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Pharmacokinetics and Tissue Penetration of Tazobactam Administered Alone and with Piperacillin

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The pharmacokinetics of tazobactam (500 mg) administered intravenously alone were compared with the pharmacokinetics of tazobactam coadministered with piperacillin (4 g), and the penetration into an inflammatory exudate in six healthy males was studied. Piperacillin influenced the pharmacokinetics of tazobactam. The mean levels of tazobactam in plasma at 4 h were 0.6 μg/ml when it was given alone and 1.2 μg/ml when it was given with piperacillin ($P = 0.0003$). The mean total clearances of tazobactam were 203.5 and 134.2 ml/min ($P = 0.035$) when it was given alone and with piperacillin, respectively. There were no significant differences in the elimination half lives, areas under the concentration-time curve from 0 h to infinity, or volumes of distribution. Inflammatory exudate penetration was rapid, and the mean maximum levels of tazobactam attained were 6.4 and 11.3 μg/ml when it was given alone or with piperacillin, respectively ($P < 0.06$). The mean percent penetration of tazobactam and the area under the concentration-time curve from 0 h to infinity in inflammatory exudate were greater when tazobactam was given with piperacillin. The mean 24-h urinary recoveries of tazobactam were 63.7% ± 7.9% when it was given alone and 56.8% ± 2.7% when it was given with piperacillin. The explanation for the differences in the pharmacokinetics of tazobactam when it was administered alone compared with those when it was given with piperacillin was unclear.

Piperacillin, a broad-spectrum penicillin (13), is susceptible to hydrolysis by a range of β-lactamases, including the plasmid-mediated enzymes found in the members of the family *Enterobacteriaceae* and other genera such as Richmond and Sykes group III (12) and the enzymes commonly found in *Staphylococcus aureus* and *Bacteroides fragilis*. A number of β-lactamase inhibitors have been combined with other broad-spectrum penicillins, such as clavulanic acid with amoxicillin (8) and ticarcillin (1, 8) and sulbactam with ampicillin (6), which are protective of the active β-lactam. Tazobactam has been combined with piperacillin in a combination of 1:8 (9, 10), and preliminary studies suggest that the pharmacokinetics of these two agents are well matched. Results of preliminary studies in humans (3) and rats (16) suggest that the elimination of tazobactam is slower in the presence of piperacillin than when tazobactam is administered alone. In the present study, the pharmacokinetics and penetration into an inflammatory fluid of tazobactam alone and tazobactam combined with piperacillin were investigated in healthy volunteers by using a cantharidine-induced blister model (15).

MATERIALS AND METHODS

Six healthy adult male volunteers participated in the study after Ethical Committee approval and written informed consent were obtained. The volunteers were aged 22 to 38 years (mean age, 29.7 years), weighed between 66.2 and 82.5 kg (mean weight, 72.9 kg), and had a mean height of 1.77 m (range, 1.72 to 1.81 m). The body weights were within 10% for their age and height. Their medical histories indicated no significant episodes or allergies to β-lactam antibiotics. Hematological and biochemical profiles, including tests of renal and hepatic functions, were normal. One week prior to the first study, all volunteers underwent a detailed physical examination and were considered normal. On the night before the first study, two 0.2% cantharides-impregnated plasters (1 by 1 cm) were applied to the anterior surface of one forearm of each volunteer and were taped in place. After overnight fasting, the subjects were given a single 500-mg intravenous injection of tazobactam dissolved in 20 ml of water; this was infused over 30 min. Solid food and drink were taken after 2 h. Blood was drawn through an intravenous canula (which was kept patent with 2-ml doses of heparinized saline [100 IU/ml]) immediately prior to infusion and then at 30 and 60 min and 2, 3, 4, 5, 6, 7, 8, and 10 h after dosing. Urine samples were collected from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h. Inflammatory exudate from the blisters was sampled with a micropipette predose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 10 h after dosing. The integrity of the blisters was maintained by spraying them with a fast-drying plastic dressing (Nobecutane; Astra Pharmaceuticals Ltd., Kings Langley, United Kingdom). At approximately 6 weeks after the first phase of the study (to allow blister healing), the volunteers were given tazobactam (500 mg) plus piperacillin (4 g) by the same intravenous route, and the same inflammatory fluid and plasma samples were collected.

Antibiotic assays were performed within 1 h of sample collection by the following microbiological methods. For tazobactam, the indicator organism was *Klebsiella aerogenes* ATCC 29665 and piperacillin (100 mg/liter) was incorporated into the medium, antibiotic medium no. 2. (Oxoid, Basingstoke, United Kingdom), the lower limit of sensitivity was 0.25 mg/liter, and the between-assay confidence limits were 6.2% at a concentration of 6 μg/ml and 8.7% at a concentration of 0.8 μg/ml. For piperacillin, the indicator organism was *Pseudomonas aeruginosa* NCTC 10701 and the medium was Oxoid antibiotic medium no. 1. The lower limit of sensitivity was 4 μg/ml, and the between-assay confidence limits were 5.8% at a concentration of 50 μg/ml and 3.7% at a concentration of 6 μg/ml.

Piperacillin at 128 μg/ml did not affect the tazobactam assay, and tazobactam at 16 μg/ml had no effect on the piperacillin assay. The piperacillin assay standard curve was

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TABLE 1. Pharmacokinetics of piperacillin following a 4-g intravenous injection when administered with 0.5 g of tazobactam

Parameter[a]	Mean ± SD	Range
Plasma		
$C_{0.5}$ (μg/ml)	223.7 ± 49.7	136–290.4
C_4 (μg/ml)	9.4 ± 3.2	5.4–13.6
$t_{1/2}$ (h)	1.0 ± 0.15	0.82–1.2
$AUC_{0-\infty}$ (μg · h/ml)	485 ± 82.1	370–592
Total clearance (ml/min)	145 ± 22.7	107–166
Renal clearance (mg/min)	73.1 ± 6.5	69.0–86.2
Inflammatory fluid		
C_{max} (μg/ml)	77.2 ± 32.6	42.8–126
T_{max} (h)	2.1 ± 1.1	0.5–3
$AUC_{0-\infty}$ (μg · h/ml)	237 ± 20.9	207–257
% Penetration	49.6 ± 5.9	41.8–55.9
Urine, % excretion (24 h)	49.8 ± 4.7	42.6–55.5

[a] $C_{0.5}$ and C_4, concentrations in plasma at 0.5 and 4 h postinjection, respectively; $t_{1/2}$, plasma elimination half-life; $AUC_{0-\infty}$, area under the plasma (or inflammatory fluid) concentration-time curve from 0 h to infinity; C_{max}, maximum concentration in inflammatory fluid; T_{max}, time to reach the maximum concentration in inflammatory fluid.

linear from 64 to 4 μg/ml, and the tazobactam assay standard curve was linear from 0.5 to 8 μg/ml. Specimens were diluted (if necessary) to ensure that they fell within these ranges.

Incubation for both assays was at 37°C. Standards were prepared by using human plasma for plasma samples (pooled human plasma; Flow Laboratories, Irvine, United Kingdom) and 70% human plasma in phosphate buffer (pH 7) for blister inflammatory exudates. Urine samples were diluted and prepared in phosphate buffer (pH 7). Results were calculated by using the correction of Bennett et al. (2).

Pharmacokinetic analysis of plasma samples was performed by using the GPHARM program (7), assuming a two-compartment model by fitting the data with a weighted least-squares algorithm. No corrections were applied for the 30-min infusion. In particular, the total clearance was calculated by dividing the dose by the extrapolated area under the plasma concentration-time curve (AUC); the renal clearance was calculated by dividing the cumulative renal excretion by the extrapolated AUC. The volume of distribution at steady state was calculated as the product of the total clearance and the mean residence time. Pharmacokinetic parameters for the inflammatory fluid were determined by standard graphical methods (14). This included calculation of the AUC by a log-linear trapezoidal procedure. The percent penetration of the agents into inflammatory fluid was calculated by comparing the AUC from 0 h to infinity ($AUC_{0-\infty}$) in the inflammatory fluid with that in serum.

The Wilcoxon signed rank test was used to check for statistical differences. A P value of <0.06 was considered significant.

RESULTS

The pharmacokinetics of piperacillin (when coadministered with tazobactam) are given in Table 1. The levels in plasma 0.5 h after the injection were 223.7 μg/ml and fell to 9.2 μg/ml by 4 h. The concentrations of piperacillin were fairly consistent among the members of the group at any one time point, with the exception of one volunteer (volunteer 6), in whom consistently lower levels were noted; he was the tallest and heaviest member of the group. The mean plasma elimination half-life of piperacillin was 1.0 h with little individual variation, although the half-life was shortest in volunteer 6 (0.82 h). The mean total and renal clearances of piperacillin were 145 and 73.1 mg/min, respectively, and 49.8% of the administered drug was recovered in the urine in 24 h.

Inflammatory fluid was rapidly penetrated by piperacillin. The peak level occurred at a mean time of 2.1 h, and the mean maximum concentration was 77.2 μg/ml. Again, considerable variation was seen, with the most rapid and extensive penetration being in volunteer 6 (126 μg/ml at 0.5 h after infusion). The mean percent penetration calculated by the ratio of $AUC_{0-\infty}$ in inflammatory fluid to that in plasma was 49.8%.

The pharmacokinetics of tazobactam (Table 2) were influenced by the presence of piperacillin. Although the mean concentrations in plasma 0.5 h after administration were not statistically significantly different, higher levels of tazobactam were noted when tazobactam was given with piperacillin (27.2 μg/ml), whereas the level was 24.3 μg/ml when tazobactam was given alone. The levels then declined, and at 4 h there was a significant difference between the levels of tazobactam when it was given with piperacillin and when it was given alone, 1.2 and 0.6 μg/ml, respectively; when the volunteers received piperacillin, the level of tazobactam was almost twice the level when it was given alone. The mean elimination half-lives of tazobactam did not differ in the two studies (1.1 h).

There were significant differences in the total and renal clearances of tazobactam, with both being more rapid when tazobactam was given alone. The renal elimination of tazobactam over 24 h was greater when the drug was given alone (63.7% of the administered dose); renal elimination was 56.8% when tazobactam was coadministered with piperacillin.

Tazobactam penetrated the inflammatory exudate rapidly; the maximum concentration was attained at 1.6 to 1.8 h postadministration, and there were no significant differences between the two studies. There was, however, a significant increase in the maximum concentration attained in the inflammatory exudate if piperacillin was coadministered with tazobactam; the mean maximum concentrations in inflammatory fluid were 6.4 μg/ml when tazobactam was given alone and 11.3 μg/ml when it was given with piperacillin. There was also a significantly longer elimination half-life from the inflammatory fluid when piperacillin was coadministered with tazobactam than when tazobactam was given alone (means, 1.3 and 0.94 h, respectively).

The percent penetration of tazobactam into the inflammatory exudate was greater after coadministration of piperacillin (67.7%) than when it was given alone (46.7%), although the individual variations were considerable.

In Table 3 the ratios of piperacillin to tazobactam in serum and inflammatory exudate are given. In plasma, the initial 8:1 ratio was maintained over 6 h; there was no significant difference between the values at 0.5 and 6 h ($P > 0.06$). The ratio of piperacillin to tazobactam in inflammatory fluid appeared to increase with time; however, there were no significant differences between the ratios at 0.5 or 1 h and 5 or 6 h; the apparent increase was due to occasionally large ratios and was reflected in the large standard deviations. The mean value of all the piperacillin:tazobactam ratios in inflammatory fluid was 8.1:1 (standard deviation, ±5.1). No side effects or chemical or hematological abnormalities attributable to the compounds were noted.

TABLE 2. Pharmacokinetics of tazobactam alone and in combination with piperacillin

Parameter[a]	Drug[b]	Mean ± SD	Range	P value[c]
Plasma				
$C_{0.5}$ (μg/ml)	A	24.3 ± 8.0	13.7–37.1	
	B	27.2 ± 6.2	16.8–36.3	>0.06
C_4 (μg/ml)	A	0.6 ± 0.12	0.44–0.74	
	B	1.2 ± 0.25	0.9–1.5	<0.06
$t_{1/2}$ (h)	A	1.13 ± 0.21	0.94–1.5	
	B	1.11 ± 0.31	0.90–1.67	>0.06
$AUC_{0-\infty}$ (μg · h/ml)	A	42.4 ± 15.8	23.0–66.9	
	B	49.0 ± 12.4	34.5–68.1	<0.06
Total clearance (ml/min)	A	203.5 ± 74.0	123.1–296	
	B	134.2 ± 39.7	97.6–21	<0.06
Renal clearance (ml/min)	A	130.3 ± 51.3	66.7–206.7	
	B	75.7 ± 19.9	60.1–115	<0.06
V_{ss} (liters)	A	225 ± 8.2	10.5–35.3	
	B	14.6 ± 3.2	11.5–20.5	>0.06
Blister				
C_{max} (μg/ml)	A	6.4 ± 2.2	4.7–10.7	<0.06
	B	11.3 ± 8.2	5.8–27.1	
T_{max} (h)	A	0.94 ± 0.7	0.5–2.0	>0.06
	B	1.83 ± 1.3	0.5–3	
$t_{1/2}$ (h)	A	0.94 ± 0.14	0.66–1.0	<0.06
	B	1.3 ± 0.4	0.76–1.8	
$AUC_{0-\infty}$ μg · h/ml	A	18.0 ± 1.29	16.5–19.7	<0.06
	B	30.8 ± 4.9	24.6–37.8	
% Penetration	A	46.7 ± 15.0	28.3–71.3	<0.06
	B	67.7 ± 25.9	43.9–108.6	
Urine, % excretion at 24 h	A	63.7 ± 7.9	54.2–75.3	
	B	56.8 ± 2.7	54.1–61.4	<0.06

[a] V_{ss}, volume of distribution at steady state; for definitions of other parameters, see footnote *a* of Table 1.
[b] A, tazobactam alone; B, tazobactam in combination with piperacillin.
[c] *P* values were determined by the Wilcoxon signed rank test.

DISCUSSION

The pharmacokinetics of piperacillin found in this study agreed with those described previously (4), with the exception that the previous investigators described a renal recovery of 79.8% in 24 h. We noted a 49.6% recovery in 24 h, a value similar to the 49% recovered when piperacillin was administered alone and 46% when it was administered together with tazobactam in preliminary studies (11).

The major finding in this study was the influence of piperacillin on the pharmacokinetics of tazobactam. The concentrations of tazobactam in serum and inflammatory fluid were greater when tazobactam was given with 4 g of piperacillin, and the $AUC_{0-\infty}$ of tazobactam was similarly greater when the two agents were coadministered. However, the plasma elimination half-life of tazobactam was not significantly different following piperacillin coadministration. The plasma and renal clearances of tazobactam were reduced in the presence of piperacillin, and a possible explanation may well be the inhibition of the tubular secretion of tazobactam (if this occurs) by piperacillin. Piperacillin, when given alone, has a renal clearance of 213 ml/min (4), which argues strongly that piperacillin undergoes active renal secretion. It would be of value to undertake studies of the pharmacokinetics of tazobactam alone and with probenecid to elucidate this point further. It was also interesting that the urinary recovery of tazobactam was lower following coadministration with piperacillin, again suggesting that a reduction in urinary elimination is the major reason for the pharmacokinetic differences. Against this proposed mechanism, it could be argued that the competition of two similar anions (i.e., β-lactams) for the selective pump at the proximal tubule would probably cause the renal clearances of both agents to be lowered. It would be of interest to study a 1:1 ratio of the two agents to assist in clarifying this point.

TABLE 3. Ratio of piperacillin:tazobactam in plasma and inflammatory exudate

Time (h)	Piperacillin:tazobactam concn ratio (SD)	
	Plasma	Inflammatory exudate
0.5	8.2:1 (0.14)	5.1:1 (0.7)
1	7.5:1 (0.60)	6.1:1 (0.64)
2	7.6:1 (1.2)	11.9:1 (9.4)
3	7.0:1 (0.3)	9.5:1 (7.6)
4	7.9:1 (1.7)	7.7:1 (2.8)
5	9.2:1 (1.7)	7.5:1 (3.2)
6	10.0:1 (4.5)	9.1:1 (1.7)

Another possible explanation might be that elimination by another route is affected by piperacillin, and data on biliary excretion and metabolism of tazobactam are awaited.

The coadministration of tazobactam and piperacillin also increased the concentration of tazobactam in inflammatory fluid and the percent penetration of tazobactam in comparison with the valves when it was administered as a single agent.

Tazobactam is similar or slightly superior to clavulanic acid in its ability to protect piperacillin from hydrolysis by a wide range of plasmid- and chromosome-mediated β-lactam-

ases (1, 5, 10), and in vitro studies have shown that a ratio of piperacillin to tazobactam of 4:1 to 8:1 reduces the piperacillin MIC for 90% of strains for the majority of β-lactamase-producing strains of the family *Enterobacteriaceae*, *S. aureus* (but not methicillin-resistant strains), and *B. fragilis* to 32 μg/ml or less. Exceptions include certain strains that possess chromosomal cephalosporinases (10). In this study we showed that the ratio of drugs administered (8:1) is maintained over 6 h in both serum and an inflammatory exudate. The use of tazobactam against systemic infections should be studied in clinical trials because of its role of protecting piperacillin against hydrolysis by β-lactamase-producing bacterial pathogens.

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