Vancomycin Dosing Adjustment: Comparison Between Trough and AUC Method

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Abstract

Introduction: Vancomycin trough-based dosing adjustment method has been postulated to increase the incidence of vancomycin induced acute kidney injury (AKI) due to overexposure to Vancomycin. Hence the vancomycin 24 hour area under the curve to minimum inhibitory concentration (AUC24/MIC) based dosing has been reintroduced.

Objective: This study aimed to compare the occurrence of AKI, resolution of infection, average total daily dose, and the duration of treatment between the trough-based and AUC24/MIC-based methods.

Methods: This is a combination of retrospective (for trough-based) and prospective (for AUC24/MIC-based) study involving patients with normal renal function who were prescribed vancomycin for the treatment of indicated infection based on culture and sensitivity testing in Hospital Melaka. In the trough-based arm, patients' vancomycin doses were adjusted to achieve the trough level of 15-20µg/mL. Whereas in the AUC24-based arm, vancomycin doses were adjusted to achieve AUC24 target of 400-600 mg.h/liter and trough level of 10-20µg/mL.

Result: A total of 152 patients were included, with 70 patients in trough-based arm and 82 patients in AUC24/MIC-based arm. The indications of vancomycin were mainly for bone Methicillin Resistant *Staphylococcus Aureus* (MRSA) (30, 19.7%), swab MRSA (24, 15.8%), and tissue MRSA (19, 12.5%). There was no statistically significant difference in the occurrence of AKI between the AUC24/MIC-based arm (n=5, 45.5%) and trough-based arm (n=6, 54.5%) (p=0.557). There were also no statistically significant differences between the AUC24/MIC-based arm and trough-based arm in terms of number of patients with resolution of infection [64 (91.4%) vs 79 (96.3%), *p*=0.116)] average total vancomycin dose [1757.10mg (standard deviation, SD 826.85mg) vs 2125.00mg (SD 986.21mg), *p*=0.350)], and duration of treatment [13.96 days (SD 9.50 days) vs 13.39 days (SD 9.54 days), *p*=0.661)].

Conclusion: This study found no reduced incidence of AKI with AUC24/MIC-based vancomycin dosing method. The average daily dose, treatment duration, and rate of resolution of infection were the same between trough-based and AUC24-based dosing adjustment methods. Further study with large sample size is warranted.

Keywords: Vancomycin, trough-based, AUC24/MIC-based, acute kidney injury

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Introduction

Vancomycin is a glycopeptide antibiotic with bactericidal microbial activity, inhibiting the synthesis of cell wall of susceptible microorganisms (1). In Malaysia, vancomycin is widely used, either empirically or specifically, to treat infections by gram positive microorganisms, notably in cases where these infections are or at high risk instigated by MRSA (2). Since vancomycin was introduced in 1958, contributing factors such as persistent infection, prolonged vancomycin duration, treatment failure and recurrent hospitalisation have led to the emergence of vancomycin intermediate resistant *staphylococcus aureus* (VISA) and vancomycin resistant *staphylococcus aureus* (VRSA) in the past 20 years, threatening the role of vancomycin as first line treatment, and rendering health care professional to the use of second line treatment such as daptomycin, linezolid, which are of higher costs (3).

The emergence of VISA and VRSA has alerted the health care community on the importance of optimisation of vancomycin treatment (4). The ratio of AUC24/MIC is the pharmacodynamic target in assessing the adequacy of exposure and coverage by Vancomycin (5-8). However due to the requirement of multiple serum samples in this method, implicating in higher medical expenses and inconveniency, the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists in their published consensus guidelines in year 2009 has recommended MRSA infection to target trough level 15-20 mcg/mL in order to achieve AUC24 required for treatment efficacy of > 400 mg.h/liter, if the MIC was ≤ 1 mcg/mL in patient with normal renal function (9).

Vancomycin overdosing is more prevalent in trough level guided dosing compared to AUC24/MIC guided dosing. Around 60% of patients with normal renal function and therapeutic AUC of ≥400 mg.h/liter were expected to have trough concentration below 15 mcg/mL (10). Therefore, trough level orientated dosing may lead to higher risk of nephrotoxicity (9). The extent of vancomycin induced acute kidney injury and histopathologic renal damage increases with the daily exposure of vancomycin and the duration of treatment in animal model studies and human exposure-response data (11, 12).

In February 2020, the vancomycin AUC24/MIC-based protocol was implemented in Hospital Melaka for patients with normal renal function. In order to assess the impact of changing current local practice on trough level guided vancomycin dosing to AUC24/MIC guided vancomycin dosing, this research aimed to assess and compare the occurrence of AKI, clinical outcome (resolution of infection), average daily dosing, and duration of vancomycin treatment between these two methods of vancomycin dosing in our population.

Methods

This was a retrospective (for trough level guided dosing adjustment method) and prospective (for AUC24/MIC guided dosing adjustment method) observational study conducted in Hospital Melaka, Malaysia. The study was registered with the National Medical Research Registry (NMRR 20-263-53121) and approval to conduct the study was obtained from the Ministry of Health Malaysia Medical Research and Ethics Committee (MREC) and Hospital Melaka's Hospital Research Review Committee (HRRC). The study population involved patients admitted to Hospital Melaka with normal renal function (creatinine clearance ≥ 50 ml/min) who received vancomycin for the treatment of indicated infection based on culture and sensitivity testing. Patients in the critical care setting were also included. Patients were excluded from the study if the infection of concerned was meningitis or infection involved central nervous system, if vancomycin was administered for surgical prophylaxis purpose, or if the patient aged 18 years old and below.

Patients in the trough-based arm were identified retrospectively from 1st July 2019 to 31st January 2020, while patients in the AUC24/MIC-based arm were included prospectively from March 2020 to June 2021. This adjustment in the study design was prompted by the changes in the vancomycin dosing practice at Hospital Melaka, as mentioned previously. In the trough-based arm, vancomycin dosing was adjusted based on pre vancomycin administration blood sample level, which was also known as trough level in this study, to make sure that the trough level was maintained within the therapeutic range of 15-20 mcg/mL. No calculation is needed for this approach. In the AUC24/MIC-based arm, two blood samples, pre and post administration of vancomycin, were taken to calculate the AUC24/MIC using the calculation protocol as shown in Appendix 1 (9, 13). Vancomycin dosing was adjusted to maintain the AUC24/MIC within the therapeutic range of 400-600 mg.h/liter and trough level between 10 to 20 mcg/mL (10). The vancomycin serum concentrations were analysed in the Biochemistry Unit, Department of Pathology of Hospital Melaka using Siemens Atellica with particle-enhanced turbidimetric inhibition immunoassay (PETINIA) method. PETINIA is a homogeneous competitive immunoassay and the rate of absorbance is inversely proportional to the concentration of drug in the sample (14).

In Hospital Melaka, Vancomycin samplings and duration of follow up were carried out according to the Clinical Pharmacokinetics Pharmacy Handbook 2019 (15). In both methods, the trough level (pre sample) was obtained before the fourth or fifth dose of vancomycin and was collected 30 minutes or one hour before the administration of vancomycin. However, an additional post sample was required for AUC24/MIC-based method which was taken one hour after the vancomycin infusion was completed. If the vancomycin trough concentration or AUC24/MIC level were within the therapeutic targets, the dosing of vancomycin will be maintained and the monitoring process will be repeated after a week. If the trough concentration or AUC24/MIC level were not within the therapeutic targets, the dosing of vancomycin will be adjusted and the monitoring processes will be repeated after the dose adjustment. The duration of follow

up in this study was from the initiation of vancomycin until its completion or discontinuation, which ranged from 1 week to 3 months, or until patients were discharged or deceased. During the follow period, all patients were monitored routinely on creatinine, blood urea and serum electrolytes. Furthermore, daily monitoring of input/output chart, and daily review of patient's clinical response which included wound condition, vital signs, and repeated cultures for microorganism clearance were carried out.

Sample size was calculated using PS: Power and Sample Size Calculation by Vanderbilt University, and online software calculator for power analysis. All power analyses were assuming an alpha=0.05, power of 80%, m=1, dichotomous, two proportions, and independent analysis. The sample size required for this study was 206 patients. To cater for incomplete medical records, an additional 20% of samples was added to the required sample sizes. The final sample size targeted was 248 patients.

Patients in the two arms were compared for the occurrence of AKI and proportion of resolved infection using Chi-Square test. The average total daily dose, duration of treatment and the trough level collected during the treatment period between both arms were compared using Independent t-test, with significance defined as p <0.05. All statistical analyses were performed using IBM Statistical Package for Social Science (IBM SPSS) programme version 22.0 and Microsoft Excel version 2013.

Result

In total, 183 patients were evaluated for study inclusion, and 152 patients were included for analysis. The remaining were excluded due to missing of vancomycin level. There were 70 patients in the trough-guided dosing arm and 82 in the AUC24/MIC-guided dosing arm. The mean (SD) age of our study population in trough-based arm and AUC24/MIC-based arm was 50.3 (18.8) and 47.1 (16.5) years, respectively. Most of the patients in both arms were Malay and male (Table 1). The baseline median (IQR) renal function in trough-based and AUC24/MIC-based group before the vancomycin treatment was 109.5 (90.0) ml/min and 96.5 (75.0) ml/min respectively. The renal function of patients for both arms did not change much at the end of vancomycin treatment. Seven cases (10%) in trough-based group and 17 cases (20.7%) in AUC24/MIC-based group were concomitantly administered with nephrotoxic medication like amikacin, gentamicin, and amphotericin B.

Table 1: Baseline characteristics of study population (n=152)

Variables	Trough-based	AUC24-based
Age, year mean (SD)	50.3 (18.8)	47.1 (16.5)
Weight, kg median (IQR)	65.0 (26.0)	65.0 (22.0)
Gender, n (%)		
Male	42 (60.0)	55 (67.1)
Female	28 (40.0)	27 (32.9)
Race, n (%)		
Malay	51 (72.9)	52 (63.4)
Chinese	12 (17.1)	19 (23.2)
Indians	7 (10.0)	7 (8.5)
Other	0	4 (4.9)
Renal Function, ml/min, median (IQR)		
CrCL (Baseline)	109.5 (90.0)	96.5 (75.0)
CrCL (End of treatment)	105.5 (105.0)	91.5 (59.0)
Concurrent nephrotoxic drugs, n (%)	7 (10.0)	17 (20.7)
Pharmacokinetics Profile, median (IQR)		
Trough level, mcg/mL	13.9 (10.1)	10.5 (8.7)
Ke, hr-1		0.11 (0.08)
Vd, L/kg		0.75 (0.38)
AUC24/MIC		445.2 (228.2)

Abbreviation: SD = Standard deviation; IQR = Interquatile range; CrCL = Creatinine clearance (using Cockcroft-Gault); Ke = Elimination rate constant; Vd = Volume of distribution; AUC24/MIC = Area under the curve to minimum inhibitory ratio

In our study population the primary indications of vancomycin were bone MRSA (30, 19.7%), followed by swab MRSA (24, 15.8%) and tissue MRSA (19, 12.5%) (Table 2). A total of 6 (8.6%) patients from trough level guided dosing and 5 (6.1%) from AUC24/MIC-based dosing arm had observed AKI, as defined by Acute Kidney Injury Network (AKIN) (16). There was no significant difference on the occurrence of AKI between these two groups (p=0.557) (Table 3). In terms of resolution of infection, there was also no significant difference between the two groups (p=0.116) (Table 3).

Table 2: Indication of Vancomycin treatment (n=152)

Indication	Proportion, n (%)
Bone MRSA	30 (19.7)
Swab MRSA	23 (15.1)
Tissue MRSA	19 (12.5)
Blood MRSA	18 (11.8)
Pus MRSA	6 (3.9)
ETT, Sputum, Bronchoaveolar MRSA	6 (4)
Non-MRSA infection [#]	50 (33)

[#] Included corynebacterium, enterococcus, rhodococcus, staphylococcus coagulase negative, and as empirical treatment of neutropenic sepsis in patients who received chemotherapy.
Abbreviation: MRSA = Methicillin resistance staphylococcus aureus; ETT = Endotracheal tube

Table 3: The development of AKI and resolution of infection in trough-based and AUC24-based groups

Parameters	Trough-based (n=70)	AUC24-based (n=82)	Statistics[a]	
			X^2 (df)	p-value
AKI, n (%)				
Yes	6 (8.6)	5 (6.1)	0.344 (1)	0.557
No	64 (91.4)	77 (93.9)		
Infection resolved, n (%)				
Resolved	64 (91.4)	79 (96.3)	2.47 (1)	0.116
Not resolved/ death	6 (8.6)	3 (3.7)		

[a] Chi-Square test
Abbreviation: AKI = Acute Kidney Injury; SD = Standard deviation

The mean trough level of AUC24/MIC-based dosing arm (11.9mcg/mL, SD 5.8) was significantly lower than the trough-guided dosing group (15.3 mcg/mL, SD 8.2) (p=0.032). Nonetheless, there was no statistically significant difference in the mean total average vancomycin dose (p=0.35) and mean duration of treatment in both groups (p=0.661) (Table 4).

Table 4: Comparison of the measured total trough level, total daily dose and duration of treatment between trough-based and AUC24-based

Parameters	Trough-based	AUC24-based	Statistics [b]	
			t (df)	p-value
Through level, *µg/mL*, mean (SD)	15.25 (8.23)	11.93 (5.75)	2.92 (150)	0.032
Daily vancomycin dose, *mg*, mean (SD)	1757.1 (862.85)	2125.0 (986.21)	-2.43 (150)	0.350
Duration of treatment, *day*, mean (SD)	13.96 (9.50)	13.39 (9.54)	0.37 (150)	0.661

[b] Independent-*t* test
Abbreviation: SD = Standard deviation

Discussion

Nephrotoxicity is a common side effect in vancomycin-treated patients (9,17). Our analysis showed there was no significant difference in terms of AKI between AUC24/MIC-based and trough-based dosing

adjustment. Our study only managed to analyse 152 patients instead of the minimum sample size of 206 patients, hence might not be able to detect significant differences between the two arms. A systemic review and meta-analysis by Tsutsuura *et al.* in 2021 that reviewed four studies comparing between AUC24/MIC-guided and trough-guided methods concluded that the incidence of vancomycin induced nephrotoxicity (VIN) was lower with AUC24/MIC-guided method. Nevertheless, it was noted that their findings might be compromised by differences in AUC24/MIC estimation methods and therapeutic range used in these four studies (18). In another study by Philips *et al.* that recruited 2,507 patients for the trough arm and 2,471 patients for the AUC24/MIC arms across 12 hospitals, there was no differences in the incidence of VIN and duration of vancomycin therapy (19). These findings were similar to our study. The background of this study was more comparable to our research as it was conducted in hospital setting, recruited all cases of vancomycin including the empirical cases, adapted the same AUC24/MIC therapeutic range (400-600 mg.h/liter), and AKIN criteria for determination of kidney injury, as well as pharmacist-driven dosing adjustments.

The AUC24/MIC-based arm has significantly lower trough level as compared to trough-based arm while still achieving the therapeutic range. This indicated that sufficient vancomycin exposure can be achieved without having high trough level. Consequently, this approach reduces the frequency of dosing titration and therapeutic monitoring sampling to achieve high trough level as with previous trough-based dosing methods in Malaysian hospital-care. This is especially beneficial in settings with limited access to Therapeutic Drug Monitoring (TDM) services. This result was in line with the statement by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists revised concensus guideline in 2020 where AUC24/MIC can be achieved with lower trough level, hence avoiding toxicity risk from over-exposure of vancomycin (17). Our findings, however, did not show differences in the average total daily dose needed to achieve therapeutic range in both arms, hence postulating no cost-saving in term of the vancomycin usage between both arms. In contrast, study by Lee BV *et al* found that there were significant institutional cost reduction using two sample AUC24 or single sample Bayesian methods as compared to trough dosing monitoring of vancomycin (20).

Similarly, the duration of Vancomycin treatment, which averaged around 14 days, was not significantly different in both arms. This may indicate the non-inferiority of AUC24/MIC-based dosing approach as compared to trough-based dosing method. The duration of intravenous antibiotics would only be extended if there is deterioration of infected wound infection (8, 21). In terms of resolution of infection, there was also no significant difference between the two arms, although AUC24/MIC-based arm recorded slightly less patients with unresolved infections. In a study by Marko *et al.*, the treatment failure was 34 percent in which the initiation of vancomycin after the first positive culture result and the time to AUC24 target attainment longer than four days were predictive of treatment failure (22). Besides that, a study by Johnston *et al.* revealed that treatment failure was more common with trough level below 10.6 mcg/mL or AUC24 below 410 mg.h/liter (23). Hence, maintaining the therapeutic range of 400-600 mg.h/liter and trough level between 10 to 20 mcg/mL in the AUC24/MIC-based doing method would be important to ensure treatment response.

Our study had several limitations. Firstly, our sample size was relatively small and only conducted in single institution which means the result cannot be generalised. Secondly, the baseline characteristics was not controlled and compared in this study, so the outcome of this study needs to be interpreted with caution. Additionally, all patients who received vancomycin were included in this study, including critically ill or neutropenic patients. As these patients often had more complications, poor organ functions and were usually on multiple medications and concomitant nephrotoxins, which could introduce remarkable changes in their pharmacodynamics and pharmacokinetics (24).

Conclusion

Our study showed that there was no difference in the occurrence of AKI among patients treated with vancomycin using the AUC24/MIC-based and trough-based dosing adjustment methods. However, the AUC24/MIC-based method can maintain patients at lower vancomycin trough concentration without being inferior to trough-based method in term of the resolution of infection and duration of treatment. Further study could be conducted to explore the differences in vancomycin therapeutic range between MRSA and non-MRSA infections.

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Conflict of interest statement
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Appendix 1

Vancomycin: AUC-Guided Dosing Approach

Equation-based approach:

i. Based on first-order pharmacokinetic equations to estimate the AUC value
ii. Required collection of two timed steady-state vancomycin concentrations
iii. Trapezoidal equations are one of the most commonly used method

Overestimate AUC Method

A. To estimate elimination rate constant, Ke

$$Ke\ (hr^{-1}) = \frac{\ln C\ post(mcg/mL) - \ln C\ pre\ (mcg/mL)}{\tau - (t\ infusion + t\ pre + t\ post)}$$

T	:	Dosing interval (hours)
t infusion	:	Infusion time (hours)
t pre	:	Interval between pre sampling and administration time (hours)
t post	:	Interval between end of infusion and post sampling (hours)

B. To calculate expected C naught (C_0)

C naught (C_0) is an extrapolated concentration at the start of infusion

$$C_0\ (mcg/mL) = C\ post\ \times\ e^{ke\ t0}$$

C_0	:	Extrapolated concentration at the start of infusion (mcg/ml)
C_{post}	:	Measured post level (mcg/ml)
Ke	:	Elimination rate constant (hr^{-1})
t_0	:	Time between start of infusion and post sampling (hours)

C. To calculate AUC (single interval)

$$AUC\ (single\ interval) = \frac{C_0(mcg/ml) - C\ pre\ (mcg/ml)}{Ke}$$

D. To calculate total AUC

$$AUC\ (total) = AUC\ (single\ interval) \times Dosing\ frequency$$

Dosing frequency	:	If dosing frequency is 12 hourly, hence need to X 2 If dosing frequency is 8 hourly, hence need to X 3