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Note

Evaluation for optimal dosing of vancomycin in patients with different physical types☆

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ABSTRACT

The sufficient dose to obtain an optimal trough concentration of vancomycin (VCM) in patients with non-standard physical types remains controversial. In this study, we examined the relationship between the dose and physical type in patients in whom an optimal trough concentration was obtained among VCM-treated patients. We retrospectively investigated the dose of VCM and physical type in patients treated with VCM between January 2012 and January 2017 at two medical institutions (n = 272). The physical type was classified using the body mass index (BMI). Patients with a BMI of <18.5 kg/m^2 were assigned to the lean group, those with a BMI of 18.5–24.9 kg/m^2 were assigned to the standard group, and those with a BMI of ≥25 kg/m^2 were assigned to the obesity group. The mean doses of VCM per time (mg/kg) to achieve the target trough concentration of VCM, 15–20 μg/mL, were 19.8 ± 4.3, 16.5 ± 3.7, and 13.7 ± 2.7 mg/kg in the lean, standard, and obesity groups, respectively. The dose per time to achieve the target trough concentration decreased significantly in association with an increase of BMI. The upper limit of the recommended dose (15–20 mg/kg) or higher in lean patients, and the lower dose in obese patients than the recommended dose might be appropriate to achieve the target trough concentration when we calculated the dose per time based on actual body weight.

Vancomycin (VCM) is a glycopeptide antibiotic that is used to treat gram-positive bacterial infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase negative *staphylococci* (MRCNS), and other gram-positive organisms such as *Enterococcus faecium* [1,2]. An area under the blood concentration-time curve (AUC)/minimal inhibitory concentration (MIC) ratio of ≥400 is considered to be the pharmacokinetic/pharmacodynamic (PK/PD) parameter associated with a clinical and bacteriological response to VCM therapy [3]. It is recommended to use the trough concentration as a surrogate of AUC for maximizing the efficacy while minimizing the onset of toxicity instead of routine AUC in the practice guidelines for therapeutic drug monitoring of vancomycin [4].

The trough concentration should be maintained at ≥10 μg/mL to improve the clinical outcome of MRSA infections and to avoid the development of resistance [5], and at ≤20 μg/mL to avoid nephrotoxicity [6]. An initial dose of 15–20 mg/kg (as actual body weight) every 12 h was recommended to achieve the target trough concentration for patients with normal renal function [4]. However, several studies reported that it was difficult to predict the trough concentration of VCM in non-standard-physical-type patients (lean and obese patients), even if the recommended dose of VCM is administered [7]. Thus, an optimal administration design for non-standard-physical-type patients is needed to be established. No useful standard index of the dose of VCM had been reported for non-standard-physical-type patients despite the existence of numerous studies regarding optimal administration methods since indices of therapeutic drug monitoring (TDM) of VCM were published in the United Kingdom in 2006, in the United States in 2009, and in Japan in 2012. In addition, no study has sufficiently examined whether international patient data can be adapted to Japanese patients due to differences in the patient background.

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In this study, we retrospectively investigated the dose, trough concentration, and physical type in VCM-treated patients, and aimed to clarify the relationships among these parameters to collect basic information to establish an optimal administration design based on the physical type.

Prior to this study, its protocol was approved by the Ethics Review Board of Keio University School of Medicine (Approval No.: 20140032) and the Ethics Review Board of Showa General Hospital (Approval No.: REC-184). Among patients in whom TDM of VCM was performed at Keio University Hospital or Showa General Hospital between January 2012 and January 2017, those meeting the following criteria were selected: 1) age: ≥18 years, 2) treated with VCM twice a day, 3) an estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73 m^2, 4) in whom the trough concentration was measured ≥3 days after the initial administration, 5) in whom the dose was not changed before the initial trough-concentration measurement, and 6) a trough concentration of 10–20 μg/mL.

The sex, age (year), height (m), body weight (kg), date of initial administration, date of TDM, dose of VCM (mg/day), trough concentration of VCM (μg/mL), serum creatinine (Cre) level (mg/dL), and blood urea nitrogen (BUN) level (mg/dL) were extracted from electronic charts. The body mass index (BMI) and eGFR were calculated using the following formulae. In females, the eGFR was corrected by multiplying by 0.739.

$$\mathrm{BMI} = \text{body weight}/(\text{height})^2$$

$$\mathrm{eGFR\ (mL/min)} = 194 \times \mathrm{Cre}^{-1.094} \times \mathrm{age}^{-0.287} \times \mathrm{weight}^{0.425} \times \mathrm{height}^{0.725} \times 0.007184/1.73$$

The subjects were divided into 3 groups according to the criteria for the physical status prepared by the Japan Society for the Study of Obesity: lean group (BMI: <18.5 kg/m^2), standard group (18.5 kg/m^2≤BMI<25 kg/m^2), and obesity group (BMI: ≥25 kg/m^2). We compared the dose per time (mg/kg) in patients in whom the initial trough concentration of VCM reached the target of 10–20 μg/mL. The dose per time was calculated by dividing the dose of VCM administered per time by the patient's actual body weight.

To compare the patient background and dose with respect to the physical type, isovariance was evaluated using Levene's test. When variance was equivalent, one-way variance analysis was conducted. When variance differed, the Kruskal-Wallis test was used. When there were significant differences among the 3 groups, the Bonferroni test was used in the presence of equal variances, and the Steel-Dwass test was used in the presence of different variances. A p-value of 0.05 was regarded as significant. For analysis, we used SPSS statistics ver. 24 software (IBM, Armonk, NY, USA).

The background of patients at two institutions (Keio University Hospital and Showa General Hospital) is presented in Table 1. A total of 272 patients were analyzed, consisting of 42 in the lean group, 180 in the standard group, and 50 in the obesity group. There were no significant differences in age, BUN, eGFR, dose of VCM and day of TDM among the groups. Trough concentration of VCM (μg/mL) was significantly higher in lean group compared with normal or obesity group ($p < 0.05$), however; trough concentration of VCM adjusted by dose per time (μg*kg/(mL*mg)) was higher in obese group compared with lean group but not normal group ($p < 0.01$).

We compared the dose per time (mg/kg) in patients in whom the initial trough concentration of VCM reached 10–20 μg/mL as shown in Fig. 1A. The mean doses per time in the lean, standard, and obesity groups were 19.8 ± 4.3, 16.5 ± 3.7, and 13.7 ± 2.7 mg/kg, respectively. There were significant differences between lean, standard and obesity groups ($p < 0.01$). The dose per time to achieve the target trough concentration decreased significantly in association with an increase of BMI.

We conducted a retrospective study to evaluate the influence of physical types on dosing designs of VCM and revealed that the necessary initial dose of VCM per body weight to achieve the target trough concentration was higher in the lean patients and lower in the obese patients than that in the standard-physical-type patients.

The median doses of VCM per time (minimum-maximum) (mg/kg) in patients in whom the initial trough concentration of VCM reached the target significantly decreased in association with an increase of BMI. In the standard group, the median was within the range of the dose per time (15–20 mg/kg) recommended in the practice guidelines for TDM of vancomycin in Japan. However, the median exceeded 20 mg/kg in the lean group, and it was below 15 mg/kg in the obese group. One previous study found no difference in the absolute volume of distribution (Vd) for VCM between lean and standard-physical-type patients (Vd (L), lean: 43.8, standard: 44.4, no significant difference) [8]. The Vd per body weight (L/kg, range) based on these values was larger in lean patients, which were 0.83 (0.74–0.92, lean) and 0.64 (0.62–0.66, standard), respectively ($p < 0.01$) [8]. When the trough VCM concentration was corrected with the dose per patient body weight based on the results from in Table 1, it was significantly increased in the obese patients compared with the lean patients. It is clarified that the blood VCM concentration is readily increased in obese patients even though the dose per body weight was lower than lean patients, and it is validated that the Vd per body weight in obese patients is smaller than lean patients. Therefore, the dose of VCM per body weight in lean patients required higher than that in standard-physical-type patients to achieve a target trough concentration.

Our data revealed that the median doses of VCM per time (mg/kg) was 13.7 in the obese patients, which was lower than the

Table 1
Patients characteristics.

(n)	Lean (42)	Normal (180)	Obesity (50)	P value
Male/female	27/15	121/59	31/19	
Age (year)	61.9 ± 17.7	65.2 ± 14.6	64.6 ± 13.9	0.421[a]
Body weight (kg)	45.6 ± 7.2[c]	56.8 ± 8.0[c]	71.4 ± 10.2[c]	<0.01[a]
BMI (kg/m^2)	16.9 ± 1.3[d]	21.5 ± 1.8[d]	28.2 ± 3.2[d]	<0.01[b]
BUN (mg/dL)	13.1 ± 5.8	13.6 ± 6.1	15.0 ± 9.3	0.303[a]
eGFR (mL/min)	92.9 ± 29.3	90.2 ± 30.5	86.2 ± 23.0	0.526[a]
Dose of VCM (mg/once)	898.8 ± 202.9	923.1 ± 188.9	965.0 ± 151.6	0.207[a]
Day of TDM (day)	4.1 ± 1.3	4.2 ± 2.0	4.1 ± 1.8	0.909[a]
Trough conc (μg/mL)	15.0 ± 2.7[c]	13.8 ± 2.7	13.3 ± 2.8	<0.05[a]
Trough conc/dose (μg/mL)/(mg/kg)	0.78 ± 0.17	0.89 ± 0.28	1.00 ± 0.25[e]	<0.01[a]

a; one-way analysis of variance, b; Kruskal-Wallis test, c; Bonferroni test ($p < 0.01$ between each group), d; Steel-Dwass test ($p < 0.01$ between each group), e; Bonferroni test ($p < 0.01$ vs lean).

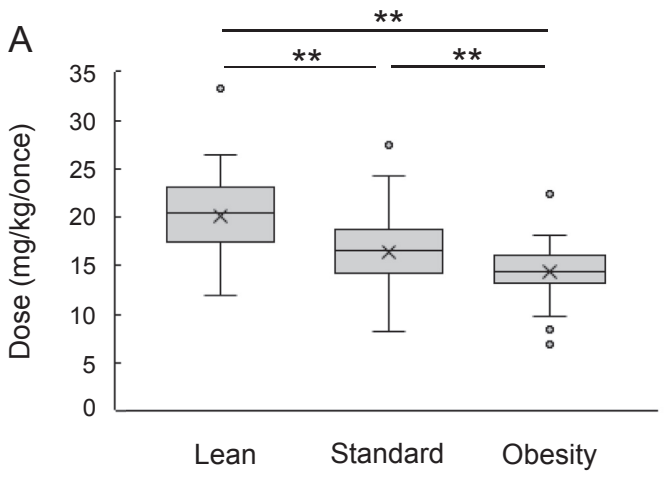

Fig. 1. Dose per time with respect to the physical type in patients in whom the trough concentration of VCM reached the target on initial TDM. Steel-Dwass test; $^{**}p < 0.01$.

recommended initial dose in the guidelines. Hong et al. reported that the mean Vd per body weight in obese patients with a BMI of 30–39.9 kg/m^2 was 0.736 ± 0.266 L/kg and that in those with a BMI of >40 kg/m^2 was 0.481 ± 0.154 L/kg, indicating that the Vd per body weight decreased with an increase in the BMI [9]. Richardson et al. demonstrated that an increase in the BMI was correlated with an increased trough concentration of VCM in obese patients. According to their study, the trough concentration of VCM at 23.9 mg/kg/day (mean dose) in obese patients was 16.5 μg/mL, whereas that at 26.0 mg/kg/day (mean dose) in non-obese patients was 12.1 μg/mL. Furthermore, the rate of obese patients in whom the trough concentration exceeded 20 μg/mL was higher than that of non-obese patients, whereas that below 15 μg/mL was lower [10]. Another retrospective study that investigated the dose to achieve optimal trough concentration of VCM in a patient population with a BMI of 30–40 or higher regarding the necessity of the dose reduction with an increase in the BMI reported that the daily dose of VCM was 30 mg/kg in patients with a BMI of 30–39, whereas it was 20–25 mg/kg in those with a BMI of ≥40 [11]. It might be appropriate to administer VCM to obese patients at a lower dose than that in non-obese patients to avoid nephrotoxicity, and the dose should be regulated by TDM [12].

To minimize the influence of confounding factors other than the physical type in the subjects, the age and frequency of administration per day were unified to ≥18 years and twice, respectively. A patient population with normal renal function was investigated. Inclusion criteria for the age and dose were ≥18 years and twice-a-day administration, respectively, based on the practice guidelines for TDM of vancomycin in Japan [4]. Regarding renal function assessment, Cockcroft-Gault's formula is routinely used, but it is influenced by the body weight [13]; therefore, we used a renal-function-estimating formula for Japanese patients involving the Cre level, age, and sex, but not the body weight, proposed by Matsuo et al. [14]. An eGFR of ≥60 mL/min/1.73 m^2 was adopted as a criterion. This value corresponds to normal or mild renal hypofunction in the severity classification of chronic kidney disease. In this study, the influence of the renal function on changes in the trough concentration may have been low.

Though similar trends are observed in a dose per time of VCM to obtain the target trough concentration through different races, the patient background markedly differs between Japan and other countries; therefore, caution is needed when extrapolating data from other countries to Japanese people. This study demonstrated that the dose per time (mg/kg) calculated using the body weight of obese patients was below the dose recommended in the practice guidelines for TDM of vancomycin in Japan, 15–20 mg/kg (Fig. 1). One previous study suggested that the risk of renal impairment may be reduced by designing a regimen based on an ideal body weight in obese patients [15]. Further data must be accumulated to examine whether an ideal body weight should be used to design a regimen for non-standard physical types to maximize the efficacy and minimize the onset of toxicity.

We revealed that the necessary initial dose of VCM per body weight to achieve the target trough concentration was higher in the lean patients and lower in the obese patients than that in the standard-physical-type patients. It is important to optimize the administration design based on the physical type.

Conflicts of interest

All authors report no conflicts of interest.

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