Indonesian Journal of Pharmacy

VOL 33 (3) 2022: 484–492 | RESEARCH ARTICLE

Evaluation of Trough-Based Vancomycin Therapy in Achieving Targeted Area Under the Curve in Haemodialysis Cases

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Submitted: 17-04-2022
Revised: 10-09-2022
Accepted: 15-09-2022

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ABSTRACT

Recently published Infectious Diseases Society of America (IDSA) guidelines on vancomycin dosing no longer advocates the use of trough concentrations as surrogate markers for clinical efficacy. Protocols developed prior to revised targets may not reflect to the true efficacy marker for vancomycin that is area under the curve divided by minimum inhibitory concentration (AUC/MIC) 400-600 mg.hr/L. This study aimed to evaluate the local vancomycin dosing protocol in achieving the target trough concentration and extrapolated AUC/MIC of 400-600 mg.hr/L in patients with haemodialysis. A retrospective analysis of therapeutic drug monitoring forms and individual medical records of hemodialysis patients was conducted. Vancomycin AUC of each individual was extrapolated via the use of a pharmacokinetic modelling software, PrecisePK®. Chi-square test of independence was used to determine the association of factors affecting AUC/MIC. A *p* value of less than 0.05 was considered statistically significant. A total number of 80 hemodialysis-dependent cases who were on vancomycin were recruited. More than 62% of hemodialysis patients showed AUC/MIC > 800 mg.hr/L. AUC/MIC was heavily influenced by minimum inhibitory concentration of the infecting microorganism. Exclusive trough-guided dosing may not translate well in achieving clinical efficacy of vancomycin in hemodialysis patients. The observed small values of MIC account for large AUC/MIC. Adjusting the dose to achieve AUC/MIC of 400 – 600 mg.hr/L requires a lower dose of vancomycin in almost 80% of the cases. The clinical impact of this dosage revision should be investigated to ensure that vancomycin efficacy will be maintained. If vancomycin efficacy is preserved, the reduced dose would be helpful to maintain the residual kidney function; a factor which is associated with overall mortality of HD patients.

Keywords: Vancomycin, Hemodialysis, Trough concentration, Dosage adjustment, Bayesian pharmacokinetics

INTRODUCTION

The use of central venous catheters that create direct access into the bloodstream and the potential transmission of the microorganism make the patients on haemodialysis (HD) to be highly susceptible to the methicillin-resistant *Staphylococcus aureus* (MRSA) infections (Al-Talib et al., 2010; Eleftheriadis et al., 2011). A study shows the prevalence of MRSA infections as high as 15.1% amongst HD patients compared to a mere 5.8% of all admitted cases (Yeoh et al., 2014). The findings highlight the need to preserve vancomycin's use against MRSA especially in HD patients that spend a significant amount of time in various healthcare settings. The dosing of vancomycin in HD patients, however, is a complicated matter due to the diversity of residual renal function, non-renal drug elimination, type,

and intensity of infection on one hand and the type of dialyzer and flux membrane, duration and frequency of haemodialysis, and blood and dialysate flow rates, on the other hand (Launay-Vacher et al., 2002; Rybak et al., 2020).

Conventionally, the dosing of vancomycin in HD patients follows a local protocol in combination with individualized therapy based upon therapeutic drug monitoring (TDM) results. This protocol provides guidance on the amount of stat dose, timing of supplemental dose (either intra or post haemodynamically) and the monitoring schedule which denotes sampling for pre-haemodialysis trough values. Subsequent doses would rely essentially on the pre-haemodialysis trough values.

As vancomycin is a time-dependant antibiotic, the accepted efficacy marker for vancomycin's bactericidal activity against MRSA infections is the area under the curve over minimum inhibitory concentration (AUC/MIC), within the range of 400 to 600. The trough concentrations were regarded as accepted surrogate markers in place of AUC/MIC and therefore conventional dosing protocols rely heavily on trough concentrations. With continued research into vancomycin use and its outcomes, trough-guided dosing has now proven inadequate, as it does not necessarily translate to the desired AUC/MIC (Rybak et al., 2020).

The 2020 vancomycin dosing guidelines released by the Infectious Disease Society of America (IDSA) no longer advocates the use of trough concentrations between 15 and 20 mg/L as a surrogate marker for AUC/MIC. The guidelines explain that although a trough concentration ensures the minimal cumulative exposure, a wide range of concentration-time profiles can result in identical trough values. This is alarming as the time-dependant killing nature of vancomycin, relies heavily on the cumulative exposure of the drug over MIC within a given interval. IDSA now recommends a monitoring of AUC/MIC between 400 and 600 that will ensure clinical efficacy; and assuming the MIC is 1 mg/L, the AUC range of 400 to 600 could be associated with lower rate of acute kidney injury (AKI). (Rybak et al., 2020) Vancomycin-associated nephrotoxicity is an important parameter of interest for HD patients as preserving residual kidney function confers for many physiological benefit, namely mortality (Krediet, 2017). Current evidence shows that AUC/MIC to an extent of 800 is still a reasonable threshold for vancomycin induced toxicity, above which the risk of nephrotoxicity increased by 3 to 4 folds (Zasowski et al., 2017).

In the past, AUC/MIC calculations were impractical in a clinical setting due to the sheer number of samples required for calculations. Fundamentally, two concentrations, a peak and a trough in a mathematical hand calculated approach can be used to quantify the AUC (Pai et al., 2014). Practically, this may not suffice, as it would require for a subsequent sampling (post dose), increased waiting time for each patient, and increased use of laboratory facilities which ultimately increases the cost borne by the healthcare facility (Surendra et al., 2018). Additionally, reducing phlebotomy in haemodialysis preserves vascular access of the peripheral veins that may serve needful for future dialysis purposes in HD patients (McCoy et al., 2020). Thus, AUC quantification via manual calculation may not prove a viable option. Instead with technological advancements, and pharmacokinetic (PK) modelling software, AUC can be calculated with minimal samplings. The software tends to utilize probability statistics, and computational mathematics to build a pharmacokinetic model that serves as a canvas over which individual patient information can be fed to build a concentration-time profile. The software thus helps to predict and provide guidance in dosing aspects. A Bayesian PK software requires only a single concentration to provide AUC-guided dosing recommendations (Rybak et al., 2020; Turner et al., 2018).

Vancomycin protocols developed prior to this latest advancement, rely on target trough concentrations instead, and may not adequately reflect the new revised target of AUC/MIC 400-600. The absence of a fixed dosage plan and trough only guided dosing, as well as the scarcity of available studies creates interest in the HD population as the likelihood of not attaining target trough concentrations is high. It was therefore crucial to evaluate the appropriateness of current dosing protocol amongst dialysis patients. Through this and since vancomycin plasma concentrations affected by a multitude of factors, we intended to determine the correlation between trough concentrations and the AUC/MIC.

This study served to evaluate the current vancomycin dosing protocol for HD patients in the Hospital Tengku Ampuan Rahimah Klang (HTAR), Klang, Malaysia by using a validated cloud-based software (PrecisePK®) that utilizes Bayesian approaches for the extrapolation of AUC values from respective trough values. In doing so, we

intended to determine the appropriateness of the given doses in reference to the main suggested efficacy indicator, the ratio of AUC/MIC.

MATERIAL AND METHODS

Our study was conducted in HTAR, a public tertiary care facility situated in the city of Klang with 850 inpatient beds. The approval for the project was initially obtained from the Faculty Research and Scholarly Activities (FRSA), Faculty of Pharmaceutical Sciences, UCSI University. The project subsequently received a grant from the Centre of Excellence for Research, Value Innovation and Entrepreneurship (CERVIE), UCSI University (grant code REIG-FPS-2020-053). Ethical clearance was then sought from the Medical Research and Ethics Committee (MREC) for which the study was registered under the National Medical Research Registry (NMRR), Ministry of Health with a research code of NMRR-20-1568-55655(IIR).

The design of the study followed a retrospective, non-comparative case series approach. All required data were pre-agreed upon prior to extraction, based on a data collection form.

The calculated target sample size was 80, based on the online case-series calculator (Musonda) and other similar studies involving smaller sample sets. (Barth & DeVincenzo, 1996; Pai & Pai, 2004) All data were extracted from internal therapeutic drug monitoring (TDM) forms, patient medical records and the hospital database. Patients were recruited in a sequential manner between December 2019 and January 2021 until the targeted sample size was achieved. Eligible cases involved end-stage renal disease (ESRD) patients on HD currently receiving IV vancomycin therapy with at least a single TDM report. Cases were excluded if the HD patients were not monitored whilst on vancomycin therapy, were on ambulatory dialysis or received haemodialysis outside the hospital setting. There was no age limit imposed on the study, as the age of the subjects assumed to be not an indicator for considered outcomes.

The duration of the study proceeded between December 2020 and February 2021 in which the data was concurrently fed into a pharmacokinetic (PK) modelling software, PrecisePK® version v2.0.0.2.0.0 under lease from Healthware Inc, USA for AUC extrapolation. The Bayesian PK modelling software utilized population kinetics and individual vancomycin samples to model a time-concentration curve specific to each patient. The PrecisePK® database includes the dialysis patients, as well (Avent & Rogers, 2019).

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 20 (Chicago, IL). A *p*-value of less than 0.05 was considered statistically significant. Descriptive statistics was used to analyze demographic data for which either mean or median was used based on the nature of distribution of the data. A chi-square test of independence was used to determine the association between multiple ranges of extrapolated trough concentrations and isolated microorganisms to calculated AUC/MIC in 4 district categories of AUC/MIC (<400, between 401 and 600, between 601 and 799, and ≥800 mg.hr/L). Additionally, a scatterplot of measured vancomycin concentration to post-dose sampling time was plotted to provide a visual inspection of the actual sampling outlook in HD patients and highlight the short-comings of trough-guided dosing.

RESULT AND DISCUSSION

Our study involved 80 eligible haemodialysis patients, screened, and identified between December 2019 and Jan 2021 (Table I).

The haemodialysis sessions in HTAR on average lasted for a minimum of 3 h per session with the frequency of haemodialysis sessions being thrice weekly. The median blood flow rate of the study population was 180 mL/min (IQR 180-200) while its respective median dialysate flow rate was 500 mL/min (IQR 500-800). It was noted that unrecorded dialysate flow rates were implied as 800 mL/min in accordance with the haemodialysis protocol at HTAR unless stated otherwise. Additionally, the haemodialysis units at HTAR are fitted with a high-flux membrane.

The total vancomycin exposure of the study participants is summarized **in Table 2**. The patients' characteristics, vancomycin dose and MIC were extracted from the patients' files and TDM reports. The individualized AUC and extrapolated trough level for each case were calculated by the pharmacokinetic modelling software, PrecisePK® version v2.0.0.2.0.0 which is evaluated as high quality and validated software (Kantasiripitak et al., 2020).

The HD patients on average were subjected to 3 HD sessions weekly and therefore, if required a vancomycin sample was drawn prior to each session. Thus, the actual number of drawn vancomycin samples was greater than the total number of the recruited patients.

Table I. Demographic data of haemodialysis patients in HTAR

Variables	Variables
Age (Mean years ± SD)	51.25 ± 14.76
SCr (Mean µmol/L ± SD)	592.25 ± 233.57
Gender	
Female No. (%)	21 (26.3)
Male No. (%)	59 (73.8)
Ethnicity No. (%)	
Malay	52 (65)
Chinese	14 (17.5)
Indian	14 (17.5)
Weight (kg) (Median IQR)	65 (55-75)
Height (m) (Median IQR)	1.65 (1.45-1.8)
BMI (kg/m^2) (Median IQR)	23.84 (21.63-27.10)
Intrinsic Vancomycin Clearance (L/hr) (Median IQR)	0.41 (0.31- 0.60)
Indication for Vancomycin Use No. (%)	
CRBSI	50 (62.5)
SSTI	11 (13.8)
Intra-Abdominal Infection	13 (16.3)
Sepsis	3 (3.8)
Diabetic Foot Infection	1 (1.3)
Others	2 (2.5)

SCr, Serum Creatinine; BMI, Body Mass Index; IQR, Interquartile Range; CRBSI, Catheter-Related Bloodstream Infection; SSTI, Skin and Soft Tissue Infection

Table II. Summary of total vancomycin exposure variables

Vancomycin Exposure	Values
Vancomycin dose (mg) (Median IQR)	1000 (750 -1500)
Vancomycin dose/kg (mg/kg) (Median IQR)	15.5 (11.6 - 20.00)
AUC/MIC (Median IQR)	1251.78 (702.69 - 2315.5)
Measured concentration (µg/mL) (Mean ± SD)	22.96 ± 7.85
Extrapolated trough concentration (µg/mL) (Mean± SD)	15.13 ± 6.00

IQR, Interquartile Range; SD, Standard Deviation

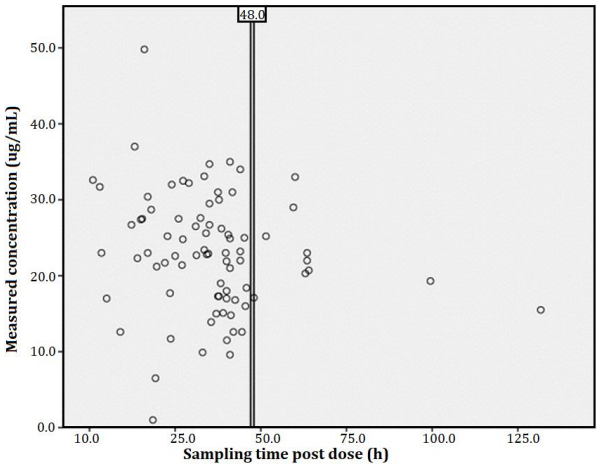

Figure 1. Scatterplot of measured concentration against post sampling time of vancomycin in haemodialysis patients

Only samples that meet the inclusion criteria and were used and allowed for better modelling of the pharmacokinetic profile of the study patients. The detected plasma concentration of vancomycin versus the post-dose sampling time is plotted to investigate the appropriateness of the practice of trough-guided dosing of vancomycin (Figure 1).

As indicated (Table III) MRSA is the predominant culture amongst our study population of haemodialysis patients in HTAR. It accounts for more than half of the cases investigated (53.5%). Approximately 26% of the patients were colonized by Coagulase Negative Staphylococci (CoNS) infection while the *Enterococcus* species accounted for 7.5% of the study population. Other identified cultures included Gram-positive bacilli and cocci.

Table III. Distribution of microbiology culture

Species	**No. (%) of patients**
MRSA	43 (53.8)
CoNS	21 (26.3)
Enterococcus sp.	6 (7.5)
Corynebacterium Striatum	3 (3.8)
Bacillus sp.	2 (2.5)
Brevibacterium sp.	2 (2.5)
Clostridium Difficile	1 (1.3)
MSSA	1 (1.3)
Micrococcus sp.	1 (1.3)
Total	80

With reference (Table IV) the highest frequency of detected levels falls within the category of AUC/MIC beyond 800 which accounts for 65% of the study population. In comparison to this, the group of AUC/MIC (400-600) that denotes the efficacy marker for vancomycin's bactericidal activity records the lowest number of individuals, involving only 8.75% of the haemodialysis patients studied. Only 5% of the study population recorded trough values above 25 mg/L, while most individuals have trough values ranging either less than 15 mg/L or within the range of 15 to 25 mg/L that recorded as 46.25% and 48.75% of the haemodialysis patients, respectively. The desired AUC/MIC, as well as the two extremes of AUC/MIC could be obtained from different intermittent stat doses of vancomycin (Table V).

Table 5 denotes the association between the ranges of AUC/MIC and the predominant culture present in the study group, namely MRSA, CoNS and *Enterococcus sp.* Over 62% of the cases fall in the AUC/MIC category of 800 and above. MRSA isolates records the highest number of cases in this group with a total of 43 (61.4%) individuals (Table III). All Enterococcus species recorded AUC/MIC values below 400. Of the 3 isolates, CoNS was the only microbiology culture with recorded isolates in all 4 groups of AUC/MIC. Upon comparison, MRSA and Enterococcus are cultures that do not record a single isolate within the vancomycin efficacy spectrum of AUC/MIC between 400-600.

Most of the MRSA cases tend to record AUC/MIC values above 800, with the mean average of this category above the 2000 range. As MIC and AUC/MIC share a reciprocal relationship, the resulting value is large as the distribution of MIC in this study is heavily influenced by MRSA cases that predominantly record MIC values of 0.38 mg/L (< 1 mg/L).

Previous studies had reported on the drawbacks of trough-guided vancomycin therapy and suggested the surrogate to be replaced by AUC/MIC (Michael J Rybak et al., 2020; M. J. Rybak et al., 2020). The findings of this study show that in haemodialysis cases whose vancomycin dose is determined by pre-dialysis trough level, there is no correlation between trough levels and desired AUC/MIC (Spearman's rho 0.164, p = 0.631). The current practice of trough-based vancomycin therapy in HD-dependent cases not only fails in providing the desired AUC/MIC in the majority of the patients, but also results in a very high AUC/MIC in a big fraction of the patients, especially those with lower MIC levels such as MRSA-infected cases. This unnecessary exposure to high levels of vancomycin in end-stage renal disease patients is a risk factor to diminish the residual kidney function. Although it may be argued that haemodialysis patients have lost substantial kidney function and thus rely on an external unit for the purpose of filtration of waste, preserving residual kidney function in such individuals have been postulated to confer many survival benefits. Authors Li et al. (2019) have reported that residual kidney function remains an important and favorable prognostic factor for that of reduced mortality, reduced morbidity and improved quality of life. In preserving the residual kidney function, tertiary care tends to benefit from reduced patient load with lower hospital stays and cost reduction seen from precision to medication and individualized therapy (Li et al., 2019).

Table IV. Chi-Square analysis for AUC/MIC against extrapolated trough values

Parameters		AUC/MIC				Total, N (%)
		< 400	400 - 600	601 - 799	≥ 800	
Extrapolated trough concentration (mg/L)	≥ 25	0	0	1	3	4 (5)
	15 - 24	2	6	3	28	39 (48.75)
	< 15	8	1	7	21	37 (46.25)
Total, N (%)		10 (12.5)	7(8.75)	11(13.75)	52 (65)	80

Table V. The frequency of AUC/MIC categories versus given stat dose

		Dose (mg)				Total
		< 750	750<n<1200	1200<n<1550	> 1550	
AUC/MIC	< 400	1	6	3	0	10
	400<n<600	0	4	3	0	7
	600<n<800	2	4	4	1	11
	> 800	7	31	12	2	52
Total		10	45	22	3	80

Previously recommended plasma concentration of 15 to 20 mg/L appeared to produce the vancomycin AUC/MIC above 800 in the present study. According to Rybak et al. (2020) a varying number of concentration-time curves can eventually lead to the same trough values and thus accounts for the degree in variability between AUC/MIC. Additionally, it was interesting to note that trough concentrations of below 15 mg/L also displayed AUC/MIC in the range of above 800. It thus indicates that lower values of trough concentrations are able to reduce the vancomycin exposure, yet maintain adequate AUC/MIC values in its therapeutic range of 400 to 600 (Finch et al., 2017).

Applying a certain dosage regimen of vancomycin in HD-dependent patients may not be feasible. Shifting from current trough-based dosing to the recommended AUC/MIC target, brings the importance of MIC into the center of attention, as it is the denominator of the target value and any variation in the MIC would result in drastic changes in the dosage regimen. According to our findings wherever the AUC/MIC was higher than 800 mg.hr/L the reported MIC of the microorganism was lower than 1 mg/L. The question that further studies must try to answer is whether the benefits of reducing the dose to maintain the AUC/MIC within 400 – 600 mg.hr/L overweigh the possible suboptimal level of trough concentration of vancomycin. Although AUC/MIC values of 400 to 600 mg.hr/L serves as a guide for vancomycin specific to MRSA cases, vancomycin is nonetheless used for other Gram-positive infections. A study claims that it is still reasonable to employ this guide in those microorganisms, as well (Neely et al., 2018). Furthermore, the dose regimen across all 4 categories of AUC/MIC lies within similar ranges. This shows that dosing strategies should not rely on mere weight-based dosing, but to investigate other factors such as MIC that can influence the efficacy marker of AUC/MIC.

However, some have argued the accuracy and reproducibility of AUC/MIC (Revolinski & Doern, 2021). The argument focuses on two major points. The first argument is about the inadequacy and controversy of available evidence to correlate the clinical response with the level of AUC/MIC. The second argument is regarding the potential for diverse and erroneous reported MICs that eventually variates the value of AUC/MIC. In general, the stated level of MIC is not accurate, in nature (Charlton Carmen et al., 2014) and Etest® data, for instance are typically overreported. Where mean and median MIC for MRSA were 0.45 mg/L and 0.38 mg/L, respectively in present study, the same measure in other studies is reported, differently. For example, a study from USA (Musta et al., 2009) reported the MIC as ≤1, 1.5, 2, and 3 mg/L for 74 (15.1%), 355 (72.6%), 50 (10.2%), and 10 (2.1%) isolates, respectively. The diversity is evident when MIC of the isolates in Taiwan is as follows: 21.1% had a MIC = 2 mg/L, 76.4% had a MIC = 1 mg/L and 2.4% had MIC = 0.5 mg/L (Wang et al., 2010). Obviously, the high AUC/MIC, reported in our study is primarily due to the low

MIC level. The potential diversity of MIC is stemmed not only from the nature of MIC value (as a range), but also from the quality control violations.

With regards to the use of trough-guided dosing, the assumption of its surrogacy only holds valid for when the true trough concentration is used for guidance. In a simple 3-time a week session, the patient will be given a supplemental dose following each HD session, and its respective trough concentration is to be measured prior to the subsequent session, primarily 48 hours later. In allowing a generous 3 hours prior to haemodialysis session (considering the extremely high half-life in ESRD) as acceptable trough concentration sampling period, only 5 % of the study population were able to achieve the targeted trough. The observed variability of trough sampling among HD patients in our study population may lead the researchers to the point that the majority of 'trough concentrations' would provide misleading interpretations as it does not reflect the targets of it assumptions (Neely et al., 2018).

The limitations of this study arise from the single healthcare centre. The protocol of vancomycin therapy and microbiology investigations may differ across other institutions. As vancomycin was usually started on the initial order of the prescriber, many cases were excluded as they did not show true infections with recorded MIC values necessary for analysis. Another limitation noted was the lack of validation for the extrapolated AUC obtained from the PrecisePK® software. This was due to the inability to obtain two samples within the same dosing frame to manually calculate the actual AUC which could then be referenced as a control for the study.

CONCLUSION

Vancomycin dosing strategy in dialysis-dependent patients remains to be TDM-guided stat dosing. In addition to the patients' clinical response, AUC/MIC can be deployed as the dominant surrogate. However, vancomycin prescribers should account for the specific MIC of the infecting microorganism that has been noted to heavily influence the AUC/MIC. At the same time, the hospital settings should be equipped with validated software to allow the clinicians extrapolate AUCs and trough levels where needed. Achieving the optimal dose of vancomycin, especially in dialysis-dependent patients, probably would not be possible without considering a collection of parameters, including the clinical response, trough level and AUC/MIC. Future work with increased sample size may be necessary to further evaluate the impact of these high levels of AUC on the residual renal clearance in renal replacement therapy patients that confers for clinical benefit.

ACKNOWLEDGMENT

The authors would like to appreciate the Pharmacy Division and the management of Hospital Tengku Ampuan Rahimah Klang, Malaysia for their kind cooperation with the research team and the Director General of Health, Malaysia for his permission to publish this article. The consistent support of PrecisePK® team is also appreciated.

FUNDING

This study received an internal grant from the Centre of Excellence for Research, Value Innovation and Entrepreneurship (CERVIE), ****(covered for peer review) University.

TRANSPARENCY DECLARATION

The authors declare no conflict of interests.

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