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Aztreonam Concentrations in Human Tissues Obtained During Thoracic and Gynecologic Surgery

T. R. BEAM, JR.,[1] R. P. GALASK,[2] L. T. FRIEDHOFF,[3]* T. B. PLATT,[3] AND M. A. LEITZ[3]

Buffalo Veterans Administration Medical Center, Buffalo, New York 14215[1]; University of Iowa Hospital and Clinic, Iowa City, Iowa 52242[2]; and The Squibb Institute for Medical Research, Princeton, New Jersey 08540[3]

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The concentrations of aztreonam in human tissues obtained during surgery were measured after a single 2-g intravenous dose. The average concentration in the skeletal muscle, atrial appendage, lung, sternum, pericardial fluid, endometrium, myometrium, fallopian tube, and ovary varied from 3 to 33 μg/g (or μg/ml). These concentrations significantly exceed the MIC for 90% of strains for most members of the family *Enterobacteriaceae*.

Single parenteral doses of aztreonam produce significant concentrations in serum (14), cerebrospinal fluid (3, 5), bile (9), blister fluid (17), peritoneal fluid (16), peritoneal dialysate (4), the prostate (8), and bronchial secretions (1). The study reported here was undertaken to determine the extent of aztreonam penetration into tissues and fluids obtained during thoracic and gynecologic surgery which had not been evaluated previously.

Patients. Fifty-one patients scheduled for elective thoracic surgery at the Buffalo Veterans Administration Medical Center and 18 patients scheduled for elective gynecologic surgery at the University of Iowa Hospital and Clinic were enrolled in this study. All patients had normal renal and hepatic function. The average ages were 60 years (range, 46 to 75 years) and 46 years (range, 27 to 73 years) for the candidates for thoracic and gynecologic surgery, respectively. The average weights were 76.8 kg (range, 56 to 105 kg) and 75.6 kg (range, 47.5 to 132.4 kg), respectively.

Drug administration. Aztreonam was supplied by The Squibb Institute for Medical Research and was administered as a single 2-g intravenous dose given over 5 min in the immediate preoperative period.

Surgical procedures. Fluid and tissue samples were obtained by standard surgical procedures. For gynecologic samples, the sampling time was the moment when the blood supply to the tissue was completely interrupted, and for thoracic samples the sampling time was the time of actual surgical excision. Serum for aztreonam assay was obtained at the time that fluid or tissue was sampled. Except for single specimens of squamous cell and epidermoid cell lung carcinomas, all samples assayed were normal tissue. No samples had evidence of active infection. The samples were stored at −20°C or below until assayed.

Aztreonam assays. Skeletal muscle, atrial appendage, sternum, and lung tissue samples were minced into very small pieces and weighed. The sternum samples were pulverized with a Spex 6700 Freezer/Mill (Spex Industries, Metuchen, N.J.). The tissues were then diluted with 1 ml of 0.1 M phosphate buffer (pH 6.0) per g of sample. After dilution, the samples were homogenized for 1 min by using a Tekmar homogenizer (Tekmar, Cincinnati, Ohio). The homogenates were diluted with 3 ml of 50% methanol (in pH 6.0 phosphate buffer) per g of homogenate. The diluted homogenates were then centrifuged, and the supernatant was decanted and saved.

The pellet was extracted twice with 5 ml of 30% methanol (in pH 6 phosphate buffer) per g of pellet. Filtered (Millex, 0.45-μm pore size; Millipore Corp., Bedford, Mass.) extracts were assayed by high-pressure liquid chromatography equipment that was previously described (11). Serum obtained simultaneously with thoracic tissues and fluids was assayed by a previously described high-pressure liquid chromatography method (11), and a similar method was used to assay pericardial and pleural fluid.

Commercially obtained samples of tissue or body fluid (Agrilab Inc., Bridgewater, N.J.) were mixed with known amounts of aztreonam at the time the specimens were obtained from study patients. These spiked samples were assayed for aztreonam, and the results were used to correct clinical specimen assay results for losses during storage.

The limit of detection, assay coefficient of variability, and recovery from spiked samples for each type of high-pressure liquid chromatography assay ranged from 0.5 to 1.3 μg/g (or μg/ml), 5.3 to 14.7%, and 80.4 to 101%, respectively.

Gynecologic tissue and simultaneous serum were assayed by microbiologic methods. The method for serum was previously described (14).

Frozen tissue samples were thawed and cut into small pieces, and 0.2-g samples were weighed into a labeled test tube. These samples were refrozen at −78°C until assayed. On the day of assay, the samples were extracted by a procedure similar to that used for the high-pressure liquid chromatography assay of thoracic tissues. The extracts were added to cylinders on seeded agar plates (Penassay Seed Agar-B263; Difco Laboratories, Detroit, Mich.) and incubated at 37°C for 16 to 20 h.

Standards were prepared in 30% methanol. The quantitation limits for the assays were 0.04 μg/ml and 0.2 μg/g for serum and tissue, respectively. Standard preparations of aztreonam in both serum and gynecologic tissue were prepared at the time the clinical samples were obtained from patients and used to correct the assay results for activity lost during storage. Mean recovery from standards was 79% and about 100% for gynecologic tissue and serum standards, respectively.

* Corresponding author.

TABLE 1. Results of thoracic tissue and fluid aztreonam assays

Type of tissue or fluid	Tissue or fluid sampling time (h)	No. of samples	Tissue or fluid aztreonam concn (μg/g or μg/ml)[a]	Serum aztreonam concn (μg/ml)[a]	Tissue or fluid concn/serum concn ratio[a]
Skeletal muscle	0.25–0.68	6	16 ± 2	108 ± 18	0.20 ± 0.07
	0.75–1.03	12	14 ± 2	82 ± 7	0.17 ± 0.02
	1.05–1.60	17	10 ± 2	74 ± 3	0.14 ± 0.03
	1.66–2.66	7	9 ± 2	55 ± 5	0.15 ± 0.03
	2.91–3.83	5	5 ± 1	36 ± 8	0.17 ± 0.05
Atrial appendage	0.91–1.58	12	22 ± 2	76 ± 5	0.29 ± 0.02
	1.60–2.08	6	19 ± 2	55 ± 5	0.36 ± 0.05
	2.11–4.03	5	13 ± 3	40 ± 6	0.32 ± 0.05
Lung	1.20–2.08	6	22 ± 7	61 ± 3	0.35 ± 0.11
	2.13–4.58	7	19 ± 3	41 ± 5	0.46 ± 0.08
Sternum	0.46–0.78	6	3 ± 3	105 ± 5	0.03 ± 0.03
	0.80–1.05	6	6 ± 3	79 ± 13	0.07 ± 0.02
	1.06–1.70	6	5 ± 2	78 ± 8	0.08 ± 0.04
	1.85–3.83	4	3 ± 2	43 ± 10	0.07 ± 0.02
Pericardial fluid	0.35–0.95	6	23 ± 3	76 ± 7	0.32 ± 0.05
	1.00–1.13	6	33 ± 6	87 ± 5	0.38 ± 0.08
	1.21–1.85	12	24 ± 5	70 ± 6	0.38 ± 0.08
	2.00–3.83	5	27 ± 7	41 ± 7	0.64 ± 0.18
Pleural fluid	1.08–2.96	3	51 ± 31	64 ± 12	0.69 ± 0.32

[a] Values are means ± standard error of the mean.

The hemoglobin content of tissue and fluid specimens was used to correct the assay results for aztreonam in contaminating blood (8). Samples that contained more than 50% blood were excluded.

The aztreonam concentrations in tissues and fluids obtained during thoracic and gynecologic surgery are shown in Tables 1 and 2. Mean concentrations in the skeletal muscle, atrial appendage, lung, pericardial fluid, endometrium, myometrium, ovary, and fallopian tube ranged between 4 and 33 μg/g (or μg/ml), depending on the type of specimen and the time after administration of the drug. Mean sternum concentrations ranged between 3 and 6 μg/g. Only three samples of pleural fluid were obtained, with a mean drug concentration of 51 μg/ml. The ratios of the tissue or fluid concentration to the serum concentration were relatively constant over time, suggesting rapid equilibration of serum and tissue or fluid aztreonam concentrations.

The mean levels of aztreonam in tissues and fluids obtained during thoracic surgery were generally similar to or exceeded mean drug concentrations produced in these tissues after similar doses of cefotaxime, ceftazidime, or cefonacid (7, 13, 10). Mean aztreonam levels in gynecologic tissues exceeded mean drug levels produced after a 7-g dose of cefmenoxime or a 1-g dose of moxalactam (2, 12).

The mean tissue and fluid aztreonam concentrations observed in this study were 3 to 33 times the MIC for 90% of strains for most members of the family *Enterobactericeae* (15). These results provide support for the reported therapeutic efficacy of aztreonam in skin, soft tissue, pulmonary, and gynecologic infections (6) and support future studies to evaluate the use of aztreonam for prophylaxis.

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TABLE 2. Results of gynecologic tissue aztreonam assays

Type of tissue or fluid	Tissue or fluid sampling time (h)	No. of samples	Tissue aztreonam concn (μg/g)[a]	Serum aztreonam concn (μg/ml)[a]	Tissue concn/serum concn ratio[a]
Endometrium	0.73–1.92	4	9 ± 3	63 ± 11	0.13 ± 0.05
	2.50–4.05	7	4 ± 1	32 ± 6	0.16 ± 0.05
Myometrium	0.73–1.92	9	11 ± 3	63 ± 8	0.17 ± 0.05
	2.50–4.05	9	6 ± 1	32 ± 5	0.20 ± 0.04
Ovary	0.73–1.92	7	13 ± 4	59 ± 9	0.23 ± 0.05
	2.50–4.05	5	7 ± 3	35 ± 9	0.22 ± 0.09
Fallopian tube	0.73–1.92	8	12 ± 3	62 ± 9	0.20 ± 0.06
	2.50–4.05	7	7 ± 2	32 ± 6	0.22 ± 0.08

[a] Values are means ± standard error of the mean.

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