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Comparative Pharmacokinetics and Tissue Penetration of Sulbactam and Ampicillin After Concurrent Intravenous Administration

R. M. BROWN, R. WISE,* J. M. ANDREWS, AND J. HANCOX

Department of Medical Microbiology, Dudley Road Hospital, Birmingham, United Kingdom

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A combination of 500 mg each of sulbactam and ampicillin was administered intravenously into six healthy male volunteers, and subsequent serum and blister fluid levels were measured. Both drugs had similar serum half-lives of about 1 h. The concentrations of sulbactam in serum and blister fluid were about 1.5 times those of ampicillin, and appeared to be pharmacokinetically well matched when administered in equal doses.

Sulbactam (penicillanic acid sulfone), a β-lactamase inhibitor with very limited antibacterial activity, has properties similar to clavulanic acid (6). Although less active than the latter compound sulbactam clearly enhances the activity of penicillin G, ampicillin, and carbenicillin against certain β-lactamase-producing bacteria both in vitro and in vivo. Because of its greater stability in solution, sulbactam may have an advantage over clavulanic acid as a companion drug to various β-lactams (2, 6).

In this study, the pharmacokinetics of sulbactam and ampicillin were investigated in healthy volunteers after intravenous administration of the two drugs simultaneously. The tissue penetration in skin blister fluid was also measured.

MATERIALS AND METHODS

The subjects were six healthy male volunteers between the ages of 25 and 39 years. They had normal body builds with mean weights and heights of 71.67 kg (range, 63.6 to 74.5 kg) and 1.78 m (range, 1.70 to 1.83 m), respectively. At the time of the experiment, no subject was receiving any medication. Written informed consent was obtained. There was no history of atopy, known previous allergy to β-lactam compounds, diabetes mellitus, glycogen storage disease, hepatic or renal disease, or gastrointestinal disease. Hepatic and renal functions were normal as assessed by hepatic enzymes, prothrombin time, and urea and creatinine estimations. Full haematological profiles were also normal.

On the evening before the experiment, two 1- by 1-cm 0.2% cantharides plasters were taped to the front of the forearm of each volunteer. On the morning of the experiment, the volunteers ate a light breakfast. Blood samples were taken for repeat laboratory tests and predose base-line assays, and the volunteers emptied their urinary bladders. An intravenous cannula was inserted into a forearm vein and was kept patent by a small flushing dose of heparinized saline (100 U/ml). A combination of 500 mg of the sodium salt of sulbactam dissolved in sterile water and 500 mg of ampicillin dissolved in sterile water was injected intravenously in a total volume of 8 ml into the contralateral arm (the arm with the blisters) over 2 to 4 min.

Blood samples were taken from the cannula (after discarding the first 2 ml) at 10, 20, 30, 45, 60 and 90 min, and 2, 3, 4, 5, 6, and 8 h after the dose of sulbactam and ampicillin. Urine samples were collected at 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h after the dosage. The volumes were measured, and the samples were taken for assay. The cantharides-induced blisters were sampled at 0.5, 1, 2, 3, 4, 5, 6, and 8 h. In each volunteer, one blister was sampled until empty. The fluid removed from the blisters in approximately equal volumes was placed on four preweighed, sterile, 6-mm assay disks (two each for ampicillin and sulbactam determinations), which were reweighed to measure the amount of fluid on the disks.

All assays were performed within 2 h of sample collection. The assays for sulbactam were performed by a routine agar plate diffusion technique with *Escherichia coli* 273 (Pfizer Inc., New York, N.Y.) as the indicator organism and Oxoid (Basingstoke, U.K.) brain heart infusion agar (with ampicillin incorporated at a final concentration of 50 μg/ml) as the antibiotic medium. This method is similar to that described for clavulanic acid (1). Serum standards were prepared in Flow (Flow Laboratories, Inc., McLean, Va.) human serum and urine standards were prepared in phosphate-buffered saline (pH 7.0) in which the urine samples were diluted when necessary. Blister fluid sample standards made in 70% Flow human serum, so as to simulate the protein content of the blister fluid (7), were applied in triplicate on identical disks in the same volume as that calculated by weighing on the test disks. The assays for ampicillin were performed by a routine agar plate diffusion technique with *Sarcina lutea* 9341 as the indicator organism and Penassay 2 as the antibiotic medium (Difco Laboratories, Detroit, Mich.). The ampicillin assay was not interfered with by concentrations of sulbactam up to 60 μg/ml. Serum standards were prepared in horse serum (having previously been shown to be equivalent in this assay to human serum), and urine standards were prepared in

TABLE 1. Mean concentrations of sulbactam and ampicillin in serum and blister fluid[a]

Time (h) after i.v. injection[b]	Sulbactam concn (μg/ml)		Ampicillin concn (μg/ml)	
	Serum	Fluid	Serum	Fluid
0.166	43.2 ± 12.9		30.3 ± 5.4	
0.33	28.1 ± 5.8		20.4 ± 2.4	
0.5	19.8 ± 2.9	19.2 ± 9.8	14.1 ± 1.9	8.1 ± 3.1
0.75	14.8 ± 1.2		10.0 ± 1.8	
1.0	12.5 ± 1.9	13.7 ± 4.1	8.2 ± 2.8	7.9 ± 2.9
1.5	6.9 ± 2.2		5.0 ± 1.0	
2.0	5.5 ± 2.6	9.9 ± 2.2	2.8 ± 0.7	5.7 ± 1.1
3.0	2.3 ± 0.9	5.3 ± 2.3	1.5 ± 0.6	4.6 ± 1.7
4.0	1.6 ± 0.6	3.2 ± 1.3	0.9 ± 0.4	2.0 ± 0.8
5.0	ND[c]	ND	ND	1.1 ± 0.5
6.0	ND	ND	ND	ND
8.0	ND	ND	ND	ND

[a] Values are means ± standard deviation.
[b] i.v., Intravenous.
[c] ND, Not detectable.

phosphate-buffered saline (pH 7.0) in which the urine samples were diluted when necessary. Blister fluid standards for ampicillin assay were made in 70% horse serum and applied in triplicate on identical disks in the same volume as that calculated by weighing on the test disks. Internal controls of predicted levels were included in the assay containing both ampicillin and sulbactam, and no interference of one agent by the other was noted. The pharmacokinetic analysis of the individual data was performed by graphic methods (4).

RESULTS

The levels of each antibiotic at various times are shown in Table 1, and the pharmacokinetic data are shown in Table 2.

The serum levels of both drugs showed a rapid initial distribution phase followed by a gradual steady decline, suggesting that the data fits a two-compartment open model.

The mean serum levels of the compounds 30 min after dosing were approximately 20 μg/ml for sulbactam and 14 μg/ml for ampicillin and were greater than 2 and 1 μg/ml for sulbactam and ampicillin, respectively, for 3 h. No detectable levels were found at 5 h and after. Generally, the serum levels of sulbactam were 1.5 times those of ampicillin. Since one volunteer failed to produce adequate blisters, the blister level data were derived from five subjects. Both drugs penetrated blister fluid rapidly. The sulbactam levels were approximately equal in serum and blister fluid at 0.5 h. The ampicillin levels in serum and blister fluid were approximately equal at 1 h. The rate of elimination of both drugs from blister fluid was similar to that from serum. The areas under the concentration-time curves (AUCs) for blister fluid for both drugs were not statistically different from the serum values. Previous studies (7) have shown that the blister fluid is similar in composition to a superficial burn (5). The 1.5:1 ratio of sulbactam to ampicillin was maintained in blister fluid as it was in serum.

The mean value of the initial concentration of sulbactam (C_0) was almost twice as high as that of ampicillin. The mean values of first-order rate constant for the terminal elimination phase of the drug by all routes were similar for sulbactam and ampicillin. Higher values of AUC were obtained for sulbactam than ampicillin, their

TABLE 2. Pharmacokinetics of sulbactam and ampicillin[a]

Drug	C_0 (μg/ml)	β (h^{-1})	$t_{1/2\beta}$ (h)	$AUC_{0-\infty}$ (μg/ml.h)	Drug recovery in urine in 24 h (% of dose)	Cl_p (ml/min)	Cl_r (ml/min)	V_{cc} (liters)	AUC in blister (μg/ml.h)
Sulbactam	93.5 ±62.02	0.708 ±0.08	0.99 ±0.111	43.67 ±12.1	85.15 ±21.34	200.5 ±42.89	169.44 ±54.5	7.34 ±3.73	42.115 ±5.41
Ampicillin	49.6 ±19.1	0.7117 ±0.12	1.04 ±0.189	28.37 ±11.37	83.22 ±11.08	296.15 ±28.6	261.2 ±46.9	11.22 ±3.76	26.553 ±2.97

[a] Values are means ± standard deviation. Abbreviations: C_0, initial fictive concentration of each drug; β, first-order rate constant for the terminal elimination phase of the drug by all routes; $t_{1/2\beta}$, serum half-life of each drug during the elimination phase; $AUC_{0-\infty}$, area under the curve to zero time to infinity; Cl_p, plasma clearance; Cl_r, renal clearance; and V_{cc}, apparent distribution volume of each drug in the central compartment.

mean values being 43.67 and 28.37 μg/ml. h, respectively. Sulbactam and ampicillin had a similar serum half-life during the elimination phase: 0.99 and 1.04 h, respectively. The mean value of the apparent distribution volume of the drug in the central compartment for ampicillin was greater than that of sulbactam. The total clearance of the drug was calculated from dose at $AUC_{0-\infty}$, and the renal clearance was calculated from the drug recovery in urine at $AUC_{0-\infty}$. The clearance values for ampicillin were greater than sulbactam. Approximately 85% of both drugs was excreted in urine by 24 h.

There were no side effects experienced by any of the volunteers after administration of the two drugs. Repeat laboratory tests (biochemical and hematological) taken 24 h after administration of the drugs remained normal in all six volunteers.

DISCUSSION

In choosing a β-lactam to accompany a β-lactamase inhibitor, it is necessary to ensure that the in vitro activity and the pharmacological properties are such that synergistic interaction occurs in vivo. For ampicillin-resistant strains of *Bacteroides fragilis, Staphylococcus aureus*, and *E. coli*, it was found that the optimum ratio of ampicillin to sulbactam was about 1:2 (6). In this study, when equal doses of sulbactam and ampicillin were administered, the serum levels achieved were close to this ratio, i.e., the sulbactam levels were 1.5 times the levels of ampicillin. In other respects, the pharmacokinetics of the two compounds were very similar. The mean terminal (β-phase) half-lives of each agent were each about 1 h, so that the ratio of the two agents was maintained throughout each dosing interval.

The pharmacokinetics of ampicillin corresponded well to those previously described (3), except that the total and renal clearance was somewhat lower in this study. This may be because of the different methods of calculating the clearances or because sulbactam competed with ampicillin for tubular secretion. On this point, specific studies should be undertaken by administering each drug separately.

The apparent distribution volume of ampicillin in the central compartment was greater than that of sulbactam, but both corresponded to the volume of the vascular compartment plus the well-perfused organs. The renal clearance of ampicillin was approximately 50% greater than that of sulbactam, but the total renal excretion of each drug was similar. This difference can probably be explained by the larger distribution volume of ampicillin and the considerable intersubject variation of the clearances themselves.

The final formulation of sulbactam and ampicillin has not yet been decided. Because sulbactam and ampicillin appear to be pharmacokinetically well matched in equal doses, our data suggest that 0.5 or 1 g of each at 6-h intervals would be applicable in patients with normal renal function.

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LITERATURE CITED

1. **Edberg, S. C., and L. D. Sabath.** 1980. Determination of antibiotic levels in body fluids. *In* Antibiotics in laboratory medicine. The Williams & Wilkins Co., Baltimore, Md.
2. **English, A. R., J. A. Retsema, A. E. Girard, J. E. Lynch, and W. E. Barth.** 1978. CP-45,899, a beta-lactamase inhibitor that extends the antibacterial spectrum of beta-lactams: initial bacteriological characterization. Antimicrob. Agents Chemother. **14**:414–419.
3. **Gasko, J. J., G. P. Lewis, and G. W. Schmitt.** 1973. Ampicillin and hetacillin pharmacokinetics in normal and nephric subjects. Clin. Pharmacol. Ther. **14**:90–99.
4. **Greenblatt, D. J., and J. Koch-Weser.** 1975. Clinical pharmacokinetics. N. Engl. J. Med. **297**:702–705.
5. **Sevitt, S.** 1957. *In* Pathology and therapeutic applications 37–38. Butterworth & Co. Ltd., London.
6. **Wise, R., J. M. Andrews, and K. A. Bedford.** 1980. Clavulanic acid and CP-45,899: a comparison of their *in vitro* activity in combination with penicillins. J. Antimicrob. Chemother. **6**:197–206.
7. **Wise, R., A. P. Gillett, B. Cadge, S. R. Durham, and S. Baker.** 1980. The influence of protein binding upon tissue fluid levels of six β-lactam antibiotics. J. Infect. Dis. **142**:77–82.