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Kinetics of Piperacillin and Tazobactam in Ventricular Cerebrospinal Fluid of Hydrocephalic Patients†

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Its broad antibacterial spectrum qualifies the combination of piperacillin and tazobactam for therapy of nosocomial bacterial central nervous system (CNS) infections. Since these infections sometimes are accompanied by only minor dysfunction of the blood-cerebrospinal fluid (CSF) barrier, patients with noninflammatory occlusive hydrocephalus who had undergone external ventriculostomy were studied ($n = 9$; age range, 48 to 75 years). After administration of the first dose of piperacillin (6 g)-tazobactam (0.5 g) over 30 min intravenously, serum and CSF were drawn repeatedly and analyzed by high-performance liquid chromatography. Pharmacokinetics were determined by noncompartmental analysis. Maximum concentrations of piperacillin in CSF ranged from 8.67 to <0.37 mg/liter (median, 3.42 mg/liter), and those of tazobactam ranged from 1.37 to 0.11 mg/liter (median, 0.45 mg/liter). CSF maxima were observed, in median, 1.5 and 2 h after the end of the infusion. Elimination in CSF was considerably slower than in serum (median half-life at beta phase for piperacillin, 5.9 h in CSF versus 1.47 h in serum; for tazobactam, 6.1 h versus 1.34 h). For tazobactam, the ratio of the area under the concentration-time curve (AUC) in CSF to the AUC in serum was approximately three times as high as that for piperacillin (medians, 0.106 versus 0.034). In view of the tazobactam concentrations in CSF observed in this study, the practice of using a constant concentration of 4 mg of tazobactam per liter for MIC determination is inadequate for intracranial infections. Larger amounts of tazobactam than the standard dose of 0.5 g three times daily may be necessary for CNS infections.

The antibiotic combination of piperacillin and tazobactam has a broad antibacterial spectrum, including most of the pathogens responsible for bacterial central nervous system (CNS) infections. Unlike newer cephalosporins, piperacillin is active against enterococci, many anaerobes, and *Listeria monocytogenes*. Piperacillin has been shown to be effective in experimental and human *Pseudomonas aeruginosa*, *Escherichia coli*, and *Streptococcus* sp. meningitis (4, 25). The combination of piperacillin and tazobactam was as potent as ceftriaxone in meningitis caused by a β-lactamase-producing *E. coli* strain (10). The combination also appears promising for the therapy of β-lactamase-producing *P. aeruginosa*, *Acinetobacter* sp., and *Staphylococcus aureus* CNS infections. In particular, piperacillin and tazobactam may be of value in CNS infections caused by *Enterobacteriaceae* producing extended-spectrum β-lactamases which hydrolyze newer cephalosporins (12).

Many CNS infections caused by the pathogens mentioned are of nosocomial origin and are sometimes accompanied by only minor disruption of the blood-cerebrospinal fluid (CSF) barrier. For this reason, we studied the kinetics of piperacillin and tazobactam in the ventricular CSF of patients with external ventriculostomy in the absence of pronounced meningeal inflammation.

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MATERIALS AND METHODS

Nine patients (three females, six males; age range, 48 to 75 years; serum creatinine, 0.6 to 1.8 mg/dl) with extracerebral infections caused by bacteria with either proven or (when treatment had to be initiated before susceptibility data were available) presumed susceptibility to piperacillin-tazobactam were included in this study. They had undergone external ventriculostomy due to noninflammatory occlusive hydrocephalus (CSF erythrocyte count, 1 to 106 mm^{-3} [median, 9 mm^{-3}]; CSF protein content, 172 to 1,990 mg/liter [median, 948 mg/liter]) and received a first dose of 6 g of piperacillin and 0.5 g of tazobactam (4.5 g of Tazobac and 2 g of Pipril; Lederle Arzneimittel GmbH & Co., Wolfratshausen, Germany) simultaneously over 30 min via a single venous catheter. These doses were chosen because 6 g is the highest single piperacillin dose and 0.5 g is the highest single tazobactam dose approved by the German drug regulatory authorities. At 16 h later, treatment was continued with 4.5 g of Tazobac three times daily or twice daily. Further information on the patients studied is in Table 1.

Arterial blood and ventricular CSF from indwelling catheters were sampled before and at the end of the infusion and at 10 and 30 min and 1, 2, 4, 7, 10, 13, and 16 h after the end of the infusion. Ventriculostomy samples were obtained from the port nearest the site of insertion, and 1 ml of CSF was discarded before the CSF sample (1 ml) was collected. Blood was allowed to clot, and then blood and CSF were centrifuged immediately and the supernatants were frozen at −70°C.

Informed consent for participation was obtained from the nearest relative. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Göttingen.

After deproteinization with acetonitrile, drug concentrations in serum and CSF were measured by high-performance liquid chromatography (HPLC). Piperacillin was separated by using a potassium dihydrogen phosphate-acetonitrile mobile phase and a LiChrosphere-C_{18}, 5-μm column and detected at 220 nm. Tazobactam was separated on a dual-column HPLC system (precolumn, RP 2, 10 μm; analytical column, Spherisorb ODS II, 5 μm; mobile phase, 100 mM sodium dihydrogen phosphate, 5 mM tetrabutylammonium hydrogen sulfate, 5% (precolumn) or 10% (analytical column) acetonitrile, pH 6.5) and detected at 210 nm. The serum and CSF samples were measured against a calibration series prepared with drug-free serum and CSF, respectively. No interference was observed in serum and CSF for tazobactam, piperacillin, or the internal standards, except for the CSF of patient 4, where tazobactam could not be quantified due to peak interference. Quantification was carried out by weighted (1/concentration) linear regression. Linearity of tazobactam and piperacillin calibration curves in serum was demonstrated between 0.084 and 49 mg/liter and between 0.35 and 200 mg/liter. In CSF, linearity in the following concentration ranges was found: tazobactam, 0.087 to 51.5 mg/liter; piperacillin, 0.37 to 200 mg/liter. The

TABLE 1. Characterization of the patients investigated in the sequence of descending peak piperacillin concentrations in CSF

Patient no.	Age (yrs), sex[a]	Wt (kg)	Disease	Time interval (days)[b]	Osmotherapy, corticoids	Serum creatinine (mg/dl)	CSF analysis[c]			
							Protein (mg/liter)	Q_{Alb} (10^{-3})	WBC/mm^3	RBC/mm^3
1	48, M	85	Intracerebral hemorrhage	5	Mannitol	1.2	948	5.8	106	14,933
2	50, M	100	Intracerebral hemorrhage	8		1.8	838	2.9	65	29,400
3	70, M	85	Intracerebral hemorrhage	3	Mannitol	1.0	1,990	5.4	9	7,723
4	60, M	80	Subarachnoid hemorrhage	9	Mannitol, dexamethasone	1.0	1,674	6.9	49	33,877
5	52, F	65	Subarachnoid hemorrhage	15		0.8	1,882	3.8	16	8,533
6	60, F	70	Subarachnoid hemorrhage	3	Dexamethasone	0.9	172	2.7	4	512
7	63, F	80	Subarachnoid hemorrhage	12	Glycerol, dexamethasone	0.6	387	2.8	9	5,034
8	49, M	90	Infratentorial infarction	6		1.1	418	6.7	1	20
9	75, M	80	Subarachnoid hemorrhage	5	Mannitol, dexamethasone	1.2	1,444	25.3	2	853

[a] M, male; F, female.
[b] Time interval between insertion of external ventriculostomy and the first piperacillin-tazobactam infusion. The laboratory results presented were obtained on the day of drug administration.
[c] Q_{Alb}, CSF-to-serum albumin ratio; WBC, leukocytes; RBC, erythrocytes.

lowest calibration levels were taken as quantification limits. Samples with drug concentrations above the quantification limits were prediluted with tested drug-free plasma.

For determination of interassay variation, spiked quality control samples were prepared by adding defined amounts of piperacillin and tazobactam to tested drug-free serum and CSF. The levels of interassay precision of the spiked tazobactam quality controls in serum were 3.6% (39.8 mg/liter), 3.7% (3.5 mg/liter) and 4.3% (0.34 mg/liter). For piperacillin, the levels of interassay precision in serum found were 4.5% (146 mg/liter), 0.4% (29.1 mg/liter), 2.8% (5.69 mg/liter), and 3.4% (1.12 mg/liter). The accuracy of the tazobactam standards in serum ranged from 99.9 to 100.5%, and that of piperacillin standards ranged from 102.1 to 104.5%. The levels of interassay precision of the spiked tazobactam quality controls in CSF were 4.9% (39.9 mg/liter), 5.2% (3.88 mg/liter), and 2.6% (0.39 mg/liter). For piperacillin, the levels of interassay precision in CSF were 2.2% (154 mg/liter), 1.3% (30.6 mg/liter), 2.7% (6.07 mg/liter), and 1.4% (1.20 mg/liter). The accuracy of the tazobactam standards in CSF ranged from 99.9 to 101.4%, and that of piperacillin standards ranged from 96.6 to 102.0%.

Concentration-time curves for serum and CSF were analyzed by noncompartmental methods by using the program Topfit 2.0 (Gödecke-Schering-Thomae). Peak drug concentrations in serum and CSF (C_{maxS} and C_{maxCSF}, respectively) and time from the end of the infusion to the concentration peak (t_{maxS} and t_{maxCSF}) were taken directly from the concentration-time curves. Elimination rate constants (k_β) were determined by log-linear regression analysis [weighting function $g(y_i) = 1/y_i$, where $g(y_i)$ is the weighted concentration and y_i is the individual concentration as determined by HPLC], and half-lives ($t_{1/2\beta}$) as $\ln 2/k_\beta$. The areas under the concentration-time curves for serum and CSF up to the last measurable drug concentration (AUC_{S0-t} and AUC_{CSF0-t}) were estimated by the linear trapezoidal rule. Extrapolation to infinity (AUC_S and AUC_{CSF}) was done by dividing the last measurable drug concentration (C_l) by the k_β, and the ratio of $AUC_{CSFextrapolated}$ to AUC_{CSF} was expressed as a percentage. Total clearance from serum (CL) was calculated as dose/AUC_S, and the apparent volume of distribution (V_β) was calculated as dose/$AUC_S \cdot k_\beta$. The volume of distribution at steady state (V_{ss}) was determined as CL · (mean residence time − infusion time/2), where the mean residence time is defined as $\int_0^\infty C_S(t) \cdot t\,dt/AUC_S$, where C_S is the drug concentration in serum.

Data were expressed as medians and ranges. For median determination and rank correlation analysis, the maximum piperacillin concentration (C_{maxCSF}), AUC_{CSF}, and AUC_{CSF}/AUC_S of patient 9, all of whose drug concentrations in CSF were below the quantification limit of 0.37 mg/liter, were assigned the lowest rank. For median t_{maxCSF} and $t_{1/2\beta CSF}$ of piperacillin, patient 9 was not considered. Since the tazobactam concentrations in the CSF of patient 4 could not be measured because of peak interference and were not necessarily below the quantification limit, this patient was not considered for the determination of all medians of tazobactam parameters in CSF.

Although some kinetic parameters did not obey Gaussian distribution (especially t_{maxCSF} and AUC_{CSF}/AUC_S of tazobactam), means ± standard deviations (SD) were also provided to facilitate comparison with data on the CSF penetration of other compounds.

RESULTS

At the end of the infusion, piperacillin concentrations in serum were more than 10 times as high as those of tazobactam. The CL and k_β of both drugs in serum were almost identical, whereas the V_{ss} of tazobactam was consistently higher than that of piperacillin (medians, 23.3 and 18.3 liters) (Table 2).

C_{maxCSF} of piperacillin ranged from below the quantification limit of 0.37 to 8.67 mg/liter, and the tazobactam maxima in CSF were 0.11 to 1.37 mg/liter (Table 3). The C_{maxCSF} of piperacillin and tazobactam showed a moderate correlation (Spearman's rank correlation coefficient $r_S = 0.52$, $n = 8$, $P = 0.20$). The AUC_{CSF}/AUC_S of piperacillin correlated with the AUC_{CSF}/AUC_S of tazobactam at a low level ($r_S = 0.19$, $n = 8$, $P = 0.66$). In five patients, the t_{maxCSF} of both compounds occurred during the first 2 h after the end of the infusion. In three patients, however, tazobactam CSF maxima were reached 10 to 16 h after the end of the infusion. The $t_{1/2CSF}$ values of both drugs were similar and consistently greater than

TABLE 2. Kinetic properties of piperacillin and tazobactam in serum after simultaneous i.v. administration of 6 and 0.5 g

Drug and patient no.	C_{max} (mg/liter)	AUC (mg · h/liter)	CL (ml/min)	$t_{1/2\beta}$ (h)	V_β (liters)	V_{ss} (liters)	$AUC_{piperacillin}/AUC_{tazobactam}$
Piperacillin							
1	292	381	263	1.11	25.2	21.6	12.5
2	404	630	159	1.40	19.3	16.1	15.1
3	333	495	202	1.19	20.8	17.8	11.4
4	355	438	228	1.59	31.4	16.9	12.7
5	348	470	213	1.48	27.3	20.5	11.3
6	482	699	143	1.47	18.2	13.7	12.0
7	334	382	262	1.14	25.7	19.5	16.2
8	354	531	188	1.47	24.0	18.3	11.9
9	317	586	171	1.75	25.8	20.3	10.4
Median	348	495	202	1.47	25.2	18.3	12.0
Mean	358	512	203	1.40	24.2	18.3	12.6
SD	56	110	43	0.22	4.2	2.5	1.9
Tazobactam							
1	20.2	30.4	274	1.11	26.3	24.4	
2	29.0	41.6	200	1.24	21.5	18.2	
3	25.2	43.3	193	1.24	20.7	27.4	
4	31.7	34.4	242	1.72	36.0	19.9	
5	28.7	41.5	201	2.38	41.3	25.9	
6	36.6	58.3	143	1.63	20.2	15.8	
7	21.3	23.6	353	1.27	38.8	25.2	
8	29.0	44.6	187	1.34	21.6	19.1	
9	27.4	56.2	148	2.12	27.2	23.3	
Median	28.7	41.6	200	1.34	26.3	23.3	
Mean	27.7	41.5	216	1.56	28.2	22.1	
SD	5.0	11.2	66	0.44	8.4	4.0	

TABLE 3. Kinetic properties of piperacillin and tazobactam in CSF after simultaneous i.v. administration of 6 and 0.5 g[a]

Drug and patient no.	C_{max} (mg/liter)	t_{max} (h)	AUC (mg · h/liter)	Extrapolated AUC (%)	$t_{1/2\beta}$ (h)	AUC_{CSF}/AUC_S	$AUC_{piperacillin}/AUC_{tazobactam}$
Piperacillin							
1	8.67	0.17	18.1	6.3	3.0	0.048	9.1
2	4.26	0.5	21.3	1.4	4.5	0.034	4.6
3	4.23	2	35.3	10.8	4.6	0.071	8.0
4	3.89	4	54.5	20.3	5.8	0.124	
5	3.42	0.5	29.9	17.2	6.1	0.064	6.4
6	1.15	2	19.4	33.0	10.9	0.028	3.5
7	0.87	1	9.3	15.2	5.9	0.024	0.5
8	0.59	2	9.6	30.3	9.5	0.018	2.0
9	BQL[a]		BQL				
Median	3.42	1.5	19.4	16.2	5.9	0.034	4.6
Mean	3.39	1.5	24.7	16.8	6.3	0.051	4.9
SD	2.64	1.3	15.0	11.0	2.6	0.035	3.1
Tazobactam							
1	0.46	0.5	2.0	30.4	2.4	0.064	
2	0.64	2	4.6	21.5	7.4	0.110	
3	0.57	2	4.4	12.2	4.0	0.103	
4	PI[b]		PI			PI	
5	0.44	0.5	4.7	26.8	8.2	0.114	
6	0.20	2	5.5	54.9	17.9	0.094	
7	1.37	10	17.4	23.0	4.8	0.739	
8	0.23	16	4.8[c]	42.5		0.108	
9	0.11	10	1.7[c]	57.4		0.030	
Median	0.45	2	4.7	28.6	6.1	0.106	
Mean	0.50	5.4	5.6	33.6	7.4	0.170	
SD	0.40	5.8	4.9	16.4	5.6	0.232	

[a] BQL, below the quantification limit of 0.37 mg/liter.
[b] PI, peak interference.
[c] The median k_β was used to estimate AUC_{CSF} and AUC_{CSF}/AUC_S.

the $t_{1/2S}$ values (Table 3). The concentration-time curves of piperacillin and tazobactam in serum and CSF constructed from the median concentrations of all patients are shown in Fig. 1. AUC_{CSF}/AUC_S, as a measure of overall CSF penetration, was approximately three times as high with tazobactam as with piperacillin (Table 3).

DISCUSSION

For piperacillin, the median AUC in serum was somewhat higher (495 versus 452 mg · h/liter) and the $t_{1/2}$ was longer (1.47 versus 1.05 h) than average values found in healthy adults (data summarized in reference 7). Although serum creatinine was elevated only in patient 2, this reflects a moderate impairment of renal function in our patients, which is often observed in elderly and intensive care patients despite normal plasma creatinine values. The CL, V, and $t_{1/2S}$ observed in this study compared well with data obtained from elderly patients undergoing colorectal surgery (11). Probably reflecting its lower molecular weight, the V of tazobactam in our patients and in those with colorectal surgery was slightly higher than that of piperacillin (11).

The disturbance of the blood-CSF barrier of our patients, as estimated by the CSF protein content and by the CSF-to-serum albumin ratio, ranged from not detectable to moderate. Similar conditions can be encountered in CNS infections with an absent or mild inflammatory host reaction, as in the immunocompromised and in patients with septic encephalitis, and ventriculitis. Even early bacterial meningitis can occur with minimal or absent CSF abnormalities (14). Furthermore, the

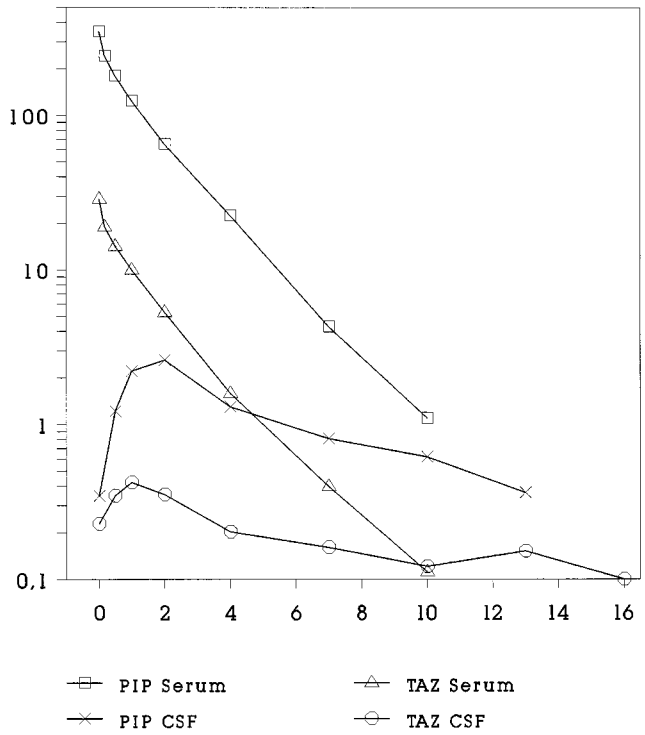

FIG. 1. Concentration-time curves of piperacillin (PIP) and tazobactam (TAZ) in serum and CSF. The graph represents the medians of nine patients. Note the slow elimination of both drugs from the CSF compartment.

use of corticoids impedes the CSF penetration of antibiotics (2). For these reasons, the drug concentrations in CSF measured by us are probably the minimum concentrations which can be counted upon in bacterial CNS infections. The current practice of measuring concentrations of antibiotics in lumbar CSF and assuming identical antibiotic concentrations in all parts of the CSF compartment overestimates the antibiotic concentrations in the vicinity of the brain. From differences in the concentrations of protein and other compounds in lumbar, cisternal, and ventricular CSF samples, it is well known that the single parts of the CSF compartment do not fully equilibrate (5). In a recent study done with primates, the AUC of lamivudine was approximately five times as high in the lumbar CSF as in the ventricular CSF after intravenous infusion (1).

In fully developed meningitis, higher piperacillin concentrations in CSF than those found by us have been observed. In this condition, concentrations in lumbar CSF of 7 to 10 mg/liter are usually present during high-dose intravenous (i.v.) therapy (3, 4), and concentrations in lumbar CSF of up to 35 mg/liter may occur (3, 4, 7).

In the present study, after a single dose of 6 g, maximum concentrations of piperacillin in CSF (median, 3.42 mg/liter) were approximately eight times higher than those after a 2-g i.v. dose of cefotaxime or ceftriaxone (19) and the median was twice that seen after administration of 3 g of ceftazidime (18). Despite similar clinical characterizations of patients participating in both studies, the range of the maximum concentrations in CSF was much greater with piperacillin (below the quantitation limit of 0.37 mg/liter up to 8.67 mg/liter) than with ceftazidime. The median AUC_{CSF}/AUC_S ratio of piperacillin (0.034) compared well with the median AUC_{CSF}/AUC_S ratio of ceftazidime (0.054) (18) but was below that of cefotaxime (0.12) and approximately five times the median AUC_{CSF}/AUC_S of ceftriaxone (0.007) (19).

At physiological pH, tazobactam is a highly hydrophilic drug. The pK_a is 2.1; i.e., at pH 7.4, the drug is almost completely ionized (15). The pK_a of piperacillin is 4.14. The degree of ionization at pH 7.4, therefore, is slightly lower. Since on reversed-phase HPLC columns its retention time is longer than that of tazobactam, piperacillin appears to be somewhat less hydrophilic than tazobactam (15). The protein binding of both compounds in human plasma is approximately 20% (23). The CSF penetration of tazobactam, as assessed by the AUC_{CSF}/AUC_S, was three times as great as that of piperacillin; i.e., the lower molecular mass of tazobactam (322 versus 540 Da) probably outweighed its higher hydrophilicity (22).

As observed with other hydrophilic drugs (16, 18–20), elimination of both compounds from CSF was considerably slower than that from serum. The long elimination half-life of piperacillin and tazobactam in CSF suggests likely accumulation after repeated dosing. Assuming linear kinetics, mean steady-state concentrations in CSF can be estimated from single-dose kinetic data by dividing the AUC_{CSF} by the dosing interval (17). Using the median AUC_{CSF} of tazobactam of 4.7 mg · h/liter and administering the commercial product of 6 g of piperacillin and 0.75 g of tazobactam every 6 h would lead to an estimated mean steady-state tazobactam concentration of 1.18 mg/liter of CSF.

For determination of the MIC of the piperacillin-tazobactam combination, a constant concentration of 4 mg of tazobactam per liter, which is derived from concentrations observed in serum, is usually added to decreasing piperacillin concentrations. With the restriction that the MIC was determined in the presence of 4 mg of tazobactam per liter, the maximum drug concentrations in CSF in this study were above the MICs for approximately 90% of the *Acinetobacter* sp. and *S. aureus* strains isolated in Germany but above those of only 25% of the *P. aeruginosa* strains tested (6). However, with the drug levels in CSF observed in this study, a piperacillin concentration/MIC ratio above 10, which is necessary for a rapid bactericidal effect in experimental meningitis (21, 24), can be attained only in the presence of highly susceptible pathogens.

Although the AUC_{CSF}/AUC_S ratio of tazobactam was comparatively high, the absolute tazobactam concentrations in CSF were far below 4 mg/liter. Tazobactam is a high-affinity β-lactamase inhibitor active against most plasmid-mediated and chromosomal β-lactamases. In some cases, the concentrations encountered by us in CSF are probably sufficient for protection of piperacillin. However, in *E. coli* isolates with different levels of piperacillin resistance due to TEM-1 β-lactamase activity, the tazobactam concentrations required to reduce the piperacillin MIC to 1 mg/liter ranged from 1.2 to 8.1 mg/liter (13). In the rabbit model of TEM-3 β-lactamase producing *Klebsiella pneumoniae* meningitis, a dose of 10 mg of tazobactam and 80 mg of piperacillin per kg per h was much less effective than a combination of 25 mg of tazobactam and 80 mg of piperacillin per kg per h (12). These experimental data and our kinetic data imply that administration of 0.5 g of tazobactam three times daily may not be adequate for bacterial meningitis and other CNS infections. Even when accumulation in the CSF compartment and an increase in the daily dose of the commercial product (Tazobac) containing tazobactam and piperacillin in a 1:8 ratio are taken into account, the tazobactam concentrations in ventricular CSF will probably stay substantially below 4 mg/liter.

For these reasons, either the MIC of piperacillin should be determined in the presence of 0.4 mg of tazobactam per liter or the tazobactam dose should be increased, if the use of piperacillin-tazobactam for CNS infections is considered. For other infections, e.g., lung, bone, and intraabdominal infections, the kinetic data available suggest that MIC determination with a constant tazobactam concentration of 4 mg/liter is appropriate (8, 9, 11).

In conclusion, in the presence of minor impairment of the blood-CSF barrier, concentrations of piperacillin in CSF after an i.v. infusion of 6 g showed high interindividual variability, with a median C_{maxCSF} of 3.42 mg/liter. Maximum tazobactam concentrations in CSF after i.v. administration of 0.5 g (median, 0.45 mg/liter) were approximately 1 order of magnitude lower than the constant concentration of 4 mg/liter used for MIC determination. For this reason, current in vitro testing appears to be inadequate when the use of piperacillin-tazobactam for intracranial infections is anticipated. The usual doses of tazobactam may not be sufficient to supply adequate drug concentrations in CSF for the treatment of CNS infections.

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