AMPICILLIN AND SULBACTAM PHARMACOKINETICS AND PHARMACODYNAMICS IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS PATIENTS

BY

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Continuous ambulatory peritoneal dialysis (CAPD) is becoming a widely accepted and frequently utilized procedure for the management of renal failure patients. A major consequence of this technique is the risk of peritonitis, which requires either intravenous or intraperitoneal antibiotics, and may lead to hospitalization and removal of the peritoneal catheter. Approximately two thirds of peritonitis episodes are caused by gram-positive organisms.[1] The combination of ampicillin and sulbactam, an investigational beta-lactamase enzyme inhibitor, is highly active against most organisms causing CAPD-peritonitis.[2,3,4] Sulbactam has limited intrinsic antibacterial activity with the notable exception of N. gonorrhoeae.[5,6] Sulbactam has been shown to expand the spectrum of activity of beta-lactam antibiotics such as ampicillin to include beta-lactamase producing organisms.[2,3,4]

The purpose of this study was to characterize the absorption and elimination of a single dose of a fixed combination of ampicillin and sulbactam following two way cross-over intravenous and intraperitoneal administration to non-infected CAPD patients. The in-vitro antimicrobial activity of this combination against selected bacterial isolates was determined in dialysate collected from these patients.

METHODS

Patient Population

Eight non-infected CAPD patients between the ages of 33 and 83 participated in this study. The mean weight of the patients ranged from 54 to 89.5 kg. The mean estimated body surface area[7] was 2.0 m^2 (range, 1.7 - 2.7 m^2). Prior to the study, no patient had received antibiotics for seven days, but all patients were allowed to take any other medications prescribed for the management of chronic renal failure. Three patients had

diabetes mellitus, one had hereditary nephritis, one had medullary cystic disease, one had polycystic kidney disease, one had hypertension, and one had chronic renal failure for unknown reasons. Written informed consent was obtained from all patients. One patient had a history of allergy to cephalosporins, and no patients were allergic to penicillins. All patients had normal hepatic function. Hematologic profiles were normal except for the anemia of chronic renal failure. Immediately following intraperitoneal administration of the antibiotic combination, patient 4 complained of itching and a warm feeling in his lower back. The antibiotic-containing dialysate just infused was drained to remove any drug in the peritoneal cavity and diphenhydramine was administered orally. Patient 7 developed cloudy dialysis fluid within 6 hours after the dose was administered. The dialysate contained an elevated number of white blood cells, which continued to increase during the next dialysis exchange. Although the patient experienced no abdominal pain, the patient was treated with cefazolin and gentamicin. Both patients were removed from the study and neither suffered any sequelae.

Dosing

Ampicillin/sulbactam was administered as a single dose in a randomized cross-over fashion, intravenously (IV) and intraperitoneally (IP). Each dose consisted of ampicillin 2 g and sulbactam 1 g. There was at least a ten day washout period between doses.

Samples

Prior to drug administration, an intravenous cannula was inserted into a forearm vein. Dextrose 5% in Water was infused continuously at a rate of 30ml/hr through this cannula via a three-way stopcock. All blood samples were drawn through this stopcock after a 5 ml sample was removed to prevent any dilutional effect of the intravenous fluid. For intravenous drug

administration, a temporary intravenous catheter was inserted into the opposite arm and removed after drug administration. The IV dose, reconstituted with sterile water per the manufacturer's instructions, was added to 50 ml of Dextrose 5% in Water, and infused over fifteen minutes. Blood samples were drawn at the end of the infusion and this was considered time 0.

Prior to drug administration, each patient's indwelling peritoneal catheter was equipped with a 3-way stopcock and a 50 ml plastic syringe. Sampling of the dialysate was performed by withdrawing 50 ml of dialysate into the syringe and then forcefully reinfusing this sample. This procedure was repeated twice prior to each sample withdrawal to thoroughly mix the dialysate within the peritoneal cavity. A 5 ml sample was then withdrawn and saved for analysis. The IP dose was also reconstituted per the manufacturer's instructions, then injected through the medication port into the dialysate bag just prior to administration. The dialysate was infused over fifteen minutes. The 0 time sample was collected at the end of the IP infusion. Dialysate exchanges were performed every six hours during the study.

All patients received 2.08 liters of dialysate (Dianeal®, Travenol Laboratories, Inc., Deerfield, Ill.) containing 1.5% hydrous glucose. Heparin (500 units/liter) and insulin were added as required to the dialysate. No other additives were permitted.

Blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24 and 48 hours following the IV and IP doses. Samples were also collected at 3 and 5 hours following the IP dose. The blood was centrifuged and serum drawn off. Dialysate samples were collected at 0, 0.25, 0.5, 1, 2, 4, 6, 6.5, 7, 8, 10, 12, 13, 14, 16, 18, 19, 20, 21, 24, 30, 36, 42 and 48 hours following the IV and IP doses. Additional samples were collected at 3

and 5 hours following the IP dose. After each 6 hour exchange, the dialysate was drained and the dialysate volume measured. Urine was collected during the intervals of 0-2, 2-4, 4-8, 8-12, 12-24, and 24-48 hours, and samples were saved for analysis. All serum, dialysate, and urine samples were immediately stored at -70°C until assayed.

Susceptibility Testing

The 6 h and 24 h dialysate samples following IV dosing were utilized to determine the antimicrobial activity of ampicillin/sulbactam. Each sample was diluted 1:1 with Mueller-Hinton broth prior to microtiter testing. The 6 hour sample contained the peak concentration of ampicillin and the 24 hour sample was defined as representing the trough concentration. Susceptibility testing was performed using one standard laboratory strain and four clinical isolates: Escherichia coli, ATCC 25922; Escherichia coli-ampicillin resistant, 35; Klebsiella pnuemoniae, UCLA 5166; Staphylococcus epidermidis, isolated from a patient with CAPD peritonitis; and Staphylococcus aureus-ampicillin sensitive.

Minimum inhibitory (MICs) and bactericidal (MBCs) concentrations in the dialysate-Mueller-Hinton broth mixture for ampicillin and sulbactam alone and at a ratio of 1:1 and 2:1 were determined in standard fashion using a microdilution technique.[9] Bacterial inocula of approximately 5×10^4 colony forming units (CFUs) were placed in microdilution wells (0.1 ml volume) with ampicillin and sulbactam in 50% Mueller-Hinton broth-50% fresh dialysate. The microdilution plates were incubated at 35°C for 18-24 h. 25µl from each clear well was plated on Mueller-Hinton agar for CFU determinations. A 99.9% reduction in CFU from initial inoculum was used as the bactericidal endpoint.

Inhibitory and bactericidal titers were determined following serial dilutions of the 6 and 24 hour samples. The dilutions were incubated at 35°C

for 18-24 hours and processed as above to determine bactericidal endpoints. In addition, a predicted inhibitory/bactericidal titer was calculated by dividing observed ampicillin concentrations in dialysate at 6 and 24 hours by the MIC/MBC for each organism. Linear regression analysis was performed on the predicted and observed mean bactericidal titers for all patients and all organisms. Titers > 1:1024 were arbitrarily assigned a value of 1:2048. Titers < 1:2 were not included in the calculation.

Pharmacokinetic Analysis

Semilogarithmic plots were constructed of the ampicillin and sulbactam serum concentrations versus time for both IV and IP dosing. The slope of the terminal elimination phase, k_{el}, was determined by linear regression. The elimination half-life in serum, $t_{1/2\beta}$, was calculated as: $t_{1/2\beta} = (\ln 2)/k_{el}$. The area under the serum concentration time curve to time t (mg x hrs/liter), following IV and IP dosing was calculated by the linear trapezoidal rule. The residual area from the last measurable serum concentration to infinity was estimated by dividing the last measurable serum concentration by k_{el}. The absolute bioavailability of the IP dose was calculated by dividing the AUC(IP) by the AUC(IV).

Total body clearance (Cl_{TB}) was determined by: $Cl_{TB} = \frac{Dose}{AUC}$

Dialysis clearance (Cl_D) was determined by: $Cl_D = Cl_{TB}$ x the fraction of the dose recovered in dialysate.

Renal clearance (Cl_R) was determined by: $Cl_R = Cl_{TB}$ x fraction of the dose recovered in urine.

Volume of distribution (V) was calculated: $V = \frac{Cl_{TB}}{k_{el}}$

The V following IV dosing was also calculated by a noncompartmental determination of steady-state volume of distribution, corrected for infusion time:[8]

V_{ss} = [dose x AUMC/$(AUC)^2$] - [t' (dose)/2 (AUC)], where t' is the infusion time and AUMC is the area under the first moment curve measured with the linear trapezoidal rule.

The data presented in this paper are expressed as mean ± SD.

RESULTS

The mean serum and dialysate ampicillin and sulbactam concentrations following IV dosing are presented in figures 1 and 2, respectively. The concentrations following the IP doses are presented in figures 3 and 4. Following either route of administration, both drugs readily crossed the peritoneal membrane and appeared to achieve near equilibrium between serum and dialysate by 6 hours. Both drugs are best described by a one-compartment model.

Tables 1 and 3 include the pharmacokinetic parameters for ampicillin following IV and IP dosing respectively. Following IV administration, 1% of the dose was recovered in the dialysate and 7.2% of the dose was recovered in the urine in 48 hours. Following the IP dose, 6.7% of the dose was recovered in the urine.

The pharmacokinetic parameters for sulbactam following the IV and IP doses are presented in tables 3 and 4. Following IV administration, 11% of the dose was recovered in the dialysate and 5.0% of the dose was recovered in the urine in 48 hours. Following the IP dose, 5.0% of the dose was recovered in the urine.

Susceptibility Testing

Peak ampicillin concentrations in dialysate occurred at 6 hours following IV dosing and declined over the 48 hours of the study. Because 6 and 24 hours represented reasonable dosing intervals, the ratios of ampicillin to sulbactam concentrations occurring at those times were calculated. The

data are presented in table 5. MICs for ampicillin and sulbactam were determined for each drug alone and for ampicillin/sulbactam in combination in the ratios of 1:1 and 2:1. These ratios were used because they corresponded to the range of ampicillin/sulbactam ratios observed at 6 and 24 hours. The ampicillin MICs of the various test organisms in the presence of sulbactam were determined for the range of ampicillin/sulbactam concentration ratios obtained from each patient. These MICs showed essentially no change over the ratios of ampicillin to sulbactam of 0.007-1024. For S. aureus, the ampicillin MIC was 2μg/ml; for S. epidermidis, the MIC was 0.06μg/ml; for K. pneumoniae, the MIC was 4μg/ml, for the standard strain of E. coli (ATCC 25922), the MIC was 2μg/ml; and for ampicillin resistant E. coli, the MIC was 64μg/ml.

Bactericidal titers for the 6 and 24 h D-MH samples were identical to inhibitory titers for each organism. The mean observed reciprocal titers are presented in Table 6. A predicted inhibitory/bactericidal titer was calculated by dividing observed ampicillin concentrations in dialysate at 6 and 24 h by the corresponding MIC/MBC for the organism. Regression analysis revealed a highly significant correlation between predicted and observed bactericidal titers for all patients and all organisms (r^2 = 0.95, y = 0.692 + 1.01x).

DISCUSSION

The pharmacokinetic parameter values of ampicillin observed in this study are similar to those previously reported for patients with renal dysfunction and also for patients on CAPD.[10,11] It has been shown that renal clearance plays a major role in the elimination of ampicillin in patients with normal renal function. Approximately 85% of the dose is eliminated in the urine and the half-life is reported to be 1 hour in patients

with normal renal function.[12,13] Dialysis clearance plays a very minimal role in the removal of ampicillin for CAPD patients as evidenced by removal of only 1% of the dose in the dialysate after 48 hours. Intraperitoneal drug administration was well tolerated. From these data, it appears that ampicillin may be dosed IP or IV every 12-24 hours in patients with severe renal insufficiency.

Previous reports have shown that renal clearance is also the primary method of sulbactam elimination.[14-17] In patients with normal renal function, renal clearance represents approximately 80% of total clearance with 75-85% of the dose being recovered in the urine within 24 hours.[14] An elimination half-life of 1 hour has been observed.[14,] Following IV administration of sulbactam to CAPD patients, only 11% of the dose was recovered in the dialysate in 48 hours. Co-administration of ampicillin and sulbactam has been shown to have no effect on the pharmacokinetics of either drug.[14] The pharmacokinetics of ampicillin and sulbactam are almost identical in patients with normal renal function.[14] The pharmacokinetic parameters of ampicillin and sulbactam remain virtually identical in chronic renal failure, as evidenced by our study.

The present study demonstrates a marked reduction in total ampicillin and sulbactam clearance in patients on CAPD. Reduced elimination of ampicillin and sulbactam led to a half-life of approximately 9.5 hours for each drug. Therefore, it should be possible to dose ampicillin and sulbactam in combination every 12-24 hours to patients undergoing CAPD. The specific dosing interval should be determined by the susceptibility of the causative organism.

The importance of protein binding in determining drug transfer across the peritoneal membrane is not well understood. The drugs used in this study

present slightly different protein binding characteristics. Sulbactam has a minimal degree of binding, while ampicillin is approximately 15-25% bound to serum proteins.(12,13) Of interest are the concurrent serum and dialysate drug concentrations seen in this study and in a similar study with cefoperazone and sulbactam.(18) At the end of each 6 hour exchange, the simultaneous serum and dialysate sulbactam concentrations are similar, suggesting free movement of the drug across the peritoneal membrane. The ampicillin serum and dialysate concentrations at each 6 hour exchange are not quite equivalent, with lower concentrations in dialysate. This suggests that only unbound drug is free to cross the peritoneal membrane. Since at least 75% of an ampicillin dose is not bound to serum proteins, IV administration still leads to therapeutic concentrations in the peritoneal cavity for many CAPD-associated pathogens as shown by the pharmacodynamic data presented in this report.

Verbrugh, et al., addressed the issue of decreased antibacterial activity of antibiotics in CAPD fluid.(19) They observed that tobramycin had only 10% of its bactericidal activity in dialysate when compared to Mueller-Hinton broth. The beta-lactam, imipenim, lost no activity. In another study, cefoperazone also did not seem to lose any bactericidal activity.(18) The results of our study indicate that ampicillin in combination with sulbactam also maintains its predicted inhibitory and bactericidal activity in dialysate.

A comparison of the peak and trough inhibitory and bactericidal titers in dialysate revealed that higher titers were obtained with IP dosing than with IV dosing. Both IP and IV administration provided therapeutic, (> 1:8) inhibitory and bactericidal titers, at the 6 hour peak for all organisms except the ampicillin-resistant *E. coli*. The titers at 24 hours were

therapeutic only for S. epidermidis, which was exquisitely sensitive to the ampicillin/sulbactam combination. A good correlation through linear regression was obtained between observed bactericidal titers and titers predicted from dialysate drug concentrations and organism MICs to ampicillin/sulbactam, (r^2 = 0.95). During episodes of CAPD-associated peritonitis, it should be possible to predict therapeutic efficacy from the ampicillin/sulbactam concentrations achieved in dialysate if the MIC of the causative organism is known. We recommend clinical trials with infected patients to confirm this hypothesis. In many cases, it should be possible to treat CAPD-associated peritonitis with ampicillin/sulbactam IP every 12 hours. It should also be possible to treat the patient at home by allowing the patient to administer the antibiotic combination intraperitoneally, avoiding the costs and inconvenience of hospitalization. In most cases, IV administration of this combination should also be efficacious, as evidenced by the pharmacodynamic data from this study.

The data generated from this study were obtained from 6 non-infected CAPD patients. Because the effects of peritonitis on pharmacokinetics remain unknown, it will be necessary to confirm our results in studies with infected patients.(20) Similarly, it is necessary to confirm the susceptibility data presented here in studies involving infected CAPD patients.

REFERENCES

1. Vas SI. Peritonitis, p. 418. In K.D. Nolph (ed.) Peritoneal dialysis. 2nd ed. 1985 Martinus Nijhoff, Boston.
2. Fu Kwung P, Neu Harold C. Comparative inhibition of ß-lactamases by novel ß-lactam compounds. Antimicrob. Agents Chemother 1979; 15:171-76.
3. Lees L, Milson JA, Knirsch AK. Sulbactam plus ampicillin: Interim review of efficacy and safety for therapeutic and prophylactic use. Rev Infect Diseases 1986; 8:S644-S650.
4. Retsema JA, English AR, Girard A, et al. Sulbactam/ampicillin: In vitro spectrum, potency, and activity in models of acute infection. Rev Infect Diseases 1986; 8:S528-S534.
5. Retsema JA, English AR, Girard AE. CP-45899 in combination with penicillin or ampicillin against pencillin-resistant stayphylococcus, Hemophilus influenzae, and Bacteroides. Antimicrob Agents Chemother 1980; 16:615-622.
6. Caine VA, Foulds G, Handsfield HH. Therapeutic trial and pharmacokinetics of sulbactam for uncomplicated gonorrhea in men. Antimicrob Agents Chemother 1984; 26:683-685.
7. Diem K, and Lentner C. Scientific tables, p. 537. 1985 In, Geigy Pharmaceuticals, Ardsley NY.
8. Benet LZ, Galeazzi RL. Noncompartmental determination of steady-state volume of distribution. J Pharm Sci 1979; 68:1071-1074.
9. Lenette E.H., et al. (editors), Manual of Clinical Microbiology, 4th ed., American Society for Microbiology, Washington D.C., 1985, pp. 972-977.

10. Bennett WM, Aronoff GR, Morrison G, et al. Drug prescribing in renal failure: dosing guidelines for adults. Amer J Kidney Dis 1983; III:155-184.

11. Jackson EA, McLeod DC. Pharmacokinetics and dosing of antimicrobial agents in renal impairment, part i. Amer J Hosp Pharm 1985; 31:36-52.

12. Kucer A, Bennett N Mck. (eds), The use of antibiotics. 3rd edition. 1979. William Heinemann Medical Books Ltd., London. pp. 99-131.

13. Wright AJ, Wilkowsek CJ. The penicillins. Mayo Clin Proc 1983; 58:21-32.

14. Foulds G., et al., Pharmacokinetics of sulbactam in humans. Antimicrob Agents Chemother 1983; 23:696-699

15. Brown RM, Wise R, Andrews JM, et al. Comparative pharmacokinetics and tissue penetration of sulbactam and ampicillin after concurrent intravenous administration. Antimicrob Agents Chemother 1982; 21:565-67.

16. Schad VB, Guenin K, Straehl P. Single-dose pharmacokinetics of intravenous sulbactam in pediatric patients. Rev Infect Diseases 1986; 8:S512-17.

17. Rogers HJ, Bradbrook ID, Morrison PG, et al. Pharmacokinetics and bioavailability of sultamicillin estimated by high performance liquid chromatography. J Antimicrob Chemother 1983; 11:435-44.

18. Johnson CA, et al. Pharmacokinetics and pharmacodynamics of cefoperazone/sulbactam in continuous ambulatory peritoneal dialysis patients. Antimicrob Agents Chemother Submitted for publication.

19. Verbrugh HA, Keane WF, Conroy WE, et al. Bacterial growth and killing in chronic ambulatory dialysis fluids. J Clin Microbiol 1984; 20:199-203.

20. Johnson CA, Zimmerman SW, Rogge M. The pharmacokinetics of antibiotics used to treat peritoneal dialysis-associated peritonitis. Am J Kidney Dis 1984; 4:3-17.

FIGURE LEGENDS

Fig. 1 Mean ampicillin concentrations in serum and dialysate following 2-g ampicillin/1-g sulbactam IV dose. Ampicillin concentrations were detectable in serum and dialysate for 48 hours.

Fig. 2 Mean sulbactam concentrations in serum and dialysate following 2-g ampicillin/1-g sulbactam IV dose. Sulbactam was detectable in serum and dialysate for 48 hours.

Fig. 3 Mean ampicillin concentrations in serum and dialysate following 2-g ampicillin/1-g sulbactam IP dose. Ampicillin was detectable in serum and dialysate for 48 hours.

Fig. 4 Mean sulbactam concentrations in serum and dialysate following 2-g ampicillin/1-g sulbactam IP dose. Sulbactam was detectable in serum and dialysate for 48 hours.

FIGURE 1. Ampicillin serum and dialysate concentrations after a 2-g ampicillin/1-g sulbactam dose IV

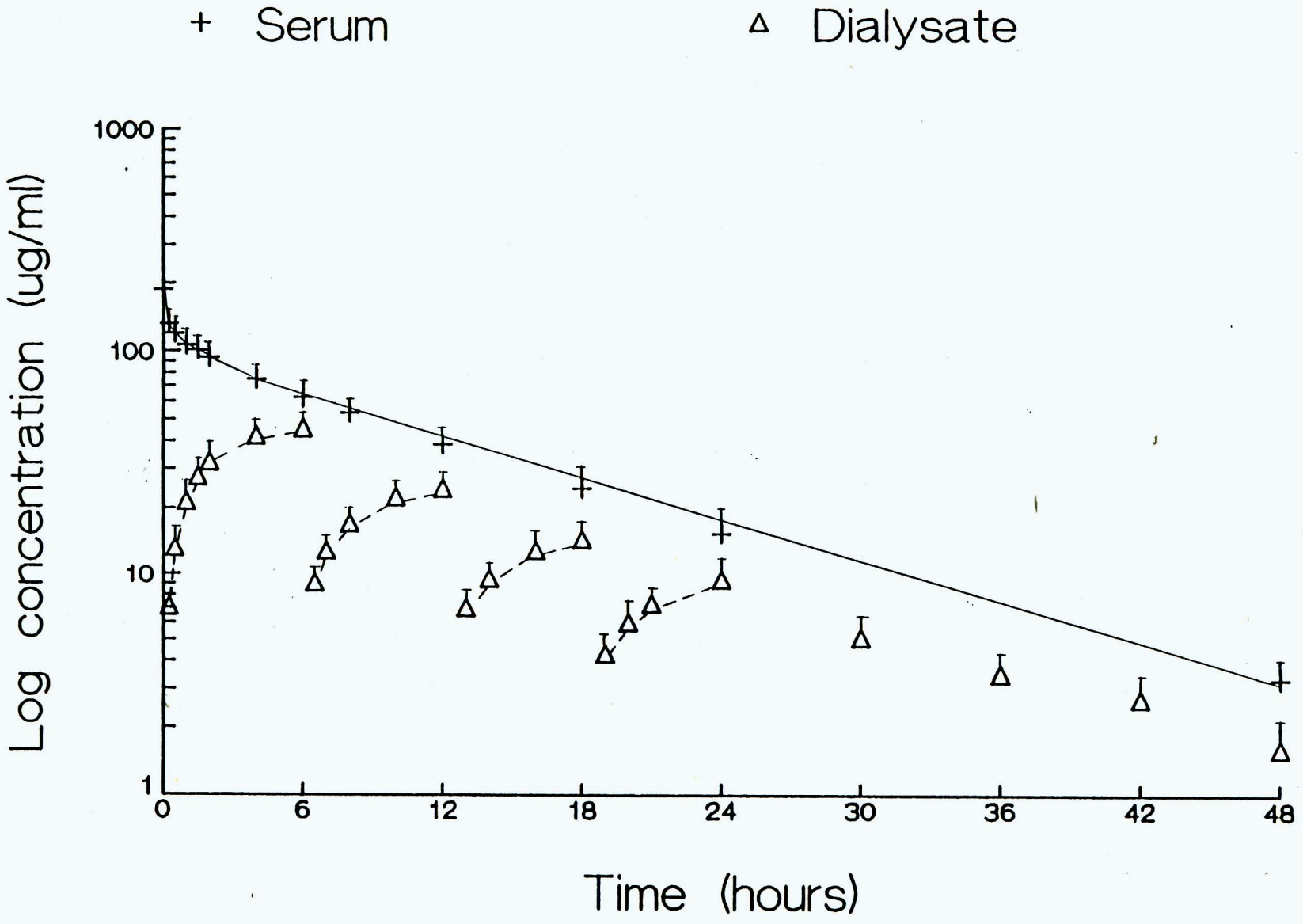

FIGURE 2. Sulbactam serum and dialysate concentrations after a 2-g ampicillin/1-g sulbactam dose IV

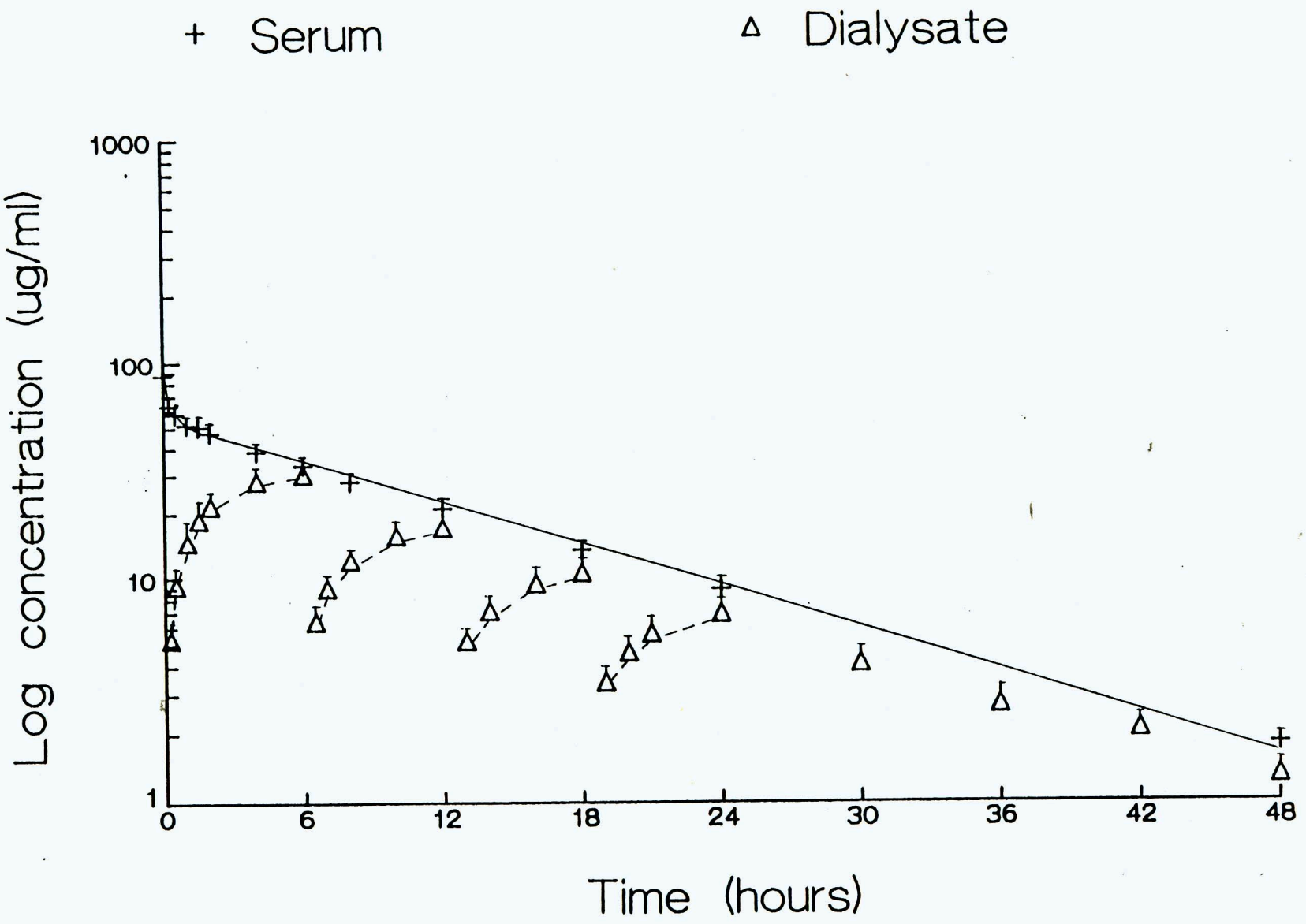

FIGURE 3. Ampicillin serum and dialysate concentrations after a 2-g ampcillin/1-g sulbactam dose IP

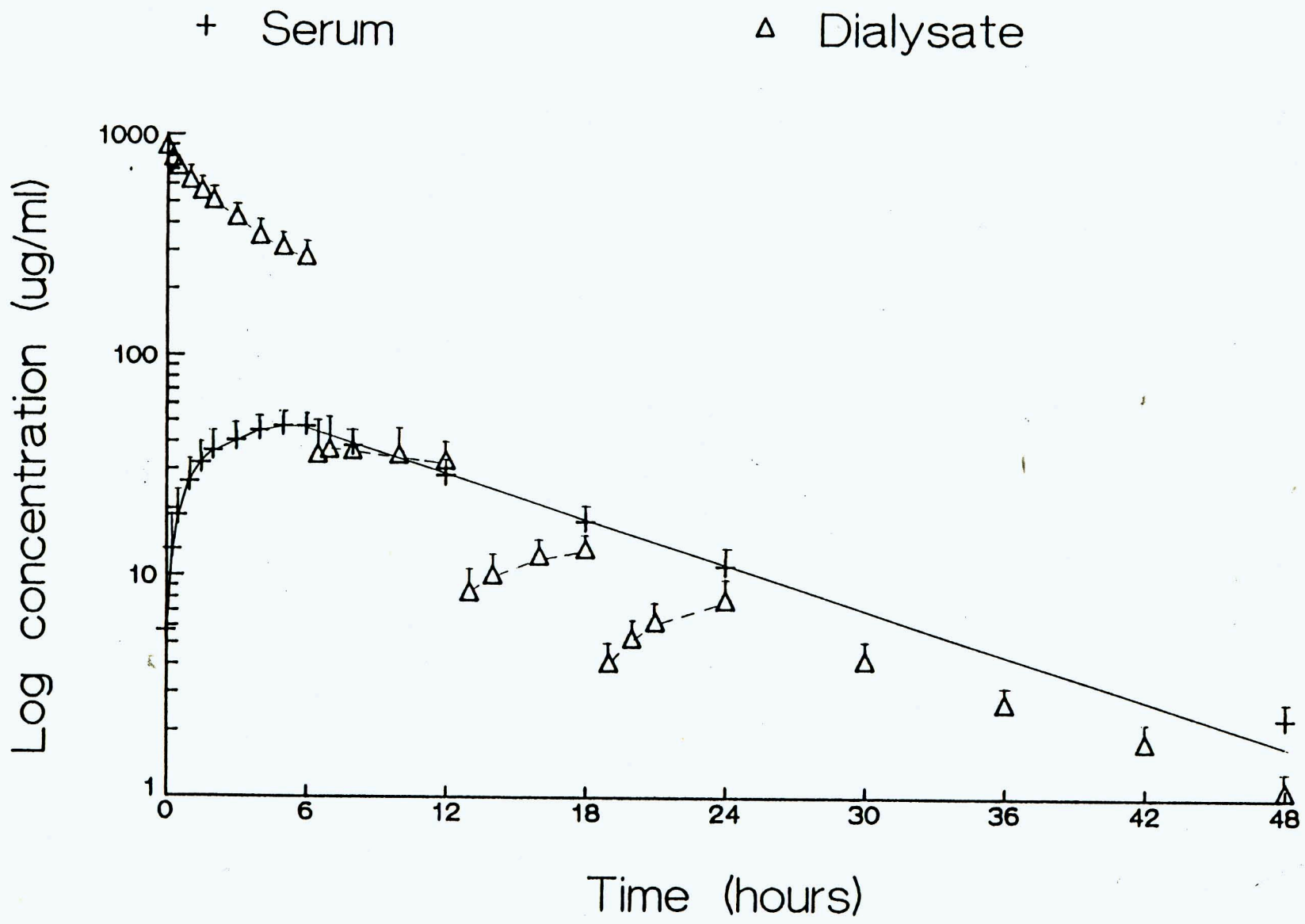

FIGURE 4. Sulbactam serum and dialysate concentrations after a 2-g ampicillin/1-g sulbactam dose IP

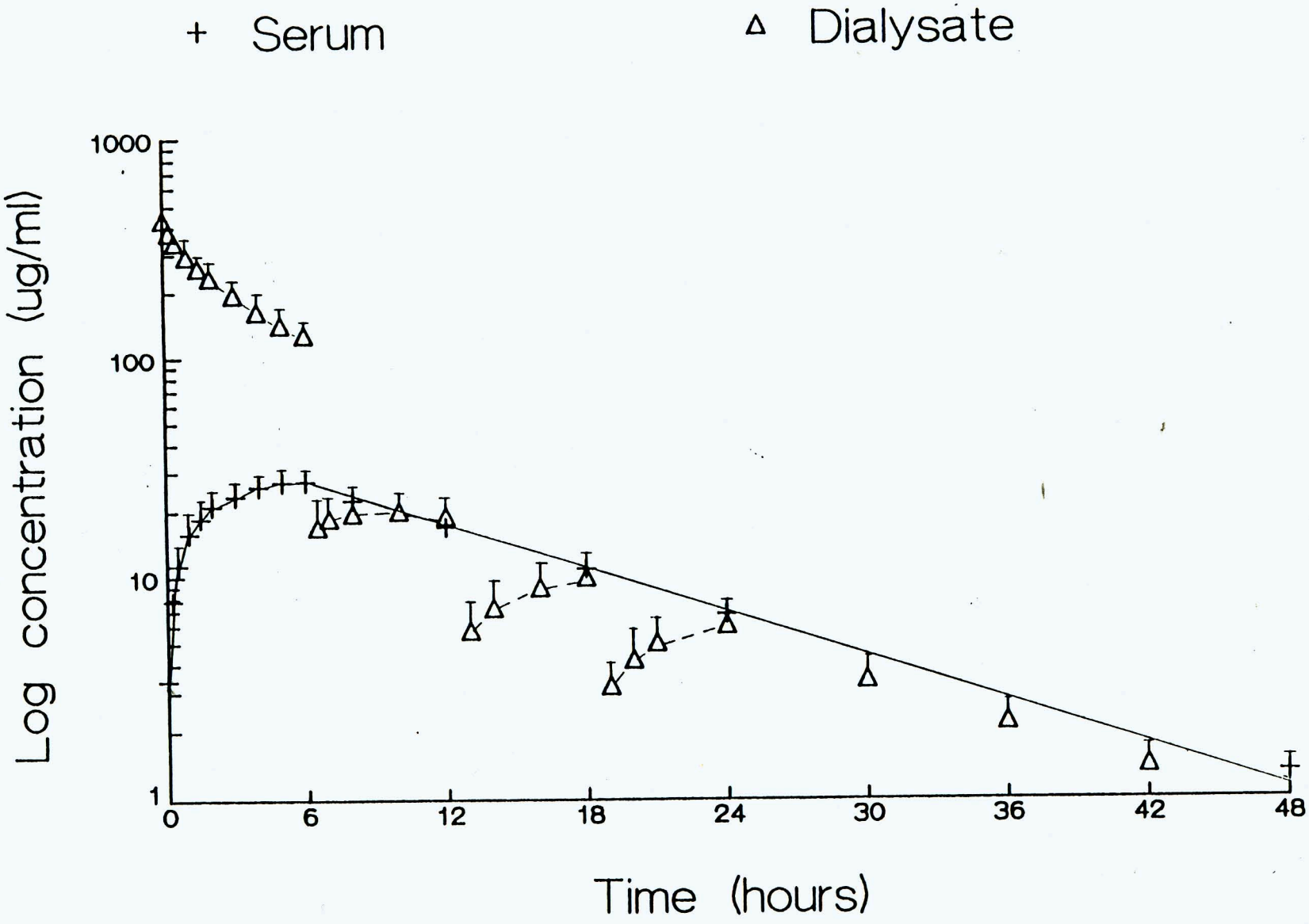

Table 1. Ampicillin Pharmacokinetics After a 2-g Ampicillin/1-g Sulbactam IV dose over 15 min.

Patient	k_{el} (h^{-1})	$t_{\frac{1}{2}\beta}$ (h)	C_o (μg/ml)	AUC $\left(\frac{mg \cdot h}{l}\right)$	V_{ss} (l)[b]	V_β (l)[c]	Cl_{TB} (ml/min)	Cl_R (ml/min)	Cl_D (ml/min)
1	.062	11.1	182.3	1795.2	16.6	17.9	18.6	1.6	2.4
2	.052	13.3	202.8	1790.1	17.8	21.4	18.6	2.5	2.4
3	.069	10.0	257.9	1491.9	17.5	19.3	22.3	0.1	2.5
5	.094	7.4	99.4[a]	1154.7	17.8	18.4	28.9	0.2	2.7
6	.083	8.3	152.8	1441.8	16.1	16.6	23.1	4.5	2.4
8	.102	6.8	127.2	860.6	19.6	22.8	38.7	0.2	3.6
Mean ± SD	$\bar{X}$ = .077 ± .019	$\bar{X}$ = 9.5 ± 2.2	$\bar{X}$ = 170.3 ± 56.6	$\bar{X}$ = 1422.4 ± 365.2	$\bar{X}$ = 17.6 ± 1.2	$\bar{X}$ = 19.4 ± 2.3	$\bar{X}$ = 25.0 ± 7.7	$\bar{X}$ = 1.5 ± 1.6	$\bar{X}$ = 2.7 ± 0.5

NOTE: Patients 4 and 7 did not complete the study

a. Technical difficulties were encountered withdrawing C_o blood sample in patient No. 5. This may explain this apparently low value.

b. V as calculated by noncompartmental determination of steady-state V_D, corrected for infusion time.

c. V as calculated by $\frac{Cl_{TB}}{k_{el}}$

Table 2. Sulbactam Pharmacokinetics After a 2-g Ampicillin/1-g Sulbactam IV Dose Over 15 Minutes

Patient	k_{el} (h^{-1})	$t_{\frac{1}{2}\beta}$ (h)	C_o (μg/ml)	AUC $\left(\frac{mg \cdot h}{l}\right)$	V_{ss} (l)[b]	V_β (l)[c]	Cl_{TB} (ml/min)	Cl_R (ml/min)	Cl_D (ml/min)
1	.067	10.3	84.7	814.2	16.7	18.2	20.5	1.9	3.3
2	.055	12.5	97.0	799.1	21.1	22.6	20.9	2.7	3.4
3	.059	11.8	128.5	926.6	16.9	18.4	18.0	0.1	3.2
5	.084	8.3	43.5[a]	692.4	16.9	17.2	24.1	0.2	3.3
6	.101	6.8	66.3	632.9	14.9	15.6	26.3	4.2	3.2
8	.082	8.5	105.1	653.0	17.0	18.7	25.5	0.6	4.4
Mean ± SD	$\bar{X}$ = .075 ± .017	$\bar{X}$ = 9.7 ± 2.2	$\bar{X}$ = 87.5 ± 29.9	$\bar{X}$ = 753.0 ± 113.2	$\bar{X}$ = 17.3 ± 2.0	$\bar{X}$ = 18.5 ± 2.3	$\bar{X}$ = 22.6 ± 3.2	$\bar{X}$ = 1.5 ± 1.5	$\bar{X}$ = 3.5 ± 0.5

NOTE: Patients 4 and 7 did not complete the study

a. Technical difficulties were encountered withdrawing C_o blood sample in patient No. 5. This may explain this apparently low value.

b. V as calculated by noncompartmental determination of steady-state V_D, corrected for infusion time.

c. V as calculated by $\frac{Cl_{TB}}{k_{el}}$

Table 3. Ampicillin Pharmacokinetics after a 2-g Ampicillin/1-g Sulbactam IP Dose Over 15 Minutes

Patient	k_{el} (h^{-1})	$t_{\frac{1}{2}\beta}$ (h)[a]	C_{peak} (μg/ml)	t_{max} (h)	AUC $\left(\frac{mg \cdot h}{l}\right)$	Absolute Bioavailability	V_β (l)	Cl_{TB} (ml/min)	Cl_R (ml/min)
1	.063	11.0	44.9	6	916.5	.51	17.6	18.6	0.8
2	.057	12.2	53.5	6	1160.0	.65	19.6	18.6	2.1
3	.053	13.1	35.5	5	801.7	.46	21.2	22.3	0.03
5	.100	6.9	48.0	6	686.2	.59	17.3	28.9	0.1
6	.095	7.3	57.5	5	893.7	.62	14.6	23.1	3.2
8	.099	7.0	48.5	5	664.8	.77	23.4	38.7	0.1
Mean ± SD	$\bar{X}$ = .078 ± .022	$\bar{X}$ = 9.6 ± 2.6	$\bar{X}$ = 48.0 ± 7.6		$\bar{X}$ = 853.8 ± 182.1	$\bar{X}$ = .60 ± 0.11	$\bar{X}$ = 19.0 ± 3.1	$\bar{X}$ = 25.0 ± 7.7	$\bar{X}$ = 1.0 ± 1.2

NOTE: Patients 4 and 7 did not complete the study.

a. k_{el} was calcuated from the slope of the β phase of elimination beginning at t = 6h.

Table 4. Sulbactam Pharmacokinetics After a 2-g Ampicillin/1-g Sulbactam IP Dose Over 15 Minutes

Patient	k_{el} (h^{-1})	$t_{\frac{1}{2}\beta}$ (h)[a]	C_{peak} (μg/ml)	t_{max} (h)	AUC $\left(\frac{mg \cdot h}{l}\right)$	Absolute Bioavailability	V_β (l)	Cl_{TB} (ml/min)	Cl_R (ml/min)
1	.067	10.4	25.3	6	491.7	.60	18.4	20.5	0.8
2	.060	11.7	30.5	6	646.6	.81	21.0	20.9	2.3
3	.059	11.8	20.5	5	457.4	.49	18.4	18.0	0.03
5	.088	7.9	28.8	6	464.3	.67	16.4	24.1	0.2
6	.108	6.4	30.8	5	434.8	.69	14.6	26.3	3.7
8	.082	8.5	30.7	5	539.9	.83	18.7	25.5	0.1
Mean ± SD	$\bar{X}$ = .077 ± .019	$\bar{X}$ = 9.4 ± 2.3	$\bar{X}$ = 27.8 ± 4.1		$\bar{X}$ = 505.8 ± 77.8	$\bar{X}$ = .68 ± 0.13	$\bar{X}$ = 17.9 ± 2.2	$\bar{X}$ = 22.6 ± 3.2	$\bar{X}$ = 1.1 ± 1.3

NOTE: Patients 4 and 7 did not complete the study.

a. k_{el} was calculated from the slope of the β phase of elimination beginning at t = 6h.

TABLE 5. $\frac{\text{Ampicillin}}{\text{Sulbactam}}$ concentrations (ug/ml) and ratios which occurred in dialysate 6 and 24 h after 2-g ampicillin/1-g sulbactam IV and IP dosing.

	IV				IP			
Patient No.	P[a] (µg/ml)	$\frac{\text{Ampicillin}}{\text{Sulbactam}}$	T[b] (µg/ml)	$\frac{\text{Ampicillin}}{\text{Sulbactam}}$	P (µg/ml)	$\frac{\text{Ampicillin}}{\text{Sulbactam}}$	T (µg/ml)	$\frac{\text{Ampicillin}}{\text{Sulbactam}}$
1	$\frac{45}{29}$	1.6	$\frac{12}{7}$	1.7	$\frac{347}{156}$	2.2	$\frac{8}{5}$	1.6
2	$\frac{46}{28}$	1.6	$\frac{16}{10}$	1.6	$\frac{268}{126}$	2.1	$\frac{12}{8}$	1.5
3	$\frac{41}{29}$	1.4	$\frac{10}{8}$	1.3	$\frac{348}{162}$	2.1	$\frac{7}{6}$	1.2
5	$\frac{43}{29}$	1.5	$\frac{6}{5}$	1.2	$\frac{248}{107}$	2.3	$\frac{6}{5}$	1.2
6	$\frac{53}{32}$	1.7	$\frac{8}{4}$	2	$\frac{300}{134}$	2.2	$\frac{7}{4}$	1.8
8	$\frac{35}{47}$	1.3	$\frac{5}{7}$	0.7	$\frac{181}{82}$	2.2	$\frac{6}{8}$	0.8

a. P = Peak ampicillin concentration (6 h after dosing)

b. T = Trough ampicillin concentration (24 h after dosing)

Table 6. Geometric mean[a] observed reciprocal inhibitory/bactericidal titers occurring in D-MH samples 6 and 24 h after 2-g ampicillin/1-g sulbactam dose

Organism	IV		IP	
	P[c]	T[c]	P	T
S. aureus	6.0	< 2.0	34.7	< 2.0
S. epidermidis	682.7	106.7	1962	128
E. coli, ampicillin-resistant (29522)	8.7	< 2.0	68.5	3.2
E. coli (35)	< 2.0	< 2.0	4.0	< 2.0
K. pneumoniae	5.3	< 2.0	22.7	< 2.0

a. Geometric mean of 2 replicates.

b. P = inhibitory/bactericidal reciprocal titers observed in D-MH containing the peak ampicillin concentration (6 h after dose).

c. T = inhibitory/bactericidal reciprocal titers observed in D-MH containing the trough ampicillin concentration (24 h after dose).