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Effect of Cardiopulmonary Bypass on Vancomycin and Netilmicin Disposition

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The effect of cardiopulmonary bypass (CPB) on the disposition of vancomycin (15 mg/kg) and of netilmicin (3 mg/kg) was studied in 10 adults. The concentration-time profile of the drug in serum and renal clearance were characterized pre-CPB, during CPB, and post-CPB. Vancomycin and netilmicin exhibited initial decreases in mean concentrations in serum of 4.0 mg/liter (16.8%) and 2.2 mg/liter (29.1%), respectively, upon initiation of CPB. Netilmicin concentrations in serum rebounded to a mean of 0.6 mg/liter (15.4%) within 90 min on CPB and then continuously decreased. Vancomycin concentrations in serum demonstrated a rebound increase of 2.3 mg/liter (23.5%) at the end of CPB when the aorta was unclamped. Mean renal clearance throughout CPB was decreased for vancomycin (58.4 to 43.4 ml/min per m^2) and netilmicin (53.4 to 31.5 ml/min per m^2). The rebound in vancomycin concentration in serum strongly correlated with the length of time between unclamping the aorta and coming off CPB ($r = 0.94$), as well as with the increase in temperature upon rewarming ($r = 0.92$).

Antimicrobial prophylaxis for cardiopulmonary bypass (CPB) surgery is routinely prescribed to prevent endocarditis or sternal and costochondral infections (7, 26). Selection of an appropriate antibiotic is directed against *Staphylococcus aureus* and *Staphylococcus epidermidis*, which account for the majority of bacterial infections, and also against the gram-negative bacilli (2, 3, 7, 26). The increasing incidence of methicillin-resistant staphylococci has led to the recommendation that vancomycin be administered prophylactically for cardiothoracic surgery in hospitals in which methicillin-resistant staphylococci are prevalent (3, 15, 16). Aminoglycosides have been recommended for prophylaxis against the gram-negative pathogens on the cardiac valves and the sternum and for some prophylactic effect against staphylococci (16).

Many physiologic changes occur in patients placed on CPB. These changes, including decreased cardiac output and organ perfusion, can alter drug absorption, distribution, metabolism, and excretion (13, 14). Studies with prophylactic vancomycin and netilmicin in CPB surgery are very limited. Only two reports have examined vancomycin concentrations in serum during CPB surgery, and both sought to determine appropriate dosing, rather than drug disposition (4, 10).

One published report of aminoglycoside prophylaxis in open-heart surgery has addressed netilmicin concentrations in pericardial fluid, atrial appendage, and serum but only in the intraoperative phase of CPB (27). Therefore, this study was designed to investigate what effect CPB surgery has on the disposition of two renally excreted prophylactic antibiotics, vancomycin and netilmicin, before, during, and after CPB.

MATERIALS AND METHODS

A total of 10 adult patients scheduled for elective coronary artery bypass grafting or cardiac valve replacement surgery requiring CPB were studied. All patients gave written informed consent to participate in this protocol, which was approved by the University Institutional Review Board. Patients included for data analysis did not undergo multiple cardiothoracic procedures, require intra-aortic balloon pump assist, or receive antibiotics within the preceding 24 h. Those patients scheduled for coronary artery bypass grafting were maintained on nitrates, beta-blockers, or calcium channel blockers, while those patients scheduled for valve replacement were maintained on digoxin and diuretics. All cardiac and antihypertensive medications were continued through the morning of surgery, while all other medications were discontinued 12 to 24 h before surgery. Volume status, renal and hepatic function tests, and routine biochemical tests were within normal limits before CPB.

All patients were premedicated with 10 mg of oral diazepam, 0.1 mg of intramuscular morphine sulfate per kg, and 0.4 mg of intramuscular scopolamine approximately 1 h before anesthesia. At 30 to 60 min before CPB was initiated, anesthesia was induced with 50 μg of fentanyl per kg, with or without 0.5 to 1% isoflurane inhalation anesthesia, and maintained with 100% oxygen and additional doses of fentanyl and vecuronium. Monitoring lines were established and included two-lead electrocardiogram (leads I and V5), arterial catheter, Swan-Ganz catheter, end-tidal-CO_2, tympanic and rectal temperature probes, and Foley catheter.

Each patient received, through the central venous catheter, vancomycin (1,000 mg diluted in 250 ml of 5% glucose in water over 1 h via a controlled-infusion device) and netilmicin (3 mg/kg in 50 ml of 5% glucose in water over 30 min). Netilmicin and vancomycin infusions ended a mean of 1.75 ± 0.9 and 1.0 ± 0.5 h, respectively, before CPB.

CPB was conducted in the standard fashion with a Shiley S-100A HED oxygenator with integral heat exchanger and a Sarns 5000 extracorporeal pump. The routinely monitored CPB parameters included myocardial temperature, core temperature, CPB flow rate, cardioplegia volume, hemoconcentrator volume, and CPB pump priming volume. The mean pump prime volume was 2.0 liters and consisted of 1.8 liters of Plasma-lyte A injection with 50 meq of sodium bicarbonate, 100 ml of albumin (25%), and 50 ml of mannitol (12.5 g). Heparin, 300 IU/kg of body weight, was injected

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before insertion of the aortic and vena caval cannulae. The aorta was cross-clamped (AoX on) to provide a quiet, flaccid, bloodless heart, and hyperkalemic cardioplegic solutions, 1,000 to 2,000 ml, were infused (19). CPB involved moderate hypothermia (27 to 28°C), when pump flow rates were 1.7 to 1.8 liters/min per m^2, mean arterial pressures were 55 to 65 mm Hg, and hemodilution was used to maintain a hematocrit of 25%. Rewarming was started, and then the aortic cross-clamp was removed (AoX off) to resume total cardiac perfusion. The heparin anticoagulant effect was monitored by the activated clotting time and neutralized with protamine at the completion of CPB. Clot formation was evaluated by using thromboelastography after normalization of the activated clotting time. The patients were allowed to recover spontaneously from neuromuscular blockade over the course of that evening. Ventilation was controlled for 18 to 24 h after surgery.

All blood samples were drawn from systemic arterial catheters. Pre-CPB samples (n = 3 to 5) were collected immediately postinfusion, approximately 30 min postinfusion, and every 30 min thereafter until the patient was placed on CPB, with one sample always obtained just before placement on CPB. Intra-operative samples (n = 5 to 8) were collected immediately after placement on CPB and every 30 min thereafter. Post-CPB samples (n = 3 to 4) were drawn immediately after CPB, 1 hour after CPB, and just before the first maintenance dose. A mean of 13 blood samples per patient were collected during the study period, with a minimum of three samples in each of the phases.

Urine was collected for determining vancomycin and netilmicin renal clearance by sampling from a Foley catheter placed in the bladder of the patient at the time of anesthetic induction. The urine collection schedule consisted of 2-h timed intervals, beginning at the start of the antibiotic infusions and continuing for a total of 24 h. Duplicate samples were retained for analysis.

The exact sampling time for both blood and urine collections was recorded and used in the pharmacokinetic analysis of data. Blood samples were allowed to clot and were then centrifuged to separate the serum. The serum samples, as well as the urine samples, were frozen at −70°C until assayed. At the time of analysis, the serum and urine samples for each patient were allowed to thaw at room temperature and were analyzed on the same day.

The assay procedure for vancomycin concentration in serum and urine used an automated fluorescence polarization immunoassay (TDx; Abbott Laboratories, Diagnostic Div., Irving, Tex.). The respective intra- and interday coefficients of variation for the assay with replicate samples (n = 6) were 3.7 and 4.9% at 7.5 mg/liter, 4.7 and 6.1% at 35 mg/liter, and 3.8 and 5.5% at 75 mg/liter. The sensitivity of the assay was 0.6 mg/liter. Vancomycin concentrations in the urine samples were determined by using a modification of the assay for vancomycin in serum. The urine samples were initially diluted 1:17 with distilled water and were then analyzed by the same assay procedure. Urine samples which contained ≤200 mg of vancomycin per liter were reassayed by using a 1:5 dilution with distilled water. Three control samples of vancomycin, 200, 500, and 1,000 mg/liter, were prepared in drug-free urine and analyzed with each assay. The respective concentrations for these control samples from six assay runs over a 3-month period, reported as the mean ± the standard deviation [SD]), were 211.2 ± 7.2, 516.9 ± 23.2, and 980.9 ± 55.6 mg/liter. The intra- and interassay coefficients of variation for replicate control samples (n = 6) were less than 4.0 and 6.0%, respectively. Cross-reactivity between numerous agents and the vancomycin assay has been reported as <1% (25).

Netilmicin concentrations in serum and urine were determined by the enzyme-multiplied immunoassay technique (EMIT with Stasar III spectrophotometer; Syva Company, Palo Alto, Calif.). The respective intra- and interday coefficients of variation for the assay with replicate samples (n = 6) were 2.7 and 2.3% at 4.0 mg/liter and 2.3 and 1.9% at 8.0 mg/liter. Netilmicin concentrations in the urine samples were determined by using a modification of the assay for netilmicin in serum. The urine samples were initially diluted 1:17 with distilled water and were then analyzed by the same assay procedure. Urine samples which contained ≤50 mg of netilmicin per liter were reassayed by using a 1:9 dilution with distilled water. Two control samples of netilmicin, 50 and 150 mg/liter, were prepared in drug-free urine and analyzed with each assay. The respective concentrations for these control samples (n = 10), reported as the mean ± SD, were 53.8 ± 1.3 and 157.1 ± 2.6 mg/liter, respectively. The intra- and interday coefficient of variation for the assay with replicate control samples was less than 3.0% at both concentrations. Cross-reactivity with the netilmicin assay had not been observed previously (28).

Pharmacokinetic parameters for vancomycin and netilmicin total-body clearance and the apparent volume of distribution at steady state (V_{ss}) were calculated by the model-independent method. The total body clearance of the drug was obtained by dividing the dose by the area under the concentration-time curve (AUC) from 0 to infinity. The V_{ss} was determined by dividing the product of the dose and the area under the first moment of the concentration-time curve (AUMC) from 0 to infinity by AUC^2 from 0 to infinity. Both AUMC and AUC were approximated by the linear trapezoidal rule to the last measured drug concentration in serum. The calculation of the residual areas for both AUC and AUMC required a value for the elimination rate constant estimated by linear regression from the terminal postdistributive phase of the concentration-time curve. Linear regression analysis was also used to estimate the concentration of vancomycin and netilmicin in serum from each individual patient at the following times: postinfusion, pre-CPB, CPB, and post-CPB. Vancomycin concentrations in serum at AoX on and at off-CPB are measured concentration-time data. The renal clearance was determined by dividing the amount of antibiotic excreted unchanged in the urine during the collection interval by the area under the curve for that interval. Data were analyzed by linear regression to determine the relationship between drug concentration in serum versus time data and CPB monitoring parameters. Analysis of variance was used to evaluate differences in renal clearance pre-CPB, during CPB, and post-CPB.

RESULTS

The four women and six men studied ranged in age from 42 to 73 (mean ± SD = 59.8 ± 10.4) years, with five undergoing valvular heart surgery and five undergoing coronary artery bypass surgery. Patient characteristics included the following: normal body indices of weight, 66.9 ± 14.3 kg; height, 64.4 ± 5.1 in. (1 in. = 2.54 cm); and body surface area, 1.72 ± 0.23 m^2. Renal indices were also within normal limits and included serum creatinine of 1.1 ± 0.3 mg/dl, blood urea nitrogen of 20.4 ± 6.8 mg/dl, and calculated creatinine clearance of 57.2 ± 18.3 ml/min (5).

Routine surgical events in the 10 study patients included hypothermia to a mean core temperature of 28.3°C, a net

TABLE 1. Vancomycin and netilmicin concentrations in serum over the time course of CPB[a]

Drug	Dose (mg/kg)	Concn in serum (mg/liter)				
		Postinfusion	Pre-CPB	CPB	AoX off	Post-CPB
Vancomycin (n = 10)	15.8 ± 3.2	53.8 ± 36.1	23.3 ± 10.1	19.3 ± 8.5	14.0 ± 5.9	16.3 ± 5.6
Netilmicin (n = 10)	3.0 ± 0	11.0 ± 1.5	7.1 ± 3.2	4.9 ± 2.1	4.6 ± 1.5	4.2 ± 1.4

[a] Data are mean ± SD.

increase of 2 liters of fluid (input of pump prime and cardioplegia volume minus the hemoconcentrated volume), a mean cardiac index of 1.57 liters/min per m^2, and mean arterial pressure of 54.2 mm Hg. The total CPB time was 157 ± 49 min, with the aorta being cross-clamped for 88 ± 26 min. The time between unclamping the aorta and off-CPB was 32.8 ± 18.7 min.

The drug concentrations in serum during CPB for vancomycin and netilmicin were >5.2 and >2.4 mg/liter, respectively. Throughout the entire 8-h study interval, the respective vancomycin and netilmicin mean trough drug concentrations in serum were 9.5 ± 2.4 and 2.4 ± 0.5 mg/liter, and the lowest trough concentrations were 6.2 and 1.6 mg/ml, respectively. The mean concentrations for vancomycin and netilmicin in serum at specific perioperative times during CPB are shown in Table 1. Vancomycin and netilmicin exhibited an initial decrease in the mean drug concentration in serum of 4.0 mg/liter (16.8%) and 2.2 mg/liter (29.1%), respectively, upon initiation of CPB. Netilmicin concentrations in serum rebounded a mean of 0.6 mg/liter (15.4%) within 90 min on CPB and then continuously decreased. Vancomycin concentrations in serum demonstrated a rebound increase of 2.3 mg/liter (23.5%) at the end of CPB when the aorta was unclamped.

The actual pharmacokinetic parameters calculated are summarized in Table 2. The AUC and V_{ss} reported for both vancomycin and netilmicin are similar to those reported in the literature for patients not undergoing CPB (6, 24). Vancomycin and netilmicin demonstrated a decrease in renal clearance during CPB, although there was not a statistically significant difference ($P > 0.05$) between the three phases.

Vancomycin. The disposition of vancomycin during the perioperative period of CPB began with an abrupt decrease in drug concentration in serum (mean of 4.0 mg/liter, 16.8%) upon initiation of CPB. The drug concentration in serum continued to steadily decline during CPB until the aorta was unclamped. Aortic cross-clamping divided the disposition during CPB into two distinct phases (AoX on and AoX off). During rewarming, which corresponds to the time between unclamping the aorta (AoX off) and the termination of CPB, a progressive rise in vancomycin concentration in serum occurred (mean of 2.3 mg/liter, 23.5%). This increase in vancomycin concentration in serum strongly correlated with the degree of temperature elevation (r = 0.92) (Fig. 1) and the length of time allowed for rewarming (r = 0.94; $y = 0.71x - 7.19$; $P < 0.001$). During CPB, renal vancomycin clearance had decreased approximately 30% from that calculated pre-CPB (Table 2). In the post-CPB phase, drug concentrations in serum continued to decrease, while renal clearance increased and returned to that observed pre-CPB.

Netilmicin. The disposition of netilmicin throughout the perioperative period of CPB demonstrated a similar sharp decrease in mean drug concentration in serum of 2.2 mg/liter (29.1%) upon initiation of CPB. Mean drug concentrations in serum immediately pre-CPB were 4.9 ± 2.1 mg/liter and demonstrated a rebound increase to 5.5 ± 2.1 mg/liter (15.4%) within 30 to 90 min into CPB, which gradually and continuously decreased thereafter. During CPB, renal netilmicin clearance decreased from a pre-CPB rate of 53.4 to 31.5 ml/min per m^2. Post-CPB drug concentrations in serum continued to decrease, while renal clearance began to increase toward pre-CPB rates.

DISCUSSION

Vancomycin and netilmicin are antibiotics which are renally excreted, primarily through glomerular filtration. Our study demonstrated different concentration-time profiles for both agents in serum during CPB. First, vancomycin and netilmicin concentrations initially decreased when the patient was placed on CPB. The sharp fall in the drug concentration in serum for both vancomycin and netilmicin (16.8 ± 11.3% and 29.1 ± 3.6%, respectively) with the onset of CPB has been described for other drugs (1, 21, 22). Theories proposed to account for the decreased drug concentrations in serum include hemodilution, protein binding changes, tissue distribution, and sequestration in CPB apparatus (10, 18).

In our study, the dilutional effect of CPB was estimated as a percentage of total volume as suggested by Koren et al. (17). Total volume was calculated by adding the priming volume to an assumed blood volume of 80 ml/kg of body weight (8). The mean dilutional effect of the priming volume was 26.3%, while the apparent decrease in drug concentration in serum observed was 16.8% for vancomycin and 29.1% for netilmicin. Hemodilution alone may not account entirely for the changes observed with netilmicin.

Protein binding could be an additional factor accounting for the changes observed in drug concentrations in serum

TABLE 2. Vancomycin and netilmicin pharmacokinetic parameters over the time course of CPB[a]

Drug	AUC (mg · h/liter)	V_{ss} (liter/kg)	CL[b] (ml/min per 1.73 m^2)	CL_R[c] (ml/min per 1.73 m^2)		
				Pre-CPB	CPB	Post-CPB
Vancomycin (n = 10)	199.0 ± 59.7	0.49 ± 0.17	91.6 ± 25.9	58.4 ± 35.3	43.4 ± 29.5	72.5 ± 38.8
Netilmicin (n = 10)	52.8 ± 11.1	0.37 ± 0.17	64.2 ± 10.1	53.4 ± 18.9	31.5 ± 23.9	38.5 ± 22.2

[a] Data are mean ± SD.
[b] CL, Clearance.
[c] CL_R, Renal clearance.

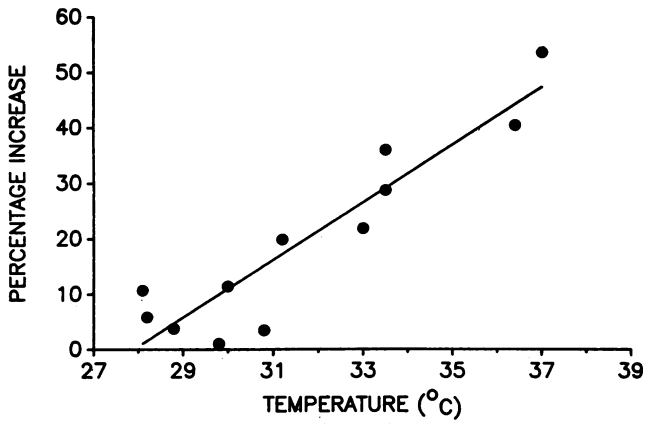

FIG. 1. Correlation between the whole body temperature after unclamping the aorta and post-CPB versus the percentage increase in vancomycin concentrations in serum. The linear regression is: $y = 5.19x - 144.94$ ($r = 0.92$; $P < 0.001$).

during CPB for vancomycin, which is 30 to 60% protein bound, but is unlikely for netilmicin, which is less than 10% protein bound (16, 29, 30). However, retrospective protein binding studies could not be performed, because temperature and storage conditions of the serum affect unbound drug concentrations and the concentrations of free fatty acid (23). We hypothesize that hemodilution and the initial changes in albumin concentrations could partially explain the decrease in vancomycin concentration at the beginning of CPB but not the increases observed after aortic cross-clamping.

Tissue distribution is another explanation, since the drug distributes to the lung and peripheral tissues until CPB is begun. Although actual tissue samples were not obtained, it is known that netilmicin, like other aminoglycosides, distributes primarily to the extracellular fluid compartments (12, 30). Since the initial decrease in netilmicin concentration rebounded within 90 min (mean of 48 min) into CPB, a dilutional effect is more likely than a distributive effect. In contrast, vancomycin distributes to the extracellular and the intracellular spaces (11, 12). The vancomycin concentrations continued to progressively decline after the initial drop from CPB, which we hypothesize to be due to vancomycin distribution into tissues, since it did not rebound as netilmicin did.

Lastly, drug sequestration within the CPB circuit is a possibility and has been demonstrated by Koren et al. (17) for fentanyl and by Dasta et al. (9) for nitroglycerin. We are currently conducting investigations to determine the possibility and extent of sequestration of vancomycin and netilmicin within the CPB apparatus.

A second important observation, besides the initial decrease in concentrations in serum secondary to CPB initiation, was a dramatically different time course for the rebound in drug concentration in serum observed for both vancomycin and netilmicin. Netilmicin concentrations in serum rebounded a mean of 0.6 mg/liter (15.4%) within 90 min into CPB. Throughout the remainder of the CPB phase, drug concentrations in serum slowly declined, despite a 44% decrease in renal netilmicin clearance. Vancomycin did not demonstrate a rebound increase until the aorta was unclamped. Reperfusion of blood and rewarming of the patient followed release of the aortic cross-clamp. The strong correlation demonstrated between the increased vancomycin concentrations in serum and the length of time allowed for rewarming ($r = 0.94$) and the actual temperature elevation ($r = 0.92$) support the theory of vancomycin tissue redistribution. The steady increase in drug concentration in serum occurred despite a 30% reduction in renal vancomycin clearance observed between pre-CPB (58.4 ± 35.3 ml/min per 1.73 m^2) and CPB (43.4 ± 29.5 ml/min per 1.73 m^2). This would suggest that diminished perfusion (mean flow rate of 1.57 ± 0.16 liter/min per m^2) with a diluted blood volume allows for greater permeability and distribution of vancomycin to tissue sites. Upon rewarming and increased blood circulation (AoX off), vancomycin returned to the intravascular volume from these sites, as well as from tissues which were isolated from the CPB circuit, since mean drug concentrations in serum rose from 14.0 ± 5.9 to 16.3 ± 5.6 mg/liter. This was not observed with netilmicin, since the drug distributes poorly to extravascular sites but is influenced by intravascular volume changes. A similar redistribution phenomenon (rebound) has been reported with vancomycin after hemofiltration (20). However, this is the first report to identify a rebound at the time of reperfusion and rewarming. Studies during CPB specifically addressing drug rebound with AoX off are needed to confirm this occurrence.

The two findings of a decrease in drug concentration in serum at the initiation of CPB and subsequent rebound during different stages of CPB were reconfirmed in all patients by examining the individual concentration-time data of the drug in serum. Despite the changes observed during CPB, the pre-CPB concentration-time data aligned with the post-CPB concentration-time data. We postulated this was due to the rebound in drug concentration in serum observed during CPB with and after aortic cross-clamping. Although further analyses are necessary, significant changes in the concentration-time profile for vancomycin and netilmicin in serum occur during CPB.

In summary, both vancomycin and netilmicin exhibited an initial decrease in drug concentrations in serum upon initiation of CPB. Netilmicin concentrations in serum rebounded early into CPB; however, in contrast, vancomycin demonstrated a rebound increase toward the end of CPB when the aorta was unclamped. The rebound in netilmicin concentration in serum did not correlate with any one factor from those routinely monitored during the procedure and could not be entirely accounted for by hemodilution. The rebound in vancomycin concentration in serum did correlate with the length of time between unclamping the aorta and coming off CPB, as well as with the increase in temperature upon rewarming. The data suggest that vancomycin exhibits a tissue redistribution due to CPB; however, further studies examining vancomycin concentrations in actual tissue during the three phases of CPB need to be conducted.

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