Vancomycin plasma concentrations in cardiac surgery with the use of profound hypothermic circulatory arrest

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Abstract

Objective: This study was undertaken to compare the effect of deep hypothermic circulatory arrest, compared with moderate hypothermia, on the plasma concentrations and pharmacokinetic profile of vancomycin, administered as prophylaxis, in patients undergoing cardiac surgery with cardiopulmonary bypass. Methods: Two groups of adult cardiac surgery patients were prospectively studied. One group consisted of 12 patients undergoing valvular surgery with moderate hypothermia, and another group was of 12 patients undergoing surgery with the use of profound hypothermic circulatory arrest. Vancomycin was administered before skin incision, and plasma levels were measured at regular intervals for 24 h. Results: The plasma concentrations of vancomycin showed a similar pattern in both groups. The pharmacokinetic profile showed a three-compartment model in both groups. Conclusion: The dosing of vancomycin, if used as antibiotic prophylaxis, does not need to be adjusted in cardiac surgery patients when undergoing profound hypothermic circulatory arrest, since the plasma concentrations and pharmacokinetic profile are similar to patients with moderate hypothermia. The pharmacokinetic profile, consisting of three compartments, was not changed by the differences in temperature.

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1. Introduction

Antibiotic prophylaxis is a mainstay in the prevention of surgical wound infection. In cardiac surgery, cephalosporins are routinely given, but in case of penicillin allergy alternative antibiotics such as clindamycin or vancomycin are used [1]. In conditions where a high prevalence of methicillin-resistant Staphylococcus aureus (MRSA) exists, vancomycin is preferred. In patients undergoing cardiac surgery with the use of profound hypothermic circulatory arrest (PHCA) the pharmacokinetic profile of antibiotics may be different than in those requiring only moderate or mild hypothermia, as was recently shown in a study from this institution [2]. We present the first study of the pharmacokinetic profile of vancomycin in patients undergoing PHCA.

2. Materials and methods

Two groups of 12 elective adult cardiac surgery patients were selected for this prospective study, which was approved by the Institutional Review Board of Stanford University. Written informed consent was obtained from all patients. Group A consisted of patients undergoing uncomplicated aortic and valve surgery with the use of cardiopulmonary bypass (CPB) and moderate hypothermia; group B consisted of patients undergoing complicated aortic and valve surgery with the use of CPB and PHCA because the aortic arch had to be repaired or replaced. All patients had normal preoperative renal function. In the PHCA group, the patients were systemically cooled, aiming at a tympanic temperature of 20 °C. Before circulatory arrest, mannitol 0.5 mg kg⁻¹ and furosemide 0.5 mg kg⁻¹ were administered, as well as thiopental 30 mg kg⁻¹ and hydrocortisone 1.5 mg kg⁻¹ for neurologic protection. During circulatory arrest, selective antegrade cerebral perfusion (SACP) was employed through either a graft anastomosed to the axillary artery or a graft attached to the innominate artery at a flow rate of 10 ml kg⁻¹ min⁻¹ cold blood.

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Anaesthetic and surgical techniques were standardised. Both bladder and tympanic temperatures were simultaneously recorded. The CPB circuit was primed with a 20 ml kg\(^{-1}\) solution of crystalloid and albumin in a 4:1 volume ratio. After insertion of a radial artery catheter, a blood sample was collected for the assessment of the vancomycin plasma concentration (control value), followed by the infusion of vancomycin, 15 mg kg\(^{-1}\) IV over 30 min by means of an infusion pump. Blood pressure and heart rate were continuously monitored during the infusion, watching for any signs of hypotension or tachycardia. Arterial blood samples were collected at 5, 10, 15, 30 and 60 min after finishing the infusion, and just before the start of CPB, 5, 10, 15, 30, 60, 120 and 180 min on beginning CPB, at the end of CPB, at the end of the surgical procedure, and in the Intensive Care Unit 24 h after the control value was assessed.

Surgical incision was performed within 60 min after the administration of vancomycin in all patients, as recommended [3]. In both groups, the lowest bladder temperature was recorded, as well as CPB time, aortic clamp (AC) time and SAPC time. Vancomycin plasma concentrations were determined with the use of high-performance liquid chromatography [4].

2.1. Statistical analysis

Data are reported as median (interquartile range). Continuous variables were compared by the Wilcoxon test. Categorical variables were compared by Fisher’s exact test or Pearson’s chi-square test. A non-linear mixed-effect modelling approach (NONMEM version VI.2, NONMEM Project Group, ICON Development Solutions, USA) was used to perform the population pharmacokinetic analysis using the first-order conditional estimation (FOCE) method and the interaction option. Inter-patient variability was modelled exponentially and a proportional error model was used to account for the residual variability. The initial step in the modelling process was the definition of a basic structural model without covariates. One-, two- and three-compartment models were tested. Model parameters were clearances and volumes of distribution. Model selection was based on the precision of the parameter estimates and visual inspection of the scatter plots of observed concentrations versus population and individual predictions and residuals versus population predictions and time. A decrease of 3.84 in the objective function (-2 log likelihood) provided by NONMEM was considered statistically significant for the addition of one parameter (\(P < 0.05\)). Then, the covariate effects of moderate or deep hypothermia, total body weight, lean body weight and creatinine clearance were examined. Creatinine clearance was calculated with the Cockcroft–Gault equation. Lean body weight was calculated using the equations of Jammahasation et al. [5]. Each covariate was added individually to the base model. Thereafter, covariates with a significant effect were added one by one, starting with the one with the largest drop in the objective function and was included in the model if a significant increase in the objective function was obtained. Backward elimination was then performed where each covariate was independently removed from the model. An increase in the objective function value (\(\Delta\) log likelihood) provided by NONMEM was considered statistically significant for the addition of one covariate (\(P < 0.05\)). Then, the covariate effects of

Table 1.

<table>
<thead>
<tr>
<th>Patient demographic data.</th>
<th>Moderate hypothermia ((N = 12))</th>
<th>Profound hypothermia ((N = 12))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>11/1</td>
<td>9/3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.0 (36.5–73.0)</td>
<td>52.5 (49.2–64.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.7 (77.2–85.7)</td>
<td>84.0 (66.0–94.2)</td>
</tr>
<tr>
<td>CrCl (ml min(^{-1}))</td>
<td>58.3 (51.1–80.7)</td>
<td>61.4 (44.2–74.4)</td>
</tr>
<tr>
<td>Lowest bladder temp (°C)</td>
<td>28.1 (27.6–29.9)</td>
<td>22.5 (20.5–23.8)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>231 (193–264)</td>
<td>260 (214–288)</td>
</tr>
<tr>
<td>Aortic clamp time (min)</td>
<td>166 (124–197)</td>
<td>180 (138–224)</td>
</tr>
<tr>
<td>SAPC time (min)</td>
<td>33 (29–37)</td>
<td></td>
</tr>
</tbody>
</table>

All data are presented with (SD). CrCl: creatinine clearance; CPB: cardiopulmonary bypass; SAPC: selective antegrade cerebral perfusion. Data: median (interquartile range).

* Significant difference (\(P < 0.05\)) between the groups.

Fig. 1. Vancomycin plasma concentration versus time profiles for individual patients. Cp: plasma concentration.

function 6.7 (\(P < 0.01\)) was used to confirm that the covariate was significant.

3. Results

Table 1 shows the demographic parameters of the patients in the moderate and deep hypothermia group. Except for a difference in bladder temperature, there were no significant differences between the groups. The pharmacokinetic analysis included 381 vancomycin plasma concentrations. The plasma concentration versus time profile for each individual patient is shown in Fig. 1. There were no differences in vancomycin plasma concentrations between the moderate and deep hypothermia group in the period pre-CPB, during CPB, and post-CPB (Fig. 2). A three-compartment model best fit the data (Fig. 3). The calculated volume of distribution was 76 l, and elimination half-life was 16.7 h. Total clearance was 82 ml min\(^{-1}\). Of the covariates, lean body mass had a significant effect (\(P < 0.002\)) on clearance\(_1\) (CL\(_1\)), but not on the other model parameters shown in Table 2.
for the prevention of surgical wound infection [6]. Cephalosporins, in particular cefazolin, are recommended as first choice [1]. In case of cephalosporin or penicillin allergy, clindamycin or vancomycin is preferred [7], and in conditions of a high likelihood of colonisation with MRSA, vancomycin is chosen as alternative or additional antibiotic agent [7–9]. Since in some intensive care units, MRSA has been the most frequently isolated micro-organism after cardiac surgery [10], vancomycin has been used more frequently. This has recently shown to be effective in the reduction of postoperative surgical site infections [11].

It is recommended to infuse vancomycin over a period of 60 min to avoid adverse reactions such as hypotension, maculopapular erythema (‘Red-Man’ syndrome), and bronchospasm [12]. In our study, we have chosen for a controlled 30 min infusion time for practical reasons, without observing any adverse reactions. Vancomycin is a soluble glycopeptide antibiotic with 55% binding to protein, and is 90% excreted unchanged by the kidney. The therapeutic range of vancomycin administered intravenously is commonly reported as a peak level of 20–40 μg ml⁻¹ and a trough level of 5–10 μg ml⁻¹ [13].

More recent studies were unable to show that greater vancomycin trough concentrations improved outcome [14]. The pharmacokinetic profile of vancomycin has been studied earlier in cardiac surgery patients, but only those under mild or moderate hypothermia. Vancomycin elimination half-life was 8–9 h, volume of distribution was 51 l, and a total clearance of 78 ml min⁻¹ [15–17] was reported. A significant increase in its volume of distribution is reported during CPB [17]. In almost all previous studies, a steep decrease of plasma level is observed after the start of CPB, which is attributed not only to haemodilution but also to sequestration of vancomycin in the bypass circuit [16]. Only one report found a small, but significant increase, followed by a steady decrease in vancomycin concentration [18]. Our observations in the moderate hypothermia group were concordant with these earlier reports [15]. The volume of distribution was larger, and elimination half-life was longer, mainly because our sampling times were longer. We were particularly interested in the changes in vancomycin plasma concentrations in patients undergoing cardiac surgery with PHCA, since the blood flow to the kidneys is temporarily interrupted during circulatory arrest. It is possible that collateral blood flow from the antegrade cerebral perfusion is responsible for some residual renal blood flow during PHCA, but this was not assessed in this study.

We speculated that circulatory arrest, in combination with a very low body temperature, may lead to an increase in plasma levels, which could justify an adjustment of dosing and timing of ensuing antibiotic administration. Our results show that PHCA does not significantly change the pharmacokinetic profile of vancomycin. There may be several explanations for this phenomenon, including adequate renal protection mainly due to profound hypothermia, perhaps also by the administration of mannitol and furosemide, although their role in protecting the kidney from acute injury is controversial [19,20]. Hyperaemia after reperfusion and warming could contribute as well. This leads to the conclusion that adjustment in dosing regimen of vancomycin for procedures using PHCA is not justified in the presence of a normal renal function.

Table 2
Pharmacokinetic model parameters.

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (l)</td>
<td>6.9</td>
</tr>
<tr>
<td>V2 (l)</td>
<td>10.2</td>
</tr>
<tr>
<td>V3 (l)</td>
<td>59.2</td>
</tr>
<tr>
<td>CL1 (l min⁻¹)</td>
<td>0.063 + 0.002* (LBW-60)</td>
</tr>
<tr>
<td>CL2 (l min⁻¹)</td>
<td>0.559</td>
</tr>
<tr>
<td>CL3 (l min⁻¹)</td>
<td>0.201</td>
</tr>
</tbody>
</table>


* Significant effect (P < 0.05) of LBW on CL1.

4. Discussion

These results show that the pharmacokinetic profile of vancomycin in patients undergoing cardiac surgery with PHCA is similar to that in patients who undergo operation with moderate hypothermia. Antibiotic prophylaxis is important for the prevention of surgical wound infection [6]. Cephalosporin prophylaxis is important for the prevention of surgical wound infection [6].


References


