ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1983, p. 394–400
0066-4804/83/090394-07$02.00/0

Vol. 24, No. 3

Metabolism and Pharmacokinetics of Aztreonam in Healthy Subjects

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Received 1 April 1983/Accepted 27 June 1983

The metabolism and pharmacokinetics of aztreonam (SQ 26,776) were studied in four healthy male volunteers, each of whom received single 500-mg intravenous and intramuscular doses of ^{14}C-labeled drug according to a two-way crossover design. Serial samples of serum, urine, and feces were assayed for aztreonam and metabolites. Serum pharmacokinetics of aztreonam administered intravenously were described by an open, linear, two-compartment kinetic model. Kinetics of intramuscular aztreonam followed a one-compartment model with first-order absorption and elimination. Intramuscular bioavailability was 100%. After either intravenous or intramuscular administration, aztreonam was eliminated primarily by urinary excretion of unchanged drug (about 66% of dose), whereas only 1% of the dose was found as unchanged drug in the feces, presumably owing to biliary secretion. The average elimination half-life of aztreonam was 1.6 and 1.7 h, respectively, for intravenous and intramuscular administration. Aztreonam did not undergo extensive metabolism; the most prominent biotransformation product of aztreonam was SQ 26,992, the compound resulting from the hydrolytic opening of the beta-lactam ring. Urinary and fecal SQ 26,992 constituted 7 and 3% of the administered dose, respectively. SQ 26,992 was eliminated at a considerably slower rate than was aztreonam.

The monobactam aztreonam, in single-dose studies in healthy male volunteers, displays linear kinetics, as determined by microbiological and high-pressure liquid chromatography assays over an intravenous dose range of 125 to 4,000 mg and an intramuscular dose range of 250 to 1,000 mg, with a terminal half-life of between 1.3 and 2 h (10). Multiple intravenous and intramuscular 500- and 1,000-mg doses, administered every 8 h resulted in no significant change in pharmacokinetic parameters. Serum protein binding of aztreonam averages 56%. SQ 26,992 is a microbiologically inactive biotransformation product of aztreonam and is formed in humans by the hydrolytic opening of the beta-lactam ring of aztreonam, as determined by high-pressure liquid chromatography (9).

The purpose of this study was to investigate further the metabolism and pharmacokinetics of aztreonam by using, for the first time, the radiolabeled drug administered both intravenously and intramuscularly to the same subjects.

MATERIALS AND METHODS

Subjects. Six healthy male subjects participated in this study; however, urine collections for two were incomplete. The latter two subjects were excluded from any further consideration in this report. The four remaining subjects had a mean age of 28 years (range, 21 to 30), mean height of 177 cm (range, 168 to 187), and mean weight of 73.3 kg (range, 69.2 to 80.1). All four subjects were considered healthy as determined by normal physical examination, 12-lead electrocardiogram, complete blood count, urinalysis, and serum chemistry profile. None had a history of chronic disease, drug abuse, recent drug ingestion, or allergy to any drug or other substances. All of the subjects gave informed, written consent before entry into this study. The study protocol was approved by the Institutional Review Board of The Medical Center at Princeton.

Administration of drug. Each volunteer received two 500-mg doses of aztreonam administered as single 2-min intravenous infusions and as intramuscular injections in the gluteus maximus according to a two-way crossover design with a 15-day washout period between doses. The adequacy of the washout period was shown by negative drug and radioactivity assay results in serum, urine, and feces obtained just before the second dose. Each dose contained ca. 50 μCi of ^{14}C in the 2-position of the thiazolyl ring. The aztreonam was formulated with L-arginine as a buffering agent in a ratio of 1 g of aztreonam to 0.7 g of L-arginine. This powder blend was reconstituted with sterile water to a final volume of 2.5 ml before administration. 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.

The following series of tests was performed on each subject before and after drug administration: physical examination (including multiple determination of vital signs), electrocardiogram, complete blood count, serum chemistry profile (sodium, potassium, chloride, fasting glucose, urea nitrogen, creatinine, uric acid, calcium, inorganic phosphorus, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase, and creatine phosphokinase), and urinalysis.

Collection of biological specimens. Samples of blood for assay of aztreonam were drawn before and 5, 10, 20, and 30 min and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 h after completion of each dose. Serum was prepared and stored at −20°C for subsequent analyses. Protein-free filtrate (PFF) was prepared by ultrafiltration of serum obtained at 0.5, 1, and 3 h (7). Urine samples were obtained before injection of the drug, and total urine collections were obtained for the intervals 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, and 120 to 144 h. Fecal samples were obtained before injection of the drug, and total fecal collections were obtained for the intervals 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, and 120 to 144 h.

Microbiological assay. The details of the microbiological assay for aztreonam have been described previously (8). Aztreonam concentrations in serum and urine samples (but not PFF or feces) were determined by the agar diffusion method which had quantitation limits of 0.04 μg/ml for serum and 0.08 μg/ml for urine. The specificity and precision of the method were shown previously by negative results for all predose specimens and by coefficients of variation of 3 to 5%.

Radiochemical assay. Concentrations of total radioactivity in serum, PFF, urine, and feces were determined by liquid scintillation counting. A 0.1-ml volume of serum was digested in 1.0 ml of Soluene-350 (Packard Instrument Co., Downers Grove, Ill.), neutralized with 0.1 ml of PGM (a saturated solution of sodium pyruvate in methanol, glacial acetic acid, and methanol, in a volume ratio of 4:3:1), and mixed with 15 ml of scintillation cocktail (1). PFF (0.05 ml) was counted directly in 15 ml of scintillation cocktail. A 0.2-ml sample of urine was digested in 1.0 ml of Soluene-350, neutralized with 0.1 ml of PGM, and mixed with 15 ml of scintillation cocktail. Samples of feces were shaken with about 3 to 5 volumes of water for 16 h. A portion of the homogenate (0.2 g) was digested by shaking for about 48 h with 1 ml of Soluene-350. The digested sample was bleached with 1.0 ml of a 20% solution of benzoyl peroxide in toluene and mixed with 0.1 ml of PGM and 15 ml of scintillation cocktail.

All samples were counted in either a Model 2425 or 3380 Packard Tri-Carb liquid scintillation spectrometer (Packard Instrument Co., Rockville, Md.). Samples prepared from thin-layer chromatograms (see below) were counted in an Intertechnique Model SL-4200 scintillation spectrometer (IN/US Service Corporation, Fairfield, N.J.). Counting efficiency was determined with automatic external standardization and the use of previously prepared quench curves. The quantitation limit for total radioactivity in serum, PFF, and urine was 0.2 μg/ml; the limit in feces was 1 μg/g.

TLRC. Homogenates of feces (5 g) were extracted five times with 8 ml of methanol. Portions (1.0 ml) of the combined methanolic extracts were assayed by thin-layer radiochromatography (TLRC) for total radioactivity. The remainder of each extract was filtered through glass wool and evaporated to dryness in vacuo at about 25°C. The residue then was reconstituted in 0.6 ml of methanol.

Samples of urine (25 μl) and the reconstituted methanolic extracts of feces (100 μl) were chromatographed on 0.25-mm silica gel GF plates (Analtech, Inc., Newark, Del.) in 1-butanol-ethyl acetate-acetic acid-water (1:1:1:1). Aztreonam and SQ 26,992 were used as reference compounds. Chromatograms were visualized under short-wavelength UV light. Each chromatogram was divided into six zones consisting of aztreonam, SQ 26,992, and unknown compounds. All

TABLE 1. Concentrations of aztreonam and total radioactivity in serum after parenteral administration of 500-mg doses to healthy male volunteers[a]

Time after injection (h)	Mean ± SEM concn (μg/ml) in serum as tested by:			
	Intravenous route		Intramuscular route	
	Aztreonam bioassay	Total radioactivity	Aztreonam bioassay	Total radioactivity
0.08	56.3 ± 3.8	67.2 ± 5.3	6.7 ± 2.5	8.5 ± 3.2
0.17	45.6 ± 2.6	54.2 ± 3.0	11.7 ± 3.3	15.0 ± 4.8
0.33	37.4 ± 2.3	43.3 ± 3.3	16.6 ± 2.8	20.2 ± 3.1
0.50	31.6 ± 2.2	36.4 ± 2.6	19.0 ± 2.0	23.6 ± 3.3
1	20.0 ± 1.0	24.2 ± 1.6	21.0 ± 1.3	26.7 ± 1.5
1.5	15.0 ± 0.7	19.0 ± 1.1	19.7 ± 0.6	24.4 ± 1.2
2	12.6 ± 0.7	15.4 ± 0.8	17.2 ± 0:8	21.4 ± 1.2
3	8.0 ± 0.6	10.7 ± 0.5	12.6 ± 0.5	16.1 ± 0.8
4	5.3 ± 0.3	7.6 ± 0.5	8.6 ± 0.5	11.2 ± 0.8
6	2.2 ± 0.2	4.0 ± 0.3	3.8 ± 0.3	5.9 ± 0.4
8	0.8 ± 0.1	2.4 ± 0.1	1.5 ± 0.2	3.3 ± 0.2
12	0.1 ± 0.0	1.6 ± 0.1	0.2 ± 0.0	1.7 ± 0.7
16	0.0 ± 0.0	1.3 ± 0.1	0.0 ± 0.0	1.4 ± 0.1

[a] $n = 4$.

the silica gel in each zone was scraped from the plate, mixed with 1 ml of a 50:50 (vol/vol) mixture of methanol and water, and counted in 15 ml of the scintillation cocktail.

The quantitation limits for aztreonam and SQ 26,992 in urine were 2.0 μg/ml. Recovery of both aztreonam and SQ 26,992 from spiked urine samples prepared at several concentrations was generally greater than 96%. The recoveries of aztreonam and SQ 26,992 from spiked fecal samples were 90 and 93%, respectively. Recovery of aztreonam from spiked serum samples was 70%. Although application of a correction factor gave aztreonam concentrations in serum consistent with bioassay results, only values for total radioactivity levels in serum are reported.

Calculations used in radiochemical assays. The concentration of total radioactivity in serum was expressed as microgram equivalents of aztreonam per milliliter. The concentration of unchanged aztreonam in urine was calculated by multiplying the fraction of total radioactivity in the aztreonam zone of the thin-layer chromatogram by the concentration of total radioactivity present in the corresponding sample. The concentration of unchanged aztreonam in feces was obtained by multiplying the concentration of total radioactivity in feces (as equivalents of aztreonam) by the product of the fraction extracted into methanol and by the fraction of total radioactivity in the extract present as aztreonam.

Pharmacokinetic methods. A standard two-compartment open model was used to calculate aztreonam pharmacokinetic parameters for individual subjects after intravenous infusion, as described previously (8). Nonlinear regression analysis was performed, using the computer programs AUTOAN and NONLIN (5). The following pharmacokinetic parameters were determined by standard methods (4): 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-lives for the α-distribution phase and the β-elimination phase; serum clearance; and area under the curve (AUC) based on the trapezoidal rule. The 2-min duration of the intravenous infusion was accounted for in the pharmacokinetic analysis.

After intravenous administration of drug, the urinary excretion rates (amount, ΔM_u, of compound excreted in the urine over a collection interval of duration Δt) of aztreonam and SQ 26,992 were calculated, plotted versus midpoints of urine collection times, and fitted by linear regression analysis for each subject. The slope of the $\ln(\Delta M_u/\Delta t)$ versus t relationship was used to calculate elimination half-life by using the relationship, $t_{1/2u} = (\ln 2)/\text{slope}$ (4).

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 intrave-

TABLE 2. Pharmacokinetic parameters for aztreonam administered as 500-mg doses to healthy male volunteers[a]

Parameter	Mean ± SEM (n = 4)	
	Intravenous	Intramuscular
Absorption		
Extent		
bioavailability, % of dose	NA	101 ± 3
Rate		
t_{peak} (h)	NA	0.88 ± 0.12
$t_{1/2a}$ (h)	NA	0.42 ± 0.21
K_a (h^{-1})	NA	2.83 ± 0.87
Distribution		
Extent, liters kg^{-1}		
V_1	0.11 ± 0.01	NA
V_{ss}	0.18 ± 0.00	NA
V_{area}	0.21 ± 0.00	0.21 ± 0.01
Rate		
$t_{1/2\alpha}$ (h)	0.23 ± 0.03	NA
K_{12} (h^{-1})	1.19 ± 0.27	NA
K_{21} (h^{-1})	1.64 ± 0.15	NA
Elimination		
Extent, 0 to 144 h		
urine (% of dose)	67.3 ± 2.0	64.5 ± 1.7
feces (% of dose)	NA	NA
serum clearance (ml min^{-1} kg^{-1})	1.53 ± 0.04	1.46 ± 0.02
renal clearance (ml min^{-1} kg^{-1})	1.03 ± 0.04	0.94 ± 0.03
Rate[b]		
$t_{1/2\beta}$ or $t_{1/2el}$ (h)	1.59 ± 0.03	1.70 ± 0.09
K_{10} or K_{el} (h^{-1})	0.85 ± 0.06	0.41 ± 0.02

[a] Values are based on the results of microbiological assays. NA, Not applicable.
[b] $t_{1/2\beta}$ and K_{10} are for the intravenous route, $t_{1/2el}$ and $K_{1/2el}$ are for the intramuscular route.

nous study (10). The following pharmacokinetic parameters were determined by standard methods for each subject (4): 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-lives for the absorption and elimination phases; serum clearance; and AUC.

The percentage of radioactivity bound to serum proteins was calculated from the relationship, 100 × (serum concentration − PFF concentration)/serum concentration. The percent binding values calculated by this method represent total binding (covalent and noncovalent) of radioactivity to serum proteins.

Concentrations of unchanged aztreonam measured by microbiological assay in serum after intravenous and intramuscular administration of aztreonam were used for pharmacokinetic evaluations. Urinary excretion data for unchanged aztreonam and SQ 26,992 (measured by TLRC) were also used for the determination of the terminal half-life of elimination of aztreonam and SQ 26,992, respectively.

RESULTS

The mean concentrations of total radioactivity in serum are shown in Table 1 for four subjects receiving both intravenous and intramuscular doses of aztreonam. The initial concentrations of total radioactivity immediately after intravenous administration were higher than those after intramuscular administration, as might be expected. However, between 2 and 12 h, the concentrations of total radioactivity were generally higher for intramuscular than for intravenous administration. The 1- and 1.5-h concentrations were similar for both routes of administration. The terminal elimination phase for the total radioactivity in serum was nonlinear for individual subjects; this may have been due to differing rates of formation or elimination of aztreonam and its metabolites (not quantitated in serum by radiochemical assay).

The mean concentrations of aztreonam in serum, as measured by bioassay, are shown in Table 1. After intravenous administration, the decline of aztreonam levels in serum was biphasic over a 1,000-fold range of concentrations in serum. After intramuscular administration, levels of aztreonam in serum displayed first-order ascending-absorption and descending-elimination phases.

The pharmacokinetic parameter values are summarized in Table 2. Based on a comparison of serum AUC values for unchanged aztreonam after intravenous and intramuscular administration, the absolute bioavailability of aztreonam after intramuscular administration was 101 ± 3%. Absorption of aztreonam from the intramuscular injection site was also rapid ($t_{1/2a}$ = 0.42 h). The apparent volume of distribution (V_{area}) was the same for both routes of administration. The extent of urinary aztreonam elimination over 6 days for intravenous and intramuscular dosing was 67 and 64%, respectively. Values for serum and renal clearance were also similar, and the terminal half-life was 1.6 and 1.7 h for intravenous and intramuscular administrations, respectively.

Serum protein binding based on total radioactivity was independent of sampling time and averaged 69.5 and 71.7% after intravenous and intramuscular dosing, respectively.

The time course of mean urinary and fecal excretion of total radioactivity is shown in Fig. 1 for both routes of drug administration. Urinary and fecal excretion was essentially complete by 12 and 48 h after dosing, respectively. Figure 2 shows the time course of mean cumulative aztreonam and SQ 26,992 excretion in urine, as assayed by TLRC methods. Table 3 shows that the concentrations of aztreonam in urine, measured by bioassay and TLRC compared favor-

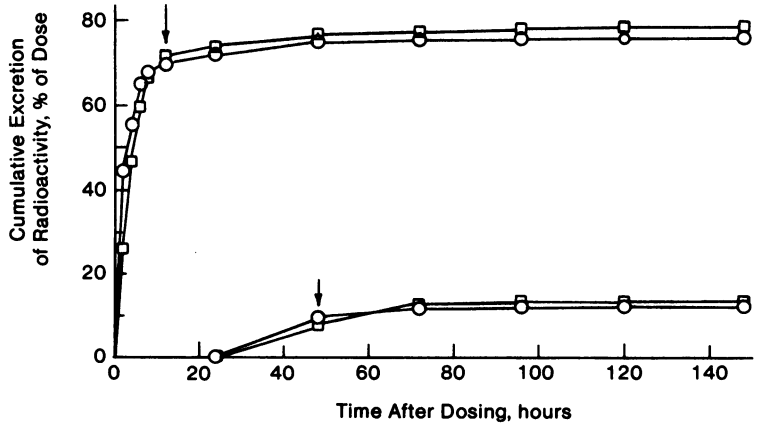

FIG. 1. Mean cumulative urinary (top curves) and fecal (bottom curves) excretion of total radioactivity. Symbols: ○, 500-mg intravenous dosage; □, 500-mg intramuscular dosage. On the top curves, arrow indicates 12 h; on the bottom curves, arrow indicates 48 h.

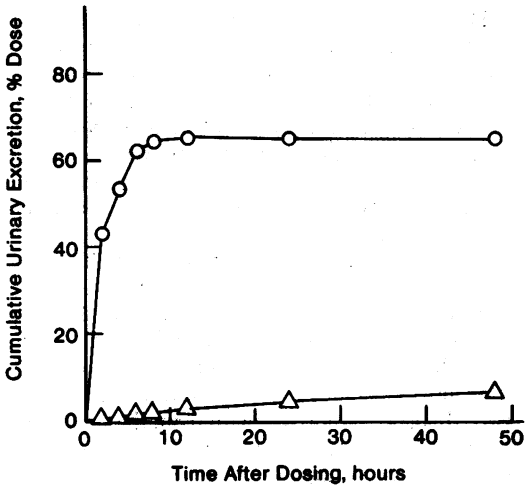

FIG. 2. Mean cumulative excretion of aztreonam (O) and SQ 26,992 (Δ) in urine, as measured by radiochemical assays. ^{14}C-labeled aztreonam (500 mg) was administered in 2-min intravenous infusions.

ably, indicating the absence of bioactive metabolites of the monobactam. The aztreonam concentration in pooled fecal specimens for all subjects between 24 and 96 h after dosing was in the range of 10 to 20 μg/gm of feces. Table 4 summarizes recovery of total radioactivity in urine and feces and the components of total radioactivity, i.e., aztreonam, SQ 26,992, and unknown (extractable and nonextractable) metabolites.

There were no important differences in biotransformation profiles and recoveries of total radioactivity for the two routes of administration. Approximately 90% of the total dose was accounted for. Aztreonam and SQ 26,992 in urine represented a mean of about 66 and 7% of the dose, respectively, and in feces, about 1 and 3% of the dose.

The radioactivity in the TLRC zone for SQ 26,992 was positively identified as SQ 26,992 by chromatographic, spectrometric, and spectroscopic methods. Radioactivity in each of the four TLRC zones, other than those for unchanged aztreonam and SQ 26,992, constituted only 0.1 to 1.1% of the dose and was therefore not characterized further.

Figure 2 indicates that aztreonam elimination in urine was nearly complete by about 6 h; however, SQ 26,992 was excreted for at least 48 h. This finding was analyzed further by using a plot of urinary excretion rate versus time, as shown in Fig. 3. The apparent half-life for aztreonam by this method (1.77 ± 0.05 h) compared favorably with the value obtained from data for serum (1.59 ± 0.03 h), whereas the half-life for SQ 26,992 was 25.8 ± 1.9 h, more than 10 times longer than that of unchanged aztreonam.

Aztreonam, given in a single intravenous infusion over 2 min and as an intramuscular injection, was tolerated well by healthy male subjects and produced no consistent effects on vital signs, electrocardiographic tracings, peripheral blood counts, serum chemistry values, or urinary findings. One subject complained of a mild taste alteration during the 2-min intravenous infusion.

DISCUSSION

In the present study, aztreonam administered as a single 500-mg intravenous or intramuscular dose produced concentrations in serum and urine that would be potentially therapeutic for commonly encountered members of the family *Enterobacteriaceae*. Eradication of *Pseudomonas aeruginosa* strains would probably require a higher dosage. When intramuscularly administered, aztreonam was completely bioavailable to systemic circulation. Aztreonam was not extensively metabolized and was primarily eliminated unchanged in the urine. This study showed that SQ 26,992 was the most prominent biotransformation product of aztreonam in healthy humans and was eliminated in the urine more slowly than was the parent compound. The site of formation of SQ 26,992 is unknown. It is also the most

TABLE 3. Aztreonam concentrations in urine after parenteral administration of 500-mg doses to healthy male volunteers[a]

Time after injection (h)	Mean ± SEM concn (μg/ml) in urine as tested by:			
	Intravenous route		Intramuscular route	
	Bioassay	TLRC	Bioassay	TLRC
0–2	1479 ± 286	1419 ± 286	906 ± 208	912 ± 220
2–4	419 ± 171	419 ± 164	394 ± 129	403 ± 116
4–6	251 ± 63	250 ± 64	542 ± 35	549 ± 33
6–8	79 ± 14	83 ± 13	216 ± 18	228 ± 28
8–12	16 ± 4	18 ± 4	45 ± 7	50 ± 9
12–24	1.6 ± 0.4	2 ± 0	3.8 ± 0.6	6 ± 1
24–48	0.0 ± 0.0	0 ± 0	0.1 ± 0.0	0 ± 0

[a] $n = 4$.

TABLE 4. Cumulative recoveries of radioactivity from urine and feces after administration of 500-mg doses of ^{14}C-labeled aztreonam to healthy male volunteers[a]

Cumulative parameter (over 0–144 h)	Mean ± SEM % total radioactive dose	
	Intravenous	Intramuscular
Components of urinary radioactivity:		
Aztreonam	65.9 ± 1.5	66.3 ± 2.1
SQ 26,992	6.9 ± 0.5	7.6 ± 0.4
Unknown metabolites	3.2 ± 2.2	3.8 ± 0.1
Total	76.1 ± 1.4	77.7 ± 2.3
Components of fecal radioactivity:		
Aztreonam	1.4 ± 0.0	1.0 ± 0.0
SQ 26,992	3.4 ± 0.1	3.2 ± 0.1
Unknown metabolites	7.5 ± 0.1	10.8 ± 0.4
Total	12.3 ± 0.2	15.0 ± 0.6
Total urinary and fecal excretion[b]	88.4 ± 1.4 (86.0–92.0)	92.8 ± 2.3 (86.2–96.3)

[a] $n = 4$.
[b] Numbers in parentheses represent ranges.

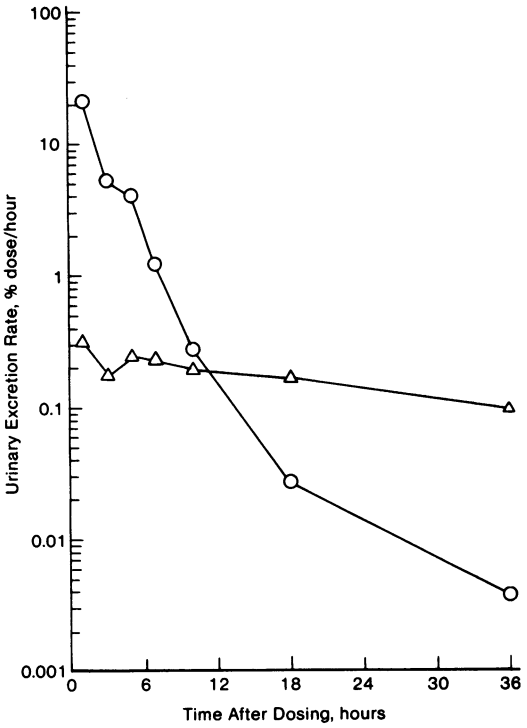

FIG. 3. Mean excretion rates of aztreonam (○) and SQ 26,992 (△) in urine, as measured by radiochemical assays. Aztreonam (500 mg) was administered in 2-min intravenous infusions. For aztreonam, $t_{1/2\beta}$ = 1.77 ± 0.05 h; for SQ 26,992, $t_{1/2\beta}$ = 25.8 ± 1.9 h.

prominent metabolite of aztreonam in rats, dogs, and monkeys (data on file, The Squibb Institute for Medical Research).

Measurable amounts of aztreonam and metabolites in feces suggest that parenterally administered aztreonam is excreted in the bile and consequently may be capable of destroying aerobic gram-negative bacteria commonly present in the colon. In view of the less than 1% oral bioavailability of aztreonam (11), it is unlikely that a significant amount of the monobactam secreted in the bile is reabsorbed during transit through the intestinal tract. Fecal concentrations of aztreonam exceeded the minimal inhibitory concentrations for most *Enterobacteriaceae*. Such organisms serve as a source of infection in the immunocompromised patient and tend to overgrow when colonization resistance is impaired, e.g., when broad-spectrum antibiotics suppress the normal gram-positive and anaerobic gut flora.

The value for serum protein binding of total radioactivity found in this study, 71%, exceeded previously reported values for binding of aztreonam, 56% (10) and 58% (J. C. L. Mihindu, N. D. Bolton, W. M. Scheld, D. A. Spyker, E. A. Swabb, and W. K. Bolton, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami, Fla., abstr. no. 141, p. 90, 1982) in healthy subjects, perhaps owing to binding of both aztreonam and radiolabeled metabolites to serum proteins. However, in vitro antimicrobial activity of aztreonam is not significantly affected by the presence of human serum (6).

The apparent half-life of the elimination of SQ 26,992 was more than 10 times that of aztreonam, based on urinary excretion data. Slow formation or elimination of SQ 26,992 may account for much of the total serum radioactivity measured 4 h or more after dosing. Unfortunately, an accurate method for measuring SQ 26,992 in human serum was not available at the time of this study. There have been suggestions in the literature that penicilloic acids (analogous to SQ 26,992), formed after administration of penicillin, also are eliminated more slowly than the parent compound (2, 3). A previous study (9) of multiple doses of aztreonam administered at 8-h intervals for 7 days to healthy volunteers has suggested accumulation of SQ 26,992, which is consistent with the finding in the present study that the half-life of SQ 26,992 is longer than 20 h.

ACKNOWLEDGMENTS

The thoughtful guidance of D. N. McKinstry, B. H. Migdalof, and T. B. Platt is gratefully appreciated. We thank J. Blue, S. Lubin, and the nursing staff of the Clinical Pharmacology Unit of The Medical Center at Princeton for their outstanding cooperation. J. Shaw, J. Ross, C. Ita, C. Mondi, R. Ratoff, and L. Boor provided technical assistance. ^{14}C-labeled az-

treonam and ^{14}C-labeled SQ 26,992 were synthesized by P. Egli. Isolation and identification of SQ 26,992 as the metabolite of aztreonam was carried out by D. W. Everett.

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