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Association between single trough-based area under the curve estimation of vancomycin and treatment outcome among methicillin-resistant *Staphylococcus aureus* bacteremia patients

Mohd Makmor-Bakry[1], Azmi Nor Mohd Farez Ahmat[1], Ahmad Fuad Shamsuddin[1], Chee-Lan Lau[2], Ramliza Ramli[3]

[1]*Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*
[2]*Department of Pharmacy, Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur, Malaysia*
[3]*Department of Medical Microbiology and Immunology, Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur, Malaysia*

Abstract

Background: Failure of antibiotic treatment increases mortality of critically ill patients. This study investigated the association between the treatment resolution of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and vancomycin pharmacokinetic variables.

Methods: A total of 28 critically ill patients were included in this study. All data were collected from medical, microbiology and pharmacokinetic records. The clinical response was evaluated on the basis of clinical and microbiological parameters. The 24-h area under the curve (AUC_{0-24}) was estimated from a single trough level using established equations.

Results: Out of the 28 patients, 46% were classified as responders to vancomycin treatment. The trough vancomycin concentration did not differ between the responders and non-responders (15.02 ± 6.16 and 14.83 ± 4.80 μg mL^{-1}; $P = 0.929$). High vancomycin minimum inhibitory concentration (MIC) was observed among the non-responders ($P = 0.007$). The ratio between vancomycin trough concentration and vancomycin MIC was significantly lower in the non-responder group (8.76 ± 3.43 vs. 12.29 ± 4.85 μg mL^{-1}; $P = 0.034$). The mean ratio of estimated AUC_{0-24} and vancomycin MIC was 313.78 ± 117.17 μg h mL^{-1} in the non-responder group and 464.44 ± 139.06 μg h mL^{-1} in the responder group ($P = 0.004$). AUC_{0-24}/MIC of ≥ 400 μg h mL^{-1} was documented for 77% of the responders and 27% of the non-responders ($\chi^2 = 7.03$; $P = 0.008$).

Conclusions: Ratio of trough concentration/MIC and AUC_{0-24}/MIC of vancomycin are better predictors for MRSA treatment outcomes than trough vancomycin concentration or AUC_{0-24} alone. The single trough-based estimated AUC may be sufficient for the monitoring of treatment response with vancomycin.

Key words: vancomycin, MRSA, critical care, AUC, MIC, trough concentration.

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CORRESPONDING AUTHOR:

Mohd Makmor-Bakry, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia, phone: +603 9289 7244, fax: +6032698 3271, e-mail: mohdclinpharm@ukm.edu.my

Methicillin-resistant *Staphylococcus aureus* (MRSA) is amongst the most serious infections of hospitalized patients. MRSA infections are associated with high mortality, especially amongst critically ill patients [1]. A recent clinical guideline recommends a higher serum trough concentration (15–20 μg mL^{-1}) for patients with complicated MRSA bacteremia [2]. Even though a higher trough concentrations has being associated with a better treatment response [3], clinical failure remains common even in patients who have achieved the recommended target for vancomycin trough concentration. Clinical failure in patients with a higher trough concentration was reported to be associated with high minimum inhibitory concentration (MIC) of vancomycin towards MRSA [1, 4–7].

Beside treatment failure, an increased mortality rate has also been observed in patients with higher vancomycin MIC [8–11]. These issues complicate the role of vancomycin as a gold standard in the treatment of MRSA bacteremia. In Malaysia, a higher vancomycin MIC value has being reported in six major hospitals [12]. Treatment failure with vanco-

mycin is not uncommon even with MIC < 2 μg mL^{-1}. The Clinical and Laboratory Standards Institute has also changed the vancomycin susceptibility breakpoint against MRSA from 4 μg mL^{-1} or less to 2 μg mL^{-1} or less [13].

Commonly, vancomycin trough concentration alone has being used to predict vancomycin treatment efficacy. However, conflicting evidence has been published for the relationship between vancomycin trough concentration and treatment response [3–5]. The pharmacokinetic/pharmacodynamic (PK/PD) profiles for vancomycin have being investigated over the past decade. The ratio of area under the plasma concentration-time-curve (AUC) and MIC has being proposed as the appropriate PK/PD variable to represent vancomycin effectiveness. Several studies have shown that higher AUC/MIC (> 400 μg h mL^{-1}) has being associated with improved treatment outcomes and faster bacterial killing [14–16]. On the other hand, two studies reported a lower effective AUC/MIC ratio cut-off point at 300 μg h mL^{-1} [17, 18].

In Malaysia and most of the developing countries, standard monitoring of trough vancomycin concentration is widely practiced as a supportive indicator for vancomycin effectiveness. This PK variable may not be able to appropriately represent the vancomycin PK-response relationship with the current increase in vancomycin MIC among MRSA. As such, this study aimed to investigate the relationship between the resolution of MRSA bacteremia and vancomycin PK variables, namely AUC_{0-24}, AUC_{0-24}/MIC, trough concentration and trough concentration/MIC, on treatment response among critically ill patients.

METHODS

This retrospective study was conducted in Universiti Kebangsaan Malaysia Medical Center involving critically ill patients with MRSA bacteremia. The study proposal has been approved by Universiti Kebangsaan Malaysia Research Ethics Committee (UKM1.5.3.5/244/NF-014-2013).

Patients included in this study were those over 18 years old, with MRSA bacteremia, treated with vancomycin for at least 72 hours. Vancomycin was administered through intermittent intravenous short infusion, having the serum vancomycin trough concentration monitored, with MIC vancomycin measured using an E-test (E-test; BioMerieux, USA), with baseline white blood cell and neutrophil counts of more than two serial readings. Body temperature was recorded daily throughout the ICU stay. Patients treated with vancomycin for other indications beside MRSA and patients who were concurrently being treated with other antibiotics for MRSA bacteremia were excluded from this study. A positive culture for MRSA was isolated in 68 patients, but only 36 patients were treated with vancomycin. From the 36 patients, 28 fulfilled the inclusion and exclusion criteria.

Medical, microbiological and pharmacokinetic records of the eligible patients were retrieved and reviewed. Appropriate demographic, laboratory and clinical data were collected using a structured data collection form. These data included: age, sex, body mass, acute physiology and chronic health evaluation II (APACHE II) score upon ICU admission, duration of ICU admission, co-morbid conditions, white blood cell with neutrophil count, culture and sensitivity, daily body temperature, type and duration of ventilator support, use and duration of inotropic support and concurrent antibiotics for other indications beside MRSA. Information regarding the vancomycin therapy was also collected. These data included dose, frequency, timing of dose, vancomycin MIC values, serum vancomycin concentration and timing of sampling.

Due to the nature of standard monitoring practice in the study site and study design, only trough vancomycin concentrations were available for the estimation of PK variables. Vancomycin trough concentration was defined as the concentration before the next scheduled vancomycin dose at steady-state level. The serum vancomycin concentration was measured using automated fluorescence polarization immunoassay (COBAS Integra 800 System, ROCHE, USA). The maximum vancomycin concentration and AUC_{0-24} were estimated from the trough level and published vancomycin population PK values by using established equations [19, 20].

The primary end-point measured was clinical response to vancomycin therapy and was identified as either responder or non-responder. As such the PK profile of vancomycin was compared based on these two groups. 'Response' was defined as improvement of infection related parameters; such as decreasing white blood cell (WBC)/neutrophil count, resolving local signs of infections, decreasing body temperature, change of invasive ventilation support to non-invasive ventilation support, and discontinuation of inotropic support. 'Non-response' was defined as no improvement or worsening of signs and symptoms of infection as described in 'Response', or a change of antibiotic from vancomycin to alternative agents (teicoplanin, linezolid and daptomycin) based on the clinical judgment of clinicians and with or without persistent positive culture.

All discrete data were presented as frequencies and percentage and continuous variables were summarized as mean ± SD where appropriate. Appropriate contingency table tests were used to compare the

nominal data and Student's *t*-test was used for normally distributed continuous data. Statistical significant difference was set at $P < 0.05$. All statistical data were analyzed using IBM SPSS version 21 for Windows.

RESULTS

The 28 patients were categorized into two groups based on clinical response as either responders ($n = 13$) or non-responders ($n = 15$). Table 1 shows the demographic data and clinical profile of the patients. The majority of patients in both groups were male. The average mean age (± SD) for the responder and non-responder groups was 55.92 ± 16.74 and 62.07 ± 12.60 years, respectively. The distribution of co-morbid conditions was comparable between the two groups. The mean APACHE II score in the responder group was 22.69 ± 5.04 and in the non-responder group was 23.87 ± 8.38 ($P = 0.663$). The use of steroids, incidence of shock and mortality were comparable between the groups. The most common concurrent antibiotic used was carbapenem followed by polymyxin-B.

The main isolation sources were from trachea aspirate and blood. Overall, a higher MIC value was

TABLE 1. Demographic data and clinical profile of the patients

Variables	Responders ($n = 13$)	Non-responders ($n = 15$)	*P*-value
Age, years (mean ± SD)	55.92 ± 16.74	62.07 ± 12.60	0.279
Body mass, kg (mean ± SD)	64.25 ± 10.43	68.29 ± 13.18	0.460
Gender, *n* (%)			
Male	12 (92)	10 (67)	0.173
Female	1 (8)	5 (33)	
Co-morbid condition, *n* (%)			
Hypertension	11 (85)	10 (67)	0.396
Cerebrovascular accident	2 (15)	4 (27)	0.655
Cerebrovascular disease	7 (54)	6 (40)	0.705
Diabetes mellitus	9 (69)	10 (67)	1.000
Chronic kidney disease	7 (54)	6 (40)	0.705
Liver disease	2 (15)	1 (7)	0.583
Pulmonary disease	1 (8)	3 (20)	0.600
Alcohol	2 (15)	1 (7)	0.583
Trauma	1 (8)	1 (7)	1.000
Surgery	8 (62)	8 (53)	0.718
Malignancy	2 (15)	4 (27)	0.655
Obesity	2 (15)	4 (27)	0.655
APACHE II score (mean ± SD)	22.69 ± 5.04	23.87 ± 8.38	0.663
Shock, *n* (%)	8 (62)	6 (40)	0.449
Mortality, *n* (%)	5 (39)	8 (53)	0.476
Steroid, *n* (%)	2 (15)	7 (47)	0.114
Concurrent antibiotics, *n* (%)	12 (92)	14 (93)	1.000
Carbapenem	5 (38)	7 (47)	
Polymyxin-B	3 (23)	4 (27)	
Piperacillin/tazobactam	1 (8)	2 (13)	
4th generation cephalosporin	1 (8)	2 (13)	
Vasopressor, *n* (%)	7 (54)	9 (60)	1.000
Length of ICU stay, day (mean ± SD)*	6.88 ± 5.69	16.57 ± 15.79	0.094
Length of ventilation, day (mean ± SD)*	2.63 ± 5.85	12.85 ± 17.39	0.097
Baseline WBC, × 10^9 L^{-1} (mean ± SD)	20.18 ± 8.12	18.57 ± 7.29	0.523
Baseline neutrophils, % (mean ± SD)	87.23 ± 5.16	88.51 ± 8.90	0.654

*Calculated in survived patient only, SD – standard deviation, APACHE II – acute physiology and chronic health evaluation II, ICU – intensive care unit, WBC – white blood cells

TABLE 2. Distribution of methicillin-resistant *Staphylococcus aureus* isolates in relation to specimen site and MIC value

Variables	Responders ($n = 13$)	Non-responders ($n = 15$)	*P*-value
Sample source, *n* (%)			
Wound/swab/pus	3 (23)	4 (27)	0.998
Sputum	1 (8)	–	
Trachea aspirate	5 (38)	5 (33)	
Blood	4 (31)	5 (33)	
BAL	–	1 (7)	
MIC (μg mL^{-1})			
Mean ± SD	1.29 ± 0.41	1.77 ± 0.46	0.004
Range	0.75-2.0	1.0-3.0	

SD – standard deviation, BAL – bronchoalveolar lavage, MIC – minimum inhibitory concentration

TABLE 3. Vancomycin dose and pharmacokinetics/pharmacodynamics characteristics between responders and non-responders to vancomycin therapy

Variables (mean ± SD)	Responders ($n = 13$)	Non-responders ($n = 15$)	*P*-value
Baseline creatinine clearance, mL min^{-1}	42.58 ± 35.25	54.33 ± 35.79	0.391
Clearance vancomycin, L h^{-1}	1.65 ± 1.53	2.09 ± 1.33	0.209
Vd, L	40.25 ± 5.78	42.96 ± 6.25	0.247
Ke, h^{-1}	0.042 ± 0.035	0.038 ± 0.024	0.612
Half-life, h	29.65 ± 20.99	24.16 ± 15.35	0.433
Vancomycin dose, mg kg^{-1} day^{-1}	25 ± 16.4	17 ± 9.5	0.106
Duration of therapy, days	9.25 ± 4.06	9.85 ± 5.33	0.807
Vancomycin trough concentration, μg mL^{-1}	15.02 ± 6.16	14.83 ± 4.80	0.971
< 15 μg mL^{-1}, *n* (%)	7 (54)	6 (40)	0.705
≥ 15 μg mL^{-1}, *n* (%)	6 (46)	9 (60)	
Trough/MIC, μg mL^{-1}	12.29 ± 4.85	8.77 ± 3.43	0.034*
Vancomycin peak concentration, μg mL^{-1}	29.39 ± 11.44	33.93 ± 12.48	0.327
AUC_{0-24}, μg h mL^{-1}	563.44 ± 151.12	523.66 ± 128.44	0.458
AUC_{0-24}/MIC, μg h mL^{-1}	464.44 ± 139.06	313.78 ± 117.17	0.004*
< 400 μg h mL^{-1}, *n* (%)	3 (23)	11 (73)	0.008*
≥ 400 μg h mL^{-1}, *n* (%)	10 (77)	4 (27)	

Vd – volume of distribution, Ke – elimination rate constant, AUC_{0-24} – 24-hour area under the curve, MIC – minimum inhibitory concentration

documented in the non-responder group ($P = 0.007$). The lowest MIC was recorded in the responder group (MIC = 0.75 μg mL^{-1}) and the highest MIC was recorded in the non-responder group (MIC = 3 μg mL^{-1}). Table 2 shows the distribution of MRSA isolates in relation to specimen site and MIC value.

There was no significant difference in terms of creatinine clearance, vancomycin clearance, volume of distribution, elimination half-life, or elimination rate constant ($P > 0.05$). Comparable vancomycin daily dose and duration of therapy between the groups were also documented. No significant difference was observed between the groups in terms of trough concentrations (15.02 ± 6.16 vs. 14.83 ± 4.80; $P = 0.929$). Based on the cut-off point of the vancomycin trough concentration at 15 μg mL^{-1}, no significant difference was found in the distribution of subjects between these groups ($P = 0.705$). The ratio between vancomycin trough concentration and MIC was significantly higher in the responder group (12.29 ± 4.85 vs. 8.77 ± 3.43; $P = 0.034$). The mean AUC0-24 was comparable between the responder group (563.44 ± 151.12 μg h mL^{-1}) and non-responder group (523.66 ± 128.44 μg h mL^{-1}; $P = 0.458$). There was a significant difference in terms of AUC0-24/MIC ratio between the groups (464.44 ± 139.06 μg h mL^{-1} vs. 313.78 ± 117.17 μg h mL^{-1}, $P = 0.004$). Table 3 shows the pharmacokinetics profile of the study cohort. When a cut-off point of AUC_{0-24}/MIC was set at 400 μg h mL^{-1}, the percentage

of responders who achieved at least the set value was 77% and among the non-responders was 27% ($\chi^2 = 7.03$; $P = 0.008$).

DISCUSSION

The vancomycin trough concentrations were similar in the therapy responder and non-responder groups. This finding however contradicted previous reports by Cheong *et al.* [3] and Zelenitsky *et al.* [16]. Both studies found that higher vancomycin trough concentrations were associated with improves treatment outcomes. The current study demonstrated that higher vancomycin trough concentration > 15 μg mL^{-1} were not associated with improved treatment outcomes. This finding showed that vancomycin trough concentration alone is not a good indicator for the treatment outcomes. Similarly, several other studies have also shown that vancomycin trough concentration > 15 μg mL^{-1} did not improve treatment outcomes, especially in the presence of higher vancomycin MIC for MRSA [4, 5, 7].

The vancomycin trough concentration/MIC ratio was higher among responders. This finding supported previous research that found that higher vancomycin trough concentration is needed in patients with higher vancomycin MIC [1, 7]. The ratio of 12.29 ± 4.85 μg mL^{-1} was associated with improved treatment outcomes. This effective trough concentration/MIC ratio can be achieved with higher vancomycin trough concentration in high MIC vancomycin-MRSA cases. Nevertheless, this approach may significantly increase the risk for nephrotoxicity. Hence, close monitoring of renal function is imperative.

Our findings also showed no significant difference in the AUC_{0-24} values when compared between the groups. However, the ratio of AUC_{0-24}/MIC was significantly higher in the responder group. Higher ratio in the responder group indicated that MIC of vancomycin-MRSA had an important influence on vancomycin treatment outcomes in patients with MRSA bacteremia. The effective AUC_{0-24}/MIC ratio of 464.44 μg h mL^{-1} found in the current study was similar to that suggested and reported earlier (400 μg h mL^{-1}) [14–16]. This finding also supported the appropriateness of using a single trough vancomycin concentration to estimate the AUC_{0-24} for the monitoring of vancomycin treatment response.

The findings presented above showed that the effective ratio can be achieved with the recommended trough concentration of around 15 μg mL^{-1} as long as the vancomycin MIC is equal to or less than 1 μg mL^{-1}. If the isolated MRSA strain is associated with higher vancomycin MIC, both the ratios of trough concentration/MIC and AUC_{0-24}/MIC may become better predictors for vancomycin effectiveness. This supports the value of MIC monitoring in vancomycin treated patients especially in the critically ill setting. One more element that could also influence the outcome is the genetic virulence factors of the MRSA which involve the Panton-Valentine leukocidin (PVL) strains: a positive PVL presence was associated with severe disease and poor clinical outcome [21, 22]. Nevertheless, this genetic factor was not available and considered in this study.

Even though the current study findings have highlighted the value of MIC data in the estimation of vancomycin PK variables in the management of MRSA bacteremia, generalization of the findings should be done with caution due to several limitations. Given the retrospective nature of the study design, the risk of unmeasured confounding effects and introduction of bias was unavoidable. The sample size in this study was limited due to vigorous inclusion and exclusion criteria especially in critically ill patients. Hence, the power of the study might have been compromised. The estimation of AUC_{0-24} in this study was based on a single trough concentration and clearance of vancomycin calculated from the established population equation and the nearest available serum creatinine. As such, this estimation may also be one of the limitations of this study. AUC_{0-24} estimated using multiple points of concentrations is more appropriate.

CONCLUSIONS

Higher vancomycin MIC was associated with poor clinical outcomes. The serum trough vancomycin concentration alone is not clearly associated with improved treatment outcomes. Given the significant influence of vancomycin MIC on the treatment outcomes, the ratios of trough concentration/MIC and AUC_{0-24}/MIC are better predictors for vancomycin effectiveness in critically ill patients with MRSA bacteremia. The estimated AUC_{0-24} based on a single trough concentration with stable renal function may be appropriate for vancomycin treatment monitoring.

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