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NOTES

Penetration of Aztreonam into Human Bronchial Secretions

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Nine intubated patients were given a single, 2-g intravenous dose of aztreonam over 5 min. Samples of serum and bronchial secretion were obtained 2, 4, and 8 h after administration and assayed for aztreonam content. The mean concentrations in bronchial secretion ranged from 1.9 to 5.2 μg/ml and tended to be highest at 4 h. The concentrations in bronchial secretion varied from patient to patient, but each patient had one or more bronchial secretion samples that contained at least 2.7 μg of drug per ml.

Aztreonam is a monobactam antibiotic with excellent activity against gram-negative bacteria (2). After intravenous administration, concentrations in blister and peritoneal fluids rapidly rise toward those found in serum (N. E. Winslade, I. L. Smith, G. Simons, D. J. Swanson, A. Vigano, P. B. Wels, and J. J. Schentag, Rev. Infect. Dis., in press). Since antibiotic concentrations in bronchial secretion often differ from levels in serum (4), we undertook a study of aztreonam penetration in the bronchial secretions of patients given a single, 2-g intravenous dose.

Nine patients who required endotracheal intubation because of respiratory failure were enrolled in this study. Written informed consent was obtained from all patients before enrollment. All patients had normal serum creatinine and blood urea nitrogen. The average age of the patients was 46 years (range, 20 to 57 years), and the average weight was 71.1 kg (range, 45 to 90.9 kg). All patients produced purulent sputum. Two patients had pneumonia and seven had tracheobronchitis. Aztreonam, supplied by The Squibb Institute for Medical Research, was administered intravenously as a single 2-g dose over 5 min. Samples of bronchial secretion were obtained with a suction catheter inserted into the pulmonary tree via the endotracheal tube. Samples were then frozen at −78°C until assayed. Specimens containing gross blood were excluded.

Serum bioassay was performed by a cylinder-plate agar diffusion method. Thawed samples were diluted 1:20 in 0.1 M phosphate buffer (pH 6). The diluted serum was then rediluted with 5% serum in phosphate buffer. Standard solution were also prepared in 5% serum in phosphate buffer. Diluted samples were bioassayed with petri dishes prepared with 7 ml of Difco Penassay seed agar inoculated with *E. coli* SC12155. Cylinders were placed on each plate and filled with unknown or known standard solutions. Each plate contained three identical standards and three samples of unknown content. Petri dishes were incubated at 37°C for 16 to 20 h, and zone sizes were measured. The lower limit of detection was 0.4 μg/ml, and the coefficient of variation was 3.4%.

A similar procedure was used for bioassay of bronchial secretions. A measured volume of each sample was diluted with an equal volume of methanol and centrifuged. The supernatant was diluted 1:1.25 with 0.1 M phosphate buffer (pH 6) and then further diluted with 40% methanol to achieve an expected concentration of 0.02 to 0.1 μg of aztreonam per ml. Standard solutions of known aztreonam concentrations were also prepared in 40% methanol. Samples were then bioassayed as described above for serum. The lower limit of detection was approximately 0.05 μg/ml, and the coefficient of variation was 11.7%.

Samples of bronchial secretion or expectorated sputum, containing known amounts of aztreonam, were prepared on the day specimens were obtained from patients. The known samples were assayed in parallel with the samples from patients. The results of the known-sample assays were used to correct the results of the patient sample assays for aztreonam recovery. Recovery from known samples averaged 88.1%. Antibiotics other than aztreonam were administered concomitantly to some patients. These antibiotics showed no in vitro cross-reactivity in the aztreonam assay. Body surface area was calculated by published methods (1).

Aztreonam was well tolerated. Physical examinations and laboratory studies performed before and after aztreonam administration revealed no adverse reactions. The results of all serum and bronchial secretion bioassays are shown in Table 1. The highest mean concentration in serum, 80.1 μg/ml, was achieved at 30 min, the earliest post-dosing time examined. The variability of the concentrations in serum may be due to subclinical variations in renal function and variations in binding of aztreonam to serum proteins.

The mean concentration in bronchial secretion reached a maximum of 5.2 μg/ml at 4 h after dosing. Individual concentrations ranged from 0.04 to 14.1 μg/ml at 2 h, 2.1 to 10.7 μg/ml at 4 h, and 0.5 to 4.5 μg/ml at 8 h after aztreonam administration. Penetration of bronchial secretions, calculated from the ratio of the area under the curve for concentration in bronchial secretion to the area under the curve for concentration in serum versus time, ranged from 6 to 55% and averaged 17%. This type of variability of antibiotic concentrations in bronchial secretion has been reported previously for other antibiotics (4). Every patient had one or more bronchial secretion samples that contained at least 2.7 μg of aztreonam per ml.

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TABLE 1. Serum and bronchial secretion assays

Patient no.	Dose (mg/m²)[a]	Aztreonam concn (μg/ml) in following body fluid at indicated time:									
		Serum				Bronchial secretion			Ratio of concn in bronchial secretion to concn in serum		
		0.5 h	2 h	4 h	8 h	2 h	4 h	8 h	2 h	4 h	8 h
001	1,097	59.9	13.7	6.4	1.3	14.1	10.7	2.5	1.03	1.67	1.92
002	953	96.8	37.0	28.8	15.7	3.7	2.9	>2.0[b]	0.10	0.10	
003	902	85.0	40.0	17.4	4.1	7.4	10.5	2.8	0.19	0.60	0.68
004	1,063	75.8	34.3	13.3	2.6	2.6	2.7	0.8	0.08	0.20	0.31
005	1,228	63.0	69.0	52.7	22.6	3.6	4.9	4.5	0.05	0.09	0.20
006	962	40.0	12.0	5.2	1.2	4.9	2.1	0.6	0.41	0.40	0.50
007	1,274	120.0	46.8	23.6	3.6	0.04	6.9	0.5	0.00	0.29	0.14
008	974	77.4	36.3	15.1	3.1	1.0	2.7	1.5	0.03	0.18	0.48
009	1,375	103.0	61.7	36.8	12.8	0.7	3.4	2.6[c]	0.01	0.09	
Mean ± SD	1,092 ± 165	80.1 ± 24.4	39.0 ± 19.0	22.1 ± 15.3	7.4 ± 7.7	4.2 ± 4.4	5.2 ± 3.4	1.9 ± 1.4	0.21 ± 0.33	0.40 ± 0.50	0.60 ± 0.61

[a] All patients received a single, 2g intravenous dose.
[b] Although the concentration was greater than 2 μg/ml, the exact potency could not be quantitated because of limited sample volume.
[c] Eight-hour bronchial secretion data excluded from mean. Specimen contained gross blood.

In this study, the mean concentrations of aztreonam in bronchial secretion ranged from 1.9 to 5.2 μg/ml at 2 to 8 h after a single, 2-g intravenous dose. This may be compared with the MIC of aztreonam for 90% of common *Enterobacteriaceae* strains, which is usually 1.0 μg/ml or less (2). The aztreonam concentrations found in this study are consistent with initial reports of the high microbiological cure rate of aztreonam in patients with lower respiratory tract infections caused by these organisms (J. Rodriguez and C. H. Ramirez-Ronda, Abstr. Int. Congr. Chemother. 13th, Vienna, Austria, abstr. no. SY61-7, 1983).

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