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Pharmacology of Aztreonam After Intravenous Infusion

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The pharmacokinetics of aztreonam, a monocyclic β-lactam which inhibits most members of the family *Enterobacteriaceae* at concentrations of <1 μg/ml and most *Pseudomonas aeruginosa* isolates at concentrations of <16 μg/ml, were examined in healthy male volunteers after 30-min intravenous infusions of 0.5, 1, and 2 g of the drug. Mean peak levels of the drug in serum at the end of infusion were 65.5, 164, and 255 μg/ml after 0.5, 1, and 2 g, respectively, with levels of the drug in serum of 1.8, 3, and 8.5 μg/ml at 8.5 h for the three doses, respectively. The half-life was approximately 2 h for all three doses. The total serum clearance averaged 1 ml/min per kg. The apparent volume of distribution averaged 0.17 liter/kg for the three doses. Overall excretion of the drug in urine was 61%, with mean levels in urine of 23, 52, and 109 μg/ml at 8.5 to 12.5 h after 0.5, 1, and 2 g of aztreonam, respectively. Concentrations of the drug in serum after a 1-g dose exceeded the minimal inhibitory concentration for 90% of the members of the *Enterobacteriaceae* by four- to eightfold for 8 h and exceeded the minimal inhibitory concentration for *P. aeruginosa* isolates for 4 h.

Aztreonam is a monocyclic β-lactam antibiotic which has been shown to have activity against the majority of gram-negative aerobic bacteria. It inhibits the majority of the members of the family *Enterobacteriaceae* at concentrations of <1 μg/ml and most *Pseudomonas aeruginosa* isolates at concentrations of <16 μg/ml (8, 10, 15). With this in vitro activity, aztreonam has promise in the therapy of infections due to organisms resistant to older cephalosporins and to aminoglycosides. Previous studies of the pharmacology of aztreonam have been performed with bolus intravenous administration of aztreonam or by the intramuscular route (13). In the United States, most antimicrobial agents are administered by infusion; therefore, we wished to determine the pharmocokinetic parameters of aztreonam after infusion over 30 min in accordance with standard clinical practice. We also wished to compare the pharmacokinetics of aztreonam with other new cephalosporins which had been studied in our laboratory (2, 5, 6, 9, 11, 12).

MATERIALS AND METHODS

Drug. Aztreonam was supplied by The Squibb Institute for Medical Research, Princeton, N.J.

Subjects. Six normal male volunteers between the ages of 22 and 32 years (mean, 26 years) were the subjects of the study. Informed written consent in accordance with federal guidelines was obtained from each individual. Their mean weight was 70 kg (range, 64 to 77 kg). The mean body surface area was 1.84 m^2 (range, 1.73 to 2.05 m^2). All subjects were judged to be healthy on the basis of history, physical examination, electrocardiogram, chemistry profile (SMAC and Technicon), complete blood count, and urinalysis. Subjects with known allergies to penicillins or cephalosporins were excluded from the study. None of the subjects had received antimicrobial agents in the prior 2 weeks. All subjects were admitted to the General Research Center at Columbia Presbyterian Medical Center the night before infusion of the drug and remained in the center during the study. Chemical, hematological, or urine tests were performed immediately before and 72 h after each dose of aztreonam.

Drug administration. Each of the six subjects received, by random assignment, 0.5, 1, or 2 g of aztreonam on day 1 of the study and an alternate dose 1 and 2 weeks later. Serum samples were obtained at 0, 0.25, 0.5, 1, 1.5, 2.5, 4.5, 6.5, 8.5, and 12.5 h after beginning infusion of the drug. Aztreonam was infused via a small bore needle over 30 min at a rate of 1 ml/min by using a syringe pump. Blood samples were divided into equal portions, immediately frozen, and stored at −70°C until assayed. Aztreonam in urine, serum, and phosphate buffer (pH 7, 0.05 M) has been shown to be stable under these conditions at concentrations of 2, 10, and 100 μg/ml for the period of storage. Urine samples were collected immediately before injection and at 0 to 2.5, 2.5 to 4.5, 4.5 to 8.5, and 8.5 to 12.5 h after the start of infusion.

Assays. Aztreonam was assayed by the agar well diffusion technique with antibiotic medium no. 2 (Difco Laboratories) as previously described for assays of other antibiotics (2, 9). Antibiotic standards for assay of serum samples were prepared in pooled normal human serum from the subjects who had been shown to lack antibacterial activity against the assay organisms. Urine samples were diluted in 0.05 M potassium phosphate buffer, pH 7. The assay organism

was *Escherichia coli* 3989 (from our collection). Serum and urine samples were assayed in quadruplicate, and five standards were used on each plate. Concentrations of aztreonam were calculated by using a linear semilogarithmic plot generated with a computer.

The assay for aztreonam could detect 0.15 mg/ml and gave linear results over a concentration range of 0.2 to 80 μg/ml. Serum samples which gave results outside the linear part of the curve were diluted with normal serum, and urine samples were diluted in phosphate buffer. Samples were thawed only once. Spiked samples, which were prepared at the time of infusion and stored in a manner similar to that of samples from the study subjects, showed no evidence of significant decomposition of aztreonam.

Pharmacokinetic and statistical methods. A two-compartment, open model was used to calculate the pharmacokinetic parameters for aztreonam after intravenous infusion (3). Because aztreonam was infused over 30 min, the exponential equation $C = Re^{-\alpha t} + Se^{-\beta t}$ was used to express the concentration of the drug in serum (C, micrograms per milliliter)-versus-time (t, hour) data. Curve stripping of C-versus-t (time after the end of the 30-min infusion) data and optimization of coefficients R, S, α, and β by nonlinear regression analysis were performed with the computer programs AUTOAN and NONLIN (4) on an IBM 370 digital computer. All serum data were weighted according to their reciprocals for computer analysis. The relationships between coefficients R and S and coefficients A and B for this model were $A = (R\alpha T)/[1 - \exp(-\alpha T)]$ and $B = (S\beta T)/[1 - \exp(-\beta T)]$, where α and β were hybrid rate constants and T was the duration of the infusion. The volume of distribution of the central compartment was expressed as $V_1 = \text{dose}/[(A + B)W]$, where W was the body weight in kilograms. The volume of distribution based on the area under the serum concentration-time curve, $V_{D_{area}}$, was expressed as $\text{dose}/(\beta W(A/\alpha) + (B/\beta))$. The volume of distribution based on an extrapolation of the beta-phase elimination curve was calculated by using $V_{D_{ext}} = \text{dose}/B$. The volume of distribution at the steady state was expressed as $V_{ss} = V_1 [1 + (K_{12}/K_{21})]$, where the intercompartmental rate constants were expressed as $K_{21} = (A\beta + B\alpha)/(A + B)$ and $K_{12} = \alpha + \beta - K_{21} - K_{10}$. In addition, the rate constant for elimination from the central compartment was expressed as $K_{10} = \alpha\beta/K_{21}$. Half-lives for the distribution and elimination phases of the serum concentration-time data were expressed as $t_{1/2\alpha} = (\ln 2)/\alpha$ and $t_{1/2\beta} = (\ln 2)/\beta$, respectively. Serum clearance was expressed as $Cl_s = V_1K_{10}/W$. The area under the serum concentration-time curve was calculated by using the trapezoidal rule with $C = 0$ at the start of the infusion. The cumulative excretion of aztreonam in urine was determined.

Statistical evaluation was performed using analysis of variance for the crossover design. Geometric means were compared by Duncan's multiple-range test. Linear regression analysis was used to test for a dose-response relationship for pharmacokinetic parameters.

RESULTS

The results of the infusion of the three doses are given in Table 1. At the end of infusion of 0.5, 1, and 2 g of aztreonam, the mean concentrations of the drug in serum were 65.5, 164, and 255 μg/ml, respectively. Mean levels of the drug in serum of 14, 35, and 67 μg/ml were present 2 h after the end of infusion (2.5 h after the beginning of infusion). At 4 h after dosing, aztreonam levels were 7.0, 16, and 36 μg/ml, whereas at 8 h, levels of 1.8, 3, and 8.5 μg/ml were present. Even at 12 h after the end of infusion, aztreonam could be detected, and levels of 0.92 and 1.87 μg/ml were found after the 1- and 2-g doses, respectively.

The pharmacokinetic characteristics of the three infusions are noted in Table 2. There was rapid distribution of the compound after all three doses. The calculated serum half-life of the drug ranged from 1.90 ± 0.21 h for the 1-g dose to 2.16 ± 0.38 h for the 2-g dose. These differences were not statistically significant. The various volumes of distribution, particularly the calculated apparent volume of distribution at the steady state, were similar for all three doses. Serum clearance of aztreonam was similar for all doses, with values of 1.08 ± 0.14, 0.91 ± 0.06,

TABLE 1. Concentrations of aztreonam in serum of six healthy male subjects after 30-min infusions of 0.5, 1, and 2 g

Time after start of infusion (h)	Mean concn (μg/ml) of drug in serum after dose of:		
	0.5 g	1 g	2 g
0.5	65.5 (50.7–98.2)[a]	164 (148–169)	255 (184–320)
0.75	42.5 (32.4–58.7)	117 (86–139)	200 (175–232)
1.0	32.5 (29.3–42.8)	72.9 (62.1–86.1)	155 (116–191)
1.5	23.1 (18.5–26.3)	48.8 (22.8–61.6)	111 (69–160)
2.0	17.7 (13.6–22.2)	47.3 (34.0–65.9)	76.8 (60–102)
2.5	13.8 (10.9–15.2)	35.1 (26.9–42.4)	66.9 (42.5–95.4)
4.5	6.97 (5.67–7.57)	16.2 (11.0–24.7)	35.5 (24.9–40.2)
6.5	3.49 (2.50–5.03)	8.48 (5.59–13.01)	14.6 (9.5–19.8)
8.5	1.75 (1.05–3.23)	3.02 (1.4–5.4)	8.54 (5.73–11.52)
12.5	0.17 (ND[b]–0.59)	0.92 (0.4–1.3)	1.87 (1.23–2.67)

[a] Range is given in parentheses.
[b] ND, Not detected.

TABLE 2. Pharmacokinetic parameters (mean ± standard deviation) of aztreonam after intravenous infusion

Parameter	Dose (g)		
	0.5	1	2
$t_{1/2\alpha}$ (h)	0.33 ± 0.24	0.22 ± 0.06	0.36 ± 0.14
$t_{1/2\beta}$ (h)	1.98 ± 0.43	1.90 ± 0.21	2.16 ± 0.38
K_{12} (h^{-1})	1.89 ± 1.57	1.46 ± 0.60	0.75 ± 0.36
K_{21} (h^{-1})	1.48 ± 0.78	1.21 ± 0.48	1.02 ± 0.44
K_{10} (h^{-1})	0.97 ± 0.23	1.05 ± 0.19	0.70 ± 0.04
V_1 (liter/kg)	0.07 ± 0.02	0.05 ± 0.01	0.08 ± 0.01
V_{ss} (liter/kg)	0.15 ± 0.03	0.11 ± 0.01	0.14 ± 0.04
V_2 (liter/kg)	0.08 ± 0.02	0.06 ± 0.01	0.06 ± 0.03
$V_{D_{ss}}$ (liter/kg)	0.23 ± 0.07	0.20 ± 0.05	0.26 ± 0.01
$V_{D_{area}}$ (liter/kg)	0.18 ± 0.04	0.15 ± 0.02	0.18 ± 0.05
Serum clearance (ml/min per kg)	1.08 ± 0.14	0.91 ± 0.06	0.98 ± 0.14
Renal clearance (ml/min per kg)	0.60 ± 0.21	0.59 ± 0.14	0.60 ± 0.19
Area under curve (μg · h/ml)	109.6 ± 15.5	271.2 ± 24.3	511.2 ± 91

and 0.98 ± 0.14 ml/min per kg for the 0.5-, 1-, and 2-g doses, respectively. Mean renal clearances ranged from 0.59 to 0.60 ml/min per kg.

The areas under the curve for the three doses were 110 ± 15, 271 ± 98, and 511 ± 91 μg h/ml. These normalized to 220, 271, and 256 μg h/ml, but these differences were not statistically significant.

The recovery of aztreonam from urine is shown in Fig. 1. There was 37 to 40% recovery of the drug in the 0- to 2.5-h period (which included 0.5 h of drug infusion). By 12.5 h, recovery of the drug from urine was 57, 65, and 60% for the 0.5-, 1-, and 2-g doses, respectively. Mean concentrations of the drug in urine and ranges of values are given in Table 3. These values ranged from mean levels of 5,657 μg/ml with the 2-g dose and 1,027 μg/ml with the 0.5-g dose in the first 2.5-h period to mean levels in the 8- to 12-h period of 23, 52, and 110 μg/ml for the 0.5-, 1, and 2-g doses, respectively.

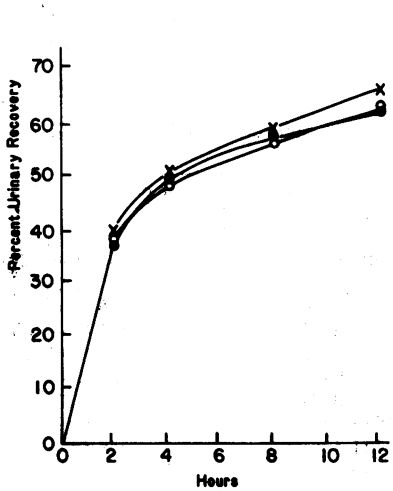

FIG. 1. Cumulative excretion of aztreonam after intravenous infusion of 2 g (●), 1 g (×), and 0.5 g (○).

Tolerance. Aztreonam administered as a single infusion of 0.5, 1, and 2 g was well tolerated. Phlebitis was not encountered with the single intravenous infusion, nor was there any evidence of hepatic, renal, or hematological dysfunction. No apparent allergic reactions occurred during the 3-week period.

DISCUSSION

Aztreonam is a unique molecule in that it contains the β-lactam nucleus with an acidic function on the nitrogen, an α-methyl group on the ring structure, and an aminothiazolyl side chain with an iminocarboxyl propyl substitution, which provides β-lactamase stability and activity against *P. aeruginosa* (1). Aztreonam has been shown to inhibit most members of the family *Enterobacteriaceae* at concentrations of <1 μg/ml. Indeed, 90% of the *E. coli*, *Klebsiella*, and *Proteus* isolates are inhibited by <0.2 μg/ml, including isolates resistant to ampicillin, carbenicillin, cefazolin, and cefamandole (8, 10, 15). Equally important, the minimal bactericidal concentrations for the majority of bacterial isolates are within a single dilution of the minimal inhibitory concentrations (MICs). Aztreonam inhibits *Haemophilus influenzae* at concentrations of <0.1 μg/ml. Furthermore, it inhibits most *P. aeruginosa* isolates at concentrations of <16 μg/ml, including carbenicillin-resistant isolates (8, 10). In a recent clinical study, all *P. aeruginosa* isolates tested were inhibited by 12.5 μg of aztreonam per ml (B. Scully and H. C. Neu, manuscript in preparation).

The pharmacology of aztreonam shown in this study was compared with the MICs of blood culture isolates during the past 2 years in our laboratory (Fig. 2). After a 1-g dose, levels of aztreonam in serum remain well above the MICs

TABLE 3. Concentrations of aztreonam in urine of six healthy male subjects after 30-min infusions of 0.5, 1, and 2 g

Time interval (h)	Mean concn (μg/ml) of drug in urine after dose of:		
	0.5 g	1 g	2 g
0–2.5	1,027 (602–1,493)[a]	3,158 (997–5,228)	5,657 (2,333–8,286)
2.5–4.5	246 (109–478)	690 (372–1,290)	1,720 (455–3,186)
4.5–8.5	88 (35–147)	363 (101–748)	449 (145–725)
8.5–12.5	23 (10–38)	52 (10–85)	110 (34–145)

[a] Range is given in parentheses.

for *H. influenzae*, *E. coli*, *Klebsiella* spp., *Proteus* spp., *Morganella* spp., and *Providencia* spp. for 12 h and *Citrobacter* spp. and *Serratia* spp. for at least 6 h. Furthermore, levels of the drug in serum above the MICs for *Enterobacter* spp. and *P. aeruginosa* are present for 4 h after a 1-g infusion and for 6 h after a 2-g dose. Because aztreonam is only 56% protein bound (14) and because we have shown earlier that serum does not alter MICs (8), the data of this study indicated that the compound could be administered every 8 h as a 0.5- or 1-g infusion to produce therapeutic concentrations against the majority of the members of the *Enterobacteriaceae*. Use of the 2-g dose would produce levels of aztreonam in serum of two to four times the MIC for *P. aeruginosa* for at least 4 h. Only *Acinetobacter* spp. would not be inhibited.

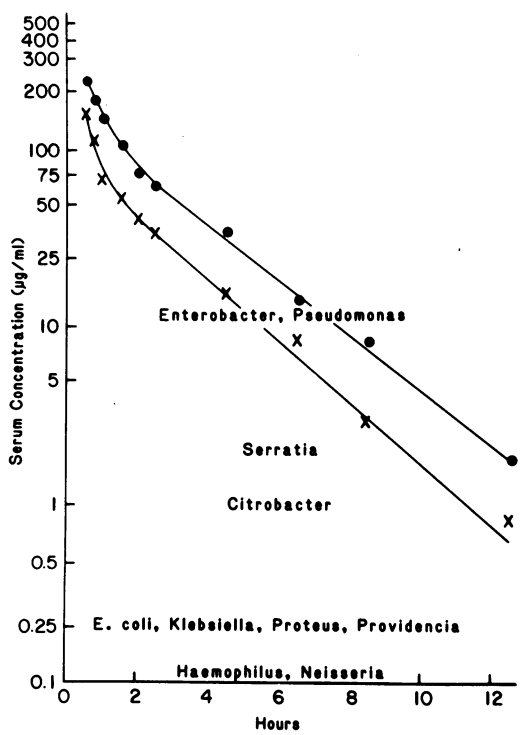

FIG. 2. Plot illustrating the relation of levels of aztreonam in serum after 2 g (●) and 1 g (×) of drug infused over 30 min to MIC_{90}s for the bacterial species listed, based on data from references 8, 10, and 14.

By utilizing the data of Table 3, it is clear that aztreonam will provide concentrations in urine against nosocomial urinary pathogens *E. coli*, *Klebsiella* spp., *Proteus* spp., and *P. aeruginosa* (7) which will exceed the MICs and minimal bactericidal concentrations for 12 h, even after a 0.5-g intravenous dose. A dosage regimen of 1 g of aztreonam twice daily should, in fact, inhibit most *P. aeruginosa* and *Serratia* isolates and be able to replace aminoglycosides.

The overall comparison of the pharmacokinetics of aztreonam and other agents studied at our center (2, 5, 9, 11, 12) is shown in Table 4. A dose of 1 g was used for comparison. In those situations in which a 2-g dose was used, the results were normalized to provide comparative 1-g values. Aztreonam administered by infusion yielded higher mean levels of the drug in serum than did cefamandole, cefoxitin, cefotaxime, ceftizoxime, moxalactam, and ceftazidime. The mean peak levels of cefoperazone and ceftriazone were similar, but these agents were 85 and 90% protein bound, respectively. Aztreonam had a half-life similar to that of ceftazidime and a slightly shorter half-life than that of moxalactam. Only ceftriaxone had a significantly longer half-life of 8 h. The recovery of aztreonam from

TABLE 4. Comparison of aztreonam pharmacokinetics and third-generation β-lactam antibiotics studied in our laboratory

Agent	$t_{1/2}$ (h)	Peak levels in serum[a] (μg/ml)	Recovery in urine (% of dose)
Aztreonam	1.9	164	65
Cefotaxime	1.1	42	55
Ceftizoxime	1.4	87	85
Cefoperazone	1.9	125	25
Moxalactam	2.3	62	75
Ceftazidime	1.8	80	75
Ceftriaxone	8	140	50

[a] Based on intravenous infusion of 1 g of antibiotic over 15 to 30 min.

urine was slightly lower than that of ceftizoxime, ceftazidime, and moxalactam, but greater than that of cefoperazone.

Mean values for the aztreonam half-life obtained in this study were slightly longer than the mean value of 1.7 h obtained in earlier studies of normal volunteers who received intravenous bolus injections, but were nevertheless within the previously reported range of calculated half-lives (13).

Overall, the pharmacological profile of aztreonam is superior to that of first- and second-generation cephalosporins and similar to or improved over that of the third-generation agents. Administration schedules of two or three times daily would seem to be a reasonable program. Indeed, we have already determined that such a dosage program is reasonable, effective, and safe (B. Scully and H. C. Neu, 3rd Mediterr. Congr. Chemother., Dubrovnik, Yugoslavia, 1982) in the therapy of serious infections due to multiresistant gram-negative bacteria.

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