Pharmacokinetics and Ex Vivo Susceptibility of Cefpodoxime Proxetil in Patients Receiving Continuous Ambulatory Peritoneal Dialysis

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Pharmacokinetics of cefpodoxime, an extended-spectrum cephalosporin, were determined for eight noninfected patients on continuous ambulatory peritoneal dialysis (CAPD) and eight healthy volunteers. Subjects were matched for sex, age (± 6 years), and body weight (± 10 kg, except for one pair) and received a single 200-mg (cefpodoxime equivalents) oral dose of the prodrug cefpodoxime proxetil in an open-label, paired-design fashion. Dialysate (CAPD group only), plasma, and urine samples were collected and assayed for cefpodoxime by a microbiologic method. In addition, mean bactericidal titers of the effluent dialysate against selected bacterial strains often associated with CAPD-related peritonitis were determined at 6 and 24 h after the dose. There was a significant difference ($P < 0.05$) in all pharmacokinetic parameters between healthy and CAPD subjects, except for lag time to absorption. The mean peak plasma cefpodoxime concentration of 1.88 ± 0.6 $\mu\text{g/ml}$ occurred at 2.44 ± 0.5 h for healthy volunteers, while the peak concentration of 3.25 ± 1.4 $\mu\text{g/ml}$ occurred at 12.0 ± 4.2 h for patients on CAPD. The average elimination half-life in CAPD patients was approximately 12 times greater than that seen in healthy volunteers. Peritoneal dialysis had a minimal effect on cefpodoxime clearance. In healthy volunteers, $24.2\% \pm 13\%$ of the dose was recovered from the urine, in contrast to only $5.59\% \pm 6.9\%$ for CAPD patients. The mean bactericidal titers for all CAPD patients, at 6 and 24 h, were mostly less than 1:2 and did not exceed 1:4 for any of the isolates. Because of the decreased renal clearance and negligible dialysate clearance of cefpodoxime, and delayed drug absorption, the dosage interval for cefpodoxime proxetil may need to be extended in CAPD patients.

Cefpodoxime proxetil is an orally administered cephalosporin ester that is converted to the free acid cefpodoxime, an extended-spectrum cephalosporin. Presumably, this conversion occurs upon contact with nonspecific intestinal brush border esterases (13, 15). Cefpodoxime, through binding and inhibiting various penicillin-binding proteins (22), is active in vitro against many gram-positive and gram-negative bacteria, except *Pseudomonas* spp., enterococci, and methicillin-resistant staphylococci (6, 13, 14, 22). The drug is highly stable against different chromosome- and plasmid-mediated β -lactamases (22). Clinically, in doses of 100 to 200 mg (cefpodoxime equivalents), cefpodoxime proxetil is effective in treating skin and soft tissue, upper and lower respiratory tract, and urinary tract infections due to susceptible organisms (7, 8, 10, 20).

Previous studies have indicated that the half-life of cefpodoxime is prolonged in patients with renal impairment, with a positive correlation established between the drug's renal clearance and its half-life (2). Hemodialysis removes nearly one-quarter of the administered dose (3).

This open-label, single-dose, paired-design study was conducted to evaluate the disposition of cefpodoxime following oral administration of a single 200-mg dose of cefpodoxime proxetil to patients on continuous ambulatory peritoneal dialysis (CAPD). Additionally, mean bactericidal titers (MBTs) of the effluent dialysate were determined against

selected bacterial strains often associated with CAPD-related peritonitis.

MATERIALS AND METHODS

Subjects. Eight noninfected CAPD patients and eight healthy volunteers participated in this paired-design study. Each CAPD patient was matched with a healthy volunteer with respect to sex, age (± 6 years), and body weight (± 10 kg, except for pair 8). Pair 8 consisted of two females with a history of cholecystectomy; therefore, the weight requirement was waived for this pair. All subjects were within 20% of the desired body weights (16a). At the time of the study, no patient was taking any other antibiotics; however, the CAPD patients were allowed to take other medications prescribed for the management of chronic renal failure, except for any known hepatic enzyme-inducing agents, antacids, metoclopramide, and histamine₂ receptor antagonists, which were not allowed within 4 days of dosing. Aluminum hydroxide-containing antacids, citrate salts (e.g., Shohl's solution), or calcium supplements were not taken for 4 h before and 4 h after dosing. Prior to dosing, three CAPD patients were taking ranitidine, and two were taking metoclopramide. Patients had no known history of penicillin or cephalosporin allergy. All laboratory parameters (i.e., hepatic, renal, and hematologic parameters and electrolytes) were within normal limits (healthy volunteers) or consistent with chronic renal failure (CAPD patients). All patients gave written informed consent prior to enrollment in the study.

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This study was approved by the Human Subjects Committee of the University of Wisconsin Center for Health Sciences.

Dosing. All participants were admitted to the University of Wisconsin-General Clinical Research Center at least 12 h prior to drug administration. Ten hours prior to dosing, a standardized light snack was served. The subjects continued fasting for 4 h postdose, at which time lunch was consumed. For CAPD patients, the peritoneal space was completely drained in the morning prior to dosing. Then, immediately after complete instillation of a fresh volume of dialysate fluid in the peritoneal cavity, the patients were dosed. Each subject ingested one 200-mg (cefpodoxime equivalents) film-coated cefpodoxime proxetil tablet (lot 25,693; The Upjohn Company, Kalamazoo, Mich.) with 180 ml of water.

Samples. Blood samples (5 ml) were collected in vacuum tubes (Becton-Dickinson, Rutherford, N.J.) containing freeze-dried EDTA as an anticoagulant. For CAPD patients, blood samples were collected just prior to drug administration (0 h) and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 6.5, 7, 8, 10, 12, 13, 14, 16, 18, 20, 22, 24, 26, 30, 36, 42, 48, 54, 60, 66, and 72 h following dosing. From healthy volunteers, blood samples were collected just prior to drug administration (0 h) and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h following dosing. Plasma was harvested within 1 h of sample collection and frozen and stored at -20°C until assayed.

Urine was collected from all subjects before drug administration (-12 to 0 h) and during the following intervals: 0 to 6 , 6 to 12 , 12 to 18 , 18 to 24 , 24 to 36 , and 36 to 48 h after dosing. For CAPD patients, urine collection was extended into 48 - to 60 - and 60 - to 72 -h-postdose intervals. The volume of urine was measured, and a 12 -ml aliquot was frozen and stored at -20°C until assayed.

In CAPD patients, peritoneal dialysis exchanges were done every 6 h throughout the study with 2.08 -liter solutions containing 1.5 , 2.5 , or 4.25% hydrous glucose (Dianeal; Baxter, Deerfield, Ill.). Heparin (500 U/liter) and insulin were added as required to the dialysate. No other additive was permitted. Before drug administration, the indwelling peritoneal catheter of each CAPD patient was equipped with a three-way stopcock and a 50 -ml plastic syringe. Sampling of the dialysate was performed by withdrawing 50 ml of dialysate into the syringe and reinfusing the fluid into the peritoneum. This was done twice before a 10 -ml sample for analysis was withdrawn. This technique was used to mix the dialysate within the peritoneum. Dialysate samples were collected just prior to drug administration (0 h) and at 0.33 , 0.67 , 1 , 1.5 , 2 , 2.5 , 3 , 4 , 6 , 6.5 , 7 , 8 , 10 , 12 , 13 , 14 , 16 , 18 , 19 , 20 , 22 , 24 , 26 , 30 , 36 , 42 , 48 , 54 , 60 , 66 , and 72 h after dosing. Dialysate effluent was drained in the usual manner by gravity-dependent flow. Dialysate samples were frozen and stored at -70°C until assayed. At the end of each dialysis exchange, the volume of the spent dialysate was measured.

Drug analysis. Plasma, urine, and dialysate samples were analyzed for cefpodoxime concentration by a microbiologic procedure. A seed layer of agar containing antibiotic medium (Difco, Chicago, Ill.) seeded with 0.15% *Providencia rettgeri* UC-12186 (CDC 4334-69; Bronson Methodist Hospital, Kalamazoo, Mich.) was poured into a Nunc plate. After the agar solidified, 6 -mm agar wells were cut into each plate, and subsequently, 30 μl of the analytical, reference standard, or quality control sample was applied to each well. The samples diffused into the agar, and if they contained cefpodoxime, growth of the bacteria in the seed layer was inhibited, creating a circular inhibition zone. Zone diameters were measured with a Mitutoyo Digital Caliper (500 Series;

Mitutoyo Manufacturing Co.). Data were collected by a Mitutoyo Digimatic Logger (model DL-10; Mitutoyo Manufacturing Co.) and transferred to an acquisition computer program. An unweighted linear regression of zone diameter versus natural log of cefpodoxime concentration was plotted for the reference standards and used to determine slopes, intercepts, and correlation coefficients. The cefpodoxime concentrations were calculated by using the resulting parameters:

$$\text{natural log sample concentration} = \frac{\text{zone diameter} - y \text{ intercept}}{\text{slope}}$$

The linear range for analysis of cefpodoxime concentrations was 0.04 to 2.56 $\mu\text{g/ml}$ for plasma and urine and 0.08 to 2.56 $\mu\text{g/ml}$ for dialysate samples. Specimens with concentrations greater than 2.56 $\mu\text{g/ml}$ were diluted. For plasma, assay precision, measured as the coefficient of variation for estimated concentrations of quality control samples, was as follows: 12.8% for the 0.15 - $\mu\text{g/ml}$ sample, 18.1% for the 0.5 - $\mu\text{g/ml}$ sample, and 15.7% for the 1.0 - $\mu\text{g/ml}$ sample. For urine, assay precision was 14.9% for the 0.15 - $\mu\text{g/ml}$ sample, 13.4% for the 0.5 - $\mu\text{g/ml}$ sample, and 17.2% for the 1.0 - $\mu\text{g/ml}$ sample. For dialysate, assay precision was 13.2% for the 0.15 - $\mu\text{g/ml}$ sample, 10.9% for the 0.5 - $\mu\text{g/ml}$ sample, and 13.4% for the 1.0 - $\mu\text{g/ml}$ sample. Limit of quantitation was 0.04 $\mu\text{g/ml}$ for plasma and urine and 0.08 $\mu\text{g/ml}$ for dialysate.

The assay accuracy for plasma was 101.3% for the 0.15 - $\mu\text{g/ml}$ sample, 99.6% for the 0.5 - $\mu\text{g/ml}$ sample, and 102% for the 1.0 - $\mu\text{g/ml}$ sample. For urine, assay accuracy measured 109.3% for the 0.15 - $\mu\text{g/ml}$ sample, 110.3% for the 0.5 - $\mu\text{g/ml}$ sample, and 89.2% for the 1.0 - $\mu\text{g/ml}$ sample. For dialysate, assay accuracy was 99.3% for the 0.15 - $\mu\text{g/ml}$ sample, 81.6% for the 0.5 - $\mu\text{g/ml}$ sample, and 94.2% for the 1.0 - $\mu\text{g/ml}$ sample. The interday coefficients of variation for the calibration standards ranged from 9.1 to 12.8% (plasma), 9.5 to 13.2% (urine), and 7.8 to 10.6% (dialysate).

Specificity of this microbiologic method for cefpodoxime has been demonstrated previously in studies comparing high-performance liquid chromatography and microbiologic assay results; excellent correlations between the two methods were observed for cefpodoxime concentrations in urine and in plasma, with close agreement between assays (4). Additionally, cefpodoxime undergoes minimal biotransformation in humans (2), which greatly reduces the potential for assay interference due to active metabolites.

Pharmacokinetic analysis. Noncompartmental techniques were used for pharmacokinetic analysis of data. The maximum concentration in plasma (C_{max}) of cefpodoxime and the time to maximum concentration (T_{max}) were determined by visual inspection of the data. Lag time to absorption (t_{lag}) and linearity of absorption were calculated by the residual-concentration technique (18). Natural log-transformed concentrations in plasma were plotted against time, and linear regression analysis was performed on the terminal portion of the curve to determine the slope, which represented the terminal rate constant (k_{term}). Terminal half-life was determined by dividing $\ln 2$ by k_{term} . Cefpodoxime area under the plasma drug concentration-time curve from time zero to infinity ($\text{AUC}_{0-\infty}$) was calculated by the linear trapezoidal rule from time zero to the time of the last plasma drug concentration (AUC_{0-t}) and extrapolated to infinity by dividing the last determined plasma drug concentration by k_{term} and adding the value to AUC_{0-t} . Area under the first moment

TABLE 1. Pairing scheme and demographics

Pair	Sex	Trait of subject				
		Healthy		CAPD		
		Age (yr)	Wt (kg)	Age (yr)	Wt (kg)	Renal disease
1	Male	31	97.3	38	95.5	MCD ^a
2	Male	49	80.0	50	78.1	DN ^b
3	Male	36	78.6	37	74.4	DN
4	Male	28	75.0	31	72.3	DN
5	Male	32	75.2	35	79.7	DN
6	Male	45	62.2	43	62.3	DN
7	Male	31	73.2	31	76.5	DN
8	Female	43	61.4	43	81.4	DN

^a MCD, medullary cystic disease.^b DN, diabetic nephropathy.

of the curve from time zero to infinity was also determined by the linear trapezoidal rule. Mean residence time was calculated by dividing area under the first moment of the curve from time zero to infinity by $AUC_{0-\infty}$.

Plasma data were fitted to a nonlinear model, with SAS statistical analysis software (release 6.07), to ascertain the absorption pattern of cefpodoxime.

Renal clearance (CL_R) and dialysis clearance values for cefpodoxime were calculated by dividing the total amount of drug recovered in the urine and dialysate, respectively, by the AUC_{0-r} .

Statistical analysis. The Wilcoxon signed-rank test was performed to detect group differences in the aforementioned pharmacokinetic parameters; α was set at 0.05. Data are expressed as mean $\pm$ standard deviation (SD).

Ex vivo susceptibility. The antimicrobial activity of cefpodoxime was measured in the 6- and 24-h dialysate samples by a microtiter technique. Because T_{max} is prolonged in patients with end-stage renal disease (9) and because the dosage interval will need to be extended in such patients (2, 9), these sample times were chosen to represent anticipated peak and trough concentrations. Susceptibility studies were conducted against a standard strain (ATCC 25922) and a clinical isolate (ampicillin resistant) of *Escherichia coli*, a clinical isolate of *Klebsiella pneumoniae* (UCLA 5166), a clinical isolate of *Staphylococcus aureus* (methicillin sensitive and penicillin resistant), and a clinical isolate of *Staphylococcus epidermidis* (methicillin and penicillin sensitive).

MICs and MBCs of cefpodoxime in a 1:1 mixture of Mueller-Hinton broth and dialysate were determined by a microdilution technique (1). Bacterial inocula of 5×10^5 CFU/ml were placed in microdilution wells (0.1-ml volume) with serial dilutions of a 1:1 mixture of Mueller-Hinton broth and dialysate. The microdilution plates were incubated at 35°C for 18 to 24 h. A 25- μ l sample from each clear well was plated on Mueller-Hinton agar for CFU determination. The bactericidal endpoint was defined as 99.9% reduction in

FIG. 1. Mean plasma cefpodoxime concentration-time profile in CAPD patients and healthy volunteers following a single dose of 200 mg of cefpodoxime proxetil (expressed as mean $\pm$ SD).

CFU from the initial inoculum. Inhibitory and bactericidal titers were similarly determined after serial dilutions of the 6- and 24-h dialysate samples. In addition, a predicted inhibitory or bactericidal titer was calculated by dividing the observed cefpodoxime concentrations in the dialysate at 6 and 24 h by the MIC or MBC for the organism. Linear regression analysis was performed on the predicted and observed MBTs for all patients and all organisms. Titers less than 1:2 were not included in the calculation.

RESULTS

All 16 subjects completed the study. Demographic data are presented in Table 1. Three CAPD patients were anuric. The pharmacokinetic parameters are presented in Table 2. The mean plasma cefpodoxime concentration-time profiles are presented in Fig. 1. Patients on CAPD exhibited delayed absorption of cefpodoxime as evidenced by the prolonged mean T_{max} . Nonlinear analysis of the CAPD plasma data indicated a biexponential absorption pattern. This translated into the presence of two separate, unequal peaks for all but one CAPD subject. Figure 2 illustrates this pattern for one of the subjects. The first, smaller peak occurred around 6 h, and the second, higher peak occurred around 12 h postdose. There was no difference in k_{term} between nonlinear analysis and linear regression of the data.

There was a trend toward statistical significance for the t_{lag} values. The average terminal half-life in CAPD patients (24.4 ± 18 h) was approximately 12 times greater than that seen in healthy volunteers (1.98 ± 0.4 h). The mean values for

TABLE 2. Cefpodoxime pharmacokinetic parameters^a

Subject group	C_{max} (μ g/ml)	T_{max} (h)	k_{term} (h^{-1})	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μ g $\cdot$ h/ml)	t_{lag} (h)	MRT (h)	Urinary recovery (%)	CL_R (ml/min/kg)	Dialysate recovery (%)	CL_D (ml/min/kg)
Healthy	1.88 ± 0.6	2.44 ± 0.5	0.36 ± 0.1	1.98 ± 0.4	10.2 ± 2.8	0.21 ± 0.3	4.90 ± 0.4	24.2 ± 13	1.13 ± 0.6		
CAPD	3.25 ± 1.4	12.0 ± 4.2	0.04 ± 0.0	24.4 ± 18	107 ± 79	0.56 ± 0.5	38.4 ± 21	5.59 ± 6.9^b	0.04 ± 0.1^b	5.74 ± 3.1	0.03 ± 0.0

^a Expressed as mean $\pm$ SD. $P < 0.05$ for all parameters, except t_{lag} , $t_{1/2}$, terminal half-life; MRT, mean residence time; CL_D , dialysis clearance.

^b $n = 5$ CAPD patients only.

FIG. 2. Plasma cefpodoxime concentration-time data for CAPD subject no. 4 (dashed curve indicates a simulated simple oral absorption pattern, as seen in healthy subjects; solid curve is from fit of data to a biexponential nonlinear model).

$AUC_{0-\infty}$ and mean residence time were also significantly higher for CAPD patients.

Only $5.74\% \pm 3.1\%$ of the dose was recovered from the dialysate. In healthy volunteers, $24.2\% \pm 13\%$ of the dose was recovered from the urine, in contrast to only $5.59\% \pm 6.9\%$ for the five nonanuric CAPD patients. There was a more than 26-fold reduction in CL_R of cefpodoxime in CAPD patients.

MBTs. Peak dialysate cefpodoxime concentrations occurred on the average 14.8 ± 6.0 h after the dose, with a mean C_{max} of 1.06 ± 0.4 µg/ml. At 6 and 24 h, mean dialysate drug concentrations were 0.62 ± 0.4 and 0.37 ± 0.4 µg/ml, respectively (Fig. 3). The MICs of cefpodoxime against the four challenge strains varied from 0.12 to 4 µg/ml. Not surprisingly, the MBTs (observed and calculated) for all CAPD patients' dialysates at 6 and 24 h were mostly less than 1:2 and did not exceed 1:4 for any of the isolates.

FIG. 3. Plasma and dialysate cefpodoxime concentration-time profiles in CAPD patients following a single dose of 200 mg of cefpodoxime proxetil (dialysate concentrations not connected with lines represent new dialysis bag exchange); expressed as mean + SD.

DISCUSSION

Cefpodoxime proxetil is a prodrug which, upon de-esterification of the carboxyl group on the cephem nucleus, is converted to the extended-spectrum cephalosporin cefpodoxime. Our pharmacokinetic data for healthy volunteers are consistent with those previously reported (2). As anticipated, the C_{max} and $AUC_{0-\infty}$ in CAPD patients were significantly increased over the values for healthy subjects. Although our subjects were fasting for 10 h before and until 4 h after dosing, absorption was still ongoing in CAPD patients when the fast was broken. Food can increase the C_{max} and AUC of cefpodoxime, but the T_{max} remains unaffected (11, 12).

Neither the cause nor the clinical significance of the double-peak absorption phenomenon is known at this time. However, previously published data, and the presence of a smaller initial peak, compared with the larger second peak, argue against enterohepatic circulation as a possible cause for this absorption pattern in the CAPD subjects. The presence of this double-peak phenomenon in the CAPD subjects, but not in the healthy volunteers, may be suggestive of an effect exerted by the peritoneal dialysis process on the oral absorption of drugs.

The T_{max} of a drug increases as the rate of elimination and/or the rate of absorption decreases. In CAPD patients, cefpodoxime T_{max} was delayed extensively, which cannot be attributed to a difference in t_{lag} . Decreased systemic clearance of cefpodoxime was most likely responsible for the delayed T_{max} in these patients. However, other factors primarily affecting the rate of absorption, such as delayed gastric emptying, also may have contributed. Hughes et al. (12) showed that propantheline, an anticholinergic agent which can delay gastric emptying, caused a 47% increase in T_{max} of cefpodoxime, independent of its antisecretory capacity. Interestingly, metoclopramide, a prokinetic agent, failed to affect the T_{max} as might have been expected (12). Seven of our CAPD patients had diabetes, and, although not assessed, it is conceivable that each had diabetic gastroparesis to some extent (two were taking metoclopramide chronically). Another possible mechanism for the delayed gastric emptying in CAPD patients involves instillation of dialysate in the peritoneal cavity, leading to gastric motor dysfunction. CAPD patients with a full peritoneal cavity can have a significant delay in gastric emptying of indigestible solids (5). This phenomenon is not observed when the peritoneal cavity is drained (5), nor has it been observed in hemodialysis and predialysis patients with end-stage renal disease (16, 23). However, it is uncertain whether gastric emptying of liquids and digestible solids is similarly delayed, because the digestive mechanisms differ from that for indigestible solids (17).

Gastric pH is an additional factor affecting cefpodoxime absorption. By increasing gastric pH, ranitidine can delay T_{max} by nearly 50% (11). The three CAPD patients who were taking ranitidine discontinued the medication 4 days prior to dosing; thus, the role of this agent in delaying T_{max} is highly improbable. Likewise, the 4-day medication washout period was sufficient for dissipation of pharmacologic effect of gastric drugs (i.e., antacids, metoclopramide, and histamine₂ receptor antagonists); however, this washout period is generally not adequate for the disappearance of the enzyme-inducing or enzyme-inhibiting effect of most drugs. Nonetheless, given that cefpodoxime undergoes minimal biotransformation in humans (2), this limitation is likely of no significance in this study.

As seen in Table 3, the T_{max} of cefpodoxime appears to

TABLE 3. Comparison of cefpodoxime $C_{\max}$ and $T_{\max}$ (mean $\pm$ SD) following oral administration of cefpodoxime proxetil^a

Reference	n	CL _{cr} ^b (ml/min) or type	$C_{\max}$ (μ g/ml)	$T_{\max}$ (h)
Present study	8	Normal	1.9 $\pm$ 0.6	2.4 $\pm$ 0.5
4	8	Normal	2.3 $\pm$ 0.8	2.3 $\pm$ 0.5
19	6	118 $\pm$ 31	2.3 $\pm$ 0.5	2.5 $\pm$ 0.5
19	6	70 $\pm$ 11	3.5 $\pm$ 0.6	2.5 $\pm$ 0.8
19	6	38 $\pm$ 3	3.0 $\pm$ 0.9	3.7 $\pm$ 1.2
19	6	18 $\pm$ 7	3.7 $\pm$ 0.9	3.8 $\pm$ 1.3
3	6	Hemodialysis	4.8 $\pm$ 1.2	5.0 $\pm$ 2.1
9	8	Hemodialysis	3.7 $\pm$ 1.0	5.4 $\pm$ 1.0
Present study	8	CAPD	3.3 $\pm$ 1.4	12 $\pm$ 4.2

^a Cefpodoxime equivalents (200 mg).^b Creatinine clearance.

increase with decreasing renal function, with dialysis patients having the highest values (3, 4, 9, 19). As noted earlier, this is likely due to decreasing systemic elimination of the drug as renal function decreases. Unfortunately, however, in most of these studies the number of diabetic patients was not reported; thus, the effect, if any, of diabetic gastroparesis on the $T_{\max}$ values cannot be assessed. It would also be of interest to determine whether the accumulated uremic toxins denature or competitively inhibit the intestinal brush border enzymes and lead to delayed absorption of cefpodoxime. However, even if such an effect were to exist, it would not explain the substantial difference in $T_{\max}$ between hemodialysis and CAPD patients.

Cefpodoxime is primarily excreted via the kidneys (21). We recovered from the urine 24.2 and 5.59% of the dose in healthy subjects and CAPD patients, respectively. The remainder of the dose not excreted in the urine was likely to have been extensively transformed in the gastrointestinal tract and excreted in the feces (2).

Expectedly, CL_R was significantly reduced in CAPD patients. While dialysate drains were occasionally incomplete, total dialysate recovery during the entire study permitted accurate dialysate clearance calculations. Unlike hemodialysis (3, 9), peritoneal dialysis was not efficient in removing cefpodoxime. Because of decreased renal clearance and negligible dialysate clearance, CAPD patients should be dosed with 200 mg of cefpodoxime every 24 h, as suggested for predialysis patients with end-stage renal disease (19).

At the present time, orally administered cephalosporins are not routinely used for the treatment of CAPD-associated peritonitis; however, because of its extended spectrum, we evaluated cefpodoxime's potential in this role. Although the expected dialysate $T_{\max}$ (6 h) was underestimated and we did not measure the MBTs at peak dialysate drug concentrations, dialysate cefpodoxime $C_{\max}$ was still less than a third of plasma cefpodoxime $C_{\max}$. It is doubtful that MBTs at such a time point would have been of clinical significance. Because of increased permeability, the dialysate pharmacokinetics of cefpodoxime during bouts of peritonitis potentially differ from those in the noninfected state. Nonetheless, the low MBTs in the dialysate currently preclude the use of cefpodoxime, at this dose, for oral treatment of CAPD-associated peritonitis.

In conclusion, the delay in $T_{\max}$ is most likely the result of decreased systemic elimination of cefpodoxime; however, conditions affecting absorption of cefpodoxime, such as delayed gastric emptying secondary to diabetes and peritoneal dialysate-induced gastric motor dysfunction, may have

contributed. As peritoneal dialysis does not remove cefpodoxime to any appreciable extent, a single daily dose of 200 mg of cefpodoxime should be adequate for CAPD patients in treating systemic infections due to susceptible organisms.

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