Aztreonam Penetration into Synovial Fluid and Bone

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Eighteen patients with uncomplicated degenerative joint disease requiring joint replacement (hip or knee) were given a single 2-g intravenous dose of aztreonam over a 5-min period preoperatively. The mean concentration in synovial fluid of 83.0 ± 9.2 µg/ml averaged 0.99 times the concomitant levels in serum. The mean concentration in cancellous bone of 16.0 ± 4.3 µg/g averaged 0.20 times the concomitant levels in serum.

The increasing incidence of gram-negative bone and joint infections (14, 19), particularly in patients with underlying diseases (13), combined with a higher incidence of poor therapeutic outcome in patients with such infections treated with available antimicrobial agents (10, 29), has stimulated a search for improved therapeutic modalities. Aztreonam, a monobactam agent with excellent gram-negative antibacterial activity, is being evaluated as a treatment for gram-negative bacillary osteomyelitis and arthritis. This paper presents data from a clinical study designed to determine penetration of aztreonam into bone and synovial fluid.

Patients admitted to the orthopedic service of Rush-Presbyterian-St. Luke’s Medical Center, Chicago, Ill., requiring elective hip or knee joint replacement were eligible to participate in the study. Patients with suspected or proven joint inflammation, infection, hemorrhage, or aseptic necrosis were excluded, as were patients with significant underlying disease such as renal or cardiovascular impairment, liver dysfunction, or penicillin allergy. Eighteen patients with degenerative joint disease, aged 39 to 78 years (mean, 61 years) and weighing 53.6 to 93.0 kg (mean weight, 71.8 kg), were entered into the study after giving written informed consent. Seventeen underwent total hip replacement, and one underwent knee replacement. Within 7 days of aztreonam administration, eligible patients were screened by clinical history and physical examination, testing of vital signs, a battery of laboratory tests, and an electrocardiogram to verify lack of underlying disease. The physical examination, testing of vital signs, and laboratory studies were repeated at the end of the study.

Aztreonam, supplied by The Squibb Institute for Medical Research, Princeton, N.J., was administered intravenously as a 2-g dose over 5 min into a peripheral vein. Blood samples for aztreonam assay were obtained immediately before and 35 min after the start of aztreonam infusion and at the time of joint fluid and bone sampling.

Synovial fluid was aspirated by needle from the affected joint prior to incision to minimize blood contamination. At least 1 g of cancellous bone was taken from the head or epicondyle of the femur at the time of its removal. Single samples of bone, synovial fluid, or both were obtained from each patient and stored at −70°C prior to assay. During knee surgery, sampling was done prior to application of the tourniquet used to improve control of hemostasis.

All assays of aztreonam were conducted at The Squibb Institute for Medical Research. Samples obtained from patients 1 and 2 were assayed for aztreonam by a microbiological technique. Samples obtained from patients 3 through 18 were assayed for aztreonam by high-pressure liquid chromatography with an external standard.

Serum was assayed by previously reported methods (20). Standard preparations of bone and synovial fluid containing known amounts of aztreonam were prepared and assayed daily. Microbiological assay of bone was performed by a procedure similar to that used for prostate tissue in a previously reported study (17), except that the samples were pulverized with a Spex freezer-mill prior to assay. The limit of detection of the assay was 0.1 µg/g of bone. The coefficient of variation and mean recovery from standards were 8.0 and 79.0%, respectively.

Bone samples were prepared for high-pressure liquid chromatography by a procedure identical to that used for the bioassay and then filtered (Millex; 0.45 µm [pore size]; Millipore Corp., Bedford, Mass.). They were then analyzed with a high-pressure liquid chromatography system consisting of an Altex model 110A pump set for 2 ml/min, a 37- to 50-µm silica gel precolumn, a 30- to 38-µm C18 guard column, a Waters Associates, Inc., 10-µm µBondpak analytical column (150 by 3.9 mm), and a UV detector set for 290 nm. The mobile phase was 85 parts 5 mM tetrabutylammonium sulfate, adjusted to pH 2.85 with 1 M KH2PO4, and 15 parts acetonitrile. Samples were introduced via a 20-µl precision loop injector. The limit of detection was 1 µg/g, the coefficient of variation was 8.1%, and the mean recovery from standards was 87.0%.

The method used for microbiological assay of synovial fluid was identical to that previously reported for urine (20), except that samples were diluted 1:20 in 0.1 M phosphate buffer (pH 6) prior to assay. The limit of detection was 0.4 µg/ml. The coefficient of variation and mean recovery were 3.5 and 98%, respectively. The high-pressure liquid chromatographic assay of synovial fluid was done by a method identical to that previously reported for serum (20). The limit of detection was 0.5 µg/ml. The coefficient of variation and recovery from standards were 8.5 and 98%, respectively.

Assays of hemoglobin in blood, bone, and synovial fluid and correction of aztreonam concentrations for blood contamination were performed by previously described methods (17). Samples whose blood contents were 51% or more were excluded from analysis. No specimens suitable for assay could be obtained from patient 6.

Results of the aztreonam assays are listed in Table 1. The mean concentration in serum at the time of bone and synovial fluid removal was 78 µg/ml. The mean concentration in bone was 16 µg/g. Concentrations of aztreonam in individual bone specimens were variable but showed a
Table 1. Aztreonam concentration data

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Aztreonam concn in serum (μg/ml)</th>
<th>Simultaneous with SF and bone samples</th>
<th>Time of SS * sample (h)</th>
<th>Aztreonam concn in SF * (μg/ml)</th>
<th>SF/SS concn ratio</th>
<th>Time of SF sample (h)</th>
<th>Aztreonam concn in bone (μg/ml)</th>
<th>Bone/SS concn ratio</th>
<th>Time of bone sample (h)</th>
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<td>111.0</td>
<td>1.65</td>
<td>88.9</td>
<td>0.80</td>
<td>1.60</td>
<td>30.3</td>
<td>0.27</td>
<td>1.80</td>
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<td>2</td>
<td>167.9</td>
<td>95.1</td>
<td>1.25</td>
<td>162.2</td>
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<td>1.20</td>
<td>40.9</td>
<td>0.43</td>
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<td>92.1</td>
<td>69.1</td>
<td>1.11</td>
<td>84.6</td>
<td>1.22</td>
<td>0.80</td>
<td>49.0</td>
<td>0.71</td>
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<tr>
<td>4</td>
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<td>116.0</td>
<td>1.25</td>
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<td>NS</td>
<td>NS</td>
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<td>0.37</td>
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<td>5</td>
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<td>129.0</td>
<td>1.00</td>
<td>&gt;88.8</td>
<td>0.88</td>
<td>0.91</td>
<td>NS</td>
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<tr>
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<td>1.06</td>
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<td>4.4</td>
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<tr>
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<td>87.3</td>
<td>1.16</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.00</td>
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<td>1.03</td>
<td>98.0</td>
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<td>0.93</td>
<td>9.5</td>
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<td>1.05</td>
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<td>63.0</td>
<td>2.11</td>
<td>51.8</td>
<td>0.82</td>
<td>1.91</td>
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<td>59.3</td>
<td>1.50</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>5.2</td>
<td>0.09</td>
<td>1.43</td>
</tr>
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Mean ± SEM 122.0 ± 8.4 77.8 ± 5.1 1.41 ± 0.08 83.0 ± 9.2 0.99 ± 0.08 1.24 ± 0.11 16.0 ± 4.3 0.20 ± 0.05 1.48 ± 0.09

\* SS, Simultaneous serum.
\* SF, Synovial fluid.
\* NS, No sample assayable.
\d Specimen obtained at 1.01 h for assay.

tendency to decrease with time. Patients 15 and 17 had values of 0 μg/g. These low values may have been due to inaccurate correction for aztreonam in tissue blood. The uncorrected aztreonam concentrations for these two patients were 6.8 and 5.2 μg/g, respectively. The ratios of bone to serum concentrations averaged 0.20 and were also quite variable. The mean concentration of aztreonam in synovial fluid was 83 μg/ml, and the average ratio of the concentration in synovial fluid to that in serum was 0.99. Although drug concentrations in synovial fluid were variable, they exceeded 0.8 times the simultaneous concentrations in serum for all specimens. Mean ratios of drug concentrations in bone and synovial fluid to that in serum at 0.5 h were 0.66 and 0.13, respectively.

No definite adverse reactions to aztreonam were noted during this study. Patients 7 and 12 had postdose serum glutamic pyruvic transaminase elevations of 2.4 and 6.4 times normal, respectively. Patient 12 also had elevated postdose serum glutamic oxalacetic transaminase (6.2 times normal) and lactate dehydrogenase (1.3 times normal) levels. Patients 8 and 9 had minor (less than twice normal) postdose elevations of serum glutamic oxalacetic transaminase and glutamic pyruvic transaminase, and patient 9 had a minor elevation of lactate dehydrogenase (1.2 times normal). These abnormalities were not associated with symptoms, required no treatment, and were considered to be possibly related to aztreonam.

Antibiotic efficacy in joint and bone infections requires an adequate spectrum of activity against the causative organism(s) in the environment of the infection (often anaerobic and acidic) and penetration in adequate concentrations to the site of infection. The spectrum of activity of aztreonam against aerobic gram-negative bacilli is well documented. Aztreonam maintains good activity in an anaerobic environment, in contrast to the aminoglycosides (4).

Penetration of a wide variety of antimicrobial agents into joints has been reported. In general, single-dose (versus multiple-dose) studies (8, 21) and studies that corrected for blood contamination (1, 21, 24) detected lower penetration values. In dogs, cefazolin, penicillin, and cefamandole in serum rapidly equilibrate with the interstitial fluid of bone (5, 11, 16). Specimens assayed after crushing gave lower assay results than specimens assayed by elution (15). Some authors have reported that inflammation has little effect on the penetration of antibiotics into joint or bone (27).

The ratio of the aztreonam concentration in synovial fluid to that in serum compares favorably with that of streptomycin (50 to 75%) (30), trimethoprim-sulfamethoxazole (100%) (31), cefadroxil (43%) (23), cephalothin (20 to 53%) (9, 26), cefamandole (28.1%) (26), gentamicin (88%) (6), and tobramycin (95%) (6). Aztreonam concentrations in cancellous bone (mean, 20% of that in concomitant serum) are similar to those of moxalactam (18%) (21), cefazolin (18%) (21), cefadroxil (23%) (23), cephalothin (5 to 33%) (7, 9, 26), cefamandole (5 to 20%) (18, 24, 26), cefuroxime (10 to 70%) (7), clindamycin (10 to 50%) (1, 28), ceftazidime (54%) (1), and amoxicillin (16.4%) (2). However, the ranges for all these antibiotics were very wide (25, 28), with some specimens showing no detectable concentrations. This may have been due to the variability of the specimens taken from patients with significant bone disease. There are few data available on the bone penetration of aminoglycosides, but clinical studies have shown a high failure rate when they are used as the sole treatment of gram-negative osteomyelitis (29).

Because of the high treatment failure and morbidity rates seen in gram-negative bactillary arthritis and osteomyelitis (3, 10, 29), newer, more active agents are required. Aztreonam has excellent activity against gram-negative microorganisms, beta-lactamase stability, activity in anaerobic and acidic milieu, and good penetration into both synovial fluid and bone. These qualities are consistent with early reports of its efficacy in the treatment of gram-negative bone and joint infections (12, 22).
LITERATURE CITED


