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Pharmacokinetics and Tissue Penetration of Ticarcillin Combined with Clavulanic Acid

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A combination of 3 g of ticarcillin and 200 mg of clavulanic acid was administered intravenously to six healthy male volunteers, after which the concentrations of these agents in serum and blister fluid were measured. The ratio of the two drugs in serum varied from 15:1 (ticarcillin-clavulanic acid) at the time of administration to 28:1 at 30 min and 62:1 at 5 h after injection. Both agents penetrated blister fluid rapidly, the ratio being 33:1 at 1 h and 66:1 at 3 h. The elimination rates of these agents were different, but for each compound they were similar in serum and blister fluid.

Ticarcillin, a wide-spectrum penicillin (7), is susceptible to a number of β-lactamases, including the plasmid-mediated enzymes found in the *Enterobacteriaceae* (and other genera) such as the Richmond and Sykes group III (6) and the β-lactamases of *Bacteroides fragilis* and *Staphylococcus aureus*. Clavulanic acid is a potent inhibitor of many such enzymes (5, 9). In vitro studies (1, 4) have shown that in combination these agents are highly synergistic. Preliminary animal studies on a combination of ticarcillin and clavulanic acid in a ratio of 15:1 suggest that these agents are pharmacokineticaly well matched (L. Mizen and G. Woodnut, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami, Fla., abstr. no. 294, 1982.), and human volunteer studies of a 5:1 ratio confirmed this (D. H. Staniforth, D. Jackson, and R. Horton, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr, no. 443, 1981.). In the present study, the pharmacokinetics and tissue penetration of a 15:1 combination of ticarcillin with clavulanic acid were investigated in healthy volunteers by using a blister model (10).

MATERIALS AND METHODS

The subjects were six male volunteers between the ages of 24 and 40 years. They were of normal body build and had a mean (± standard deviation) weight and height of 78.7 ± 8.1 kg and 1.78 ± 0.07 m, respectively. At the time of the study, no subject was receiving any form of medication. Written informed consent was obtained. One week before the trial, a full medical history, physical examination, and biochemical and hematological profiles were obtained; hepatic and renal function were assessed as normal, and no previous history of atopy, allergy to β-lactam compounds, or hepatic, renal, or gastrointestinal disease was found.

To induce blisters, two 1-cm^2 0.2% cantharides plasters were taped to the flexor aspect of a forearm of each volunteer the evening before the study.

At the start of the study, an intravenous cannula was inserted into a vein in the other forearm and was kept patent with 1-ml doses of heparinized saline (100 U/ml). The subjects emptied their bladders, and predose blood samples were taken for base-line assay. Ticarcillin (3 g) and clavulanic acid (0.2 g) (batch no. Ct11B01; Beecham Research Laboratories) dissolved in 20 ml of sterile water were injected into the antecubital vein of the opposite arm over 3 min at time 0 h.

After discarding the first 2 ml, blood samples were taken from the cannula at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h. Blister fluid was collected at 0.5, 1, 2, 3, 4, 5, 6, and 7 h and placed on six sterile 6-mm assay disks. The volume of fluid taken was measured by reweighing these disks and was found to be about 20 μl. Urine collections were taken at 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h. The volume and pH were noted, and a 20-ml sample was kept for assay.

Assays were performed within 2 h of sample collection. The assay for ticarcillin was carried out by a routine agar plate diffusion technique with *Pseudomonas aeruginosa* NCTC 10701 as the indicator organism and Penassay no. 1 (Oxoid, Basingstoke, U.K.) as the antibiotic medium. Serum standards were prepared in human serum, and urine standards were prepared in phosphate-buffered saline (pH 6.6) in which urine samples were diluted when necessary. Blister fluid sample standards were made up in 70% serum, thus simulating the protein content of actual blister fluid (10).

The assay for clavulanic acid was performed in a similar manner. The medium used was Penassay no. 2 (Oxoid) incorporating 35 μg of benzylpenicillin per ml, and the indicator organism was *Klebsiella pneumoniae*. The plates were used within 3 h of pouring. Standards in this method were made up in 100% horse serum and 70% horse serum for serum and blister fluid, respectively, it having previously been shown that horse serum and human serum gave equivalent results (preliminary results, data not shown). The 95%

confidence limits of the serum assays were 16.4 and 16.8%, respectively, for ticarcillin and clavulanic acid.

The pharmacokinetic analysis of individual data was performed by standard graphical methods.

RESULTS

The levels of ticarcillin and clavulanic acid in serum and blister fluid at various times are shown in Table 1. The pharmacokinetic data are shown in Table 2. The serum concentration-time curves for both agents appeared essentially to fit a two-compartment open model.

The serum level of ticarcillin showed a very rapid initial distribution, and there were too few sampling times within the first hour to accurately calculate serum half-life in the distribution phase in four of the six subjects for this agent. The mean levels 30 min postdose were approximately 200 μg/ml for ticarcillin and 7.5 μg/ml for clavulanic acid, a ratio of 28:1. At 4 h postadministration, the ratio of ticarcillin to clavulanic acid was about 40:1, and at 5 h (at which time the limits of sensitivity of the clavulanic acid assay were being reached), the ratio was about 60:1. The terminal (or β-phase) half-lives were 66 and 91 min for ticarcillin and of clavulanic acid, respectively, but there was considerable intersubject variation in the case of clavulanic acid.

Both agents rapidly penetrated into blister fluid. At 1 h, the percent penetrations [i.e., (blister fluid level/serum level) × 100] were 58 and 77% for ticarcillin and of clavulanic acid, respectively. The maximum blister fluid levels were attained between 1 to 2 h, and the terminal elimination rate of each agent from blister fluid was similar to the terminal serum half-life. The ratio of ticarcillin to clavulanic acid in blister fluid at 1 h postdose was 33:1, increasing to 66:1 at 3 h and then declining to about 40:1 at 5 to 6 h.

The volume of distribution of clavulanic acid was approximately twice that of ticarcillin, clavulanic acid distributing itself to approximately 25% of the mean body weight. By 24 h, 77% of ticarcillin and 45% of clavulanic acid had been recovered in the urine. Although the plasma clearance of clavulanic acid (241 ml/min) was about twice that of ticarcillin (116 ml/min), the renal clearances of each agent were similar.

DISCUSSION

The pharmacokinetics of intravenously coadministered ticarcillin and clavulanic acid are generally in agreement with the perliminary results of others (Staniforth et al., 21st ICAAC, abstr. no. 443), with the exception of the longer serum half-life of clavulanic acid found in the present study (however, there was considerable subject to subject variation in this study). The pharmacokinetics of ticarcillin do not appear to be influenced by the presence of clavulanic acid, as this data is similar to that found after the administration of ticarcillin alone (3). It is not known whether the coadministration of ticarcillin influences the pharmacokinetics of clavulanic acid.

Although ticarcillin and clavulanic acid were administered at a 15:1 ratio, the ratios in serum and blister fluid were considerably different, there being a relative decrease in the amount of clavulanic acid present, so that, for instance, by 4 h the ratio was about 40:1 in serum and 55:1 in blister fluid, and at 5 h the ratios were 62:1 and 48:1, respectively. This decrease cannot be explained by a relatively shorter half-life of clavu-

TABLE 1. Mean concentrations (± standard deviation) of ticarcillin and clavulanic acid in serum and blister fluid

Time (h) after i.v. injection[a]	Serum concn (μg/ml)		Ratio[b]	Blister fluid concn (μg/ml)		Ratio[b]
	Ticarcillin	Clavulanic acid		Ticarcillin	Clavulanic acid	
0.25	277.1 ± 117.6	11.4 ± 3.4	24			
0.5	205.8 ± 84.9	7.4 ± 2.0	28	57.9 ± 64	3.4 ± 2.4	17
0.75	182.1 ± 69	6.2 ± 1.9	29			
1.0	158.4 ± 58.5	3.6 ± 1.1	44	92.6 ± 66.6	2.8 ± 1.1	33
1.5	114.1 ± 39.5	2.3 ± 0.6	49			
2.0	83.6 ± 26	1.35 ± 0.3	62	73.5 ± 25.8	2.0 ± 1.4	37
3.0	43.3 ± 17.3	0.7 ± 0.3	62	53.1 ± 13.1	0.8 ± 0.3	66
4.0	24.8 ± 10.6	0.63 ± 0.3	39	33.4 ± 15.8	0.6 ± 0.3	56
5.0	12.4 ± 4.8	0.2 ± 0.2	62	28.7 ± 14	0.6 ± 0.3	48
6.0	6.9 ± 3.4	0.1 ± 0.1	69	12.9 ± 9.9	0.3 ± 0.1	43
7.0	3.4 ± 1.7	ND[c]		9.6 ± 8.1	0.2 ± 0.1	48
8.0	1.7 ± 0.7	ND				

[a] i.v., Intravenous.
[b] Ticarcillin/clavulanic acid ratio.
[c] ND, Not done.

TABLE 2. Pharmacokinetics of ticarcillin and clavulanic acid

Parameter (U)[a]	Mean ± SD	
	Ticarcillin	Clavulanic acid
C_0 (μg/ml)	603 ± 13.4	16.3 ± 2.9
$t_{1/2\alpha}$ (min)	16.4 ± 2.05	25.0 ± 10
$t_{1/2\beta}$ (min)	66.0 ± 6	91.0 ± 31
$AUC^{0-\infty}$ (μg · h/ml)	475 ± 169	14.6 ± 3.7
V_d (liters)	10.8 ± 43	20.33 ± 8.0
Cl_p (ml/min)	116 ± 40.1	241 ± 61
Cl_r (ml/min)	86.7 ± 23.7	107 ± 48
24-h urine recovery (%)	76.6 ± 13.5	44.9 ± 17.7
$t_{1/2}$ blister (min)	78.0 ± 9.0	85.8 ± 25.8
t_{max} blister (min)	105 ± 57.6	75.0 ± 36
C_{max} blister (μg/ml)	114.5 ± 54	3.7 ± 1.96

[a] C_0, Initial fictive concentration of each drug; $t_{1/2\alpha}$, serum half-life in the distribution phase; $t_{1/2\beta}$, serum half-life in the elimination phase; $AUC^{0-\infty}$, area under the curve from time zero to infinity; V_d, volume of distribution at steady state; Cl_p, plasma clearance; Cl_r, renal clearance; $t_{1/2}$ blister, terminal half-life in blister fluid; t_{max} blister, time of maximum concentration (C_{max}) in blister fluid.

lanic acid but is possibly related to the greater volume of distribution of clavulanic acid. There was also a greater nonrenal elimination of clavulanic acid as compared with ticarcillin, a result presumably related to the metabolism of clavulanic acid (2).

When formulating a mixture of β-lactamase inhibitors and β-lactams, it is important to know how much inhibitor to have present to protect the β-lactam. In vitro studies of ticarcillin-resistant *Enterobacteriaceae* (4) suggest that between 5 and 10 μg of clavulanic acid per ml are required before clinically relevant synergy (i.e., a reduction in the minimal inhibitory concentration of ticarcillin to ≤16 μg/ml) is obtained. If this were the case, then this formulation of ticarcillin and clavulanic acid would not be expected to be active clinically, as levels of greater than 5 μg/ml are obtained in the serum only in the first hour and do not reach 5 μg/ml at all in blister fluid. However, a dynamic in vitro model which simulated the expected in vivo levels (R. J. Boon, P. Masters, and R. Sutherland, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami, Fla., abstr. no. 293, 1982) showed this combination did produce a 99.9% kill of ticarcillin-resistant *Enterobacteriaceae* and *P. aeruginosa*. Similarly, a soft-tissue infection model in animals has demonstrated efficacy of the combination, whereas ticarcillin alone failed (R. J. Boon, A. S. Beale, C. V. Pierce, and R. Sutherland, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami, Fla., abstr. no. 295, 1982.). To date, there is no clinical information to confirm these experiments. Clinical studies on amoxicillin (1 g) plus clavulanic acid (0.2 g), which have similar pharmacokinetics to this present combination (9a) indicate that such a combination is efficacious at preventing sepsis after appendectomy (R. Wise and I. A. Donovan, unpublished data), and it might be expected that ticarcillin plus clavulanic acid would also be clinically efficacious. It is possible that in vivo levels of clavulanic acid need be present for only short periods of time to inhibit susceptible β-lactamases and allow the ticarcillin to exert its bactericidal effects. Studies on this point should be performed. In the case of β-lactamase-producing *B. fragilis, S. aureus, Haemophilus influenzae*, and *Neisseria gonorrhoeae* strains which are resistant to ticarcillin, it is known that lower amounts of clavulanic acid are required to inhibit β-lactamases (8, 9).

This combination of β-lactams plus inhibitor should prove to be efficacious against a wide range of bacterial pathogens, including *P. aeruginosa*, the *Enterobacteriaceae, S. aureus*, and gram-negative anaerobic bacilli. The results of clinical trials are awaited with interest.

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