

Comparison of Cephalothin and Cefamandole Prophylaxis During Insertion of Prosthetic Heart Valves

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Cefamandole nafate (CM) and cephalothin sodium (CP) were administered as prophylaxis in a randomized, prospective study to 30 consecutive patients undergoing prosthetic cardiac valve insertion. A single dose of 20 mg/kg was given intramuscularly during anesthesia induction, and serial plasma antibiotic concentrations, atrial muscle and cardiac valve tissue antibiotic levels, plasma bactericidal activity against pathogenic staphylococci, and infectious complications were determined and compared for the two drugs. Both antibiotics produced high plasma levels ($>20 \mu\text{g/ml}$ 30 min after injection) which fell less than 25% during the period of cardiopulmonary bypass. However, CM levels were significantly higher at most time periods ($P < 0.05$) than CP levels. CP levels were undetectable in atrial muscle from 14 of 15 patients and in valves from 10 of 15 patients. In contrast, CM bioactivity was found in all tissues. Differences in tissue antibiotic concentration could not be accounted for by differences in plasma concentrations or by CP tissue binding and were assumed to be caused by differences in penetration. Plasma bactericidal activity against staphylococci was equal for the two drugs (median titer, 1:16). No infections were seen in either group. CM appeared to be an effective and perhaps preferable prophylactic antibiotic for use during cardiac surgery.

Antibiotics are routinely administered before the insertion of prosthetic heart valves in order to prevent prosthetic valve endocarditis (PVE). Staphylococci are the most common organisms causing PVE and are thus the bacteria against which most of these antibiotics are directed (4, 19). Although cephalosporins and semisynthetic penicillins are equally active in vitro against *Staphylococcus aureus*, cephalosporins are more active against *Staphylococcus epidermidis* and in addition protect against many gram-negative bacilli which may cause PVE and postoperative infections (10, 14, 20, 23). Thus, cephalosporins have been recommended as the prophylactic antibiotics of choice during cardiac surgery to repair or replace damaged valves (6, 14). However, because of the low incidence of PVE, studies assessing the efficacy of various prophylactic antibiotics have been unable to show significant differences in the ability of these antibiotics to prevent endocarditis (3, 5, 7, 14).

The present study was designed to investigate aspects of antibiotic prophylaxis that may be relevant to the prevention of infection around the valve prosthesis. Two cephalosporin antibiotics were chosen to be compared in a random-

ized, prospective study. These antibiotics were cephalothin, the antibiotic currently used most often for prophylaxis, and cefamandole (Eli Lilly and Co., Indianapolis, Ind.), a new cephalosporin with activity against staphylococci similar to that of cephalothin and greater activity than cephalothin against many gram-negative bacilli (15).

The specific aspects of prophylaxis investigated were (i) antibiotic concentration in plasma before and during cardiopulmonary bypass (CPB); (ii) antibiotic concentration in cardiac tissue; (iii) the incidence of bacterial contamination of cardiac tissue and pump blood during surgery; (iv) the bactericidal activity of plasma obtained at the time of valve insertion against a panel of staphylococci isolated from patients with PVE; and (v) the effect of prophylaxis on the incidence of postoperative infections.

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MATERIALS AND METHODS

Patients. Thirty consecutive patients admitted to the cardiovascular surgery service at the Medical College of Virginia Hospitals were assigned from a table

of random numbers to receive either cephalothin sodium (CP; 15 patients) or cefamandole nafate (CM; 15 patients). All patients had porcine xenograft cardiac valves (Hancock Laboratories, Anaheim, Calif.) inserted in either the aortic or mitral position, and all surgery was performed by the same surgeon and surgical team. No patient needed to be excluded from the study because of a history of serious allergic reactions to either penicillin or cephalosporin drugs. Informed consent was obtained from each patient before entry into the study. Patients were followed postoperatively until discharge, a mean of 10 days after surgery, for signs of wound, urinary tract, respiratory, or prosthetic valve infections.

CPB. Nonpulsatile blood flow was maintained at 50 ml/kg per min during CPB, and blood temperature during bypass was 32 to 34°C. The mean arterial pressure varied from 50 to 100 mm of Hg. The pump was primed with 2,000 ml of Normosol R (Abbott Laboratories, North Chicago, Ill.) plus 300 ml (75 g) of albumin for mitral valve surgery and 1,500 ml of whole blood, 500 ml of Normosol R, and 50 ml (12.5 g) of albumin for aortic valve replacement. The beginning of bypass was assumed to occur when the venous clamp was opened, initiating mixing of the priming fluid with the patient's blood. The end of bypass coincided with clamping of the venous return.

Drug dosage and administration. Antibiotics were administered in a single dose of 20 mg per kg of total body weight. They were given by intramuscular (i.m.) injection into the deltoid muscles at the time of anesthesia induction. No other antibiotic was administered before or during surgery, but the surgeons' antibiotics of choice were given for 48 to 72 h postoperatively. These antibiotics were streptomycin (500 mg i.m. every 12 h), aqueous penicillin G (10^6 U intravenously [i.v.] every 6 h), and sodium nafcillin (1 g i.v. every 6 h).

Samples. Plasma (patients were heparinized before and during CPB) was obtained either from the arterial line before bypass or from the pump oxygenator during bypass. The adequacy of the oxygenator as a sampling site was tested by drawing simultaneous pump and arterial blood during bypass; there was no difference in antibiotic concentration from either site at any time during bypass. Samples were obtained at the following times: 30 and 60 min after drug administration, immediately before CPB, 10 min after CPB, every 30 min during CPB, and at the end of bypass. Atrial appendage muscle, excised in order to insert venous lines during the pre-bypass period, and valve tissues removed before insertion of the prosthesis were also saved. These tissues were obtained from all patients in the study. Plasma and tissues were either assayed immediately for antibiotic content or frozen at -70°C and assayed the next day.

Assays. Plasma and tissue antibiotic concentration were assayed by the paper disk diffusion method (18) on Mueller-Hinton agar (BBL, Cockeysville, Md.) with *Bacillus subtilis* ATCC 6633 as the test organism. All determinations were done in duplicate and read by the same technician. Standards for plasma antibiotic assays were made in normal human serum with cefamandole lithium and cephalothin sodium powders, weight corrected for potency. The lower limit of sensitivity of the plasma antibiotic assay was 0.25 µg/ml

for cefamandole and 0.3 µg/ml for cephalothin.

Tissue was washed free of adherent blood, weighed, and homogenized with a mortar and pestle after the addition of phosphate-buffered saline (PBS, pH 7.2). Valves were homogenized in a ratio of 1 ml of PBS per 200 mg of tissue; the ratio for atrial appendages was 1 ml/100 mg because less tissue was available, and 1 ml was the minimum volume required for grinding. The difference in tissue dilution produced differences in the lower limit of sensitivity of the assay for the two tissues. Sterile sand, the weight equal to that of the tissue, was added to facilitate grinding. The homogenate was removed from the mortar with a Pasteur pipette and centrifuged at 6,000 rpm for 10 min. The supernatant was assayed for antibiotic activity against standards made in PBS. The lower limits of sensitivity of the tissue assays were as follows: CM, 0.625 µg/g (valve) and 1.25 µg/g (atrial appendage); CP, 1.0 µg/g (valve) and 2.0 µg/g (atrial appendage). No attempt was made to estimate the amount of antibiotic-containing blood in tissue. Pieces of valve and atrial appendage tissue with no bioactivity were used to calculate the amount of drug activity lost during homogenization. After the addition of 20 µg of either antibiotic per ml and incubation for 30 min, the activities of the tissue supernatants were only 4% (CM) and 8% (CP) lower than standards.

Tissue with supernatants producing no zone of activity on bioassay were treated in the following manner. Tissue was homogenized as described above, with 10% trichloroacetic acid substituted for PBS. The homogenate was incubated for 30 min at 37°C and then centrifuged. The supernatant was neutralized to pH 7.2 with 1 N NaOH and bioassayed. Standards were made in PBS with an antibiotic whose concentration was adjusted by the number of drops required to bring the trichloroacetic acid supernatant to neutrality. The effect of trichloroacetic acid on the activities of CP and CM was assessed by incubating the antibiotics and trichloroacetic acid at concentrations of 1.5, 5, 10, and 20 µg/ml for 1 h at 37°C. After neutralization, there was no loss in bioactivity of the antibiotics in trichloroacetic acid as compared with appropriate standards. The acid-extracted (before neutralization) and PBS supernatants of some tissues with no bioactivity were further analyzed by high-performance liquid chromatography (Hewlett-Packard 1084, Avondale, Pa.), using a reverse-phase microparticulate C-8 column (Hewlett-Packard) according to the method of Wold (22). High-performance liquid chromatography was also used to confirm the absence of degradation of the cephalosporins by trichloroacetic acid.

Serum bactericidal titers were determined by the microtiter twofold dilution system (8) in Mueller-Hinton broth (BBL, Cockeysville, Md.), using an inoculum of 10^5 colony-forming units/ml. Inhibitory titers were read after 24 h, and all wells were subcultured to Mueller-Hinton agar by the use of a replicating device which delivered approximately 0.01 ml by means of stainless-steel rods. The highest dilution of serum which resulted in no growth on agar after 18 h of incubation was considered the bactericidal titer.

Culturing. The valve ring of each patient was cultured with cotton swabs just before insertion of the prosthesis. One swab was used to streak Trypticase soy agar, whereas the other was placed in a tube of

brain heart infusion broth. In addition, a 2-ml sample of blood was taken from a sterile, unused stopcock on the pump oxygenator of each patient just before the end of CPB. The blood was inoculated into 10 ml of brain heart infusion broth. All broth was observed for 1 week and subcultured to Trypticase soy agar at the end of the week or if the broth became cloudy before this time.

Statistics. The comparison of all differences between groups was made by Student's *t* test. A *P* value of <0.05 was considered significant.

RESULTS

The patients in the two groups were comparable in terms of age, sex, type of valve replaced, and length of surgery (Table 1).

Plasma antibiotic concentration. The levels of CP and CM in plasma after i.m. injection are shown in Table 2. High concentrations of both antibiotics were present 30 min after injection, ranging from 25 to 66 $\mu\text{g}/\text{ml}$ for CM and 20 to 40 $\mu\text{g}/\text{ml}$ for CP. The levels fell slowly during the pre-bypass period, dropped less than 10% when the patients were placed on CPB, and remained above 6 $\mu\text{g}/\text{ml}$ until the end of bypass periods lasting 220 (CP) and 203 (CM) min. Although there was no significant difference in the rate of decline of CM and CP concentrations during CPB, CM levels were significantly higher than CP levels at each time period studied except at the end of bypass.

Tissue antibiotic concentration. Tissue and concomitant plasma antibiotic concentrations are shown in Fig. 1. The atrial appendage was removed during the pre-bypass period, a

mean (\pm standard deviation [SD]) of 35.0 ± 5.6 (CP) and 43.8 ± 9.0 (CM) min after antibiotic administration. The valves were excised a mean (\pm SD) of 12 ± 4.2 (CP) and 19 ± 10 (CM) min after the patient was begun on CPB. The times of tissue removal were not significantly different for the two groups. CP was not detected in 14 of 15 atrial appendage samples, nor was it found in 10 of 15 valve specimens; three of the five valves having bioactivity had concentrations of $<6 \mu\text{g}/\text{g}$ of tissue. No additional tissue-bound activity was extractable from any valve with trichloroacetic acid. Likewise, no CP peak corresponding to known standards was seen by using high-performance liquid chromatography of both trichloroacetic acid and PBS tissue extracts. In contrast, all tissue from patients receiving CM had bioactivity, with mean levels (\pm SD) of $26.7 \pm 14.3 \mu\text{g}/\text{g}$ in atrial appendages and $16.2 \pm 8.5 \mu\text{g}/\text{g}$ in valves. The differences in tissue concentrations were not accounted for by differences in concomitant plasma antibiotic concentrations. Although plasma concentrations of CM were significantly higher than those of CP at most times sampled (Table 2), the tissue antibiotic concentrations of CM were a significantly higher percentage of concomitant plasma levels than were those of CP (the lower limit of sensitivity of the assay for CP was used as the antibiotic concentration for tissue extracts producing no zone on bioassay). These relationships [(tissue/plasma) \times 100] were $39 \pm 19\%$ (mean \pm SD) and $51 \pm 21\%$ for CM valve and atrial appendage tissues, respectively, and $12 \pm 11\%$

TABLE 1. Characteristics of study groups

Antibiotic	Patient age (yr)	Patient sex		Valve replaced		Time (min)	
		Male	Female	Mitral	Aortic	Drug administration to CPB	Beginning to end of CPB
Cephalothin	54 (14-70) ^a	10	5	5	10	45 (34-70) ^a	94 (60-220)
Cefamandole	56 (29-69)	9	6	7	8	52 (40-90)	97 (60-203)

^a Mean (range).

TABLE 2. Plasma concentrations of cephalothin and cefamandole in cardiac surgery patients after a single 20-mg/kg i.m. injection

Antibiotic	Antibiotic level ($\mu\text{g}/\text{ml}$)					
	30 min after dose	Pre-bypass	On bypass			Off bypass
			10 min	30 min	60 min	
Cefamandole (15) ^a	47.3 ± 15.3^b	47.1 ± 15.7	43.8 ± 11.3	41.0 ± 11.3	38.5 ± 11.6	33.3 ± 12.1
Cephalothin (15)	33.6 ± 13.0	29.7 ± 5.2	29.1 ± 16.0	31.4 ± 15.7	28.5 ± 16.2	26.9 ± 18.4
<i>P</i> value ^c	<0.01	<0.005	<0.005	<0.05	<0.05	>0.05

^a Number of samples at each time.

^b Mean \pm SD.

^c Student's *t* test.

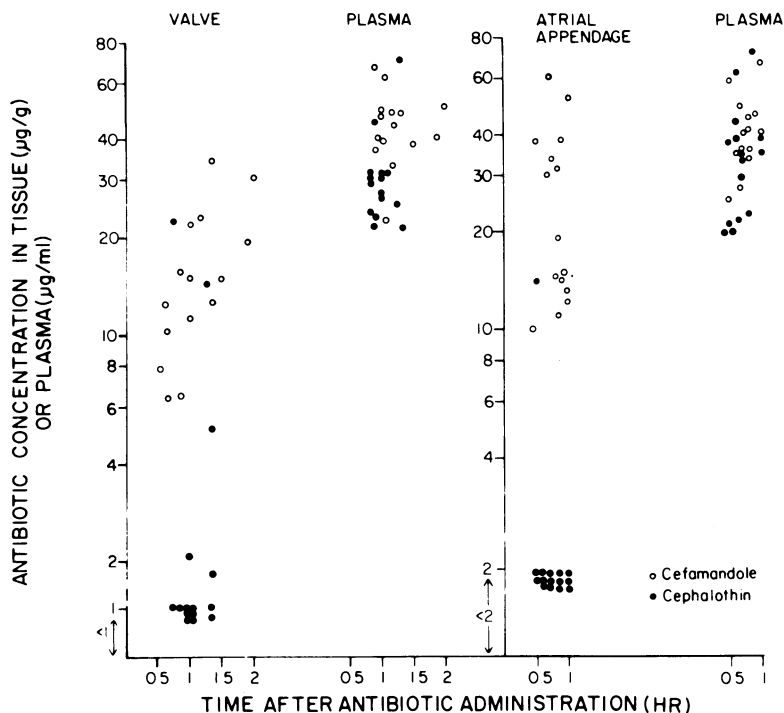


FIG. 1. Comparison of cephalothin and cefamandole tissue and concomitant plasma concentrations after the i.m. injection of 20 mg/kg to patients undergoing prosthetic valve insertions.

and $13 \pm 4.0\%$ for CP valve and atrial appendage tissues, respectively. All aortic valves were heavily calcified, whereas only one of the mitral valves contained any calcium. There was no difference in antibiotic concentration between calcified and uncalcified tissue.

Plasma bactericidal activity. The bactericidal activity of plasma obtained at the time of valve removal was tested against a panel of ten isolates of *S. epidermidis* and five isolates of *S. aureus* that had been recovered from the blood or tissue of patients with PVE. The titers were similar for patients receiving either CM or CP. The lowest titer of any plasma specimen against any bacterial isolate was 1:8, with the median titer 1:16 (range, 1:8 to 1:64).

Bacterial contamination during surgery. All valve ring swabs and pump blood cultures yielded no growth.

Infection and drug toxicity. There were no infections during the immediate postoperative period in any of the 30 patients in this study, nor has there been a case of endocarditis in any patient in over 6 months of follow-up since discharge.

Although three patients in the study gave a history of urticarial or maculopapular rashes after receiving penicillin (two CP and one CM),

none of the three had any signs or symptoms compatible with a drug reaction after receiving cephalosporins. These patients received both the study cephalosporin intraoperatively and CP instead of penicillin and nafcillin postoperatively. One patient with no allergic history developed a pruritic maculopapular rash 10 days postoperatively, but the offending drug could not be identified. There were mild abnormalities in renal and hepatic function during the postoperative period in most patients in the study. However, these are common in patients who have been on CPB and could not be directly attributed to any drug. No abnormalities persisted at the time of discharge.

DISCUSSION

The goal of antibiotic prophylaxis during cardiac surgery is to have antibacterial activity present at the site of potential bacterial contamination in sufficient concentration to prevent bacterial implantation and subsequent infection. Prevention of postoperative wound infections may be possible with appropriate antibiotic prophylaxis (14), but the major aim of prophylaxis is to prevent infection around the inserted prosthetic valve. In this study we have compared the properties of two cephalosporin antibiotics

which may influence their value as prophylactic agents. We also attempted to define the proper antibiotic dose and time of administration so that the concentrations of such drugs in plasma and tissue during surgery would be optimum. The study revealed the following.

First, the administration of 20 mg of either CP or CM per kg in the operating room during anesthesia induction produced high plasma levels ($\geq 20 \mu\text{g/ml}$) within 0.5 h which remained elevated throughout surgery. Plasma or serum levels of antibiotics administered "on call" or "on the morning of surgery" may be very low or undetectable during surgery, and thus contaminating organisms may gain access to and persist in tissues. Kluge et al. (11) measured $< 1 \mu\text{g}$ of CP per ml in plasma during surgery in 69% of patients who were begun on CPB more than 5 h after the last dose of CP. As a possible consequence of low antibiotic levels, contaminating organisms, particularly *S. epidermidis* and diphtheroids, were recovered from cardiac tissue in 71% of these patients (12). In contrast, during our study, with the administration of CM and CP in the operating room during anesthesia induction, there were no contaminating organisms cultured from pump blood or cardiac tissues during surgery, and serum inhibitory and bactericidal titers at the time of valve insertion were $\geq 1:16$ in 28 of 30 patients. The lowest antibiotic concentration at the end of CPB was $6 \mu\text{g/ml}$ after 5 h of surgery in one patient who received CP. This value is still many times the minimal inhibitory concentration of most contaminating staphylococci and diphtheroids (9, 17).

CM and CP levels fell less than 25% during a mean of 2 h on CPB. This was consistent with a recent study which suggested that elimination of CP was markedly slowed after patients were begun on CPB (21).

Second, CM levels were significantly higher than CP levels at all times sampled except at the end of bypass, even though the rate of decline in plasma antibiotic concentration was similar for the two drugs. The persistence of higher blood levels of CM than CP in normal volunteers after both i.v. and i.m. administration has been noted by others (5).

Levels of CM attained during CPB may also be affected by the route of administration. The CM levels during bypass obtained in this study after i.m. injection were compared with levels from patients undergoing coronary artery bypass surgery who received the drug as a 15-min i.v. infusion in a separate study; the doses and times of administration were the same for both routes. Although peak levels of i.v. CM exceeded peak i.m. CM levels, the plasma antibiotic concentra-

tions after 60 min on bypass were significantly higher with i.m. than i.v. administration ($38.5 \pm 11.6 \mu\text{g/ml}$ i.m.; $28.2 \pm 7.9 \mu\text{g/ml}$ i.v. [mean \pm SD]; $P < 0.01$ [16]). Higher levels may have been maintained after i.m. administration because of decreased tissue perfusion due to a fall in mean arterial pressure during bypass, resulting in slowed antibiotic absorption from injection sites.

Third, valve and atrial appendage levels of CM were at least three to five times higher than those of CP, based on comparisons of tissue antibiotic concentrations expressed as percentages of concomitant plasma levels. Although the presence of blood in atrial muscle might falsely elevate the absolute concentration of drug in such tissue, the use of tissue/plasma ratios makes comparisons of antibiotic tissue concentrations valid and suggests that cardiac tissue penetration by CM might be greater than by CP. The fact that a similar difference of concentrations also existed for valve tissue, which is avascular, further supports this contention.

The explanation for the higher tissue levels of CM than CP is not readily apparent. A recent study by Bergeron et al. (2) found an increased concentration of CM as compared with CP in subcutaneous fibrin clots implanted in rabbits; the amount of CM in clots as a percentage of serum levels was also higher for CM than CP. This difference was related to the presence in the serum of desacetylcephalothin, a metabolite of CP, which comprised 75% of the total serum antibiotic and penetrated clots poorly. An additional factor contributing to the difference was a shorter half-life of CP than CM. However, the role played by either of these factors in our study is questionable. The concentration of desacetylcephalothin in human serum is only 5 to 15% of the concentration of the parent drug (5). Unless there was competition for penetration or tissue binding sites between desacetylcephalothin and CP, the presence of the metabolite probably did not contribute significantly to the differences in tissue concentrations observed in our study. In addition, the half-lives of CP and CM before and during CPB in our study were similar. Protein binding may determine tissue penetration, but, since there is little difference in protein binding between CP (65%) and CM (67 to 74%) in humans (1), this is also not a likely explanation for higher CM tissue levels. The difference in penetration of CM when compared with CP may be related to physical characteristics of the CM molecule such as pK_a and lipophilia.

No additional bioactive or chromatographically detected CP was found in tissue after protein denaturation with trichloroacetic acid. This is in contrast to the finding of Kornguth and

Kunin (13), who demonstrated the release of large amounts of tissue-bound aminoglycosides from rabbit myocardium after trichloroacetic acid treatment. These results further suggest that the failure to detect CP in the tissues studied was due to poor penetration of the antibiotic and not to tissue binding after penetration had occurred.

Although it is not clear whether the penetration of antibiotics into cardiac tissue is important for prophylaxis to be effective, high concentrations of CM in the perivalvular area may provide continued bactericidal activity against implanted organisms after the valve is sewn into place. Furthermore, the penetration of CM into valves, many of them deformed and calcified, suggests that it may be a more effective cephalosporin than CP for treating endocarditis due to cephalosporin-susceptible organisms in the penicillin-allergic patient.

In summary, this study has shown that the i.m. administration of 20 mg of CM or CP per kg to patients undergoing prosthetic cardiac valve insertion gives sustained plasma levels that are maintained for up to 3.5 h on CPB. CPB does not diminish and, in fact, appears to prolong the duration of effective plasma levels of these cephalosporins. Because CM gives higher plasma levels after i.m. injection than CP, valve and atrial appendage levels are markedly higher with CM than with CP, and CM and CP show equal bactericidal activity in plasma against pathogenic staphylococci, CM may be a better antibiotic for prophylaxis during cardiac surgery than CP and should be evaluated clinically for potential superiority in treating bacterial endocarditis in penicillin-allergic patients.

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