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Single-Dose Pharmacokinetics of Aztreonam in Pediatric Patients

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Single intravenous doses (30 mg/kg) of aztreonam, a novel monobactam antibiotic, were administered to 29 children from 2 days to 11 years old. Serum, urine, and, when possible, cerebrospinal fluid samples were analyzed by high-pressure liquid chromatography and microbiological methods. The concentration of aztreonam in serum 15 min after drug administration was approximately 100 μg/ml in all age groups. The elimination half-life varied inversely, and the clearance from serum varied directly, with age. Aztreonam pharmacokinetics in 2- to 12-year-olds were similar to those in adults. The concentration in urine was high and prolonged, with potentially therapeutic concentrations still present 12 to 24 h after infusion in all age groups. Penetration into cerebrospinal fluid averaged 17.3% in children with inflamed meninges. Standard clinical and laboratory measurements revealed no untoward reactions. The 30-mg/kg dose of aztreonam produced potentially therapeutic concentrations in serum, urine, and cerebrospinal fluid. A dosage schedule of every 6 to 8 h in older children and every 8 to 12 h in neonates is suggested for multiple-dose clinical trials.

Aztreonam is a novel monocyclic beta-lactam antibiotic with excellent activity against a broad range of gram-negative aerobic bacteria, including *Pseudomonas aeruginosa* (3, 13). The frequency of gram-negative infections in neonates and infants (9) and the problems associated with treating such infections with broad-spectrum antimicrobial agents (6) make aztreonam of special interest in pediatric therapeutics. This led us to study the pharmacokinetics of aztreonam in selected pediatric patients, and the results are recorded in this report.

MATERIALS AND METHODS

Subjects. All 29 subjects included in this study (Table 1) were inpatients at the Oklahoma Teaching Hospitals during, and for at least 48 h after, aztreonam administration. Each was receiving concurrent therapy, including antibiotics, for suspected or proven infection. Before the study, each patient's medical history was recorded, and a physical examination and battery of laboratory tests were performed. Subjects with a history of allergy to beta-lactam drugs or with abnormal hepatic or renal function were excluded. The parent(s) of each subject gave written informed consent for the child's participation after the study protocol had been explained. The study protocol was approved by the Institutional Review Board of the Oklahoma University Health Sciences Center.

Drug administration. Each subject received 30 mg of aztreonam per kg intravenously over 3 min into an indwelling intravenous catheter or needle. If the calculated dose was more than 100 mg, it was rounded to the nearest 10 mg. Aztreonam was formulated with L-arginine as a buffering agent in a ratio of 1,000 mg of aztreonam to 780 mg of L-arginine. Each single-dose vial was reconstituted with 8.7 ml of sterile water to a final volume of 10 ml (100 mg/ml).

Safety evaluation. The following studies were done for each subject before and 48 h after drug administration: history, physical examination, hemogram, urinalysis, and serum chemistry profile (glucose, urea nitrogen, creatinine, electrolytes, bilirubin, alkaline phosphatase, and alanine aminotransferase). If possible, studies were also done for calcium, phosphorus, total protein, albumin, and lactic acid dehydrogenase. In addition, vital signs were monitored and the injection site was inspected before and at 0.5, 1, 8, 24, and 48 h after drug administration.

Sampling for drug assay. Serum samples for aztreonam assay were obtained before and at 0.25, 1, 3, and 6 h after drug administration and frozen at −70°C until analysis was done. Urine samples were obtained before drug injection, when possible, and during the following time intervals: 0 to 3, 3 to 6, 6 to 12, and 12 to 24 h. Cumulative urine collections were obtained for older children. In children under 2 years, from whom urine could not be obtained on demand, random urine samples were obtained during each time interval. Cerebrospinal fluid (CSF) samples were obtained, during the 6-h period after aztreonam administration, from children undergoing lumbar puncture for therapeutic or diagnostic reasons.

Assays. Serum, urine, and CSF samples were analyzed for concentrations of aztreonam and its open-lactam-ring metabolite, SQ 26,992, by high-pressure liquid chromatography (10). Serum samples obtained 15 min and 6 h after drug administration were also assayed microbiologically to determine the inhibitory and killing power of aztreonam in serum. Stock organisms resistant to other antimicrobial agents the patient was receiving were used to standardize these results. Three different bacteria, each an *Escherichia coli* strain with an aztreonam MIC of 0.12 μg/ml, were used at an inoculum of 5×10^5 CFU/ml. None of these strains was synergistically inhibited by the combination of aztreonam with the other antimicrobial agents (ampicillin, chloramphenicol, and gentamicin). The microtiter broth method was used to measure the inhibitory power, and 0.01 ml was subcultured onto antibiotic-free agar to determine the bactericidal (killing) power (1).

Pharmacokinetic methods. Data on the concentration of aztreonam in serum were analyzed by moment analysis (4). The elimination rate constant, λ_2, was derived from fitting a one- or two-exponent equation to the serum concentration-time data with the computer programs AUTOAN and NONLIN (7). The elimination half-life was calculated as $t_{1/2} = \ln 2/\lambda_2$. The serum clearance ($CL_S$) was calculated as dose/AUC, where AUC is the area under the serum concentra-

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TABLE 1. Demographic summary of patients receiving single-dose intravenous aztreonam

Age	No. of patients (no. of males)	Mean age (range)	Mean (cm) (range)	Mean (kg) (range)
Newborns				
<7 days, <2,500 g	6 (2)	3 days (2–4 days)	41 (34–45)	1.6 (0.8–2.3)
<7 days, >2,500 g	6 (5)	3 days (2–5 days)	52 (44–59)	3.2 (2.7–3.7)
1 wk–1 mo	5 (2)	19 days (7–30 days)	54 (48–59)	4.0 (2.7–4.7)
Infants (>1 mo–2 yr)	6 (2)	9.5 mo (2–21 mo)	70 (64–80)	7.7 (5.7–9.1)
Children (>2–12 yr)	6 (3)	5.5 yr (2–11.4 yr)	103 (72–152)	16.7 (6.0–38.4)

tion-time curve, estimated by the trapezoidal rule. The volume of distribution at steady state (V_{ss}) was calculated as dose times AUMC/AUC^2, where AUMC is the area under the first moment of the serum concentration-time curve (2).

Statistical evaluation. Differences in the pharmacokinetic parameters for the five age groups were determined by analysis of variance. The data were transformed to natural logarithms to make the distributions more Gaussian, fulfilling statistical test assumptions. Pearson's r test was also used when appropriate.

RESULTS

Selected aztreonam concentrations in serum and urine and standard pharmacokinetic parameters were determined (Table 2). Three patterns of drug elimination are evident from these data. Premature newborns in the first week of life eliminated aztreonam at the slowest rate. Full-term newborns and infants up to 2 years had similar but more rapid drug elimination profiles. Children from 2 to 12 years eliminated the drug most rapidly.

Peak concentrations in serum did not vary significantly with age ($P > 0.10$), but drug half-life was inversely related to age ($r = -0.71$, $P < 0.001$). Bioavailability, as estimated by the AUC, showed a similar age dependency. The data for clearance of aztreonam from serum explain these elimination patterns, since premature infants had the lowest clearance rate and older children, in whom the drug had the shortest half-life, had the highest clearance rate. The kinetic variables were analyzed with a noncompartmental model because of the lack of multiple specimens during the distribution phase. However, the concentrations in serum measured 15 min after infusion varied little from those estimated from elimination-phase measurements, suggesting that the distribution phase was somewhat shorter than 15 min in all the age groups studied.

The concentration of aztreonam in urine varied widely (Table 2). Aztreonam was eliminated primarily in unchanged form, as previously noted for adults (12). The concentration of SQ 26,992, the open-lactam-ring metabolite, in urine was approximately 2 to 10% of the aztreonam concentration. In one infant and three children who provided cumulative urine collections, the mean ± standard error of the mean recoveries of aztreonam and SQ 26,992 were 74 ± 16 and 4.4 ± 1.7% of the total dose, respectively.

The concentration of aztreonam in CSF was measured for six patients (Table 3). Five patients who received aztreonam 24 to 72 h after acute bacterial meningitis was diagnosed had a mean CSF-to-serum ratio for aztreonam concentration of 17.3%. A patient studied at the completion of a 14-day course of therapy for pneumococcal meningitis had a CSF-to-serum concentration ratio of 3.1%.

Microbiological assay for the inhibitory and killing activity of aztreonam in serum showed excellent agreement with the values obtained by high-pressure liquid chromatography. All paired inhibitory and killing titers were identical, except for two for which there was a twofold difference. The median killing activity titer at 15 min after infusion was 1:512, and at 6 h it was 1:64. Multiplying the measured inhibitory power

TABLE 2. Selected drug concentrations in serum and urine and pharmacokinetic parameters in children receiving single-dose intravenous aztreonam

Age	No. of subjects	Mean drug concn (μg/ml) in: Serum (mean ± SEM) 15 min	Serum 6 h	Urine (range) 0–3 h	Urine 18–24 h	$t_{1/2}$(h)[a]	AUC (μg · h/ml)[a]	V_{ss} (liters/kg)[a]	CL_S (ml/min per kg)[a]
Newborns									
<7 days, <2,500 g	6	83.0 ± 21.3	31.7 ± 3.3	786 (246–2,141)	76 (26–129)	5.71 ± 1.63	325.2 ± 18.5	0.36 ± 0.04	0.94 ± 0.14
<7 days, >2,500 g	6	97.8 ± 5.0	17.6 ± 3.8	656 (11–1,430)	345 (32–712)	2.56 ± 0.20[b]	306.7 ± 23.7	0.26 ± 0.02	1.41 ± 0.15
1 wk–1 mo	5	97.4 ± 4.3	14.1 ± 2.7	993 (641–1,450)	56 (5–114)	2.43 ± 0.35[b]	256.8 ± 17.8	0.30 ± 0.02	1.68 ± 0.16[b]
Infants (>1 mo–2 yr)	6	118.7 ± 6.7	11.8 ± 5.3	1,414 (610–2,235)	110 (3–495)	1.70 ± 0.16[b]	228.9 ± 20.4[b]	0.20 ± 0.03[b]	1.87 ± 0.31[b]
Children (>2–12 yr)	6	96.9 ± 16.2[c]	5.8 ± 1.2	3,727 (1,290–7,190)	111 (7–334)	1.67 ± 0.21[b]	189.4 ± 14.1[d]	0.29 ± 0.07	2.50 ± 0.15[e]

[a] Mean ± standard error of the mean.
[b] Significantly different from newborns, <7 days, <2,500 g ($P < 0.05$).
[c] The data for one child with a concentration of 380 μg/ml (probable distribution phase) were omitted from this calculation.
[d] Significantly different from newborns, <7 days ($P < 0.05$).
[e] Significantly different from all other groups ($P < 0.05$).

TABLE 3. Concentrations of aztreonam in the CSF of children receiving a single intravenous dose

Age	Aztreonam given (days after initial diagnosis)	Sample obtained (h postinfusion)	Concn of aztreonam in CSF (μg/ml)	CSF/serum concn ratio (%)
7 days	1	1.3	13.3	18.8
3 mo	3	3.0	10.1	19.2
7 mo	2	0.75	20.8	24.1
8 mo	2	4.3	2.1	18.3
2 yr	2	1.1	3.4	6.1
22 days	14	0.75	2.4	3.1

by the MIC for the test organism gave values within one dilution of the concentration measured by high-pressure liquid chromatography in 17 of 21 patients.

Tolerance of single intravenous doses was satisfactory at all ages. An 11-year-old girl complained of an unusual taste sensation during the 3-min infusion. In five patients, the number of eosinophils increased to 5 to 9% of total leukocytes; this was unrelated to more generalized hypersensitivity reactions and did not require treatment. No other significant abnormalities were detected. No patient showed evidence of phlebitis or inflammation at the injection site.

DISCUSSION

In healthy adults, Swabb et al. (12) found a $t_{1/2}$ in serum of 1.65 h, with a mean peak concentration of 99.5 μg/ml, an AUC of 168.4 μg · h/ml, and a CL_S of 1.67 ml/min per kg after a 1,000-mg intravenous dose of aztreonam. These values were similar to those found in our 2- to 12 year-old group after the administration of 30 mg of aztreonam per kg. Not unexpectedly, the slower rate at which the drug was cleared from the serum of younger infants and newborns resulted in prolonged half-lives and increased bioavailability (AUC).

The pharmacokinetic data presented indicate that a 30-mg/kg intravenous dose produces concentrations in serum that exceed the MICs for most gram-negative bacteria of clinical interest (*Enterobacteriaceae*, *Neisseria* spp., and *Haemophilus* spp.) for 8 to 12 h. The MIC of aztreonam that inhibits 90% of *Pseudomonas aeruginosa* strains, 12 μg/ml (13), was exceeded for approximately 8 to 12 h in premature newborns, 6 to 8 h in full-term newborns and older infants, and 4 h in children. These data suggest that a dosage interval of 8 to 12 h in neonates and 6 to 8 h in children older than 1 month would be appropriate for initial multiple-dose clinical trials. Documented *Pseudomonas* infections, however, may require larger individual doses or a narrower dosage interval.

The concentration of aztreonam in urine was consistent with its primarily renal, unmetabolized, excretion. Potentially therapeutic concentrations were present in the urine of all patients 24 h after the single-dose intravenous infusion, suggesting that once-daily aztreonam administration might be an appropriate regimen for renal infection uncomplicated by bacteremia. Only three patients had an aztreonam concentration in urine as low as 10 μg/ml 18 to 24 h after administration.

The CSF-to-serum concentration ratio for aztreonam in this study was slightly higher than those described in adults with inflamed meninges who were given 2 g of aztreonam intravenously (R. Greenman, S. Arcey, G. Dickinson, J. Mokhbat, L. Sabath, and L. Friedhoff, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 23rd, Las Vegas, Nev., abstr. no. 410, 1983). These drug concentrations in CSF should be adequate for the treatment of meningitis caused by gram-negative bacteria, except for *Pseudomonas*, as they were 10 to 100 times the mean MICs of aztreonam against *Enterobacteriaceae*, *Haemophilus* spp., and *Neisseria* spp. More CSF data are required, but in the presence of significant central nervous system inflammation, the concentration in CSF appeared to be comparable to or greater than that of other beta-lactams (8).

The agreement between the results of high-pressure liquid chromatography and microbiological assays for aztreonam lends additional evidence for extrapolating these data from in vitro activity to in vivo efficacy. The results also confirm the bactericidal activity of aztreonam, an important factor in the therapy of serious infections.

The single 30-mg/kg dose of aztreonam used in this study was well tolerated. The patients with mild to moderate eosinophilia showed no evidence of more generalized allergic or hypersensitivity reactions; concurrent infections or drug therapy may have contributed to the eosinophilia. These data lend additional support to the favorable therapeutic-to-toxic effect ratio of aztreonam noted in studies with animals (5) and adult humans (11).

This study of the pharmacokinetics and safety of single-dose administration suggests that aztreonam may prove to be a safe, effective antimicrobial agent in the treatment of serious gram-negative infections in children. The concentrations in urine and CSF and the microbiological activity in serum support further investigation of aztreonam in multiple-dose clinical trials in children.

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