Pharmacokinetics and tissue penetration of vancomycin continuous infusion as prophylaxis for vascular surgery

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Objectives: To determine the tissue penetration of vancomycin into perivascular fat and arterial wall during a continuous infusion of vancomycin, given as prophylaxis for vascular surgery.

Patients and methods: Patients undergoing arterial reconstruction requiring antibiotic prophylaxis were included. Patients received a loading infusion of vancomycin the evening prior to surgery followed by a continuous 24 h infusion, calculated according to renal function. Three peri-operative serum samples and intra-operative perivascular fat and arterial wall samples were collected for vancomycin assay.

Results: Twenty-eight patients were included. Three serum samples were obtained from all patients, fat samples were available from 27 (96.4%) patients and vessel wall samples were available from 23 (82.1%) patients. Serum vancomycin concentrations were maintained within a relatively narrow range, while fat and arterial wall concentrations were highly variable.

Conclusions: This study has shown that prophylactic administration of vancomycin with a loading infusion followed by a continuous infusion before and during vascular surgery achieves serum and vascular tissue concentrations that are above the MICs for most common organisms implicated in post-operative graft infection. However, penetration into perivascular fat tissues is poor.

Keywords: glycopeptides, surgical prophylaxis, tissue distribution

Introduction

Prosthetic graft infection following vascular surgery is a feared and potentially life-threatening event that complicates 3%–5% of such procedures.1 The most common pathogens are staphylococcal species, with methicillin-resistant Staphylococcus aureus (MRSA) a particular concern.2,3 Antibiotic prophylaxis for vascular surgery requiring prosthesis is routine practice.4 Vancomycin is recommended in institutions with high levels of MRSA.5

It has been shown that a loading infusion of vancomycin over 2–2.5 h followed by a continuous intravenous infusion for 24 h offered a practical approach to maintaining target serum concentrations of vancomycin during and after vascular surgery.6 However, it was not clear whether adequate tissue concentrations would be achieved with this approach. The present study was therefore conducted to determine the vancomycin concentrations achieved in perivascular fat and arterial wall during a continuous infusion of vancomycin.

Methods

Patients undergoing arterial surgery requiring a prosthetic graft or patch were eligible for inclusion. The study was approved by the NHS Research Ethics Committee and the local Research and Development group. Written consent was obtained from all patients following verbal and written explanations of the study. The night before their scheduled surgery, all patients were given a loading infusion of 1000 mg of vancomycin over 2 h if they weighed <70 kg or 1500 mg over 2.5 h if they weighed ≥70 kg. This was immediately followed by a constant rate infusion of 500–2500 mg, calculated according to renal function,7 which was maintained for 24 h. The exact dosing protocol has previously been described.8

Three blood samples were withdrawn during the surgical procedure: first, at induction of anaesthesia; second, during tissue sampling; and third, at the end of the procedure. A sample of perivascular fat and arterial wall was taken during the procedure by the operating surgeon. If a specimen of vessel wall was not obtainable, then a sample of fat alone was taken. The blood samples were centrifuged and the serum frozen.

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in secure storage. The tissue samples were rinsed with sterile saline, dried and frozen intact.

The serum and tissue samples were batch analysed at the end of the study (D. G. W. and T. Z.). Extraction procedures were as follows. Tissue samples were weighed, then homogenized with 2 mL of 0.1% formic acid containing internal standard (atenolol). Fat samples (250 mg) were added to 2 mL of 0.1% formic acid containing internal standard, then the solution was sonicated at 50 °C for 15 min. Both samples were then centrifuged at 7000 rpm for 5 min and the supernatant was filtered before solid phase extraction. A highly sensitive method for determination of vancomycin concentration by liquid chromatography–tandem mass spectrometry was applied for both the serum and tissue analysis. The assay was validated for extraction of vancomycin from serum. However, due to the small quantities of material extracted at the time of operation, validation of the tissue samples was not possible. The method was linear, in the range 0.05–10 mg/L, with a limit of quantification (LOQ) of 0.005 mg/L and a limit of detection (LOD) of 0.001 mg/L. Intra-day precision was ±3.5%, ±2.5% and ±0.7% at 0.05, 0.5 and 5 mg/L, respectively. Inter-day precision was ±7.6%, ±6.4% and ±3.9% at 0.05, 0.5 and 5 mg/L, respectively. The recovery for vancomycin was in the range of 89.2%–98.1%, with recovery for the atenolol internal standard being 97.3%.

Results
Vancomycin concentration data were available from 28 patients. The mean (range) age of the patients was 68 years (42–83 years) and the mean (SD) weight was 72.7 kg (17.1 kg), ranging from 38 to 108 kg. The mean (SD) estimated creatinine clearance was 66.5 mL/min (24.5 mL/min) and ranged from 21 to 127 mL/min. Fifteen patients (53.6%) underwent carotid surgery, seven (25.0%) patients had a lower limb bypass and to 127 mL/min. Fifteen patients (53.6%) underwent carotid surgery, seven (25.0%) patients had a lower limb bypass and six patients (21.4%) underwent aortic surgery.

Three blood samples were taken from all patients (n = 28) over a median period of 2 h (range 0.8–5 h). The first sample was taken 8.7–15.5 h (median 12.8 h) and the last was taken 10.5–19 h (median 14.8 h) after the start of the infusion. Serum concentration–time profiles during the infusion were essentially flat, with a mean (SD) vancomycin concentration of 12.2 mg/L (3.2 mg/L) (Table 1). Variability in the three concentration measurements was less than 15% in 79% of patients (n = 22); concentrations accumulated during the sampling period in four patients, fluctuated in one patient and declined in one patient. Although the serum concentrations were maintained within a relatively narrow range, both fat and arterial wall concentrations were highly variable. Samples of perivascular fat were taken at a mean (SD) of 14.3 h (1.7 h) after the start of the infusion; concentrations were available from 27 patients and ranged from 0.32 to 7.35 mg/kg. Vessel wall sampling was not possible in five patients. Concentrations in the vessel wall were significantly higher than those in subcutaneous fat [95% confidence interval (CI) of the mean difference 2–5.3 mg/kg] and ranged from 1 to 16 mg/kg. Table 1 summarizes the concentration data and Figure 1 shows the raw results.

Ratios of tissue to serum concentration are summarized in Table 1. In most cases, samples of fat or vessel wall were taken within 10 min of the serum sample; however, six fat samples and five vessel wall samples were taken at the midpoint between two serum samples. This was due to operative difficulties in sampling fat and vessel at the same time. In these cases, the mean of the serum sample concentrations was used for comparison. The average ratio for fat was 0.22 and the average ratio for vessel wall was 0.5.

Discussion
This study examined concentrations of vancomycin in subcutaneous fat and vessel wall during vancomycin prophylaxis by continuous infusion for surgical prophylaxis. To our knowledge, this is the first study to examine the tissue penetration of vancomycin in patients undergoing vascular surgery and the first to do so using continuous vancomycin infusion rather than bolus administration.

Vancomycin is known to distribute well into most body spaces and fluids, although penetration into the CSF is low unless the meninges are inflamed. Cruciani et al. found ratios of lung to serum vancomycin concentrations ranging from 0 to 1.1 at various times after a single dose of 1000 mg. The mean ratio was 0.41 at 12 h after the dose, which is similar to the mean tissue-to-serum ratio of 0.50 for vessel wall (range 0.09–1.2) in the present study. However, lung tissue concentrations were generally below the MIC breakpoint value of 4 mg/L beyond 3 h after an intermittent infusion and the authors suggested that administration by constant rate infusion might be a better approach.

The penetration of vancomycin into capsular and pericapsular tissue was investigated by Luzzati et al. in patients undergoing breast surgery. They found that although tissue concentrations were low or undetectable 1 h after the end of a 1000 mg infusion, they were above the breakpoint value of 4 mg/L in most patients 4–8 h post-dose. Tissue-to-serum ratios at 8 h ranged from 0.5 to 1.48 in capsular tissue and 0.7 to 2.8 in pericapsular tissue. In the present study, 61% of patients had vessel wall concentrations >4 mg/kg at the time of sampling.

In cardiac surgery, Martin et al. compared serum and cardiac tissue concentrations of vancomycin in a group of patients who received a single dose of 15 mg/kg before surgery with those who received an additional 7.5 mg/kg after the start of

Table 1. Summary of vancomycin serum and tissue concentrations and ratios from samples taken during vascular surgery

<table>
<thead>
<tr>
<th></th>
<th>Number of samples</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum concentration (mg/L)</td>
<td>84</td>
<td>12.2</td>
<td>3.2</td>
<td>11.0</td>
<td>6.8</td>
<td>23.1</td>
</tr>
<tr>
<td>Fat concentration (mg/kg)</td>
<td>27</td>
<td>2.41</td>
<td>1.85</td>
<td>1.80</td>
<td>0.32</td>
<td>7.35</td>
</tr>
<tr>
<td>Fat-to-serum ratio</td>
<td>27</td>
<td>0.216</td>
<td>0.185</td>
<td>0.153</td>
<td>0.024</td>
<td>0.862</td>
</tr>
<tr>
<td>Vessel wall concentration (mg/kg)</td>
<td>23</td>
<td>5.93</td>
<td>4.21</td>
<td>5.07</td>
<td>1.02</td>
<td>16.0</td>
</tr>
<tr>
<td>Vessel wall-to-serum ratio</td>
<td>23</td>
<td>0.498</td>
<td>0.335</td>
<td>0.463</td>
<td>0.086</td>
<td>1.18</td>
</tr>
</tbody>
</table>
cardiopulmonary bypass (CPB). Despite achieving higher serum concentrations in the second group, there were no significant differences in tissue concentrations. The authors commented that exclusion of cardiac tissue during CPB and the redistribution phenomena following discontinuation of CPB might have contributed to this finding. Concentrations were similar in thoracic wall fat and sternal bone, but higher in pericardial tissue, and achieved values above the MIC90s of *S. aureus* (1 mg/L) and *Staphylococcus epidermidis* (2 mg/L) in 72%–100% of patients, depending on group, time and sampling matrix. In the present study, vessel wall concentrations were also higher than fat concentrations. In tissue, concentrations were >2 mg/kg in 78% of patients and >1 mg/kg in all patients, but in fat, only 44% of concentrations were >2 mg/kg and 85% were >1 mg/L. Vancomycin tissue concentrations during cardiac surgery were also investigated by Kitzes-Cohen et al., following a single dose of 15 mg/kg over 1 h. Before the start of CPB, concentrations in sternal cortex and marrow and in skin were similar, at around 10 mg/kg, but fat concentrations were lower (4–6 mg/kg). During and after CPB the ratios of tissue to serum concentration ranged from around 1.6 to 2.1 for pericardium and atrium through 0.2 to 1.4 for skin and 0.2 to 0.4 for fat.

The impact of multiple doses of vancomycin was investigated in two further studies conducted in cardiac surgery patients. Massias et al. administered 10 mg/kg by infusion over 1 h every 8 h for 2 days and achieved average sternal bone concentrations during surgery of 4–14 mg/kg and tissue-to-plasma ratios ranging from 0.31 to 0.95 (mean 0.57). Unbound vancomycin concentrations during administration by continuous infusion were examined by Skhirtladze et al. in diabetic and non-diabetic patients following cardiac surgery. A loading infusion of 1000 mg over 60 min was followed by a continuous infusion of 80–120 mg/h (2000–3000 mg/day). Interstitial fluid samples were collected by microdialysis and concurrent plasma samples were collected hourly for 6 h. Median plasma vancomycin concentrations were similar in diabetic and non-diabetic patients (36.5 and 37.6 mg/L, respectively), but interstitial fluid concentrations and concentration ratios were significantly lower in diabetic patients [3.7 mg/L compared with 11.9 mg/L and 0.1 (range 0–0.45) compared with 0.3 (range 0.46–0.94)].

Clearly, the MIC for target organisms (i.e. *S. aureus*, and in particular MRSA) needs to be considered. While cases of reduced susceptibility to vancomycin have been reported, the accepted MIC breakpoint for *S. aureus* susceptibility to vancomycin is ≤4 mg/L. Serum levels with this continuous infusion were ≥4 mg/L in 100% of samples. Vessel wall concentrations were ≥4 mg/L in 61% of samples, but in only 19% of fat samples.

A common feature of all previous studies and the present study is wide inter-patient variability in both tissue concentrations and the ratio of tissue to plasma or serum concentrations. Penetration into fat is consistently lower than into other tissues, which reflects the low lipid solubility of vancomycin and poor vascularization of fat. Previous studies have identified time-dependent variability in the penetration of tissue and a rapid decline in plasma concentrations after a single dose. In the present study, serum concentrations were maintained by giving a constant rate intravenous infusion after the initial loading dose, and since samples were taken 9–19 h after the start of therapy, serum concentrations should have been close to steady state. Mean fluctuations in serum concentration of 0.3 mg/L (range 0.2–9 mg/L) were observed over a sampling period of 1–5 h and may have reflected a combination of variable input rates, concurrent fluid administration and assay variability.
Conclusions

Single bolus doses of vancomycin are commonly used in the prophylaxis of infection during vascular surgery. Administration of an individualized loading dose and continuous infusion can avoid the potential for sub-therapeutic concentrations if surgery is delayed or prolonged and excessive concentrations if additional doses are given to patients with renal impairment. This study has shown that during surgery this approach achieves both serum and vascular tissue concentrations that are above the MICs for most common organisms implicated in graft infection. However, penetration into perivascular fat is poor.

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Transparency declarations

None to declare.

References