is absorbed at the same rate but not as well as cefpodoxime proxetil and is eliminated faster (8).

The minor adverse reactions (headaches, loose stools) experienced by some of the participants after these single doses are most likely coincidental and in part due to the changes in diet and sleeping habits necessary for these trials. This is supported by the fact that more symptoms occurred following the lower dose of 0.1 g than after the 0.2-g dose of cefpodoxime proxetil. Any further interpretation of symptoms is restricted by the open-label design of this study.

Study 2. Modern antibiotic therapy is often accompanied by simultaneous therapy of underlying diseases. Famotidine, an H_2 receptor antagonist, and Maalox 70, an antacid, are both characterized by their abilities to elevate gastric pH. This makes them common drugs for the treatment of peptic ulcers.

Both famotidine and Maalox 70 significantly reduced the bioavailability of cefpodoxime proxetil to a relative bioavailability of 60% compared with that of the control. A change in gastric pH seems to influence the bioavailability of cefpodoxime proxetil. The stability and the dissolution rate of cefpodoxime proxetil in vitro depend on the pH of the test solution (20). The solubility of cefpodoxime proxetil in aqueous solution is reduced from approximately 11 mg/ml at pH 1.5 to only 0.4 mg/ml at pH 6.0 to 7.0. Spontaneous hydrolysis can be observed for 3% of the dose at pH 6.0 but for 7% of the dose at pH 7.0. Raising the pH from 1.2 to 6.8 causes no marked change in the in vitro disintegration time of the tablet (5 to 7 min) (20). These data suggest that the decrease in the bioavailability of cefpodoxime proxetil, when administered simultaneously with Maalox 70 or famotidine, results from incomplete dissolution of the drug in the stomach at the increased gastric pH. The same mechanism seems to be responsible for a similar reduction in the bioavailability of enoxacin after pretreatment with ranitidine, another H_2 receptor antagonist (9).

Other authors have been able to show that administration of cefpodoxime proxetil after a meal enhances the bioavailability of the antibiotic (14). Hughes et al. (11) administered cefpodoxime proxetil to fasting subjects and after intervention with pentagastrin, ranitidine, sodium bicarbonate, and aluminum hydroxide. The highest peak concentrations were achieved in fasting subjects and after pentagastrin. All other interventions reduced the C_{max} and the AUC by 35 to 50%. The gastric pH and the C_{max} and the AUC were inversely related. Giving cefpodoxime proxetil at the midpoint of the fourth meal of various diets resulted in a rise in the C_{max} of 22 to 34% for all regimens.

These findings are important for clinical therapy, since the simultaneous administration of cefpodoxime proxetil and H_2 receptor antagonist or antacid drugs, especially in the fasting patient, may reduce the efficacy of the antibiotic. To achieve sufficient serum levels, administration of cefpodoxime at least 2 h after the administration of an antacid or famotidine is recommended. Postprandial administration has been successfully used with concomitant administration of cefuroxime axetil and an H_2 receptor antagonist (19).

The changes in urine recoveries were in agreement with the variations in concentrations of cefpodoxime in serum for both interventions.

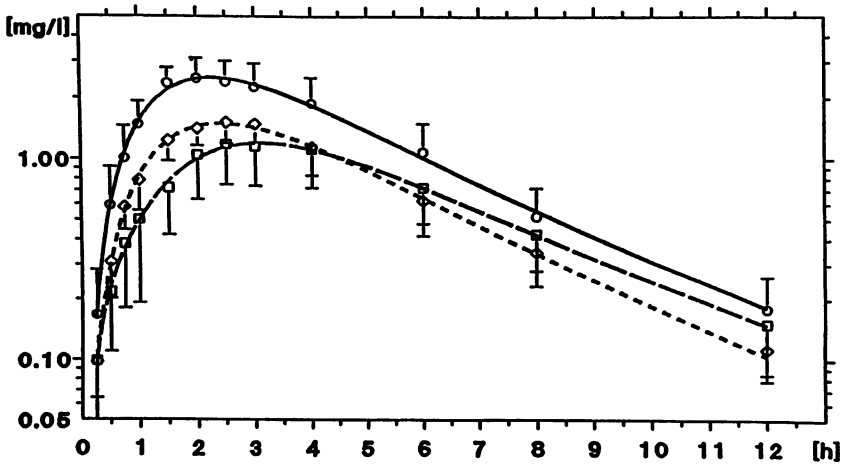

FIG. 3. Arithmetic means and SD for cefpodoxime after oral administration of 0.2 g of cefpodoxime proxetil (○), 0.2 g of cefpodoxime proxetil concomitant with 40 mg of famotidine (□), and 20 ml of Maalox 70 (◇).

In conclusion, optimal absorption of cefpodoxime requires low gastric pH, which allows sufficient dissolution of cefpodoxime. The evaluation of adverse events observed during this interaction study is even more limited than in study 1. It is nearly impossible to assign symptoms to any specific drugs, since the antibiotic was given simultaneously with an antacid and an H_2 receptor antagonist. Overall, we were able to observe good tolerance of cefpodoxime proxetil in this single-dose study.

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