ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1988, p. 51–56
0066-4804/88/010051-06$02.00/0

Vol. 32, No. 1

Pharmacokinetics and Pharmacodynamics of Cefoperazone-Sulbactam in Patients on Continuous Ambulatory Peritoneal Dialysis

CURTIS A. JOHNSON,[1]* STEPHEN W. ZIMMERMAN,[2] DONALD P. REITBERG,[3] THOMAS J. WHALL,[4] JAMES E. LEGGETT,[5] AND WILLIAM A. CRAIG[5]

School of Pharmacy, University of Wisconsin, 425 North Charter Street, Madison, Wisconsin 53706[1]; School of Medicine, University of Wisconsin, Madison, Wisconsin 53792[2]; Pfizer Pharmaceuticals, Inc., New York, New York 10017[3]; Pfizer Quality Control, Groton, Connecticut 06340[4]; and Department of Medicine, Veterans Administration Hospital, Madison, Wisconsin 53705[5]

Received 27 April 1987/Accepted 8 October 1987

This study was conducted to determine the pharmacokinetics of the fixed combination antibiotic cefoperazone-sulbactam in patients receiving continuous ambulatory peritoneal dialysis (CAPD). In addition, the pharmacodynamic profile of this combination was determined by the use of mean bactericidal titers against selected bacterial strains. Six noninfected CAPD patients were given a fixed dose of cefoperazone (2 g) and sulbactam (1 g) either intravenously or intraperitoneally over 10 min in a randomized, two-way crossover fashion. The mean peak cefoperazone concentration in serum after intravenous administration was 280.9 μg/ml. The mean peak concentration in serum after intraperitoneal cefoperazone administration was 38.9 μg/ml and occurred 2 to 4 h postdose. The mean peak sulbactam concentration in serum after intravenous administration was 82.2 μg/ml. The mean peak concentration in serum after intraperitoneal sulbactam administration was 24.4 μg/ml and occurred at 6 h. The absolute bioavailability of the intraperitoneal dose was 61% for cefoperazone and 70% for sulbactam. Cefoperazone total body and renal clearances were unaffected by renal failure and dialysis. However, both clearance values for sulbactam were reduced markedly. Only intraperitoneal dosing provided peak inhibitory and bactericidal titers in dialysate for all organisms tested. Intravenous dosing provided satisfactory dialysate titers only for very susceptible bacterial strains. End-stage renal disease and CAPD do not alter cefoperazone pharmacokinetics; however, sulbactam dosing may need to be adjusted.

Continuous ambulatory peritoneal dialysis (CAPD) is widely recommended as an alternative to hemodialysis in the treatment of end-stage renal disease. However, a major disadvantage of CAPD is peritonitis. Approximately two-thirds of dialysis-related peritonitis is caused by gram-positive organisms, whereas gram-negative bacteria cause about 25% of the cases (13). Treatment has consisted of intravenous (i.v.) and intraperitoneal (i.p.) antibiotics, primarily cephalosporins and aminoglycosides (10). Cefoperazone has a broad spectrum of activity against both gram-positive and gram-negative bacteria, which makes it a suitable choice for the treatment of CAPD peritonitis. Sulbactam, a beta-lactamase inhibitor, has been shown to enhance the in vitro spectrum of cefoperazone (8).

This study was conducted to characterize the absorption and elimination of a single dose of a fixed combination of cefoperazone and sulbactam after two-way crossover i.v. and i.p. administration to noninfected CAPD patients. In addition, the in vitro antimicrobial activity of this antibiotic combination against selected bacterial strains was determined in dialysates collected from these patients.

MATERIALS AND METHODS

Patients. Six noninfected CAPD patients between 29 and 81 years old participated in this study. The weight of the patients ranged from 69.4 to 100.8 kg. The mean estimated body surface area (4) was 2.0 m^2 (range, 1.84 to 2.19 m^2). At the time of the study, no patient was taking any other antibiotic; however, the patients were allowed to take any other medications prescribed for the management of chronic renal failure. Four patients had diabetes mellitus, one had familial nephritis, and one had chronic glomerulonephritis. All patients gave written informed consent. There were no histories of allergy to penicillin. All patients had normal hepatic function as determined by routine liver function tests. The serum albumin concentration was greater than 3.4 g/dl in all patients. Hematologic profiles were normal except for the anemia of chronic renal failure.

Dosing. Cefoperazone-sulbactam was administered as a single dose in a randomized crossover fashion, i.v. and i.p. Each dose consisted of 2 g of cefoperazone and 1 g of sulbactam. The washout period between doses was at least 1 week.

Samples. Before drug administration, an i.v. cannula was inserted in a forearm vein. Glucose (5% in water) was infused continuously into this cannula through a three-way stopcock at a rate not exceeding 30 ml/h. All blood samples were withdrawn through this cannula after an initial 5 ml of blood was withdrawn to eliminate any dilution effect of the i.v. fluid. For i.v. drug administration, a temporary i.v. catheter was inserted in the opposite arm. After the drug was infused, this catheter was withdrawn. The i.v. dose, dissolved in sterile water as recommended by the manufacturer, was added to 50 ml of glucose (5% in water) and infused over 15 min. The zero-time samples were obtained at the end of the infusion.

Before drug administration, the indwelling peritoneal catheter of each patient was equipped with a three-way stopcock and a 50-ml plastic syringe. Sampling of the dialysate was

* Corresponding author.

performed by withdrawing 50 ml of dialysate into the syringe and reinfusing the fluid into the peritoneum; this was done twice before a 5-ml sample for analysis was withdrawn. This technique was used to mix the dialysate within the peritoneum. The i.p. dose was dissolved in sterile water and injected through the medication port into the dialysate bag. The dialysate was infused over 15 min. The zero-time samples were obtained at the end of the infusion. Dialysate exchanges were performed every 6 h throughout the study.

All dialysate used was 2.08 liters (Dianeal; Baxter, Deerfield, Ill.) containing 1.5% hydrous glucose. Heparin (500 U/liter) and insulin were added as required to the dialysate. No other additives were permitted.

Blood samples were taken at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, and 48 h after the i.v. and i.p. doses. Additional samples were obtained at 3 and 5 h after the i.p. dose. Serum was obtained by centrifugation. Blood collection was associated with a mild reduction in hematocrit in three patients. No transfusions were required. Dialysate samples were obtained at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 6.5, 7, 8, 10, 12, 13, 14, 16, 18, 19, 20, 21, 24, and 48 h after the i.v. and i.p. doses. Additional samples were obtained at 3 and 5 h after the i.p. dose. At the end of each 6-h exchange, all drained dialysate was measured. Urine was collected during the intervals of 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 h. Portions of dialysate and urine were saved for analysis. All samples were stored at −60°C until assayed.

Drug analysis. Cefoperazone and sulbactam concentrations in serum and urine were determined by high-performance liquid chromatography as described by Reitberg et al. (11). There were several differences in analytical methodology, as described below.

In the present study, the serum analysis was performed using a Dupont Zorbax Phenyl analytical column (4.6 mm [inside diameter {i.d.}] by 25 cm; particle size, 6 μm) preceded by a Brownlee Phenyl, Spheri-5 guard column (4.6 mm [i.d.] by 3 cm; particle size, 5 μm). The mobile phase for the assay of both drugs was 0.02 M tetrabutylammonium phosphate–0.005 M tribasic sodium phosphate in acetonitrile-water (25:75, vol/vol) (pH 4.0) with a flow rate of 2.0 ml/min. An internal standard of cefamandole was used. The sample size was 50 μl. The wavelength for detection was 205 nm (0.02 absorbance units, full scale [AUFS]). Before analysis of the serum samples, an extraction procedure was performed as described by Reitberg et al. (11); however, back extraction was done using 0.02 M Na_3PO_4.

The urine analysis for sulbactam was done with a Rainen Microsorb C_{18} analytical column (4.6 mm [i.d.] by 25 cm; particle size, 5 μm) preceded by a Brownlee C_{18}, Spheri-5 guard column. The mobile phase was 0.005 M tetrabutylammonium phosphate in acetonitrile-water (17:83, vol/vol) (pH 5.0). The flow rate was 1.8 ml/min. An analytical wavelength of 205 nm (0.01 AUFS) was used for detection.

The urine analysis for cefoperazone was done with a Waters Novapak C_{18} analytical column (3.9 mm [i.d.] by 15 cm; particle size, 4 μm). The mobile phase was in an acetonitrile-water mixture (9:91, vol/vol).

The analysis of both drugs in dialysate was performed using a Waters 6000A solvent delivery system, a Micromeritics 725 autoinjector, an SF773 variable-wavelength detector, and a Spectra Physics 4270 computing integrator. The analytical column for the cefoperazone dialysate assays was a Waters Novapak C_{18} column (3.9 mm [i.d.] by 15 cm; particle size, 4 μm). A Brownlee RP-18 New Guard guard column was used. The analytical column used for dialysate sulbactam analyses was a Rainen Microsorb C_{18} column (4.6 mm [i.d.] by 25 cm; particle size, 5 μm). In addition, a Brownlee RP-18, Spheri-5 guard column was used. No precolumn was used for cefoperazone in dialysate but was used for sulbactam.

The mobile phase for cefoperazone assays in dialysate was 0.0012 M triethylammonium acetate and 0.0028 M acetic acid in acetonitrile-water (9:91, vol/vol). The flow rate was 2.0 ml/min. The sample size was 50 to 100 μl. The cefoperazone retention time was about 12 min. A wavelength of 254 nm was used (0.01 AUFS). The mobile phase for sulbactam assays in dialysate was 0.005 M tetrabutylammonium phosphate in acetonitrile-water (17:83, vol/vol) (pH 5.0). The flow rate was 1.8 ml/min. The sample size was 50 μl. The retention time for sulbactam was about 17 min. The wavelength used was 205 nm (0.01 AUFS). The dialysate cefoperazone and sulbactam analyses were performed using external standards.

Dialysate containing cefoperazone was diluted in the mobile phase sufficiently to bring the concentration to the range of the assay. After the high-performance liquid chromatography analysis described above, the final cefoperazone concentration was determined by comparison of its peak height to that of the average peak height of the bracketing standard solutions.

Dialysate sulbactam analyses were performed after the dialysate was treated in a manner similar that used for urine. Final urine and dialysate sulbactam concentrations were determined by linear regression analysis by using peak heights.

Cefoperazone recovery in dialysate was ≥90% over a range of 1 to 170 μg/ml, with a detection limit of 1 μg/ml. Sulbactam recovery in dialysate was 99% over a range of 2.5 to 400 μg/ml, with a detection limit of 2 μg/ml. Studies of blank uremic dialysate revealed that no significant endogenous substances eluted at the retention time of cefoperazone, sulbactam, or cefamandole. The within-day precision of the dialysate assay for sulbactam (2.5 to 100 μg/ml) was <8% relative standard deviation; for cefoperazone (1 to 160 μg/ml), it was <2% relative standard deviation.

Microbiology. The antimicrobial activity of cefoperazone-sulbactam in dialysate samples taken at 4 and 12 h were determined by a microtiter technique. The dialysate samples were diluted 1:1 with Mueller-Hinton broth (D-MH). The 4-h dialysate samples contained the peak cefoperazone concentration after i.v. dosing; the 12-h samples contained the cefoperazone concentration after two 6-h dialysis exchanges. Since cefoperazone is usually given at 12-h intervals, these 12-h samples contained what will be referred to as trough concentrations. Susceptibility studies were conducted against two laboratory strains (*Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* UCLA 5166) and six clinical isolates (*Staphylococcus aureus* [methicillin susceptible and penicillin resistant]; *Staphylococcus epidermidis*, isolated from a patient with CAPD peritonitis; *E. coli* 35 and 14 [ampicillin resistant]; and *Pseudomonas aeruginosa* 1 and 2).

The MICs and MBCs of cefoperazone in D-MH at various concentrations of sulbactam were determined by a checkerboard dilution technique that provided various ratios of cefoperazone to sulbactam. Bacterial inocula of approximately 5×10^5 CFU/ml were placed in microdilution wells (0.1-ml volume) with serial dilutions of both cefoperazone and sulbactam in 50% Mueller-Hinton broth–50% fresh dialysate. The microdilution plates were incubated at 35°C for 18 to 24 h. A 25-μl sample from each clear well was plated on Mueller-Hinton agar for CFU determinations. A

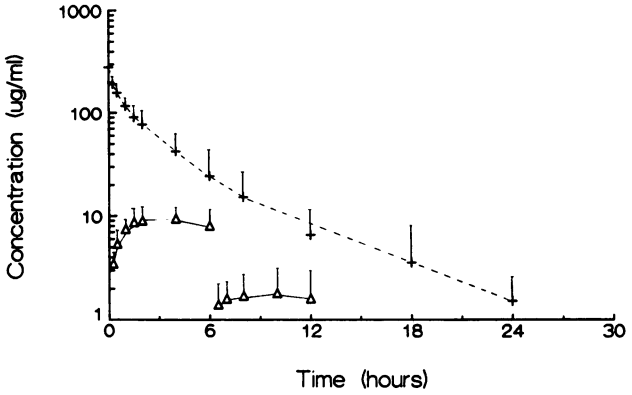

FIG. 1. Mean cefoperazone concentrations in serum (+) and dialysate (△) after a cefoperazone (2 g)-sulbactam (1 g) i.v. dose. No cefoperazone was detectable in dialysate after 12 h; in serum, none was detectable after 18 h.

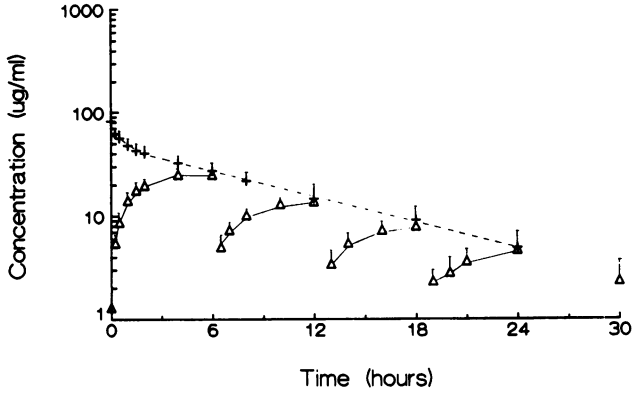

FIG. 3. Mean sulbactam concentrations in serum (+) and dialysate (△) after a cefoperazone (2 g)-sulbactam (1 g) i.v. dose. No sulbactam was detectable in serum at 30 h.

99.9% reduction in CFU from the initial inoculum was used as the bactericidal endpoint.

Inhibitory and bactericidal titers were determined after serial dilutions of the 4- and 12-h D-MH samples. The dilutions were incubated at 35°C for 18 to 24 h and processed as described above to determine bactericidal endpoints. In addition, a predicted inhibitory/bactericidal titer was calculated by dividing the observed cefoperazone concentrations in dialysate at 4 and 12 h by the MIC or MBC for the organism. Cefoperazone MICs and MBCs used for predicted titer calculation were those appearing on the checkerboard at locations containing cefoperazone/sulbactam ratios similar to those in the 4- and 12-h dialysate samples for each patient. Linear regression analysis was performed on the predicted and observed mean bactericidal titers for all patients and all organisms. Titers >1:1,024 were arbitrarily assigned a value of 1:2,048. Titers <1:2 were not included in the calculation.

Pharmacokinetic analysis. A semilogarithmic plot was constructed of the cefoperazone and sulbactam concentrations in serum versus time after the i.v. and i.p. doses. The slope of the terminal elimination phase (k_{el}) was determined by linear regression. The serum half-life for the elimination phase ($t_{1/2\beta}$) was calculated as follows: $t_{1/2\beta} = (\ln_2)/k_{el}$. The area under the serum concentration-time curve to time t (AUC_{0-t}; mg · h/liter) after the i.v. and i.p. doses was calculated by the linear trapezoidal rule. The residual area from the final measurable concentration in serum to infinity was estimated by dividing the final measured concentration by k_{el}. The absolute bioavailability of the i.p. dose was calculated by the equation $AUC_{0-\infty i.p.}/AUC_{0-\infty i.v.}$

Total body clearance (CL_{TB}) was determined by the equation $CL_{TB} = \text{Dose}/AUC_{0-\infty}$. Dialysis clearance ($CL_D$) was determined by the equation $CL_D = CL_{TB} \times$ fraction of dose recovered in dialysate. Renal clearance (CL_R) was determined by the equation $CL_R = CL_{TB} \times$ fraction of dose recovered in urine. The volume of distribution (V) was calculated as follows: $V = CL_{TB}/k_{el}$. V after i.v. dosing was also calculated by a noncompartmental determination of the volume of distribution at steady state (V_{ss}) (1), corrected for infusion time:

$$V_{ss} = [\text{dose} \times AUMC_{0-\infty}/(AUC_{0-\infty})^2] - [t'(\text{dose})/2(AUC_{0-\infty})]$$

where t' is the infusion time and $AUMC_{0-\infty}$ is the area under the first moment of the concentration-time curve measured with the linear trapezoidal rule to time t, with residual added, calculated as $(t^*C_p^*/k_{el}) + (C_p^*/k_{el})$, where t* is the time of the final measured concentration and C_p^* is the final measured concentration.

The data presented are expressed as mean ± standard deviations.

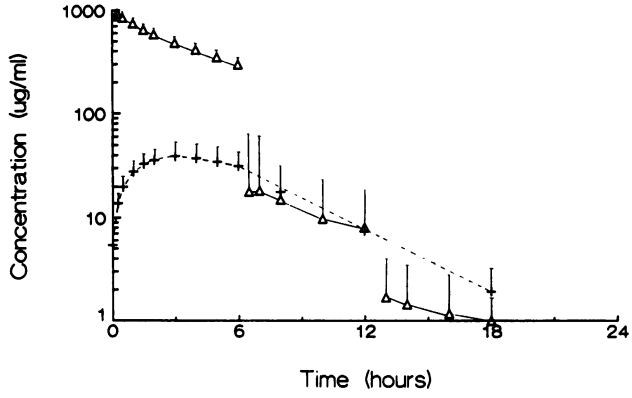

FIG. 2. Mean cefoperazone concentrations in serum (+) and dialysate (△) after a cefoperazone (2 g)-sulbactam (1 g) i.p. dose. No cefoperazone was detectable after 18 h.

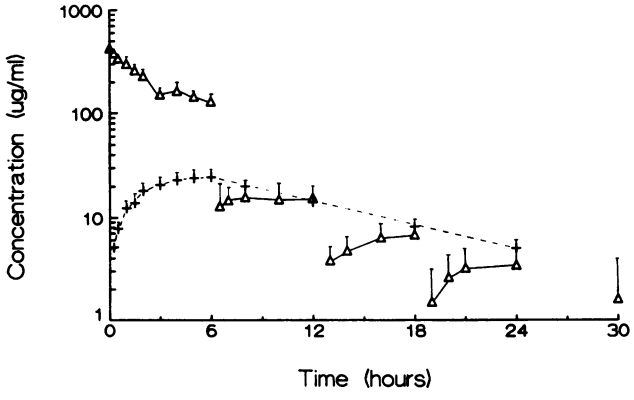

FIG. 4. Mean sulbactam concentrations in serum (+) and dialysate (△) after a cefoperazone (2 g)-sulbactam (1 g) i.p. dose. No sulbactam was detectable in serum at 30 h.

TABLE 1. Cefoperazone pharmacokinetics after a cefoperazone (2 g)-sulbactam (1 g) i.v. dose over 15 min

Patient	k_{el} (h^{-1})	$t_{1/2\beta}$ (h)	Peak concn in serum (μg/ml)	$AUC_{0-\infty}$ (mg · h/liter)	V_{ss} (liters)[a]	V_{β} (liters)[b]	CL_{TB} (ml/min)	CL_R (ml/min)	CL_D (ml/min)
1	0.223	3.10	253.8	659.1	12.6	14.0	52.0	No urine	0.6
2	0.459	1.51	283.6	376.5	9.1	11.8	90.4	0.7	0.4
3	0.173	4.01	284.9	918.4	11.9	12.8	36.9	1.3	0.6
4	0.271	2.55	261.6	761.7	9.1	9.9	44.6	0.2	0.6
5	0.379	1.83	288.1	409.2	10.5	13.1	82.9	0.9	0.5
6	0.493	1.41	313.4	264.2	9.9	15.1	124.3	1.0	0.6
Mean ± SD	0.333 ± 0.13	2.08 ± 0.82	280.9 ± 21.2	564.9 ± 254.0	10.5 ± 1.5	12.8 ± 1.8	71.9 ± 33.4	0.7 ± 0.5	0.55 ± 0.08

[a] Calculated by noncompartmental determination of V_{ss}, corrected for infusion time.
[b] Calculated by CL_{TB}/k_{el}.

RESULTS

The mean serum and dialysate cefoperazone and sulbactam concentrations after i.v. dosing are presented in Fig. 1 and 2, respectively. The corresponding results after the i.p. doses are presented in Fig. 3 and 4. After either route of administration there was rapid movement of both drugs across the peritoneal membrane, with rapid equilibration between the central and peritoneal compartments. Both drugs are best described by a one-compartment model.

The pharmacokinetic calculations for cefoperazone after the i.v. and i.p. doses are presented in Tables 1 and 2. After i.v. administration, 1% of the dose was recovered in the urine in 48 h, and 1% was recovered in the dialysate. After the i.p. dose, less than 1% was recovered in the urine.

The pharmacokinetic calculations for sulbactam after the i.v. and i.p. doses are presented in Tables 3 and 4. After i.v. administration, 10.8% ± 8.2% of the dose was recovered in the urine in 48 h, and 11.1% ± 1.4% was recovered in the dialysate. After the i.p. dose, 9.2% ± 7.4% was recovered in the urine.

There was no correlation between the duration of dialysis treatment or the patients' peritonitis histories with either drug clearance or i.p. drug bioavailability.

Susceptibility testing. The peak and trough concentrations of cefoperazone in dialysate after the i.v. dose occurred at 4 and 12 h, respectively. A ratio of the cefoperazone to sulbactam concentrations occurring at 4 and 12 h was calculated (Table 5). Similar ratios were established for 4 and 12 h after the i.p. dose (Table 5). The cefoperazone MICs for the various test organisms were determined for the range of cefoperazone-sulbactam concentration ratios obtained from each patient. These MICs showed essentially no change over cefoperazone/sulbactam ratios of 0.002 to 1,024. For *S. aureus*, the cefoperazone MIC was 2 μg/ml; for *S. epidermidis*, the MIC was 0.5 μg/ml. For the standard strain of *E. coli* (ATCC 25922), the MIC was 0.12 to 0.25 μg/ml; for the clinical isolates of *E. coli*, the MICs were 4 to 8 μg/ml. For *K. pneumoniae*, the MIC was 0.25 to 0.5 μg/ml, and for both strains of *P. aeruginosa*, the MIC was 16 μg/ml.

Bactericidal titers for the 4- and 12-h D-MH samples were identical to the inhibitory titers for each organism. The mean observed reciprocal titers are presented in Table 6. A predicted inhibitory/bactericidal titer was then calculated based on the observed cefoperazone concentrations in dialysate at 4 and 12 h and the corresponding MIC or MBC ratio for the organism (e.g., patient 1: the peak dialysate cefoperazone concentration after the i.v. dose was 9.9 μg/ml; the MIC and MBC for *S. aureus* were 2 μg/ml; therefore, the predicted inhibitory/bactericidal titer was only 1:5). Regression analysis revealed a highly significant correlation between predicted and observed bactericidal titers for all patients and all organisms ($r^2 = 0.756$) (Fig. 5).

DISCUSSION

The pharmacokinetic parameter values for cefoperazone observed in this study are similar to those previously described for normal volunteers and patients with renal dysfunction (3). Our pharmacokinetic data are also in agreement with results of previous studies involving patients on CAPD (6, 9). It is apparent that CL_R and CL_D contribute little to total cefoperazone clearance. i.p. drug administration was tolerated well, with the i.p. dose approximately 60% absorbed in 6 h as calculated by the AUC ratios of the i.p. and i.v. doses. It appears cefoperazone can be given either i.v. or i.p. with no dosage adjustments required for end-stage renal disease or peritoneal dialysis.

Previous reports have shown that CL_R is the primary method of sulbactam elimination (2, 5). In patients with normal renal function, CL_R has represented approximately 80% of total clearance, with 75 to 85% of the dose recovered in the urine within 24 h. A $t_{1/2\beta}$ of 1 h has been observed. Coadministration of cefoperazone and sulbactam has been

TABLE 2. Cefoperazone pharmacokinetics after a cefoperazone (2 g)-sulbactam (1 g) i.p. dose

Patient	k_{el} (h^{-1})[a]	$t_{1/2\beta}$ (h)	Peak concn in serum (μg/ml)	T_{max} (h)[b]	$AUC_{0-\infty}$ (mg · h/liter)	Absolute bioavailability (%)	V (liters)	CL_{TB} (ml/min)	CL_R (ml/min)
1	0.143	4.85	42.8	4	444.9	0.69	21.7	52.0	No urine
2	0.317	2.19	31.8	2	256.0	0.69	17.0	90.4	0.3
3	0.193	3.60	60.9	3	686.5	0.76	11.5	36.9	0.7
4	0.302	2.30	38.4	3	287.0	0.38	8.8	44.6	0.1
5	0.339	2.04	34.8	4	242.9	0.60	14.5	82.9	0.4
6	0.494	1.40	24.8	2	138.0	0.51	15.0	124.3	0.5
Mean ± SD	0.298 ± 0.123	2.33 ± 0.96	38.9 ± 12.4		342.5 ± 195.5	0.61 ± 0.14	14.8 ± 4.5	71.9 ± 33.4	0.3 ± 0.3

[a] k_{el} was calculated from the slope of the β phase of elimination beginning at $t = 6$ h.
[b] T_{max}, Time to maximum concentration of drug in serum.

TABLE 3. Sulbactam pharmacokinetics after a cefoperazone (2 g)-sulbactam (1 g) i.v. dose over 15 min

Patient	k_{el} (h^{-1})	$t_{1/2\beta}$ (h)	Peak concn in serum (μg/ml)	$AUC_{0-\infty}$ (mg · h/liter)	V_{ss} (liters)[a]	V_{β} (liters)[b]	CL_{TB} (ml/min)	CL_R (ml/min)	CL_D (ml/min)
1	0.093	7.43	69.2	540.2	19.6	20.1	31.3	No urine	3.5
2	0.143	4.83	72.7	454.4	15.0	15.6	37.3	4.0	3.6
3	0.078	8.91	86.9	563.7	22.9	23.5	30.5	6.8	3.5
4	0.078	8.89	67.9	664.7	18.8	19.5	25.3	1.2	3.4
5	0.108	6.39	85.8	429.7	21.1	22.1	39.9	7.1	3.8
6	0.105	6.58	110.6	479.0	18.7	20.4	35.8	3.5	3.9
Mean ± SD	0.101 ± 0.024	6.86 ± 1.67	82.2 ± 16.2	521.9 ± 86.5	19.4 ± 2.7	20.2 ± 2.7	33.4 ± 5.3	3.8 ± 2.9	3.6 ± 0.2

[a] Calculated by noncompartmental determination V_{ss}, corrected for infusion time.
[b] Calculated by CL_{TB}/k_{el}.

TABLE 4. Sulbactam pharmacokinetics after a cefoperazone (2 g)-sulbactam (1 g) i.p. dose

Patient	k_{el} (h^{-1})	$t_{1/2\beta}$ (h)	Peak concn in serum (μg/ml)[a]	$AUC_{0-\infty}$ (mg · h/liter)	Absolute bioavailability (%)	V (liters)	CL_{TB} (ml/min)	CL_R (ml/min)
1	0.080	8.62	25.8	422.5	0.79	23.3	31.3	No urine
2	0.143	4.85	26.8	344.6	0.77	15.6	37.3	4.2
3	0.139	4.97	25.2	338.0	0.62	13.2	30.5	5.8
4	0.098	7.12	24.1	362.3	0.55	15.6	25.3	0.5
5	0.093	7.48	21.4	328.0	0.78	26.0	39.9	6.1
6	0.112	6.21	23.0	323.2	0.69	19.4	35.8	2.9
Mean ± SD	0.111 ± 0.026	6.26 ± 1.45	24.4 ± 2.0	353.1 ± 36.7	0.70 ± 0.10	18.9 ± 5.0	33.4 ± 5.3	3.25 ± 2.6

[a] The peak concentration in serum occurred at 6 h in all patients except patient 6 (5 h).

TABLE 5. Cefoperazone and sulbactam concentrations and ratios which occurred in dialysate 4 and 12 h after cefoperazone (2 g)-sulbactam (1 g) i.v. and i.p. doses

Patient	i.v.				i.p.			
	4 h		12 h		4 h		12 h	
	P[a] (μg/ml)	Cefoperazone/sulbactam	T[b] (μg/ml)	Cefoperazone/sulbactam	P (μg/ml)	Cefoperazone/sulbactam	T (μg/ml)	Cefoperazone/sulbactam
1	9.9/26.3	0.4	2.3/15.6	0.1	450/112	4	12/16.2	0.7
2	5.2/24.3	0.2	0.6/13.4	0.04	380/183	2	44/27.5	1.6
3	16/24.5	0.6	3.9/14.3	0.3	380/149	2.5	6.8/15.9	0.4
4	12/24.2	0.5	2.1/15.1	0.1	530/213	2.5	5.6/7.7	0.7
5	8.0/23.7	0.3	0.6/12.2	0.05	380/163	2.3	11/12.7	0.9
6	5.2/27.6	0.2	0.1/11	0.01	340/158	2.2	4.4/12.2	0.4

[a] P, Cefoperazone concentration/sulbactam concentration at 4 h.
[b] T, Cefoperazone concentration/sulbactam concentration at 12 h.

shown to have no effect on the pharmacokinetics of either drug (5).

The present study demonstrates a marked reduction in total and renal sulbactam clearance in patients receiving CAPD. After either route of administration, approximately 10% of the dose was recovered in the urine in 48 h. After the i.v. dose, 11% of the dose was recovered in the dialysate. CL_D and CL_R each represented only 10% of total clearance. Reduced sulbactam elimination led to a $t_{1/2\beta}$ of about 7 h. Based on these data, it appears sulbactam should be given every 24 h in the presence of severe renal insufficiency, whereas cefoperazone may be given every 12 h.

The importance of protein binding in determining drug transfer across the peritoneal membrane is not well understood. The drugs used in this study present contrasting protein-binding characteristics. Sulbactam has a low degree of binding, whereas cefoperazone is approximately 90% bound to serum proteins (3). Of interest are the concurrent serum and dialysate drug concentrations seen in this study. At the end of each 6-h exchange, the simultaneous serum and dialysate sulbactam concentrations were similar, suggesting free movement of the drug across the serum-dialysate concentration gradient. However dialysate cefoperazone concentrations were lower than simultaneous concentrations in serum, supporting the concept of dialyzability of the unbound drug fraction only. Relatively low dialysate cefoperazone concentrations after i.v. dosing may lead to diminished i.p. antibacterial activity, as shown by the pharmacodynamic data presented in this report.

The bacterial killing effects of antibiotics in CAPD fluid have been addressed by Verbrugh et al. (14). They observed that the aminoglycoside tobramycin had only 10% of its bactericidal activity in dialysate compared with that in Mueller-Hinton broth. The beta-lactam imipenem lost no activity in dialysate. The results of the present study reveal that the beta-lactam cefoperazone in combination with sulbactam also maintains its predicted inhibitory and bactericidal activity in D-MH.

A comparison of the peak and trough inhibitory and bactericidal titers in dialysate revealed that higher titers

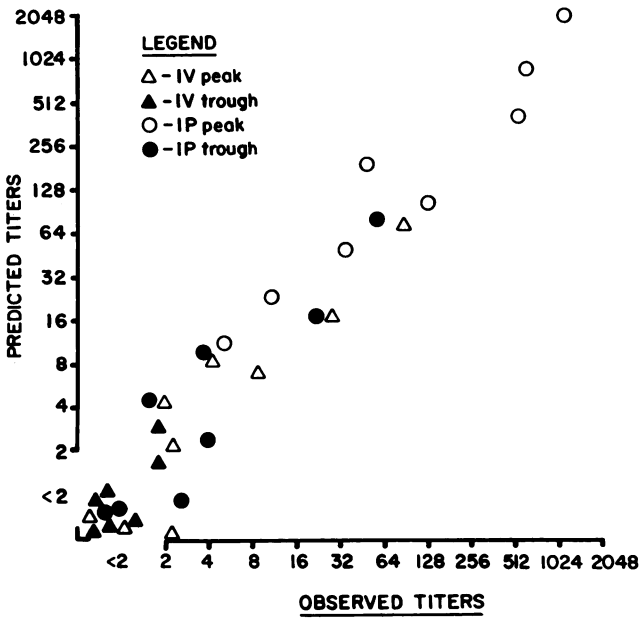

FIG. 5. Mean predicted versus observed reciprocal inhibitory/bactericidal titer values. $y = 0.2661 + 0.8149x$; $r^2 = 0.756$. Each symbol represents a mean reciprocal titer value (n = six patients) for each organism tested.

were obtained with i.p. dosing than with i.v. dosing. Only the i.p. doses provided potentially therapeutic peak inhibitory and bactericidal titers for all the organisms tested, including the two clinical strains of *P. aeruginosa*. Peak bactericidal titers after i.v. dosing were greater than 8 only for very susceptible bacterial strains (MIC, <1.0 μg/ml). A good correlation was obtained between observed bactericidal titers and titers predicted from dialysate drug concentrations and the MICs of cefoperazone-sulbactam combinations for the organism. During episodes of CAPD-associated peritonitis, if the MIC for the organism is known, it should be possible to predict therapeutic efficacy from the cefoperazone and sulbactam concentrations achieved in dialysate. However, clinical trials involving infected patients need to be conducted to confirm this prediction. It may be important not to rely on i.v. therapy alone for dialysis-related peritonitis. Cefoperazone and sulbactam can be given safely and effectively via i.p. administration.

TABLE 6. Geometric mean[a] reciprocal inhibitory/bactericidal titers occurring in D-MH samples 4 and 12 h after a cefoperazone (2 g)-sulbactam (1 g) dose

Organism	i.v.		i.p.	
	P[b]	T[c]	P	T
S. aureus	2.5	<2	91	3.2
S. epidermidis	8.4	1.5	1,346	22
E. coli 25922	195	14.8	1,446	74
E. coli 35	3	1.8	51	3.5
E. coli 14	3	1.5	293	8.3
K. pneumoniae	50	5.5	981	47
P. aeruginosa 1	<2	<2	10	<2
P. aeruginosa 2	<2	<2	20	<2

[a] Geometric mean of two to six replicates.
[b] P, Inhibitory/bactericidal reciprocal titers observed in D-MH containing the peak cefoperazone concentration (4 h after dose).
[c] T, Inhibitory/bactericidal reciprocal titers observed in D-MH containing the trough cefoperazone concentration (12 h after dose).

The data generated in this study were obtained from noninfected CAPD patients. Because the effects of peritonitis on pharmacokinetics remain unknown (7), it will be necessary to confirm the data in studies involving infected patients. Previous studies have shown that peritoneal clearance of solutes such as urea, creatinine, and protein may be altered during peritonitis (12). It is quite possible that peritoneal transfer of drugs also may change in the presence of an inflamed peritoneal membrane. The application of the susceptibility data presented here will also need additional confirmation in efficacy trials with patients with CAPD-associated peritonitis.

ACKNOWLEDGMENTS

We thank the nursing staff of the University of Wisconsin Hospital Peritoneal Dialysis Program for their assistance. We acknowledge the technical assistance of J. A. Bowman, M. P. DeLude, and W. C. Leonard.

This work was supported by Pfizer Pharmaceuticals, Inc.

LITERATURE CITED

1. **Benet, L. Z., and R. L. Galeazzi.** 1979. Noncompartmental determination of steady-state volume of distribution. J. Pharm. Sci. **68**:1071–1074.
2. **Brown, R. M., R. Wise, J. M. Andrews, and J. Hancox.** 1982. Comparative pharmacokinetics and tissue penetration of sulbactam and ampicillin after concurrent intravenous administration. Antimicrob. Agents Chemother. **21**:565–567.
3. **Craig, W. A., and A. U. Gerber.** 1981. Pharmacokinetics of cefoperazone: a review. Drugs **22**(Suppl.1):35–45.
4. **Diem, K., and C. Lentner.** 1970. Scientific tables, p. 537. Geigy Pharmaceuticals, Ardsley, N.Y.
5. **Foulds, G., J. P. Stankewich, D. C. Marshall, M. M. O'Brien, S. L. Hayes, D. J. Weidler, and F. G. McMahon.** 1983. Pharmacokinetics of sulbactam in humans. Antimicrob. Agents Chemother. **23**:692–699.
6. **Hodler, J. E., R. L. Galeazzi, B. Frey, M. Rudhardt, and A. J. Seiler.** 1984. Pharmacokinetics of cefoperazone in patients undergoing chronic ambulatory peritoneal dialysis: clinical and pathophysiological implications. Eur. J. Clin. Pharmacol. **26**: 609–612.
7. **Johnson, C. A., S. W. Zimmerman, and M. Rogge.** 1984. The pharmacokinetics of antibiotics used to treat peritoneal dialysis-associated peritonitis. Am. J. Kidney Dis. **4**:3–17.
8. **Jones, R. N., H. W. Wilson, C. Thornsberry, and A. L. Barry.** 1985. In vitro antimicrobial activity of cefoperazone-sulbactam combinations against 554 clinical isolates including a review and β-lactamase studies. Diagn. Microbiol. Infect. Dis. **3**:489–499.
9. **Keller, E., A. Jansen, K. Pelz, G. Hoppe-Seyler, and P. Schollmeyer.** 1984. Intraperitoneal and intravenous cefoperazone kinetics during continuous ambulatory peritoneal dialysis. Clin. Pharmacol. Ther. **35**:208–213.
10. **Oreopoulos, D. G., P. Williams, R. Khanna, and S. Vas.** 1981. Treatment of peritonitis. Peritoneal Dial. Bull. **1**(Suppl.): S17–S19.
11. **Reitberg, D. P., T. S. Whall, M. Chung, D. Blickens, H. Swarz, and J. Arnold.** 1988. Multiple-dose pharmacokinetics and toleration of intravenously administered cefoperazone and sulbactam when given as single agents or in combination. Antimicrob. Agents Chemother. **32**:42–46.
12. **Rubin, J., R. Ray, T. Barnes, and J. Bower.** 1981. Peritoneal abnormalities during infectious episodes of continuous ambulatory peritoneal dialysis. Nephron **29**:124–127.
13. **Vas, S. I.** 1985. Peritonitis, p. 403–439. *In* K. D. Nolph (ed.), Peritoneal dialysis, 2nd ed. Martinus Nijhoff, Boston.
14. **Verbrugh, H. A., W. F. Keane, W. E. Conroy, and P. K. Peterson.** 1984. Bacterial growth and killing in chronic ambulatory peritoneal dialysis fluids. J. Clin. Microbiol. **20**:199–203.