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Pharmacokinetics of Sulbactam in Humans

GEORGE FOULDS,[1]* JOSEPH P. STANKEWICH,[2] DAVID C. MARSHALL,† MARK M. O'BRIEN,‡ SHERRARD L. HAYES,§ DONALD J. WEIDLER,[3] AND F. GILBERT McMAHON[4]

Central Research Division[1] and Quality Control Division,[2] Pfizer Inc., Groton, Connecticut 06340; Division of Clinical Pharmacology, University of Miami, Miami, Florida 33103[3]; and Clinical Research Center, Inc., New Orleans, Louisiana 70112[4]

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Sulbactam, a new β-lactamase inhibitor, has pharmacokinetic characteristics in humans similar to those of ampicillin and amoxicillin. Its half-life in humans is approximately 1 h. In a two-compartment pharmacokinetic model, the apparent volume of distribution for the central compartment is approximately 12 liters, and half of the dose is found in the central compartment in the postdistributive phase. Approximately 75% of a parenteral dose is excreted unchanged in urine. The coadministration of sulbactam with ampicillin, penicillin G, or cefoperazone has essentially no effect upon the kinetics of either the β-lactam antibiotic or sulbactam.

Since the introduction of β-lactam antibiotics, many organisms previously susceptible to the penicillins have developed resistance. This resistance is often due to the presence of a β-lactamase, an enzyme that is capable of hydrolyzing the β-lactam ring of penicillins, thereby destroying their antibiotic activity (16, 18). One way to restore the susceptibility of resistant strains of bacteria to the antibiotic is to coadminister a β-lactamase inhibitor, that is, a compound which will inactivate the enzyme. Such a compound is sulbactam (CP-45,899, penicillanic acid sulfone), a competitive and noncompetitive β-lactamase inhibitor (4, 14, 15) presently under clinical investigation. Although it has relatively little intrinsic biological activity, sulbactam has been shown to extend the in vitro spectrum of β-lactam antibiotics to a number of resistant organisms (1, 8, 9, 17). This report describes the parenteral pharmacokinetics of sulbactam in humans.

Since the efficacy of sulbactam requires concomitant administration of a β-lactam antibiotic, emphasis has been placed upon comparisons of the pharmacokinetics of sulbactam with those of and in combination with parenteral antibiotics such as ampicillin, penicillin G, and cefoperazone.

MATERIALS AND METHODS

Assay of sulbactam: bioassay. During the single- and multiple-dose studies in which sulbactam was given alone, sulbactam levels in serum and urine were assayed by a microbiological cylinder plate technique, essentially described in the *United States Pharmacopoeia XX* (20). The assay employed *Comamonas terrigena* ATCC 8461 at a concentration of approximately 10^7 organisms per ml of Antibiotic Medium A (BBL Microbiology Systems) as the test medium. A single seeded 12-ml agar layer in plastic petri dishes (20 by 100 mm) was used to enhance sensitivity.

The serum samples were analyzed against a standard curve prepared in pooled human control serum. The standard curve ranged from 1 to 3 μg/ml with a limit of detection of approximately 0.5 μg/ml. When necessary, the serum samples were diluted with pooled human control serum to approximately 2 μg/ml. The standard curve (1.4 to 4.0 μg/ml) for the analysis of urine samples was prepared in 1% potassium phosphate buffer (pH 6.0). All urine samples were diluted a minimum of 10-fold with 1% potassium phosphate buffer (pH 6.0) to eliminate any sample interference and, if necessary, additionally to approximately 2 μg/ml. The resulting limit of detection in undiluted urine was approximately 7 μg/ml.

Each standard curve sample was plated in triplicate on each of nine agar plates. The serum and urine specimens were plated in triplicate on each of three agar plates. The test agar plates were then incubated at 32 to 35°C for approximately 18 h. The resulting zones of inhibition were read by an automated zone reader, and the calculations were performed by a PDP-8E computer hard-wired to the reader (6). A linear regression analysis was performed on the log of the concentration of standards versus the zone diameter. In all bioassays described in this paper, samples for which the initial assay indicated a value outside the range of the standard curve were rediluted, to bring the concentration within the range of the standard curve, and then were reassayed.

Fresh sulbactam standards were prepared in control serum or 1% pH 6.0 buffer and analyzed on each test day as controls for the serum and urine assays, respectively. The mean recovery for 14 fortified urine con-

† Present address: Ethicon, Sommerville, NJ 08876.
‡ Present address: University Affiliated Cincinnati Center for Developmental Disabilities, Cincinnati, OH 45229.
§ Present address: 1600 South 4th Street, Fort Pierce, FL 33450.

trols over 8 assay days was 98.4% with a relative standard deviation of 1.4%. The mean recovery for 22 fortified serum controls over 11 assay days was 99.5% with a relative standard deviation of 2.3%.

Assay of sulbactam: GC-MS. During studies in which sulbactam was coadministered with an antibiotic, the methyl ester of sulbactam was prepared and analyzed by gas chromatography with mass spectrometry detection (GC-MS). To 0.50 ml of serum or 30 μl of urine, 100 μl of a solution of the sodium salt of penicillanic acid (CP-12,943), equivalent to 0.04 mg of free acid per ml, was added as an internal standard. The mixture was acidified with 0.5 ml of 0.25 N HCl and extracted with 5 ml of ethyl acetate. The extracts were methylated with diazomethane (11). After methylation, the extracts were reduced in volume to 0.5 ml and stored in a freezer until they were injected into the gas chromatograph. Portions (1 to 5 μl) of the extracts were injected into a Finnigan 3200 gas chromatograph-mass spectrometer with chemical ionization and specific ion monitoring under the following conditions: column, 1.5 m by 2.2 mm, 3% OV-1 on GCQ 60/80; column temperature, 170°C; source temperature, 165°C; carrier gas, methane; ion source pressure, 750 μm; attenuation, 10^{-8}; filter, 0.5. Detection was by specific ion monitoring: sulbactam (*m/e* 206) and CP-12,943 (*m/e* 244).

The retention time for the sulbactam peak (*m/e* 206) was approximately 60 s. The retention time for the internal standard peak (penicillanic acid, *m/e* 244) was approximately 25 s. Standard curves prepared by fortification of blank serum or urine with a solution of sulbactam in ethyl acetate (1 mg/10 ml) were prepared in parallel with the samples. Quantitation was by comparison of log *R* (the ratio of peak height of sulbactam to peak height of the internal standard) with the least-squares regression of log concentration of standards versus log *R* of standards. Standard curves were injected after every set of 10 to 20 samples. The GC-MS assay was linear over the range of 0.1 μg/ml to greater than 400 μg/ml. To examine the reproducibility and precision of the assay, triplicate samples in dog serum and urine were prepared and assayed. The correlation coefficients of log peak height versus log concentration were greater than 0.9970. The relative standard deviations were between 2.1 and 8.9%. Comparison of peak heights of drug extracted from dog serum, plasma, and urine and human serum with peak heights of drug prepared in ethyl acetate indicated that the extraction procedure recovered essentially all of the sulbactam and that the apparent extent of recovery was constant over the range of 0.1 to greater than 100 μg/ml in all media tested. For examination of interference by β-lactam antibiotics, standard curves of human serum fortified with between 0.2 and 10 μg of sulbactam per ml, alone and in combination with 50-μg/ml concentrations of ampicillin, amoxicillin, penicillin G, cefoperazone, or cephalothin, were assayed for sulbactam. No significant change was produced in either the slope or intercept of the standard curves by the addition of the antibiotic. All of the correlation coefficients were above 0.996. Additionally, assays of ampicillin at 50 μg/ml, cefoperazone at 100 μg/ml, cefazolin at 100 μg/ml, or cephalothin at 50 μg/ml produced no detectable response corresponding to either sulbactam or the internal standard (penicillanic acid).

Studies were conducted to determine the stability of sulbactam in frozen human serum and urine. Fortified sulbactam samples were prepared in pooled human control urine and pooled human control serum at 302 and 2.0 μg of sulbactam per ml, respectively, and were assayed. The samples were then subdivided, frozen at approximately −60°C, and assayed periodically. Sulbactam in human serum retained full activity when stored at −60°C for 6 weeks. Sulbactam in human urine retained at least 94% of initial activity. Additional stability studies showed that human serum samples fortified with 2 or 20 μg of sulbactam per ml retained 96 or 98% of their initial activity after 13 days of storage at −20°C. However, samples fortified with 2, 5, or 10 μg of sulbactam per ml lost approximately 24% of their activity upon storage at −10°C for 37 days. These results indicate that samples of human serum to be assayed for sulbactam should be stored at or below −20°C.

Assay of ampicillin, penicillin G, and cefoperazone. Ampicillin, penicillin G, and cefoperazone concentrations in serum and urine were determined by a microbiological cylinder plate technique essentially identical to that described in the *United States Pharmacopoeia XX* (20). The organism used for these assays was *Micrococcus luteus* ATCC 9341 at a concentration of approximately 10^7 organisms per ml in Antibiotic Medium C (BBL Microbiology Systems) for ampicillin and penicillin G or Medium A for cefoperazone. A single seeded agar layer of approximately 12 ml in plastic petri dishes (20 by 100 mm) was used to improve sensitivity. Compensatory standard curves for each antibiotic were prepared in pooled control human serum. For assays of drug in urine, standard curves were prepared in 1% potassium phosphate buffer (pH 6.0). Each standard curve concentration was plated in triplicate on each of nine agar plates. Serum and urine specimens were plated in triplicate on each of three agar plates. After incubation at 32 to 35°C for approximately 18 h, zones of inhibition were read by the automated zone reader and calculated as described above.

Ampicillin concentrations in the serum standard curves ranged from 0.04 to 0.14 μg/ml, and the penicillin G standard curves ranged from 0.05 to 0.4 μg/ml. The buffer standard curves for assay of urine samples ranged from 0.03 to 0.12 μg of ampicillin per ml or 0.03 to 0.20 μg of penicillin G per ml. If necessary, serum samples were diluted to approximately the midpoint of the appropriate standard curve with pooled human control serum. All urine samples were diluted a minimum of 10-fold with the 1% phosphate buffer to eliminate any sample interferences. They were then diluted further, if necessary, to bring the expected assay concentration near the midpoint of the standard curve. During the study of the interaction of ampicillin or penicillin G and sulbactam in humans (described below), the mean recoveries of ampicillin in fortified serum and urine controls were 98 and 100%, respectively, with relative standard deviations of 1.7 and 2.7%, respectively. The mean recoveries for the penicillin G serum and urine controls were 100 and 97% with relative standard deviations of 4.3 and 1.8%, respectively.

For the assay of cefoperazone, the standard curves ranged from 1.5 to 6 μg/ml in serum and 0.3 to 1.2 μg/ml in urine. The limits of sensitivity were approxi-

mately 0.7 μg/ml in serum and, because of the 10-fold dilution in buffer, 2 μg/ml in urine. For a typical cefoperazone study the mean recovery for 17 serum controls over 6 assay days was 101% with a relative standard deviation of 3.2%. The mean recovery for 13 urine controls over 6 assay days was 101% with a relative standard deviation of 2.3%.

Since a primary purpose of this work was to examine the influence of sulbactam on the kinetics of β-lactam antibiotics, the possible interference of sulbactam in the above assays was investigated. Even when sulbactam was added at 10 times the levels of ampicillin and penicillin G to control samples in serum, no interference was detected in either of these assays. Sulbactam also had no effect on the assays for cefoperazone, even when the sulbactam concentrations were twice those of the cefoperazone. Additionally, 50 μg of sulbactam per ml alone produced no response in the assay for cefoperazone. These results were expected since *M. luteus* is not known to produce any β-lactamase enzymes.

A study was conducted to determine the stability of cefoperazone in human serum and urine under several storage conditions. Cefoperazone samples were prepared in pooled human control urine and pooled human control serum at 300 and 60 μg of cefoperazone per ml, respectively, and were assayed. The samples were then subdivided into individual tubes, stored at 5, −20, or −60°C, and assayed periodically. Cefoperazone in serum retained at least 95% of initial activity after 3 months at −20°C and 100% of initial activity after 3 months at −60°C. Cefoperazone in urine was completely stable for 3 months even when only refrigerated at 5°C, but the cefoperazone serum samples were relatively unstable under this condition.

All clinical samples for bioassay were stored in a Revco freezer at −60°C before being assayed. All bioassays were complete within 6 weeks. Samples for GC-MS assay of sulbactam were stored at −20°C and assayed within 8 weeks of receipt.

Human studies. (i) Single dose. To assess single-dose pharmacokinetics, healthy male volunteers were given doses of 125 to 1,000 mg of sulbactam by intramuscular (i.m.) injection or 30-min intravenous (i.v.) infusion. Samples of serum and urine from each volunteer were assayed for intact sulbactam by bioassay.

(ii) Multiple dose. To assess the possible increase in drug concentrations during a multiple-dose regimen, healthy male volunteers received either i.m. or 30-min i.v. doses of 500 mg of sulbactam every 6 h for 3 days. Samples of serum were obtained after the first dose and after the second dose on day 3. The serum samples were assayed for sulbactam by bioassay.

Interaction studies. To assess the possible pharmacokinetic interaction of sulbactam with penicillin G and ampicillin, six healthy male volunteers received 500 mg of sulbactam alone, 500 mg of penicillin G alone, and the combination by 30-min infusions in a three-way crossover experiment. Similarly, another set of six volunteers received 500 mg of sulbactam alone, 500 mg of penicillin G alone, and the combination by i.m. injection. A third set of six volunteers received 500 mg of sulbactam alone, 500 mg of ampicillin alone, and the combination by i.v. bolus. After each dose, serum and urine samples from each subject were assayed for sulbactam (GC-MS), ampicillin, or penicillin G, as appropriate.

To assess the possible pharmacokinetic interaction of sulbactam and cefoperazone, healthy male subjects were administered 2 g of cefoperazone, alone or in combination with 1 g of sulbactam, by 1-h i.v. infusion or i.v. bolus injection twice a day for 5 days. Serum and urine samples were obtained on days 1 and 5 and analyzed for sulbactam (GC-MS) and cefoperazone.

Pharmacokinetics. Serum concentrations of sulbactam or the coadministered β-lactam antibiotic were fitted to equation 1 by using an iterative least-squares computer program and interpreted as one- or two-compartment pharmacokinetic models by standard methods (10, 21).

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

In all cases, more complex models did not provide a substantial improvement in the fit of the model to the data. The goodness of fit (r^2) usually exceeded 0.96.

Areas under the serum concentration versus time curves (AUCs) for comparisons of the availability of doses of sulbactam were calculated by the trapezoidal method. Where appropriate, they were extrapolated to infinity: $AUC_{0-\infty} = AUC_{0-t} + C_t/\beta$, where β is the slope of ln C versus time for the last three to five time points. Half-lives were calculated as 0.693/β.

Renal clearances (Cl_r) were calculated from $AUC_{0-\infty}$ from the best fit of the data to the curve after 30-min i.v. infusions and the recovery of drug in urine: $Cl_r = X_U/AUC_{0-\infty}$, where X_U is the amount of drug recovered in urine.

Furthermore, $AUC_{0-\infty} = A_1/\alpha + B_1/\beta$, where A_1 and B_1 are A and B from equation 1 corrected for 30-min infusion.

Total clearance (Cl_T) of drug from blood was calculated from $AUC_{0-\infty}$ (as above) and the dose, as follows: Cl_T = dose/$AUC_{0-\infty}$.

Nonrenal clearance (Cl_N) was also calculated: $Cl_N = Cl_T - Cl_r$.

RESULTS

Single dose. After a 30-min infusion of 500 mg of sulbactam, a peak serum concentration of approximately 20 μg/ml was obtained; 1,000 mg produced a peak of 43 μg/ml (Fig. 1). The half-life for elimination was about 1.0 h. The data were interpreted as a two-compartment pharmacokinetic model. The results (Table 1) are compatible with i.v. infusion followed by moderate rates of distribution into and out of a peripheral compartment ($k_{12} = 0.9\ h^{-1}$; $k_{21} = 1.8\ h^{-1}$) and a moderate elimination rate ($k_{10} = 1.4\ h^{-1}$). The apparent volume of distribution for the central compartment (serum and rapidly equilibrating tissues) was between 9 and 16 liters, and the total apparent volume of distribution was between 19 and 28 liters. Approximately 51% of the drug was in the central compartment in the postdistributive phase. Calculated steady-state serum concentrations were proportional to dose. These pharmacokinetic parameters are very close to those of amoxicillin for which the following parameters have been reported: $t_{1/2}$ = 1.05; V_c = 13.9 liters; V_b = 22.3 liters; f_c = 0.46; and C_{ss} = 14.6 μg/ml for 250 mg infused over 33

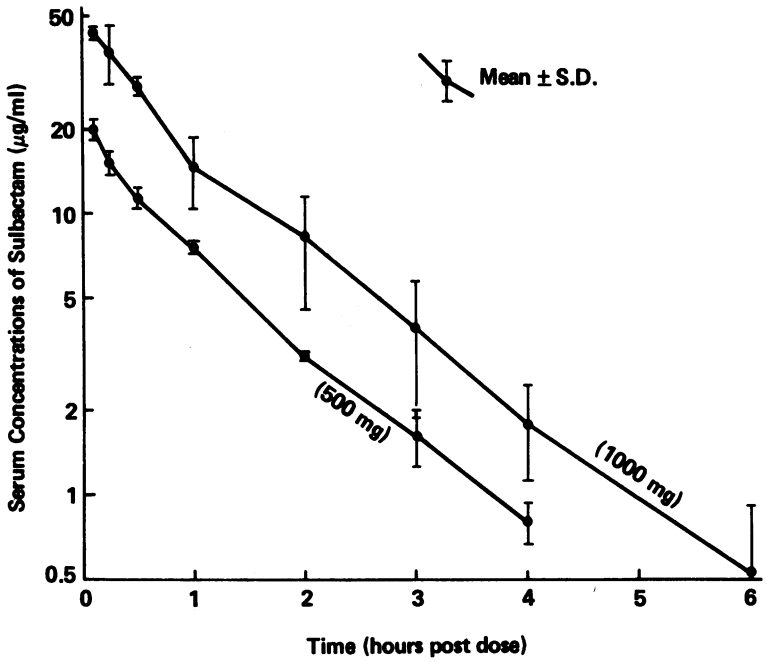

FIG. 1. Serum concentrations of sulbactam after 30-min infusions to men (four subjects per dose regimen). S.D., Standard deviation.

min (22). The parameters are also similar to those of ampicillin: $t_{1/2}$ = 1.31; V_c = 12.3 liters; V_b = 18.5 liters; f_c = 0.66 (12); C_{ss} = 29.0 μg/ml for continuous infusion of 500 μg/h (19). The results show that parenteral sulbactam acts like a typical penicillin in humans. Sulbactam has also been administered to humans by bolus i.v. injections: 500 mg produced a peak serum concentration of approximately 32 μg/ml.

After i.m. administration of 500 mg of sulbactam, the mean peak serum concentration was 13 μg/ml; 1,000 mg produced a peak of 28 μg/ml (Fig. 2). The elimination half-life was approximately 1.2 h. Comparison of AUCs and urinary recoveries with those obtained after i.v. doses indicated that the i.m. dose was completely bioavailable.

The only side effect observed after the parenteral administration of sulbactam to humans was pain at the site of i.m. injection. The pain subsided rapidly and disappeared completely within 1 h. In these studies, approximately 70%

TABLE 1. Pharmacokinetic parameters of sulbactam in humans: two-compartment open model, 30-min i.v. infusion

Sulbactam dose (mg)	N	$t_{1/2}$ (h)	V_c (liters)	V_B (liters)	f_c[a]	C_{ss}[b] (μg/ml)	$AUC_{0-\infty}$[c] (μg · h/ml)	Sulbactam recovery in urine (mg)	Clearance (ml/min)		
									Renal	Total	Nonrenal
125	1	0.89		27.06[d]		11.9	5.9	98.2	277.4	357.1	75.7
250	1	1.09	5.79	19.98	0.29	11.5	19.8	188.6	158.8	210.4	51.6
500	4	0.96	12.96	24.00	0.54	31.1	28.9	362.6	211.8	270.9	74.6
1,000	4	0.95	11.34[e]	21.81	0.52	64.1	66.4	784.6[f]	204.1	254.0	54.0
Mean (all doses)		0.97	11.73	22.82	0.51			75.5% of dose	203.8	266.3	65.3
S.D. (all doses)		0.10	3.56	3.07	0.13			±5.5%	±44.4	±47.4	±17.7

[a] Fraction of drug in central compartment in postdistributive phase (= β/k_{10}).
[b] Calculated (= $k_0/k_{10}\ V_B$).
[c] From fit of equation 1 to the data and corrected for 30-min infusion.
[d] One compartment (= β).
[e] Mean of three; one subject could only be fitted to a one-compartment model.
[f] Mean of three; no urine sample was obtained from one subject.

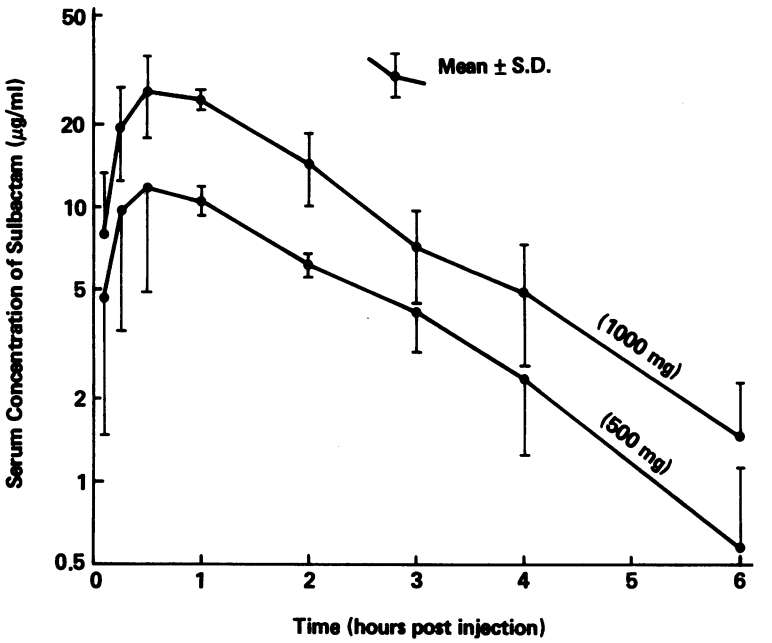

FIG. 2. Serum concentrations of sulbactam after i.m. injections to men (four subjects per dose regimen). Mean ± standard deviation (S.D.) one-sided where necessary to avoid confusion.

of a parenteral dose of sulbactam was excreted in the urine between 0 and 6 h, with an additional recovery of 5% between 6 and 12 h postdose.

The urinary recovery data after the 30-min i.v. infusions were analyzed in more detail (Table 1). The renal clearance was approximately 204 ml/min and was not dose dependent. The total clearance of drug from the serum was 266 ml/min. The nonrenal clearance was 65 ml/min.

Multiple-dose study. After multiple doses of sulbactam by 30-min i.v. infusion or i.m. injections of 500 mg every 6 h for 3 days, no significant changes were observed in either AUCs or peak serum concentrations between dose 1 and dose 10 (Fig. 3).

Coadministration studies. The pharmacokinetic interaction of sulbactam with several β-lactam antibiotics was examined in humans. Only minor changes in serum concentrations or urinary recoveries of sulbactam were observed after administration of 500 mg of sulbactam alone and with 500 mg of penicillin G by 30-min i.v. infusion or i.m. injection or with 500 ampicillin by i.v. bolus (Fig. 4 and Table 2). Similarly, only minor changes in the serum concentrations or urinary recoveries of penicillin G or ampicillin were observed upon coadministration of sulbactam (Fig. 4 and Table 2). No significant changes in the apparent volumes of distribution of the central compartment or f_c were observed, owing due to coadministration of sulbactam and penicillin G or ampicillin.

Sulbactam was also coadministered with cefoperazone. Coadministration of 1-g doses of sulbactam with 2-g doses of cefoperazone, either by 1-h infusion or i.v. bolus injection, twice a

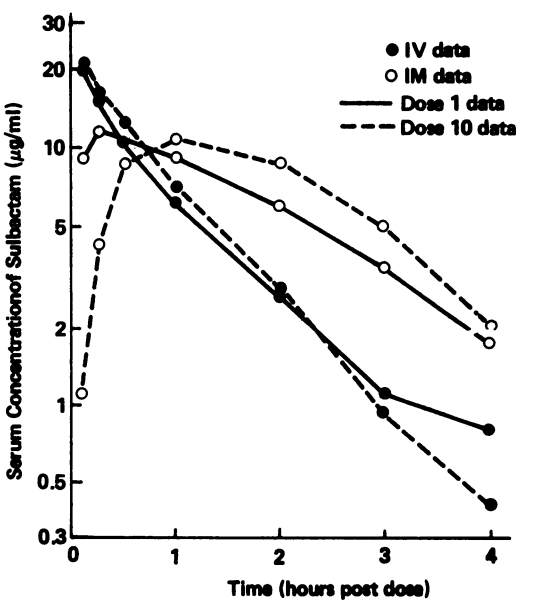

FIG. 3. Mean serum concentrations of sulbactam after i.v. or i.m. administration of 500 mg every 6 h for 3 days to three men per dose regimen.

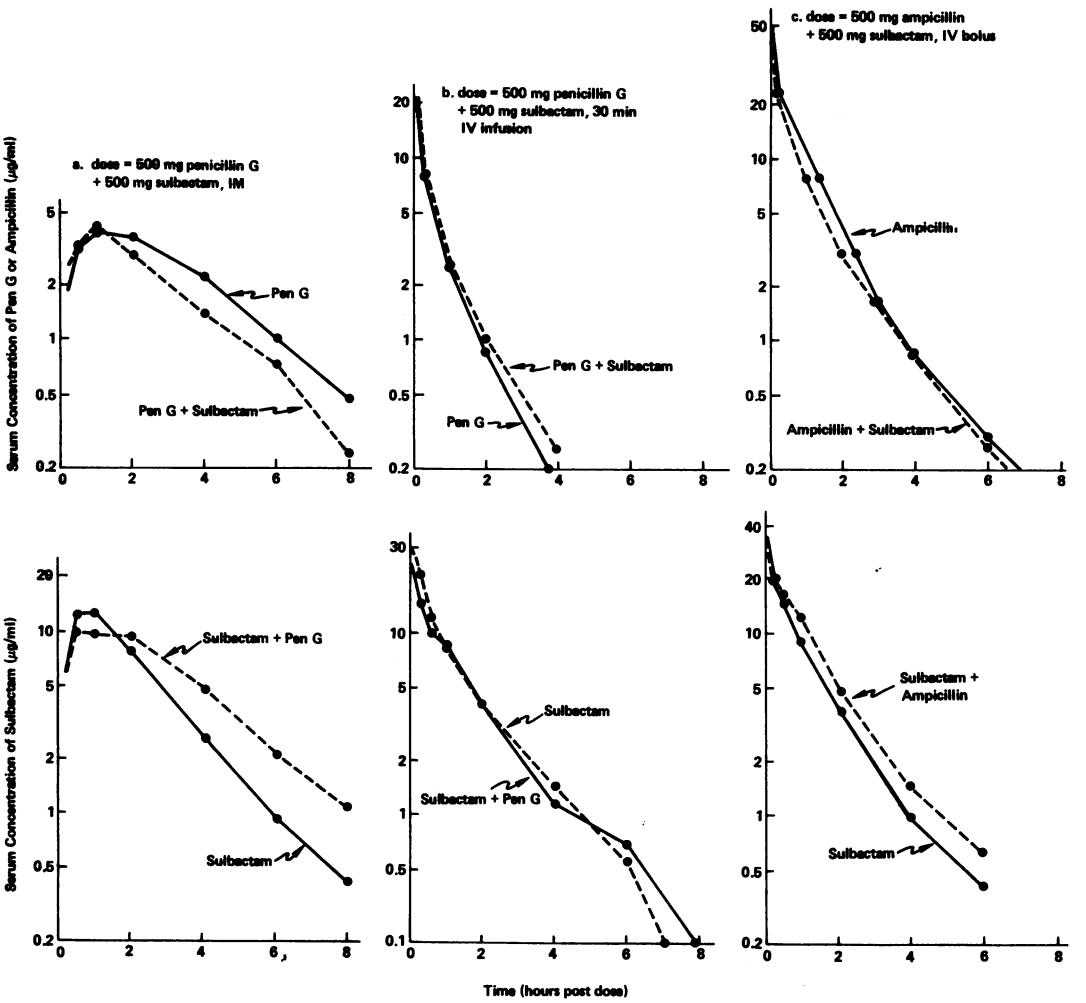

FIG. 4. Interaction of sulbactam with penicillin G or ampicillin. Mean (N = 6) concentrations after 500 mg of each component was administered alone or in combination. (———) Concentration of drug alone; (– – – –) concentration in combination.

day for 5 days, did not significantly affect the peak serum concentration, AUCs, or urinary recoveries of cefoperazone (Table 2). Furthermore, no major accumulation of cefoperazone or sulbactam was observed during either study.

DISCUSSION

The pharmacokinetics of sulbactam in humans are similar to those of ampicillin or amoxicillin, with a half-life of approximately 1 h. The principal mode of elimination is excretion in urine with a renal clearance of approximately 204 ml/min, a value similar to that reported elsewhere for sulbactam and ampicillin (5). An additional similarity to the β-lactam antibiotics is the increase in the half-life of sulbactam of approximately 40% in humans due to a prior dose of probenecid (V. A. Caine, K. K. Holmes, G. Foulds, and H. H. Handsfield, Abstr. Annu. Meet. Am. Soc. Microbiol. 1981, A72, p. 13), a response similar to that for ampicillin (7, 13) or penicillin G (2). This response suggests that sulbactam is excreted by the same mechanism in the kidney, i.e., mainly tubular secretion (3). Multiple dosing at rates as high as 500 mg every 6 h (i.m.) or 1 g twice a day (1 h infusions or i.v. bolus) does not appear to lead to accumulation of drug as indicated by an increase in peak serum concentrations or AUCs. Coadministration of sulbactam appears to have very little effect on the pharmacokinetics of ampicillin, penicillin G, or cefoper-

TABLE 2. Mean AUCs, peak serum concentrations, and urinary recoveries of sulbactam and β-lactam antibiotics after administration alone or in combination to healthy subjects

Dose			No. of subjects	Drug assayed	Mean value		
Route	Drug[a]	(mg)			AUC (μg · h/ml)	Peak concn (μg/ml)	Recovery (% of dose)
30-min i.v.	SUL	500	6	SUL	34.4	23.3	72.9
	SUL	500	6	SUL	36.0	28.4	77.8
	PG	500		PG	18.6	22.5	80.8
	PG	500	6	PG	16.0	16.6	86.1
i.m.	SUL	500	6	SUL	35.5	14.2	76.5
	SUL	500	6	SUL	43.1	11.1	97.4
	PG	500		PG	14.6[b]	4.68	76.9
	PG	500	6	PG	18.2[b]	4.62	68.1
i.v. bolus	SUL	500	6	SUL	29.6	31.8	109.5
	SUL	500	6	SUL	36.6	30.4	89.2
	AMP	500		AMP	24.7	23.2	59.9
	AMP	500	6	AMP	30.3	27.6	64.2
1-h i.v., dose 1	CF	2,000	24	CF	381.0	176.0	17.8
	CF	2,000	24	CF	378.0	168.0	15.5
	SUL	1,000		SUL	53.5	38.3	38.9
1-h i.v., t.i.d.,[c] day 5	CF	2,000	24	CF	403.0	159.0	18.3
	CF	2,000	24	CF	390.0	159.0	15.9
	SUL	1,000		SUL	50.2	35.2	46.8
i.v. bolus, dose 1	CF	2,000	24	CF	449.0	266.0	24.1
	CF	2,000	24	CF	439.0	254.0[d]	25.2
	SUL	1,000		SUL	69.9	76.0	101.0
i.v. bolus, t.i.d., day 5	CF	2,000	24	CF	438	276	15.9
	CF	2,000	24	CF	461	282[d]	18.6
	SUL	1,000		SUL	67.3	77.6	92.4

[a] SUL, Sulbactam; PG, penicillin G; AMP, ampicillin; CF, cefoperazone. Braces indicate coadministration of indicated dose.

[b,d] These pairs of values were different (paired t test, two-tailed, $P < 0.05$).

[c] t.i.d., Three doses per day.

azone, suggesting that coadministration of sulbactam will not affect the usual dosing regimens for these β-lactam antibiotics.

Sulbactam appears to equilibrate rapidly between the serum and the peripheral compartment. The apparent volume of distribution of the central compartment of 9 to 16 liters is in the range of total extracellular fluid in humans (approximately 15 liters) and suggests that sulbactam is widely distributed in the extracellular fluid. Furthermore, the total apparent volume of distribution of between 19 and 28 liters is over half that of the total body fluid, approximately 40 liters in a 70-kg human, suggesting that sulbactam may be widely distributed into the tissues.

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