ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1982, p. 969-971
0066-4804/82/120969-03$02.00/0

Vol. 22, No. 6

Pharmacokinetics and Tissue Penetration of Azthreonam

R. WISE,* A. DYAS, A. HEGARTY, AND J. M. ANDREWS

Department of Medical Microbiology, Dudley Road Hospital, Birmingham, England

Received 27 August 1982/Accepted 9 September 1982

Six healthy male volunteers received 1 g of azthreonam each as an intravenous injection. Serial blood and cantharides-induced blister fluid samples were taken over the next 8 h. Urine samples were collected over 24 h. The concentration of azthreonam in serum was about 50 μg/ml at 0.5 h after injection and fell to 2 to 3 μg/ml at 8 h; the serum half-life was 1.93 h, and the volume of distribution was equivalent to 12% of the mean body weight. The plasma clearance was 89.0 ml/min, 73.7% of the dose being recovered in the urine within 24 h. Azthreonam rapidly penetrated blister fluid, reaching a maximum of 25.4 μg/ml at 1.8 h after administration.

Azthreonam (SQ 26,776) is a new synthetic antimicrobial agent belonging to the monobactam group of beta-lactams (5). The activity of this compound is confined to aerobic gram-negative bacteria, against which it possesses considerable potency and stability to β-lactamases (4, 6). Preliminary studies (3) have shown that this agent is well tolerated after parenteral administration, that its serum half-life is somewhat longer than those of other β-lactams (1.66 h), and that it is eliminated predominantly through the kidneys. This report is concerned with the pharmacokinetics of azthreonam in healthy volunteers and with its tissue penetration as measured by a skin blister model.

MATERIALS AND METHODS

The subjects were six male volunteers between the ages of 24 and 40 years. They had normal body builds with a mean weight of 76.8 kg (standard deviation, 3.7 kg) and a mean height of 1.78 m (standard deviation, 0.04 m). At the time of the study, no subject was receiving any medication. Written informed consent was obtained. After a medical history and physical examination, the volunteers were considered healthy; in particular, there was no history of atopy, known previous allergy to β-lactam compounds, diabetes mellitus, or hepatic, renal, or gastrointestinal disease. Hepatic and renal functions were normal as assessed by hepatic enzyme activity, prothrombin time, and serum concentrations of bilirubin, urea, and creatinine. Full hematological profiles were also normal.

On the evening before the study, two 0.2% cantharides plasters (1 by 1 cm) were taped to the front of the forearm of each volunteer. On the morning of the study, each volunteer ate a light breakfast of cereal or toast and one cup of tea or coffee. Blood samples were taken for repeat laboratory tests and for the predose base-line assay, and the volunteers emptied their urinary bladders. An intravenous cannula was inserted into a forearm vein and was kept patent by a small flushing dose of heparinized saline (100 U/ml). A 1-g dose of azthreonam (E. R. Squibb & Sons, Princeton, N.J.; batch MNB 864H/RA29) dissolved in 10 ml of sterile water was injected intravenously into the contralateral arm (the arm with the blisters) over 2 min.

Blood samples were taken from the cannula (after discarding the first 2 ml) at 15, 30, 45, 60, and 90 min and at 2, 3, 4, 5, 6, 7, and 8 h after the dose of azthreonam. Urine samples were collected at 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h after the dose. The volumes were measured, and the samples were taken for assay. The two cantharides-induced blisters were sampled alternately at 30 min and at 1, 2, 3, 4, 5, 6, 7, and 8 h. The fluid removed from the blisters was placed on three preweighed sterile 6-mm assay disks and was reweighed to measure the amount of fluid on each disk.

All assays were performed within 2 h of sample collection. The assays for azthreonam were performed by a routine agar plate diffusion technique with *Escherichia coli* SC12655 (Squibb) as the indicator organism and Penassay no. 1 (Oxoid Ltd., Basingstoke, United Kingdom) as the antibiotic medium. Serum standards were prepared in horse serum, which has been shown to be equivalent in this assay to human serum. Urine standards were prepared in phosphate-buffered saline (pH 7.0) in which the urine samples were diluted when necessary. Blister fluid sample standards made in 70% horse serum, so as to simulate the protein content of the blister fluid (7), were applied in triplicate on identical disks in the same volume as that calculated by weighing on the test disks. The 95% confidence limits of the microbiological serum assay were better than ±18.2%. The urine samples and selected blood samples (those taken at 0.5, 1, 2, 4, and 8 h) were also assayed by high-pressure liquid chromatography (HPLC). In the HPLC assay, a μ Bondapak C_{18} column in a Z-module radial compression system (Waters Associates, Milford, Mass.) was used, the solvents being 12.5% methanol and 1% acetic acid at a flow rate of 2.5 ml/min. Detection was at 254 nM. The retention time of azthreonam was 9 min. The correlation coefficient between HPLC and the bioassay was 0.98, slope 0.9, intercept 0.14. An examination of the HPLC tracings for possible serum and urinary metabolites was made. The pharmacokinetic analysis of the individual data was performed by standard graphic methods (1, 2).

RESULTS

The levels of azthreonam in serum and blister fluid at various times are shown in Table 1. The blister fluid data are derived from five volunteers because of poor blister formation in one subject. The pharmacokinetic data are shown in Table 2.

The serum level of azthreonam showed a rapid initial distribution phase (which was essentially complete by 1 h) followed by a gradual steady decline, suggesting that the data fit a two-compartment open model.

The mean serum level of azthreonam 30 min after the dose was approximately 50 μg/ml; it fell to 2 to 3 μg/ml after 8 h. The terminal serum half-life was 1.93 h. The drug rapidly penetrated the blister fluid, and at 1 h the level in the fluid was about one-half that in serum. The maximum level in blister fluid was attained between 1 and 2 h. After 4 h, the rate of elimination from blister fluid (terminal half-life, 2.14 h) was very similar to the terminal serum half-life. By 8 h, the level in blister fluid had declined to about 5 μg/ml.

Azthreonam initially distributed itself to approximately 12% of the mean body weight. A total of 73.7% of the administered drug was found in the urine by 24 h; the renal clearance of azthreonam was 65.9 ml/min. No metabolites of azthreonam could be detected in the HPLC assay of urine and serum samples.

No side effects were experienced by any volunteer after azthreonam administration. Repeat laboratory tests (biochemical and hematological) taken 24 h after administration of the drug remained normal for all six volunteers.

TABLE 1. Concentrations of azthreonam in serum and blister fluid

Time (h) after intravenous injection	Mean azthreonam concn (μg/ml)	
	Serum	Blister fluid
0.25	72.5 ± 12.6	ND[a]
0.5	53.5 ± 4.9	16.2 ± 8.9
0.75	47.5 ± 6.1	ND
1.0	42.1 ± 6.1	22.7 ± 8.4
1.5	30.1 ± 2.9	ND
2.0	24.1 ± 3.5	21.8 ± 3.8
3.0	16.0 ± 2.6	21.7 ± 4.1
4.0	11.0 ± 1.7	16.1 ± 2.9
5	7.6 ± 0.9	11.8 ± 1.6
6.0	5.3 ± 0.7	10.0 ± 1.9
7.0	3.9 ± 0.9	6.72 ± 1.5
8.0	2.6 ± 0.7	4.9 ± 1.0

[a] ND, Not determined.

TABLE 2. Pharmacokinetics of azthreonam

Parameter (unit)	Value (mean ± SD)
Initial fictive concn (μg/ml)	115.0 ± 43.8
First-order rate constant (h^{-1})	
Initial distribution	3.38 ± 2.97
Overall elimination	0.361 ± 0.028
Serum half-life during elimination phase (h)	1.93 ± 0.14
Area under the curve, time zero to infinity (μg · h/ml)	189.3 ± 16.6
Apparent volume of distribution (liters)	
Central compartment	9.61 ± 3.1
β Method	17.2 ± 3.1
Clearance (ml/min)	
Plasma	89.0 ± 7.1
Renal	65.9 ± 10.5
Recovery in urine, 24 h (%)	73.7 ± 6.41
Blister fluid data	
Terminal half-life (h)	2.14 ± 0.14
Time (h) of maximum concn	1.8 ± 0.83
Maximum concn (μg/ml)	25.4 ± 5.9

DISCUSSION

The pharmacokinetics of azthreonam described in this study are essentially similar to those previously described (3). The only point of significant difference is that the terminal half-life measured here (1.93 h) is somewhat longer than that found previously (1.66 h). It is unlikely that individual variations can explain this difference since both studies had very narrow ranges of half-lives as shown by the small standard deviations. The method of calculating the half-life may account for the difference.

Azthreonam appears to be eliminated predominantly by the kidneys, the rate of renal elimination being approximately half the glomerular filtration rate. The fate of the azthreonam unaccounted for by urinary recovery (25% of the administered dose) is unknown. No microbiologically active metabolites were found in urine, and there was a close correlation between the HPLC and the microbiological assays. Our search for serum and urinary metabolites by HPLC was not exhaustive, so metabolism and consequent renal elimination might occur undetected by our methods. There is some preliminary information that 1 to 5% of the drug is eliminated as a hydrolysis product (E. A. Swabb, personal communication). It is also possible that biliary elimination may account for the portion of the dose not recovered in the urine.

It has been shown previously that the blister fluid model simulates the fluid obtained in a mild inflammatory exudate (7) such as a first-degree

burn. Azthreonam is very active against the majority of *Enterobacteriaceae*, the minimum inhibitory concentration of 90% of such strains being ≤0.5 μg/ml. From extrapolation of the data obtained in this study, the levels in serum and blister fluid will exceed 0.5 μg/ml for about 12 h after a 1-g dose, suggesting that dosing twice daily should be clinically effective. Since azthreonam is less active against *Pseudomonas aeruginosa* (90% minimum inhibitory concentration, 8 μg/ml, with levels in serum and blister fluid falling below 8 μg/ml between 5 and 7 h), either a higher dose or more frequent administration of 1 g is indicated.

Our study shows that azthreonam possesses useful pharmacokinetic properties and deserves further clinical evaluation.

ACKNOWLEDGMENT

We thank W. Weston-Davies of Squibb Laboratories for his advice and support.

LITERATURE CITED

1. **Greenblatt, D. J., and J. Koch-Weser.** 1975. Clinical pharmacokinetics. N. Engl. J. Med. **297**:702–705.
2. **Ritschel, W. A.** 1976. Handbook of basic pharmacokinetics. Drug Intelligence Publications. Hamilton, Ill.
3. **Swabb, E. A., A. A. Sugerman, T. B. Platt, F. G. Pilkiewicz, and M. Frantz.** 1982. Single-dose pharmacokinetics of the monobactam azthreonam (SQ 26,776) in healthy subjects. Antimicrob. Agents Chemother. **21**:944–949.
4. **Sykes, R. B., D. P. Bonner, K. Bush, N. H. Georgopapadakou, and J. S. Wells.** 1981. Monobactams—monocyclic β-lactam antibiotics produced by bacteria. J. Antimicrob. Chemother. **8**(Suppl. E):1–16.
5. **Sykes, R. B., C. M. Cimarusti, D. P. Bonner, K. Bush, D. M. Floyd, N. H. Georgopapadakou, W. H. Koster, W. C. Liu, W. L. Parker, P. A. Principe, M. L. Rathnum, W. A. Slusarchyk, W. H. Trejo, and J. S. Wells.** 1981. Monocyclic β-lactam antibiotic produced by bacteria. Nature (London) **291**:489–491.
6. **Wise, R., J. M. Andrews, and J. Hancox.** 1981. SQ 26, 776, a novel β-lactam: an in vitro comparison with other antimicrobial agents. J. Antimicrob. Chemother. **8**(Suppl. E):39–47.
7. **Wise, R., A. P. Gillett, B. Cadge, S. R. Durham, and S. Baker.** 1980. The influence of protein binding upon tissue fluid level of six β-lactam antibiotics. J. Infect. Dis. **142**:77–82.