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Single-Dose Pharmacokinetics of the Monobactam Azthreonam (SQ 26,776) in Healthy Subjects

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Azthreonam (SQ 26,776) is a new, completely synthetic, monocyclic beta-lactam antimicrobial agent that is highly active in vitro against most gram-negative bacteria. The pharmacokinetics of single intravenous doses of 125 to 4,000 mg, studied in 36 healthy male subjects, were best described by an open, linear, two-compartment kinetic model. The mean peak serum levels at 5 min after completion of 3-min infusions of 500-, 1,000- and 2,000-mg doses were 58, 125, and 242 μg/ml, respectively. The mean terminal serum half-life for all doses was 1.66 h, and the apparent volume of distribution was 0.18 liter/kg. The mean serum clearance was 1.27 ml min^{-1} kg^{-1}, and urinary excretion averaged 68% of the doses administered. The pharmacokinetics of single intramuscular doses of 250 to 1,000 mg, studied in 18 subjects, were best described by a linear, one-compartment model, with first-order absorption and elimination. The mean peak serum levels occurring at 1 h after doses of 250, 500, and 1,000 mg were 12, 22, and 46 μg/ml, respectively. Other kinetic parameters were similar to those for intravenous administration. Tolerance of azthreonam was good, with only a mild rash in one subject and with mild to moderate transient elevations in serum transaminases and lactate dehydrogenase in two subjects.

Azthreonam (SQ 26,776) (Fig. 1) is a new, synthetic, beta-lactam antimicrobial agent in the recently defined family of monobactam antimicrobial compounds (10). Azthreonam possesses potent antibacterial activity against a broad spectrum of aerobic gram-negative bacteria in vitro, as indicated by minimal inhibitory concentration (MIC) values for 90% of the isolates (MIC_{90}), which are often below 0.5 μg/ml (7). The antimicrobial activity of azthreonam is maintained in the presence of various beta-lactamases, pH values ranging from 6 to 8, or human serum. Toxicological (5) and therapeutic (2) investigations of this compound in several animal species have shown it to be well tolerated and efficacious. The purpose of this ascending-dose study was to describe the pharmacokinetics and safety of single intravenous and intramuscular doses of azthreonam in healthy human subjects.

MATERIALS AND METHODS

Subjects. Characteristics of the 72 healthy male subjects participating in this study are listed in Table 1. All of the subjects were considered healthy based on normal physical examinations, 12-lead electrocardiograms, complete blood counts, urinalyses, and serum chemistry profiles. Subjects giving histories of chronic disease, drug abuse, recent drug ingestion, or allergy to any drug or other substances were excluded.

All of the subjects gave informed, written consent before entry into this study. The protocols for this study were approved by the Institutional Review Board of The Medical Center at Princeton.

Administration of the drug. In the initial intravenous study, 48 subjects were divided at random into a drug or placebo group. Azthreonam was administered intravenously to 36 subjects, and a normal saline placebo was given to the 12 other subjects. The drug and placebo were administered in a blind fashion for tolerance testing purposes. The intravenous doses of azthreonam were 125, 250, 500, 1,000, 2,000, and 4,000 mg. Six subjects received the drug, and two subjects received placebo in each of the six treatment groups. Azthreonam was formulated with L-arginine as a buffering agent in a weight ratio of 1 g of azthreonam:0.78 g of L-arginine. The powder blend was reconstituted with sterile water to a final volume of 10 to 13 ml. Solutions of azthreonam or 10-ml volumes of normal saline placebo were given intravenously over 3 min through a small-bore catheter placed in an antecubital vein.

In a second study, 24 subjects received by random assignment intramuscular injections of either 250, 500, or 1,000 mg of azthreonam or an identical volume of normal saline placebo. Six subjects were given azthreonam, and two received placebo in each of the three treatment groups. Drug or placebo was injected into the right gluteus maximus. The powder blend of azthreonam and L-arginine described previously was reconstituted with sterile water to a final volume of 3.5 ml.

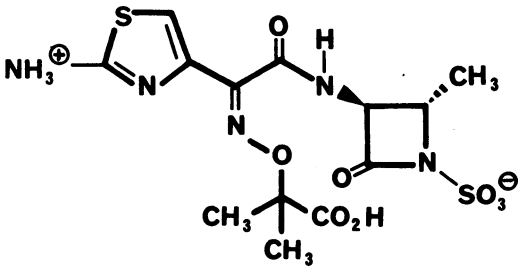

FIG. 1. Azthreonam (SQ 26, 776).

(In both studies azthreonam was prepared in vials containing the indicated dosages plus 5% overage to compensate for mechanical losses. The coefficient of variation for the actual vial contents was less than 0.6%).

Safety evaluation. The following series of tests was performed on each subject before and several times after drug administration: physical examination (including multiple vital signs and evaluation of the injection site), electrocardiogram, complete blood count, serum chemistry profile, urinalysis, and urine chemistry battery (including creatinine clearance). Hematological evaluation and serum and urine chemistry batteries were conducted at 24 and 72 h after injection of the drug.

Sampling of biological fluids for drug assay. Samples of blood for assay of azthreonam were drawn before drug administration and at 5, 10, 20, and 30 min, and at 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the end of the 3-min intravenous infusion or the intramuscular injection. Serum was prepared for subsequent analyses. Urine samples were obtained before injection of the drug, and cumulative urine collections were obtained in the intervals 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 16, 16 to 24, and 24 to 48 h. Approximately 250 ml of water was ingested at the time of drug administration and at 1 and 2 h after dosing to promote urine formation. Water was taken ad libitum during the remainder of the study. Subjects fasted overnight before dosing and for 4 h after dosing.

Assays. The details of the microbiological and high-pressure liquid chromatography (HPLC) assays for azthreonam have been described previously (9). Azthreonam concentrations in serum and urine samples from the intravenous and intramuscular studies were determined by the microbiological agar diffusion method, which had quantitation limits of 0.03 μg/ml for serum and 0.06 μg/ml for urine. Biological samples from the intravenous study were also assayed by the HPLC method, which had quantitation limits of 1.0 μg/ml for serum and 5.0 μg/ml for urine. The specificity and precision of each method were shown by negative results for all predose specimens and by coefficients of variation of 3 to 5%.

Pharmacokinetic methods. A standard two-compartment open model was used to calculate azthreonam pharmacokinetic parameters after intravenous infusion, as described previously (9). Nonlinear regression analysis was performed, using the computer programs AUTOAN and NONLIN (6). The following pharmacokinetic parameters were determined by standard methods (3): V_1, volume of distribution of the central compartment; V_{area}, volume of distribution based on area under the serum concentration time curve; V_{ss}, volume of distribution at steady state; k_{12} and k_{21}, intercompartmental transfer rate constants; k_{10}, elimination rate constant; $t_{1/2\alpha}$ and $t_{1/2\beta}$, half-times for the α-distribution phase and the β-elimination phase; serum clearance; and area under the curve (AUC) based on the trapezoidal rule. The 3-min duration of the intravenous infusion was accounted for in the pharmacokinetic analysis.

A one-compartment first-order absorption and elimination model was used to calculate the pharmacokinetic parameters after intramuscular injection in a manner similar to that just described for the intravenous study. The following pharmacokinetic parameters were determined by standard methods (3): V_{area}; t peak, the time until peak of measured serum concentration; k_a, rate constant for absorption from the intramuscular injection site; k_{el}, rate constant for elimination; $t_{1/2a}$ and $t_{1/2el}$, half-times for the absorption and elimination phases; serum clearance; and AUC.

RESULTS

Intravenous pharmacokinetics. The bioassay and the HPLC assay for azthreonam in serum and urine gave, for all practical purposes, equivalent results. The results of the bioassay will be described in detail below, because this method had lower quantitation limits.

Figure 2 shows the mean serum concentrations of azthreonam as measured by bioassay after single 125- to 4,000-mg intravenous doses. Mean values represent six subjects at each dose. Serum concentrations at 24 h could be measured only after the 4,000-mg dose. The decline in serum levels of azthreonam was biphasic over a 10,000-fold range in serum concentration. The parallel, equally spaced, curves indicated visually that the monobactam obeyed linear kinetics. This was confirmed by linear regression analysis of AUC (micrograms per hour per milliliter) versus dose (milligrams): AUC = 0.176 dose + 8.12, r = 0.981. Table 2 summarizes the mean serum concentrations at selected times, with AUC values for the 500- and 1,000-mg doses. These data also indicate that serum concentration and AUC were proportional to dose.

The cumulative urinary excretion of azthreonam after intravenous administration is shown in Fig. 3. Measurable urinary excretion was essentially complete after 12 h and was dose independent, with a mean value of 68% of the

TABLE 1. Characteristics of study subjects[a]

Study group	Age (yr)	Ht (cm)	Wt (kg)	No. of subjects
Drug	22 (18–31)	178 (166–193)	74 (55–90)	54
Placebo	21 (18–28)	178 (160–193)	77 (61–96)	18

[a] Data are mean values, with respective ranges in parentheses.

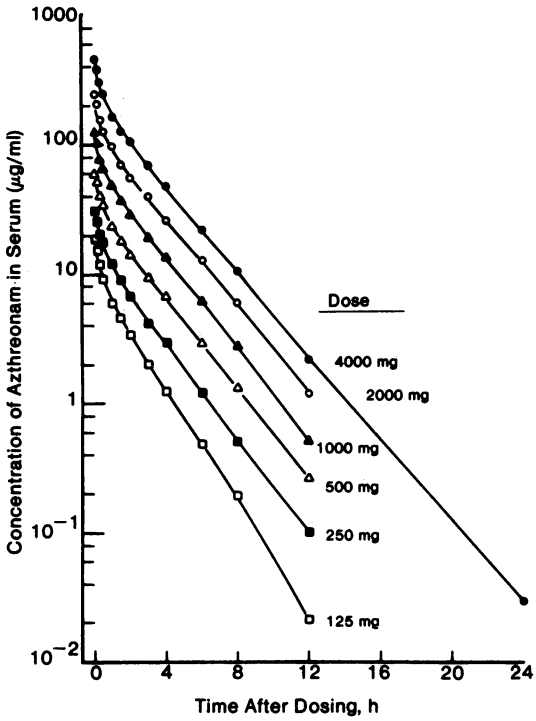

FIG. 2. Mean serum concentration of azthreonam after 3-min intravenous infusions of 125 (□), 250 (■), 500 (△), 1,000 (▲), 2,000 (○), and 4,000 mg (●).

administered dose. The good agreement between bioassay and HPLC results (not shown in detail) for urinary excretion suggested the absence of important amounts of bioactive metabolites of azthreonam. The primary method of elimination appeared to be urinary excretion of unchanged drug.

The concentrations of azthreonam in the urine at various time periods are listed in Table 3 for the 500- and 1,000-mg intravenous doses. A comparison with Table 2 indicates that urine concentrations generally exceeded concurrently measured serum concentrations by a factor of 10 to 100.

The serum pharmacokinetics of azthreonam administered intravenously were described by an open, linear, two-compartment model; kinetic parameters are shown in Table 4. Parameters describing the extent and rate of distribution and elimination are listed for both bioassay and HPLC methods, which gave equivalent results. There were no important variations in kinetics with dose; therefore, overall means, standard deviations, and ranges were calculated for all of the 36 subjects who received the drug.

The extent of distribution was described by V_1, V_{ss}, and V_{area}, which had mean values of 0.09, 0.16, and 0.18 liters/kg of body weight, respectively. The rate of distribution was represented by $t_{1/2\alpha}$, with a mean value of 0.2 h for the initial rapid decline in serum concentration (α-phase). The rate of elimination of azthreonam was described by $t_{1/2\beta}$, which had a mean value of 1.66 h for the terminal decline in serum concentration (β-phase). A mean value of 1.27 ml min^{-1} kg^{-1} was obtained for whole-body or serum clearance.

Intramuscular pharmacokinetics. Figure 4 summarizes the mean serum concentrations of azthreonam as measured by bioassay after single 250- to 1,000-mg intramuscular doses. Mean values represent six subjects at each dose. The first-order ascending-absorption and descending-elimination phases are evident. Table 2 gives the serum concentrations at selected times, with AUC values for 500- and 1,000-mg doses. These data indicate that serum concentration and AUC were proportional to dose.

The concentrations of azthreonam in the urine after the 500 and 1,000-mg intramuscular doses are shown in Table 3. Urine concentrations generally exceeded concurrently measured serum concentrations by a factor of 10 to 100, as indicated by comparing the data in Tables 2 and 3.

TABLE 2. Serum concentrations of azthreonam after intravenous and intramuscular administration[a]

Time after injection	Intravenous dose (mg)		Intramuscular dose (mg)	
	500	1,000	500	1,000
5 min	58.2 ± 3.4	125 ± 4	4.8 ± 1.0	8.6 ± 2.3
1 h	23.3 ± 0.8	48.6 ± 1.6	22.0 ± 1.8	46.5 ± 2.8
4 h	6.7 ± 0.2	13.2 ± 0.3	8.9 ± 0.5	18.4 ± 0.6
6 h	2.9 ± 0.2	6.0 ± 0.3	3.8 ± 0.3	8.2 ± 0.4
8 h	1.3 ± 0.1	2.7 ± 0.1	1.7 ± 0.2	3.5 ± 0.2
12 h	0.26 ± 0.04	0.51 ± 0.02	0.30 ± 0.05	0.65 ± 0.09
AUC[b]	94 ± 2	191 ± 5	84 ± 3	180 ± 4

[a] Serum concentration values measured by bioassay are expressed as the mean ± the standard error of the mean. Units, micrograms per milliliter; six different subjects were used at each dose.

[b] AUC values, micrograms hour per milliliter (0 to 24 h).

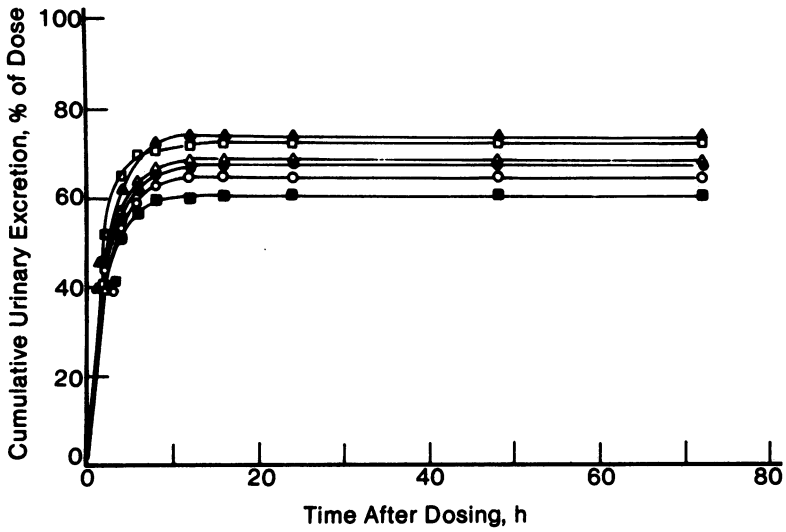

FIG. 3. Mean cumulative urinary excretion of azthreonam after 3-min intravenous infusions of 125 (□), 250 (■), 500 (△), 1,000 (▲), 2,000 (○), and 4,000 mg (●).

The serum pharmacokinetics of azthreonam administered intramuscularly were described by an open one-compartment model with first-order absorption and elimination processes. Because there were no important variations in kinetic values with dose, the overall means, standard deviations, and ranges were computed for all of the 18 subjects who received the drug. The apparent rate of absorption from the intramuscular injection site was described by t peak and $t_{1/2a}$, which had mean values of 0.9 and 0.4 h, respectively (Table 4). Values for distribution and elimination parameters after intramuscular injection were very similar to those listed in Table 4 for intravenous administration. For example, values of k_{el} and $t_{1/2el}$ from intramuscular doses were statistically indistinguishable from values of β and $t_{1/2\beta}$, respectively, from intravenous doses.

Safety. Human tolerance of single intravenous and intramuscular doses of azthreonam was acceptable, based on the results of physical examinations, extensive laboratory tests, electrocardiograms, and examination of injection sites. One subject developed a mild, pruritic, erythematous rash on both arms shortly after administration of a 250-mg intravenous dose. Another subject, who received 250 mg intravenously, had mild-to-moderate transient elevations in serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and lactate dehydrogenase. Another subject, who received 1,000 mg intramuscularly, had similar increases in serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase. These elevations were first noted 72 h after dosing in the absence of any subjective or objective findings. In all of the subjects, phlebitis or inflammation of the injection site was absent. There were no significant changes in hematological, renal, cardiac, gastrointestinal, respiratory, or neurological function.

TABLE 3. Urinary concentrations of azthreonam after intravenous and intramuscular administration[a]

Time after injection (h)	Intravenous dose (mg)		Intramuscular dose (mg)	
	500	1,000	500	1,000
0–2	1,400 ± 200	3,000 ± 1,200	520 ± 190	1,200 ± 320
2–4	250 ± 58	710 ± 370	380 ± 170	650 ± 84
4–6	330 ± 57	720 ± 190	420 ± 87	640 ± 200
6–8	140 ± 27	300 ± 73	180 ± 31	470 ± 140
8–12	50 ± 8	70 ± 10	27 ± 8	140 ± 28
12–16	8.2 ± 1.6	11 ± 3	6 ± 1	25 ± 4
16–24	1.9 ± 0.4	2.8 ± 0.5	1.3 ± 0.3	5 ± 2.7

[a] Urine concentration values measured by bioassay are expressed as mean ± standard error of the mean (micrograms per milliliter) for cumulative urine collections over the indicated time intervals; six different subjects were used at each dose.

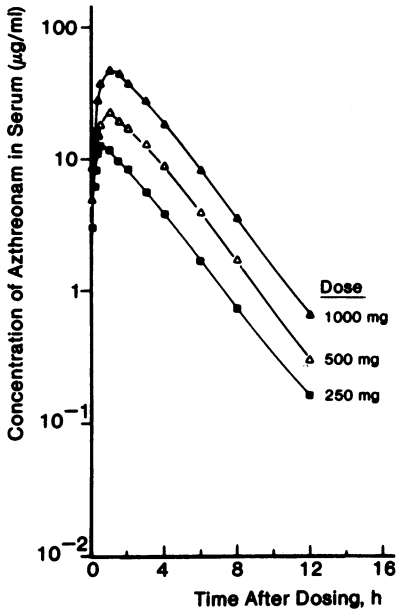

FIG. 4. Mean serum concentrations of azthreonam after intramuscular injections of 250 (□), 500 (△), and 1,000 mg (▲).

DISCUSSION

Azthreonam differs from the commercially available beta-lactams (penicillins, cephalosporins, and cephamycins) by its (i) fundamentally new molecular structure, which places it in a completely different family of antimicrobial agents, (ii) entirely synthetic origin obviating synthesis by bacterial fermentation, (iii) greater in vitro activity against most of the clinically important *Enterobacteriaceae* and *Pseudomonas aeruginosa* strains, and (iv) lack of significant activity against gram-positive organisms and anaerobes.

Azthreonam has a spectrum similar to that of commercially available aminoglycosides in that both have potent gram-negative activity. However, unlike gentamicin, azthreonam retains its in vitro bactericidal activity under anaerobic conditions (7). Because azthreonam lacks significant activity against gram-positive organisms, initial therapy of life-threatening bacterial infections before identification of the pathogen would require coadministration of azthreonam with another agent having adequate gram-positive activity.

The pharmacokinetics of azthreonam described in this study suggest that intravenous

TABLE 4. Summary of pharmacokinetics of azthreonam in healthy subjects[a]

Parameter	Bioassay			HPLC assay		
	Mean	SD	Range	Mean	SD	Range
Absorption (i.m.)						
Rate (apparent)						
t peak (h)	0.94	0.34	0.42–1.50	NA	NA	NA
$t_{1/2a}$ (h)	0.40	0.23	0.16–0.90	NA	NA	NA
k_a (h^{-1})	2.24	1.10	0.77–4.30	NA	NA	NA
Distribution (i.v.)						
Extent						
V_1 (liters/kg)	0.09	0.02	0.06–0.12	0.09	0.02	0.06–0.14
V_{ss} (liters/kg)	0.16	0.02	0.11–0.20	0.16	0.02	0.12–0.20
V_{area} (liters/kg)	0.18	0.02	0.13–0.23	0.18	0.03	0.14–0.27
Rate						
$t_{1/2\alpha}$ (h)	0.20	0.07	0.12–0.53	0.23	0.11	0.09–0.74
k_{12} (h^{-1})	1.44	0.52	0.26–2.52	1.44	0.69	0.17–3.84
k_{21} (h^{-1})	1.78	0.39	0.80–2.81	1.60	0.57	0.48–3.24
Elimination (i.v.)						
Extent						
24 h urinary excretion (% of dose)	68	7	52–82	70	13	42–94
Serum Cl (ml min^{-1} kg^{-1})	1.27	0.14	0.98–1.60	1.14	0.20	0.81–1.68
Rate[b]						
$t_{1/2\beta}$ (h)	1.66	0.19	1.30–1.95	1.88	0.27	1.27–2.49
k_{10} (h^{-1})	0.87	0.13	0.62–1.22	0.82	0.18	0.56–1.48

[a] Absorption parameters for 18 subjects receiving intramuscular (i.m.) injections were independent of dose in the range of 250 to 1,000 mg. Distribution and elimination parameters for 36 subjects receiving intravenous (i.v.) injections were independent of dose in the range of 125 to 4,000 mg.

[b] After intramuscular doses, values were as follows: $t_{1/2el}$, 1.64 ± 0.21 (standard deviation), 1.23 to 2.21 h (range); k_{el}, 0.43 ± 0.06 (standard deviation), 0.31 to 0.56 h^{-1} (range). After intravenous doses, values were: β, 0.42 ± 0.05 (standard deviation), 0.36 to 0.53 h^{-1} (range).

doses of 500 to 2,000 mg would produce serum concentrations that would readily inhibit commonly encountered members of *Enterobacteriaceae*, as well as *Pseudomonas aeruginosa*. A single 500- to 1,000-mg dose of azthreonam may produce concentrations inhibiting the majority of *Enterobacteriaceae* in urine for 16 to 24 h. The elimination-phase half-life of azthreonam appeared to be longer than that of many first and second generation cephalosporins (1) and was comparable to that of the third generation cephalosporin ceftazidime (8). Azthreonam was associated with a low incidence of elevated liver function tests as has also been noted for many other penicillins and cephalosporins (4). Additional studies of the safety and kinetics of multiple parenteral doses of azthreonam in healthy subjects are in progress.

The in vitro antibacterial activity and the overall acceptable tolerance and pharmacokinetics of azthreonam in humans suggest that it may prove to be an effective chemotherapeutic agent for infections due to gram-negative bacteria. It may be possible to treat respiratory, soft-tissue, and urinary tract infections due to susceptible organisms with lower and less frequent doses than has been necessary with both first- and second-generation cephalosporins. In addition, the striking similarity between the antibacterial spectrum and potency of azthreonam and aminoglycosides suggests a new alternative therapy for the initial treatment of bacterial infections before laboratory identification of a pathogen. This would be particularly feasible if azthreonam, a beta-lactam antibiotic, proves to have a more favorable safety profile than aminoglycosides, as suggested by early studies in animals (5).

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