Penetration of Vancomycin into Mediastinal and Cardiac Tissues in Humans

CLAUDE MARTIN,1* MAJED ALAYA,2 MARIE-NOELLE MALLET,3 XAVIER VIVIAND,1 KARIM ENNABLI,2 RACHID SAID,2 AND PHILIPPE DE MICCO3

Department of Anesthesia and Intensive Care, Hopital Nord, 1 and Department of Microbiology, Hopital Salvador, 3
13915 Marseilles Cedex 20, France, and Department of Anesthesia and Department of Cardiac Surgery, Hopital Sehoul, Sousse, Tunisia2

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Vancomycin penetration into heart tissues (valves, myocardium, auricles, and pericardium) and mediastinal tissues (fat and sternal bone) was evaluated after two regimens of vancomycin administration. Ten patients were given 15 mg of vancomycin per kg of body weight before anesthesia. Ten other patients received the same dose and then a second 7.5-mg/kg dose at the time of initiation of cardiopulmonary bypass. Similar and satisfactory vancomycin tissue penetrations were observed in both groups. However, for some patients in the two groups, vancomycin levels in tissue were less than the MICs for potential pathogens (Staphylococcus aureus and Staphylococcus epidermidis).

Cardiac surgery is a clean surgery but requires antibiotic prophylaxis to prevent serious postoperative infections of the cardiac valves or the mediastinal tissues (1). Antibiotic prophylaxis is used to protect against pathogens most likely to contaminate the surgical wound, that is, methicillin-resistant or susceptible staphylococci. Cephalosporins (cefazolin, cefamandole) are widely used for that purpose, but vancomycin is an alternative for prophylaxis in allergic patients or when a risk of postoperative infections because of methicillin-resistant staphylococci exists (6, 8). Vancomycin is characterized by a slow killing rate of bacteria, and this is particularly true for low levels of the drug (half the MIC) (16). Given this time dependency for bacterial killing, exposure of bacteria to antibiotic concentrations greater than the MIC for long periods of time seems desirable. For prophylaxis for postoperative infections, such adequate antibiotic concentrations should probably be achieved in all potential sites of infection (2, 13).

The present study was designed to determine whether two different dose regimens could result in the achievement and maintenance of adequate concentrations in sternal bone, mediastinal fat, and heart tissues. Levels in tissue greater than or equal to the MIC for 90% of methicillin-susceptible or resistant Staphylococcus aureus (1 μg/ml) and coagulase-negative staphylococci (2 μg/ml) tested (19) were considered adequate.

Subject and study design. The study received the approval of the Ethics Committee of our institution (Hopital Nord), and all patients gave informed consent. The study was prospective and randomized and was designed to compare the penetration of vancomycin after either a single (group 1) or two (group 2) intraoperative intravenous doses in patients undergoing mitral or aortic valve replacement. Twenty patients, divided into two groups of 10 patients each, were included in the study. Criteria for inclusion were as follows: 18 years of age or older, absence of prior history of hepatic or renal disease, elective surgery, and no clinical or laboratory signs of infection.

Antibiotic administration. Group 1 patients were given 15 mg of vancomycin (Eli Lilly & Co.) per kg of body weight administered intravenously over a 60-min period. Infusion was started 90 min before the surgical incision. Group 2 patients were given the same dose following the same protocol. A second dose of vancomycin (7.5 mg/kg over 30 min) was given immediately after the cardiopulmonary bypass (CPB) was instituted. In both groups, vancomycin (10 mg/kg over 60 min) was given at 8, 16, and 24 h after the first infusion.

Blood and tissue sampling. Blood samples (10 ml each) were collected from an arterial catheter and were centrifuged (800 × g for 20 min). Tissue samples were immediately rinsed in normal saline and were pressed in sterile gauze to eliminate contaminating blood. Serum and tissue samples were stored at −80°C until assay. Simultaneous blood and tissue samples were obtained, as follows: from the thorax opening (thoracic wall fat, sternal bone [a mixture of cancellous and cortical bone], and pericardium); during CPB (ventricular myocardium [cardiac apex or papillary muscle], a fragment of the resected valve, and a fragment of the right auricle); and at the time of thorax closure (pericardium, sternal bone, and thoracic wall fat). Additional blood samples were obtained at the following periods: before vancomycin infusion (control), 10 min after the end of vancomycin infusion (peak level), before the initiation of CPB, 10 min after the end of the second vancomycin infusion (group 2; second peak level), at the end of aortic cross-clamping, at the end of CPB, and on hour 8 (prior to the first postoperative vancomycin infusion).

Vancomycin assay. Vancomycin was assayed in plasma and tissues by a fluorescence polarization immunoassay (TDX; Abbott Laboratories). Tissue specimens were reduced to a fine powder with a SPEX 6700 crusher (SPEX Industries, Edison, N.J.). The frozen tissue fragments were pulverized under liquid nitrogen for 1 min. The resulting powder was taken up in phosphate buffer, and the mixture was shaken for 24 h at 4°C. The homogenate was centrifuged and filtered. Vancomycin was then assayed in the supernatant (Cs; in micrograms per milliliter) and was converted to the concentration of vancomycin in tissues (Cv; in micrograms per gram) by the equation $C_v = C_s \times V_s / W_s$, where $V_s$ is the volume of the supernatant and $W_s$ is the weight of the tissues sample (in grams). The sensitivity of the assay was 0.1 μg/g. Within-day and between-day reproducibilities were 7.1 and 8.2%, respectively, at 5
FIG. 1. Plasma vancomycin levels at different periods during the surgical procedures. Patients in group 1 received one intraoperative dose of 15 mg of vancomycin per kg. Patients in group 2 received a second dose of 7.5 mg/kg at the time of initiation of CPB (results are means ± standard deviations). T0, control, before vancomycin injection; T1, 10 min after the end of the first vancomycin infusion (71 ± 1 min); T2, opening of the thorax (101 ± 10 min); T3, initiation of CPB (126 ± 20 min); T4, 40 min after the initiation of CPB (10 min after the second vancomycin injection for patients in group 2) (156 ± 17 min); T5, end of aortic cross-clamping (173 ± 23 min); T6, end of CPB (195 ± 28 min); T7, thoracic closure, end of surgery (218 ± 29 min); T8, hour 8, before the first vancomycin postoperative injection (483 ± 2 min). *, P < 0.05 between the groups.

μg/ml, 3.9 and 5.2%, respectively, at 25 μg/ml, and 2.3 and 4.6%, respectively, at 75 μg/ml.

CPB. Anticoagulation was induced with heparin (300 IU/kg) and was monitored by the activated clotting time (over 400 s during CPB). The CPB pump (SARNS 9000; 3M Santé Laboratory, Malakoff, France) was primed with 500 ml of lactated Ringer solution, 500 ml of 14% bicarbonate, and 500 ml of dextran (molecular weight, 60,000). The pump flow rate was 2 liters/m², and blood was oxygenated with a membrane oxygenator (William Harvey, Bard). The mean blood pressure was maintained at about 80 mm Hg during CPB, and the core body temperature was decreased to approximately 28°C. Cardiac arrest was instituted by infusion of cold cardioplegia solution (hyperpotassic blood) into the aorta. A core body temperature of ≥34°C was required to achieve CPB. After CPB, heparin was neutralized with protamine (1.5 dose of protamine per dose of heparin).

Statistical analysis. Results are expressed as means ± standard deviations. Analysis of variance, t test with the Bonferroni correction, and the chi-square test were performed when appropriate. A P value of <0.05 was considered significant.

The two groups were matched for the studied parameters. In group 1 (10 patients), the mean age was 48 ± 10 years, the duration of CPB was 63 ± 9 min, and the duration of aortic cross-clamping was 37 ± 19 min. In group 2 (10 patients), the mean age was 43 ± 20 years, the duration of CPB was 76 ± 22 min, and the duration of aortic cross-clamping was 50 ± 14 min.

Vancomycin levels in plasma. Figure 1 shows the evolution of vancomycin levels in the plasma of both groups at different periods. Plasma vancomycin levels were strictly identical in the two groups until T3 (initiation of CPB). Peak levels (T1) were 34.2 ± 12.1 mg/liter in group 1 and 37.5 ± 10.5 mg/liter in group 2. At T3 (132 ± 17 min), patients in group 2 received a second infusion of vancomycin (7.5 mg/kg). A second peak of vancomycin (48 ± 12 mg/liter) was observed in group 2 at T4. From T4 to T7 (closure of the thorax), plasma vancomycin levels were significantly higher in group 2 patients than in group 1 patients (P < 0.05). At hour 8 after the first infusion (T8) both groups had similar plasma vancomycin levels (group 1, 6 ± 4.2 mg/liter; group 2, 9.8 ± 5.1 mg/liter). At that time, both groups received a second (group 1) or a third (group 2) vancomycin injection of 10 mg/kg and then similar injections at hours 16 and 24 after the first infusion.

FIG. 2. Penetration of vancomycin into mediastinal and cardiac tissues during cardiac surgery. Patients in group 1 received one intraoperative dose of 15 mg of vancomycin per kg. Patients in group 2 received a second intraoperative dose of 7.5 mg of vancomycin per kg at the time of initiation of CPB (results are means ± standard deviations). Fat, thoracic wall fat; stern, sternal bone; peric, pericardium; myoc, myocardium; endoc, resected valve; auric, auricle; MIC 90, MICs for 90% of isolates tested.
TABLE 1. Proportion of patients with vancomycin concentrations in tissues greater than or equal to the MIC90 for S. aureus and S. epidermidis testeda

<table>
<thead>
<tr>
<th>Sampling time and tissue</th>
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<tr>
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<td>Group 1</td>
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a Patients in group 1 received one intraoperative dose of 15 mg of vancomycin per kg. Patients in group 2 received a second intraoperative dose of 7.5 mg of vancomycin per kg at the time of initiation of CPB.

Vancomycin penetration in mediastinal and cardiac tissues.

Figure 2 shows the vancomycin concentrations in various tissues during surgery in both groups. During the beginning stages of surgery, before CPB, a higher level of drug penetration was observed in the pericardium than in thoracic wall fat and sternal bone. During the second period (CBP), similar vancomycin concentrations were achieved in the myocardium and auricle and concentrations in the resected valves were slightly lower. During the third period (end of surgery), the pattern of vancomycin penetration in tissues (pericardium, sternal bone, and thoracic wall fat) was similar to that observed during the first period. When the two regimens of vancomycin administration were compared, no significant difference between concentrations in tissue was observed. During the third period, concentrations in sternal bone and thoracic wall fat were higher in group 2 (7.1 ± 6.6 and 5.0 ± 4.6 μg/g, respectively) than in group 1 (4.6 ± 4.1 and 4.6 ± 3.0 μg/g, respectively), but this difference did not reach the level of significance (Fig. 2).

In both groups, the ratios of tissue concentrations/MICs for 90% of staphylococci (Staphylococcus aureus, 1 μg/g; Staphylococcus epidermidis, 2 μg/g) tested (MIC90) were calculated in order to evaluate the potential clinical efficacy of vancomycin concentrations achieved with both regimens of administration. Ratios were between 3 and 20. For S. aureus, the ratios were between 6 and 20, and for S. epidermidis, the ratios were between 3 and 10. When the two regimens of vancomycin administration were compared, no significant difference was observed between the ratios achieved during surgery. When tissues were compared, higher ratios (between 7.5 and 20) were achieved in the myocardium and pericardium (P < 0.05).

The proportion of patients with vancomycin concentrations in tissue that were greater than or equal to the MIC90 for S. aureus and S. epidermidis were calculated for both groups during the different periods studied. When the two regimens of vancomycin administration were compared, no significant difference was observed between the two groups (Table 1).

Previous studies have established the basic principles of antibiotic prophylaxis in surgical procedures, and the main points are (i) that the antibiotic must be present in the involved tissues before surgery, allowing bacterial contamination; and (ii) that the drug must attain and maintain concentrations in plasma and tissues high enough to inhibit the growth of contaminating pathogens (9, 17, 18). The present study confirms the effective penetration of vancomycin into human mediastinal and heart tissues. Concentrations in the heart valves, myocardium, and right auricle were high and in most cases greater than or equal to the MIC90 for usually susceptible pathogens. Furthermore, very satisfactory levels were also achieved in the pericardium, sternal bone, and thoracic wall fat. For instance, in sternal bone, vancomycin concentrations were 30 to 60% of the concentrations in plasma, confirming the results of a previous report (12). This penetration was greater than the 20 to 30% reported for cefazolin (14) and cefamandole (7). In most cases, these levels in tissue were also greater than the MIC90 for pathogens usually responsible for infections following cardiac surgery. Interestingly, similar levels of vancomycin penetration were achieved in the thoracic wall fat (a poorly vascularized tissue) and in the sternal bone at times of thoracic opening and closure as well. This is of great clinical interest, since mediastinal infections are among the most severe complications after cardiac surgery. This finding is true even when the usual modalities of surgical antibiotic prophylaxis which call for the immediate (less than 2 h) preoperative administration of the chosen drug are used (3, 4).

In the present study, we compared two regimens of vancomycin administration, and one group of patients (group 2) received a second intraoperative dose of 7.5 mg of vancomycin per kg at the time of initiation of CPB. To prevent such an effect, one of our groups received a second dose of vancomycin when CPB was started. This resulted in significantly higher plasma vancomycin levels in group 2 up to T7 (end of surgery). Levels in tissue were not different between the two groups during the period of CPB since cardiac tissues were excluded from the general circulation. After aortic unclamping, an increase (although nonsignificant) in plasma vancomycin levels was observed at T6 and T7. This was probably explained by the fact that upon rewarming and increased blood circulation, vancomycin returned to the intravascular volume from peripheral tissues, as well as from tissues which were isolated from the CPB circuit (10). This increase in plasma vancomycin levels in group 1 patients probably explained why the concentrations in tissue were not different between the two groups at the end of surgery.

Achieving and maintaining sufficient drug concentrations in tissues to avert the risk of postoperative infection are important goals when using antibiotics with a time-dependent efficacies, such as vancomycin. Optimal concentrations should be maintained throughout the surgical procedures. With vancomycin, efficacy is directly related to the time during which its concentration in target tissues exceeds the MIC for the offending organism. Little gain in the rate or extent of killing is obtained by increasing concentrations above that level.

In conclusion, the use of vancomycin at 15 mg/kg before cardiac surgery allowed us to achieve and maintain throughout
the operative procedures antibiotic concentrations in tissues greater than the MIC for *S. aureus* and *S. epidermidis* in most of the patients who we studied. In some patients, however, this dose regimen did not result in adequate concentrations in tissues. The use of a second intraoperative dose of 7.5 mg of vancomycin per kg at the time of institution of CPB resulted in higher levels in plasma, but penetration into tissue was not significantly improved. With both drug administration regimens that we tested, some patients remained at risk of postoperative infection.

REFERENCES