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Comparison of vancomycin calculation programs in predicting steady state vancomycin trough concentrations among Thai septic patients

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Introduction

Vancomycin, a glycopeptide group, is an antimicrobial agent that has been used for infections caused by Gram-positive bacteria especially, methicillin-resistant *Staphylococcus aureus* (MRSA) or *S. epidermidis* (MRSE) and ampicillin-non susceptible *Enterococci*.¹ However, the efficacy of treatment with vancomycin is well correlated with the adequate serum vancomycin concentration. Moreover, the risk of nephrotoxicity due to vancomycin is also associated with an undesirable high serum concentration.² Thus, the therapeutic drug monitoring is necessary to adjust the vancomycin dosing regimen giving the better efficacy and the lesser nephrotoxicity as well.¹

Owing to the variable pharmacokinetic properties among patients received vancomycin treatment, the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) have launched a consensus statement of therapeutic monitoring of vancomycin for patient care.¹ Practically, trough serum vancomycin concentrations obtained before the fourth dose in patients with normal renal function, are the most method for monitoring vancomycin efficacy and safety. The recommended trough serum vancomycin concentrations are 15–20 mg/L correlated with the area under the curve (AUC) at approximately 400.³

Unfortunately, the therapeutic monitoring of vancomycin is unavailable in somewhere. The various programs for design of vancomycin dosing regimen are applied in the real practice. Taylor and Sarkisoff revealed that among the vancomycin calculation programs [Therapeutic Drug Monitoring System (TDMS) vs GlobalRph vs Clinical Pharmacology], TDMS is the most accurate vancomycin trough calculator.⁴ Contrastingly, Aubron et al. indicated that the MM-USCPACK program is a useful and reliable tool for prediction of serum vancomycin concentrations.⁵

As described above, the limitation of available vancomycin therapeutic monitoring and uncertain of vancomycin calculation programs for vancomycin prediction. With our study objective, we sought for the suitable vancomycin calculation programs in order to predict the concentrations of serum vancomycin for Thai patients treated with vancomycin.

Methods

Study protocol

We performed a retrospective review study of adult patients admitted to Phramongkutklao Hospital, a 1200-bed university hospital in Bangkok, Thailand during January 2013-February 2017. This study was approved by the institutional review board of the Royal Thai Army Medical Department and Phramongkutklao Hospital, Bangkok, Thailand (approval No. Q002h/60 issued on 25th March 2017). The inclusion criteria for this study were 1) age ≥ 18 years old and 2) patients having the steady state vancomycin trough concentrations. Patients with end-stage renal disease (CrCl less than 15 mL/min), renal replacement therapy

(patients with hemodialysis, peritoneal dialysis or continuous renal replacement therapy), acute kidney injury or sample time of vancomycin trough concentration more than 1 hour before giving the next dose, were excluded.

The patient data were recorded including demographic characteristics, weight, height, comorbidities, ICU admission, serum albumin and serum creatinine. Details of vancomycin dosing regimen (dose, interval, and infusion time) and concentrations (trough levels and exact times of blood sampling) were also collected.

Vancomycin calculation programs

For the vancomycin calculation programs based on permissible programs and giving the vancomycin trough levels, twelve programs of vancomycin level prediction were determined including 8 programs on web-based applications (Vancomycin Calculator, Therapeutic Drug Monitoring Calculator, Globalph, Traditional Dosing Vancomycin, Vancomycin Level Prediction from Maintenance Dosing, MedCalc, Vancomycin Pharmacokinetics, and Vancomycin Initial Dosing), 2 programs operating in a personal computer (UCSF Vanco Dosing Calculator and TDMS2000) and 2 programs operating as mobile application (Rx Calc and Antibiotic Kinetics Lite).

Statistical analysis

We compared the measured serum vancomycin trough concentrations at the steady state with those predicted by each of vancomycin calculation programs. We calculated mean error (ME) and root mean square error (RMSE) as following formula

$$ME = \sum \frac{(\text{Predicted value} - \text{Observed value})}{N} \quad RMSE = \sum \frac{\sqrt{(\text{Predicted value} - \text{Observed value})^2}}{\sqrt{N}}$$

Whereas Observed value = measured serum trough concentrations at the steady state

Predicted value = calculated serum vancomycin trough concentrations from the programs

N = number of samples

ME and RMSE were used to assess accuracy (bias) and precision of each vancomycin calculation programs, respectively.

Results

During the study period, a total of 48 patients were included. The characteristics of patients and details of vancomycin dosing regimens were shown in Table 1. The bias and precision of each vancomycin calculation programs were shown in Table 2. The accuracy (ME) ranged from -15.10 µg/mL (MedCalc) to 0.25 µg/mL (Vancomycin Initial Dosing). The program of Vancomycin Initial Dosing showed the least bias of vancomycin trough concentrations (ME 0.25 µg/mL; 95%CI -1.49, 1.99). Moreover, vancomycin trough concentrations also revealed the highest precision at RMSE of 5.92 µg/mL (95%CI 4.46, 7.08).

Table 1. Characteristics of patients (N=48)

Male, n (%)	31 (65%)
Age, years, mean±SD	60.65±23.63
Weight, kg, mean±SD	58.46±12.55
Height, cm, mean±SD	165.42±8.42
Serum creatinine, mg/dL, mean±SD	0.77±0.33
Creatinine clearance (Cockcroft-Gault formula), mL/min, mean±SD	95.10±52.15
Vancomycin maintenance dose, mg/dose, mean±SD	1,000±103.14
Dosing interval, hr, mean±SD	15.00±5.63
Infusion time, hr, mean±SD	2.00±0.21

Table 2. Mean error (ME) and root mean square error (RMSE) in each vancomycin calculation programs.

Program	ME (95% CI)	RMSE (95% CI)	Ranking of accuracy	Ranking of precision
Vancomycin Calculator	-9.44 (-12.12,-6.76)	13.14 (10.49,15.34)	11	11
Therapeutic Drug Monitoring Calculator	6.01 (4.28,7.75)	8.43 (5.96,10.32)	10	5
Globalrph	-5.89 (-7.91,-3.86)	9.15 (7.08,0.01)	9	7
Traditional Dosing Vancomycin	0.78 (-1.20,2.77)	6.80 (4.70,8.40)	2	2
Vancomycin Level Prediction from Maintenance Dosing	-5.47 (-7.83,-3.10)	9.74 (7.71,11.42)	8	8
MedCalc	-15.10 (-18.76,-11.43)	19.59 (15.11,23.23)	12	12
Vancomycin Pharmacokinetics	-4.50 (-7.57,-1.42)	11.41 (6.16,14.91)	6	10
Vancomycin Initial Dosing	0.25 (-1.49,1.99)	5.92 (4.46,7.08)	1	1
UCSF Vanco Dosing Calculator	-1.89 (-3.91,0.12)	7.11 (5.51,8.42)	3	3
TDMS2000	3.86 (1.94,5.77)	7.59 (4.92,9.53)	4	4
Rx Calc	-5.04 (-7.21,-2.87)	8.94 (7.17,10.42)	7	6
Antibiotic Kinetics Lite	4.12 (1.22,7.02)	10.72 (8.76,12.38)	5	9

Discussion

In this study, we summarized that the Vancomycin Initial Dosing as vancomycin calculation programs gave the least bias and the highest precision in predicting the serum vancomycin trough concentrations at the steady state in this population. This program which seems to be suitable for predicting serum vancomycin concentrations, might be from some limited. Patients with age below 18 years old, unstable renal function, hemodialysis or severe renal impairment (CrCl <25 mL/min) have to be restricted for program use.⁶ These conditions were similar to our inclusion and exclusion criteria. Not surprisingly, Vancomycin Initial Dosing yielded the least ME and RMSE.

However, Traditional Dosing Vancomycin and UCSF Vanco Dosing Calculator were also an acceptable program as the second and the third rank of the least ME and RMSE. The UCSF Vanco Dosing Calculator could not be used in patients with hemodialysis, continuous renal replacement therapy (CRRT) and unstable renal function like our population.⁷ For Traditional Dosing Vancomycin, we could not explain why this program gave the minute ME and RMSE because of inaccessible details of program.

Above three programs such as Vancomycin Initial Dosing, Traditional Dosing Vancomycin and UCSF Vanco Dosing Calculator were not mentioned or compared for predicting vancomycin trough levels in any previous studies. Among many calculators, Only Therapeutic Drug Monitoring System (TDMS), GlobalRph and Clinical Pharmacology were assessed by Taylor et al. study. They evaluate and compare them to actual measured vancomycin troughs indicating TDMS was the most accurate vancomycin trough calculator.⁴ This finding similar to our results showing TDMS with more accuracy and precision as compared to GlobalRph.

However, the Vancomycin Initial Dosing was the best calculator of serum vancomycin trough concentrations in our population. The vancomycin dosing calculators need to be further evaluated in the other Thai patient group such as patients with chronic kidney disease, RRT or patients with age <18 years old.

The Vancomycin Initial Dosing was the most accurate and the least bias program. Patients with less than 18 years of age, unstable renal function, severe renal impairment (CrCl <25 mL/min), hemodialysis or hematological malignancies could not be applicable because this program was formulated from patients without such factors.

Moreover, the applicable program might be difficult in real practice because Vancomycin Initial Dosing, Traditional Dosing Vancomycin and UCSF Vanco Dosing Calculator operate on web-based applications and in a personal computer, respectively. Thus, the development of mentioned calculators as mobile application on smartphone makes them convenient to practically use.

Conclusion

Vancomycin Initial Dosing as vancomycin calculation programs gave the least bias and the highest precision in predicting the serum vancomycin trough concentrations at the steady state among Thai septic patients. The patients other than our inclusion and exclusion criteria might not be applicable.

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