Serum Antibiotic Concentrations Pre- and Postcardiopulmonary Bypass

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Serum concentrations of cephalothin or kanamycin, or both, were determined in 53 patients undergoing cardiopulmonary bypass. Conventional doses of these antibiotics did not provide serum levels above the accepted minimum inhibitory concentrations in children. Adults had adequate serum antibiotic concentrations only when the antimicrobials were administered within 4 hr of beginning cardiopulmonary bypass. The impact of these variations upon the occurrence of infectious endocarditis could not be appraised since no cases of infective endocarditis were seen during a 4-month postoperative period.

The administration of prophylactic antibiotics to patients undergoing cardiac surgery is an accepted practice (1, 4, 9, 11, 12, 14, 15, 17). The effectiveness of this practice in preventing postoperative infections, including endocarditis, has not been established (7, 8, 10). Typically, antimicrobial prophylaxis is initiated the day before surgery to ensure adequate serum and tissue levels at the time of the operative procedure. Postoperative infective endocarditis remains a significant problem despite the use of prophylactic antibiotics (1, 8, 10, 15–17).

An important variable which until recently has not been considered in the issue of antibiotic chemoprophylaxis of this patient population is the effect of cardiopulmonary bypass on serum antibiotic levels (14). Lower serum and tissue antibiotic concentrations, sufficient to allow the establishment of infection, might be predicted due to the dilutional effect of the pump-priming volume or other factors related to the extracorporeal circulation. Indeed, Benner (2) reported that penicillins and cephalosporins disappeared from the serum of 15 of 18 patients within 15 min after beginning cardiopulmonary bypass.

Cephalothin and kanamycin are used at the University of Maryland Hospital for chemoprophylaxis of open-heart patients. We measured serum concentrations of these antibiotics in patients undergoing cardiopulmonary bypass (CPB).

**MATERIALS AND METHODS**

Fifty-three patients, 38 adults (aged 20–69 years, mean 47.2 years) and 15 children (aged 3–12 years, mean 7.3 years), scheduled for cardiac surgery requiring cardiopulmonary bypass were included in the study. The Division of Thoracic Surgery routinely uses the following program of antibiotic prophylaxis: beginning 24 hr before surgery and continuing for 7 to 10 days. One gram of cephalothin was administered intramuscularly every 6 hr, and 0.5 g of kanamycin was administered intramuscularly every 12 hr for most adults. Some adult patients received smaller doses of antibiotics at the discretion of their physicians. Children received antibiotic dosages adjusted according to weight. For cephalothin, the dose (in milligrams per kilogram per 24 hr) ranged between 30 and 90 and averaged 52; for kanamycin the dose ranged between 11 and 20 and averaged 13.6 (Table 1). Patients received antibiotics early on the morning of surgery.

Serum samples for determination of antibiotic concentrations were obtained immediately before the institution of cardiopulmonary bypass, at 15, 30, and 60 min after bypass was begun, and immediately after the termination of bypass. (Because of technical problems, e.g., difficulty placing sumps or other catheters which delayed onset of CPB or difficulty in maintaining the patient's blood pressure which required precipitous use of CPB, the timing of the sample drawn before CPB did not always accurately designate time zero. The time elapsed, therefore, between time zero samples and the 15-min CPB samples ranged between 15 to 30 minutes.) Serum was frozen and shipped to Bristol Laboratories in Syracuse, N.Y. for processing. Both antibiotics were assayed by modification of the agar diffusion technique. The test organism used for cephalothin determination was Sarcina lutea, and that for kanamycin was Bacillus subtilis. Tissue antibiotic concentrations were not determined.

Baseline blood urea nitrogen and serum creatinine were measured on each patient before antibiotic prophylaxis was initiated.

Serum concentrations of cephalothin alone were
determined in 13 patients, kanamycin alone in 5 patients, and both antibiotics in 35 patients. The distribution of antibiotic dosages appears in Table 2.

Patients were placed into one of three groups based on the time interval between antibiotic administration and the institution of cardiopulmonary bypass: a 3- to 4-h interval group, a 4- to 5-h interval group, and a group composed of patients who received their drug more than 5 h before bypass (range 5 to 12 h).

**RESULTS**

Serum levels of cephalothin varied widely but correlated roughly with the elapsed time between antibiotic administration and initiation of cardiopulmonary bypass. The serum cephalothin determination in all patients obtained just before the beginning of cardiopulmonary bypass (time zero) appear in Fig. 1. Values for patients in the 3- to 4-h interval group ranged between 0 and 20 μg/ml at time zero. Serum cephalothin concentrations were generally lower in children.

**Table 1. Mean antibiotic dosages**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosea</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>Children</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>57.1</td>
<td>51.8</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>14.2</td>
<td>13.6</td>
</tr>
</tbody>
</table>

*a Expressed as milligrams per kilogram per 24 h.

**Table 2. Antibiotic dosages given before institution of cardiopulmonary bypass**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Cephalothin (6 h before bypass)</th>
<th>Kanamycin (12 h before bypass)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>28</td>
<td>1.0 g</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.5 g</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>0.5 g</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.5 g</td>
</tr>
<tr>
<td>Children</td>
<td>12</td>
<td>13 mg/kg (avg)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1.** Serum cephalothin determination in all patients obtained before the beginning of cardiopulmonary bypass (time zero).
despite the fact that they received doses on a body weight basis comparable with adults. Only one of 12 children studied had a serum concentration of cephalothin above 1 µg/ml at the termination of cardiopulmonary bypass. Of adults placed on cardiopulmonary bypass 3 to 4 h after receiving cephalothin, 95% still had serum concentrations of 1 µg/ml or greater at the end of bypass time (Fig. 2). In sharp contrast, only 23% of those adults placed on cardiopulmonary bypass more than 5 h after the last dose of cephalothin had serum levels above 1 µg/ml by the end of bypass. In fact, only 31% of this group had serum concentrations of cephalothin above 1 µg/ml after 15 min of cardiopulmonary bypass (Fig. 3). Intermediate results were obtained in the group of patients going on bypass 4 to 5 h after receiving cephalothin; 50% had serum concentrations of 1 µg/ml or greater at the end of cardiopulmonary bypass.

Serum kanamycin levels varied widely also and correlated roughly with the time elapsed between antibiotic administration and initiation of cardiopulmonary bypass. The serum concentrations of kanamycin in all patients obtained just before the institution of cardiopulmonary bypass (time zero) are depicted in Fig. 4. Patients in the 3- to 4-h interval group had serum kanamycin concentrations ranging between 4.5 to 23 µg/ml at time zero. Again, children had generally lower values than adults, despite the fact that they received similar milligram-to-kilogram doses. None of the 8 children studied had kanamycin levels above 5 µg/ml at the end of bypass. Of those adult patients begun on cardiopulmonary bypass within 3 to 4 h after receiving the antibiotic, 72% had serum concentrations of 5 µg/ml or greater at the end of bypass (Fig. 5). In contrast, none of the patients who received antibiotics more than 5 h before cardiopulmonary bypass was initiated had serum levels of kanamycin above 5 µg/ml at the termination of the bypass procedure (Fig. 6). Only 25% of this patient group had levels above 5 µg/ml 15 min after beginning cardiopulmonary bypass. Intermediate values were obtained in the group placed on bypass 4 to 5 h after receiving kanamycin, and 50% had serum concentrations of 5 µg/ml or greater at the end of bypass time.

All patients had normal blood urea nitrogen and serum creatinine values before the initiation of antibiotic administration.

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**Fig. 2.** Serum cephalothin concentrations obtained 3 to 4 h after antibiotic administration.
Fig. 3. Serum cephalothin concentrations obtained more than 5 h after antibiotic administration.

Fig. 4. Serum kanamycin concentrations in all patients obtained before cardiopulmonary bypass.
SERUM CONCENTRATIONS 3–4 HOURS POST ANTIBIOTIC ADMINISTRATION

- Adults, 0.5 gram 10
- Adults, 0.25 gram 8
- Children 1

Fig. 5. Serum kanamycin concentrations obtained 3 to 4 h after antibiotic administration.

SERUM CONCENTRATIONS > 5 HOURS POST ANTIBIOTIC ADMINISTRATION

- Adults, 0.5 gram 6
- Adults, 0.25 gram 2
- Children 11

Fig. 6. Serum kanamycin concentrations obtained more than 5 h after antibiotic administration.
tion of cardiopulmonary bypass. Patients were followed for a minimum of 4 months postoperatively. During the observation period, no infective endocarditis occurred.

**DISCUSSION**

The reported incidence of infective endocarditis after cardiopulmonary bypass varies between 1 and 10% (1, 4, 6, 8, 10, 13, 15, 17). The infection is sometimes difficult to identify because unusual or "nonpathogenic" organisms are recovered and disregarded as contaminants (1, 3, 4, 8, 13, 16). The delay in recognition, antibiotic resistance of the organisms, and presence of foreign bodies are factors which compound the complexity of the problem (7, 8, 10, 17). The mortality rate of postoperative infective endocarditis in several large series ranged between 33 and 83% (1, 4, 8, 10, 13, 15, 17). Prophylactic antibiotics have been used to decrease the incidence and mortality of this complication of open-heart surgery (1, 4, 9, 12, 15). Controlled studies confirming the efficacy of antimicrobial prophylaxis in preventing postoperative infections, including endocarditis, are not available (6-8, 10). Despite this, patients continue to receive prophylactic antimicrobials during cardiopulmonary bypass in most institutions in this country.

Burke (5) demonstrated that prophylactic antibiotics would prevent infections in animals only if adequate serum concentrations were present when the microorganisms were introduced into the operative site. His studies have served as the rationale for instituting antibiotic prophylaxis before open-heart surgery (1, 8). Whether or not patients actually have adequate serum and tissue levels of antibiotics while undergoing extracorporeal circulation, therefore, is basic. Benner (2) noted the disappearance of penicillins and cephalosporins from the serum of patients within 15 min after being placed on cardiopulmonary bypass; the exact time intervals between administration of antibiotics and sampling of serum were not reported.

The minimum inhibitory concentration of cephalothin for most susceptible gram-positive organisms is 1 µg/ml or less. Kanamycin has a minimum inhibitory concentration of 5 to 10 µg/ml for susceptible gram-negative organisms. Our results demonstrate that children did not have serum levels of either antibiotic above the minimum inhibitory concentrations during the total interval of bypass time. The majority of our adult patients maintained adequate serum antibiotic concentrations only if brought to cardiopulmonary bypass within 4 h of receiving the last dose. If prophylactic antibiotics (in particular, serum levels during cardiopulmonary bypass) have a significant role in the prevention of postoperative infections, then it is clear that (i) doses in children should be increased, (ii) antibiotics should be administered within 4 h (preferably less) of initiating cardiopulmonary bypass, and (iii) other prophylactic regimens should be carefully studied to determine appropriate dose-time relationships for each antibiotic.

**ACKNOWLEDGMENTS**

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**LITERATURE CITED**

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