

Original Article

Low Correlation Between Vancomycin Area Under the Curve Over 24 Hours to the MIC (AUC/MIC ratio) and the Trough Concentration at Steady State in Methicillin-Resistant *Staphylococcus Aureus* Pneumonia

You Min Sohn^{a*}, Hyo Jung Park^{a*}, Jee Eun Chung^b, Kyungmin Huh^c, Kyeongman Jeon^d,
Yong Seok Lee^a and Myung Sook Min^{a†}

Department of Pharmaceutical Services, Samsung Medical Center,

81 Irwon-ro, Gangnam-gu, Seoul, 06351, Republic of Korea^a

College of Pharmacy, Hanyang University,

55 Hanyangdaehak-ro, Sangnok-gu, Ansan, Gyeonggi-do, 15588, Republic of Korea^b

Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University

School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 06351, Republic of Korea^c

Department of Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University

School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 06351, Republic of Korea^d

Background : Vancomycin is a mainstay of treatment of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The recently published guideline on vancomycin monitoring recommends that a vancomycin loading dose can be considered and an individualized target AUC/MIC ratio of 400–600 and should be advocated to achieve clinical efficacy while improving safety in patients with the suspected or definitive MRSA infections.

Methods : To evaluate the correlation between the vancomycin trough concentration and the area under the curve over 24 hours to the MIC (AUC/MIC) ratio according to the guideline recently published. A retrospective cohort study was conducted on adult patients treated for MRSA proven pneumonia with the vancomycin. We enrolled patients administered with the vancomy-

*You Min Sohn and Hyo Jung Park contributed equally to this study and are considered cofirst authors.

투고일자 2020.8.19; 심사완료일자 2020.9.15; 게재확정일자 2020.10.21

†교신저자 Myung Sook Min Tel:82-2-3410-3370 E-mail:msook.min@samsung.com

cin loading dose before the maintenance dose and the monitored vancomycin trough concentrations at the steady state in medical intensive care units April 2017–March 2020. We calculated the vancomycin AUC/MIC ratio based on the trough concentration measured for each patient using the Bayesian software. The difference between the microbiological cure, all-cause mortality, and nephrotoxicity for each group was studied.

Results : There was low correlation between the vancomycin AUC/MIC and trough concentration in MRSA pneumonia. A total of 35 patients were included. Thirty-one patients (88.6%) were above the AUC/MIC ratio 400, while 19 patients (54.3%) were in the trough range above 15 mcg/ml. Although there was a weak correlation between the vancomycin trough concentration and the AUC/MIC ratio ($r=0.427$, $p=0.010$), the vancomycin through concentrations at the steady state within the therapeutic ranges did not mean the vancomycin AUC/MIC ratio within the therapeutic ranges ($p=0.580$). No significant difference was observed in the microbiological cure, all-cause mortality, and incidence of acute kidney injury in each group.

Conclusion : The trough level-guided monitoring of the vancomycin should be replaced by the AUC/MIC ratio-guided monitoring in the clinical practice in Korea.

[Key words] Vancomycin, Trough concentration, AUC/MIC ratio, MRSA pneumonia

Vancomycin is a mainstay of treatment of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Since the first guideline in 2009 for the therapeutic drug monitoring on vancomycin for adult patients with severe MRSA infection, the optimal trough concentration with 15 to 20 mg/L had been considered as the surrogate marker for the most accurate and practical method to monitor efficacy and toxicity.¹⁾ Because it could be very difficult to obtain multiple vancomycin concentrations to calculate the AUC and AUC/MIC ratio in the clinical situation, trough concentration monitoring was used as a surrogate marker for AUC.

Recently published guideline on vancomycin monitoring recommends that a vancomycin loading dose of 20 to 35 mg/kg can be considered and that an individualized target

AUC/MIC ratio of 400 to 600 should be advocated to achieve clinical efficacy while improving patient safety in patients with suspected or definitive serious MRSA infections.²⁾ However, in Samsung Medical Center (SMC), the vancomycin's dosage regimen with loading dose still has been adjusted by using the through concentration of 15 to 20 mg/L to treat MRSA pneumonia.

The objective of this study was to evaluate retrospectively the correlation between vancomycin trough concentration and the AUC/MIC ratio in MRSA pneumonia.

Methods

Study design and population

A retrospective cohort study was conducted at SMC, a 1989-bed university affiliated

tertiary referral hospital in Seoul, South Korea. The records of adult patients treated for MRSA proven pneumonia with vancomycin in medical intensive care unit. The study period was from April 2017 to March 2020. Patients who received vancomycin for less than 72 h and patients without a vancomycin trough concentration were excluded from the analysis. Patient's demographics characteristics, laboratory data and underlying diseases were collected from electronic medical records. This study was approved by the hospital's Institutional Review Board (IRB No. 2020-04-217).

SMC IV vancomycin protocol

Vancomycin loading dose (LD) regimen was developed in April 2017 in SMC to attain therapeutic vancomycin concentration rapidly and optimize AUC/MIC ratio.³⁾ Initial vancomycin dose of 25 mg/kg of actual body weight was recommend in our hospital's guideline as a loading dose. And then followed by 15~20 mg/kg every 12 hours for the maintenance doses. Vancomycin trough concentration (C_{trough}) was obtained just before the fourth dose at steady-state conditions. Vancomycin concentrations were analyzed using a kinetic interaction of microparticles in a solution (cobas c702 module, Roche Diagnostics GmbH, Germany). The therapeutic drug monitoring of C_{trough} was conducted by clinical pharmacist during the ICU multidisciplinary team rounding. Target C_{trough} was 15~20 mg/L.

Estimation of vancomycin AUC/MIC ratio

From the previous vancomycin concentrations, dosing interval, doses, patient sex,

age, weight, serum creatinine level, and MIC, we retrospectively estimated vancomycin AUC/MIC ratio for each patient using Antibiotic Kinetics™ software (RxKinetics, School of Pharmacy and Health Profession, Creighton University, USA).⁴⁾

Outcome measures

We evaluated the correlation of vancomycin AUC/MIC ratio value versus C_{trough}. The patients with AUC/MIC ratio were divided into three groups of less than 400, between 400 and 600, and over 600. Based on trough concentrations for the same patients, they were divided into less than 15 mg/L, between 15 and 20 mg/L, and over 20 mg/L. The difference among these groups was studied in microbiological cure, all-cause mortality and the incidence of acute kidney injury.

Statistical analysis

Descriptive data were summarized by median with IQR and percentages. Categorical variables were analyzed using Chi-square test. Comparisons between the three groups were performed using either Kruskal-Wallis test or ANOVA. The correlation analysis was performed to identify the correlation between continuous variables after normality test. All statistical analyses were performed using SPSS statistics software version 25 (SPSS Inc., Chicago, IL, USA).

Results

Demographic patient characteristics

A total of 128 presumed MRSA pneumonia

Table 1 Demographic data

| Characteristics (n= 35) | Median, IQR |
|--|-------------------|
| Age, years | 63 (22-84) |
| Male | 23 (66) |
| Weight | 59 (32-98) |
| BMI*, kg/m ² | 22.0 (13.0-35.1) |
| CRP†, mg/dL | 12.1 (0.9-34.1) |
| Serum lactate, mmol/dL | 1.5 (1.1-2.0) |
| Blood urea nitrogen, mg/dL | 22 (9.3-46.8) |
| Serum creatinine, mg/dL | 0.76 (0.27-2.72) |
| Estimated GFR‡, L/min/1.73 m ² | 98.9 (18.5-170.4) |
| Comorbidities | |
| Diabetes | 9 (25.7) |
| Cardiovascular disease | 4 (11.4) |
| Cerebrovascular disease | 1 (2.9) |
| Chronic lung disease | 8 (22.9) |
| Chronic kidney disease | 1 (2.9) |
| Dialysis | 0 (0.0) |
| Chronic liver disease | 4 (11.4) |
| Solid cancer | 7 (20) |
| Hematological malignancy | 3 (8.6) |
| Solid organ transplant | 2 (5.9) |
| Autoimmune disease | 3 (8.6) |
| Immunosuppressant use | 6 (17.1) |
| Vancomycin MICs | |
| ≤ 0.5 | 8 (22.8) |
| 1 | 22 (62.9) |
| 2 | 5 (14.3) |
| Concomitant medication with nephrotoxicity | |
| Colistin | 13 (37.1) |
| Piperacillin/tazobactam | 11 (31.4) |

Values are median with IQR or no (%).
 MRSA, methicillin-resistant Staphylococcus aureus; *BMI: body mass index; †CRP, C-reactive protein; ‡GFR, glomerular filtration rate; §MIC, minimum inhibitory concentration

patients was screened, and 35 culture proven MRSA pneumonia patients were enrolled in the study. Demographics for the enrolled patients that received vancomycin are described in Table 1. Of those patients the median age was 63 (22~84) years, mean weight 59 (32~98) kg, and 23 patients were male.

Twenty-two patients (62.9%) were the MIC 1 mg/mL of vancomycin, 8 patients (22.8%) were MIC ≤ 0.5 mg/L, and 5 patients (14.3%) were MIC of 2 mg/L. All patients received their vancomycin per SMC protocol.

Correlation of vancomycin AUC/MIC ratio and trough concentration

There was a positive correlation between the vancomycin AUC/MIC ratio and C_{trough} (Fig. 1). As the result of correlation analysis by non-parametric test, Spearman's rho was 0.427 (p < 0.010).

Twelve patients (34.3%) were in target AUC/MIC ratio (AUC/MIC ratio 400 to 600), 19 patients (54.3%) were above target AUC/MIC ratio (AUC/MIC ratio > 600) and 4 patients (11.4%) were below the AUC/MIC ratio (AUC/MIC ratio < 400). Seventeen patients (48.6%) were in the target trough level (15~20 mg/L), 2 patients (5.7%) were above trough level (trough > 20 mg/L) and 16 patients (45.7%) were below trough level (trough < 15 mg/L) (Table 2). It was 35.3% of target AUC/MIC ratio in the target trough level group (Fig. 2). Thirty-one patients (88.6%) were shown above AUC/MIC 400.

Clinical outcomes

There were no significant differences in microbiological cure (p > 0.999), all-cause mortality within 90 days (p=0.126), and ne-

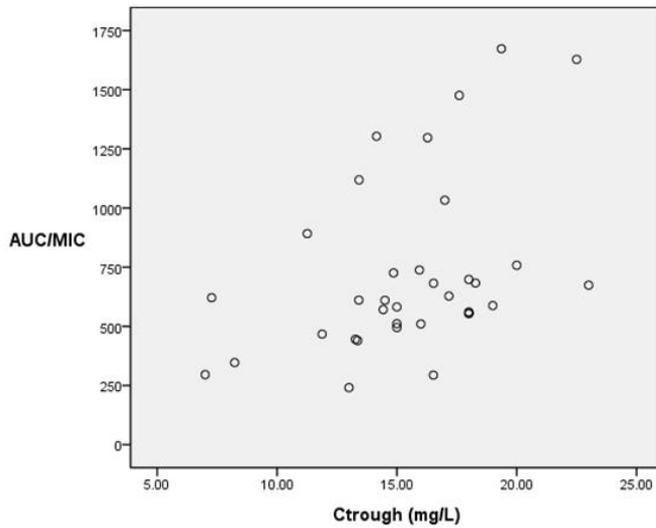


Fig. 1 Scatter gram of vancomycin trough level versus AUC/MIC ratio (Spearman's rho, $r=0.427$, $p=0.010$)

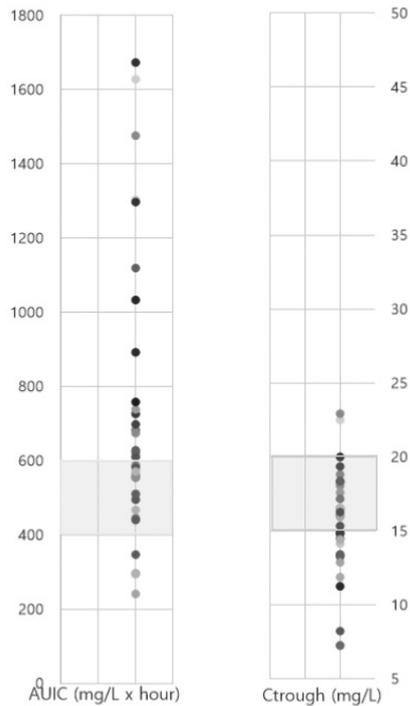


Fig. 2 Discrepancy between vancomycin target AUC/MIC ratio and trough concentration ($p = 0.580$)

AUC: AUC/MIC ratio, area under the curve over 24 hours to MIC; Ctrough: trough concentration at steady state. The gray area means an optimal therapeutic range.

Table 2 Discrepancy between vancomycin AUC/MIC ratio and trough concentration (p=0.580)[§]

| | | Treatment | | | | Total Patient Number |
|----------------------|-------|-------------------|---------------|----------------|-----------|----------------------|
| | | < 400 | 400 ~ 600 | > 600 | | |
| | | 295 (241-340) | 533 (440-588) | 738 (610-1673) | | |
| Trough (mg/L) | < 15 | 13.38(7.24-14.86) | 3 (18.8) | 6 (37.5) | 7 (43.8) | 16 (45.7) |
| | 15~20 | 17.6(15.34-20) | 1 (5.9) | 6 (35.3) | 10 (58.8) | 17 (48.6) |
| | > 20 | (22.5, 22.93) | 0 (0) | 0 (0) | 2 (100) | 2 (5.7) |
| Total Patient Number | | | 4 (11.4) | 12 (34.3) | 19 (54.3) | 35 (100.0) |

[§]Fisher's exact test

Values are mediana with IQR or n (%).

Table 3 Clinical outcomes in Ctrough groups and AUC/MIC ratio groups

| Clinical outcome | Target trough (15 - 20 mcg/mL) n (%) | p-value | Target AUC/MIC (400 - 600) n (%) | p-value |
|----------------------|---|---------|-------------------------------------|---------|
| Microbiological cure | 13 (76.5%) | > 0.999 | 10 (83.3 %) | > 0.999 |
| All-cause mortality | 7 (41.2 %) | 0.126 | 4 (33.3 %) | 0.259 |
| Nephrotoxicity | 7 (41.2%) | > 0.999 | 6 (50%) | 0.799 |

n, patient number

phrotoxicity (p > 0.999) in target Ctrough groups (15~20 mcg/ml). There was also no significant differences in microbiological cure (p > 0.999), all-cause mortality within 90 days (p=0.259), and nephrotoxicity (p=0.799) in target AUC/MIC ratio groups (400~600) (Table 3).

Discussion

This is the first study in Korea to show the correlation between vancomycin trough concentration at steady-state and AUC/MIC in critically ill patients with microbiologically confirmed MRSA pneumonia.

Most current data have demonstrated that trough concentrations may not be optimal

surrogate marker for AUC values. Trough-only monitoring, with a target of 15 to 20 mg/L, is no longer recommended based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA.^{5),6)}

Vancomycin is a large-weighted and hydrophilic molecule that penetrated the lung parenchyma poorly even that is inflamed. The past clinical guidelines on vancomycin monitoring recommended high trough levels within 15 to 20 mg/L to achieve successful treatment for MRSA infection. However, recent studies have been showing that using the optimal AUC/MIC ratio calculated with MIC to MRSA and AUC of vancomycin rather than through concentration to adjust the vancomycin dosage regimen increases the

clinical outcomes and decreases vancomycin induced toxicity.³⁾⁻⁷⁾

We demonstrated that the vancomycin through concentrations within the therapeutic ranges did not mean that the vancomycin AUC/MIC ratio within the therapeutic ranges though there was a positive correlation between AUC/MIC ratio values and trough levels at steady state. Only thirty-five percent of the trough concentrations within therapeutic range was optimal AUC/MIC ratio with 400 to 600. This discordance between optimal AUC/MIC ratio and trough ranges showed the trough value, a single exposure point before administration is not the surrogate pharmacokinetic factor that integrated quantity of cumulative vancomycin exposure.

Especially, among sixteen patients below trough level (trough < 15 mg/L), thirteen patients (81.3%) were shown above AUC/MIC 400. According to 2009 guideline on vancomycin trough monitoring, even though AUC/MIC ratio was above 400, the doses of vancomycin could be increased to maintain the trough concentration of 15 to 20 mg/L. It might be that the vancomycin dose was unnecessarily overdosed.

Neely and colleagues⁸⁾ simulated that therapeutic AUC of ≥ 400 mg·h/liter for an organism for which the vancomycin MIC is 1 mg/L approximately 60% are expected to have a trough concentration below the suggested minimum target of 15 mg/L for serious infections, which could result in needlessly increased doses and a risk of toxicity. Like our study results, they indicated that adjustment of vancomycin doses on the basis of trough concentrations without a Bayesian tool resulted in poor achievement of maximally safe drug exposures in plasma and

that many adults could have an adequate vancomycin AUC with a trough concentration of <15 mg/L. While it has been difficult to calculate AUC in the clinical setting in the past, recently Bayesian software programs can be used to generate accurate and reliable estimates of the daily AUC values with peak and trough PK sampling. The AUC/MIC ratio-guided monitoring of vancomycin should be considered instead of trough level-guided monitoring to provide appropriate and safe dosage.

In vancomycin pharmacokinetic and pharmacodynamics aspects, its activities are time-dependent and slow bactericidal effect. In vancomycin, pharmacodynamic parameter associated with clinical effectiveness is therapeutic AUC/MIC ratio.^{9),10)} AUC/MIC ratio-guided vancomycin dosing is needed to replace trough-only monitoring in practice to improve clinical outcome.^{11),12)}

In critically ill patients with MRSA pneumonia, the clinical outcome is known to be affected by many factors such as comorbidities, severity of infection and organ dysfunctions. It might be very encouraging if we confirmed the appropriate vancomycin AUC/MIC ratio could be increased the clinical cure in critically ill patients with MRSA pneumonia.

However, in our study the therapeutic range of the through concentration as well as AUC/MIC ratio had no relation with clinical outcomes or nephrotoxicity. Unfortunately, this study might lack power to discriminate relationship between AUC/MIC ratio and clinical outcomes that could be caused by the small sample size of thirty-five patients enrolled.

Although the vancomycin AUC/MIC ratio of 400 to 600 was recommended to be optimal in

serious infection to achieve clinical efficacy and improve patient safety,^{13),14)} our study demonstrated that nephrotoxicity was not related to AUC/MIC ratio even more than 600. Considering poor penetration of vancomycin to lung parenchyma, even in pneumonia, higher target AUC/MIC ratio might be optimal. Prospective studies with large patients are warranted to confirm the optimal AUC/MIC ratio therapeutic range in MRSA pneumonia.

As with any major practice of change in therapeutic drug monitoring, education is essential to the implementation of AUC/MIC ratio-based dosing under the initiative of a clinical pharmacist. Clinical pharmacist should provide the background and rationale for AUC/MIC ratio based vancomycin dosing.

Clinical pharmacist can provide our study as a good evidence for adjusting the vancomycin's dosage to AUC/MIC ratio rather than the minimum concentration and change the old-fashioned practice of vancomycin trough-only monitoring.

There are several limitations in our study. First, the sample size was quite small. Especially, there were only four patients under 400 of vancomycin AUC/MIC ratio. Second, this was a retrospective study and there were difficulties in evaluating the effects or side effects of vancomycin. Third, pharmacokinetic parameters were estimated on the Bayesian method by the software using one vancomycin trough concentration measured at fourth dose after administration of vancomycin. Not all C_{trough} samples might be within the first 24 to 48 hours. It's very important to achieve early therapeutic AUC/MIC ratio within the first 24 to 48 hours to improve clinical outcome.¹⁵⁾ A follow-up

study of AUC/MIC ratio calculated based on the concentration of vancomycin within the first 24 to 48 hours is needed.

In conclusion, we confirmed a low correlation between vancomycin trough concentration and AUC/MIC ratio and discordance between optimal AUC/MIC ratio and trough ranges. Trough level-guided monitoring of vancomycin should be replaced by AUC/MIC ratio-guided monitoring.

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