Risk factors for nephrotoxicity associated with continuous vancomycin infusion in outpatient parenteral antibiotic therapy

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Objectives: Continuous vancomycin infusion is increasingly used for outpatient management of infections, but the relationship between vancomycin and nephrotoxicity is controversial. We investigated the risk factors associated with nephrotoxicity in this setting.

Methods: A retrospective cohort study of patients receiving continuous vancomycin infusion as outpatient parenteral antibiotic therapy (OPAT) was performed. The likelihood of developing nephrotoxicity (≥50% increase in serum creatinine from baseline) was evaluated in relation to demographic variables, underlying co-morbidities, infectious disease diagnoses, concomitant drug exposures and vancomycin concentration. Logistic regression was used to determine the association of various variables. Classification and regression tree analysis was used to determine the most significant breakpoint for continuous variables.

Results: We examined 102 adult patients between January 2004 and June 2007. The mean ± SD age, baseline serum creatinine and steady-state vancomycin concentration were 48.2 ± 17.6 years, 78.0 ± 32.5 μmol/L and 15.5 ± 10.8 mg/L, respectively. The majority of the patients (66.7%) were treated for bone and joint infection. The cumulative incidence of nephrotoxicity was 15.7%. Nephrotoxicity was found to be associated with hypertension [odds ratio (OR) 5.302 (95% confidence interval (CI) 1.159–24.246), P = 0.031], exposure to aminoglycosides [OR 6.594 (95% CI 1.026–42.385), P = 0.047], loop diuretics [OR 8.123 (95% CI 1.449–45.528), P = 0.017], and steady-state vancomycin concentration ≥28 mg/L [OR 21.236 (95% CI 2.687–167.857), P = 0.004].

Conclusions: We have identified independent risk factors for nephrotoxicity in patients receiving continuous infusion vancomycin in OPAT. A serum steady-state vancomycin concentration ≥28 mg/L markedly increases the risk.

Keywords: renal dysfunction, vancomycin monitoring, continuous infusion, OPAT

Introduction

The relationship between vancomycin and nephrotoxicity is unclear, with a cumulative incidence of 0% to 17%.¹ Although its pathophysiology is not well understood, observational studies have demonstrated vancomycin trough levels to be an important predictor of risk. Other risk factors are duration of therapy and aminoglycoside use.² Studies on this subject are, however, confounded by concomitant use of other nephrotoxins, small sample sizes and focus on inpatients likely to be at higher risk of nephrotoxicity.

Continuous vancomycin infusion is increasingly used in the outpatient parenteral antibiotic therapy (OPAT) setting. It requires less frequent therapeutic drug monitoring, is cheaper,³ leads to faster attainment of therapeutic concentrations and is associated with fewer adverse events when compared with intermittent dosing.⁴ However, the incidence and predictors of vancomycin-related nephrotoxicity in patients receiving OPAT are less clearly defined than in inpatients. Outpatients are likely to be at lower risk because of less frequent intercurrent renal insults such as surgery, radiologic contrast, acute sepsis and
Nephrotoxicity with vancomycin in OPAT

nephrotoxic medications. In low-risk populations, the cost effectiveness of routine repeated monitoring of renal function and vancomycin serum concentration has been questioned. It has been proposed that a more targeted approach should be adopted, although the relative importance of various risk factors has not been adequately elucidated.

The comparative clinical effectiveness and nephrotoxicity of continuous versus intermittent intravenous antibiotics have not been thoroughly elucidated. In this study, we examined the relationship between vancomycin use and nephrotoxicity in the OPAT setting. The objectives of the study were to identify risk factors for nephrotoxicity and to identify patients at higher risk of nephrotoxicity. Such a clinical prediction tool could allow more selective monitoring of renal function and serum vancomycin concentrations in the OPAT setting, reducing costs and minimizing the risk of nephrotoxicity.

Patients and methods

Study sites

The study was conducted at the OPAT units of National University Hospital and Tan Tock Seng Hospital, two large tertiary-care hospitals in Singapore.

Study design

We conducted a retrospective cohort study of OPAT patients administered intravenous vancomycin between January 2004 and June 2007. The study was approved by the Domain-specific Institution Review Board covering both hospitals. In view of the retrospective nature of the study, the need for informed consent from subjects was waived.

Patients

All adult patients (18 years of age or greater) prescribed continuous vancomycin infusion as outpatients during the study period were identified from the OPAT database. Continuous infusions of vancomycin were administered through a peripherally inserted central catheter using an elastomeric infusion device. Vancomycin and creatinine concentrations were measured weekly and steady-state concentrations of 20–25 mg/L were targeted. Patients who underwent dialysis, experienced systolic blood pressure <90 mmHg, potentially resulting in renal dysfunction (e.g. septic shock, cardiac arrest) or met the criterion of nephrotoxicity while on vancomycin therapy in the hospital were excluded.

Data retrieval

Pertinent data were retrieved from patients’ medical records and laboratory database, including demographic characteristics (age, ethnicity, gender and serum creatinine), co-morbidities (hypertension, congestive cardiac failure, diabetes mellitus and renal diseases), indications for vancomycin therapy, microorganisms isolated, concomitant exposure to potential nephrotoxins (aminoglycosides), dose and duration of vancomycin therapy. Serum creatinine and vancomycin concentration measurements were performed routinely (weekly) during OPAT follow-up clinic visits. Mean outpatient weighted vancomycin steady-state concentrations were calculated by summing measured steady-state concentrations multiplied by the number of days at that concentration, divided by the total number of treatment days. The primary endpoint of the study was the development of nephrotoxicity (defined as more than 50% increase in serum creatinine compared with baseline) during vancomycin therapy. Only vancomycin concentrations measured prior to nephrotoxicity were used in the analysis if nephrotoxicity developed during the course of therapy.

Statistical analysis

Logistic regression was used to explore various risk factors associated with the primary endpoint of the study. Univariate analyses were performed separately for each of the risk factor variables to ascertain the odds ratio and 95% confidence interval (CI). For continuous variables found significant in the analysis, classification and regression tree (CART) analysis was used to determine the threshold breakpoint and further analysis with Fisher’s exact test was used. Variables with a P value of <0.2 in the univariate analyses were included in the logistic regression model for the multivariate analysis. A backward selection process was utilized. A P value of ≤0.05 was considered significant unless stated otherwise. All statistical analyses were performed using Systat® version 12.0 (Systat Software, Inc., Point Richmond, CA, USA).

Results

Patients

A total of 102 adult patients receiving continuous vancomycin infusion as OPAT were examined. All patients received vancomycin in hospital (as intermittent dosing) prior to OPAT. The ethnic background of the patients comprised 53.9% Chinese (55 patients), 23.5% Malay (24 patients), 19.6% Indian (20 patients) and 2.9% others (3 patients); 73.5% were male (75 patients). The mean ± SD age, baseline serum creatinine and steady-state vancomycin concentration were 48.2 ± 17.6 years, 78.0 ± 32.5 µmol/L and 15.5 ± 10.8 mg/L, respectively. The majority of patients (66.7%) were treated for bone and joint infection. Most infections were due to methicillin-resistant Staphylococcus aureus (84 patients) and coagulase-negative Staphylococcus (7 patients). The patients received vancomycin for 12.3 ± 9.3 days in the hospital and 23.8 ± 16.9 days as OPAT (before the onset of nephrotoxicity, if nephrotoxicity was observed).

Risk factors of nephrotoxicity

The cumulative incidence of nephrotoxicity was 15.7% (16 patients). In the univariate analysis, risk factors associated with nephrotoxicity are shown in Table 1. The probability of developing nephrotoxicity during therapy in relation to steady-state vancomycin concentration is shown in Figure 1. Using CART analysis, the threshold breakpoint in steady-state vancomycin concentration was 28 mg/L; nephrotoxicity occurred in 11.6% (11 out of 95) and 71.4% (5 out of 7) of patients with vancomycin concentration of <28 mg/L and equal to 28 mg/L or greater, respectively (P = 0.001). Neither the cumulative dose nor the duration of vancomycin therapy was found to be a risk factor (P > 0.2). In the multivariate analysis, nephrotoxicity was associated with hypertension, concomitant exposure to aminoglycosides or loop diuretics, and vancomycin concentration of 28 mg/L or greater (Table 1). In
this cohort, patients were much more likely (~21 times) to develop nephrotoxicity during therapy if their steady-state vancomycin concentration was 28 mg/L or greater ($P = 0.004$).

### Discussion

The incidence of nephrotoxicity associated with vancomycin therapy remains controversial. The risk (if any) of developing nephrotoxicity during therapy is thought to be even lower in the OPAT setting, as patients are less critically ill and other nephrotoxins are less likely to be encountered. The cumulative incidence of nephrotoxicity observed in our patients (15.7%) was consistent with several previous studies with smaller sample sizes.7,8 We believe that this is the largest study to date assessing continuous vancomycin infusion in the OPAT setting.

We identified multiple independent risk factors of nephrotoxicity initially in the univariate analysis (Table 1). After adjusting for other potentially confounding variables in the multivariate analysis, four factors remained. Steady-state vancomycin concentration (as a dichotomous variable of 28 mg/L or greater) was found to have the most significant association with subsequent nephrotoxicity during therapy. Recently, increasing vancomycin inhibitory concentrations in staphylococci associated with treatment failures9 have prompted recommendation of a higher vancomycin target concentration for patients receiving intermittent infusions. There are no existing guidelines for a target serum concentration for continuous infusion dosing. Consequently practice varies widely, with target steady-state concentrations ranging from 20 to 35 mg/L.8,10 A French study of 957 patients treated with continuous vancomycin infusion reported steady-state concentration to be $<10$ mg/L (7.9%), 10–30 mg/L (71.2%) or $>30$ mg/L (20.9%).11 Collectively, these figures suggest that a significant proportion of patients receiving vancomycin by continuous infusion may be at high risk of nephrotoxicity. Hypertensive patients on loop diuretics or who are receiving aminoglycosides appear to be at greatest risk and should have therapeutic drug monitoring while on vancomycin continuous infusion as OPAT.

Our study has several limitations including the fact that severity of illness was not assessed when vancomycin therapy was started. We assumed that all patients were clinically stable (well enough to be discharged for OPAT). Furthermore, patients who developed nephrotoxicity did not appear to have a higher

### Table 1. Logistic regression analysis of nephrotoxicity associated with continuous vancomycin infusion

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis odds ratio (95% CI)</th>
<th>$P$ value</th>
<th>Multivariate analysis odds ratio (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Malay</td>
<td>3.157 (1.029–9.688)</td>
<td>0.049</td>
<td></td>
<td></td>
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<tr>
<td>Indian</td>
<td>0.235 (0.029–1.896)</td>
<td>0.174</td>
<td></td>
<td></td>
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<tr>
<td>male</td>
<td>0.390 (0.129–1.179)</td>
<td>0.095</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline serum creatinine $\geq$133 $\mu$mol/L</td>
<td>14,000 (2.310–84.859)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone and joint infections</td>
<td>0.433 (0.147–1.279)</td>
<td>0.130</td>
<td></td>
<td></td>
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<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>hypertension</td>
<td>3.321 (1.112–9.922)</td>
<td>0.032</td>
<td>5.302 (1.159–24.246)</td>
<td>0.031</td>
</tr>
<tr>
<td>congestive cardiac failure</td>
<td>3.952 (0.605–25.816)</td>
<td>0.151</td>
<td></td>
<td></td>
</tr>
<tr>
<td>renal diseases</td>
<td>6.833 (1.506–31.011)</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant exposure to aminoglycosides</td>
<td>3.455 (0.994–12.008)</td>
<td>0.051</td>
<td>6.594 (1.026–42.385)</td>
<td>0.047</td>
</tr>
<tr>
<td>loop diuretics</td>
<td>4.444 (1.093–18.079)</td>
<td>0.037</td>
<td>8.123 (1.449–45.528)</td>
<td>0.017</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>3.700 (1.135–12.062)</td>
<td>0.030</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin concentration $\geq$28 mg/L</td>
<td>1.079 (1.023–1.139)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin concentration $\geq$28 mg/L</td>
<td>19.091 (3.297–110.536)</td>
<td>0.001</td>
<td>21.236 (2.687–167.857)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

Note: only variables with $P < 0.2$ in the univariate analysis are shown.

*aSteady-state concentration evaluated as a continuous variable.

Figure 1. Relationship between vancomycin concentration and the likelihood of nephrotoxicity. Note: $C_v =$ steady-state vancomycin concentration; relationship based on estimates from univariate analysis.
baseline serum creatinine, longer hospitalization or duration of inpatient vancomycin (data not shown). We did not compare the incidence of nephrotoxicity between OPAT patients given vancomycin as intermittent and continuous infusion (focus of an ongoing investigation). Patients who developed nephrotoxicity in the hospital (deemed to be ‘high risk’) were also not included in this study. There have been several studies examining continuous vancomycin therapy in the inpatient setting.3,7,8,10,12 However, most of these studies had limited sample size (<25), which made the nephrotoxicity risk factor(s) difficult to assess. Finally, it is not easy to establish a causal relationship between vancomycin and nephrotoxicity as vancomycin is dependent on glomerular filtration rate for elimination.

In conclusion, our data support selective monitoring of renal function in OPAT patients at high risk of developing nephrotoxicity during vancomycin therapy and dose adjustment to achieve a constant serum vancomycin concentration of <28 mg/L. A larger prospective study is warranted to validate our findings.

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Transparency declarations

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