Penetration of Sulbactam and Ampicillin into Cerebrospinal Fluid of Infants and Young Children with Meningitis

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Infusions of 50 mg of sulbactam per kg per day and 400 mg of ampicillin per kg per day in divided doses to infants and children with bacterial meningitis produced levels in cerebrospinal fluid approximately one-third those in serum. Concentrations in cerebrospinal fluid of 5.5 µg of sulbactam per ml and 16.0 µg of ampicillin per ml declined within a few days of therapy to 1.9 µg of sulbactam per ml and 5.2 µg of ampicillin per ml.

Haemophilus influenzae, Neisseria meningitidis, and *Streptococcus pneumoniae* are the leading pathogens causing bacterial meningitis in children (16, 22). For years, ampicillin was the mainstay of therapy (4). However, its effectiveness was compromised by the emergence (9, 11, 21) and increasing incidence (8, 16, 18, 19, 21) of strains of *H. influenzae* which produce β-lactamase enzymes that hydrolyze ampicillin, destroying its activity.

Sulbactam, a β-lactamase inhibitor which combines with β-lactamases to destroy their activity (10) and prevent the destruction of β-lactams, is under clinical development for coadministration with ampicillin for treatment of infections. The activity of sulbactam plus ampicillin against ampicillin-resistant strains of *H. influenzae* and *S. pneumoniae* (1, 3, 12, 13, 23) and the enhanced penetration of sulbactam through inflamed meninges (7, 17) suggested that this combination might be useful in the treatment of bacterial meningitis in children.

Therefore, we examined the efficacy of ampicillin plus sulbactam in the treatment of meningitis in infants and young children and compared this therapy with the standard therapy of ampicillin plus chloramphenicol. The results (reported previously on 41 of 53 patients receiving sulbactam plus ampicillin [14]) showed eradication of bacteria, including four ampicillin-resistant pathogens, from cerebrospinal fluid (CSF) from 34 of 35 evaluable patients during therapy with ampicillin plus sulbactam. As a part of this study, we also examined the penetration of sulbactam and ampicillin into CSF.

MATERIALS AND METHODS

A total of 53 children and infants admitted to Children's Hospital National Medical Center, Washington, D.C., or the Robert Reid Cabral Children's Hospital, Santo Domingo, Dominican Republic, with a clinical diagnosis of meningitis were given ampicillin plus sulbactam. The mean age of the 48 patients from whom samples were obtained was 17.6 months (standard deviation [SD], 28.3 months; median, 8.5 months; range, 1 to 176 months), and the mean weight was 9.8 kg (SD, 6.35 kg; median, 8.0 kg; range, 3 to 34 kg). Of these patients, 42 suffered from concurrent diseases (anemia, 35; malnutrition, 14; septicemia, 9; pneumonia, 1; congenital

hydrocephalus, 1; sickle-cell anemia, 1; Down's syndrome, 1; and cardiac murmurs, 1). Microbiological evaluation of baseline CSF samples revealed *H. influenzae* (21 isolates), *S. pneumoniae* (5 isolates), *N. meningitidis* (5 isolates), and single isolates each of *Neisseria* sp., *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Listeria monocytogenes*.

Sulbactam (50 mg/kg per day) plus 400 mg of ampicillin per kg per day were administered in four (42 patients) or six (6 patients) divided doses per day by 30- to 60-min intravenous infusions. CSF was obtained by lumbar puncture within an hour after the doses. The first sample was obtained approximately 48 h after initiation of therapy (after dose 8 or 9 in 23 patients at 4 doses per day [mean, 8.2 doses; SD, 2.4 doses; range, 1 to 13 doses]). Sample set 2 was obtained 1 to 5 (median, 3) days later and sample set 3 was obtained 6 to 11 (median, 8) days after sample set 1. Serum samples were also obtained at the time of the first sampling. Because of the nature of the patient population, sufficient volume to run the desired assays was sometimes not available. The samples were frozen until assays for ampicillin by bioassay (6) and for sulbactam by gas chromatography (5, 6) were done. Each assay was free from interference by the coadministered drug and had a coefficient of variation of less than 10% for quadruplicate assays. The few CSF samples with unusually high drug concentrations were correlated with very high concentrations in serum, suggesting that the high concentrations in CSF were not due to contamination.

Comparisons were made by means of paired *t* tests, whenever possible, to reduce the extensive variability expected from this patient population. Group *t* tests were used otherwise.

TABLE 1. Concentrations in serum after administration of ampicillin plus sulbactam to infants and children with meningitis[a]

Baseline presence of bacteria in CSF	Sulbactam		Ampicillin	
	No. of patients	Concn (SD) (µg/ml)	No. of patients	Concn (SD) (µg/ml)
No bacteria	13	13.9 (9.6)	11	85.5 (90.2)
Bacteria	35	18.6 (16.4)	33	86.0 (71.0)
Total		17.2 (14.8)		85.8 (74.8)

[a] Ampicillin (400 mg/kg per day) plus sulbactam (50 mg/kg per day) was given in four or six divided doses per day for approximately 48 h.

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TABLE 2. Concentrations in CSF after administration of ampicillin plus sulbactam to infants and children with meningitis[a]

Sample set[b]	Baseline presence of bacteria in CSF	Sulbactam			Ampicillin		
		No. of patients	Concn (SD) (μg/ml)	CSF/serum (SD)	No. of patients	Concn (SD) (μg/ml)	CSF/serum (SD)
1	No bacteria	9	1.9 (1.7)	0.11	7	2.5 (2.4)	0.05
1	Bacteria	31	5.5 (8.7)	0.34 (0.26)	26	16.0 (20.8)	0.39 (0.49)
2	Bacteria	27	1.9 (2.4)[c]		22	5.2 (4.7)[c]	
3	Bacteria	27	0.89 (1.16)[d]		25	3.6 (5.3)[d]	

[a] Ampicillin (400 mg/kg per day) plus sulbactam (50 mg/kg per day) was given in four or six divided doses.
[b] Sample set 1, samples drawn 24 to 48 h after initiation of therapy; sample set 2, samples obtained 1 to 5 days after sample 1; sample set 3, samples obtained 6 to 11 days after sample 1.
[c] Paired t tests of differences between samples in set 1 and set 2 from the same subject; sulbactam mean difference, 4.35 μg/ml; $P = 0.015$; ampicillin mean difference, 14.42 μg/ml; $P = 0.004$.
[d] Paired t tests of differences between samples in set 2 and set 3 from the same subject; sulbactam mean difference, 1.10 μg/ml; $P = 0.003$; ampicillin mean difference, 2.94 μg/ml; $P = 0.0005$.

RESULTS AND DISCUSSION

The mean concentrations in serum on day 1 of sampling were 17.2 μg of sulbactam per ml and 85.9 μg of ampicillin per ml (Table 1). The short serum half-lives of sulbactam (0.92 h) and ampicillin (0.83 h) in young children (11 to 18 months old, weighing 9 to 11 kg) (Pfizer Central Research, data on file; Pfizer, Inc., New York, N.Y.) suggest that the 4- and 6-h dosing intervals would not result in noticeable accumulation of either drug during the course of therapy. Although there was little difference in mean concentrations in serum between patients with positive CSF cultures (+M) and patients with sterile CSF (−M) on sampling day 1 (Table 1), the levels of drug in CSF were higher in +M patients (Table 2). Mean penetration ratios (concentration in CSF/ concentration in serum) in +M patients of 0.34 (sulbactam) and 0.39 (ampicillin) were much greater than those of −M patients whose ratios for sulbactam were (except one) below 0.17 and whose ratios for ampicillin were all below 0.10 (Table 2.). The concentrations of sulbactam in CSF were correlated with concentrations in serum ($r^2 = 0.665$, $P < 0.0001$) and with the concentrations of ampicillin in CSF ($r^2 = 0.790$, $P < 0.0001$).

Mean concentrations of both drugs in CSF in +M patients declined within several days to one-third those of sample 1 (Table 2.). The concentrations decreased further between sampling times 2 and 3 to produce concentrations after 1.5 weeks of dosing only one-sixth to one-fourth of those of the first sample. The decline in mean concentrations of sulbactam and ampicillin in CSF during the course of therapy was also observed in the CSF of individual patients. A total of 16 of 21 +M patients from whom three CSF samples were assayed for sulbactam showed patterns with a high concentration in CSF in sample 1, followed by a markedly lower concentration after an additional 1 to 5 days of therapy, and a concentration after further therapy equal to or lower than that of the previous sample. A similar pattern was observed for ampicillin concentrations in CSF from 14 of 17 +M patients.

The penetration ratio of ampicillin into CSF (39%) was at least as high as the penetration ratio in patients given ampicillin alone (25% on days 1 to 3 [20]), suggesting that coadministration of sulbactam does not decrease the penetration of ampicillin into CSF. As shown elsewhere for other kinetic parameters (2, 5, 6, 15), the kinetics of sulbactam and ampicillin in CSF are similar. Penetration of both drugs into CSF was greater in patients with bacterial meningitis than in patients whose CSF did not contain bacteria. Also, ratios of penetration into CSF and the decreases of concentrations in

CSF during the course of therapy with the two drugs were similar. Since sulbactam and ampicillin do not readily penetrate uninflamed meninges, the decline in concentrations of drug in CSF may be additional evidence for the meningeal healing shown by the decline in levels of leukocytes and protein in CSF within 48 to 72 h of initiation of therapy (14). Furthermore, in one patient whose meningitis (caused by *Klebsiella pneumoniae*) did not respond to treatment, the initial high concentrations of sulbactam and ampicillin did not decline during treatment.

The results of this study demonstrate that sulbactam and ampicillin readily penetrate into the CSF of patients with bacterial meningitis and the concentrations in CSF decline during the course of therapy. The high cure rates (14) indicate that this combination is highly effective in the treatment of meningitis in infants and children.

LITERATURE CITED

1. Aswopokee, N., and H. C. Neu. 1978. A sulfone beta-lactam compound which acts as a beta-lactamase inhibitor. J. Antibiot. 31:1238–1244.
2. Brown, R. M., R. Wise, J. M. Andrews, and J. Hancox. 1982. Comparative pharmacokinetics and tissue penetration of sulbactam and ampicillin after concurrent intravenous administration. Antimicrob. Agents Chemother. 21:565–567.
3. 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.
4. Fleming, P. C., J. D. M. Murray, M. W. Fujiwara, J. S. Prichard, and G. A. McNaughton. 1967. Ampicillin in the treatment of bacterial meningitis, p. 47–52. Antimicrob. Agents Chemother. 1966.
5. Foulds, G., A. K. Knirsch, J. P. Stankewich, and D. J. Weidler. 1985. The parenteral kinetics of ampicillin/sulbactam in man. Clin. Pharmacol. Res. 5:79–86.
6. Foulds, G., J. P. Stankewich, D. C. Marshall, M. M. O'Brien, S. L. Hayes, D. J. Weidler, and F. G. McMahon. 1983. Pharmacokinetics of sulbactam in humans. Antimicrob. Agents Chemother. 23:692–699.
7. Hanninen, P., and T. Rossi. 1986. Penetration of sulbactam into cerebrospinal fluid in patients with viral meningitis or without meningitis. Rev. Infect. Dis. 8(Suppl. 5):S609–S611.

8. Istre, G. R., J. S. Conner, M. P. Globe, and R. S. Hopkins. 1984. Increasing ampicillin-resistance rates in *Haemophilus influenzae* meningitis. Am. J. Dis. Child. **138:**366–369.

9. Khan, W., S. Ross, W. Rodriguez, G. Controni, and A. K. Saz. 1974. *Haemophilus influenzae* type b resistant to ampicillin. J. Am. Med. Assoc. **229:**298–301.

10. Labia, R., V. Lelievre, and J. Peduzzi. 1980. Inhibition kinetics of three R-factor-mediated β-lactamases by a new β-lactam sulfone (CP 45899). Biochim. Biophys. Acta **611:**351–357.

11. Nelson, J. D. 1974. Should ampicillin be abandoned for treatment of *Haemophilus influenzae* disease. J. Am. Med. Assoc. **229:**322–323.

12. Retsema, J. A., A. R. English, and A. E. Girard. 1980. CP-45,899 in combination with penicillin or ampicillin against penicillin-resistant *Staphylococcus, Haemophilus influenzae*, and *Bacteroides*. Antimicrob. Agents Chemother. **17:**615–622.

13. Retsema, J., A. English, A. Girard, J. Lynch, M. Anderson, L. Brennan, C. Cimochowski, J. Faiella, W. Norcia, and P. Sawyer. 1986. Sulbactam/ampicillin: in vitro spectrum, potency and activity in acute models of infection. Rev. Infect. Dis. **8**(Suppl. 5):S528–S534.

14. Rodriguez, W. J., W. Khan, J. Puig, J. Feris, S. Harmon, B. G. Gold, and S. Ahmed. 1986. Sulbactam/ampicillin vs. chloramphenicol/ampicillin for the treatment of meningitis in infants and children. Rev. Infect. Dis. **8**(Suppl. 5):S620–S629.

15. Rogers, H. J., I. D. Bradbrook, P. J. Morrison, R. G. Spector, D. A. Cox, and L. J. Lees. 1983. Pharmacokinetics and bioavailability of sultamicillin estimated by high performance liquid chromatography. J. Antimicrob. Chemother. **11:**435–445.

16. Schlech, W. F., J. I. Ward, J. D. Band, A. Hightower, D. W. Fraser, and C. V. Broome. 1985. Bacterial meningitis in the United States, 1978 through 1981. The national bacterial meningitis surveillance study. J. Am. Med. Assoc. **253:**1749–1754.

17. Stahl, J.-P., J.-P. Bru, G. Fredj, K. W. Brammer, M.-R. Mallaret, and M. Micoud. 1986. Penetration of sulbactam into the cerebrospinal fluid of patients with bacterial meningitis receiving ampicillin therapy. Rev. Infect. Dis. **8**(Suppl. 5): S612–S616.

18. Stephenson, W. P., G. Doern, N. Gantz, L. Lipworth, and K. Chapin. 1985. Pharyngeal carriage rates of *Haemophilus influenzae*, type b and non-b, and prevalence of ampicillin-resistant *Haemophilus influenzae* among healthy day-care children in central Massachusetts. Am. J. Epidemiol. **122:**868–875.

19. Thornsberry, C., and L. A. Kirven. 1974. Antimicrobial susceptibility of *Haemophilus influenzae*. Antimicrob. Agents Chemother. **6:**620–624.

20. Thrupp, L. D., J. M. Leedom, D. Ivler, P. F. Wehrle, B. Portnoy, and A. W. Mathies. 1966. Ampicillin levels in the cerebrospinal fluid during treatment of bacterial meningitis, p. 206–213. Antimicrob. Agents Chemother. 1965.

21. Tomeh, M. O., S. E. Starr, J. E. McGowan, P. M. Terry, and A. J. Nahmias. 1974. Ampicillin-resistant *Haemophilus influenzae* type b infection. J. Am. Med. Assoc. **229:**295–297.

22. Whitby, M., and R. Finch. 1986. Bacterial meningitis: rational selection and use of antibacterial drugs. Drugs **31:**266–278.

23. 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.