Assessment of vancomycin use in chronic haemodialysis patients: room for improvement

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Abstract

Background. Vancomycin is frequently prescribed for the management of infections in haemodialysis patients. We evaluated the appropriateness of vancomycin use in our chronic haemodialysis population.

Methods. Charts of all chronic haemodialysis patients who received vancomycin between 1 March 2003 and 1 March 2004 were retrospectively reviewed. Indication was assessed according to the modified Hospital Infection Control Practices Advisory Committee guidelines for vancomycin prescription. The prescribed dosing regimens were evaluated.

Results. A total of 163 courses of vancomycin in 105 patients were assessed. Of all courses, 88% were considered to be initially appropriate, but this decreased to 63% once culture and sensitivity results were available. Use of vancomycin for the management of beta-lactam-sensitive organisms accounted for the majority of inappropriate use. The most common vancomycin-dosing regimen prescribed was 500 mg intravenously at each haemodialysis session (51%); however, considerable variability was observed.

Conclusions. Although the initial indication for vancomycin use was generally appropriate, inappropriate continuation of this antibiotic, failure to obtain proper cultures to guide therapy and potentially subtherapeutic dosing regimens were some of the challenges identified. Centres providing chronic haemodialysis should take steps to optimize vancomycin prescription to improve clinical outcomes and reduce the risk of antimicrobial resistance.

Keywords: drug use evaluation; haemodialysis; vancomycin

Introduction

Vancomycin is frequently prescribed for the management of suspected or documented infections in haemodialysis pa-

tients due to its broad coverage of potential gram-positive pathogens and convenient dosing schedule [1,2]. Despite these advantages, the overuse of vancomycin is a concern as it is associated with significant risks of infection involving organisms with reduced susceptibility to the drug, such as vancomycin-resistant enterococci and vancomycin-intermediate and -resistant Staphylococcus aureus [3,4].

There have been numerous calls for judicious vancomycin prescribing, and guidelines have been prepared by the Hospital Infection Control Practices Advisory Committee (HICPAC) in the USA and by Health Canada to direct physicians in its use [3,5,6–8]. It has been suggested, however, that the HICPAC guidelines need to be modified for the haemodialysis population to allow for the use of vancomycin as empiric therapy for a febrile patient on haemodialysis with an unclear site of infection (pending culture and sensitivity data) [1]. Proper dosing of vancomycin is also an important element when considering appropriate use, as inappropriate dosing may encourage the development of resistance or increase the risk of adverse effects.

The Ottawa Hospital (TOH) is a 1000-bed tertiary care hospital with three campuses. Each campus has an outpatient dialysis unit. As of 1 March 2003, TOH provided service to 531 chronic haemodialysis patients, of which 317 were dialyzed through fistulas, 7 through grafts and 207 through central catheters. In contrast to inpatients, where clinical pharmacists monitor adherence of vancomycin therapy to hospital-based criteria for use and dosing, there is no formal monitoring of vancomycin in the outpatient dialysis population at our institution. We therefore sought to assess the utilization of vancomycin in our chronic haemodialysis population. Specifically, our aims were to evaluate the degree to which the indications for vancomycin conformed to published recommendations, treatment duration, dosing regimens and monitoring of vancomycin.

Subjects and methods

A retrospective review was conducted in TOH haemodialysis patients who had received vancomycin therapy between
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1 March 2003 and 1 March 2004. Patients were identified by means of an electronic database of all chronic haemodialysis patients at TOH. Data were collected from electronic databases and paper charts and included demographic data, allergy status, type of haemodialysis access and access site, indication for vancomycin, source of infection, culture and sensitivity results, duration of therapy, catheter removal, infectious diseases’ (ID) consultation, methicillin-resistant S. aureus (MRSA) status (if known) and vancomycin administration, including timing, dose regimen and adjustments based on serum levels.

Both the initial indication and vancomycin prescription following the availability of culture and sensitivity results were assessed. The initial indication for vancomycin was determined to be appropriate if it conformed to the HICPAC guidelines modified for the chronic haemodialysis population as recommended by Golper et al. [1,6]. Those courses that did not conform to the modified HICPAC guidelines were reviewed by an ID specialist to determine appropriateness. In courses where the only culture performed was a catheter tip culture, the exit site was considered infected if S. aureus was cultured. A documented catheter-associated infection was defined as a positive catheter tip and a positive blood culture with the same organism and antibiogram, or at least one positive blood culture for S. aureus or a gram-negative bacillus, or two positive blood cultures for coagulase-negative staphylococcus (CoNS) in the absence of a catheter tip culture or any other identified source of infection [9].

Dosing schedules and serum levels of vancomycin were recorded. Regimens were considered to have required adjustment if the pre-dialysis serum level lay outside the 7.5–20 mg/L range. Adjustments for levels falling within this range were considered inappropriate. The duration of therapy for management of intravascular catheter-related bloodstream infections (CRBSIs) was assessed according to the recommendations outlined by the Infectious Diseases Society of America based on the infecting organism and whether the catheter was removed [9]. The duration of therapy for a course of vancomycin was calculated using the number of days between and including the first and last doses.

Data were tabulated and analysed using Microsoft® Excel 2000 spreadsheets and SPSS software (Statistical Package for the Social Sciences version 11.0, Chicago, IL, USA) for analysis. The study was approved by the institution’s Research Ethics Board.

Results

Between 1 March 2003 and 1 March 2004, 108 patients were eligible for inclusion. Three patients (2.8%) were excluded due to insufficient data. This left 105 patients who received 163 courses of vancomycin. Patient characteristics are listed in Table 1.

The initial indications for vancomycin use are presented in Table 2. The most common indications were empiric therapy for a febrile patient on chronic haemodialysis with an unclear site of infection (34.4% of courses) and empiric therapy for an infected prosthetic haemodialysis access (27.6% of courses). Of the 163 courses, 143 (88%) were judged to be initially appropriate (pending culture and sensitivity results). Of these 143, 117 conformed to the modified HICPAC guidelines (Table 2) and an additional 26 prescribed for an indication that did not fit the HICPAC guidelines were judged appropriate by the ID consultant (Table 2). Of the remaining 20 courses, appropriateness could not be determined in three courses due to reported penicillin or cephalosporin allergies without reaction details documented, and 17 were considered inappropriate.

Three of the 17 inappropriate courses fulfilled the HICPAC criteria, but were judged to be inappropriate as the vancomycin was for the treatment of a catheter site swab growing CoNS. The most common suspected sources of infection were catheter related (60% of cases) and skin and soft tissue (20% of cases).

The appropriateness of the response to culture and sensitivity results could be evaluated for 145 of the 163 courses (89%). Eighteen courses were excluded because no cultures were taken (3 courses), sufficient allergy details were not available (11 courses), vancomycin was used for surgical prophylaxis (2 courses) or blood cultures were positive for CoNS, but only one blood culture was drawn (2 courses). Fifty-six percent (92/163) of the total courses were considered appropriate (Table 3). This represents 63% of all evaluable courses (92/145). The most common inappropriate response to the culture and sensitivity results was the continuation of vancomycin despite the culture of a beta-lactam-sensitive organism (40/53, 75% of all inappropriate continuation). This includes the 10 courses in which vancomycin was inappropriately initiated to treat beta-lactam-sensitive organisms.

Of all courses of suspected catheter-related infections \((n = 98)\), blood cultures were drawn in only 75 (76.5%)
Table 2. Initial indications for vancomycin

<table>
<thead>
<tr>
<th>HICPAC guideline modified for chronic haemodialysis patients [1]</th>
<th>Number (percent) of courses, n = 163</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empiric therapy for a febrile patient with an unclear site of infection, pending culture/sensitivity data</td>
<td>56 (34.4%)</td>
</tr>
<tr>
<td>Empiric therapy for an infected prosthetic haemodialysis access, pending culture and susceptibility studies</td>
<td>45 (27.6%)</td>
</tr>
<tr>
<td>Treatment of beta-lactam-resistant organisms</td>
<td>15* (9.2%)</td>
</tr>
<tr>
<td>Treatment or prophylaxis for beta-lactam-sensitive organisms in a patient with a serious beta-lactam allergy</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>Prophylaxis for surgeries which involve implantation of prosthetic material or devices in a patient with a history of colonization or previous infection with methicillin-resistant organisms</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Oral treatment of antibiotic-associated colitis after failure with metronidazole, or if there is a contraindication to therapy with metronidazole</td>
<td>0</td>
</tr>
<tr>
<td>Indication did not conform to modified HICPAC guidelines</td>
<td>43 (26.4%)</td>
</tr>
</tbody>
</table>

*Includes three patients in whom vancomycin therapy was considered inappropriate, as it was prescribed in response to a catheter site swab growing coagulase-negative staphylococcus.

Table 3. Breakdown of vancomycin orders by appropriateness

<table>
<thead>
<tr>
<th>Initial indication</th>
<th>Number (percent) of courses, n = 163</th>
<th>Mean duration (range) of vancomycin (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate</td>
<td>143 (88%)</td>
<td>11.1 (1–72)</td>
</tr>
<tr>
<td>Unable to assess</td>
<td>3 (2%)</td>
<td>14.3 (4–24)</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>17 (10%)</td>
<td>17.2 (1–59)</td>
</tr>
<tr>
<td>Treatment of beta-lactam-sensitive organisms with no significant allergy</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Infected AVF</td>
<td>3</td>
<td>14.7 (4–24)</td>
</tr>
<tr>
<td>Catheter site culture growing CoNS</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis for graft insertion</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>After culture and susceptibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate</td>
<td>92 (56%)</td>
<td>8.4 (1–66)</td>
</tr>
<tr>
<td>Unable to assess</td>
<td>18 (11%)</td>
<td>15.4 (1–80)</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>53 (33%)</td>
<td>16.7 (1–59)</td>
</tr>
<tr>
<td>Infection due to beta-lactam-sensitive organism and no significant allergy</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Catheter site swab with CoNS (no or negative blood cultures)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Negative catheter site swab (no or negative blood cultures)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other infection with GNB isolated</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

AVF, arteriovenous fistula; CoNS, coagulase-negative staphylococcus; GNB, gram-negative bacilli.

courses. In 18 cases, catheter site cultures were the only cultures performed. CRBSIs were documented in 34 of the suspected cases (34/98, 35%), including 12 due to CoNS, 13 due to S. aureus and 3 positive for enterococcus species. The remainders were due to gram-negative organisms (3), other gram-positive organisms (2) or fungi (1). Of the 34 documented CRBSIs, the catheter was removed in 25 (73.5%) cases.

The median duration and range of vancomycin therapy when used to treat documented CRBSIs due to CoNS, S. aureus and enterococcus species were 14 (1–33) days, 16 (1–30) days and 21 (16–26) days, respectively. For all patients with a documented S. aureus CRBSI who received a full course of vancomycin (n = 8), the median duration of therapy was 19.5 (range, 5–30) days. Of the seven cases of documented CRBSIs due to CoNS in which the catheter was removed, the median duration and range of therapy following catheter removal was 18 (7–33) days.

Overall, cases in which the initial indication for vancomycin was considered inappropriate resulted in a total of 309 days of unnecessary vancomycin therapy. In addition, a conservative estimate of 400 days of unnecessary vancomycin therapy resulted from the inappropriate continuation of the drug following culture and sensitivity data.

A single dose of vancomycin was given in 57/163 courses (35%). Of the 106 courses in which vancomycin was continued beyond the first dose, the most common regimens prescribed were 500 mg intravenously (IV) at each haemodialysis session (51%, 54/106) and 1000 mg IV at every second haemodialysis session (23.6%, 25/106). The remainder of patients were prescribed alternate regimens, or vancomycin was dosed intermittently on specific dates. A loading dose was administered in 38% (40/106) of these courses. When assessing the doses by weight, the median loading dose was 13 mg/kg (range, 4.9–23.8 mg/kg). The median maintenance dose was 8.8 mg/kg (range, 4.9–20 mg/kg). All vancomycin doses were administered after or during haemodialysis (usually in the last 1–1.5 h).

A total of 90 levels were requested in 44 of the 106 (41.5%) courses of vancomycin. All were drawn pre-haemodialysis. The change or lack of change in the dosing of vancomycin in response to the levels was considered inappropriate in 36% (32/90) of cases. Response could...
not be assessed in 4% (4/90), either because the drug was subsequently discontinued (n = 2) or the change in dose was not clearly documented in the chart (n = 2).

Discussion

Organisms with reduced susceptibility to vancomycin may be associated with increased morbidity and mortality [4], and have limited treatment options. As these organisms are a particular concern in haemodialysis patients [4,5,8], appropriate use of vancomycin in this population is therefore of paramount importance. In our study, inappropriate prescription resulted in ∼700 patient-days of unnecessary vancomycin therapy, a result of both inappropriate initial prescription and unnecessary continuation of therapy. Four previous studies reviewing vancomycin prescription [10–13] found that only 20–55% of vancomycin orders conformed to the HICPAC guidelines. When Green et al. used modified HICPAC guidelines to judge the appropriateness of vancomycin prescriptions for hospitalized chronic haemodialysis patients, 80% of all vancomycin doses were judged to have a suitable indication for vancomycin [14]. This is similar to the rate of 88% initially appropriate orders observed in our study.

We found, however, that only 63% of courses remained appropriate following re-evaluation once culture and sensitivity results were available. The most common inappropriate use of vancomycin in Green et al.’s study was the continued use of vancomycin for the management of beta-lactam-sensitive organisms. Likewise, we observed vancomycin therapy inappropriately continued despite negative culture results or the culture of a beta-lactam-sensitive organism. In these cases, it was not clear from the chart whether vancomycin was continued despite knowledge of the culture and sensitivity results, or if the prescriber was not aware of these results.

Although treatment of beta-lactam-sensitive organisms with vancomycin may be more convenient compared to the multiple daily doses required with most beta-lactam agents, this practice is not recommended [6], and in fact, may be detrimental, particularly for infections due to *S. aureus*. For example, Stryjewski et al. recently demonstrated that haemodialysis patients treated with vancomycin for methicillin-sensitive *S. aureus* bacteraemia had a higher rate of failure compared to those treated with cefazolin [15].

As the catheter was the most common source for suspected or documented infections treated with vancomycin in the study population, we observed a number of practices related to catheters that require review. First, blood cultures were not consistently drawn in suspected catheter-related infections. Second, vancomycin was frequently continued despite negative blood cultures, and in patients in whom the only positive culture was a catheter exit site swab isolating CoNS, which are normal flora on the skin. Third, the duration of vancomycin prescribed for the treatment of documented CRBSIs with CoNS frequently exceeded the duration of therapy recommended by the Infectious Diseases Society of America [9]. Although there was a wide variation, 45% of cases were treated longer than the recommended maximum of 14 days. Of the seven cases in which the catheter was removed, the median duration of therapy following line removal was 18 days, which is greater than the recommended 5–7 days (data not shown). Finally, catheters were only removed in 11 of 15 cases of documented *S. aureus* bacteraemia. Although recommended [9], in our study, antibiotic lock therapy was not prescribed for the four cases in which the catheter was not removed.

In addition to the indication for vancomycin and duration of therapy, dosing is an important element in determining appropriateness of therapy, as inappropriate dosing may result in treatment failure and/or encourage the development of resistance. There is currently no consensus regarding a preferred dosing regimen for vancomycin with the high-flux dialysis membranes commonly used today. However, a regimen of a 1-g loading dose, followed by 500 mg after each haemodialysis session, was shown to achieve desired pre-haemodialysis vancomycin serum concentrations in the majority of patients in two separate investigations [16,17]. This regimen is similar to dosing suggested by Touchette et al. [18] and Barth and DeVincenzo [19]. We observed a variety of dosing regimens prescribed in our study, with many of the patients receiving regimens that have not been evaluated in the literature. In addition, the majority of the patients did not receive a loading dose, as recommended by Barth and DeVincenzo [19]. As levels were not often performed, it was not possible to assess the adequacy of these dosing regimens. Although it is not usual practice to dose vancomycin based on the patient’s weight, it is important in patients who are at the extremes of weight. When assessed by weight, we observed a wide range of doses from as little as 6 mg/kg at every second haemodialysis session to as much as 20 mg/kg at each haemodialysis session (data not shown), potentially representing subtherapeutic or supratherapeutic dosing.

For convenience, vancomycin serum levels are drawn prior to haemodialysis in the outpatient setting. These levels must be interpreted with the knowledge that as much as 30–40% of vancomycin may be removed during the high-flux haemodialysis session [16,17,20]. Acceptable vancomycin serum concentrations prior to haemodialysis are therefore considered to range from 7.5 to 20 mg/L, and may be as high as 25 mg/L for the treatment of more resistant pathogens such as MRSA [17,19]. Inappropriate adjustment of dosage based on levels was observed in approximately one-third of our patients, indicating potential confusion among clinicians regarding recommendations for target levels. For instance, orders to re-dose vancomycin only if the pre-haemodialysis vancomycin level was <10 mg/L, maintenance doses of vancomycin reduced for trough levels of <15 mg/L and not increasing the dose of vancomycin for pre-haemodialysis levels <5 mg/L may have placed patients at risk of subtherapeutic serum concentrations.

Given the retrospective nature of this study, there were limitations in our ability to collect certain data, including local signs and symptoms of infection, whether clinicians were aware of culture and sensitivity results, and rationale for dosage changes. Thus, unless specifically documented in the chart, we were unable to explain the lack of response to culture results or a particular length of therapy.
Anecdotally, possible reasons to explain the discrepancies between published guidelines and clinical practice include the frequent rotation of various nephrologists in the dialysis unit without consistent means of communication and follow-up, and reluctance to switch to beta-lactam therapy, which would require insertion of an extra line and homecare involvement for regimens involving multiple daily doses. We did not undertake any evaluation of the harm that inappropriate durations or dosing may have had on clinical outcome or antibiotic resistance. An additional limitation may be that periodic variation may have led to a year in which there were fewer or greater than the average number of vancomycin courses. However, selection bias was minimized by including all patients who received vancomycin in a 12-month time frame.

In summary, specific areas to target for improvement in vancomycin prescription in the outpatient haemodialysis population at our institution were identified in this review. In particular, we found that recommendations for vancomycin use in the haemodialysis population are inconsistently followed, including indications for initiation and continuation of vancomycin, obtaining appropriate cultures, appropriate dosing regimens and response to vancomycin levels. These observations led to specific recommendations regarding vancomycin prescription and dosing in the haemodialysis population at our institution (Table 4). Optimizing vancomycin prescription should improve clinical outcomes while diminishing the risk of vancomycin-resistant organisms in this high-risk population.

Acknowledgements. The authors would like to acknowledge Marie-Josée Deschênes, B.Pharm., M.Sc., and Salmaan Kanji, Pharm.D., for their contributions to this study.

Conflict of interest statement. None declared.

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Received for publication: 15.1.08
Accepted in revised form: 26.5.08