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Pharmacokinetics of Ampicillin-Sulbactam in Healthy Elderly and Young Volunteers

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The pharmacokinetics of ampicillin-sulbactam in elderly subjects (65 to 85 years; group 3, $n = 8$), compared with those in middle-aged (41 to 64 years; group 2, $n = 8$) and younger (20 to 40 years; group 1, $n = 8$) subjects, were investigated. A single 2-g dose of ampicillin combined with 1 g of sulbactam in 60 ml of intravenous solution was administered to each subject over a 30-min period. Blood and urine samples were taken at baseline and serially over an 8.5-h period following the infusion. Ampicillin and sulbactam concentrations were assayed by high-performance liquid chromatography on a reversed-phase C-8 column. The mean levels in serum of both ampicillin and sulbactam were significantly higher for samples from group 3: for ampicillin from 1 through 8.5 h, and for sulbactam for the same time interval except at 5.5 h ($P \leq 0.05$). The mean urinary excretion of both ampicillin and sulbactam was lowest, and urinary concentrations were highest in group 3. The areas under the serum drug concentration-time curve, the half-lives, and the maximum concentrations in serum were greatest, while the total clearance was lowest, for group 3 for both ampicillin and sulbactam. These results are consistent with a prolongation of antimicrobial activity of ampicillin-sulbactam in the elderly compared with that in younger subjects.

Demographic trends over the past 50 years reveal that the elderly (over age 65) are a rapidly growing segment of the population (16). Physiologic changes in the elderly compared with younger populations have been noted (9). Age-related differences in absorption, excretion, metabolism, and distribution make it necessary to study new agents in elderly populations. In the elderly, there is an increase in body fat, a decrease in body water, and an age-related decline in renal function. Other factors that may impact on the pharmacokinetics of antimicrobial agents include serum albumin and protein binding. A guideline for the study of drugs in the elderly has recently been released (3).

Prior studies of the pharmacokinetics of antibiotics in the elderly have been recently reviewed in two publications (8, 11). Analysis of the data for beta-lactam antibiotics reveals that, in the elderly, the maximum concentrations in serum, (C_{max}), area under the concentration-time curve (AUC), and half-life ($t_{1/2\beta}$) are increased, whereas total clearance (CL_T) and renal clearance (CL_R) are decreased, compared with what is observed for younger populations.

Ampicillin-sulbactam is an antimicrobial agent that has potential for use in elderly populations in the treatment of intraabdominal, pelvic, skin/soft tissue, and pulmonary infections (1). Sulbactam is a beta-lactam agent that acts as an irreversible inhibitor of beta-lactamase activity by combining with the enzyme and rendering it inactive. The pharmacokinetics of ampicillin-sulbactam in the elderly have not been extensively studied (5, 14). In this study, we examined the pharmacokinetic parameters of ampicillin-sulbactam in three healthy groups: elderly, middle-aged, and younger subjects.

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MATERIALS AND METHODS

Three groups, each composed of eight healthy volunteers, were subjects for this study: group 1, 20 to 40 years (mean, 30 years ± 6.5 years); group 2, 41 to 64 years (mean, 51 years ± 7.3 years); and group 3, 65 to 85 years (mean, 73.9 years ± 5.1 years). The study was approved by the Institutional Review Board at the Mount Sinai School of Medicine, New York, New York. Written informed consent was obtained from all volunteers. Prestudy physical examinations, blood chemistries, blood cell counts, and urinalyses were performed on all participants. Subjects were excluded if they were allergic to penicillin(s), had a history of alcohol or drug abuse, were taking antibacterial drugs or other investigational drugs within 14 days prior to the study, were pregnant, were lactating, or had evidence of cardiovascular, hepatic, hematologic, or gastrointestinal diseases. Volunteers with a calculated creatinine clearance of <25 ml/min were excluded.

Each subject was given a single 60-ml intravenous infusion of ampicillin-sulbactam containing 2 g of ampicillin and 1 g of sulbactam delivered over a 30-min period. Blood samples were collected at the following times: 0 (prior to the start of infusion), 0.25, 0.5 (end of infusion), 1, 1.5, 2, 2.5, 3.5, 5.5, and 8.5 h. Urine samples were collected prior to dosing and at the following time intervals: 0 to 2, 2 to 4, 4 to 6, and 6 to 8.5 h. All specimens were immediately centrifuged, separated, and frozen at −70°C. The specimens were later assayed by high-performance liquid chromatography (HPLC) on a reversed-phase C-8 column. Assays of serum and urine were performed by Pfizer Research Labs, Groton, Conn. Sulbactam and ampicillin were analyzed after dilution with 5 mM sodium citrate buffer at pH 5.8. The chromatographic conditions indicated above for the serum analysis were used for urine analysis. Urine was analyzed after dilution with 5 mM sodium citrate buffer at pH 5.8. Sulbactam, ampicillin, and the internal standard cefazolin were isolated from the

TABLE 1. Demographics[a]

Group	CL_{CR}[b] (ml/min)	Creatinine (mg/liter)	Serum albumin (g/dl)	Height (cm)	Weight (kg)	Age (yr)
1	101.63 (21.13)	1.05 (0.09)	4.36 (0.28)	68.44 (2.47)	72.56 (15.20)	30.00 (6.50)
2	91.32 (14.62)	1.00 (0.23)	4.04 (0.21)	67.06 (3.59)	77.47 (9.21)	51.00 (7.35)
3	61.52 (15.13)	1.08 (0.20)	4.13 (0.29)	67.63 (3.62)	73.58 (17.76)	73.88 (5.11)

[a] Values in parentheses are standard deviations. P values for CL_{CR} are 0.01 between groups 1 and 3 and groups 2 and 3; other P values are not significant.
[b] CL_{CR}, Creatinine clearance.

serum matrix after the precipitation of serum proteins with acetonitrile. The isolate was analyzed by HPLC on a reversed-phase C-8 column. The mobile phase consisted of a mixture of trisodium tetrabutylammonium phosphate and acetonitrile in water at pH 6.8. The column effluent entered a postcolumn reactor system, where it was mixed with two solutions (1.5 N NaOH in methanol-water and a dilute solution of mercuric chloride and EDTA in methanol-water). A postcolumn degradation reaction occurred in the mixing coil of the reactor system. Detection of the degraded sulbactam and ampicillin moieties was by UV absorbance at 290 nm.

Specificity. On 3 consecutive days, a sample of pooled control serum was extracted and analyzed according to the method presented above. The chromatograms were examined for potentially interfering peaks in or around the retention times of sulbactam, ampicillin, and cefazolin. The pooled control serum chromatograms were found to have minor peaks near the retention times of sulbactam and ampicillin. However, those peaks did not appear to significantly interfere with the analysis of either moiety.

Linearity. On 3 consecutive days, the HPLC system response (peak height ratios) to sulbactam and ampicillin was tested; for sulbactam, the response was found to be linear in the range of 0.5 to greater than 50 μg/ml, and for ampicillin it was linear in the range of 1 to 100 μg/ml. On the fourth day, an extended calibration curve was prepared. The HPLC system response to sulbactam and ampicillin was against tested; for sulbactam, it was found to be linear in the range of 0.5 to greater than 75 μg/ml, and for ampicillin it was linear in the range of 1 to greater than 150 μg/ml. The peak height ratios of sulbactam/internal standard and ampicillin/internal standard were determined. Calibration curves were prepared on the basis of peak height ratios versus the concentrations of sulbactam and ampicillin in the serum matrix. A linear regression analysis of the data was used to calculate slope, intercept, and correlation coefficient for both sulbactam and ampicillin.

Accuracy and precision of the assay. The accuracy and precision (short term) of the assay were evaluated by preparing extracts of pooled control serum fortified to contain standard low-spike, mid-spike, and high-spike concentrations of sulbactam and ampicillin. For sulbactam, the concentrations (in micrograms per milliliter) and relative standard deviations were as follows: low spike, 0.51 and 21.5%; mid spike, 20.4 and 1.7%; high spike, 51.0 and 1.1%. For ampicillin, the concentrations (same units) and relative standard deviations were as follows: low spike, 1.0 and 6.0%; mid spike, 39.9 and 3.5%; high spike, 99.7 and 3.6%. Each sample was analyzed in duplicate on 3 consecutive days. Average concentrations of each moiety and relative standard deviations were then calculated for each sample. The average low-spike, mid-spike, and high-spike concentrations of sulbactam and ampicillin were found to be 0.65 and 1.4 μg/ml, 20.5 and 40.5 μg/ml, and 53.0 and 106 μg/ml, respectively. Although the average measured concentrations for sulbactam and ampicillin in the low and high spikes were slightly greater than expected, they were considered acceptable for these purposes.

Data analysis. The AUC for ampicillin and sulbactam from time 0 to 12.0 h (AUC_{0-12}) and from 0 to infinity (AUC), the C_{max}, and the time to reach maximum drug concentration in serum (T_{max}) were determined for each subject. AUC_{0-12} was calculated by the trapezoidal method. AUC was the sum of AUC_{0-12} and the residual area from 12.0 h to infinity; the residual area was calculated as the estimated concentration at 12.0 h divided by the elimination phase rate constant (beta). Beta for each subject was estimated from the slope of the log-linear segment of the serum drug concentration-time curve. Half-lives were calculated as iteratively reweighted least-squares estimates from nonlinear regressions by using a linear, two-compartment model in PCNONLIN, the half-lives, and their means and standard deviations (Table 3). Total body clearance (CL_T) was determined as dose per AUC, and volume of distribution (V) was calculated from the formula total body clearance/beta. The total amount of ampicillin and sulbactam recovered from urine from 0 to 8.5 h was also determined. Renal clearance was calculated as Dex/AUC, where Dex is the amount of drug excreted unchanged in the urine.

Bioequivalence of ampicillin and sulbactam were compared following the administration of each drug in combination with the other drug. Bioequivalence was tested by using the two one-sided tests procedure for AUC and C_{max}.

Statistical analysis. Differences in patient characteristics and pharmacokinetic parameters were compared across the three age groups by using two-tailed tests of significance. Analysis of variance was used to measure differences between groups. Significance was defined as $P \leq 0.05$. All statistical analyses were performed by using statistical package social services/PC+, version 3.1.

RESULTS

The demographic data for the three subject groups is shown in Table 1. There were no significant differences between the three age groups in mean height, weight, albumin, or serum creatinine. The mean calculated creatinine clearance (CL_{CR}) (2) was least for the elderly group 3 ($P \leq 0.0003$). Mean creatinine or calculated clearance was significantly different between groups 1 and 3 ($P \leq 0.01$) and between groups 2 and 3 ($P \leq 0.01$).

The mean levels in serum for both ampicillin and sulbactam are shown on Table 2. For time periods 0, 0.25, and 0.50 h, there were no differences among the three groups for ampicillin and sulbactam. Throughout the rest of the serial determinations, the levels for group 3 for each time period for ampicillin were greater than for groups 1 and 2 ($P \leq 0.01$

TABLE 2. Drug levels in serum

Drug and time (h)	Level in serum (mg/l ± SD)			P
	Group 1	Group 2	Group 3	
Sulbactam				
0.25	34.95 ± 12.01	33.19 ± 5.53	38.59 ± 16.57	NS
0.5	52.21 ± 14.76	41.60 ± 8.54	59.09 ± 19.92	NS
1	24.95 ± 3.33	27.49 ± 2.48	34.51 ± 9.90	≦0.05
1.5	17.16 ± 5.89	15.94 ± 4.12	24.43 ± 7.47	≦0.05
2	10.46 ± 1.64	12.59 ± 2.33	19.00 ± 6.17	≦0.01
2.5	6.93 ± 1.30	8.33 ± 1.80	14.41 ± 4.26	≦0.01
3.5	3.46 ± 0.91	4.89 ± 1.70	8.94 ± 2.61	≦0.01
5.5	1.01 ± 0.55	1.46 ± 0.66	7.81 ± 10.80	NS
8.5	0.14 ± 0.26	0.49 ± 0.53	1.21 ± 0.48	≦0.01
Ampicillin				
0.25	66.76 ± 20.60	64.61 ± 10.73	74.20 ± 30.83	NS
0.5	99.79 ± 26.94	80.67 ± 17.31	112.39 ± 34.28	NS
1	43.25 ± 4.94	46.77 ± 5.74	60.44 ± 18.03	≦0.05
1.5	28.44 ± 10.59	26.30 ± 7.14	40.30 ± 12.98	≦0.05
2	15.96 ± 1.70	19.69 ± 3.73	29.93 ± 10.32	≦0.01
2.5	10.30 ± 1.96	12.72 ± 2.67	21.86 ± 7.35	≦0.01
3.5	5.29 ± 1.59	7.26 ± 2.83	12.71 ± 4.72	≦0.01
5.5	1.60 ± 0.55	1.80 ± 1.35	5.38 ± 2.10	≦0.01
8.5	0.25 ± 0.46	0.50 ± 0.91	1.50 ± 0.93	≦0.05

to 0.05). For sulbactam, the levels for group 3 for all time periods except at 5.5 h were statistically greater ($P \leqq 0.05$).

The urinary excretion of ampicillin was 1,228 mg for group 1, 1,029 mg for group 2, and 793.4 mg for group 3 (P = not significant [NS]). Urinary excretion for sulbactam was 713.8 mg for group 1, 577.6 mg for group 2, and 446.9 mg for group 3 (P = NS).

In contrast, the mean urinary concentration of ampicillin was highest for group 3 (177.6 μg/ml, versus 91.1 μg/ml for group 2 and 44.3 μg/ml for group 1 [P = NS]). The urinary concentration of sulbactam was highest for group 3 (103.7 μg/ml, versus 56.9 μg/ml for group 2 and 30.0 μg/ml for group 1 [P = NS]).

Pharmacokinetic analysis. The $t_{1/2\beta}$ for ampicillin was greatest for group 3 (1.35 h) and decreased from group 2 to group 1 (P = 0.0002) (Table 3). For sulbactam, the results were similar: the highest $t_{1/2\beta}$ (1.58 h) was for group 3 (P = 0.0001). The AUC for ampicillin was greatest for group 3 (182.2 μg/ml ± 57.8 μg/ml [standard deviation]) and lowest for group 1 ($P \leqq 0.004$). The AUC for both ampicillin and sulbactam was significantly different between groups 1 and 3 (ampicillin, $P \leqq 0.05$; sulbactam, $P \leqq 0.01$) and between groups 2 and 3 (ampicillin, $P \leqq 0.05$; sulbactam, $P \leqq 0.01$). The C_{max} was greatest for ampicillin (112.4 μg/ml ± 34.3 μg/ml) for group 3 (P = NS). For sulbactam, the C_{max} was also greatest for group 3 (59.1 μg/ml ± 19.9 μg/ml) (P = NS). The CL_T of ampicillin and sulbactam varied inversely with age. The CL_T of ampicillin and sulbactam was significantly different between groups 1 and 3 ($P \leqq 0.01$) and between groups 2 and 3 ($P \leqq 0.05$). CL_R of both ampicillin and sulbactam was significantly different between groups 1 and 3 ($P \leqq 0.01$). Group 3 had the lowest V for ampicillin and sulbactam, but it was not statistically different from that of the other age groups.

Correlations. Age was negatively correlated with ampicillin CL_T ($r = -0.669$, $P \leqq 0.001$), sulbactam CL_T ($r = -0.722$, $P \leqq 0.001$), ampicillin CL_R ($r = -0.579$, $P \leqq 0.01$), sulbactam CL_R ($r = -0.632$, $P \leqq 0.01$), and CL_{CR} ($r = -0.732$, $P \leqq 0.001$). Ampicillin CL_T was positively correlated with sulbactam CL_T ($r = 0.967$, $P \leqq 0.001$). CL_{CR} was positively correlated with ampicillin CL_T ($r = 0.766$, $P \leqq 0.001$), sulbactam CL_T ($r = 0.810$, $P \leqq 0.001$), ampicillin CL_R ($r = 0.596$, $P \leqq 0.01$), and sulbactam CL_R ($r = 0.662$, $P \leqq 0.001$).

Adverse effects. There were two patients with adverse effects. Vomiting and a migraine headache occurred in one volunteer, and the other had pain at the site of the drug infusion. The symptoms were reversible and of short duration. There were no changes in laboratory parameters following drug administration in any of the three groups.

DISCUSSION

Analysis of the demographic data revealed no differences among the three groups; albumin levels were lower among the older patients, but not significantly. It has been shown that healthy elderly volunteers may have lower serum albumin levels than members of a younger age group (10). While this may affect the level of free drug with those agents which are highly protein bound, we would not expect any changes with either ampicillin, which is 18% protein bound, or with sulbactam, which is 38% protein bound (15). The calculated CL_{CR} was significantly lower for group 3. This is not unexpected, since renal function is known to decrease with age (11, 14).

In our study, the mean levels in serum of both ampicillin

TABLE 3. Pharmacokinetic parameters[a]

Drug and group	C_{max} (μg/ml)	V	$t_{1/2\beta}$ (h)	CL (ml/min)	AUC (mg/h/liter)	Urinary concn (μg/ml)	Urinary excretion (mg/0-8.5 h) (%)	CL_R (ml/min)
Ampicillin								
1	99.78 ± 26.94	31.4 ± 13.12	0.86 ± 0.15	289.15 ± 50.52	118.44 ± 20.99	44.31 ± 36.19	1228.02 ± 421.87 (61)	172.52 ± 61.55
2	82.44 ± 15.42	31.29 ± 8.72	1.09 ± 0.18	281.29 ± 33.64	120.13 ± 16.11	91.10 ± 64.95	1029.00 ± 424.94 (51)	143.82 ± 63.55
3	112.40 ± 34.30	26.33 ± 8.75	1.35 ± 0.29	198.02 ± 55.60	182.15 ± 57.79	177.56 ± 157.96	793.43 ± 398.46 (40)	71.54 ± 28.30
P	NS	NS	0.0002	≦0.01 (G 1, 3), ≦0.01 (G 2, 3)	≦0.05 (G 1, 2), ≦0.05 (G 1, 3)	NS	NS	≦0.1 (G 1, 3), ≦0.5 (G 2, 3)
Sulbactam								
1	52.21 ± 14.76	24.98 ± 4.66	0.93 ± 0.15	254.96 ± 53.04	67.95 ± 14.41	29.98 ± 25.15	713.75 ± 250.62 (71)	176.85 ± 66.73
2	42.52 ± 7.40	29.76 ± 10.01	1.19 ± 0.17	236.16 ± 26.98	71.46 ± 9.13	56.86 ± 38.88	577.64 ± 229.71 (58)	135.81 ± 57.60
3	59.10 ± 19.90	23.54 ± 7.71	1.58 ± 0.29	162.69 ± 46.21	110.37 ± 32.70	103.70 ± 80.97	446.93 ± 219.62 (45)	65.94 ± 24.55
P	NS	NS	0.0001	≦0.01 (G 1, 3), ≦0.05 (G 2, 3)	≦0.01 (G 1, 3), ≦0.01 (G 1, 3)	NS	NS	≦0.1 (G 1,3), ≦0.5 (G 2, 3)

[a] Values are means ± standard deviations. For P values, G is for group number; e.g., G 1, 2 indicates value for groups 1 and 2.

and sulbactam were higher for all time samples in the elderly than in the younger groups. For most of these periods, there was a statistically significant difference in antibiotic levels. This is similar to the findings of another reported study (14). The data reveal that when 2 g of ampicillin and 1 g of sulbactam are given to three groups of volunteers, the ratios of ampicillin to sulbactam (approximately 2:1) are maintained during the time period of the study. In vitro data by Retsema et al. revealed that organisms that are normally resistant to ampicillin are rendered sensitive to ampicillin-sulbactam at a ratio of 2:1 or 1:1 (13). This suggests that among both the elderly and the young, levels in serum would be sufficient to inhibit more than 90% of strains of pathogenic organisms (13).

In our study, the mean urinary excretion of both ampicillin and sulbactam was lowest for group 3; this is similar to rates of recovery in urine previously reported (14). The mean urinary concentration for both ampicillin and sulbactam was highest for the elderly group; this was not reported in the other study. These levels for ampicillin and sulbactam would exceed the MIC against a sensitive organism for 8 to 12 h.

With both ampicillin and sulbactam, the AUC was greatest for the elderly group (group 3) ($P = 0.05$ and 0.01, respectively). The CL_T of ampicillin and sulbactam was inversely proportional to age. The $t_{1/2\beta}$ for both ampicillin ($P = 0.0002$) and sulbactam ($P = 0.0001$) and the C_{max} were also greatest for group 3 (P = NS). Our data is comparable to that previously reported (14); however, in that study, the $t_{1/2\beta}$ for the subjects was greater. This observation may be explained by the greater age of their group and age-associated decline in renal function. In both studies, V was not different between the young and old volunteers. However, in our study, V was lowest for group 3 for both ampicillin and sulbactam. In a prior study on cefoperazone in elderly volunteers, similar findings were observed (9). For water-soluble drugs (polar compounds), this is not unexpected, since in the elderly, a decreased lean body mass coupled with a decrease in total body water is usually associated with a decrease in V (11).

Our data reveal a prolongation of antimicrobial activity in elderly subjects compared with younger subjects, as manifested by an increase in C_{max}, higher sustained concentrations throughout the dosing intervals, increased AUC, and decreased CL_T. This is consistent with prior studies that have correlated these pharmacokinetic parameters with antibacterial activity (4). Presumably, these changes would be further magnified in infected elderly patients. Studies with ceftazidime and cefotaxime have revealed similar changes (6, 7, 12).

Prior investigations have suggested that middle-aged adults should be studied (14) to determine the impact of age and CL_{CR} on pharmacokinetic parameters. While we noted differences in CL_{CR} between the elderly group and both younger adult groups, there were no differences in CL_{CR} between middle-aged and younger adults (P = NS). Similarly, our study also revealed no differences between middle-aged and younger adults for any of the pharmacokinetic parameters examined. This suggests that the pharmacokinetic parameters observed are a function of CL_{CR}, not of age. However, further studies with elderly volunteers with higher CL_{CR} values are needed to confirm this.

Analysis of covariance revealed that, when creatinine clearance was used as the covariate, the age group did not add any significant effect for either sulbactam clearance ($F_{(1, 19)} = 17.93$, $P = 0.001$) or ampicillin clearance ($F_{(1, 19)} = 12.62$, $P = 0.002$). The multiple R squared was 0.439 for sulbactam and 0.355 for ampicillin. Because of the high intercorrelation between age and creatinine clearance, age itself does not contribute significantly when creatinine clearance is taken into account.

Summary. Our data revealed that for the elderly (group 3), prolongation of the ampicillin and sulbactam antimicrobial activity was due to an increase in the AUC, $t_{1/2\beta}$, C_{max}, prolonged serum levels at most time intervals, and decreased CL_T and CL_R. On the basis of this analysis, treatment schedules at increased intervals warrant further investigation in a clinical setting.

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