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Multiple-Dose Pharmacokinetics of Intravenously Administered Cefoperazone and Sulbactam When Given in Combination to Infected, Seriously Ill, Elderly Patients

JULES I. SCHWARTZ,[1,2]* LUIS E. JAUREGUI,[1] KENNETH A. BACHMANN,[2] MARY E. MARTIN,[1] AND DONALD P. REITBERG[3]

St. Vincent Medical Center, Toledo, Ohio 43608[1]; College of Pharmacy, University of Toledo, Toledo, Ohio 43606[2]; and Department of Clinical and Scientific Affairs, Pfizer Pharmaceuticals, New York, New York 10017[3]

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The pharmacokinetics of cefoperazone and sulbactam in combination were evaluated in six, elderly, seriously ill patients treated with the drug combination for intra-abdominal infections. After giving informed consent, three males and three females aged 63.5 to 77.5 (mean, 67.9) years and weighing 54.5 to 86.8 (mean, 67.6) kg were treated with cefoperazone (2.0 g) and sulbactam (1.0 g) infused intravenously every 12 h for at least 5 days. Cefoperazone and sulbactam pharmacokinetics were characterized on both days 1 and 5 of treatment. Eleven serial blood samples were obtained just prior to and following dose 1 on days 1 and 5 of treatment. Mean estimates of cefoperazone maximal concentration in plasma (C_{max}), area under the curve of drug concentration in plasma versus time (AUC), half-life ($t_{1/2}$), apparent volume of distribution by the area method (V_{area}), apparent volume of distribution at steady state (V_{ss}), and total body clearance (CL) for day 1 (day 5) were 297.5 (237.5) μg/ml, 1,247 (1,063) μg · h/ml, 7.0 (4.9) h, 16.1 (13.4) liter, 13.1 (14.4) liter, and 28.9 (34.2) ml/min, respectively. Day 1 (day 5) mean values for sulbactam C_{max}, AUC, $t_{1/2}$, V_{area}, V_{ss}, and CL were 110.3 (78.0) μg/ml, 228 (217) μg · h/ml, 3.4 (2.5) h, 26.1 (18.5) liter, 18.9 (15.4) liter, and 97 (94) ml/min, respectively. Both drugs evidenced slower elimination and greater pharmacokinetic variability in these patients compared with values previously reported for normal volunteers. As patients improved during the course of therapy, the only pharmacokinetic parameter significantly changed between days 1 and 5 was a shortened sulbactam $t_{1/2}$. Our inability to find substantial evidence of pharmacokinetic normalization may have been related to sample size and study duration. Both drugs were present in potentially therapeutic concentrations for the entire 12-h dosing interval, but without undue accumulation from days 1 to 5.

The combination of cefoperazone and sulbactam is under investigation for the management of serious bacterial infections. The utility of the combination stems from the broad spectrum of antimicrobial activity of cefoperazone (9, 17) and the ability of sulbactam to inhibit some β-lactamases (15). Patients who are candidates for treatment with cefoperazone-sulbactam may be physiologically compromised and may therefore not distribute or eliminate these drugs as do healthy subjects. The pharmacokinetics of cefoperazone in healthy subjects is now well characterized (1, 7, 21), as is the pharmacokinetics of sulbactam (3, 10, 21). Furthermore, cefoperazone pharmacokinetics has been studied both in patients with chronic renal failure (1, 2, 12, 13, 19) and in patients with liver dysfunction (12). The pharmacokinetics of sulbactam has been evaluated in patients with appendicitis (11). However, reports relevant to the pharmacokinetics of these drugs in patients likely to typify the candidates for this combination, i.e., elderly with acute and serious illness, have not been published.

We evaluated the pharmacokinetics of cefoperazone and sulbactam administered in combination to six elderly, acutely ill patients with serious intra-abdominal infections.

MATERIALS AND METHODS

Patients. Six patients were entered into the study (Table 1). Each patient was hospitalized with a serious bacterial intra-abdominal infection. Patients who were terminally ill, had a known hypersensitivity to penicillins or cephalosporins, had received prior successful antimicrobial therapy within the past 4 days, were receiving antimicrobial therapy for another focus of infection, were receiving investigational drugs, exhibited suppressed immunologic function and/or leukopenia as evidenced by leukocytes less than 1,500/mm^3, who required dialysis, or who had ingested alcohol within 4 h prior to cefoperazone-sulbactam administration were excluded.

Renal function was assessed by determination of creatinine clearance by the method of Cockroft and Gault (5). Liver function was assessed by determination of alkaline phosphatase, total serum bilirubin, serum glutamic oxalacetic transaminase, and serum glutamic pyruvic transaminase. Laboratory tests were obtained immediately prior to cefoperazone-sulbactam administration and repeated when clinically needed during treatment. For all subjects, laboratory results were available within 24 h of the steady-state pharmacokinetic study period (day 5).

Study design. The investigation was conducted as an open trial with the objective of characterizing the pharmacokinetics of cefoperazone-sulbactam in elderly, infected patients on days 1 and 5 of treatment. These patients were being treated with cefoperazone-sulbactam for serious infections and gave informed consent to participate in this pharmacokinetic study. Both drugs were combined and administered intravenously in 100 ml of 5% dextrose in sterile water. The cefoperazone dose was 2 g, and the sulbactam dose was 1 g. Both drugs were given every 12 h for at least 5 days for treatment of the infection. Drugs were infused over 15 min. Blood was drawn to obtain samples for antibiotic content

* Corresponding author.

TABLE 1. Demographics of six patients studied during therapeutic administration of cefoperazone (2.0 g)-sulbactam (1.0 g)[a]

Patient	Age (yr)	Actual wt (kg)	Ideal body wt (kg)[b]	Sex[c]	Estimated creatinine clearance (ml/min)[d]		SGPT (U)[e]		SGOT (U)[f]		Alkaline phosphatase (U/liter)[g]		Serum bilirubin (mg/dl)[h]		Diagnosis[i]	Associated conditions[i]
					Day 1	Day 5[j]	Day 1	Day 5[j]	Day 1	Day 5[j]	Day 1	Day 5[j]	Day 1	Day 5[j]		
1	69	70.9	70.7	M	100	139	23	**46**	29	**66**	58	69	**0.6**	0.3	Peritonitis, LLQ abscess 2° to bowel ischemia, aortic aneurysm resection	Anemia, atherosclerosis, COPD, hypertension
2	66	80.9	77.6	M	**36**	**38**	**39**	**64**	**37**	**73**	**140**	**173**	**1.0**	**2.5**	Small bowel obstruction, small bowel fistula, intra-abdominal and wound infections	Abdominal aortic aneurysm, CVA, COPD, atherosclerosis, diabetes mellitus, chronic renal failure
3	77	54.5	56.9	M	**59**	**53**	19	20	28	**39**	**97**	**102**	**0.6**	**0.7**	Small bowel fistula, intra-abdominal and wound infections	Atrial fibrillation, coronary artery disease, COPD, seizures
4	63	56.8	57.0	F	**24**	**27**	**32**	13	**40**	14	**172**	**111**	**0.6**	0.4	Left pericolic abscess	Adenocarcinoma descending colon, angina pectoris, coronary artery disease, nonoliguric renal failure, hypertension
5	66	86.8	61.6	F	**39**	**42**	**33**	23	**38**	20	**148**	**154**	0.4	0.4	Intrahepatic abscess	Gram-negative septicemia, septic shock, acute renal failure, pulmonary edema
6	63	55.5	59.3	F	118	118	**42**	20	25	**29**	**389**	**510**	**1.7**	**1.0**	Acute cholecystitis, ascending cholangitis, liver microabscesses	COPD, diverticulosis, hypertension, malnutrition

[a] Drugs were infused intravenously over 15 min every 12 h for at least 5 days. Values in boldface are abnormal laboratory values indicating impaired renal or hepatic function.
[b] Calculated by the method of Devine (B. Devine, Drug Intell. Clin. Pharm. 8:650, 1974).
[c] M, Male; F, female.
[d] By the method of Cockroft and Gault (5); the lower weight (actual versus ideal) was used. Normal value, >90 ml/min for male and female.
[e] SGPT, Serum glutamic pyruvic transaminase. Normal range, 5 to 27 U for male and female.
[f] SGOT, Serum glutamic oxalacetic transaminase. Normal range, 20 to 35 U for males and 17 to 28 U for females.
[g] Normal range, 35 to 70 U/liter for male and female.
[h] Normal value, <0.5 mg/dl for male and female.
[i] Abbreviations: LLQ, left lower quadrant; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident.
[j] Day-5 determinations are ± 24 h.

TABLE 2. Cefoperazone-sulbactam pharmacokinetic parameters in acutely ill, elderly patients on days 1 and 5 of treatment (n = 6)

Parameter	Results with:					
	Cefoperazone			Sulbactam		
	Day 1 (mean [SD])	Day 5 (mean [SD])	P	Day 1 (mean [SD])	Day 5 (mean [SD])	P
C_{max} (μg/ml)	298 (145)	238 (61)	0.25	110 (77)	78 (30)	0.23
$t_{1/2}$ (h)	7.0 (3.5)	4.9 (1.7)	0.25	3.4 (1.2)	2.5 (0.5)	0.04
AUC[a] (μg · h/ml)	1,247 (353)	1,062 (372)	0.13	228 (115)	217 (105)	0.50
V_{area} (liter)	16.1 (5.9)	13.4 (2.0)	0.28	26.1 (16.8)	18.5 (6.1)	0.17
V_{ss} (liter)	13.1 (4.5)	14.4 (4.1)	0.57	18.9 (10.5)	15.4 (5.7)	0.17
CL (ml/min)	29 (9)	34 (10)	0.19	97 (61)	94 (47)	0.71

[a] From time 0 to infinity on day 1; from time 0 to 12 h on day 5.

prior to the infusion, immediately at the end of the infusion, and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h after the end of the infusion. Samplings were performed just prior to and after dose 1 of the drug combination and just prior to and after dose 1 of day 5. Whole blood was allowed to clot at room temperature. Serum was harvested by centrifugation at 4°C, transferred to clean tubes, and stored at −60°C until assayed.

Assays. Both cefoperazone and sulbactam were assayed in serum by using a high-pressure liquid chromatography procedure in which both drugs were separated on the same column. Assays were conducted by the Quality Control Division, Pfizer, Inc., Groton, Conn. The methods have been previously published (13, 21).

Pharmacokinetic analysis. Noncompartmental methods were used to estimate pharmacokinetic parameters (4, 20). Agreement between noncompartmental and model-dependent analysis methods has been previously reported for a cephalosporin given to critically ill patients (23). The area under the curve of drug concentration in serum versus time from 0 to 12 h (AUC_{0-12}) was calculated by linear trapezoidal approximation. For dose 1, AUC was calculated from the preinfusion (0) concentration to the 12-h concentration (AUC_{0-12}) and extrapolated to infinity with the equation:

$$AUC = AUC_{0-12} + C12/k \quad (1)$$

where C12 is the 12-h drug concentration and k is the terminal elimination rate constant determined as the slope of the terminal linear portion of the curve of log concentration versus time by using linear least-square regression analysis. It was determined that the heteroscedasticity of the data was not importantly increased by logarithmic transformation, nor was a weighting scheme appropriate because of the validated assay precision and accuracy. AUC_{0-12} at steady state was assumed equivalent to AUC following dose 1 under hypothetically linear dosing conditions. Half-life ($t_{1/2}$) was calculated from k by the equation:

$$t_{1/2} = \ln 2/k \quad (2)$$

Total body clearance, CL, was calculated by the equation:

$$CL = \text{dose}/AUC \quad (3)$$

where AUC on day 1 was from time 0 to infinity and AUC on day 5 was from time 0 to 12 h (at steady state). Apparent volume of distribution by the area method (V_{area}) was calculated as follows:

$$V_{area} = CL/k \quad (4)$$

Apparent volume of distribution at steady state (V_{ss}) was calculated as follows:

$$V_{ss} = CL \cdot MRT \quad (5)$$

where MRT was calculated as the area under the moment curve adjusted for the intravenous infusion to the single-dose intravenous bolus case divided by the AUC (4, 20). Maximal concentration in serum (C_{max}) was achieved at the end of the intravenous infusion (15 min postdose).

Statistics. Pharmacokinetic parameters for treatment days 1 and 5 were compared by Student's paired t test. Differences were considered to be statistically significant at P equal to or less than 0.05.

RESULTS

Pertinent patient characteristics are summarized in Table 1. All patients were recently subjected to surgery at the start of cefoperazone-sulbactam treatment. Most of the patients showed evidence of renal and hepatic compromise (Table 1).

Cefoperazone and sulbactam pharmacokinetic parameters for dose 1 of treatment day 1 and for dose 1 of treatment day 5 are shown in Table 2. On treatment day 5, steady state was assumed because preinfusion concentrations were essentially the same as 12-h postinfusion concentrations. However, large alterations in clinical laboratory values were common between days 1 and 5 (Table 1). Therefore, due to possible physiologic instability during the dosing period studied, the steady-state conditions observed on day 5 may have been different from that experienced during earlier or subsequent treatment.

The profiles of serum concentration versus time of cefoperazone on days 1 and 5 of treatment were similar (Fig. 1), as were the analogous sulbactam profiles (Fig. 2). Analysis of pharmacokinetic parameters between days 1 and 5 indicated that only the sulbactam $t_{1/2}$ decreased significantly (P = 0.04) between days 1 and 5.

DISCUSSION

Although this investigation was limited to the study of cefoperazone and sulbactam pharmacokinetics in acutely ill patients with intra-abdominal infections, the observed differences in the pharmacokinetics of these drugs in these patients and those reported for normal subjects warrant comment. In a study involving 14 male volunteers (21), cefoperazone (2.0 g) and sulbactam (1.0 g) were administered under conditions similar to those of the present study; assays were conducted at the same laboratory for both studies.

Following dose 1, patients exhibited a cefoperazone $t_{1/2}$ which was 3.9 times longer than that for healthy subjects; V_{area} for patients was 50% larger, and CL was 43% of normal

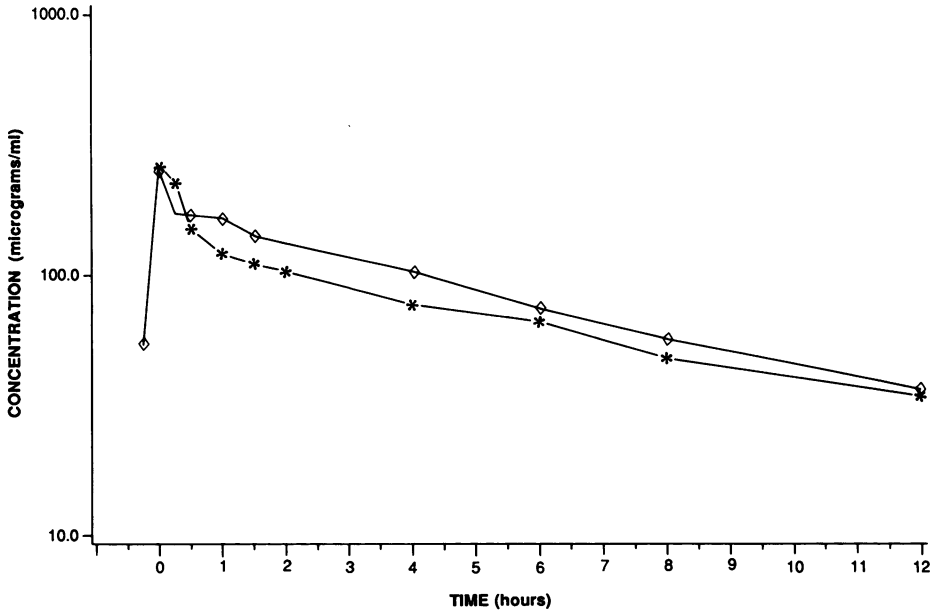

FIG. 1. Profile of log drug concentration in serum versus time for cefoperazone following intravenous infusion of cefoperazone (2 g)-sulbactam (1 g) in elderly, infected patients. Because of the log-linear format, absorption following the initial dose is not shown. *, Day 1; ◇, day 5.

values (21). Peak cefoperazone concentrations in serum, when adjusted for dose, were similar between acutely ill, elderly patients and normal volunteers (21). Thus, both a larger V_{area} and a slower CL (the parameter physiologically linked to impaired eliminating organ function) contributed quantitatively to the markedly slower cefoperazone $t_{1/2}$ in these acutely ill postsurgical patients.

Cefoperazone is cleared primarily by biliary excretion, with approximately 30% of the dose recovered in the urine of normal volunteers (16, 21), although a much greater proportion is eliminated by the renal route in biliary obstruction (12). The patients in the current study frequently experienced biliary stasis as evidenced by abnormally increased serum bilirubin and alkaline phosphatase values; this result provides a plausible explanation for changes in cefoperazone CL, which may have been dynamically changing in concordance with the disease state.

However, cefoperazone also exhibited a 50% larger V_{area}

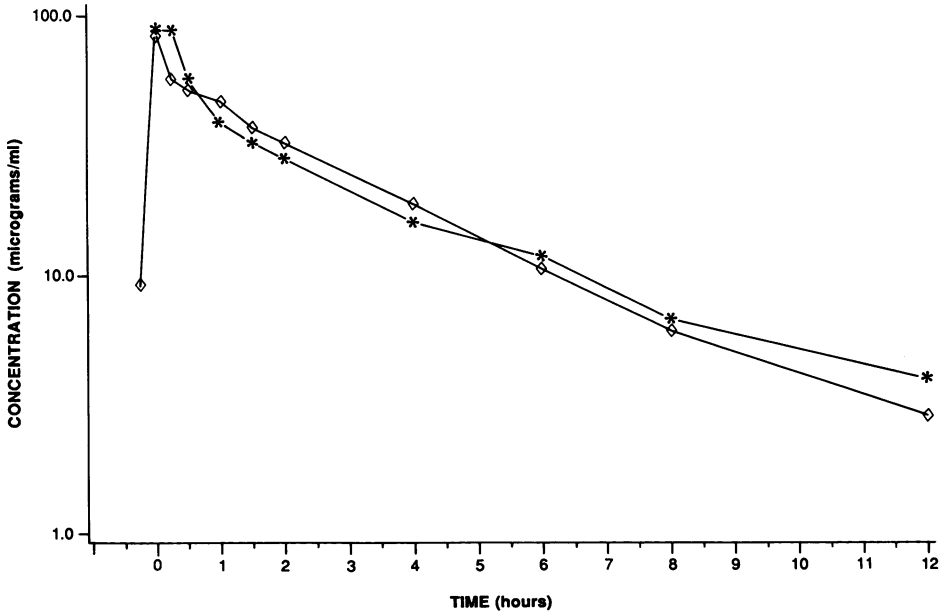

FIG. 2. Profile of log drug concentration in serum versus time for sulbactam following intravenous infusion of cefoperazone (2 g)-sulbactam (1 g) in elderly, infected patients. Because of the log-linear format absorption following the initial dose is not shown. *, Day 1; ◇, day 5.

in patients compared with normal volunteers (21), contributing quantitatively to the prolonged $t_{1/2}$. V_{area} closely approximated V_{ss}, therefore indicating that the contribution of distribution to V_{area} is proportionately much larger than that of elimination and/or absorption. V_{ss} was larger than V_{area} only for cefoperazone on dosing day 5. This result is contrary to theory (14) but may be explained by the close approximation of the two volume terms and by random error in their individual approximations.

When constant tissue binding is assumed, the effect of altered serum protein binding on distribution may be attenuated by the relative mass of drug in the extravascular volume. One possible explanation for the larger cefoperazone V_{area} in patients compared with normal volunteers stems from the fact that cefoperazone is normally extensively bound to serum protein, exhibiting a bound fraction of approximately 90% (16). Therefore, compared with that of sulbactam, perturbation of cefoperazone serum protein binding would be expected to result in a more appreciable alteration in V_{area}, since the fraction of total cefoperazone in the extravascular volume under normal conditions is relatively smaller and the fraction available for loss from the central compartment is relatively larger. Sulbactam is only 38% bound to serum protein (data on file, Pfizer Pharmaceuticals). As was observed, compared with cefoperazone, sulbactam would not be expected to show a relatively large increase in V_{area} when protein binding is impaired.

A substantial increase in cefoperazone V_{area} may be consistent with an elevated free fraction perhaps due to the marked reduction in albumin levels typically observed in these nutritionally compromised patients. However, since free fraction is expected to be related to the logarithm of albumin concentration, albumin must be depleted to values under 2 g/100 ml before extensive protein-binding alteration would be expected (8). Another explanation for a binding defect is the presence of exogenous or endogenous competitors for binding sites. This hypothesis is bolstered by the mild to moderate renal impairment in these patients and the reported defect in protein binding of acidic drugs in uremic sera (8). However, in volunteers with mild to moderate renal failure, no alteration in cefoperazone (or sulbactam) V_{ss} was discernible in a recent study (19). Therefore, the presence of competitors in serum would probably be related to hepatic impairment or to other physiologic alterations imposed by serious acute illness. For example, Shimizu (22) reported that bilirubin can displace cefoperazone from serum protein; this observation may be particularly relevant for these patients since five of six patients experienced hyperbilirubinemia (Table 1). Unfortunately, we did not measure cefoperazone free fraction, although a change in free fraction has been previously reported for the cephalosporin cefmenoxime when given to critically ill, elderly patients (18). Another possible explanation for the larger cefoperazone V_{area} found in these patients is the usual tendency toward postsurgical thirdspacing, resulting in the distribution of cefoperazone out of the central and into the peripheral compartment.

Sulbactam pharmacokinetics was also altered by serious, acute illness. Following dose 1, patients exhibited a sulbactam $t_{1/2}$ which was 3.1 times longer than that observed for healthy subjects (21). Sulbactam V_{area} for patients was similar to that for normal subjects on the initial dosing day, while sulbactam CL for patients was about one-third of that for normal subjects. This result suggests that, for sulbactam, a decrease in CL (which is physiologically linked to eliminating organ function) rather than an increase in V_{area} predominantly contributes quantitatively to the prolongation of $t_{1/2}$ in acutely ill, elderly patients. Renal impairment, observed in four of the six patients (Table 1), was frequently seen in this patient population. However, because sulbactam undergoes predominantly renal elimination, it was not surprising that the two subjects with normal creatinine clearance estimates also had the most rapid elimination of sulbactam (CL was 147 and 196 ml/min for subjects 1 and 6, respectively). Normal renal function may also explain why sulbactam elimination was not impaired in patients with appendicitis as reported by Gill et al. (11), although eliminating organ function was not documented in this paper.

As predicted from laboratory abnormalities and the antecedently greater physiologic variability experienced by these acutely ill patients compared with normal volunteers, several observations are supportive of greater intersubject pharmacokinetic variability in patients as well. The coefficient of variation for CL in these patients was approximately double for cefoperazone and threefold greater for sulbactam compared with that previously reported for normal volunteers (21). The average coefficient of variation values observed for patient drug concentrations in serum at each sampling time were one-fifth (for cefoperazone) and over 2.5 times (for sulbactam) higher following the initial dose and one-third (for cefoperazone) and two times (for sulbactam) higher at steady state compared with normal volunteer values (21) (data on file, Pfizer Pharmaceuticals). Therefore, the physiologic perturbations and variability imposed by severe illness may be manifested as enhanced pharmacokinetic intersubject variability, as well as altered mean pharmacokinetic parameter values. The current study does not, however, directly compare patients with normal volunteers, and patient sample size was limited. Therefore, the above cross-study comparisons are not definitive. However, the use of a common laboratory for drug assays reduces the assumptions required for comparisons between study sites to those antecedent to drug assay and therefore eliminates assay variability as an influence on the comparison.

When pharmacokinetic parameters from days 1 to 5 were compared, only the sulbactam $t_{1/2}$ significantly decreased with time. For sulbactam, there was a decrease in C_{max} from days 1 to 5, accompanied by decreases in V_{area} and in V_{ss}. This result suggests that the statistically significant decrease in $t_{1/2}$ during the course of treatment was quantitatively mediated by a decrease in apparent volume of distribution to values smaller than that observed in normal volunteers (21). Sulbactam CL was essentially unchanged between days 1 and 5, as expected, because of the predominantly renal elimination of sulbactam. The estimates of creatinine clearance for individual patients may have been influenced by dynamic alterations in renal function imposed by disease. However, estimated creatinine clearance was not appreciably altered between days 1 and 5 for this group of patients (means on days 1 and 5, 62.5 and 69.3 ml/min, respectively; $P = 0.36$).

For cefoperazone, the changes in pharmacokinetic parameters between days 1 and 5 were less noticeable. No statistically significant change in any pharmacokinetic parameter was found between days 1 and 5 of treatment. However, the mean $t_{1/2}$ decreased, the mean CL increased, and V_{area} decreased. V_{ss} was essentially unchanged. Cefoperazone C_{max} decreased from days 1 to 5. As cefoperazone is eliminated principally by the hepatobiliary system rather than the kidney, it is of interest that discernible improvement was not evident for any of the laboratory indices of liver function, on average, between days 1 and 5 (Table 1).

However cholestasis was present in four of six patients; they showed elevation of serum bilirubin and alkaline phosphatase throughout treatment. It is possible that the time to achieve a new steady state following reduction in cholestasis is longer for the usual laboratory markers (total bilirubin and alkaline phosphatase) than it is for cefoperazone CL. Therefore, cefoperazone CL may increase before these endogenous markers decrease; the laboratory tests may be poor indicators of drug disposition for this reason.

It can be concluded from this investigation that the elimination of both drugs is substantially slower and is more variable in elderly, acutely ill surgical patients compared with normal volunteers. This is not surprising, as the functions of eliminating organs in these patients are frequently compromised and unstable; the pharmacokinetics of cefoperazone and sulbactam appeared to appropriately reflect renal and hepatic functions. It appeared that the pharmacokinetics of both drugs may have normalized somewhat during treatment and, perhaps, posttreatment, suggesting that because of physiologically induced changes in pharmacokinetics, drug concentrations in serum are highest in compromised patients when the illness is most life threatening. However, because of the apparently large intra- and intersubject variabilities in physiology and pharmacokinetics imposed by serious disease, larger-scale studies employing longer observation periods and involving carefully selected patient populations would be needed to clearly define the effect of clinical improvement on drug pharmacokinetics. However, it is of interest that in the present study potentially therapeutic concentrations of both drugs in serum were found over the entire dosing interval and over the entire treatment period in seriously ill patients without evidence of undue accumulation.

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