Concentrations of Fusidic Acid, Cloxacillin, and Cefamandole in Sera and Atrial Appendages of Patients Undergoing Cardiac Surgery

MICHEL G. BERGERON,1,4 DENIS DESAULNIERS,2 CÉLINE LESSARD,1 MICHEL LEMIEUX,2 JEAN-PAUL DESPRÉS,2 JACQUES MÉTRAS,2 GILLES RAYMOND,2 AND GILLES BROCHU2

Département de Chirurgie Vasculaire, Institut de Cardiologie, Hôpital Laval,2 and Service d’Infectiologie, Centre Hospitalier de l’Université Laval,1 Ste-Foy, Quebec, Canada G1V 4G2

Received 27 February 1985/Accepted 8 March 1985

The concentrations of cefamandole, cloxacillin and fusidic acid were measured in the serum and heart tissue of 100 recipients of these drugs before cardiac surgery. During cardiopulmonary bypass, mean (± standard deviation) peak concentrations in serum of all patients were 63.0 ± 34.0 μg of cefamandole per ml, 30.8 ± 17.7 μg of cloxacillin per ml, and 32.4 ± 10.8 μg of fusidic acid per ml. Mean (± standard deviation) concentrations in atrial appendages taken 1 h (±15 min) after infusion were 21.3 ± 11.0 μg of cefamandole per g, 23.8 ± 17.3 μg of cloxacillin per g, and 10.7 ± 4.2 μg of fusidic acid per g. No cefamandole could be detected in 5 of 39 heart specimens. Mean tissue-to-serum ratios at 1 h for cefamandole, cloxacillin, and fusidic acid were respectively 0.35, 0.73, and 0.33. Fusidic acid, a drug which is highly effective in vitro against both methicillin-resistant Staphylococcus aureus and Staphylococcus epidermidis, was detectable in heart tissue in concentrations which were 12 times higher than the MICs of this agent against these resistant microorganisms.

There are several published reports on the penetration of cefamandole in human heart but none on either cloxacillin, a drug which in several countries of the world is used as a prophylactic agent in cardiac surgery (3, 9), or fusidic acid, an agent of some promise because of activity in vitro against both methicillin-resistant and -susceptible Staphylococcus aureus and Staphylococcus epidermidis (4, 20). The increasing incidence of severe infection due to those latter microorganisms (9, 12, 15) has stimulated us to compare the penetration of these three antibiotics in human heart.

MATERIALS AND METHODS

Patients. A total of 100 patients (69 males and 31 females) about to undergo cardiac surgery were admitted into this study. They ranged in age from 21 to 84 years old (mean, 55 years). Men constituted 65% and 55% of the cefamandole- and cloxacillin-treated groups, respectively. They accounted for 90% of the fusidic acid group. Surgeries consisted of coronary bypass (CPB) (66%) and valve replacement (32%) for the cefamandole and cloxacillin groups and CPB for the fusidic acid group. Duration of surgery varied from 3 to 5 h. Extracorporeal circulation lasted 1 to 3 h.

Drug administration. Cefamandole (Eli Lilly, Canada) was administered to 37 patients, and cloxacillin (Ayerst, Canada) was administered to 34 patients. At induction of anesthesia, both drugs were infused intravenously (i.v.) at a dose of 1 g over 5 min. Fusidate diethanolamine (Leo Laboratories, Canada) was administered to 29 patients i.v. at a dose of 580 mg over 2 h before surgery. After the first dose, fusidic acid and cloxacillin were continued every 4 h for 24 h, and fusidic acid was continued every 8 h. Each patient received a total of six injections of either drug.

Sample collection. Blood samples were collected 1, 2, 3, and 4 h after administration of either cefamandole, cloxacillin, or fusidate diethanolamine. Additional samples were collected at 5, 6, and 8 h from patients receiving fusidate diethanolamine. Portions of atrial appendage with mean weights of 0.20 g were sampled at different times after administration of the first dose of drug. Atrial appendages or valvular tissues were taken either concomitantly or within 15 min of the serum in 21 of the 37 cefamandole-treated patients, in 14 of the 34 cloxacillin-treated patients, and in 12 of the 29 fusidic acid-treated patients. In all the other patients blood and atrial samplings were not taken simultaneously.

Appropriate dilutions of patient serum containing cefamandole and cloxacillin were made in pooled human serum. Appropriate dilutions of fusidic acid were made in phosphate citrate buffer (pH 6.0) (6). For cefamandole and cloxacillin, standard curves of serum levels (concentration between 0.78 and 50 μg/ml) were prepared in serum. Standard curves for sodium fusidate (concentrations between 0.25 and 4.0 μg/ml) were prepared in phosphate citrate buffer (pH 6.0).

Atrial appendages or heart valves were rinsed three times with sterile saline, blotted dry, weighed, and then homogenized in a tissue grinder (Potter Elvejem) at 4°C with 3 or 4 volumes of 0.2 M phosphate buffer (pH 7.4) for heart tissue obtained from recipients of cefamandole or cloxacillin and with phosphate citrate buffer pH 6.0 for samples from patients receiving fusidic acid. Homogenates of a pool of atrial appendages in appropriate buffer were used to prepare standard curves for heart tissue specimens. The range of concentrations of each antibiotic was identical to that described for serum. The lower limit of detection of cefamandole and cloxacillin in the appendage was 3.9 μg/g; for fusidic acid, it was 1.0 μg/g.

Concentrations of antibiotics were determined in triplicate by microbiological agar disk diffusion assay with medium and test organism that were specific for each antibiotic. For cefamandole tryptic soy agar (Difco) was the medium used, and Bacillus subtilis (Difco) was the indicator organism. For cloxacillin the same medium was inoculated with Sarcina lutea ATCC 9341 (5 ml of 18-h culture per 100 ml of medium). For fusidic acid 1 liter of medium containing vitamin-free Casamino Acids (Difco), 15.0 g; yeast extract (Difco), 5.0 g; l-cysteine, 0.05 g; sodium chloride, 2.5 g;
glucose, 1.0 g; and agar (Difco), 24.0 g at a pH of 6.0 was inoculated with 10 ml of an 18-h culture of *Corynebacterium xerosis* Leo FF-M (6). Plates were incubated overnight at 37°C for cefamandole and fusidic acid assays and at 30°C for cloxacillin. Recovery of each antibiotic after the addition of known amounts of antibiotics in drug-free homogenates of atrial appendage was ≥95%.

The ratio of atrial appendage over serum concentration was calculated for patients from whom serum and tissue were sampled simultaneously (±15 min). Analysis of variance and Duncan multiple-range test were used for statistical analyses. Pharmacological parameters of serum (half-life, area under the curve, volume of distribution) were calculated with a one-compartment model.

**RESULTS**

From patients receiving cefamandole, cloxacillin, or fusidic acid, 115, 97, or 101 serum samples were collected, respectively. A total of 42 heart specimens (40 atrial appendages and 2 mitral valves) were taken at 20 min to 2.25 h after cefamandole injection. A total of 39 heart specimens (36 atrial appendages and 3 mitral valves) were taken at 15 min to 3.33 h after cloxacillin injection, and 23 portions of atrial appendages were sampled at 1 to 4.35 h after the beginning of fusidic acid infusion (Table 1).

**Levels of cefamandole in serum and heart tissue.** Concentrations of cefamandole in serum 1 h postinjection varied between 15.0 and 175.0 µg/ml (mean of 63.0 µg/ml). At 2 h, the drug level in serum ranged from 3.0 to 82.5 µg/ml (mean of 35.6 µg/ml), and at 4 h, it ranged from 3.5 to 38.0 µg/ml (mean of 14.7 µg/ml).

The levels of cefamandole in the 42 heart specimens collected between 16 and 135 min after injection are presented in Table 1. The lowest concentration was 7.7 µg/ml, and the highest was 55 µg/ml. Individual data for 21 of the 37 patients from whom serum and heart tissues were taken simultaneously are listed in Table 2. Mean levels in serum (± standard deviation) were 71.0 ± 36.5 µg/ml at 1 h and 39.7 ± 10.1 µg/ml at 2 h. Mean levels in corresponding appendages were 21.3 ± 11.3 and 13.5 ± 5.9 µg/ml. The mean ratio of drug concentration in heart tissue/drug concentration in serum was 0.35. The concentrations of cefamandole in the 2 mitral valves were 26.2 and 16.5 µg/g at 1.0, and 1.25 h, respectively, after administration.

**Levels of cloxacillin in serum and heart tissue.** Mean serum level of 30.8 µg/ml (7.4 to 69.7 µg/ml) was observed 1 h after bolus injection of cloxacillin. At 2 h, the value was 19.4 µg/ml (1.8 to 57.5 µg/ml), and at 4 h, the mean concentration was 12.4 µg/ml, with levels ranging from 2.4 to 35.0 µg/ml. The concentrations of cloxacillin detected in heart tissue between 16 and 200 min after the injection are shown in Table 1. The highest detectable concentration was 60.0 µg/g. No antibiotic could be detected (<3.9 µg/g) in five (13%) heart specimens. These five samples (four atrial appendages and one valve) were taken from four patients (no. 20, 27, 31, and 34). These four patients had maximal drug levels in serum of 27.5, 11.2, 23.7, and 23.5 µg/ml. The appendage sample from patient no. 20 was very small (0.023 g). The other appendage samples were large (0.08, 0.21, and 0.35 g). No drug was detectable in the mitral valve sample from patient no. 34 taken at 65 min, but the atrial appendage sample from this patient taken at 44 min had detectable levels of cloxacillin at 17.5 µg/g.

The data for 14 of the 34 patients in whom serum and atrial appendage were taken at the same time are shown in Table 2. The ratio of heart/serum concentration was quite variable, with a mean value of 0.73 (±0.63) at 1 h postinjection. The concentrations of cloxacillin in the three mitral valves were <3.9, 38.0, and 9.2 µg/g from 1.0 to 1.9 h after drug administration.

**Fusidic acid levels in serum and heart tissues.** The levels of fusidic acid in serum varied from 11.6 to 112.0 µg/ml at the end of the 2-h infusion, with a mean value of 44 µg/ml. At 3 h, drug levels in serum varied from 15.2 to 54.0 µg/ml (mean value 32.4 µg/ml). At 8 h after the beginning of infusion, drug concentrations in serum reached a mean value of 17.5 µg/ml. Atrial appendage levels of fusidic acid ranged from 4.7 to 19.2 µg/g (Table 1). The mean concentration values at 1 and 2 h (±15 min) after the end of infusion were 10.7 and 9.5 µg/g, respectively. In 12 patients in whom serum and heart specimens were taken simultaneously (Table 2), the mean level in serum 1 h after the end of infusion was 34.3 µg/ml, but it was 10.6 µg/g in the appendage sample. The mean ratio of concentration in heart tissue/concentration in serum was 0.33 (±0.19). More than 4 h after the administration of the drug, the agent was still detectable in high concentrations (6.8 µg/g). An analysis of variance of the data presented in Table 2 showed a significant difference (*P* = 0.02) between the three drugs. The tissue/serum ratios for the three antibiotics were compared by the Duncan multiple-range test. The tissue/serum ratios for cloxacillin were higher than those for cefamandole and fusidic acid (*P* = 0.05).

**Pharmacology of cefamandole, cloxacillin and fusidic acid.** The serum half-life, area under the curve, and volume of distribution of the three antibiotics administered during cardiopulmonary bypass are shown in Table 3. Fusidic acid had a significantly longer half-life than both cloxacillin and cefamandole (*P* ≤ 0.01). The area under the curve for cloxacillin was much smaller than that for cefamandole and fusidic acid (*P* ≤ 0.01). Both cloxacillin and fusidic acid exhibited a larger volume of distribution than cefamandole (*P* ≤ 0.01).

<table>
<thead>
<tr>
<th>Time post infusion (min)</th>
<th>Cefamandole concn (µg/g)</th>
<th>Cloxacillin concn (µg/g)</th>
<th>Fusidic acid concn (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>No. of heart specimens</td>
</tr>
<tr>
<td>16–45</td>
<td>21.0</td>
<td>9.5–37.5</td>
<td>12</td>
</tr>
<tr>
<td>46–75</td>
<td>21.3</td>
<td>10.5–55.0</td>
<td>21</td>
</tr>
<tr>
<td>76–105</td>
<td>20.6</td>
<td>10.0–36.9</td>
<td>3</td>
</tr>
<tr>
<td>106–135</td>
<td>16.6</td>
<td>7.7–29.5</td>
<td>6</td>
</tr>
<tr>
<td>136–200</td>
<td>ND*</td>
<td>ND*</td>
<td>ND*</td>
</tr>
</tbody>
</table>

* 99 cardiac appendages and 5 valves.
* 1 i.v. infusion over 2 h.
* ND, No data.
DISCUSSION

The present investigation clearly demonstrates that cefamandole, cloxacillin, and fusidic acid penetrated heart tissue. A great variability in antibiotic levels were observed from one patient to another. This could be explained, in part, by the different ages of the patients, their weight (each patient receiving the same dose), their variable physiological status, and finally, by the cardiopulmonary bypass (CPB) to which patients were submitted during antibiotic administration. In fact, CPB is known to modify the pharmacology of several antibiotics. We observed, in agreement with the work of others with several cephalosporins (2, 16, 18), that the elimination of both cefamandole and cloxacillin was slowed during CPB. Diminished renal perfusion and renal function, altered protein binding, or decrease in serum albumin associated with an increase in free fatty acids which also bind to serum albumin (F. P. Polyak, B. Suh, and W. A. Craig, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 186, 1979) have all been considered as possible factors affecting the pharmacology and tissue distribution of antibiotics during CPB. The pharmacology of fusidic acid, which is mainly excreted by the liver, did not seem to be affected by CPB.

Our data for cefamandole seem in accordance with those of other investigators. At 40 min after a 2-g i.v. injection of the drug, Olson and colleagues (17) detected 50 μg of cefamandole per g in the appendage; whereas at half this

<table>
<thead>
<tr>
<th>Table 3. Pharmacology of cefamandole, cloxacillin, and fusidic acid during cardiopulmonary bypass*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic (no. of patients)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Cefamandole (35)</td>
</tr>
<tr>
<td>Cloxacillin (27)</td>
</tr>
<tr>
<td>Fusidic acid (24)</td>
</tr>
</tbody>
</table>

* Results are mean ± standard error. t₁/₂, Half-life; AUC, area under the curve; V₂, volume of distribution.
dose, the levels we found were 21 µg/g. Archer et al. administered one injection (20 mg/kg) of cefamandole intramuscularly and detected levels in the appendage identical to ours and ranging from 10 to 60 µg/g with a mean of 26.7 µg/g, 44 min after antibiotic administration. Their ratio of concentration in heart tissue/concentration in serum was 0.51 for appendage and 0.39 for valvular tissue. In our study the ratios were lower, 0.37 for appendage and 0.19 for valvular tissue.

Although there are no reported data for cloxacillin levels in the heart, Kiss et al. (13), using another isoxazolyl penicillin, fluocoxacillin, at a dose of 500 mg intramuscularly could detect low concentrations of antibiotic in cardiac tissue. The concentrations varied from 2.3 to 3.5 µg/g in the auricle and from 1.1 to 2.5 µg/g in the mitral valve. They could not detect fluocoxacillin in 12 of 14 pericardial fluid specimens. In our present study, the levels were in general higher. The dose given here were twice as large. In addition, the percentage of protein binding of cloxacillin (94%) and fluocoxacillin (95%) was almost identical; this probably does not explain the difference in the penetrability of the agent. Although Austin et al. (3) did not study levels of cloxacillin in human heart, they suggested based on serum levels that a 500-mg dose should give sufficient protection against staphylococci. In our study, in which 1,000 mg was injected, 5 of the 39 heart specimens did not have any detectable levels of cloxacillin, suggesting that these patients (who all had high drug levels in serum) might not have been protected against infection. Although in one case the small size of the atrial appendage might partially explain the lack of detectability, in the other cases, no technical difficulty could explain this observation. Although we could not detect cloxacillin levels lower than 3.9 µg/g, most methicillin-resistant staphylococci have MICs of more than 4 µg/ml. In addition, in a study comparing the efficacy of cloxacillin combined with ampicillin and cefamandole as prophylactic agent in 109 patients undergoing cardiac surgery, Ghoneim et al. (9) have noted an overall rate of infection post surgery of 1.7% with cefamandole and 13.7% with the ampicillin-cloxacillin combination. The above observations coupled with our present data suggest that cloxacillin should be used with caution as a prophylactic agent in cardiac surgery.

Fusidic acid, an antibiotic derived from the fungus Fusidium coccineum, is a sodium salt of an unsaturated carboxylic acid. In contrast with the other two drugs, it has a long half-life of about 5 h and is excreted mainly by the liver (22). Like cloxacillin (94%), it is highly protein bound (97.2%). The serum levels obtained in our study were identical to those reported in the literature (22).

Its penetrance is reported to be good in bone (11), adipose tissue, aqueous humor, sputum, and pus. With a modified skin window method, Raeburn (21) described a better penetrance of fusidic acid than cephaloxin, clindamycin, or cloxacillin into inflammatory exudates. There are no reported data for heart tissue. The present clinical study demonstrated that fusidic acid can penetrate heart tissue. Mean concentrations detected in atrial appendages up to 4 h after the beginning of infusion reached values 12 times the MIC for methicillin-resistant Staphylococcus aureus (14) and Staphylococcus epidermidis (20). Maximum levels of cefamandole and cloxacillin in atrial appendages were respectively one to five times and four to eight times the MICs of those antibiotics against these pathogens (5, 14, 19). The three antibiotics reached concentrations in heart tissue well above the respective MICs of penicillinase-producing and -nonproducing S. aureus (4, 8, 10).

With the emergence of methicillin-resistant S. aureus and S. epidermidis strains that are also resistant to cephalosporins, there is an urgent need for new alternatives which can penetrate heart tissues and are active against these microorganisms. Fusidic acid has such qualities and merits further investigation as a prophylactic against infection with the above microorganisms.

ACKNOWLEDGMENTS

This study was supported by grants from Leo Laboratories Canada and Eli Lilly Co., Canada.

LITERATURE CITED


