Ceftriaxone Levels in Blood and Tissue During Cardiopulmonary Bypass Surgery

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One gram of ceftriaxone was given intravenously to 15 patients approximately 2 h before cardiopulmonary bypass surgery. Ceftriaxone levels in plasma (mean ± standard deviation) were 60.4 ± 18.8 µg/ml (range, 17.0 to 96.0 µg/ml) at the beginning of bypass, 44.2 ± 16.6 µg/ml (range, 9.4 to 78.6 µg/ml) at the end of bypass, and 19.6 ± 9.6 µg/ml (range, 4.2 to 47.1 µg/ml) the following morning, 18.1 to 24.7 h after infusion of ceftriaxone. Concentrations in the sternal bone were 4.7 ± 2.1 µg/g (range, 1.0 to 10.1 µg/g; tissue-to-plasma ratios, 0.066 ± 0.036). Concentrations in the atrial appendage were 7.7 ± 1.8 µg/g (range, 3.6 to 10.2 µg/g; tissue-to-plasma ratios, 0.143 ± 0.062). These data suggest that a single dose of ceftriaxone might be useful for prevention of infection due to susceptible pathogens.

Cephalosporins are widely used for prevention of infection in patients undergoing cardiac surgery. However, microorganisms resistant to older cephalosporins such as cephalothin, cefazolin, and cefamandole sometimes cause postoperative infections in these patients (1, 8, 10). Bor et al. (1) reported that 13 gram-negative isolates from cases of mediastinitis after cardiac surgery were resistant to antimicrobial agents used perioperatively. Thus, newer cephalosporins may find a place in such preventive therapy.

Ceftriaxone is a new cephalosporin with a broad spectrum of activity against both gram-positive and gram-negative microorganisms. Various investigators have determined that 90% of strains of most members of the family Enterobacteriaceae are inhibited by ceftriaxone concentrations of 1 µg/ml (5-7) and that 90% of Staphylococcus aureus strains are inhibited by concentrations of 3.1 to 4 µg/ml (5, 7). The elimination half-life of ceftriaxone in normal volunteers, ranging from 6 to 8.6 h (6, 9), exceeds that of all cephalosporins studied to date. We determined levels of ceftriaxone in plasma and tissue after a single intravenous dose to patients undergoing cardiopulmonary bypass surgery.

MATERIALS AND METHODS

A total of 15 patients (14 men, 1 woman) scheduled for elective saphenous vein bypass grafting for coronary artery disease were given 1 g of ceftriaxone before the procedure. The patients were 49 to 68 years of age (mean ± standard deviation, 55.6 ± 8.4), weighed 53.8 to 121.8 kg (83.8 ± 13.7), and had normal renal function and no recent history of infection or antimicrobial therapy. The protocol was approved by the institutional review boards. Patients received ceftriaxone by intravenous infusion over 20 to 30 min approximately 1 h before the anticipated skin incision and 2 h before the anticipated bypass procedure. This single dose was the only perioperative antimicrobial therapy administered to these patients.

Blood samples were collected in heparinized tubes. The first sample was obtained 20 to 50 min after completion of the infusion. At the time of median sternotomy, a portion of the xiphoid process was removed for determination of antibiotic concentration, and a second blood sample was obtained. We previously determined that removal of a portion of the xiphoid process provides a generous sample for this purpose, at little or no risk to the patient (3). Similarly, a third blood sample was obtained simultaneously with removal of a portion of the right atrial appendage for placement of the patient on cardiopulmonary bypass. A fourth blood sample was obtained at the end of cardiopulmonary bypass, and a fifth blood sample was obtained the following morning.

Blood samples were centrifuged and the plasma stored at −70°C before assay. After thawing, a 100-µl portion of plasma was combined with 200 µl of the internal standard solution (60 mg/liter). Protein was removed from this solution by adding 1.0 ml of high-pressure liquid chromatography (HPLC) grade 1-butanol (Fisher Scientific Co., Atlanta, Ga.), blending on a Vortex mixer for 30 s, and centrifuging for 10 min at 2,000 × g. The top (organic) layer and protein were removed by aspiration, and the aqueous layer was then directly taken for determination of ceftriaxone concentration by HPLC.

Bone and atrial appendage samples were frozen at −70°C immediately after collection. Before analysis, atrial appendage samples were allowed to thaw and were then rinsed thoroughly to minimize contamination due to blood. These samples were then frozen at −70°C, cut into small pieces, and weighed to the nearest 0.1 mg. The samples were then homogenized with 1 ml of cold deionized water, and the resulting mixture was subjected to the extraction procedure described below.

Bone samples free of blood were cut into pieces approximately 2 to 3 mm in diameter and were then rinsed thoroughly with sterile saline to minimize contamination due to blood. Approximately 3 g of bone was mixed with 0.125 M tris(hydroxymethyl)aminomethane (Tris) phosphate buffer (pH 7.2) to provide a 20% (wt/vol) suspension of bone in buffer. The samples were shaken in a cold room at 4°C for 6 h to extract the ceftriaxone. Extracts were then centrifuged at 1,000 × g at 4°C for 6 min, after which 200 µl of the supernatant was used in the extraction procedure described below.

Bone and atrial appendage samples were submitted to an additional extraction procedure, modified after that described by Brisson and Fourtillan (2), before determination of ceftriaxone concentrations by HPLC. The tissue samples

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were placed in 15-ml centrifuge tubes containing 300 μl of 2 M HCl, 4 ml of a 3:1 chloroform–1-butanol mixture, and an internal standard solution (100 μl of a 25-mg/liter solution for bone samples and 250 μl of a 1-mg/liter solution for atrial appendage samples). This mixture was blended in a Vortex mixer and then centrifuged for 3 min at 2,000 × g. The top (aqueous) layer was removed by aspiration, and the bottom (organic) layer was transferred to another centrifuge tube and placed in a water bath at 65°C to permit evaporation. The dry samples were then reconstituted with 200 to 300 μl of the HPLC mobile phase described below and were blended with 900 μl of HPLC-grade hexane (Fisher) in a Vortex mixer.

Cephalothin, chosen because of its similar extraction recovery and chromatographic characteristics, was used as the internal standard. Internal calibration was based on the peak height ratios of ceftriaxone to the internal standard. Separate external calibration was based on replicate standard solutions at four to five different concentration levels in deionized water. These standards were submitted to the same extraction procedures used for the samples, including the addition of the internal standard. The concentrations of ceftriaxone in the samples were determined by a straight line model based on the ratios of the chromatogram peaks to the known concentrations. The coefficient of correlation for these calibration lines was usually 0.99, and in every instance the possible lack of fit of the straight line was not significant at the 95% level of confidence (4).

Every effort was made to ensure that bone and atrial appendage samples were free from contamination due to blood. No corrections were made for possible contamination. Since the recovery of ceftriaxone and the recovery of the cephalothin internal standard from plasma, bone, and atrial appendage samples were nearly identical, and since both an internal standard and external calibration were used, the results were considered to be unaffected by possible losses in the recovery of ceftriaxone from the samples.

Determinations were made with a Waters HPLC system (Waters Associates, Milford, Mass.) equipped with a model 441 UV absorbance detector, a model 6000 pump, a model 710 autosampler, a model 720 integrator, and a model 730 system controller. A Supelcosil C-8 reversed-phase column (4.6 by 250 mm, with 5-μm packing material) fitted with a C-8 guard column (4.6 by 50 mm, with 40 μm packing material; Supelco Inc., Bellefonte, Pa.) was used. Injection volumes were 25 μl for plasma extracts and 100 μl for bone and atrial appendage extracts. The column was operated at a flow rate of 2.0 ml/min and at a pressure of 2,000 lb/in². The temperature was maintained at 40°C, and the eluant was monitored at 254 nm. Chromatographic analysis times were under 10 min.

The mobile phase for all analyses included an ion-pairing reagent, tetrabutylammonium bromide, which was found to enhance chromatographic retention and resolution of the cephalosporins. The mobile phase was prepared by adding 4 g of tetrabutylammonium bromide to 720 ml of deionized water, adjusting the pH to 7.5 by the addition of 42.5% phosphoric acid or concentrated NaOH, and then adding 280 ml of HPLC grade acetonitrile (Fisher). Freshly prepared mobile phase was sonicated before use.

**RESULTS**

Plasma concentrations determined after the 1-g ceftriaxone infusion are shown in Fig. 1. Ceftriaxone levels in the first plasma samples, obtained 0.33 to 0.83 h after the infusion (0.66 to 0.18 h) were 71.9 to 159.2 μg/ml (mean ± standard deviation, 114.8 ± 35.4 μg/ml). Ceftriaxone levels in the second and third plasma samples and simultaneous tissue levels are shown in Table 1. At the end of cardiopulmonary bypass, 2.4 to 5.7 h after the infusion (3.98 ± 0.89 h),

![FIG. 1. Ceftriaxone concentrations in plasma after a 1-g intravenous dose in samples taken 20 to 50 min after completion of the infusion (O), at the time of median sternotomy (A), at the beginning of cardiopulmonary bypass (X), at the end of cardiopulmonary bypass (△), and on the morning after surgery (●).](http://aac.asm.org/)

**TABLE 1. Simultaneous tissue (μg/g) and plasma (μg/ml) concentrations of ceftriaxone at the time of sternotomy and at the beginning of cardiopulmonary bypass**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Conc at time of sternotomy</th>
<th>Conc at the beginning of bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sternum</td>
<td>Plasma</td>
</tr>
<tr>
<td>1</td>
<td>4.6</td>
<td>69.7</td>
</tr>
<tr>
<td>2</td>
<td>4.9</td>
<td>60.2</td>
</tr>
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</tr>
<tr>
<td>15</td>
<td>2.6</td>
<td>74.0</td>
</tr>
</tbody>
</table>

| Mean    | 4.7     | 67.3   | 0.066 | 7.7             | 60.4   | 0.143 |
| Standard deviation | 2.1     | 19.5   | 0.036 | 1.8             | 18.9   | 0.062 |

a These samples were obtained 1.0 to 2.7 h after administration of ceftriaxone (mean ± standard deviation, 1.93 ± 0.41 h).

b These samples were obtained 1.5 to 2.9 h after administration of ceftriaxone (mean ± standard deviation, 2.24 ± 0.36 h).

c Ratio of tissue concentration (in micrograms per gram) to plasma concentration (in micrograms per milliliter).

d ND, Not determined.
Ceftriaxone levels in plasma were 9.4 to 78.6 µg/ml (44.2 ± 16.6 µg/ml). The morning after surgery, 18.1 to 24.7 h after the infusion (21.4 ± 2.3 h), ceftriaxone levels in plasma were 4.2 to 47.1 µg/ml (19.6 ± 9.6 µg/ml).

**DISCUSSION**

The ceftriaxone levels in plasma observed early after infusion in this study resemble those determined by Patel et al. (9), who found the mean ceftriaxone level 60 min after infusion of 1 g to be 111 µg/ml in healthy volunteers. The present data indicate that administration of 1 g of ceftriaxone before cardiopulmonary bypass results in plasma levels exceeding the minimum inhibitory concentrations against most pathogens considered to be susceptible to ceftriaxone (5–7) for up to 24 h after the infusion.

We previously determined that infusion of 2 g of cefazolin before cardiopulmonary bypass resulted in sternal bone levels of 9.9 ± 6.1 µg/g and atrial appendage levels of 16.2 ± 7.0 µg/g, whereas infusion of 2 g of cefamandole resulted in sternal bone levels of 5.0 ± 2.5 µg/g and atrial appendage levels of 7.3 ± 5.0 µg/g (3). Thus, by taking the dosage into account, the ceftriaxone levels in these tissues were similar to cefamandole and cefazolin levels determined by a similar method. That determinations of tissue levels of antimicrobial agents by different laboratories may vary substantially is well known.

These data raise the possibility that a single infusion of ceftriaxone might be useful for prevention of postoperative infection due to susceptible pathogens. It should be pointed out, however, that some bacterial species are not usually susceptible to achievable concentrations of ceftriaxone. These include some species of *Enterobacter*, *Proteus*, *Serratia*, *Pseudomonas*, *Acinetobacter*, *Bacteroides*, enterococci, and *Staphylococcus epidermidis* (5–7). Because only 50% of *S. epidermidis* strains were inhibited by a ceftriaxone concentration of 6.3 µg/ml (7), use of ceftriaxone as the sole prophylactic agent at the time of cardiac valve replacement would appear to be inadvisable. The possibility that unwanted effects of broad-spectrum prophylactic antimicrobial therapy, such as colonization by potential pathogens, might be minimized by use of only one dose awaits clarification.

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**LITERATURE CITED**