Pharmacokinetic Profiles of Ceftazidime after Intravenous Administration in Patients Undergoing Automated Peritoneal Dialysis[▽]

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The pharmacokinetics (PK) of ceftazidime after intravenous (i.v.) administration during automated peritoneal dialysis (APD) and their dependence on peritoneal membrane transport are the targets of the present study. Eleven patients receiving a single i.v. dose of ceftazidime (15 mg/kg of body weight) (seven males, median [interquartile] age, 59 [36 to 62]) were recruited. Serum and dialysate samples were collected at the beginning, middle, and end of each of the five dwells during a 24-h period, with dwells 1, 2, and 3 using an automated cycler (designated on-cycler) and dwells 4 and 5 being manual exchanges (designated off-cycler), together with urine collection during the same period. Population PK analysis was employed to estimate the PK parameters. Peritoneal equilibration tests were performed for all patients, and correlations between peritoneal clearance (CL_{PD}) for ceftazidime and dialysate-to-plasma ratios for creatinine (D/P_{cr}) were obtained using the Spearman's product correlation coefficient (ρ). Ceftazidime renal clearance (CL_{renal}) was 0.052 ml/min/kg, and CL_{PD} was 0.063 ± 0.050 ml/min/kg. CL_{PD} for on- and off-cycler were 0.071 and 0.058 ml/min/kg ($P = 0.164$), respectively. A significant correlation between CL_{PD} and D/P_{cr} was observed, with one outlier excluded, suggesting that CL_{PD} for ceftazidime during APD is dependent upon the peritoneal small-solute transport rate. A model prediction yielded adequate serum and dialysate concentrations of ceftazidime throughout a 24-h period for sensitive organisms (MIC, 8 μ g/ml) by either i.v. (at 15 mg/kg) or intraperitoneal (i.p.; at 20 mg/kg) administration during off-cycler dwells. The present study suggests that the i.v. administration of ceftazidime at 15 mg/kg or i.p. administration of ceftazidime at 20 mg/kg during a long dwell every 24 h can be recommended for treating systemic or intraperitoneal infections of APD patients.

Automated peritoneal dialysis (APD) is a rapidly growing field of dialysis therapy. APD has major advantages over continuous ambulatory peritoneal dialysis (CAPD), because it provides three or more automated exchanges using a cycler (designated on-cycler) during sleep at night, allowing the patient to have either no dwell (a so-called dry day) or only one or two manual exchanges (designated off-cycler) during the daytime. As of 2007, more than 60% of total peritoneal dialysis (PD) patients in the United States were treated by APD (15). The utilization of APD also is increasing rapidly in Europe and Asia, including Korea (15).

The drug dosing regimens established for CAPD may not be applicable to APD patients, since there are substantial differences in the dialysate volumes and dwell durations between the two modalities. However, to date few data are available on the pharmacokinetic (PK) profiles of antibiotics in APD patients except for a few agents, including cefazolin (8), tobramycin (8), vancomycin (10), piperacillin (9), fluconazole (1), and cefepime (4). Among the drugs studied, the elimination half-lives of cefazolin, tobramycin, and vancomycin proved to be

significantly shorter in on-cycler dwells than off-cycler dwells. Data are lacking for ceftazidime, an expanded-spectrum cephalosporin with potent antipseudomonal activity, which now is recommended for the initial empirical treatment of PD-associated peritonitis in combination with a narrow-spectrum cephalosporin (7).

Five to 24% of circulating ceftazidime, which has a molecular weight of 636.6, is albumin bound, and elimination takes place mostly through the urine without hepatic metabolism. The pharmacokinetics after intravenous (i.v.) or intraperitoneal (i.p.) administration in CAPD patients have been reported elsewhere (6, 13). Ceftazidime generally is administered i.v. to the CAPD patients with a regular dosing regimen of 1 g every 24 h (q24h). The present study was undertaken to determine the pharmacokinetics of ceftazidime among APD patients and to provide the proper dosing regimen while maintaining APD, thus eliminating the necessity of switching patients from APD to CAPD. This switch is not always practical because of the necessity for training users in the manual exchange technique. Besides, CAPD supplies sometimes may not be immediately available for the patients.

In our present PK study of APD patients, particular attention also was paid to the links between antibiotic clearance during a 24-h period and peritoneal solute transport characteristics.

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FIG. 1. Schematic presentation of the study.

MATERIALS AND METHODS

Eleven patients were recruited. All of the patients had been undergoing CAPD and been cared for in the Seoul National University Hospital (SNUH) PD Unit. The institutional review board of the SNUH approved the present study protocol. All patients voluntarily gave written informed consent. Inclusion criteria were the following: age greater than 18 years old, receiving PD for at least 1 month, and no liver function abnormality for 3 months. Exclusion criteria were a history of peritonitis or exit infection within 1 month, exposure to beta-lactam antibiotics within 4 weeks before the study, and known allergy to cephalosporins and positive skin test for ceftazidime just before the study. The patients' medication histories were reviewed to rule out medications that might interfere with the active tubular secretion of creatinine, such as H_2 blockers or probenecid.

Just like the APD pharmacokinetic study methods established by Manley et al. (8–10), the dialysis pattern was shifted by 8 h for the convenience of the study. Patients were instructed to arrive at the hospital at 7:30 a.m. with their abdomen emptied. Two peripheral venous catheters were inserted to administer drug and get blood samples separately. Patients with residual renal function were instructed to urinate immediately before the study, and 24-h urine samples were collected throughout the study.

The ceftazidime (Cefazime; CJ Corp., Seoul, South Korea), at 15 mg/kg (actual body weight) diluted in 10 ml normal saline, was given as an i.v. bolus injection via peripheral catheters and then flushed with another 10 ml of normal saline. Just after the ceftazidime injection, APD with a cycler was started. The patients received three cycles of 2 liters of cyclo-assisted exchange (dwells 1 to 3) with 2.5%, 3-liter dialysis fluid bags (CAPD/DPCA; Fresenius Medical Care, Bad Homburg, Germany) from 8 a.m. to 4 p.m., followed by two manual 1.5%, 2-liter dwells (dwells 4 and 5) of about 8 h each during the course of the evening and overnight (Fig. 1). Time zero (0 h) was defined as the time immediately after the bolus injection of ceftazidime was complete. Blood (5 ml) and dialysate samples (5 ml) were collected immediately after the first dialysis fluid was instilled and at the midpoint and end of the first dwell, at the midpoint and end of each of dwells 2 and 3, and at the end of dwells 4 and 5 (0, 80, 160, 240, 320, 400, 480, 960, and 1,440 min). Extra blood samples were drawn at the midpoint of two manual dwells (720 and 1,200 min) without taking the dialysate samples. The total volume of each drained dialysate was recorded. Urine samples from nonanuric patients were collected and pooled during the 24-h period. The urine volume was measured and retained for drug assay.

All of the serum, dialysate, and urine samples were immediately centrifuged and split into three batches and stored at -70°C . Ceftazidime concentrations in the serum, dialysate, and urine were assayed with a high-pressure liquid chromatography method (11). The lowest limit of quantification was $0.5\text{ }\mu\text{g/ml}$, with the calibration curve ranging from 0.5 to $200\text{ }\mu\text{g/ml}$. The intra- and interday accuracy ranged from 93.8 to 116.4%, and the intra- and interday precision, expressed as the percent coefficient of variation (CV), was less than 3.8%.

The following equations were used for pharmacokinetic analysis. Population pharmacokinetic parameter estimation and simulations were conducted using NONMEM VI level 1.2 (GloboMax, Hanover, Maryland). The first-order conditional estimation method, with the interaction option and the ADVAN6 sub-routine, was used to estimate the typical population parameters, including random interindividual variability. PK parameters, including V , k_{sd} (serum-to-dialysate transfer rate constant for drug movement from serum into the peritoneal cavity) for APD and CAPD, and k_{el} were estimated by a nonlinear mixed-effect model and were used for simulations. Two schemes of administration and dosing were simulated: (i) simulations of serum and dialysate ceftazidime concentrations at a steady state, following 15 mg/kg i.v. administration every 24 h,

were determined for a 60-kg individual with three on-cycler (dwells 1 to 3) and two off-cycler (dwells 4 and 5) exchanges; (ii) simulations of serum and dialysate ceftazidime concentrations, following 20 mg/kg i.p. administration every 24 h, were determined for a 60-kg individual. Initial dialysate ceftazidime concentrations were calculated from the i.p. dose/dialysate volume (2 liters). Simulations for both the i.v. and i.p. injection models were based on the administration at the start of the first off-cycler exchange. Renal clearance in nonanuric patients was calculated as $\text{CL}_{\text{renal}} (\text{ml/min}) = (\text{drug in urine from 0 to 24 h})/(\text{serum AUC}_{0-24})$, where AUC_{0-24} is the area under the concentration-time curve from 0 to 24 h. Peritoneal dialysis clearance was calculated as $\text{CL}_{\text{PD}} (\text{ml/min}) = (\text{drug in dialysate from 0 to 24 h})/(\text{serum AUC}_{0-24})$. Residual renal function (RRF) was estimated using the glomerular filtration rate (GFR), which was calculated with the following equations as the average of residual urea and creatinine clearance from 24 h collection of urine and normalized by the body surface area: creatinine clearance (ml/min) = (urine creatinine $\times$ 24-h urine volume)/(serum creatinine $\times$ 1,440), urea clearance (ml/min) = (urine urea nitrogen $\times$ 24-h urine volume)/(blood urea nitrogen $\times$ 1,440), and $\text{GFR} = (\text{creatinine clearance} + \text{urea clearance})/2$.

The peritoneal equilibration test (PET) is a semiquantitative assessment of peritoneal membrane transport function in patients on peritoneal dialysis (12, 14). The solute transport rates are assessed by the rates of their equilibration between the peritoneal capillary blood and dialysate. The ratio of solute concentrations in the dialysate to those in the plasma (D/P ratio) at specific times during the dwell signifies the extent of solute equilibration.

PET data were available for all subjects. The patients without PET results within 6 months before the study were instructed to perform a PET within 6 months after the PK study.

Correlation analyses were performed to compare the pharmacokinetic clearance of ceftazidime with the D/P ratio for creatinine (D/P_{cr}). The Spearman's correlation coefficient (ρ) for nonparametric analysis was obtained.

RESULTS

A total of 11 patients were enrolled in the study. The mean duration on peritoneal dialysis was 19.6 ± 15.1 months. Patient demographics are shown in the Table 1. Nine of the 11 patients were nonanuric, with residual renal creatinine clearance of $4.4 \pm 1.6\text{ ml/min/1.73 m}^2$. No patient showed any complication related to APD or known side effect of ceftazidime.

The individual and mean ceftazidime serum and dialysate concentrations at the end of each dwell (1 through 5) for all patients are shown in Fig. 2. The serum concentrations remained in excess of MICs against sensitive organisms ($8\text{ }\mu\text{g/ml}$) throughout the 24-h period. The dialysate concentrations at the end of each dwell were above the MIC as well.

The renal clearance of ceftazidime (CL_{renal}) was $0.052 \pm 0.049\text{ ml/min/kg}$ (means $\pm$ standard deviations). The mean ceftazidime CL_{PD} was $0.063 \pm 0.050\text{ ml/min/kg}$. Ceftazidime PD clearances during on- and off-cycler exchanges were 0.071 ± 0.024 and $0.058 \pm 0.029\text{ ml/min/kg}$, respectively. Estimates of population PK parameters of ceftazidime are shown in Table 2. The apparent volume of distribution was estimated at 8.56 liters. Serum-to-dialysate constants (k_{sd}) for on- and off-cycler exchanges were estimated at 0.038/h and 0.023/h. The goodness-of-fit plots are presented in Fig. 3. They indicate that the population PK model described the ceftazidime plasma concentration adequately.

Figure 4 depicts the correlation between D/P_{cr} at 4 h and the CL_{PD} of ceftazidime. No statistically significant correlations were found between D/P_{cr} at 4 h and CL_{PD} (Spearman's correlation coefficient = 0.159; $P = 0.224$). However, the correlation was statistically significant with one outlier (patient 10 in the Table 1) excluded (Spearman's correlation coefficient = 0.685; $P = 0.029$).

Model-predicted serum and dialysate ceftazidime concen-

TABLE 1. Patient characteristics^a

Patient no.	Sex	Age	Cause of ESRD	Time on PD (months)	Wt (kg)	Ht (cm)	BSA (m ²)	Ceftazidime dose (mg)	GFR (ml/min/1.73 m ²)
1	M	70	Unknown	12	53	154.5	1.51	795	4.7
2	F	23	TIN	22	52	164.8	1.54	780	2.3
3	M	34	DM	5	50	157	1.48	750	4.9
4	M	68	HT	18	82	170.5	1.97	1230	3.6
5	M	61	DM	18	51	162	1.51	765	7.8
6	M	60	DM	15	64	171	1.74	960	3.6
7	M	58	DM	3	52	164	1.54	780	5.6
8	M	55	DM	53	58	164.7	1.63	870	4.0
9	F	39	Unknown	32	49	157	1.46	735	
10	F	36	IgAN	34	50	158.4	1.48	750	
11	F	36	FSGS	4	48	158.5	1.45	720	3.2
Mean		49.1		19.6	55.4	162	1.57	830	4.4
SD		15.9		15.1	9.9	5.5	0.15	149	1.6

^a Abbreviations: M, male; F, female; ESRD, end stage renal disease; TIN, tubulointerstitial nephritis; DM, diabetes mellitus; PD, peritoneal dialysis; HT, hypertension; IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; BSA, body surface area.

trations for the 60-kg individual at steady state are shown in the Fig. 5A and B. Intravenous ceftazidime administration (15 mg/kg q24h) at the start of the first off-cycler exchange yielded adequate end-of-dwell serum and dialysate concentrations throughout the 24-h period for sensitive organisms (MIC, 8 µg/ml) (Fig. 5A). Ceftazidime administered i.p. (20 mg/kg q24h) during the first off-cycler long dwell also provided adequate serum and dialysate concentrations (Fig. 5B).

DISCUSSION

The purpose of the present study was to elucidate the pharmacokinetics of ceftazidime and provide the appropriate i.v. and i.p. dosing recommendation for APD patients using the usual three cycler exchanges during 8 h and two manual exchanges during 16 h. As shown in Fig. 2, ceftazidime diffuses from the serum into the peritoneal dialysis fluid after i.v. administration. At the end of each dwell (1 to 3 by cycler ex-

changes and 4 and 5 by manual exchanges), the dialysate is drained and new PD fluid is instilled. The ceftazidime concentration at the end of each dwell depends on the serum concentration of ceftazidime at each time point and the number of dwell hours. The serum levels at the end of the 24 h were above the upper limit of susceptibility (MIC, 8 µg/ml) for ceftazidime against nosocomial pathogens such as *Enterobacteriaceae* or *P. aeruginosa* (5). The mean dialysate concentration at the end of each dwell exceeded two times the MIC against susceptible organisms. Demotes-Mainard et al. (2) have demonstrated that the i.v. administration of 1 g ceftazidime led to serum and dialysate concentrations of ceftazidime above the MIC against susceptible pathogens for 24 h in CAPD patients. The results of the present study with APD patients showed that a single i.v. dose of ceftazidime at 15 mg/kg every 24 h can provide adequate serum and dialysate concentrations for 24 h.

Elwell et al. once reported that a trend was observed for the association between cefazolin peritoneal clearance (CL_{PD}) and the D/P_{cr} (3) during 4 h PET, which was not statistically significant. The authors suggested that the lack of correlation was due to limited subject numbers (*n* = 6) and the fact that PET and pharmacokinetic studies have been performed up to 2 years apart from each other. To overcome such limitations, we obtained PET study results for all subjects within 6 months before or after the PK study. Although the correlation between D/P_{cr} and CL_{PD} for ceftazidime was not significant, the exclusion of one outlier patient (subject 10) rendered the correlation statistically significant. Although we searched vigorously, we could not find any plausible explanations for the outlier, such as active peritonitis, aberrant solute transport character-

FIG. 2. Individual ceftazidime serum and dialysate concentrations at each time point. Horizontal bars denote mean concentrations for the serum (solid lines) and the dialysate (dashed lines). 8A, 8:00 a.m.; 4P, 4:00 p.m.; 0A, 12:00 a.m.

TABLE 2. Estimates of population pharmacokinetic parameters of ceftazidime

Parameter ^a	Population estimates	SE of estimates	Interindividual variability CV (%)
<i>V</i> _d (liter)	8.56	0.44	17.16
<i>k</i> _{el} (per h)	0.036	0.005	44.81
<i>k</i> _{sd} dwell 1 to 3 (per h)	0.038	0.004	31.68
<i>k</i> _{sd} dwell 4 to 5 (per h)	0.023	0.003	31.68

^a *k*_{sd}, elimination constant from serum to dialysate.

FIG. 3. Diagnostic scatter plots produced using the final pharmacokinetic model. (A) Observed (DV) versus population-predicted (PRED) and individual-predicted (IPRED) concentrations of ceftazidime. (B) Conditional weighted residuals (CWRES) versus PRED and time.

istics, or body habitus. Further research is warranted to explore whether dose modification is needed depending on the peritoneal transport characteristics or D/P_{cr} for peritoneal dialysis patients.

The simulation in this study modeled the 8th day of consecutive i.v. or i.p. ceftazidime administration q24h, assuming that ceftazidime has reached a steady state. Model prediction exhibited adequate serum and dialysate concentrations for sus-

ceptible microorganisms when ceftazidime is administered at 15 mg/kg i.v. or is administered at 20 mg/kg i.p. during the long dwell. PD-associated peritonitis is one of the important issues for PD patients. The intraperitoneal administration of ceftazidime is recommended as an initial empirical treatment until the causative microorganism and its antibiotic susceptibility are identified (7). Therefore, model prediction for i.p. administration in the present study could provide practical information for the PD-associated peritonitis.

In standard APD practice, manual exchanges are made in the daytime and automated exchanges are performed with a cycler machine at night during sleep. However, for the convenience of the PK study, the study patients implemented cycler-assisted exchanges in the daytime and manual exchange at night, because the majority of the blood and peritoneal samples would be taken during on-cycler exchanges. Such a shift in the dialysis pattern for APD patients was already established by Manley et al. (8–10).

Our study has some limitations. First, the number of study subjects is relatively small and we performed a single administration, although this is common for a pharmacokinetic study of peritoneal dialysis patients. Therefore, the accumulation of the test drug was not evaluated, although we simulated a steady state after consecutive administrations of ceftazidime.

FIG. 4. Correlation between the peritoneal clearance and D/P creatinine. The correlation was not significant (interrupted line A; $\rho = 0.159$; $P = 0.224$), whereas it was statistically significant with one outlier (circled dot) excluded (line B; $\rho = 0.685$; $P = 0.029$).

FIG. 5. Model predicted serum and dialysate concentrations at the steady state in a 60-kg individual. (A) Intravenous ceftazidime (15 mg/kg) administration at the first off-cycler exchange. (B) Intraperitoneal ceftazidime (20 mg/kg) administration at the first off-cycler exchange.

Second, we could not find an explanation for one particular outlier in the correlation analysis between D/P_{cr} and CL_{PD} .

In conclusion, the present pharmacokinetic study suggests that the i.v. administration of ceftazidime at 15 mg/kg or the i.p. administration of ceftazidime at 20 mg/kg during the long

dwelling q24h can be recommended for treating systemic or intraperitoneal infections in APD patients.

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