Original Article

Appropriate vancomycin use in a Malaysian tertiary hospital based on current HICPAC recommendations

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Abstract
Introduction: Antibiotic resistance is a rapidly emerging problem. A major concern is methicillin-resistant *Staphylococcus aureus* (MRSA), especially in developing countries where cost-effectiveness is imperative. Restriction of vancomycin usage is necessary to reduce the emergence of vancomycin-resistant organisms. The aim of this study was to look into the appropriate use of vancomycin based on the Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines and to investigate serum levels of vancomycin.
Methodology: The study was performed retrospectively. Medical records of patients treated with vancomycin for the past year were identified and selected.
Results: Overall, 118 patients were treated with vancomycin. Appropriate use of vancomycin was significantly higher than inappropriate use (p = 0.001). Approximately 85% (n = 100) of patients were given vancomycin for treatment, whereas the rest were given it for prophylaxis. Appropriate use of vancomycin was observed in 67% (n = 79) of patients. However, there was still a high rate of inappropriate vancomycin use for prophylaxis and treatment (n = 39, 33.1%). The most common reason for inappropriate use was non-neutropenic and non-line related sepsis (n = 36, 30.8%). Therapeutic drug monitoring of vancomycin was performed in 79 patients (67%). Most patients (n = 53, 67%) demonstrated sub-therapeutic levels during the first measurement. There was no significant difference between trough levels achieved with a higher (> 15 mg/kg) versus a lower dose (< 15 mg/kg).
Conclusions: This study demonstrates that there was still a high level of inappropriate vancomycin use, which could potentially contribute to vancomycin resistance.

Key words: vancomycin; resistant; antibiotic; appropriateness.

Introduction

Vancomycin is a glycopeptide antibiotic that is effective against Gram-positive bacteria and is clinically used to treat serious infections that are resistant to other antibiotics. However, resistance towards vancomycin has increased within the past decade [1,2]. The rise in vancomycin resistance is linked to the overuse and prolonged treatment with the glycopeptide antibiotic [3]. Reduced susceptibility of vancomycin could potentially lead to clinical failure during treatment. In view of this, various methods have been used to reduce the risk of resistance towards vancomycin. One such method is providing guidelines to ensure appropriate use of vancomycin as a means to prevent the spread of resistance to the antibiotic [4].

Appropriate use of vancomycin has been frequently reviewed in an attempt to determine whether appropriate recommendations are followed in clinical settings. Close monitoring of appropriate use of antibiotics provides a platform to review clinical practice to ensure the safeguard against antibiotic resistance. Vancomycin has been shown to be used appropriately in 30% to 50% of cases after the Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines were implemented in a tertiary care hospital [4,5]. A teaching hospital in Brazil reported that appropriate vancomycin use within the first 24 hours was demonstrated in only 34% of cases [6]. Furthermore, in this work, only 33% of cases were found to be appropriately prescribed within the recommended 72-hour window. In Iran, a review of the HICPAC guidelines demonstrated that only 6% of the cases were deemed to be appropriate for vancomycin use [7].

Another vital reason for monitoring vancomycin serum concentration during vancomycin administration is due to the narrow therapeutic range of the drug [8,9]. In view of this, vancomycin serum levels should be monitored to ensure that sub-therapeutic levels or toxicity are reduced during

clinical use. One of the main effects of vancomycin is nephrotoxicity and ototoxicity [8]. Despite this, the monitoring of vancomycin remains controversial [10], especially in patients with normal renal function and uncomplicated infections [10,11]. However, current practice suggests that monitoring serum vancomycin is vital in all patients exceeding three to five days of treatment to reduce the risk of toxicity [8].

Despite the various works on vancomycin use and monitoring of serum levels, there remains a disparity between guidelines and conformity with guidelines in clinical practice. Clearly, the incidence of appropriate vancomycin use is still poor in the clinical setting. Therefore, this work aimed to investigate the clinical conformity of vancomycin use and monitoring in a tertiary hospital in order to identify the level of appropriate vancomycin use.

Methodology

This study was performed in a local tertiary hospital. Medical records of patients treated with vancomycin over the past year were retrospectively reviewed. Patients were identified from the pharmacy information system. Patient information such as demographics, allergies, indication for vancomycin, culture and sensitivity tests, concomitant medication, serum levels of vancomycin, and diagnosis were collected. Patients with incomplete medical records or those who were not prescribed vancomycin were excluded from the study. Approval to conduct the study was obtained from the local medical research and ethics committee.

Vancomcyin utilization

The appropriateness of vancomycin use was classified according to the HICPAC guidelines [4]. The guidelines include a list of recommendations about when vancomycin use is either appropriate or acceptable, or inappropriate. The recommendations are for the prophylaxis and treatment of patients with varying degrees of infection.

The medical records were also reviewed for results of serum vancomycin levels. The serum concentration of vancomycin based on previous works [8,10,12] is a trough level of 5–10 mg/L. However, trough levels of 15–20 mg/L are recommended in more complicated infections such as endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *Staphylococcus aureus* [8,10,12]. Serum levels were divided into three categories: sub-therapeutic (< 10 mg/L for normal infections and < 15 mg/L for complicated infections); therapeutic (10–15 mg/L for

normal infections and 15–20 mg/L for complicated infections); and potential toxic (> 15 mg/L for normal infections and > 20 mg/L for complicated infections). Patients were sampled for levels immediately before the next dose. Doses of vancomycin administered to the patients were categorized based on a conventional body weight dose of 15 mg/kg [12].

Statistical analyses

Data was analysed using Statistical Package for Social Sciences (SPSS) version 15.0 for Windows and was tested with the appropriate inferential and descriptive statistics. An appropriate contingency table test (X^2 test or Fisher's exact test) at a confidence interval of 95% was used to evaluate the association between variables and outcome. Probability values of less than 0.05 ($p < 0.05$) were accepted as statistically significant.

Results
Patient demographics

A total of 118 patients were identified in the study; 64 (54.2%) were males and 54 (45.8%) were females. Half of the study population were Malay (n = 59, 50%), followed by Chinese (n = 39, 33%) and Indian (n = 12, 10.2%). There was a total of 68 (57.6%) patients < 60 years of age, with the remaining 50 (42.4%) patients ≥ 60 years of age. Approximately 46% (n = 50) of the study population were diagnosed with renal impairment prior to treatment with vancomycin. Other co-morbidities identified in the study were malignancy (n = 18, 15.3%), obesity (n = 7, 5.9%), cardiovascular disease (n = 77, 65.3%), and diabetes mellitus (n = 51, 43.2%). Drug allergies to beta-lactams and other drugs were observed in 9 (7.6%) patients. The overall length of hospital stay in this study population was 33.7 (SD ± 32.8) days.

Appropriateness of vancomycin

The use of vancomycin was identified in various wards: medical (n = 44, 37.3%), orthopedic (n = 19, 16.1%), critical care (n = 19, 16.1%), surgical (n = 18, 15.3%), and operation theaters (n = 18, 15.3%). Of the 118 patients prescribed vancomycin, more patients were given vancomycin for treatment (n = 100, 84.7%) than for prophylaxis (n = 18, 15.3%). The mean dose given to patients was 713.1 mg (SD ± 210.1 mg). The majority of the patients were given intravenous vancomycin (n = 111, 94.1%). A total of 47 (39.8%) patients were given vancomycin as monotherapy, while the remaining 71 (60.2%) patients were given combination treatment. Other antibiotics given

concomitantly were cephalosporins (n = 36, 50.7%), carbepenems (n = 22, 31%), penicillins (n = 17, 23.9%), aminoglycosides (n = 5, 7%), macrolides (n = 3, 4.2%), and others (n = 14, 19.7%).

Appropriate use of vancomycin was identified in a total of 79 (66.9%) patients (Table 1). Of these, 6 (7.6%) patients were on prophylaxis and 73 (61.8%) patients were on empirical and definitive treatment. Inappropriate use of vancomycin was identified in 39 (33.1%) patients. In the cases of inappropriate use, 12 (30.8%) patients were on prophylaxis and the remaining 27 (22.9%) patients were on empirical and definitive treatment. In this study population, it was observed that there was a significantly higher number of patients on appropriate vancomycin use than patients on inappropriate vancomycin use (p = 0.001).

Vancomycin serum level

Serum vancomycin was recommended [8,10,12] to be monitored in 100 (84.7%) patients (Table 2). However, only 79 (79%) patients were monitored for vancomycin levels in this study population. From the 79 patients who were monitored, only 18 (22.8%) were found to be within the therapeutic range. Most patients (n = 53, 67.1%) were found to have sub-therapeutic levels, with a small number (n = 8, 10.1%) achieving potentially toxic levels. When the vancomycin dose was compared with therapeutics levels, no significant difference was found between dose (< 15 mg/kg and > 15 mg/kg) and achieving serum vancomycin levels in this study population (p > 0.05) (Table 3).

Table 1. Appropriate use of vancomycin in a local tertiary hospital based on the HICPAC [4] guideline (n = 118)

Characteristics	n (%)	p value[a]
Appropriate therapy	79 (66.9)	0.001*
Prophylaxis	6 (5.1)	
Treatment	76 (64.4)	
Inappropriate therapy	39 (33.1)	
Prophylaxis	12 (10.1)	
Treatment	27 (22.9)	

[a]Chi-squared test
*p-value < 0.05 considered significant

Table 2. Vancomycin therapeutic drug monitoring in the study population

Characteristics	n (%)
Indications for monitoring (n = 118)	
Yes	100 (84.7)
No	18 (15.3)
Monitoring provided (n = 100)	
Yes	79 (79)
No	39 (39)
Vancomycin levels[a] (n = 79)	
Sub-therapeutic	53 (67.1)
Therapeutic	18 (22.8)
Potentially toxic	8 (10.1)

[a]Serum levels were divided into three categories [8,10,12]: ; Sub-therapeutic: < 10 mg/L for normal infections and < 15 mg/L for complicated infections
Therapeutic: 10–15 mg/L for normal infections and 15–20 mg/L for complicated infections; Potentially toxic: > 15 mg/L for normal infections and > 20 mg/L for complicated infections

Table 3. Association between vancomycin trough levels achieved and initial dose administered (n = 79)

Level achieved	< 15 mg/kg	≥ 15 mg/kg	p value[a]
Sub-therapeutic, n (%)	43 (70.5)	10 (55.6)	p > 0.05
Therapeutic, n (%)	15 (24.6)	3 (16.7)	
Potential toxic, n (%)	3 (4.9)	5 (27.8)	

[a]Chi-squared test; *p-value < 0.05 considered significant

Discussion

The rise in vancomycin use has been reported to be a risk factor in vancomycin-resistant *Enterococci,* vancomycin-resistant *Staphylococcus aureus* (VRSA), and vancomycin-resistant *Staphylococcus epidermis* (VRSE) [13-15]. With the challenge of producing new classes of effective antibiotics, current treatments have to be safeguarded to reduce antibiotic resistance. The main aim of this study – to investigate potential areas in which vancomycin use did not follow clinical guidelines – was achieved. This is especially vital in developing countries, where the use of antibiotics requires close monitoring to ensure effective treatment and ultimately cost reduction. The HICPAC guidelines serve as a clinical recommendation in potentially reducing the resistance of microorganisms towards vancomycin. Proper utilization of vancomycin is detailed in these guidelines because of the acknowledged importance of vancomycin resistance in the clinical setting. Although hospitals are advised to conform to these guidelines, the HICPAC does allow for changes in local settings to be applied in order to maximize the reduction in vancomycin resistance.

Vancomycin indications were appropriate in approximately 67% of the cases observed in this study population. This is in agreement with figures from other hospitals, where conformance to guidelines was found to be between 24% and 80% [16,17]. Culture and sensitivity tests were found to be the main guide in prescribing vancomycin for treatment as recommended by the HICPAC [4]. Similar to a previous work [18], MRSA was the most frequent microbe isolated in the present study. Although there have been various guidelines for prudent use of vancomycin, there is no gold standard for the use of the antibiotic. Nonetheless, culture and sensitivity tests remain the most valuable tool in determining appropriate use of the drug. The use of vancomycin in febrile neutropenic patients with catheter-related infections, severe mucositis, and suspected MRSA was also a common indication in this study population, in line with the HICPAC guidelines [4].

There was a high incidence of inappropriate use of vancomycin during the study period. Among these cases were patients requiring renal replacement therapy such as hemodialysis and peritoneal dialysis. Vancomycin is recommended for treatment of patients allergic to beta-lactam-sensitive Gram-positive bacteria in renal impairment [16]. However, during the study, only 7.6% of these patients were allergic to beta-lactam antibiotics. The high inappropriate use in this group of patients should be reviewed, as resistance could pose a problem in the future management of renal-impaired patients. In addition to this, a high rate of inappropriate vancomycin use was encountered during empirical treatment, the most common of which was the use of empirical vancomycin in the management of sepsis. Although there is no clear guideline on the use of vancomycin in sepsis secondary to infections other than vascular, line-related, or neutropenia, a previous work recommended vancomycin in view of the possibility of MRSA in high-risk areas [19]. Indeed, a detailed review is necessary of the possibility of reducing vancomycin use in this group of patients for fear of presenting an increased risk of resistance to vancomycin.

Vancomycin serum level monitoring is one method of ensuring that the serum concentration of the drug is within the therapeutic range. Although serum monitoring is recommended in most patients, approximately 80% of patients were monitored. The risk of sub-therapeutic levels is the increase in resistance to vancomycin. On the other hand, high vancomycin levels increase the risk of toxicity. Trough levels are recommended to give a more accurate and successful treatment outcome [8]. During the study period, more than half of the study population had sub-therapeutic levels during their first measurements. These levels were then adjusted based on the patients' individual requirements. The initial dosing regimens, which were based on the recommended 15 mg/kg of initial vancomycin dose, were observed not to be significantly associated with therapeutic levels of vancomycin. This is in line with previous work on vancomycin doses [20]. Thus, the monitoring of serum levels of vancomycin during initial dosing should be performed to ensure that appropriate therapeutic levels are achieved. Nonetheless, it was determined that patients who were given doses < 15 mg/kg were more likely to achieve sub-therapeutic vancomycin levels. Rybak [8] demonstrated that vancomycin doses of < 15 mg/kg were unlikely to achieve desired trough levels, and therefore recommended higher doses of between 15 and 20 mg/kg. However, further work is required to determine effective doses in the local population, as optimal dosing strategies are dependent on both pharmacokinetic and pharmacodynamic properties such as renal function, inflammation, and concomitant diseases [8,12].

Conclusions

This study provides vital information about the use of vancomycin in concordance with the HICPAC guidelines for developing countries. Findings from this

work provide a basis for improving and strengthening the use of vancomycin in local settings in order to conform to the HICPAC guidelines. More important is the recognition that reference doses of vancomycin of 15 mg/kg do not determine therapeutic levels of vancomycin in the local population. Therefore, further work should be done to identify appropriate doses for the local population. The limitation of this particular study is its retrospective design, which allowed only written clinical considerations to be assessed. To that end, further prospective work could be performed to ensure that vancomycin is prudently used in the clinical setting of tertiary local hospitals.

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