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Pharmacokinetics of Aztreonam in Patients with Various Degrees of Renal Dysfunction

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We have studied the pharmacokinetics of 1-g intravenous doses of aztreonam in four groups of six volunteers each, distinguished by their creatinine clearances (>80, 30 to 80, 10 to 29, and <10 ml/min). Subjects received 1 g of aztreonam intravenously without any complications. Aztreonam serum and urine levels were measured by microbiological methods and by high-pressure liquid chromatography, and unbound serum aztreonam was determined by ultrafiltration. Serum levels were well described by a two-compartment infusion model. From this model we determined steady-state volume of distribution, α distribution phase half-life, β elimination phase half-life, and total clearance of aztreonam. The mean of β elimination phase half-life ranged from 2 h in normal subjects to 6 h in anephric patients. The total clearance of aztreonam correlated closely with corrected creatinine clearance calculated from serum creatinine, age, and sex ($r = 0.97$, $P < 0.001$) and ranged from a mean value of 107 ml/min in normal subjects to 29 ml/min in functionally anephric patients. Some 75% of aztreonam excretion was renal. Urinary recovery of aztreonam ranged from 58% of the administered dose in normal subjects to 1.4% in uremic patients. Free aztreonam in serum correlated inversely with creatinine clearance ($P < 0.001$). A nomogram was developed as a guide for adjustment of aztreonam dosage according to renal function.

Aztreonam (SQ 26,776, formerly azthreonam) is a new synthetic β-lactam antibiotic of unique structure, characterized as a monobactam owing to the 2-oxoazetidine-1-sulfonic acid moiety (14, 15). This agent displays excellent activity in vitro against aerobic gram-negative bacteria (2, 4–6, 13, 17), including β-lactamase–producing *Haemophilus influenzae* (4), and many aminoglycoside-resistant *Enterobacteriaceae* (2, 5, 13, 17). Infections with these organisms are often acquired nosocomially by debilitated patients, including individuals with renal insufficiency.

Data on normal subjects suggest that approximately 65% of an aztreonam dose is eliminated unchanged in the urine within 24 h of parenteral administration (10, 11). Thus, knowledge of the pharmacokinetics of aztreonam in patients exhibiting renal failure is essential to provide rational dosing schedules for serious gram-negative infections. The purpose of the present study was to characterize the pharmacokinetics and safety of a single intravenous dose of aztreonam in the presence of various degrees of renal dysfunction.

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MATERIALS AND METHODS

Drug. Aztreonam was supplied by The Squibb Institute for Medical Research (lot MNB-864-H/B01) and was formulated with L-arginine as a buffering agent in a weight ratio of 1 g of aztreonam to 0.7 g of L-arginine. Aztreonam was prepared in vials containing 1 g plus 5% overage to compensate for mechanical losses. The coefficient of variation for the actual vial contents was less than 1%.

Volunteers. A total of 24 male volunteers participated in this study. Subjects with a history of penicillin or cephalosporin allergy, alcohol or drug abuse, abnormal cardiovascular or hepatic function, persistent hepatitis surface antigen, or deficiency of erythrocyte glucose-6-phosphate dehydrogenase were excluded. All of the volunteers gave written informed consent to participate in this study. The protocol for this study was approved by the Human Investigation Committee of The University of Virginia School of Medicine.

Volunteers were placed in four equal groups (I through IV) according to whether their creatinine clearance (C_{cr}) was ≥80, 30 to 79, 10 to 29, or <10 ml/min. When the subjects were screened, on the first day of the study before drug administration, and 48 h after aztreonam administration at the completion of

the study, subjects were given a complete medical history review and physical examination; 12-lead electrocardiogram; urinalysis; complete biochemical profile (sodium, potassium, chloride, total CO_2, glucose, blood urea nitrogen, serum creatinine [S_{cr}], calcium, inorganic phosphorus, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, lactic dehydrogenase, creatine kinase, and cholesterol); hematological studies (hematocrit, erythrocyte indices, total leukocyte count with differential count, platelet count, and Coombs test); and a 24-h urine test for determination of C_{cr} and total protein excretion. Blood samples for a hepatitis surface antigen test, erythrocyte glucose-6-phosphate dehydrogenase assay, and Venereal Disease Research Laboratory test, and urine samples for toxic substance tests, were obtained at screening only.

Procedures. The subjects were admitted to The University of Virginia School of Medicine Clinical Research Center the day before the study and fasted from midnight until 2 h after drug administration. After blood and urine samples for base-line determinations were obtained, 1.0 g of aztreonam reconstituted in 2.4 ml of sterile water was administered intravenously over 2 min. The patients were encouraged to be ambulatory for 2 h after drug administration. Blood samples for aztreonam levels were collected at 10, 20, and 30 min and at 1, 2, 3, 4, 6, 8, 12, 24, and 48 h after drug administration. Serum and protein-free serum filtrate samples (prepared by passage of 1- and 3-h serum specimens through ultrafiltration membrane cones, Amicon Corp.) were collected into polypropylene tubes and frozen at −70°C. Total urine collections were made for 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 h after aztreonam administration. After measurements of total urine volumes, 5-ml samples were stored at −70°C.

Assays. Aztreonam concentrations in serum, protein-free filtrate, and urine were measured within 3 weeks of specimen collection by a microbiological agar diffusion method with *Escherichia coli* SC 12155 as the test organism. Serum samples and standards prepared in pooled human serum were initially diluted 1:20 in 0.1 M phosphate buffer (pH 6). Subsequent dilutions to test level were made in a diluent of 5% serum and 95% buffer. The quantitation limit of this method was 0.45 μg/ml. Serum samples containing less than this concentration were extracted with methanol and centrifuged, and the supernatant was diluted with 0.1 M phosphate buffer (pH 6). The quantitation limit for aztreonam was 0.04 μg/ml. Standards were prepared in 0.1 M phosphate buffer (pH 6) for the assay of urine samples. The quantitation limit of the urine assay method was 0.06 μg/ml.

Concentrations of aztreonam and SQ 26,992 (the compound resulting from hydrolytic opening of the β-lactam ring of aztreonam) in serum and urine were also determined by high-pressure liquid chromatography (HPLC). Serum samples were diluted 1:2 in 30% phosphate buffer (pH 6.0) and stored at −20°C until assayed (within 3 weeks of collection). The samples were deproteinized by mixing with acetonitrile and extraction with methylene chloride. Urine samples were diluted 1:2 in 30% phosphate buffer (pH 3) and passed through Waters C18 SEP-PAK cartridges. The cartridges were washed with 3 cartridge volumes of buffer and eluted with 5 ml of a mixture of 40 parts methanol and 60 parts 1% phosphate buffer (pH 6.0).

The HPLC equipment consisted of an Altex 110A pump, a Perkin-Elmer LC-420 automatic sampler equipped with a 20-μl sample loop, a guard column (3.9 mm [inside diameter] by 3 cm) packed with Whatman CO:PELL ODS, an analytical column (3.9 mm [inside diameter] by 30 cm) packed with Waters μBondapak C18 (10 μm), a Perkin-Elmer LC-85 UV detector set at 293 nm (0.08 AUFS), and a Hewlett-Packard 3390A integrator. The mobile phase was 85% 0.005 M tetrabutylammonium hydrogen sulfate, adjusted to pH 3.0 with 1.0 M K_2HPO_4, and 15% acetonitrile. The flow rate of the mobile phase was 2.0 ml/min.

The HPLC quantitation limits in serum were 1.0 μg/ml for aztreonam and 10 μg/ml for SQ 26,992. The quantitation limit in urine was 1 μg/ml for both aztreonam and SQ 26,992.

The specificity and precision of the microbiological and HPLC methods were shown by negative results for all predose specimens and by coefficients of variation of 3 to 5%. The values obtained by the two methods were found to be comparable (±10% variation).

Pharmacokinetic and statistical analysis. The data for each subject were entered via a computer terminal, stored directly on disk files, verified, and manipulated thereafter only by pharmacokinetic and statistical programs. Serum levels were described in terms of a linear two-compartment infusion model (16): $C = [(D/T_i)V_1/k_e](C_1e^{-\alpha t} - C_2e^{-\beta t})$, where $C_1 = (1 - e^{-\alpha T_i})[(k_e - \beta)/(\alpha - \beta)]$ and $C_2 = (1 - e^{-\beta T_i})\ [(k_e - \alpha)/(\alpha - \beta)]$ and where C is the concentration of the drug in serum, C_1 and C_2 are coefficients in the equation defining C, D is the dose, t is the time after the end of infusion, T_i is the duration of the infusion, V_1 is the central volume of distribution, k_e is the elimination rate constant, α is the distribution phase decay constant, and β is the elimination phase decay constant.

The pharmacokinetic parameters were determined by an iterative least-squares method, which identifies parameter values that minimize the sum of the squares of the difference between observed and model-solution drug levels (9). Initial estimates for parameters were obtained by a curve stripping routine. The volume of distribution at steady state (V_{dss}) was calculated by the following formula (3): $V_{dss} = V_1[1 + (k_{12}/k_{21})]$ where $k_{12} = \alpha + \beta - k_{21} - k_e$; $k_{21} = (A\beta + B\alpha)/(A + B)$; $A = (\alpha D/V_1k_e)[(k_e - \beta)/(\alpha - \beta)]$; and $B = (-\beta D/V_1k_e)[(k_e - \alpha)/(\alpha - \beta)]$.

The percentage of free drug [$(C_{free}/C_{total}) \times 100$], α-phase half-life [$t_{1/2\alpha} = (\ln 2)/\alpha$], β-phase half-life [$t_{1/2\beta} = (\ln 2)/\beta$], and total drug clearance ($C_{az} = k_eV_1$) were also calculated. Lean body weight was defined for each patient as the measured weight or the expected body weight (calculated from height, age, and sex), whichever was smaller (8). Body surface area was calculated from the DuBois formula (8).

Analysis of variance and F-ratios were used to compare the patient characteristics (age, height, weight, lean body weight, and surface area) and the pharmacokinetic characteristics (percentage of free drug, α-phase half-life, β-phase half-life, total drug clearance, and urinary excretion). The V_{dss} was examined as a function of patient characteristics by using the least-squares linear regression method. Likewise,

the relationship between drug clearance and indices of renal function (C_{cr}, S_{cr}) and corrected creatinine clearance ($corC_{cr}$) were examined by using the least-squares linear regression method. The $corC_{cr}$ (in milliliters per minute, adjusted to a 70-kg body weight) was calculated for the male subjects by the method described by Cockcroft (1), with a correction for the alternative pathway, or nonrenal creatinine excretion, with rising S_{cr} (in milligrams per deciliter) by the formula (7, 8) $corC_{cr} = \{(140 - age) \times [1.015 - (0.0186 \times S_{cr})]\}/S_{cr}$. (This relationship can also be applied to females by multiplying the result by 0.85.)

RESULTS

Volunteers. The subjects ranged in age from 24 to 64 years. The subject characteristics are shown in Table 1. The means and standard deviations of each parameter are presented for the four groups, as well as the probability values from analysis of the difference. Subject heights ranged from 161 to 189 cm, and no significant differences were noted among the four groups. The lean body weights were also similar among the groups. However, the body weights were

TABLE 1. Description of subjects[a]

Group	Patient no.	Ht (cm)	Wt (kg)	Age (yr)	Lean body wt (kg)	Body surface area (m^2)	S_{cr} (mg/dl)[b]	$CorC_{cr}$ (ml/min)[c]
I	1	177	75.2	25	72.7	1.92	1.0	115
	2	176	81.8	25	72.0	1.98	1.2	95
	3	173	71.7	27	70.9	1.85	1.1	102
	4	175	74.0	33	74.0	1.89	1.3	82
	5	175	67.0	24	67.0	1.81	1.1	105
	6	185	70.3	30	70.3	1.93	0.8	138
	Mean ± SD	177 ± 4	73.3 ± 5.0	27 ± 4	71.1 ± 2.4	1.90 ± 0.06	1.1 ± 0.2	106 ± 19
II	7	180	82.1	46	82.1	2.02	2.2	42
	8	169	83.0	39	72.7	1.94	1.9	52
	9	169	87.3	52	74.1	1.98	3.1	27
	10	180	83.6	30	77.5	2.03	4.0	26
	11	189	95.0	35	86.1	2.23	2.2	46
	12	187	92.7	56	87.8	2.19	1.4	59
	Mean ± SD	179 ± 9	87.3 ± 5.4	43 ± 10	80.0 ± 6.2	2.06 ± 0.12	2.5 ± 0.9	42 ± 13
III	13	161	96.6	34	65.3	1.99	3.5	29
	14	170	83.5	41	73.9	1.95	6.9	13
	15	174	63.3	39	63.3	1.76	4.7	20
	16	170	93.8	64	72.8	2.05	3.6	20
	17	184	96.8	50	85.5	2.20	4.7	18
	18	176	83.2	34	76.2	2.00	7.0	13
	Mean ± SD	172 ± 8	86.2 ± 12.8	44 ± 12	72.8 ± 8.0	1.99 ± 0.14	5.1 ± 1.6	19 ± 6
IV	19	179	78.8	35	78.8	1.98	13.8	6
	20	174	63.2	29	63.2	1.76	14.7	6
	21	173	70.5	28	70.5	1.84	23.1	3
	22	171	80.0	45	75.3	1.92	13.8	5
	23	171	83.1	56	75.3	1.95	17.7	3
	24	180	82.6	46	82.2	2.02	16.5	4
	Mean ± SD	175 ± 4	76.4 ± 7.9	40 ± 11	74.2 ± 6.7	1.91 ± 0.10	16.6 ± 3.5	4 ± 1

[a] Patients were assigned to groups I through IV based on screening C_{cr} (not shown); values for the four groups were ≥80, 30 to 79, 10 to 29, and <10 ml/min. $CorC_{cr}$ was slightly different, explaining why patients 9 and 10 were assigned to group II. Probability values were as follows: Height, 0.358; weight, 0.019; age, 0.027; lean body weight, 0.103; body surface area, 0.052; S_{cr}, <0.001; $CorC_{cr}$, <0.001. Probability values were calculated by analysis of variance F with 3 and 19 degrees of freedom.

[b] Measured when drug was administered.

[c] Calculated from S_{cr}, age, and sex.

TABLE 2. Concentrations of aztreonam after a 1-g intravenous dose[a]

Group	Patient no.	Concn (μg/ml) after time:											
		min			h								
		10	20	30	1	2	3	4	6	8	12	24	48
I	1	73	58	50	36	25	16	12	5.4	2.7	0.8	0.0	0.0
	2	72	54	46	33	23	17	12	5.7	2.6	0.7	0.0	0.0
	3	86	63	55	39	25	16	12	5.0	2.5	0.6	0.0	0.0
	4	82	69	61	44	29	20	12	5.6	2.5	0.5	0.0	0.0
	5	80	69	61	44	28	17	11	4.8	2.5	0.5	0.0	0.0
	6	75	65	50	34	20	13	8	2.9	1.6	0.3	0.0	0.0
	Mean ± SD	78 ± 6	63 ± 6	54 ± 6	38 ± 5	25 ± 3	16 ± 2	11 ± 2	4.9 ± 1.0	2.70 ± 1.6	0.8 ± 0.3	0.0 ± 0.0	0.0 ± 0.0
II	7	93	74	64	52	36	27	21	13	9	M[b]	0.5	0.0
	8	100	65	57	41	32	21	17	9	6	1.9	0.0	0.0
	9	109	74	70	56	48	44	36	26	19	11.5	1.6	0.0
	10	117	97	85	75	55	45	38	31	23	10.6	1.2	0.0
	11	89	78	69	53	44	30	25	14	10	4.1	0.2	0.0
	12	82	71	62	45	34	24	18	10	7	2.1	0.1	0.0
	Mean ± SD	98 ± 13	76 ± 11	68 ± 10	54 ± 12	42 ± 9	32 ± 10	26 ± 9	17 ± 9	12 ± 7	6.0 ± 4.7	0.6 ± 0.6	0.0 ± 0.0
III	13	103	77	72	56	45	36	30	22	16	9	0.5	0.0
	14	133	80	67	52	42	32	25	17	11	6	0.5	0.0
	15	M	76	69	60	50	39	33	24	17	10	1.4	0.0
	16	75	66	64	52	43	39	33	27	20	13	2.8	0.1
	17	72	62	52	46	36	35	30	22	18	11	2.3	0.1
	18	109	87	74	68	58	46	42	29	22	15	3.2	0.1
	Mean ± SD	98 ± 25	75 ± 9	66 ± 8	56 ± 8	46 ± 8	38 ± 5	32 ± 6	24 ± 4	17 ± 4	11 ± 3	1.8 ± 1.2	0.0 ± 0.0
IV	19	87	69	65	58	53	46	40	38	29	19	7.6	0.7
	20	220	58	55	49	43	39	35	30	26	19	10.0	2.0
	21	227	59	58	52	44	38	32	25	18	10	2.0	0.1
	22	102	74	68	58	48	40	35	25	20	11	2.1	0.0
	23	79	66	57	50	42	37	32	23	19	12	2.3	0.1
	24	154	124	103	73	51	44	36	26	20	13	2.3	0.1
	Mean ± SD	145 ± 66	75 ± 25	68 ± 18	57 ± 9	47 ± 4	41 ± 4	35 ± 3	28 ± 6	22 ± 4	14 ± 4	4.4 ± 3.5	0.5 ± 0.8

[a] Concentrations measured by microbiological assay. Probability values were as follows: 10 min, 0.033; 20 min, 0.376; 30 min, 0.137; 1 h, 0.005; 2, 3, 4, 6, 8, and 12 h, <0.001; 24 h, 0.003; 48 h, 0.114.

[b] M, Missing data; $n = 5$ for this group.

significantly different, as were the ages and body surface areas. The normal (control) subjects tended to be younger and with lower body weights than the patients with uremia, and consequently, they had slightly smaller body surface areas than the other groups. The differences in the renal functional parameters of S_{cr}, C_{cr}, and $corC_{cr}$ were all highly significant, as anticipated, because of the segregation of the subjects into four different functional groups.

Pharmacokinetics. Table 2 lists the serum levels (in micrograms per milliliter) of aztreonam measured by microbiological assay at the various times after dosing, and Fig. 1 shows mean serum concentrations for the four groups of patients. The bioassay and HPLC assay (not shown) for aztreonam in serum and urine gave essentially idential results, indicating the absence of bioactive metabolites. Individual serum levels at 10 min ranged from 72 to 227 μg/ml and were highest in uremic subjects. Levels were not different at 20 and 30 min, but by 1 h the more rapid elimination in normal subjects became apparent. From 1 h onward, serum levels were highly significantly different. SQ 26,992 in serum was below the quantitation limit of the assay but this drug was measurable in urine.

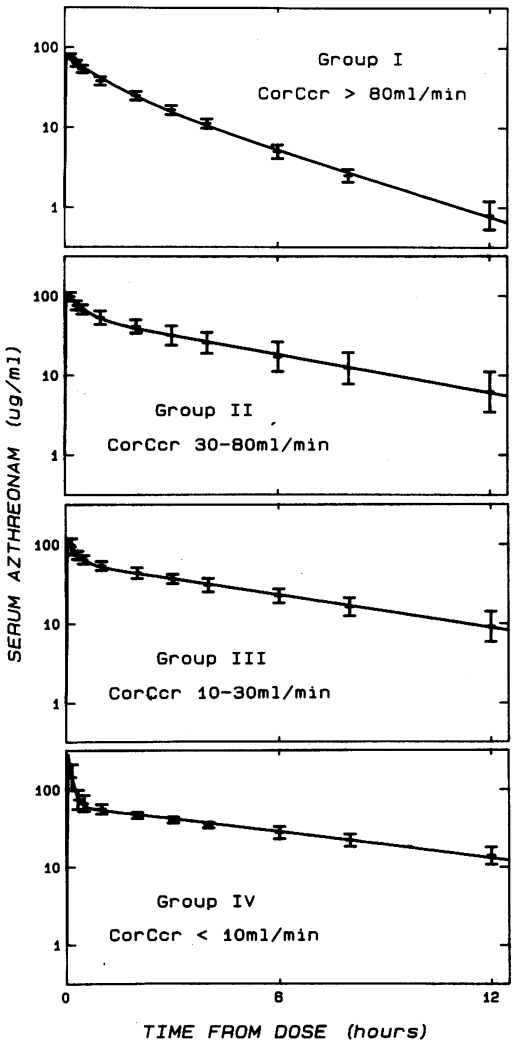

FIG. 1. Composite disappearance curves of aztreonam for the four study groups. The α distribution and β elimination phases are clearly different from the groups.

Detailed pharmacokinetic analysis was performed with total serum concentrations of aztreonam and urinary excretion data for aztreonam as measured by the microbiological assay because that analytical method had lower quantitation limits than the HPLC method. The values for the pharmacokinetic parameters derived from analysis of microbiological assay data in Table 2 are shown in Table 3. The α-phase half-life was directly related to renal function with mean values decreasing from 0.66 in normal subjects to 0.16 in subjects with $C_{cr} < 10$ ml/min ($P < 0.02$). The β-phase half-life correlated inversely with renal function, with progressive prolongation of the elimination of aztreonam from 2 h in normal subjects to 6 h in functionally anephric patients ($P < 0.001$). Differences in V_{dss} among the four groups were statistically significant but small and probably not clinically significant. V_{dss} showed no significant correlation with any of the subject characteristics. Aztreonam total body clearance was directly correlated with renal function, being 107 ml/min for normal subjects and 29 ml/min for functionally anephric patients. The percentage of free aztreonam in the serum correlated inversely with C_{cr}, i.e., there was a progressive increase in the percentage of free drug with decreasing renal function. Aztreonam excretion in the urine, as measured by microbiological assay, correlated directly with C_{cr}, with greater than half of the administered dose being excreted in normal subjects and progressively smaller amounts of drug appearing in patients whose renal function was diminished ($P < 0.001$). SQ 26,992 excretion in the urine, as measured by HPLC assay, was independent of renal function until severe renal insufficiency limited all urinary output.

Table 4 lists the urinary concentrations (in micrograms per milliliter) of aztreonam (measured by microbiological assay) and SQ 26,992 (measured by HPLC assay) during the various time intervals for total urine collections from subjects providing urine specimens. Individual urinary levels of aztreonam and SQ 26,992 ranged from 22 to 3,960 and from 0 to 194 μg/ml, respectively, during the 0-to-2-h period and were highest in healthy volunteers. Differences be-

TABLE 3. Individual and group pharmacokinetic data[a]

Group	Patient no.	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	A[b] (kg/liter)	B[c] (kg/liter)	V_{dss}[d] (kg/liter)	C_{az}[e] (ml/min)	% Free drug[f]	Recovered in urine (mg)[g]	
									Aztreonam	SQ 26,992
I	1	0.61	2.16	2.7	2.8	0.24	104	42	529	71
	2	0.17	1.99	4.0	3.7	0.23	101	45	551	73
	3	0.51	1.98	3.3	3.0	0.22	106	40	526	64
	4	1.06	1.96	3.2	2.7	0.18	92	41	678	67
	5	0.90	2.03	3.3	2.2	0.21	108	42	633	51
	6	0.69	1.80	3.4	2.1	0.23	133	41	583	72
	Mean ± SD	0.66 ± 0.31	1.98 ± 0.12	3.3 ± 0.4	2.8 ± 0.6	0.22 ± 0.02	107 ± 14	42 ± 2	583 ± 61	66 ± 8
II	7	0.84	3.85	4.4	3.0	0.20	53	46	408	101
	8	0.14	2.50	7.9	4.3	0.19	68	61	511	63
	9	0.10	4.48	10.0	5.9	0.16	30	59	217	57
	10	0.18	3.96	5.0	6.9	0.14	39	48	424	110
	11	0.54	3.13	3.4	5.5	0.15	43	48	361	210
	12	0.31	2.59	3.8	5.0	0.17	57	46	479	117
	Mean ± SD	0.35 ± 0.29	3.42 ± 0.80	5.8 ± 2.6	5.1 ± 1.4	0.17 ± 0.02	46 ± 16	51 ± 7	400 ± 104	110 ± 55
III	13	0.24	4.20	6.0	5.8	0.15	31	56	327	122
	14	0.12	3.53	13.5	4.9	0.17	43	51	133	50
	15	0.80	4.40	1.3	3.9	0.23	45	73	246	44
	16	0.33	5.62	2.6	5.2	0.18	27	54	198	29
	17	0.19	5.49	3.9	4.7	0.20	30	57	166	83
	18	0.19	5.36	5.6	5.7	0.16	25	50	191	64
	Mean ± SD	0.31 ± 0.25	4.76 ± 0.85	5.5 ± 4.3	5.0 ± 0.7	0.18 ± 0.03	34 ± 8	57 ± 8	210 ± 68	65 ± 33
IV	19	0.15	7.85	4.0	4.7	0.20	21	64	0	0
	20	0.04	8.12	126.9	3.3	0.22	26	71	0	0
	21	0.06	4.91	60.2	3.8	0.19	36	70	0	0
	22	0.16	4.90	6.1	4.9	0.19	32	69	6	0
	23	0.17	5.29	3.8	4.5	0.21	33	62	62	26
	24	0.36	5.06	9.7	5.2	0.15	27	48	18	6
	Mean ± SD	0.16 ± 0.11	6.02 ± 1.53	35.1 ± 50.0	4.4 ± 0.7	0.19 ± 0.02	29 ± 6	64 ± 9	14 ± 24	5 ± 10

[a] All pharmacokinetic parameters were based on data from microbiological assays, except that SQ 26,992 was assayed by HPLC. Probability values were as follows: $t_{1/2\alpha}$, 0.019; $t_{1/2\beta}$, <0.001; A, 0.120; B, 0.001; V_{dss}, 0.019; C_{az}, <0.001; percentage of free drug, <0.001; drug recovered in urine, <0.001 for both aztreonam and SQ 26,992.

[b] A, Intercept for distribution phase multiplied by (measured body weight/dose).

[c] B, Intercept for elimination phase multiplied by (measured body weight/dose).

[d] V_{dss}, Volume of distribution at steady state, calculated from A, B, α, and β and divided by measured body weight.

[e] Calculated from preceding parameters.

[f] Percentage of aztreonam unbound.

[g] Recovered in cumulative 0- to 48-h urine.

TABLE 4. Individual concentrations of aztreonam and SQ 26,992 after a 1-g intravenous dose[a]

Group	Patient no.	Concn (μg/ml) in sample taken at time (h): 0–2		2–4		4–8	
		Az[b]	SQ[c]	Az	SQ	Az	SQ
I	1	3,960	117	353	31.5	155	30.5
	2	3,810	42.7	1,680	52.5	286	23.3
	3	1,550	49.2	204	12.7	242	29.4
	4	3,510	194	1,030	31.5	152	12.8
	5	1,570	33.3	241	14.1	114	21.2
	6	1,350	50.0	141	25.0	115	9.3
	Mean ± SD	2,625 ± 1,254	81.0 ± 62.9	608 ± 618	27.9 ± 14.6	177 ± 71	21.1 ± 8.6
II	7	1,060	14.5	1,360	28.5	483	82.6
	8	358	tr	348	tr	144	6.1
	9	553	0.0	NR[d]	NR	172	12.1
	10	953	0.6	785	2.5	330	3.6
	11	219	7.1	247	19.4	137	10.6
	12	1,180	2.5	1,160	14.1	495	35.2
	Mean ± SD	720 ± 398	4.9 ± 6.0	80 ± 488	16.1 ± 10.9	294 ± 167	25.0 ± 30.4
III	13	327	42.9	84.7	0.0	78.1	tr
	14	289	2.0	202	4.8	126	3.7
	15	423	0.0	252	0.0	134	0.0
	16	499	0.0	NR	NR	311	0.0
	17	234	0.0	NR	NR	139	0.0
	18	272	4.8	107	2.7	95.1	4.7
	Mean ± SD	341 ± 101	8.3 ± 17.1	161 ± 79	1.9 ± 2.3	147 ± 84	1.7 ± 2.3
IV	22	NR	NR	NR	NR	NR	NR
	23	101	22.9	15.2	13.1	80.1	10.6
	24	22.0	0.0	76.2	Q[e]	80.9	0.0
	Mean ± SD	61.5 ± 55.9	11.4 ± 16.2	45.7 ± 43.1	13.1	80.5 ± 0.6	5.3 ± 7.5

[a] Probability values were as follows (the value for aztreonam is given first in each pair): 0 to 2 h, <0.001, 0.012; 2 to 4 h, 0.150, 0.033; 4 to 8 h, 0.081, 0.178; 8 to 12 h, 0.258, 0.579; 12 to 24 h, <0.001, 0.011; 24 to 48 h, 0.019, 0.160. Patients 19, 20, and 21 were anuric, and results for them are not shown.

[b] Az, Aztreonam; measured by microbiological assay.

[c] SQ, SQ 26,992; measured by HPLC.

[d] NR, Not received.

[e] Q, Insufficient sample volume.

tween mean values of aztreonam and SQ 26,992 among the four groups tended to diminish with time after drug administration. Mean SQ 26,992 concentrations exceeded those for aztreonam in groups I and II during the 12-to-24- and 24-to-48-h collection periods and in groups III and IV during the 24-to-48-h period.

Suggested modification of dosage regimen for renal dysfunction. Aztreonam clearance correlated closely with C_{cr} ($r = 0.92$) and $corC_{cr}$ ($r = 0.97$) but less well with S_{cr} ($r = 0.63$). The relationship between aztreonam clearance and $corC_{cr}$ is given in Fig. 2. The regression line is constructed showing the 95% confidence limits. The intercept of this line indicates that functionally anephric subjects had an aztreonam clearance of 25 ml/min. A normal $corC_{cr}$ of 100 ml/min corresponded to a C_{az} of 107 ml/min. Therefore, renal processes accounted for approximately 75% of total drug elimination. The regression equation of this plot provides an estimate of aztreonam clearance. From this data, we constructed a nomogram for dose adjustment in renal dysfunction. In this nomogram, the $corC_{cr}$ provides directly the required percentage of dose adjustment for a given degree of renal dysfunction; e.g., a patient with a $corC_{cr}$ of 33 ml/min would require a 50% reduction in

TABLE 4—*Continued*

8–12		12–24		24–48	
Az	SQ	Az	SQ	Az	SQ
49.8	14.1	6.5	12.7	0.3	14.3
32.1	9.0	8.8	25.5	0.1	26.3
64.7	12.1	10.9	37.9	0.2	9.8
55.5	4.8	6.4	21.8	0.2	13.5
59.4	27.5	10.6	35.7	0.1	0.0
30.8	19.4	5.0	37.0	0.0	5.3
48.7 ± 14.2	14.5 ± 8.0	8.0 ± 2.4	28.4 ± 10.2	0.2 ± 0.1	11.5 ± 9.0
214	36.3	8.2	49.1	1.5	34.6
47.5	7.5	9.9	19.3	0.2	7.5
68.2	10.6	21.5	17.3	2.7	11.8
145	6.4	56.3	38.7	2.9	58.7
56.0	8.0	15.2	32.3	1.5	42.2
135	36.4	15.1	63.7	0.3	19.8
111 ± 65	17.5 ± 14.6	21.0 ± 17.9	36.7 ± 17.8	1.5 ± 1.1	29.1 ± 19.6
71.9	18.1	14.7	18.7	0.6	17.4
45.9	5.1	9.8	6.9	0.5	14.7
62.5	12.9	24.6	23.8	1.5	6.3
230	18.8	36.7	0.0	2.5	14.3
74.9	0.0	27.0	18.2	4.7	31.7
61.3	7.0	29.8	16.1	3.3	17.6
91.1 ± 68.8	10.3 ± 7.5	23.8 ± 9.9	14.0 ± 8.8	2.2 ± 1.6	17.0 ± 8.3
NR	NR	60.6	0.0	NR	NR
44.1	15.6	129	9.0	1.3	16.8
82.8	0.0	57.6	tr	10.0	12.6
63.4 ± 27.4	7.8 ± 11.0	82.4 ± 40.4	4.5 ± 6.4	5.7 ± 6.2	14.7 ± 3.0

the aztreonam dose given at the same time interval. Alternatively, if the dosage is unmodified, then the normal time interval should be multiplied by the reciprocal of the percentage; e.g., for a corC_{cr} of 33 ml/min the standard dose of aztreonam should be administered at twice the normal time interval, and for a corC_{cr} of <10 ml/min the dose should be administered at four times the normal time interval.

Safety. Aztreonam was well tolerated by all the subjects in the study. One diabetic subject had mild diarrhea (two semiformed stools) within 1.5 h after aztreonam administration. There were no alterations in cardiovascular, renal, hepatic, or hematological function and no evidence of irritation at the injection sites.

DISCUSSION

Aztreonam has an attractive spectrum of activity in vitro against gram-negative organisms. It is likely to be widely used in critically ill patients; therefore, knowledge of its pharmacokinetics in the presence of renal failure may be especially relevant to its proper usage. We studied the pharmacokinetics of aztreonam in 24 adult male volunteers with various degrees of renal dysfunction, matched as closely as possible with the constraints of the C_{cr} classes. The control subjects with normal renal function were young athletic males, whereas the subjects in the two intermediately C_{cr} groups led sedentary lives, and those with minimal C_{cr} were more debilitated by their uremic state and dietary restrictions. However, the differences in characteristics (other than renal function) did not significantly affect aztreonam pharmacokinetic parameters.

The serum levels resulting from infusion of 1.0 g of aztreonam were described in terms of a linear two-compartment infusion model, from

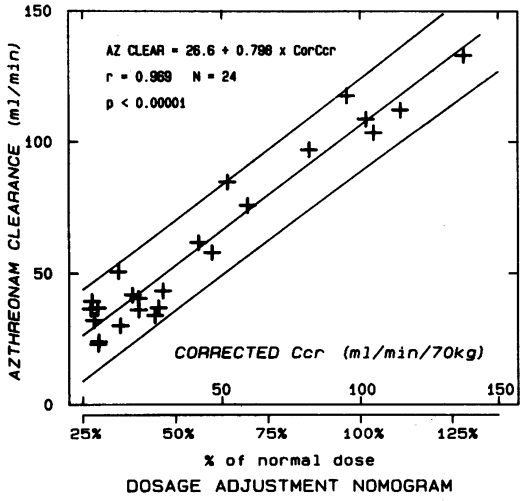

FIG. 2. Relationship between C_{az} and $corC_{cr}$. A normal $corC_{cr}$ of 100 ml/min corresponded to a C_{az} of 107 ml/min. Use of this scale for the percentage of normal dose for adjustment of dose for various degrees of renal function is explained in the text.

which V_{dss}, α distribution phase half-life, and β elimination phase half-life were determined. The V_{dss} ranged from 0.14 to 0.24 liter/kg. Several pharmacokinetic parameters were altered in patients with renal failure. The α distribution phase was significantly affected by the degree of renal dysfunction, perhaps owing to the reduced protein binding which occurs in uremia. The β half-life became progressively and significantly longer with increasing degrees of renal failure. As a corollary, serum levels of the drug were maintained at therapeutic levels for longer periods of time. Levels required for the treatment of resistant *Pseudomonas aeruginosa* (>10 μg/ml) lasted 3 to 4 h after 1.0 g of aztreonam in the normal controls, whereas in patients with $corC_{cr}$ of <10 ml/min, similar therapeutic levels were sustained for 16 h. The percentage of free drug concentration increased significantly with decreasing renal function. This may have been related to reduced protein binding in uremia, as is seen with other drugs, although other factors may be involved.

Some 58% of the administered aztreonam appeared in the urine. In normal subjects, aztreonam and SQ 26,992 recovered in the 0-to-48-h urine specimens accounted for 58 and 7% of the administered dose, respectively. Progressively lesser amounts were excreted with decreasing C_{cr}. Comparison of the intercept of the regression line in Fig. 2 for a $corC_{cr}$ of zero with the serum clearance of aztreonam in control subjects indicates that about 25% of drug clearance was nonrenal. Thus, renal excretion accounted for approximately 75% of total drug elimination, a value comparable to the sum of measured urinary excretion of aztreonam and SQ 26,992 in control subjects. Tubular secretion appears to make a significant contribution to this renal excretion (12). Urinary concentrations of aztreonam were potentially therapeutic (>1 μg/ml) for most urinary pathogens for at least 12 h in all subjects producing urine.

The aztreonam clearance correlated well with $corC_{cr}$, a calculated value using the age, sex, and S_{cr} of the individual. It is not subject to errors in calculation of C_{cr} resulting from incomplete urine collections. The $corC_{cr}$ thus provides a clinically valuable guide to dose adjustment in the presence of renal dysfunction, similar to dose adjustments for aminoglycosides (7). Our data indicate that the dose of aztreonam, given at the usual time intervals, should be 75% of the standard dose when the $corC_{cr}$ is 60 ml/min, 50% for $corC_{cr}$ of 30 ml/min, and 25% for anephric patients. Alternatively, the dose may be kept constant, and the time intervals between doses may be multiplied by the reciprocals of the stated percentages. A nomogram is provided to permit easy determination of these dosage adjustments. It should allow safe aztreonam therapy in the presence of various degrees of renal dysfunction.

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