Plasma cefazolin levels during cardiovascular surgery: Effects of cardiopulmonary bypass and profound hypothermic circulatory arrest

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Objectives: We sought to assess the effects of cardiopulmonary bypass and profound hypothermic circulatory arrest on plasma cefazolin levels administered for antimicrobial prophylaxis in cardiovascular surgery.

Methods: Four groups (10 patients per group) were prospectively studied: vascular surgery without cardiopulmonary bypass (group A), cardiac surgery with a cardiopulmonary bypass time of less than 120 minutes (group B), cardiac surgery with a cardiopulmonary bypass time of greater than 120 minutes (group C), and cardiac surgery with cardiopulmonary bypass and profound hypothermic circulatory arrest (group D). Subjects received cefazolin at induction and a second dose before wound closure. Arterial blood samples were obtained preceding cefazolin administration, at skin incision, hourly during the operation, and before redosing. Cefazolin plasma concentrations were determined by using a radial diffusion assay, with *Staphylococcus aureus* as the indicator microorganism. Cefazolin plasma concentrations were considered noninhibitory at 8 μg/mL or less, intermediate at 16 μg/mL, and inhibitory at 32 μg/mL or greater.

Results: In group A cefazolin plasma concentrations remained greater than 16 μg/mL during the complete surgical procedure. In group B cefazolin plasma concentrations diminished to 16 μg/mL or less in 30% of the patients but remained greater than 8 μg/mL. In group C cefazolin plasma concentrations decreased to less than 16 μg/mL in 60% of patients and were less than 8 μg/mL in 50% of patients. In group D cefazolin plasma concentrations reached 16 μg/mL in 66% of the patients but decreased to 8 μg/mL in only 1 patient.

Conclusions: For patients undergoing cardiac surgery with a cardiopulmonary bypass time of greater than 120 minutes, a single dose of cefazolin before skin incision with redosing at wound closure does not provide targeted antimicrobial cefazolin plasma levels during the entire surgical procedure. Patients undergoing profound hypothermic circulatory arrest are better protected, but the described protocol of prophylaxis is not optimal.

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Postoperative infection in cardiac surgical patients, mainly caused by *Staphylococcus aureus* and coagulase-negative staphylococci,[1] is a cause of major morbidity and mortality. According to the National Heart, Lung, and Blood Institute–National Institute of Allergy and Infectious Diseases Working Group, cardiovascular infections caused by *S aureus* are a serious national medical problem, with increases in the rate of *S aureus* bacteremia ranging from 122% to 283% in individual hospitals.[2]

Antimicrobial prophylaxis with cephalosporin is used routinely to reduce surgical infections after cardiovascular surgery. The use of cardiopulmonary bypass

Abbreviations and Acronyms
C_p = plasma cefazolin level
CPB = cardiopulmonary bypass

(CPB), particularly in conjunction with profound hypothermic circulatory arrest (PHCA), causes substantial profound perturbations in hemodynamics, end-organ blood flow, and temperature. Because of these changes and their influence on antibiotic pharmacokinetics, the following investigation was undertaken to determine the effect of CPB and PHCA on cefazolin plasma levels administered for antimicrobial prophylaxis in patients undergoing cardiovascular surgery.

Methods

After obtaining the approval of the Stanford Institutional Review Board and individual written informed consent, a total of 40 patients were prospectively enrolled in the study and assigned to the following groups: group A, 10 patients undergoing vascular surgery (no CPB); group B, 10 patients undergoing cardiac surgery with a CPB time of less than 120 minutes; group C, 10 patients undergoing cardiac surgery with a CPB time of greater than 120 minutes; and group D, 10 patients undergoing cardiac surgery with the use of CPB and PHCA (Table 1).

In groups B and C the target systemic (bladder) temperature was 28°C to 30°C. In group D the patients were systemically cooled during CPB to a tympanic membrane temperature of 20°C. During the PHCA period, selective antegrade cerebral perfusion was supplied through a right axillary artery cannula, with a flow of 10 mL/kg cold blood. Hydrocortisone (1 mg/kg), mannitol (0.5 g/kg), and thiopentone (15 mg/kg) were administered before the initiation of PHCA.

Other than the above mentioned differences, all participants received the same preoperative, operative, and postoperative care as nonparticipants.

Cefazolin, 1 g administered intravenously (first dose), was administered immediately after the induction of anesthesia, and a second dose was administered just before wound closure (second dose). In group A arterial blood samples drawn from a radial artery catheter were obtained before the first cefazolin dose, at skin incision, at every hour of surgical intervention, and just before the second dose of cefazolin. In groups B, C, and D additional samples were obtained before the initiation of CPB, every hour during CPB, and after weaning from CPB.

Blood samples were centrifuged, and serum was frozen to −80°C before analysis. The antibiotic plasma level (in micrograms per milliliter) of cefazolin (C_p) was then determined in vitro by using a biologic radial diffusion assay, with *S aureus* as the indicator organism.[3] Three levels of inhibition were identified: a C_p of 32 μg/mL or greater was targeted as inhibitory to *S aureus*, a Cp of 16 μg/mL was intermediate, and a C_p of 8 μg/mL or less was considered to be not inhibitory.

Data are reported as means (standard deviation) and incidence of observations, unless indicated otherwise. Differences between groups were analyzed by using analysis of variance. The Tukey method was used for multiple comparisons. For each surgical group, Kaplan-Meier actuarial estimates were calculated to quantify the time from cefazolin administration to a decrease in concentration to less than 32, 16, and 8 μg/mL; differences between curves were determined by using the log-rank test. All analyses were performed with S-PLUS version 6.2 software (Insightful Corp, Seattle, Wash).

TABLE 1. Types of operations by groups

Groups	Operations (n)
A	Abdominal aortic aneurysm repair (5)
	Thoracic aortic aneurysm (2)
	Aortofemoral bypass (2)
	Femoral-popliteal bypass (1)
B	Coronary artery bypass grafting (5)
	Aortic valve replacement (2)
	Mitral valve replacement (1)
	Tricuspid pulmonary valve replacement (1)
	Ascending aortic aneurysm (1)
C	Aortic valve and ascending aortic aneurysm replacement (4)
	Aortic, mitral, and tricuspid valve replacement (1)
	Aortic and mitral valve replacement (2)
	Aortic valve replacement and coronary artery bypass grafting (2)
	Thoracic aortic aneurysm (1)
D	Ascending aorta and arch replacement (5)
	Aortic valve, ascending aorta, and arch replacement (3)
	Thoracic aorta and arch replacement (2)

Results

The demographic data of the patients are presented in Table 2. One patient in group D was removed from analysis because of surgical complications, including severe hemorrhage. There was no difference in age, body mass index, or preoperative serum creatinine value between the groups. In group C the temperature reached a significantly lower level ($P = .01$), and the CPB time was significantly longer ($P < .01$) than in group B. There was no difference in mean surgical time between groups A and B or between groups C and D. CPB and surgical times were significantly longer in groups C and D ($P < .01$) compared with that in group B.

The plasma concentration time course of individual patients in each group is depicted in Figure 1. In group A C_p remained greater than 16 μg/mL during the complete surgical procedure. C_p diminished to 16 μg/mL or less in 30% of the patients in group B, in 60% of the patients in group C, and in 66% of the patients in group D. The Kaplan-Meier survival curves (Figure 2) show that in group C in 50% of the patients, C_p reached plasma levels of 8 μg/mL or less, and in group D this was true in 1 patient.

TABLE 2. Demographic data

Group (n)	A (10)	B (10)	C (10)	D (9)
Age (y)	66.9 ± 10.6*	57.8 ± 15.4	50.1 ± 16.8	62.0 ± 17.3
BMI (kg/m^2)	26.8 ± 4.7	24.5 ± 4.6	25.9 ± 4.2	24.8 ± 3.5
Creatinine	1.1 ± 0.2	0.9 ± 0.1	1.0 ± 0.4	1.0 ± 0.3
Male/female sex (n)	7/3	7/3	5/5	6/4
CPB time (min)	NA	109.4 ± 24.2	215.2 ± 75.7	216.7 ± 55.6
Surgical time (min)	245.5 ± 70.6	299.5 ± 70.0	447.5 ± 119.5	500.0 ± 104.0
Lowest temp (°C)	35.2 ± 0.4	30.8 ± 1.7	28.1 ± 2.3	21.2 ± 0.5

BMI, Body mass index; *CPB*, cardiopulmonary bypass; *temp*, bladder temperature. *Standard deviation.

Figure 2 shows the survival probabilities for concentrations greater than 32, 16, and 8 μg/mL. Differences between groups A, B, C, and D were not significant; however, there was a trend favoring a higher probability of concentrations greater than 32 μg/mL in group D ($P = .08$). In group A, B, C, and D the median time for concentrations greater than 32 μg/mL was 265, 210, 229, and 349 minutes, respectively. All patients in groups A and B had concentrations greater

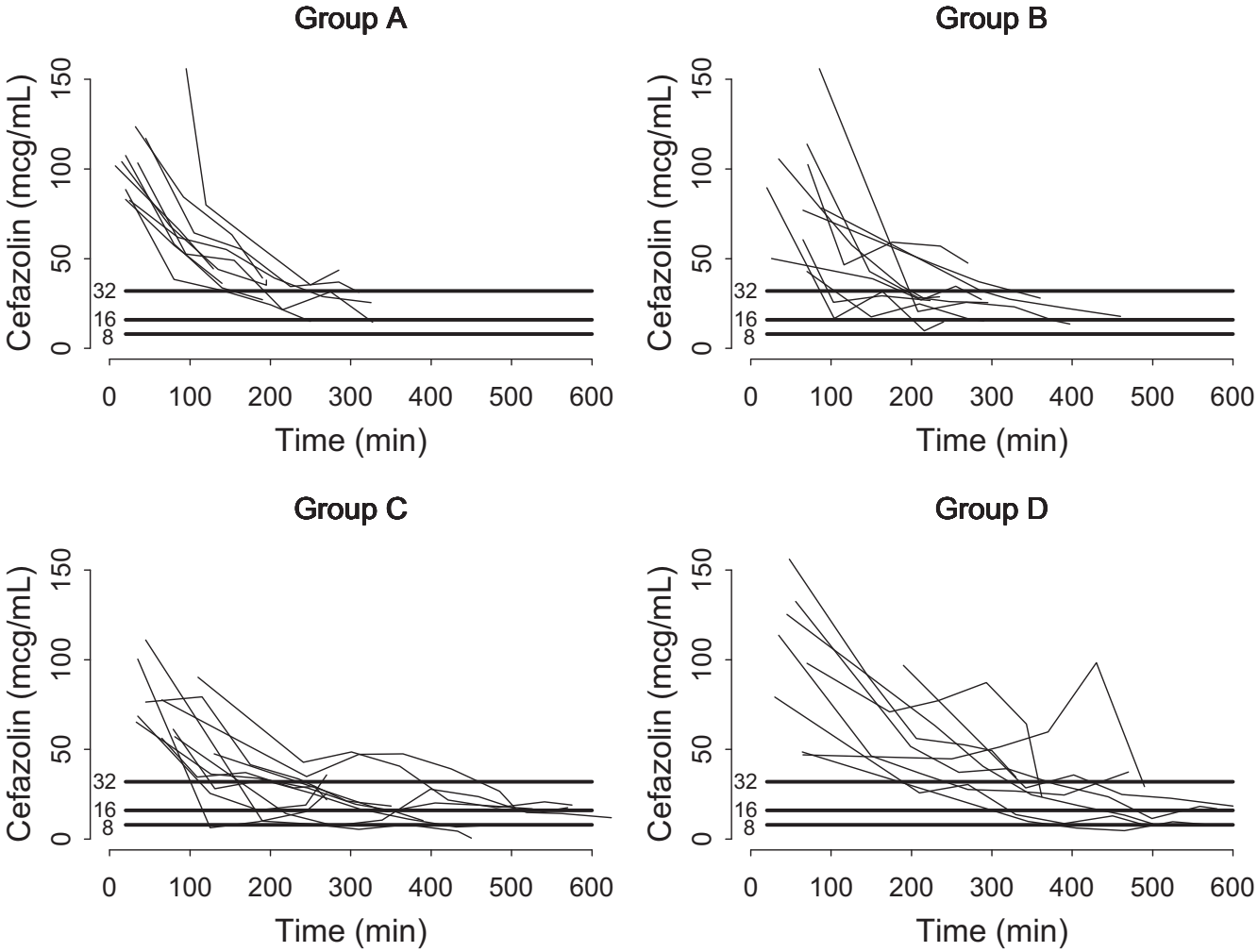

Figure 1. The cefazolin plasma concentration (C_p) time course of individual patients in each surgical group. A C_p of 8 μg/mL or less was considered to be not inhibitory, a C_p of 16 μg/mL was considered to be intermediate, and a C_p of 32 μg/mL or greater was considered to be inhibitory to *S aureus*.

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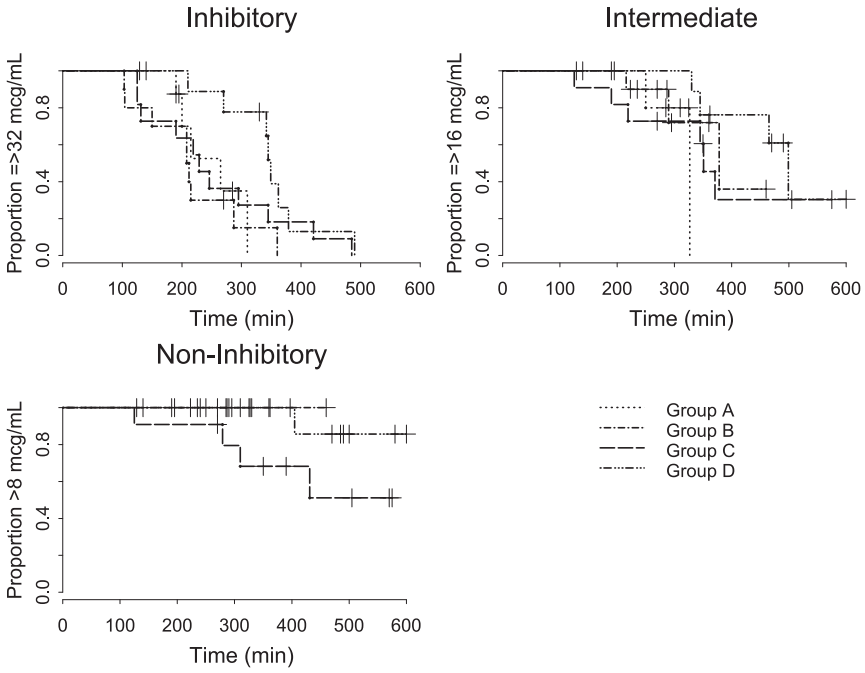

Figure 2. Kaplan-Meier survival curves for cefazolin concentrations greater than 32, 16, and 8 μg/mL in groups A, B, C, and D.

than the noninhibitory level (8 μg/mL); however, in group D the probability of concentrations of greater than 8 μg/mL was 86% compared with group C, in which the probability of concentrations greater than 8 μg/mL was only 51% before administration of the second dose of cefazolin.

Discussion

These observations demonstrate that C_p is not changed by CPB times of less than 120 minute with mild-to-moderate hypothermia, but in procedures requiring prolonged CPB time (>120 minutes) and PHCA, the dosing schedule used was not adequate to maintain targeted plasma concentrations of cefazolin.

The incidence of postoperative infection after cardiac surgery is reported to be between 7% and 18%, including deep sternal wound infections between 1% and 3%.[4] Infection is associated with increased morbidity, mortality (up to 20%),[5] hospital stay,[6] and costs.[7] Toumpoulis and colleagues[8] recently showed a 3-fold increase in 10-year mortality after initial recovery from deep sternal wound infection after coronary artery bypass surgery.

Cephalosporins, including cefazolin, are the most suitable prophylactic antibiotics because they are bactericidal, nontoxic, and active against the most common microorganisms, such as *S aureus*, *Staphylococcus epidermidis*, and *Enterobacter* species.[1,9] Cefazolin is 100% eliminated by the kidneys and 80% to 85% bound to protein.[10] Pharmacokinetic parameters of cefazolin have been determined during surgical intervention by using a model-independent method, showing an elimination half-life of 231 minutes, a total body clearance of 1.05 mL · kg^{-1} · min^{-1}, and a steady-state volume of distribution of 243 mL/kg.[11]

The prophylactic dosing schedule of cefazolin remains controversial. The recommended dose in vascular and uncomplicated cardiac surgery is 1 to 2 g administered intravenously every 8 hours for 24 to 48 hours,[12] although single preoperative dose prophylaxis is often used. Bucknell and associates[13] showed that a single dose of cefazolin, 1 g administered intravenously, before incision was as effective as redosing during 48 hours in cardiac surgery cases with a short CPB time (<120 minutes). In more prolonged procedures (surgical time >240 minutes) intraoperative redosing of cefazolin appeared to be effective in reducing surgical infection, in which the second dose of cefazolin is usually administered at fixed intervals,[14] instead of related to specific stages of the operative procedure, as in our study. Others administer a second dose of cefazolin immediately after the onset of CPB,[4] arguing that the physiologic changes associated with CPB might rapidly decrease the effective plasma level of the drug. Naziri and coworkers[15] proposed administering antibiotic prophylaxis continuously during surgical intervention to achieve constant plasma levels.

In our study the results show that the first dose of cefazolin was administered at the appropriate time before skin incision, as recommended,[16] and the C_p at incision time was inhibitory (≥32 μg/mL) in all patients. Our choice of redosing just before wound closure has not been reported elsewhere. Our argument is based on the notion that during

incision and skin closure, contamination of the wound is likely to occur. The reason for the timing of the last test sample was to verify whether our choice of redosing timing provided targeted plasma levels of cefazolin against microorganisms like *S aureus*.

Group A was the control group because CPB is not needed during vascular surgical operations and cephalosporin pharmacokinetics are predictable. This study showed that within the time period assessed for group A, cefazolin plasma levels stayed in the therapeutic range for the most common gram-positive organism causing postoperative infection, suggesting that patients are well protected against *S aureus* in accordance with earlier studies.[17] In the 3 remaining groups, CPB was used. The effects of CPB on the pharmacokinetics of cefazolin might include changes in volume of distribution and protein binding, mainly caused by a decreased temperature, hemodilution, and changes in organ perfusion.

Group B patients were comparable with subjects in earlier investigations, including a relatively short CPB time and mild hypothermia.[13] It is appropriate to compare group B with group A because age, body mass index, serum creatinine value, and surgical time were not statistically different. The results show that CPB with mild hypothermia does not change the plasma concentrations of cefazolin and that the dosing and timing schedule used kept the plasma cefazolin levels in the therapeutic range against *S aureus*. The renal clearance of cefazolin, although not measured, is apparently preserved, which might be due to the effect of hemodilution, compensating for the lower temperature.

CPB time has not been examined often in earlier studies because the length of the surgical procedure is considered to be a more important risk factor for postoperative infection.[14] Our approach of using a CPB time of greater than 120 minutes as risk factor is based on the premise that prolonged CPB might cause substantial organ dysfunction. This could lead to renal dysfunction and substantial fluid shifts. In group C, with statistically longer CPB and operative times (both $P < .01$) and a lower mean minimal temperature ($P < .01$) than in group B, the results showed that cefazolin plasma levels decreased to intermediate therapeutic levels in 60% of the patients and to ineffective levels in 50% of patients with respect to *S aureus* prophylaxis. This indicates that our choice of redosing time in this group of patients was suboptimal. A CPB time of 120 minutes is apparently a cutoff point, and the expected decrease in cefazolin excretion rate does not occur but instead follows the normal time scale, despite the lower temperature.

Patients undergoing PHCA (group D) have not previously been studied with respect to antibiotic prophylaxis. Although the mean CPB and operation times in groups C and D were not significantly different, only 1 patient in group D had a completely subtherapeutic (≤ 8 μg/mL) plasma level. Thus PHCA changes the pharmacokinetics of cefazolin considerably more than merely long CPB time, shifting the curve of the plasma level to the right. This indicates that excretion of cefazolin is delayed and that PHCA prolongs the duration of targeted cefazolin plasma levels.

Several alternative prophylactic treatments for groups C and D can be proposed, including a higher initial dose (according to body weight; ie, 30 mg/kg cefazolin), a second dose at the onset of CPB, or redosing every 240 minutes. It can be predicted that all these dosing schedules will improve the efficacy of prophylaxis in these patients, but randomized comparative studies should elucidate which prophylaxis regimen is optimal, particularly for patients requiring prolonged CPB time.

This study has several limitations. We did not measure tissue levels of cefazolin, as is recommended by others,[18] although tissue levels are reported to be directly related to cefazolin plasma levels.[19] It might even be unclear whether the laboratory technique measuring effective plasma levels is accurate to predict risk of infection because Maki and colleagues[20] observed 12% surgical wound infections after cardiac surgery in patients similar to our patients in group B in the presence of effective cefazolin plasma levels throughout surgical intervention. In our study surgical site infection was observed in 3 patients (1 in group B and 2 in group D), all with superficial infections and no cases of mediastinitis. Outcome studies with a larger number of patients would be needed to assess whether lower plasma levels of cefazolin in groups C and D actually correlated with a higher incidence of postoperative surgical site infections. Our choice for analyzing CPB time instead of surgical time as a discriminating factor can be criticized. It was mainly related to our routine to redose cefazolin at the start of wound closure and not to a fixed time interval.

We conclude that in patients undergoing long, complicated cardiac surgical procedures, our routine cefazolin prophylaxis schedule did not provide targeted plasma levels for all patients and that alternative techniques should be investigated, particularly in cardiac cases with moderate hypothermia and a prolonged CPB time.

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