Comparison of Cephalothin and Ceforanide Prophylaxis in Cardiac Surgery with Cardiopulmonary Bypass

WALTER KARNEY,1,2∗ RAPHAEL CORREA-CORONAS,1,2 RUSS ZAJTCHUK,2,3 JUDY SCHWARTZ,2,3 L. PATRICK SMITH,1,2 AND EDMUND TRAMONT2

Department of Cardiovascular Surgery3 and the Infectious Diseases Branch,1,8 National Naval Medical Center, and the Uniformed Services University of the Health Sciences,2 Bethesda, Maryland 20814

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Eighty-five patients undergoing cardiac surgery with cardiopulmonary bypass were given either cephalothin or ceforanide perioperatively in randomized, blinded fashion. The incidence of surgically related, postoperative infections was 23% for the cephalothin- and 26% for the ceforanide-treated groups. There were no statistically significant differences that could be identified between patients who became infected and those who remained free of infections, although the time spent in the operating theater was longer for the former group. Ceforanide achieves adequate levels in plasma and myocardial tissue that are sustained several hours after a 0.5-g parenteral dose and allows a 12-h interval between doses. Other currently available agents would have to be administered more frequently to achieve similar results.

Ceforanide (Cf) is a newly developed cephalosporin with a longer half-life than many of the cephalosporins currently marketed. Like cephalothin (Cp), it is inhibitory against microorganisms commonly associated with postoperative infection. Because of these attributes, a prospective study was undertaken to determine whether Cf given twice daily is as effective as Cp administered every 6 h when used prophylactically in cardiac surgery with cardiopulmonary bypass. (This paper was presented in part previously [W. Karney, R. Correa-Coronas, R. Zajtchuk, J. Schwartz, L. P. Smith, and E. Tramont. Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami Beach, Fla., abstr. no. 764, 1982]).

MATERIALS AND METHODS

From August 1980 to July 1981, 92 patients who were to undergo cardiac surgery with cardiopulmonary bypass at the National Naval Medical Center were admitted into the study after providing informed consent. (The study was approved by the institutional committee on human research.) Patients were not considered eligible if they had a history of penicillin allergy, received antibiotics during the 7 days before surgery, or had evidence of active infection. No one was admitted into the study if he or she declined participation for any reason or if the investigators felt the subject was unable to fully understand important aspects of the study explained in the consent form.

Patients were randomized to receive either six doses of 1 g of Cp or three doses of 500 mg of Cf and three doses of placebo according to the following schedule. Cp or Cf was given 1 h preinduction of anesthesia (dose 1). Cp was administered again immediately after cardiopulmonary bypass was discontinued (dose 2); after completion of surgery 6 to 8 h after dose 1 (dose 3); and at 12 (dose 4), 18 (dose 5), and 24 (dose 6) h after dose 1. Cf was given 12 and 24 h after the initial dose, with placebo substituted for the active drug for doses 2, 3, and 5. The study design was not adhered to in 12 patients recorded as given Cf for dose 3 and placebo for dose 4. The pharmacy officer who prepared the antibiotic solutions for intravenous administration was the only person at the medical center who was aware of which cephalosporin each study patient received. The randomization code was not broken in any case until after the 4- to 6-week follow-up had been accomplished.

During surgery, a portion of atrial appendage was removed, and heparinized blood specimens were drawn. Tissue and plasma specimens were immediately frozen and later transported to Bristol Laboratories, Syracuse, N.Y., where cephalosporin assays were performed. Cp concentrations in plasma and tissue samples were measured using the standard cup plate bioassay method with Sarcina lutea (ATCC 9341) as the reference organism. All samples were incubated for 16 to 18 h at 33°C. A high-pressure liquid chromatography system (methods are on file at Bristol Laboratories) was used to assay plasma and atrial appendage specimens for Cf concentrations. Complete blood count with differential, leukocyte count, urinalysis, and serum sodium, potassium, glucose, urea nitrogen, protein, and liver function tests were done day 1 preoperatively and day 2 postoperatively. Blood and urine cultures were obtained on postoperative days 1 and 2 and repeated as indicated. Wound cultures were done whenever indicated.

Each patient was seen preoperatively and followed...
closely postoperatively during the period of hospitalization by one of the investigators. Each had a Foley catheter in place during surgery and for 24 h postoperatively. Daily vital signs and conditions of the sternal and phlebectomy wounds were monitored. All evaluable patients were seen 4 to 6 weeks postoperatively, and the status of the surgical wounds was assessed. Drainage from surgical wounds was submitted for culture. The operative site was considered to be infected if any of the following criteria were met: (i) drainage from the site appeared purulent, (ii) drainage from the site was culture positive for a conventional bacterial pathogen, and (iii) there was erythema, swelling, and tenderness that required incision and drainage or antibiotics or both for treatment. Nonoperative site infections considered related to surgery also were noted.

RESULTS

Of the 92 patients who were admitted into the study, 7 (4 in the Cf- and 3 in the Cp-treated groups), were considered nonevaluable for the following reasons: death from a noninfectious cause within 12 h of surgery (2 patients), administration of additional antibiotics during the perioperative period because of major noninfectious complications (2 patients, neither of whom developed a surgically related infection), presence of intracardiac infection detected at surgery (1 patient), study aborted owing to intraoperative complications before required number of doses of study drug given (1 patient), and surgery performed did not require cardiopulmonary bypass (1 patient).

There was no significant difference in sex distribution (greater than 90% males), mean age (52 versus 51 years), or type of surgery performed for the remaining 85 patients in the two treatment groups. A total of 75 patients (38 Cp and 37 Cf) had coronary artery bypass grafting; 5 of these (3 Cp and 2 Cf) also had valve replacement. A total of 7 patients (3 Cp and 4 Cf) had valve replacement alone, and 3 (2 Cp and 1 Cf) had septal defects repaired. Surgically related infections that were detected in the 85 evaluable patients are summarized in Table 1. The infection rate (number of patients who developed infections divided by number of patients treated) for patients given Cp (23%) was not significantly different from the infection rate for patients given Cf (26%). The overall infection rate was 25% (21/85). Infection at 15 sites (nine leg wounds, two sternal wounds, one lower respiratory tract, three urinary tract) developed in 10 patients treated with Cp. Twelve sites (nine leg wounds and three sternal wounds) became infected in 11 Cf-treated patients. All five sternal wound infections were superficial. Of the 20 patients who developed postoperative wound infections, 15 had infections confined to the lower extremity phlebectomy site. The mean time postoperative when wound infections were diagnosed in the 20 patients was 2.2 weeks (range of 5 days to 5 weeks). Signs of infection did not become apparent in 12 of the 20 patients until after discharge, often at medical facilities other than the National Naval Medical Center.

The three urinary tract infections in Cp-treated patients were due to Escherichia coli that was isolated 3, 4, and 7 days postoperatively. Staphylococcus aureus was recovered from five of six draining wounds in Cf-treated patients and from two of four specimens of wound drainage in patients treated with Cp. All bacterial isolates recovered from the patients were susceptible by the disk diffusion method to both study drugs, with the exception of two Enterobacter aerogenes strains that were susceptible to Cf but resistant to Cp. Both patients from whom E. aerogenes was isolated had received Cp as the perioperative antibiotic.

Of 36 Cf-treated patients, 35 had myocardial drug levels in tissue ranging from 4.2 to 22 μg/g (Table 2). In only one patient was the concentration less than 2.5 μg/g (lower limit of the assay). The concentration of Cp in atrial appendage was less than 2.5 μg/g in 33 of 38 patients given this drug perioperatively. At the time the atrial appendage was removed, the mean serum concentration of Cf exceeded by more than threefold the mean concentration of Cp (19.2 versus 4.9 μg/ml). Since Cp was given intraoperatively, at the termination of surgery the mean serum level of both agents was greater than 8 μg/ml, which is above the minimum concentration needed to inhibit most bacterial pathogens causing surgically related infections.

The only apparent difference that was identified between the patients who remained free of infection and those who became infected was the duration of the operative procedure, and
even this difference did not reach statistical significance. The mean time of surgery for the patients who were not infected was 277 min (± 64 [standard deviation]) compared with 303 min (± 78) for the infected patients (P = 0.12 by Student’s t test with two-sample analysis). The only patient who had lower respiratory tract infection was in the operating theater for 480 min and required an intraaortic balloon for support in the immediate postoperative period. The other patient with infection at three separate sites had bypass grafting of three coronary vessels and replacement of the aortic valve that took 253 min, no more than the average time in surgery. There was no evidence of infection in the only patient who was explored for mediastinal bleeding during the early postoperative period.

There were no abnormalities detected in any of the routine lab tests that could be attributed to either of the study drugs. No other adverse effects due to Cp or Cf were identified in the 92 patients entered into the protocol.

**DISCUSSION**

In this study, the overall infection rate in patients who had cardiac surgery with cardiopulmonary bypass and who were given a cephalosporin was 25%. There was no significant difference in the infection rate between the Cf- and Cp-treated groups. However, given the study population of 85 patients, the likelihood of detecting a 15% difference in the rate of infection in the two groups was less than 0.5. In a study of similar design in which 220 patients undergoing cardiovascular surgery were enrolled, the infection rate in Cf-treated patients (14.5%) was less than the rate for those given Cp (24.5%) (R. Platt, J. Stella, J. K. Koster, J. J. Collins, L. H. Cohn, and S. Van De Vanter. Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami Beach, Fla., abstr. no. 765, 1982). The lower incidence of infection in similar patients reported from other hospitals (1, 4, 9, 10) is due in part to the following: (i) not all types of postoperative, surgically related infections (e.g., respiratory and urinary tract) are included; (ii) the definition of wound infection is variable; and (iii) the extent and duration of follow-up is inadequate. The reported incidence in well-designed studies conducted at major medical centers in which all surgically related infections have been included in the analysis has been greater than 20% (3, 6, 7). However, the wound infection rate of 24% in these 85 patients is higher than expected after a clean surgical procedure and likely was related to technique rather than antibiotic prophylaxis. While the study was in progress, the leg wound was left open for the duration of the operation and closed at the same time as the mediastinum. After completion of the study and analysis of the data, the use of perioperative antibiotics continued, but the technique for managing phlebectomy sites was altered in the following manner. Immediately after the vein was harvested, meticulous hemostasis was established and the wound was irrigated with bacitracin solution. The fascial layers were then closed with running, absorbable sutures, and the epidermis was closed with skin staples. After this technique was initiated, one leg wound infection occurred in 100 consecutive cases.

Whether antibiotics administered in prophylactic manner affect a decrease in the infection rate in cardiac surgery patients is an issue that is not yet settled. In the only valid study comparing placebo with antibiotics in patients having valve replacement, there was no significant difference in the infection rate in the placebo versus the antibiotic-treated group, and administration of antibiotics did not prevent bacterial endocarditis (7). However, because of the fear of prosthetic valve endocarditis, it is common practice to give perioperative antibiotics to all patients having valve replacement. The benefit of antimicrobial prophylaxis in coronary artery bypass surgery is even less well defined. Al-
though the results of one study indicated that patients undergoing aorta coronary bypass surgery who were given cephalosporin or Cp became infected less often than patients given placebo, the type of operation performed (e.g., valve replacement versus bypass graft) was not specified, and the 48.9% infection rate in the placebo-treated group (5) is one of the highest reported after a class I surgical procedure. The incidence of thoracic wound infection in coronary artery bypass surgery without valve replacement should be very low, even without prophylaxis (less than 1% in one large series of patients [12]). Unless there is associated valvular disease, there is no increased risk of postoperative endocarditis in these patients compared with the risk in patients undergoing noncardiac surgery. There is a consensus that whenever prophylaxis is used, there is no benefit in extending a course of antibiotics for longer than 48 h after surgery (6, 8). There is some question whether any benefit is derived from the further administration of an antimicrobial agent beyond the intraoperative period (3). The decline in infection rate seen when the technique of managing the phlebectomy site was changed after the study was completed emphasizes that surgical asepsis is the most important factor in the prevention of postoperative infections.

One of the perioperative antibiotics which has been employed in an attempt to prevent infection in patients having cardiac surgery is Cp. Cp has a broad spectrum of activity which includes coagulase-negative as well as coagulase-positive staphylococci and many of the Enterobacteriaceae. Because of its short half-life of 0.5 h, Cp is administered every 4 h when used to treat active infection. When given for prophylaxis, however, a dosage schedule after surgery of every 6 h has been employed with satisfactory results (2, 5, 6, 10). Cf, a new cephalosporin developed by Bristol Laboratories, has a serum half-life of 2.9 h and a spectrum of activity similar to Cp, although in vitro Cf is more active against certain Enterobacteriaceae and somewhat less active against staphylococci. Effective levels of Cf are maintained in plasma for at least 8 h and in myocardial tissue for at least 2 h after 0.5 g is given intramuscularly or intravenously. The very low Cp concentration in atrial appendages removed at surgery from patients in this study could be anticipated since the concentration of Cp in atrial tissue falls rapidly after parenteral administration (no measurable level after 100 min [11]). To provide adequate cardiac tissue levels during the period of cardipulmonary bypass, Cp would have to be given shortly before the patient is placed on bypass. For patients undergoing valve replacement, sustained high levels of antibiotic in cardiac tissue during and several hours after surgery could be important in preventing endocarditis. There are substantial savings that might be realized by reducing the number of times per day a parenteral antimicrobial agent must be administered. At the time of this writing, Cf has not been marketed, nor has the price it will cost per gram been determined. Until this information is available, cost analysis of potential savings comparing its use to other cephalosporins is not possible.

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LITERATURE CITED