Weight-based versus set dosing of vancomycin for coronary artery bypass grafting or aortic valve surgery

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Objectives: This study was undertaken to identify a preferred dosing strategy for patients undergoing coronary artery bypass grafting or valve replacement procedures with cardiopulmonary bypass.

Methods: Patients undergoing coronary artery bypass grafting, valve replacement surgery, or both were randomly assigned to receive either standard 1-g dosing with vancomycin before and after cardiopulmonary bypass or a single weight-based 20-mg/kg dose before surgery. The primary outcome was the percentage of time plasma concentrations were greater than 15 μg/mL during cardiopulmonary bypass and at surgical closure. Secondary outcomes included concentration of vancomycin in endothoracic tissue after vancomycin infusion, average time patients had vancomycin concentrations greater than 15 μg/mL, and vancomycin plasma and tissue pharmacokinetic parameters.

Results: Baseline characteristics were similar between the study dosing group (n = 10) and the standard dosing group (n = 10). From postinfusion to end of bypass, the median percentage of time vancomycin concentrations remained greater than 15 μg/mL was 100% (interquartile range [IQR], 72.6%-100%) for weight-based dosing versus 43.7% (IQR, 28.7%-53.4%) for standard dosing ($P = .0005$). From postinfusion to surgical closure, the percentage of time vancomycin concentrations remained greater than 15 μg/mL was significantly higher in the weight-based group (100% [IQR, 58.3%-100%] vs 34.6% [IQR, 25.3%-41.6%]; $P = .0005$). Weight-based dosing increased calculated time with vancomycin concentrations greater than 15 μg/mL and resulted in higher endothoracic tissue vancomycin concentrations.

Conclusions: Weight-based vancomycin dosing before coronary artery bypass grafting or valve replacement results in vancomycin concentrations greater than 15 μg/mL consistently more than does standard 1-g dosing. (J Thorac Cardiovasc Surg 2014;147:1925-30)

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Surgical site infections (SSIs) are estimated to add $1.6 billion annually to health care costs and are no longer being covered by Medicaid after coronary artery bypass grafting (CABG) procedures.[1] With high national rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and reimbursement incentives to avoid SSIs, hospitals commonly add vancomycin for prophylaxis in cardiac surgical procedures. One SSI study found an average per case cost for MRSA infection of $13,901 and a mortality rate of 20.7% for MRSA infection versus 6.7% for methicillin-sensitive *S aureus*.[2] By adding prophylactic vancomycin and mupirocin for carriers of MRSA, one study group was able to reduce wound infections after cardiac surgery by 93%.[3] There is no consensus regarding vancomycin use for prophylaxis; however, the clinical practice guidelines for antimicrobial prophylaxis in surgery recommend against the routine use of vancomycin prophylaxis in cardiac surgery unless the patient has a β-lactam allergy or proven MRSA colonization.[4] The overall hospital-wide rate of MRSA among *S aureus* isolates at our institution is 38%, and this has been consistent for the last 5 years. The Society of Thoracic Surgeons guidelines state that for institutions with a high incidence of MRSA or patients with a high risk of MRSA infection, vancomycin would be a reasonable addition for prophylaxis during cardiac surgical procedures (class IIB recommendation, level of evidence C).[5] The same guidelines suggest either a weight-adjusted dose of 15 mg/kg or a fixed dose of 1 to 1.5 g within 60 minutes of surgical incision.[5]

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Abbreviations and Acronyms

$AUC_{0\text{-end}}$ = area under the concentration-time curve from time 0 to the end of the dosing interval
C_{max} = maximum drug concentration in plasma
CABG = coronary artery bypass grafting
CL_s = systemic clearance
CPB = cardiopulmonary bypass
IQR = interquartile range
MIC = minimum inhibitory concentration
MRSA = methicillin-resistant *Staphylococcus aureus*
SSI = surgical site infection
V_d = volume of distribution

Patients undergoing CABG or aortic valve replacement procedures are supported by cardiopulmonary bypass (CPB), which leads to volume shifts. These shifts, combined with the stress response of surgery, cause physiologic and pharmacokinetic alterations both during and after surgery. During CPB, the patient experiences hemodilution, hypothermia, hypotension, reduction in regional blood flow, and trauma, which causes an acute increase in the volume of drug distribution, reduction in drug clearance, and alteration of protein binding.[6,7] These changes lead to alterations in vancomycin plasma and tissue concentrations with resultant variations in pharmacodynamic target attainment during cardiac surgery.

Our study aimed to compare a weight-based dosing strategy with the standard dosing strategy and to gain further understanding of the pharmacokinetics of vancomycin during CPB, as well as to evaluate endothoracic tissue concentrations 30 minutes after the end of vancomycin infusion.

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MATERIALS AND METHODS

This study was conducted between January 2011 and June 2011 at the University of Colorado Hospital and was approved by the Colorado Multiple Institutional Review Board. Written, informed consent was obtained from all patients. The data were collected and analyzed by the investigators.

Study Patients

Patients between the ages of 18 and 89 years who were scheduled to undergo CABG, valve replacement surgery, or both and who did not meet any of the exclusion criteria were eligible for this study. Exclusion criteria included patient allergy or hypersensitivity to vancomycin, impaired renal function (creatinine clearance less than 40 mL/min according to the Cockcroft-Gault equation), and inability to provide consent. Perioperative infusion-related adverse effects of vancomycin were monitored until the morning after surgery.

Treatment Assignments

Patients were randomly assigned after consent to receive either a standard 1-g dose of vancomycin with a second 1-g dose to be given after CPB, or a 20-mg/kg initial dose of vancomycin determined by actual body weight with a maximum dose of 2 g. Body weights and laboratory values were obtained the morning of surgery. The vancomycin dose was prepared by the study investigators and given to a nurse for administration. The dosing was not blinded and was known by everyone involved in the surgery. The initial vancomycin dose was infused during the course of 90 minutes and was completed shortly before incision. In addition, patients from both arms were administered cefazolin for prophylaxis according to hospital protocol.

Blood and Tissue Collection

As many as 5 blood samples (5 mL) were drawn throughout the surgery for determination of vancomycin concentrations. The first blood sample was collected after the infusion of the first dose of vancomycin. A second sample was collected 15 minutes after the start of CPB, with a third sample collected 45 minutes after the start of CPB. A fourth blood sample was drawn after the end of CPB. This blood sample was immediately sent to the hospital clinical laboratory for analysis. Patients in the weight-based group who had a vancomycin concentration less than 15 μg/mL were given an additional 1-g dose of vancomycin immediately. The patients in the weight-based group with a plasma vancomycin concentration greater than 15 μg/mL were not given a second dose until 12 hours after the initial dose, as part of the 3 postoperative vancomycin doses per hospital protocol. All patients in the standard dosing group received a second 1-gram vancomycin dose after the end of CPB during surgical closure. For patients assigned to the weight-based group who did not require an immediate second vancomycin dose, a fifth sample was obtained approximately 2 hours after the fourth sample to assist with the pharmacokinetic analysis. In addition to the blood sampling, a single sample of endothoracic fascia was collected at the surgeon's discretion, with a target of 30 minutes after the conclusion of the first vancomycin infusion.

After the pharmacokinetic analysis, patients of both arms of the study were then placed on a regimen of vancomycin 1 g every 12 hours for a total of 3 postoperative doses of vancomycin according to hospital protocol. For patients in the 20-mg/kg dose arm who did not require a second dose, 1 g of vancomycin was administered 12 hours after the first dose.

Sample Storage and Analysis

Plasma was obtained from whole blood samples not immediately analyzed by the hospital laboratory. Plasma and endothoracic tissue samples were stored at -80°C until analysis. Vancomycin concentrations were determined in the plasma and homogenate by means of liquid chromatography–mass spectrometry. The method used an Applied Biosystems Sciex 4000 (Applied Biosystems, Foster City, Calif) equipped with a Shimadzu HPLC (Shimadzu Scientific Instruments, Inc, Columbia, Md) and Leap auto-sampler (LEAP Technologies, Carrboro, NC). Liquid chromatography used a Zorbax extended-C8 50 $\times$ 4.6-mm column, 5-μm particle size (Agilent Technologies, Inc, Santa Clara, Calif), equipped with a C8 column guard and operated at 40°C with a flow rate of 0.4 mL/min. The mobile phase consisted of solvent A, 10-mmol/L ammonium acetate and 0.1% formic acid in water, and solvent B, 50:50 acetonitrile and methanol. Between samples, the auto sampler was washed with a 1:1:1:1 mixture of acetonitrile, methanol, isopropyl alcohol, and water containing 0.1% formic acid. The chromatographic method used was 95% solvent A for 0.50 minutes, brought to 40% solvent B at 5.00 minutes and held for 1.00 minutes, ramped to 95% solvent B at 7.00 minutes and held for 1.00 minutes, then brought back to 95% solvent A at 8.50 minutes and held for 1.00 minutes (9.50 minutes total run time).

Human serum (control) was used to prepare standard curves and quality control samples. These samples were extracted and processed in an analogous fashion as the in vivo samples. An extraction solution containing internal standard (ceftazidime) was freshly prepared in a 100-mL volumetric flask containing a 2:1 (vol/vol) mixture of 1:1 acetonitrile and methanol and water. In individual sets, the samples were removed from the freezer where they had been stored at -80°C $\pm$ 10°C and allowed to thaw on ice for 40 to 45 minutes. The tubes were vortex mixed for 5 seconds, and a sample (250 μL) was transferred to an Eppendorf tube (1.5 mL) and mixed with extraction solution (500 μL), vortex mixed for 5 seconds, set