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Penetration of Aztreonam into Cerebrospinal Fluid of Patients With and Without Inflamed Meninges

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Aztreonam was administered as a single, 2-g intravenous dose to 25 patients with noninflamed meninges and to 9 patients with inflamed meninges. It was well tolerated and was detected in the cerebrospinal fluid at the initial sampling period at 1 h after the end of infusion. Aztreonam levels in the cerebrospinal fluid of patients with inflamed meninges were four times higher than those recorded for the same time period in patients with noninflamed meninges. Aztreonam concentrations in cerebrospinal fluid in the presence of normal and inflamed meninges exceeded the inhibitory and bactericidal concentrations for most gram-negative bacteria. Thus, a multiple-dose treatment regimen with 2-g intravenous doses every 6 h appears to be appropriate for clinical trials of aztreonam for the treatment of gram-negative bacillary meningitis which is caused by susceptible organisms.

Aztreonam is a new, completely synthetic, beta-lactam antibiotic possessing potent antimicrobial activity against a wide variety of commonly encountered aerobic gram-negative bacilli (1, 3, 5, 7, 8). It is highly stable against TEM and class I beta-lactamases (1, 3), appears to be relatively nontoxic in humans (H. Giamarellou, N. Galanakis, G. Koratzannis, K. Kanellakopoulou, M. El Messidi, H. Kouroumalis, and G. K. Daikos, Proc. Int. Congr. Chemother. 13th, Vienna, Austria, 1983; M. Gobernado, M. Santos, V. Marco, and E. Mascaros, Proc. Int. Congr. Chemother. 13th, Vienna, Austria, 1983) is efficacious in a variety of human bacterial infections (Giamarellou et al., 13th ICC, 1983; Gobernado et al., 13th ICC, 1983), and penetrates the subarachnoid spaces of experimentally infected rabbits (6). These qualities, suggesting that aztreonam may be useful in the treatment of gram-negative bacillary meningitis in humans, led to the current study of the penetration of aztreonam into the cerebrospinal fluid (CSF) of patients with and without inflamed meninges.

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MATERIALS AND METHODS

Aztreonam was administered as a single 2-g dose diluted in 50 ml of D5W, infused intravenously over 5 min. The study was divided into two parts: (A) included 25 patients (24 male, 1 female) with noninflamed meninges (≤5 leukocytes per mm^3 of CSF), and (B) included 9 patients (6 male, 3 female) with inflamed meninges (>5 leukocytes per mm^3 of CSF).

Patients were selected for study because they were about to undergo lumbar taps for evaluation of signs or symptoms for which the differential diagnosis of a central nervous system disorder had to be considered, e.g. headaches, previous history suggesting seizures, ill-defined behavioral problems, etc. Ultimately, no patients with noninflamed meninges were found to have central nervous system disorders. Ages ranged from 21 to 64 years. Informed consent was obtained in every instance. A leukocyte count with differential, hemoglobin, hematocrit, platelet count, SMA 20 and a urine analysis were obtained before and 48 h after administration of the drug. A cell count with differential, protein, and glucose were determined in CSF specimens. Patients were excluded if they were <18 years of age, allergic to penicillin, had serum creatinine at >1.5 mg/dl, or if there were >500 erythrocytes per mm^3 of CSF.

Serum samples were obtained 0.5 h after infusion and again at the same time a CSF sample was obtained. CSF samples were removed via lumbar puncture at ca. 1, 4, 5, 6, or 8 h after infusion. Each patient provided only one CSF sample for assay.

Aztreonam assay. CSF and serum samples were transported to the laboratory in dry ice and immediately stored at −70°C before assay within 1 week from collection. Aztreonam was assayed by using a microbiological standard cup plate technique with *Escherichia coli* SC 12155 as the indicator organism (4) and also by using high-pressure liquid chromatography (HPLC) (4). The quantitation limit of the microbiological assay was 0.04 μg/ml, whereas the limit of the HPLC for aztreonam and its metabolite SQ 26,992 was 1.0 μg/ml.

Pharmacokinetic analysis. Concentration-time course data from part A for aztreonam in serum were analyzed with the following equation: $C_S = C_0 e^{-kt}$, where C_S is the concentration of aztreonam in serum, C_0 is the concentration of aztreonam in serum extrapolated to time zero, k is the rate constant for elimination of aztreonam from serum, and t is the time after drug administration. C_0 and k were optimized by nonlinear regression analysis performed by NONLIN and AUTOAN computer programs on an IBM 370 digital computer. The area under the serum concentration-time curve (AUC) from 0.5 to 8 h was calculated using the equation:

$$\text{Serum AUC}_{0.5\text{–}8} = \int_{0.5}^{8} C_S dt = \frac{-C_0}{k}(e^{-8k} - e^{-0.5k})$$

Concentration-time data for aztreonam in CSF were analyzed using the previously-described computerized regression techniques and the equation:

$$C_{CSF} = B(-e^{-k_a t} + e^{-k_{el} t}),$$

where C_{CSF} is the concentration of aztreonam in CSF, B is a

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TABLE 1. Aztreonam concentrations in blood and CSF from 25 patient volunteers with noninflamed and from 9 patient volunteers with inflamed meninges after a 2-g i.v. infusion over 5 min[a]

No. of patients in expt group	Time CSF obtained (h)	Aztreonam concn (μg/ml) in		
		Serum collected 0.5 h after infusion	CSF	Serum collected at time CSF obtained
Noninflamed				
6	1.2 ± 0.2 (1–1.5)	145 ± 16 (121–169)	0.50 ± 0.20 (0.14–0.69)	97.7 ± 18.2 (73.2–119)
5	4.1 ± 0.3 (3.9–4.5)	140 ± 43 (109–216)	0.94 ± 0.23 (0.63–1.28)	35.3 ± 12.9 (25.1–55.4)
3	4.7 ± 0.1 (4.6–4.8)	150 ± 20 (128–167)	1.03 ± 0.20 (0.83–1.22)	26.9 ± 4.1 (22.2–29.4)
5	5.9 ± 0.2 (5.7–6.1)	137 ± 22 (100–157)	0.67 ± 0.26 (0.28–0.93)	14.9 ± 8.1 (7.0–27.6)
5	8.0 ± 0.2 (7.8–8.4)	125 ± 15 (105–138)	0.94 ± 0.60 (0.51–1.97)	8.5 ± 1.3 (7.4–10.5)
1	9	130	1.19	3.2
Inflamed				
5	1.1 ± 0.2 (0.9–1.4)	126 ± 18 (100–141)	1.98 ± 3.44 (0.16–8.11)	88.4 ± 21.5 (62.6–107)
1	2.2	139	1.98	54.7
3	4.2 ± 0.2 (4.0–4.3)	112 ± 27 (84.2–139)	3.22 ± 2.99 (1.01–6.63)	18.0 ± 7.2 (9.72–22.6)

[a] The aztreonam concentrations were determined by bioassay as described in the text. Values are the means ± the standard deviations; numbers in parentheses represent ranges.

coefficient, k_a is the rate constant for absorption into CSF, and k_{el} is the rate constant for elimination from CSF.

A detailed pharmacokinetic analysis was not performed on the limited amount of data available in part B.

RESULTS

Part A. CSF values for clinical laboratory tests immediately before administration of aztreonam in the group of 25 patient volunteers with noninflamed meninges were a mean leukocyte count of 0.5/mm^3 (range, 0 to 2) round cells, mean protein of 50 mg/dl (range, 21 to 111), mean sugar of 73 mg/dl (range, 28 to 145), and a mean erythrocyte count of 23/mm^3 (range, 0 to 195).

In these patients, aztreonam was detected in the CSF as early as 1 h after infusion (Table 1), reached peak values at ca. 4 h, and then appeared to plateau at about 1.0 μg/ml. Eight hours after infusion, while aztreonam concentrations in serum were decreasing but still were in excess of 8 μg/ml, the drug concentrations in CSF remained constant and seldom exceeded 1 μg/ml (Fig. 1). The serum concentration-time data were described using the equation (see above): $C_S = 167.95\ e^{-0.405t}$, whereas the CSF data were described by the equation (see above): $C_{CSF} = 0.834\ (-e^{-0.593t} + e^{-0.0104t})$. Based on the AUCs from 0.5 to 8 h, the ratio of drug in CSF to that in serum was determined to be 0.015, representing a 1.5% penetration of aztreonam into the CSF over this time period. (Concentration data used for calculating the AUCs were those obtained by bioassay).

Part B. CSF values for clinical laboratory tests immediately before administration of aztreonam in the group of nine patient volunteers with inflamed meninges were a mean leukocyte count of 349/mm^3 (range, 8 to 1,552) with 32.7% polymorphonuclear cells, mean protein of 90 mg/dl (range, 24 to 290), mean sugar of 53 mg/dl (range, <10 to 81), and a mean erythrocyte count of 68/mm^3 (range, 0 to 220).

In these patients, aztreonam also was detectable in the CSF as early as 1 h after infusion, but values were on the average four times higher than those recorded for the same time period in the noninflamed group (Table 1). This is also depicted in Fig. 1, in which individual data for the inflamed group can be compared with individual data and regression curves for serum and CSF for the noninflamed group. CSF values for patients with inflamed meninges were more variable (range 0.16 to 8.11 μg/ml) and less predictable than those in the noninflamed group. Aztreonam concentrations in CSF of patients with inflamed meninges were determined only up to 4 h after drug administration.

Results of the bioassay and HPLC assay were closely correlated for both serum and CSF (Fig. 2), indicating the absence of biologically active metabolites of aztreonam. However, low concentrations (0.5 to 1 μg/ml) of SQ 26,992 were occasionally detected in the CSF by HPLC methods.

DISCUSSION

Gram-negative bacillary meningitis remains a serious, often fatal infection with a mortality rate of between 40 and

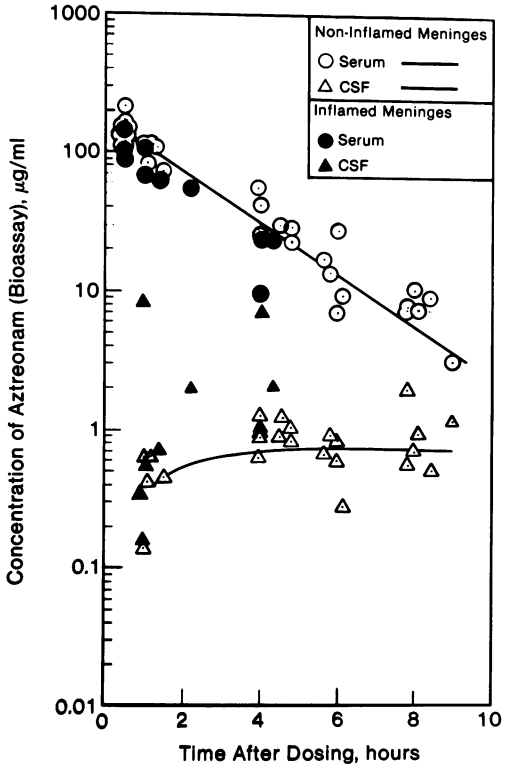

FIG. 1. Penetration of aztreonam (2 g i.v.) into the CSF of 25 adult patients with normal noninflamed meninges and 9 adult patients with inflamed meninges (see text).

80% (2). Therapeutic agents available for its treatment are few and frequently ineffective.

In this study, data regarding entry of aztreonam into the subarachnoid space was obtained by securing single samples of CSF from patient volunteers at a predetermined time after i.v. infusion of a single 2-g dose of aztreonam, and then pooling the data at specific times to construct serum and CSF time-course concentration curves. The population under study by clinical and laboratory criteria represented a homogeneous population of normal or noninflamed meninges. Thus, points could be pooled for analysis. This approach was necessary, as multiple or continuous sampling of CSF from normal humans is unethical.

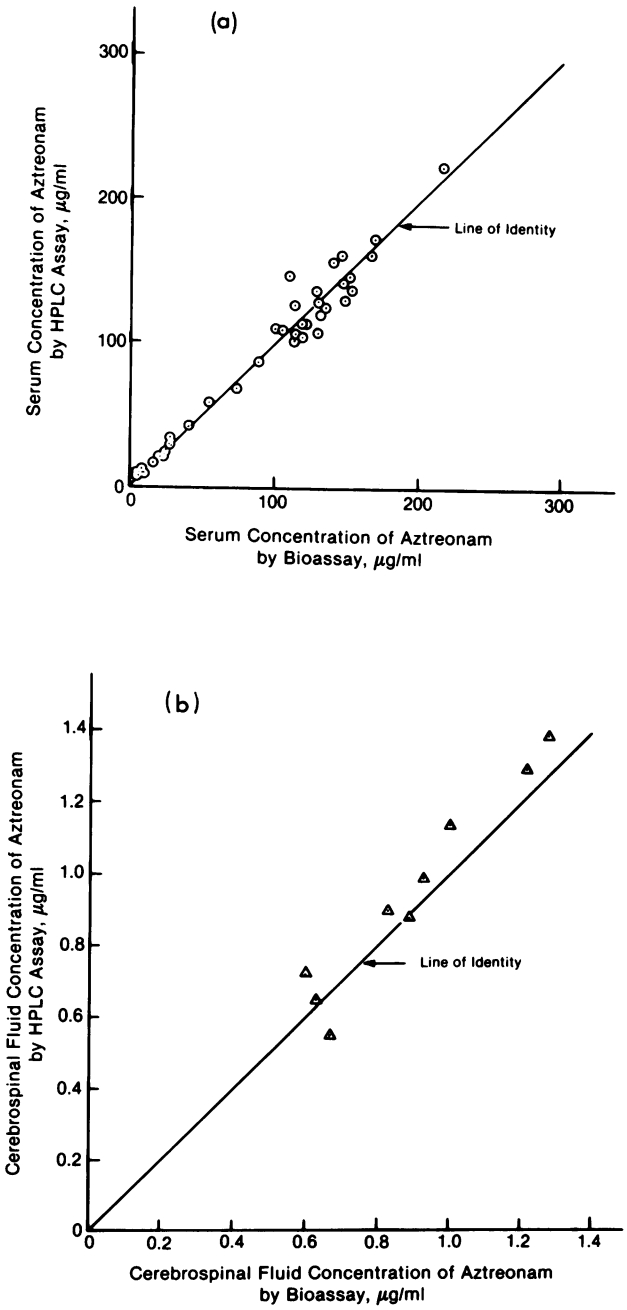

FIG. 2. Comparison of individual bioassay and HPLC values for aztreonam concentrations in serum (a) and CSF (b) of patients with normal meninges after a 2-g i.v. dose.

Although meningitis is characterized by inflamed meninges, knowledge of the CSF penetration of an antibiotic, such as aztreonam, across noninflamed meninges is necessary for two reasons. First, meningeal inflammation may be minimal and even absent early in the course of meningitis; however, this is a time when antibiotic penetration into the CSF is extremely important if progress of the disease is to be stopped. Second, immunocompromised patients, who are especially susceptible to central nervous system infections by gram-negative bacilli, may have little or no inflammatory response throughout their entire course of infection.

Aztreonam appears to penetrate the CSF adequately in the presence of either inflamed or non-inflamed meninges. In this study, after a 2-g, i.v. bolus dose, mean aztreonam concentrations in CSF in the groups of patients with noninflamed meninges were 5 to 10 times those necessary to inhibit most *Enterobacteriaceae* (1, 3, 5, 7). In addition, the drug under these conditions was well tolerated with no adverse effect observed.

The mean concentrations of aztreonam in the CSF of patients with noninflamed meninges were ca. 0.5 and 1.0 μg/ml at 1 and 4 h, respectively. After 4 h, CSF levels reached a plateau, despite drug concentrations in serum which far exceeded those in the CSF, suggesting that aztreonam levels in CSF may not be governed by diffusional processes alone. How long this plateau is maintained is unknown, but it appears to be in excess of 9 h. Thus, aztreonam given as a 2-g i.v. bolus dose rapidly achieves potentially therapeutic levels in the CSF of people with noninflamed meninges and maintains these levels for prolonged periods of time, suggesting that appropriate therapeutic regimens should consist of 2-g i.v. doses every 6 h.

In patients with inflamed meninges, like other beta-lactam antibiotics, aztreonam concentrations in the CSF exceed those found in the presence of normal meninges. Levels of aztreonam in the CSF of patients with meningitis are ca. four times higher than those of patients with noninflamed meninges, reaching levels of 1.98 and 3.22 μg/ml by 1 and 4 h, respectively. The precise factors responsible for these higher concentrations are unclear and still remain to be defined. However, such concentrations probably depend on the degree and type of inflammation present (as reflected by leukocyte and protein elevations) or on the amount of damage suffered by those cells lining the subarachnoid space and choroid plexus which control entry and exit of drugs or both.

Finally, when measuring aztreonam levels in the CSF and serum, close correlation between HPLC and microbiological assay results may be expected, suggesting that either method may be used for examination of such body fluids.

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