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Evaluation of Piperacillin-Tazobactam in Experimental Meningitis Caused by a β-Lactamase-Producing Strain of K1-Positive *Escherichia coli*

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We evaluated the pharmacokinetics and therapeutic efficacy of piperacillin combined with tazobactam, a novel β-lactamase inhibitor, in experimental meningitis due to a β-lactamase-producing strain of K1-positive *Escherichia coli*. Different doses of piperacillin and tazobactam, as single agents and combined (8:1 ratio; dosage range, 40/5 to 200/25 mg/kg per h), and of ceftriaxone were given to experimentally infected rabbits by intravenous bolus injection followed by a 5-h constant infusion. The mean (± standard deviation) rates for penetration into the cerebrospinal fluid of infected animals after coadministration of both drugs were 16.6 ± 8.4% for piperacillin and 32.5 ± 12.6% for tazobactam. Compared with either agent alone, combination treatment resulted in significantly better bactericidal activity in the cerebrospinal fluid. The bactericidal activity of piperacillin-tazobactam was dose dependent: cerebrospinal fluid bacterial titers were reduced by 0.37 ± 0.19 $\log_{10}$ CFU/ml per h with the lowest dose versus 0.96 ± 0.25 $\log_{10}$ CFU/ml per h with the highest dose ($P < 0.001$). At the relatively high doses of 160/20 and 200/25 mg of piperacillin-tazobactam per kg per h, the bactericidal activity of the combination was comparable to that of 10 and 25 mg of ceftriaxone per kg per h, respectively.

Meningitis remains a serious disease associated with high morbidity and substantial mortality (23, 26). The recently observed increase in meningeal pathogens that produce β-lactamase has prompted the search for agents that penetrate the blood-brain barrier well and show rapid bactericidal activity against such organisms in vivo. Among the agents evaluated, several broad-spectrum cephalosporins have proven to be highly effective in experimental models and in humans with meningitis due to β-lactamase-producing organisms (6, 7, 13, 15, 17, 18). An alternative approach for the treatment of meningitis due to such organisms is the use of a penicillin derivative combined with an agent that inhibits the β-lactamase elaborated by the infecting organism. Limited data on cerebrospinal fluid (CSF) penetration and efficacy of such combinations in experimental animals and humans are available (3, 5, 9, 14, 24, 28). Using a well-standardized rabbit model, we studied the pharmacokinetics and therapeutic efficacy of a novel β-lactamase inhibitor, tazobactam (CL 298,741; formerly YTR 830), combined with piperacillin, a broad-spectrum acylureido-penicillin, in experimental meningitis due to a β-lactamase-producing strain of *Escherichia coli*.

MATERIALS AND METHODS

Test organism. A K1-positive, serum-resistant strain of *E. coli*, originally isolated from a neonate with meningitis, was used. The organism produced β-lactamase, as determined by the nitrocefin chromogenic assay, and was resistant to ampicillin and piperacillin at concentrations of ≥256 μg/ml. The organism was stored on glass beads at −70°C, grown for 5 to 6 h in tryptic soy broth, washed, and diluted in saline to the desired concentration.

Antimicrobial agents. Piperacillin and tazobactam were obtained from Lederle Laboratories, American Cyanamid Co., Pearl River, N.Y. Ceftriaxone was a commercial preparation (Roche Laboratories, Nutley, N.J.).

Susceptibility tests. MICs and MBCs were measured in Mueller-Hinton broth, using the standard tube macrodilution technique, against an inoculum of 5×10^5 CFU/ml. The MIC was defined as the lowest concentration that prevented visible growth after 24 h of incubation at 35°C. The MBC, defined as the concentration that killed ≥99.9% of the original inoculum, was determined after subculturing 0.1 ml from each clear tube onto a blood agar plate and overnight incubation at 35°C.

Rabbit model. The rabbit model of experimental meningitis as described previously was used (4, 27). Briefly, New Zealand White rabbits weighing 1.8 to 2.6 kg each were anesthetized by intramuscular injection of acepromazine (3 mg/kg), ketamine (30 mg/kg), and xylazine (15 mg/kg), and a dental acrylic helmet was attached to the skull. The helmet allowed immobilization of the head in a stereotactic frame and facilitated puncture of the cisterna magna. Two to three days later, the animals were again anesthetized and inoculated intracisternally with 2×10^5 to 1×10^6 CFU of *E. coli* in 0.3 ml of saline. Some 12 to 14 h later the animals were lethargic and febrile and exhibited a mean CSF bacterial titer of 5.7 ± 1.5 CFU/ml. At that time, the animals were given an intravenous infusion of urethane (1.75 g/kg) as a long-acting anesthetic, and the antibiotic administration was started.

Drug administration. The drugs were administered through a peripheral ear vein. Different doses were used and given as a loading dose (10 ml) followed by a constant infusion (10 ml/h) over a 5-h period. Infected control rabbits

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received the same volume of saline over the same time period.

Specimen collection and processing. Serial blood from an indwelling femoral artery catheter and CSF samples from the intracisternal needle were obtained before and at 1, 3, and 5 h during the constant infusion. CSF bacterial titers were determined by quantitative cultures onto blood agar plates. The remainder of the CSF and the serum samples were stored at −70°C until drug assays were performed within 1 week. All three experimental drugs were stable for at least 3 weeks at −70°C.

Antibiotic assays. Drug concentrations in serum and CSF were determined by the agar well diffusion bioassay. *Sarcina lutea* ATCC 9341 was used as the test strain to detect piperacillin in both samples containing piperacillin alone as well as in samples containing the piperacillin-tazobactam combination. There was no inhibitory effect of tazobactam on *S. lutea*, and the results of the bioassay for piperacillin were identical whether the samples contained piperacillin alone or the combination of piperacillin and tazobactam. *E. coli* ATCC 10536 was used to detect ceftriaxone. To determine tazobactam concentrations, the β-lactamase inhibition assay with *Klebsiella pneumoniae* ATCC 29665 was used (1). This assay is based on the production of a β-lactamase by the test strain. The zone of inhibition produced by an excess amount of piperacillin added to the test samples is proportional to the amount of β-lactamase inhibitor (tazobactam) present in the sample. The lower limits of detection by bioassay were 0.5 μg/ml for both tazobactam and piperacillin and 0.25 μg/ml for ceftriaxone. Test-to-test variability for tazobactam, the compound among the three drugs with the least favorable test characteristics, was 27%.

RESULTS

In vitro susceptibility. The MICs and MBCs of the study drugs were as follows: >256 and >256 μg/ml for piperacillin and tazobactam as single agents and 0.125 and 0.25 μg/ml for ceftriaxone. The MICs of the combination of piperacillin-tazobactam were 8.0/1.0 μg/ml when tested in an 8:1 ratio, 4.0/1.0 μg/ml when tested in a 4:1 ratio, and 2.0/1.0 μg/ml when tested in a 2:1 ratio. The corresponding MBCs of piperacillin-tazobactam were 8.0/1.0 (8:1), 4.0/1.0 (4:1), and 4.0/2.0 (2:1) μg/ml, respectively.

Pharmacokinetics. Both piperacillin and tazobactam concentrations in serum tended to be higher in infected than in uninfected animals, particularly at the higher doses examined. For example, mean concentrations in serum with a dose of 200 mg of piperacillin per kg per h were 269.4 μg/ml in uninfected animals but 453.5 μg/ml in infected animals ($P < 0.05$ by Student's t test) (Tables 1 and 2). Furthermore, while piperacillin concentrations in serum of infected animals were not affected by the coadministration of tazobactam, the concentrations of tazobactam in serum were higher in animals receiving both drugs together compared with tazobactam alone ($P < 0.04$ for 10 mg/kg per h and $P < 0.07$ for 25 mg/kg per h) (Table 2).

For both piperacillin and tazobactam, the penetration into CSF in normal rabbits was low, not exceeding 0.9% for piperacillin and 2.5% for tazobactam, respectively (Table 1). In contrast, markedly improved penetration of both drugs was observed in infected rabbits (Table 2). Analysis of all animals treated with the 8:1 combination of piperacillin-tazobactam, irrespective of dose, revealed average penetrations of 32.5% for tazobactam and 16.8% for piperacillin. The calculated CSF penetration of piperacillin in animals treated with this drug alone was much lower (Table 2), but this may be due to inactivation of the drug by β-lactamases present in the CSF. Tazobactam penetration, on the other hand, appeared to increase with increasing doses when coadministered with piperacillin (from 23.4 to 43.8%; $P < 0.01$ by Student's t test) (Table 2). Due to the differences in penetration between piperacillin and tazobactam, the ratio of piperacillin/tazobactam in CSF was lower (mean, 3.5:1) than that determined in serum (mean, 7.2:1).

TABLE 1. Pharmacokinetics of piperacillin-tazobactam given by continuous infusion (8:1 ratio) in normal rabbits

Drug and dose (mg/kg per h)	No. of rabbits	Mean (± SD)[a] concn (μg/ml) in:		Mean CSF/serum penetration (%)[a]
		Serum	CSF	
Piperacillin				
40	4	34.6 ± 5.0	<0.5	
80	6	105.6 ± 57.1	0.8 ± 0.4[b]	0.6[b]
120	3	153.8 ± 46.5	1.4 ± 0.4	0.9
160	3	200.1 ± 6.9	1.7 ± 0.7	0.9
200	3	269.4 ± 7.3	2.0 ± 0.5	0.7
Tazobactam				
5	4	4.1 ± 1.2	<0.5	
10	6	10.0 ± 7.2	<0.5	
15	3	16.8 ± 0.7	<0.5	
20	3	20.9 ± 2.1	0.6[c]	2.5[c]
25	3	34.1 ± 4.6	0.9 ± 0.2	2.5

[a] Mean of all animals per group. The result for individual animals was calculated as the mean of the 1-, 3-, and 5-h samples.
[b] Only three animals with detectable levels of piperacillin in CSF are included.
[c] Only one animal with detectable levels of tazobactam in CSF is included.

The mean concentrations of ceftriaxone in serum and CSF for the two different doses used (10 and 25 mg/kg per h) and the corresponding mean penetration rates are given in Table 2.

Bactericidal activity. In control animals, a mean increase of CSF bacterial titers of 0.16 ± 0.20 $\log_{10}$ CFU/ml per h was observed during the 5-h experiment (Table 3). Administration of tazobactam or piperacillin alone was accompanied by only minor changes in CSF bacterial titers (Table 3). In contrast, when piperacillin was combined with tazobactam, a dose of piperacillin as low as 40 mg/kg per h, producing mean concentrations in CSF in the range of the MBC for the organism (4.6 and 1.3 μg/ml, respectively), showed significant bactericidal activity in the CSF. A fivefold increase in the dosage of the antibiotic combination was followed by a marked increase in bactericidal activity from 0.37 ± 0.19 to 0.96 ± 0.25 $\log_{10}$ CFU/ml per h ($P < 0.001$) (Table 3). The differences between the bactericidal activities of piperacillin-tazobactam versus piperacillin alone were statistically significant ($P < 0.001$).

When the dose of tazobactam was held constant (10 mg/kg per h) and the dose of piperacillin was increased from 80 to 200 mg/kg per h, an increase in bactericidal activity in CSF was observed ($P = 0.07$) (Table 3). In contrast, at the highest dose of piperacillin examined, increasing the tazobactam dose from 10 to 25 mg/kg per h did not influence the killing rate (Table 3).

Bacterial killing in CSF of rabbits receiving ceftriaxone also showed a dose-dependent increase (Table 3). The bactericidal activities of piperacillin-tazobactam and ceftriaxone, when adjusted for the ratio between concentrations in CSF and the MBC, were comparable (Fig. 1).

TABLE 2. Pharmacokinetics of piperacillin and tazobactam, as single agents and combined, and of ceftriaxone given by continuous infusion in experimentally infected rabbits with meningitis due to *E. coli*

Drug and dose (mg/kg per h)	No. of rabbits	Mean (± SD)[a] concn (μg/ml) in:		Mean (± SD) CSF/serum penetration (%)[a]
		Serum	CSF	
Piperacillin				
80	3	100.8 ± 27.2	4.7 ± 1.7	4.5 ± 0.7[b]
160	6	292.1 ± 68.4	7.9 ± 1.0	2.6 ± 0.7[b]
200	6	453.6 ± 125.9	14.8 ± 3.1	3.4 ± 0.8[b]
Tazobactam				
10	3	7.1 ± 3.7	2.1 ± 1.1	29.2 ± 12.4
25	3	26.2 ± 1.6	9.2 ± 1.7	34.8 ± 4.9
Piperacillin-tazobactam (8:1)				
Piperacillin				
40	6	20.2 ± 2.8	4.6 ± 2.3	22.9 ± 11.5
80	6	105.6 ± 48.6	17.4 ± 4.7	19.4 ± 9.9
120	6	213.5 ± 97.2	26.6 ± 10.0	14.0 ± 4.7
160	6	364.5 ± 62.0	53.5 ± 14.5	14.4 ± 2.2
200	6	477.6 ± 202.3	59.9 ± 27.0	13.0 ± 4.6
Tazobactam				
5	6	5.6 ± 1.5	1.3 ± 0.3	23.4 ± 11.5
10	6	16.0 ± 5.4	4.5 ± 2.0	30.3 ± 15.7
15	6	38.3 ± 23.4	9.7 ± 4.2	31.2 ± 12.2
20	6	44.7 ± 18.6	15.2 ± 6.3	33.9 ± 2.4
25	6	54.5 ± 21.0	22.4 ± 6.1	43.8 ± 12.1
Piperacillin-tazobactam (20:1)				
Piperacillin				
200	3	474.3 ± 112.1	64.9 ± 21.2	11.8 ± 1.7
Tazobactam				
10	3	12.3 ± 1.1	6.5 ± 1.6	54.2 ± 17.7
Ceftriaxone				
10	6	64.6 ± 12.8	4.2 ± 2.4	6.2 ± 2.9
25	6	79.0 ± 19.4	6.8 ± 2.3	8.9 ± 3.2

[a] Mean of all animals per group. The result for individual animals was calculated as the mean of the 1-, 3-, and 5-h samples.
[b] CSF/serum penetration rates may be low due to inactivation of the drug in CSF by the β-lactamase of the infecting organism.

DISCUSSION

Tazobactam is a novel β-lactamase inhibitor that has been shown to be highly synergistic in vitro with penicillins, especially against gram-negative bacteria (2, 10–12). The combination of tazobactam with piperacillin has been found to be one of the most promising β-lactamase inhibitor-penicillin combinations (10–12). We therefore studied the pharmacokinetics and the dose-dependent bactericidal activity of this combination in rabbits with meningitis caused by a β-lactamase-producing strain of *E. coli*.

Several pharmacokinetic findings in our study were noteworthy. First, concentrations of both piperacillin and tazobactam in serum were higher in infected animals than in controls. Since neither cardiovascular parameters nor the renal function of infected animals was monitored in this study, the reasons for the altered pharmacokinetics in infected animals are presently unclear.

Second, tazobactam, but not piperacillin, concentrations in serum were affected by the simultaneous administration of the other drug. Thus, tazobactam concentrations in serum and, correspondingly, in CSF were approximately twofold higher in the presence of piperacillin than when tazobactam was given alone. A decreased clearance and prolonged serum half-life of tazobactam after coadministration with piperacillin have also been found in other experimental animals and in humans (Lederle Laboratories, unpublished information).

Third, the penetration of tazobactam as a single agent into the CSF of infected animals was remarkably good, with a mean rate of 32.5%. A similar penetration rate has been reported for clavulanic acid in experimental meningitis in rabbits (14, 24) and for sulbactam in humans with meningitis (9). The penetration rate was not affected by the combination with piperacillin. However, we found increasing serum/CSF penetration rates of tazobactam with increasing doses after coadministration with piperacillin. The reasons for this have not been elucidated but could involve either improved penetration into the CSF at very high concentrations in serum (for example, because of free drug levels that are out of proportion with total levels in serum) or reduced elimination of the drug from CSF by a saturable export system (4).

Lastly, after coadministration with tazobactam, the penetration of piperacillin into the CSF of infected rabbits was in the range found previously in humans and in experimental animals (8, 20). As could be expected from earlier observations with ampicillin (15), concentrations of piperacillin in CSF were much lower when it was given alone. This is most probably the result of the inactivation in CSF of the drug by the β-lactamase produced by the infecting organism.

The addition of tazobactam to piperacillin in the therapy of

TABLE 3. Bacteriologic efficacy of piperacillin and tazobactam as single agents, of piperacillin combined with tazobactam, and of ceftriaxone given as a 5-h continuous infusion in experimental meningitis due to K1-positive *E. coli*

Treatment (drug and dose, mg/kg per h)	No. of rabbits	Change (mean ± SD) in CSF bacterial titers (log_{10} ml/h)
No treatment	12	+0.16 ± 0.20
Tazobactam alone		
10	3	+0.13 ± 0.26
25	3	−0.15 ± 0.20
Piperacillin alone		
80	3	−0.17 ± 0.36
160	6	−0.08 ± 0.25
200	6	−0.16 ± 0.22
Piperacillin-tazobactam		
40/5	6	−0.37 ± 0.19
80/10	6	−0.60 ± 0.23
120/15	6	−0.64 ± 0.17
160/20	6	−0.72 ± 0.14
200/25	6	−0.96 ± 0.25
200/10	3	−0.94 ± 0.24
Ceftriaxone		
10	6	−0.77 ± 0.22
25	6	−1.05 ± 0.21

rabbits with meningitis restored the bactericidal activity of piperacillin against the infecting, β-lactamase-producing *E. coli* strain. Our results show a significant dose dependency of bacterial killing in the CSF. Such a correlation between increasing antibiotic concentrations and bactericidal rates in the CSF has been found previously in experimental studies with *Streptococcus pneumoniae* (various β-lactams) (15, 24), *E. coli* (broad-spectrum cephalosporins and aminoglycosides) (6, 18, 20), and *Proteus mirabilis* (aminoglycosides) (21). Similar to the findings of these studies, rapid bactericidal activity in the present study was found when the ratio of CSF drug concentrations to the MBC was higher than 10× the MBC. That the bactericidal activity in CSF did not change when high doses of piperacillin were combined with either 10 or 25 mg of tazobactam per kg per h further indicates that there is a threshold concentration of tazobactam required to restore the bactericidal activity of piperacillin, above which tazobactam does not increase the bactericidal activity of piperacillin.

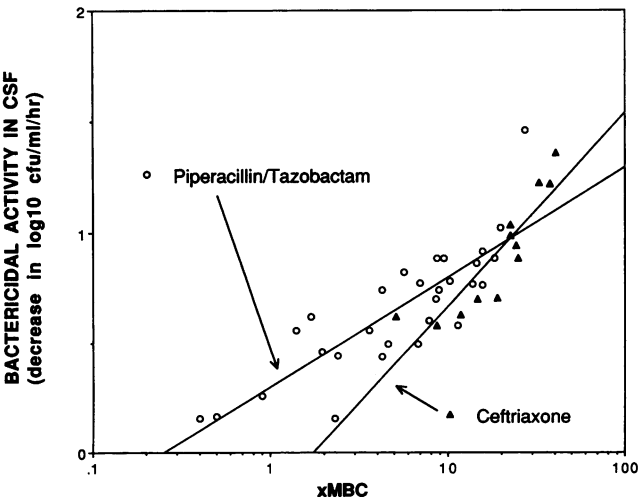

FIG. 1. Correlation between CSF drug concentration relative to the MBC and bacterial killing in CSF of experimentally infected rabbits with meningitis due to a β-lactamase-producing strain of *E. coli*. The result for each animal is plotted as ratio of the mean concentration of the drug in CSF to the MBC versus bacterial killing in CSF over the 5-h treatment period. Spearman rank correlations (r_s) were as follows: piperacillin-tazobactam, $r_s = 0.838$, $P < 0.0001$; ceftriaxone, $r_s = 0.948$, $P < 0.0001$.

Our study provides some information about the potential usefulness of piperacillin-tazobactam for the therapy of bacterial meningitis, but many aspects need to be explored in additional studies. It appears clear from our results that tazobactam has favorable CSF pharmacokinetics and can restore the bactericidal activity of piperacillin in CSF infected with a β-lactamase-producing strain. On the other hand, as exemplified by the strain used in our study, piperacillin is somewhat less active in vitro against many such strains than some of the newer cephalosporins. Even though the bactericidal activity of piperacillin-tazobactam was comparable to that of ceftriaxone, when adjusted for the CSF drug concentration/MBC ratio, the lower intrinsic activity of piperacillin may make it difficult in some cases to achieve the very high concentrations in CSF necessary for a rapid bactericidal activity. Furthermore, not all β-lactamases are effectively inhibited by tazobactam (11). Pharmacokinetic properties such as serum half-life also affect the clinical usefulness of a drug. This aspect has not been investigated in this study, which was designed to examine in a standardized fashion the CSF bactericidal activity relative to the ratio between CSF drug concentrations and the in vitro activity of the drugs. Thus, while our results suggest some interesting properties of piperacillin-tazobactam for the therapy of bacterial meningitis, more studies are needed before the role of this drug combination in the therapy of bacterial meningitis in humans can be assessed.

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