

Underestimation of the Calculated Area Under the Concentration-Time Curve Based on Serum Creatinine for Vancomycin Dosing

Sung Joon Jin¹, Ji Hyun Yoon¹, Bo Sook Ahn², Ji Ah Chung², and Young Goo Song^{1,2}

¹Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul; ²Therapeutic Drug Monitoring Team, Gangnam Severance Hospital, Seoul, Korea

Background: The ratio of the steady-state 24-hour area under the concentration-time curve (ssAUC₂₄) to the MIC (AUC₂₄/MIC) for vancomycin has been recommended as the preferred pharmacodynamic index. The aim of this study was to assess whether the calculated AUC₂₄ (cAUC₂₄) using the creatinine clearance (CLcr) differs from the ssAUC₂₄ based on the individual pharmacokinetic data estimated by a commercial software.

Materials and Methods: The cAUC₂₄ was compared with the ssAUC₂₄ with respect to age, body mass index, and trough concentration of vancomycin and the results were expressed as median and interquartile ranges. A correlation between the cAUC₂₄ and ssAUC₂₄ and the trough concentration of vancomycin was evaluated. The probability of reaching an AUC₂₄/MIC of 400 or higher was compared between the cAUC₂₄ and ssAUC₂₄ for different MICs of vancomycin and different daily doses by simulation in a subgroup with a trough concentration of 10 mg/L and higher.

Results: The cAUC₂₄ was significantly lower than the ssAUC₂₄ (392.38 vs. 418.32 mg·hr/L, $P < 0.0001$) and correlated weakly with the trough concentration ($r = 0.649$ vs. $r = 0.964$). Assuming a MIC of 1.0 mg/L, the probability of reaching the value of 400 or higher was 77.5% for the cAUC₂₄/MIC and 100% for the ssAUC₂₄/MIC in patients with a trough concentration of 10 mg/L and higher. If the MIC increased to 2.0 mg/L, the probability was 57.7% for the cAUC₂₄/MIC and 71.8% for the ssAUC₂₄/MIC at a daily vancomycin dose of 4,000 mg.

Conclusions: The cAUC₂₄ using the calculated CLcr is usually underestimated compared with the ssAUC₂₄ based on individual pharmacokinetic data. Therefore, to obtain a more accurate AUC₂₄, therapeutic monitoring of vancomycin rather than a simple calculation based on the CLcr should be performed, and a more accurate biomarker for renal function is needed.

Key Words: Vancomycin; Pharmacodynamics; Area under curve; Drug monitoring, Therapeutic

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Corresponding Author : Young Goo Song, MD, PhD

Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University

College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 135-720, Korea

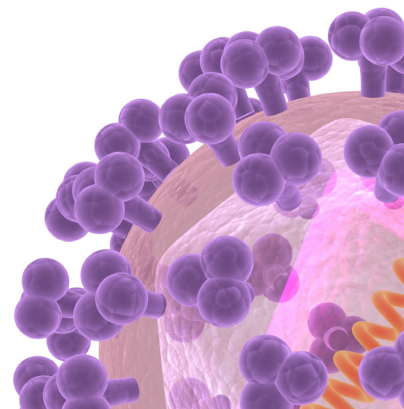
Tel.: +82-2-2019-3319, Fax: +82-2-3463-3882

E-mail: imfell@yuhs.ac

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Introduction

Traditionally, therapeutic monitoring of vancomycin has been recommended to prevent toxicity, and earlier studies established the target peak concentration for vancomycin in the range of 30 to 35 mg/L, with troughs of 5 to 10 mg/L. More recently, however, evidence has emerged that trough concentrations of 5 to 10 mg/L might be insufficient and a higher trough level, *i.e.*, exceeding 15 mg/L, has been suggested for pneumonia, meningitis, and for species that are more resistant [1, 2]. On the basis of various pharmacodynamic data, the ratio of the steady-state 24-hour area under the concentration-time curve ($ssAUC_{24}$) to the MIC ($ssAUC_{24}/MIC$) of 400 or higher has been recommended as the preferred pharmacodynamic index to achieve clinical effectiveness with vancomycin [3, 4]. Several simulation studies have suggested that the daily dose of vancomycin should be escalated to 4000 to 6000 mg to achieve the AUC_{24}/MIC ratio of 400 or higher, and, as a result, a trough concentration was increased to 15 to 20 mg/L [5, 6].

To obtain the AUC_{24} value more easily in the clinical setting, numerous previous studies have used the calculated AUC_{24} ($cAUC_{24}$) using the formula based on the CLcr (see Equation 2, below) to determining the vancomycin dose [3, 4, 7]. According to this formula, there is a possibility that the $cAUC_{24}$ might be underestimated when the CLcr is overestimated. That means that a higher dose of vancomycin could be recommended inappropriately when the CLcr is overestimated. Recently, as the vancomycin MIC against methicillin resistant *Staphylococcus aureus* (MRSA) continues to increase, several studies have reported that the trough concentration of vancomycin should be maintained at 20 mg/L or higher to reach a target value of the AUC_{24}/MIC ratio of 400 or higher, and this leads to a concern that vancomycin cannot be further used for the treatment of MRSA due to its toxicity [6, 8, 9].

The primary objective of the current study was to assess whether the $cAUC_{24}$ based on the CLcr differs from the estimated $ssAUC_{24}$ obtained from individual pharmacokinetic parameters of vancomycin in patients with normal creatinine concentrations by using a commercial software, the CAPCIL program (Simkin Inc., Gainesville, Florida, USA). Attempts were also made to compare these values ($cAUC_{24}$, $ssAUC_{24}$) with the trough concentration of vancomycin and thereby to confirm which values are more indicative of the trough concentration. Secondly, we also evaluated the proportion of patients who reached $cAUC_{24}/MIC$ and $ssAUC_{24}/MIC$ ratios of 400 or higher while altering the MIC and daily dose of vancomycin by simulation.

Materials and Methods

1. Subjects and collection of blood samples

This study was reviewed and approved by the Institutional Review Board at Gangnam Severance Hospital of Yonsei University Health System in Seoul, Korea (Reg. No. 3-2011-0082). All procedures were conducted in accordance with the guidelines of the Declaration of Helsinki. All data were collected retrospectively from patients who were receiving vancomycin at a single institution during a period ranging from June of 2006 to May of 2010. We included patients who were aged 18 years or older, patients whose serum creatinine concentration was lower than 1.2 mg/dL (normal range), patients who had vancomycin concentrations considered to have reached steady state (after administering more than 3 times), and patients who were given vancomycin at a dose of 1000 mg with a 12-hour interval. Vancomycin was dispensed in a saline (100 mL) and then intravenously infused over 1 hour. After the administration was done more than 3 times, the concentration was measured. Blood samplings were done 1 hour after the completion of vancomycin infusion (peak) and just before the next infusion (trough). The concentrations of serum creatinine and serum cystatin C were also simultaneously measured. Other clinical and demographic data were collected from the medical records of the recruited patients.

Serum vancomycin concentrations were determined by fluorescence polarization immunoassay methods (Cobas Integra 800 analyzer, Roche, Mannheim, Germany). The cystatin C concentration was measured using gold colloidal colorimetry (Hitachi 7600-110, Hitachi, Japan).

2. Individual pharmacokinetic parameters of vancomycin

The individual pharmacokinetic parameters of vancomycin were derived from the CAPCIL program. The glomerular filtration rate (GFR) was estimated by serum cystatin C rather than serum creatinine concentration. The vancomycin clearance (CL_{van}) and volume of distribution (V_d) were estimated for each patient using the CAPCIL program.

3. Individual pharmacodynamic index of vancomycin

In each patient, the $ssAUC_{24}$ was estimated based on the following formula using individual pharmacokinetic data (Equation 1). [5]

* Equation 1: $ssAUC_{24} = D/CL_{van}$

The $ssAUC_{24}$ is expressed as mg · hr/L, CL_{van} as L/hr, and D

is vancomycin dosage in mg/24 h.

Besides, the $cAUC_{24}$ was obtained with the following formula using the CLcr that has been proposed by several studies (Equation 2) [3, 4, 7].

$$* \text{Equation 2: } cAUC_{24} = D / [(CLcr \times 0.79) + 15.7] \times 0.06]$$

The $cAUC_{24}$ is expressed as mg · hr/L, CLcr as mL/min, and D is vancomycin dosage in mg/24 h.

In Equation 2, the CLcr was calculated using the Cockcroft and Gault formula (Equation 3) [10].

$$* \text{Equation 3: } CLcr \text{ (mL/min)} = [140 - \text{age (y)}] \times \text{weight (kg)} / [72 \times Scr \text{ (mg/dL)}]$$

(Female: multiplying by correction factor, 0.85)

The $cAUC_{24}$ value was compared with the $ssAUC_{24}$ according to age, body mass index (BMI), and the trough concentration of vancomycin. The correlation between the 2 AUCs ($cAUC_{24}$, $ssAUC_{24}$) and the steady-state trough concentration of vancomycin was evaluated because the trough concentration is an actual surrogate marker in clinical setting.

4. Assessment of the AUC_{24}/MIC ratio

The probability (%) of reaching a target AUC_{24}/MIC value of 400 or higher was compared between the $cAUC_{24}$ and $ssAUC_{24}$ for different vancomycin MICs (0.5, 1.0, and 2.0 mg/L) and different daily vancomycin doses (2000, 2500, 3000, 3500, and 4000 mg) by simulation. This simulation estimates the actual dose of vancomycin that is needed to reach a target value of 400 for the $cAUC_{24}/MIC$ and $ssAUC_{24}/MIC$ in cases in which the MIC of vancomycin is actually 2.0 mg/L.

5. Statistical analysis

A statistical analysis was performed using SPSS 20 for Windows (IBM, Armonk, NY, USA). Continuous data were presented as mean (standard deviation [SD]) and analyzed with the paired *t*-test if data were determined to be normally distributed or with the Wilcoxon signed-rank test for nonparametric data. The nonparametric values were expressed as median and interquartile ranges (IQR). A correlation analysis was performed using a Pearson's correlation coefficient (*r*). A *P*-value of < 0.05 was considered statistically significant.

Results

1. Clinical characteristics and pharmacokinetic parameters

A total of 596 patients (352 men and 244 women) were in-

cluded. The mean (SD) age of patients was 55.0 (16.6) years (range, 18-96) and the mean (SD) weight was 62.5 (13.3) kg. The pharmacokinetic analysis was performed using the CAP-CIL program and included a total of 1192 vancomycin concentration measurements (peak and trough) in 596 patients. The mean (SD) Vd of vancomycin was 0.73 (0.19) L/Kg, the CLvan was 5.02 (1.93) L/hr, and the half-life ($T_{1/2}$) was 6.92 (2.86) hours (Table 1).

2. Pharmacodynamic index

The $ssAUC_{24}$ was significantly higher than the $cAUC_{24}$; the median (IQR) values were 418.32 (330.35, 546.19) and 392.38 (322.63, 486.73), respectively ($P < 0.0001$; Table 2). Patients were also divided into subgroups based on age, BMI, and trough concentration. The $cAUC_{24}$ was found to be relatively lower than the $ssAUC_{24}$ in almost all subgroups. In particular, in older patients with a higher trough concentration, a higher degree of difference between the $ssAUC_{24}$ and $cAUC_{24}$ was observed (Table 2). The $ssAUC_{24}$ showed a stronger correlation with the trough concentration than the $cAUC_{24}$ ($r = 0.964$ and $r = 0.649$) (Fig. 1A, 1B).

3. Assessment of the AUC_{24}/MIC

Assuming that the MIC of vancomycin against MRSA was 1.0 mg/L, the number of patients who reached the target $cAUC_{24}/MIC$ and $ssAUC_{24}/MIC$ values of 400 or higher was 286 of 576 (48.0%) and 322 of 576 (54.0%), respectively. In patients with a trough concentration of 10 mg/L and higher (227 patients), the percentage of those who reached the $cAUC_{24}/MIC$ and $ssAUC_{24}/MIC$ values of 400 or higher was 77.5% ($n = 176$) and

Table 1. Demographic characteristics and pharmacokinetic parameters of the patients

	Mean (SD)
Sex (Male : Female) (Number)	352 : 244
Age (years)	55.0 (16.6)
Body weight (kg)	62.5 (13.3)
Serum creatinine concentration (mg/dL)	0.78 (0.19)
Serum cystatin-C concentration (mg/L)	0.98 (0.33)
Vancomycin peak concentration (mg/L)	33.88 (9.87)
Vancomycin trough concentration (mg/L)	10.04 (6.99)
Volume of distribution (Vd, L/Kg)	0.73 (0.19)
Vancomycin clearance (CLvan, L/hr)	5.02 (1.93)
Half life ($T_{1/2}$, hour)	6.92 (2.86)
Calculated creatinine clearance (CLcr, mL/min)	94.49 (40.83)

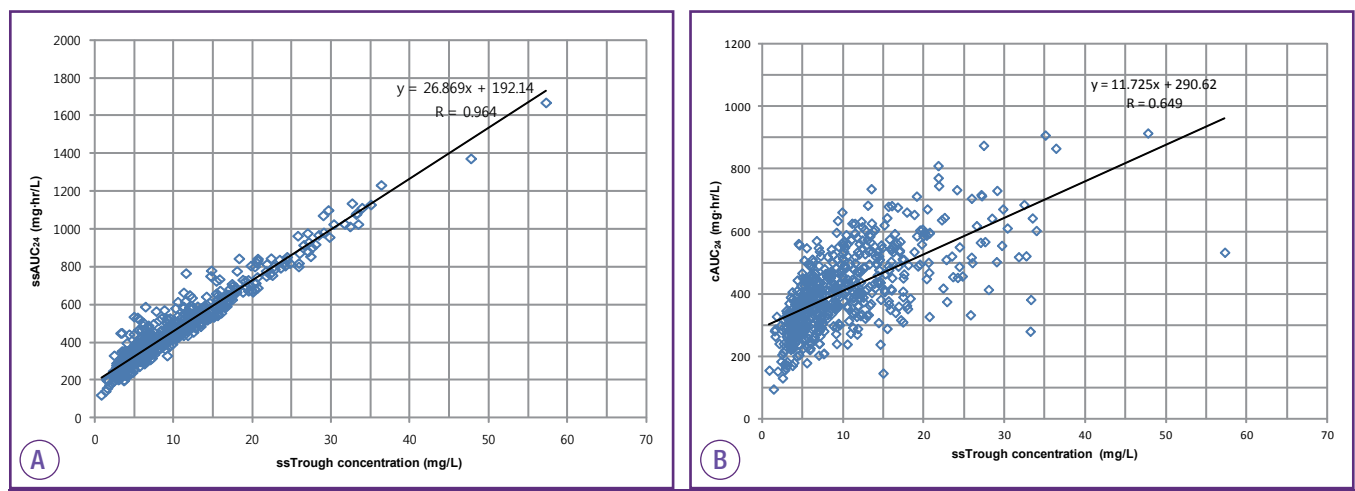
SD, standard deviation.

Table 2. Comparison of the calculated AUC₂₄ (cAUC₂₄) with 24-hour steady-state AUC (ssAUC₂₄) according to age, BMI, and the trough concentration of vancomycin

Group	Number (%)	cAUC ₂₄ (mg·hr/L) [Median (IQR)]	ssAUC ₂₄ (mg·hr/L) [Median (IQR)]	P-value ^a
Age group (year)				
< 30	58 (9.7)	292.26 (240.30, 357.09)	320.39 (250.37, 423.48)	0.0007
30-39	61 (10.2)	309.41 (259.58, 357.64)	321.32 (274.36, 441.76)	0.0007
40-49	95 (15.9)	345.52 (293.99, 388.74)	349.91 (303.10, 452.21)	0.0165
50-59	125 (21.0)	398.71 (340.89, 442.20)	418.69 (336.96, 515.45)	0.0013
60-69	131 (22.0)	429.13 (365.03, 511.71)	427.20 (361.96, 579.44)	0.0391
70-79	98 (16.4)	497.94 (433.16, 569.65)	523.98 (427.03, 629.11)	0.0114
≥ 80	28 (4.7)	619.89 (521.13, 739.49)	755.28 (563.89, 848.44)	0.0139
BMI group (kg/m ²)				
< 18.5	63 (10.6)	458.20 (382.77, 563.33)	488.99 (362.84, 635.53)	0.0897
18.5 ≤ 23	254 (42.6)	405.43 (337.05, 499.17)	413.63 (333.51, 539.80)	0.0012
23 ≤ 25	123 (20.6)	377.48 (320.17, 467.79)	422.06 (330.40, 538.05)	0.0001
25 ≤ 30	126 (21.1)	373.70 (301.94, 456.27)	396.12 (313.82, 518.44)	< 0.0001
≥30	30 (5.0)	295.34 (238.73, 419.43)	372.98 (249.42, 549.86)	< 0.0001
Trough conc. (mg/L)				
< 5	132 (22.2)	298.20 (258.68, 341.89)	279.03 (239.42, 312.13)	0.0011
5 ≤ 10	237 (39.8)	381.93 (334.69, 436.51)	386.23 (344.36, 422.70)	0.5018
10 ≤ 15	120 (20.1)	455.47 (388.80, 539.22)	523.14 (475.57, 561.70)	< 0.0001
15 ≤ 20	55 (9.2)	496.72 (409.42, 577.79)	646.91 (591.10, 691.37)	< 0.0001
≥20	52 (8.7)	580.10 (495.50, 682.68)	853.03 (801.28, 1018.68)	< 0.0001
Total	596 (100)	392.38 (322.63, 486.73)	418.32 (330.35, 546.19)	< 0.0001

AUC, area under the curve; BMI, body mass index; conc., concentration; CLcr, creatinine clearance; CLvan, vancomycin clearance; Scr, serum creatinine. cAUC₂₄ = Daily dose (mg)/[(CLcr (mL/min) × 0.79) + 15.7] × 0.06. ssAUC₂₄ = Daily dose (mg)/CLvan (L/hr). CLcr (mL/min) = [140 - age (y)] × weight (kg)/[72 × Scr (mg/dL)]. (Female: multiplying by correction factor, 0.85).

^aData analyzed with the Wilcoxon signed-rank test.

**Figure 1.** Relationship between the steady-state 24-hour AUC (ssAUC₂₄) and steady-state trough concentration of vancomycin (A), and between the calculated AUC (cAUC₂₄) and steady-state trough concentration of vancomycin (B).

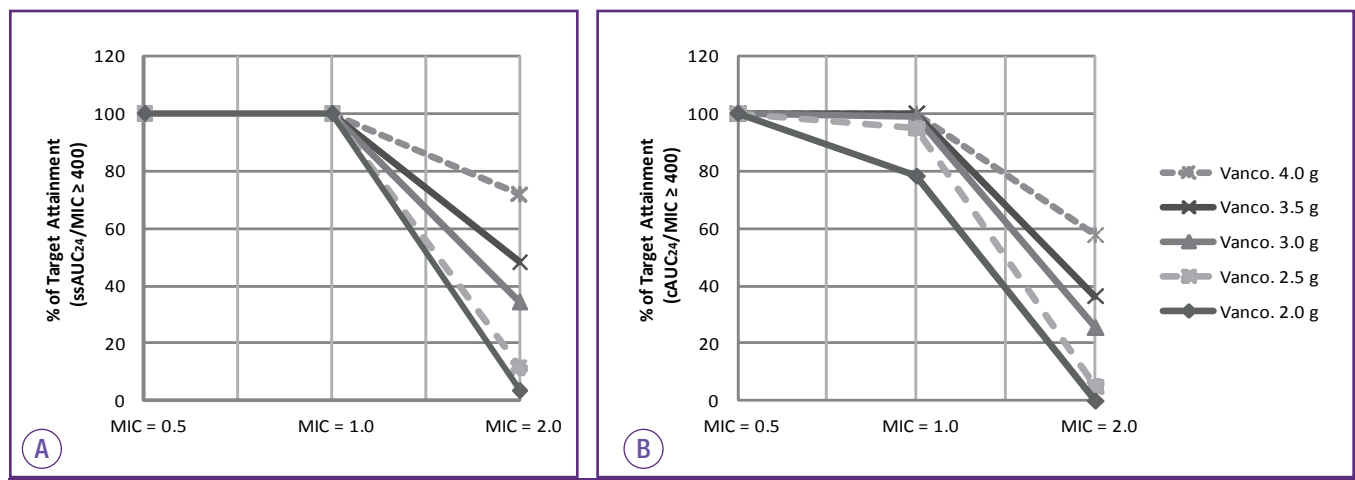


Figure 2. Probability (%) of reaching target ssAUC₂₄/MIC (A) and cAUC₂₄/MIC (B) values of 400 or higher for different MICs (0.5, 1.0, and 2.0 mg/L) and daily vancomycin doses (2,000, 2,500, 3,000, 3,500, and 4,000 mg) by simulation in patients with a trough concentration of 15 to 20 mg/L.

Table 3. Probability (%) of reaching a target AUC₂₄/MIC value of 400 or higher for different MICs and daily vancomycin doses by simulation in patients with a trough concentration of 15 to 20 mg/L.

Vancomycin dose (mg/d)	% of cAUC ₂₄ /MIC ≥ 400			% of ssAUC ₂₄ /MIC ≥ 400		
	MIC = 0.5	MIC = 1.0	MIC = 2.0	MIC = 0.5	MIC = 1.0	MIC = 2.0
2,000	100	78.2	0	100	100	3.6
2,500	100	94.9	5.1	100	100	11.5
3,000	100	98.9	25.6	100	100	34.4
3,500	100	100	36.5	100	100	48.2
4,000	100	100	57.7	100	100	71.8

AUC, area under the curve; MIC, minimal inhibitory concentration; cAUC₂₄, calculated AUC; ssAUC₂₄, steady state 24-hour AUC.

100%, respectively. However, among patients with a trough concentration from 5 to less than 10 mg/L, 50% and lesser achieved the target AUC₂₄/MIC value.

4. Simulation

Assuming that vancomycin is administered at a daily dose of 2000, 2500, 3000, 3500, and 4000 mg and the MIC of vancomycin against MRSA is 0.5, 1.0, and 2.0 mg/L, we performed a simulation to evaluate the proportion of patients whose cAUC₂₄/MIC and ssAUC₂₄/MIC ratios reached the target value of 400 or higher. When the MIC of vancomycin was 2.0 mg/L, the probability (%) of reaching the target cAUC₂₄/MIC and ssAUC₂₄/MIC values was less than 40% in patients with a trough concentration of 10 to 15 mg/L at a daily vancomycin dose of 4000 mg. In patients with a trough concentration of 15 to 20 mg/L, the probability (%) of reaching the target ssAUC₂₄/MIC and cAUC₂₄/MIC values of 400 or higher was 71.8% and 57.7%, respectively, even at a daily vancomycin dose of 4000 mg (Fig. 2, Table 3).

Discussion

The appropriate assessment of renal function and the resulting adjustment of the dose are mandatory in antibiotics such as vancomycin, which are mainly excreted from the kidney. The effective therapeutic range of vancomycin has been mainly recommended to be from 5 to 10 mg/L based on the trough concentration in consideration of the effect and safety. In recent years, however, depending on the sites of infection, the concentration has been recommended to be from 10 to 15 mg/L in patients with endocarditis and from 15 to 20 mg/L in those with pneumonia or meningitis. It has also been recommended that a therapeutic range be maintained at approximately 15 to 25 mg/L for the continuous intravenous infusion [1, 2]. According to most of the recent studies, the ssAUC₂₄/MIC ratio rather than %time > MIC has been proposed as the pharmacodynamic index indicating the clinical responses of vancomycin, and the target AUC₂₄/MIC value is recommended to be maintained at the level of 400 or higher [3, 4]. Based

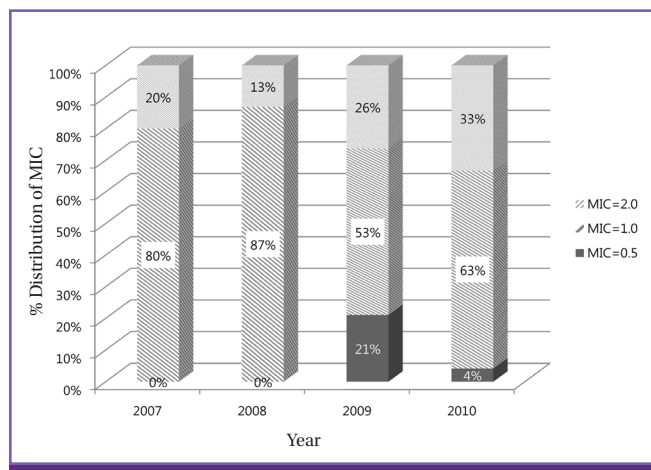


Figure 3. Percent distribution of the vancomycin MIC (by microbroth dilution method using Vitek 2 system [bioMerieux, Marcy 1'Etoile, France]) against MRSA isolated from July 2007 to June 2010 at the Gangnam Severance Hospital.

on this target, several studies have been conducted to assess the validity of the treatment dose of vancomycin and to adjust it [5, 6, 9]. However, in actual clinical settings, it can be difficult to obtain multiple serum vancomycin concentrations to determine the accurate AUC_{24} . Therefore, most of the studies have obtained the value of the $cAUC_{24}$ using the formula based on the CLcr (Equation 2) [3-5, 7]. However, according to some previous studies including ours [11, 12], serum cystatin C level rather than serum creatinine level is better indicative of the renal function. Therefore, we used serum cystatin C rather than serum creatinine to estimate individual GFR in the CAPCIL program, which is one of the applications to monitor drug therapy [13-15]. Finally, it is necessary to identify a new marker that would better reflect the renal function compared with the serum creatinine level or CLcr. Cystatin C may be considered as a good candidate for a new marker in patients with a normal creatinine concentration [11, 16-19]. Some authors have also noted that there is a tendency to overestimate the CLcr in elderly people or those with a smaller muscle mass [16-20]. Therefore, there is a possibility that the formula (Equation 2) might conversely underestimate the $cAUC_{24}$ and, as a result, a higher dose of vancomycin might be recommended inappropriately.

In particular, the MIC of vancomycin against MRSA has been recently observed to be gradually increasing, which has led to the opinions that vancomycin is no longer necessary [5, 9, 21]. This is not only because a higher dose of vancomycin should be administered at a daily dose of up to 5000 to 6000 mg to maintain the AUC_{24}/MIC of 400 or higher but also because the actual administration would be difficult because of

adverse effects such as nephrotoxicity in these cases. Furthermore, we also observed the MIC of vancomycin, by microbroth dilution method using Vitek 2 system (bioMerieux, Marcy 1'Etoile, France), to have gradually increased at our institution during a period from 2007 to 2010 (Fig. 3). Therefore, we attempted to assess whether the $cAUC_{24}$ calculated from the CLcr was different from the $ssAUC_{24}$ based on the individual pharmacokinetic parameters of vancomycin derived from a commercial software. We also attempted to investigate how much vancomycin was actually needed to reach the target AUC_{24} in a higher MIC by simulation. Finally, we examined which of the 2 AUCs ($cAUC_{24}$ or $ssAUC_{24}$) was more correlated with the trough concentration of vancomycin. The trough concentration may be used as a surrogate marker for the AUC; therefore, the analysis of the correlation between the 2 AUCs and the trough concentration is important to determine the administration dose of vancomycin.

As we expected, the $cAUC_{24}$ was found to be significantly lower compared with the $ssAUC_{24}$. In older patients with a higher trough concentration, there was a higher discrepancy between the 2 AUCs. This means that the CLcr could be overestimated and the serum creatinine concentration could not reliably reflect the renal function in those subgroups. Accordingly, it is possible that the doses of vancomycin suggested by several studies based on the $cAUC_{24}$ were too high [5, 9]. In particular, in regard to the correlation with the trough concentration, which might vary depending on the actual renal function of patients, the $ssAUC_{24}$ showed a closer relationship with the trough concentration than the $cAUC_{24}$ (Fig. 1A, 1B). Some clinicians have decreased the extent of therapeutic drug monitoring of vancomycin because there is little evidence to support a relationship between serum concentrations and efficacy and toxicity [20, 22]. However, because it may be difficult to determine the accurate AUC_{24} in the clinical setting, trough concentration monitoring can be effectively used as a surrogate marker for the AUC.

As shown in our study, assuming that the MIC of vancomycin against MRSA was 1.0 mg/L, the number of patients who reached the target $cAUC_{24}/MIC$ and $ssAUC_{24}/MIC$ values of 400 or higher were 286 of 576 (48.0%) and 322 of 576 (54.0%), respectively. In the subgroup with a trough concentration from 5 to less than 10 mg/L (237 patients), the probability of reaching a target AUC_{24}/MIC of 400 or higher was about 40% both for $ssAUC_{24}$ and $cAUC_{24}$. Therefore, it is not surprising that patients with a trough concentration of less than 10 mg/L were likely not to respond to vancomycin treatment. However, in the subgroup with a trough concentration of 10 mg/L and

higher (227 patients), the percentage of patients reaching target $cAUC_{24}/MIC$ and $ssAUC_{24}/MIC$ values was 77.5% (176 of 227) and 100%, respectively. These results are quite acceptable but the daily dose of vancomycin should be increased to 2500 mg to increase the proportion of patients reaching the target $cAUC_{24}/MIC$ value to more than 90%. In other words, there is a possibility that a higher dose of vancomycin could be recommended inappropriately if the $cAUC_{24}$ was used as the pharmacodynamic index. In a recent consensus review, it was recommended that the trough concentration should always be maintained above 10 mg/L to avoid development of resistance, and for a pathogen with a MIC of 1 mg/L, the trough concentration would have to be at least 15 mg/L to achieve the target AUC_{24}/MIC value of 400 [23]. Using the Monte Carlo simulation, Mohr and Murray determined that the probability of achieving an AUC_{24}/MIC of 400 or higher would be 100% with a MIC of 0.5 mg/L, 40% to 60% with a MIC of 1.0 mg/L, and 0% with a MIC of 2.0 mg/L [24]. Del Mar Fernández de Gatta Garcia et al. reported that a probability of 90% of reaching a target AUC_{24}/MIC value of 400 with a MIC of 1 mg/L would require a daily vancomycin dose of 3 to 4 g [5, 25]. However, in the present study, if we used the $ssAUC_{24}$ as the pharmacodynamic index rather than the $cAUC_{24}$, a daily vancomycin dose of 2 g would be enough to reach the target value at a MIC of 1 mg/L.

However, the results were different with a MIC of 2.0 mg/L. The probability of reaching target $cAUC_{24}/MIC$ and $ssAUC_{24}/MIC$ values was 0% in the subgroup with a trough concentration from 10 to less than 15 mg/L. Even in the subgroup with a higher trough concentration from 15 to less than 20 mg/L, the probability was 0% and 3.6%, respectively. Therefore, the daily dose of vancomycin should be increased to achieve a satisfactory clinical effect with a MIC of 2.0 mg/L. The simulation showed that the probability of reaching target $cAUC_{24}/MIC$ and $ssAUC_{24}/MIC$ values in patients with a trough concentration from 10 to 15 mg/L was less than 40% even at a daily vancomycin dose of 4000 mg (Table 3). This means that the trough concentration of 10 to 15 mg/L would not be acceptable with a MIC of 2.0 mg/L. The probability of reaching target $cAUC_{24}/MIC$ and $ssAUC_{24}/MIC$ values in patients with a trough concentration of 15 to 20 mg/L was 57.7% and 71.8%, respectively, at a daily vancomycin dose of 4000 mg (Table 3). A high vancomycin dose is certainly needed to reach a target AUC_{24}/MIC value with a MIC of 2.0 mg/L; however, a higher dose could be recommended when the $cAUC_{24}/MIC$ ratio was used for determining the daily dose of vancomycin.

Likewise, an extremely high dose of vancomycin can be in-

appropriately recommended when we use the $cAUC_{24}/MIC$ ratio based on the serum creatinine concentration. Instead, it would be more reasonable to monitor the trough concentration as a surrogate marker in the actual clinical setting. As shown by our study, the MIC of 1.0 mg/L or higher allows to predict that the satisfactory goals of the pharmacodynamic index may be achieved if the trough concentration is maintained at the level of 10 mg/L and higher.

Our study has several limitations. First, we could not directly confirm the correlation between the $ssAUC_{24}/MIC$ ratio and clinical outcome. In other words, we could not confirm whether the treatment effects clinically vary between patients with an $ssAUC_{24}/MIC$ value of 400 or higher and those with a $cAUC_{24}/MIC$ value of less than 400. In addition, we could not analyze the MICs of vancomycin against MRSA isolated from each patient. Therefore, further studies are needed to examine the correlations between the MICs of vancomycin against MRSA isolated from each patient and $ssAUC_{24}/MIC$ and $cAUC_{24}/MIC$, and to directly confirm the clinical outcomes. Moreover, several errors that could affect the pharmacodynamic index might have occurred at each step of the therapeutic drug monitoring (TDM) process, and they could not be completely controlled because of a retrospective design of the study. It is possible that the Cockcroft and Gault method might have caused the differences between the $cAUC_{24}$ and $ssAUC_{24}$.

In conclusion, several studies have shown that the AUC_{24}/MIC ratio is a pharmacodynamic index that reflects the effects of vancomycin [3-6, 9]. However, a more thorough study is needed to determine the administrative dose of vancomycin based on the $cAUC_{24}/MIC$ based on the CLcr. Despite the above limitations, our results showed that the $cAUC_{24}$ was clearly underestimated compared with the estimated $ssAUC_{24}$ based on individual pharmacokinetic data. Accordingly, it should be considered that a higher dose of vancomycin could be recommended inappropriately when the $cAUC_{24}$ was used. Therefore, a more accurate clinical outcome study should be performed to evaluate the appropriate dose of vancomycin. Finally, to obtain a more accurate AUC_{24} , therapeutic monitoring of vancomycin rather than simple calculation based on the CLcr should be performed, and a more accurate biomarker of the renal function is needed.

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