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Original Article

Clinical applicability of urinary creatinine clearance for determining the initial dose of vancomycin in critically ill patients

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All authors meet the ICMJE authorship criteria

YT was responsible for the organization and coordination of the trial. RM was the chief investigator and responsible for the data analysis. SI, MH and MS performed the trial design and data analysis. All authors contributed to the writing of the final manuscript.

Abstract

Introduction: The purpose of this study was to evaluate the clinical applicability of urinary creatinine clearance (CrCl) for determining the initial dose of vancomycin (VCM) in critically ill patients and to assess VCM trough plasma concentration/maintenance daily dose (C/D) ratio in patients with augmented renal clearance (ARC).

Methods: As the primary outcome measure, correlations between estimated renal function and the VCM C/D ratio were compared using the following formulas: CrCl, Cockcroft-Gault equation ($eCrCl_{C\text{-}G}$) and KineticGFR equation (KeGFR). Patients were divided into those with or without changes in renal function. The patients were further classified based on the presence or absence of ARC. The secondary outcome was the comparison of VCM C/D ratio between ARC and Non-ARC patients.

Results: A total of 65 patients were enrolled for analysis. In all groups, CrCl tended to correlate better with the VCM C/D ratio than $eCrCl_{C\text{-}G}$ and KeGFR. A significantly lower VCM C/D ratio was observed in patients with persistent ARC than in the Non-ARC group (0.24 versus 0.52 kg/L).

Conclusions: The clinical applicability of CrCl for the initial dosing design of VCM in critically ill patients was shown. Furthermore, the results indicated that patients with persistent ARC required a higher VCM dose than Non-ARC patients. Although our findings are limited, they have a value for further verification.

Keywords: Therapeutic drug monitoring, Vancomycin, Critically ill patients, Augmented renal clearance

Introduction

Accurate estimation of renal function in critically ill patients is important for designing an appropriate drug dosing regimen for renally excreted drugs. The gold standard for assessing renal function is glomerular filtration rate (GFR) [1], which is calculated from inulin clearance; nevertheless, GFR is not widely used because it is invasive and labor intensive. In clinical practice, various estimation formulas using serum creatinine (sCr) are widely used because of their simplicity [2–4]. However, these equations are inaccurate in the acute phase because they assume patients have stable renal function [5, 6]. Moreover, in critically ill patients with changing renal function, there is no established renal function assessment formula to adjust drug doses. In such cases, urinary creatinine clearance (CrCl), which measures the amount of creatinine in urine, is often used for daily renal function assessment [7–9].

Vancomycin (VCM), one of the antibiotics for methicillin-resistant *Staphylococcus aureus* (MRSA) infection, is a renally excreted drug with more than 90% of the drug being excreted unchanged in urine [10, 11]. Critically ill patients need to achieve effective VCM plasma concentration within a short period [12]; however, they are known to be at a high risk for acute kidney injury [13]. Therefore, it is recommended to adjust the dose based on their plasma concentrations via therapeutic drug monitoring (TDM) [14]. Nonetheless, prediction of VCM plasma concentration in critically ill patients is difficult because of the large variability in volume of distribution and clearance [15, 16]. Various equations for estimating renal function have been used for designing the dose regimen of VCM in critically ill patients [17–19]. However, there are only few reports comparing the usefulness of CrCl with that of other renal function estimation equations, especially in patients with variable renal function. In general, CrCl better estimates the renal function trends of critically ill patients and may be useful in designing VCM dosing; moreover, it is less expensive to determine CrCl [8]. Thus, the purpose of this study was to evaluate the clinical applicability of CrCl for the initial dosing design of VCM in critically ill patients.

In addition, there have been an increasing number of reports supporting the presence of augmented renal clearance (ARC) in some critically ill patients [20–23]. ARC is defined as increased renal excretion of circulating solutes, and the risk of decreasing plasma concentration of VCM has been reported in such cases [24–27]. There is a lack of evidence of the appropriate VCM dose in Japanese patients with ARC [28]. Moreover, there are few reports of TDM for VCM (VCM-TDM) with continuous daily measurement of CrCl [29]. Therefore, this study also evaluated the clinical applicability of CrCl in patients with ARC. In addition, we assessed whether the VCM trough plasma

concentration/maintenance daily dose (C/D) ratio was different between ARC and Non-ARC patients, taking into account their renal function changes.

Patient and Methods

Data sources

All data were obtained retrospectively from the medical records of critically ill patients who had received VCM intravenously from April 2014 to July 2020 at the Emergency Department of Hokkaido University Hospital. Patients were excluded if they were younger than 18 years, received renal replacement therapy, and changed VCM maintenance dose during the start of VCM therapy and the initial TDM.

Data collection

We collected data on age, sex, height, weight, urinary creatinine (uCr), sCr, serum albumin (sAlb), diagnosis, history of VCM dosage, and VCM trough plasma concentration. Body surface area (BSA) was calculated using the DuBois equation. The severity of each patient's illness was evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE) II scores determined on the first day of VCM administration.

Renal function estimation

The renal function was estimated using the following formulas: CrCl equation, Cockcroft-Gault equation ($eCrCl_{C\text{-}G}$), and KineticGFR equation (KeGFR).

➢CrCl formula:

$$CrCl\ (mL/min) = \frac{Volume\ urine\ (mL)\ \times\ uCr\ (mg/dL)}{Collection\ time\ (min) \times\ sCr\ (mg/dL)}$$

➢$eCrCl_{C\text{-}G}$ formula [2]:

$$eCrCl_{C-G}\ (mL/min) = \frac{(140 - Age) \times\ Body\ Weight\ (kg)}{72\ \times\ sCr\ (mg/dL)}$$

For females, the above value was multiplied by 0.85. When sCr was < 0.6 mg/dL, it was corrected to 0.6 mg/dL [30].

➢KeGFR formula [31, 32]:

$$KeGFR\ (mL/min) = \frac{SSP_{cr}\ (mg/dL)\ \times eCrCl_{C-G}\ (mL/min)}{MeanPcr\ (mg/dL)} \times \left(1 - \frac{24\ (hr/day) \times \Delta P_{cr}\ (mg/dL)}{\Delta Time\ (hr)\ \times Max\Delta P_{cr}\ (mg/dL)\ /Day}\right)$$

SSPcr is the steady-state sCr (in this analysis, sCr at the time of study enrollment). MeanPcr is the mean value of sCr measured on the day of VCM administration and the day before. ΔPcr is the difference in sCr between the two points. ΔTime is the interval in hours between two consecutive sCr measurements. MaxΔPcr is the maximum change in sCr (1.5 was used in this analysis).

Outcomes

To evaluate the clinical applicability of CrCl for the initial dose determination of VCM, we evaluated the correlation between estimated renal function on the first day of VCM administration and the VCM C/D ratio in each above-mentioned formula as the primary outcome measure. The VCM dosing design and CrCl collection are shown in Fig. 1. The VCM loading dose (only once) and maintenance dose were determined based on the physician's decision and/or pharmacist's suggestion. The maintenance dose of VCM was fixed until the first VCM-TDM. VCM-TDM was performed after day 3. CrCl was calculated from daily 8 h urine collection (22:00–6:00). Patients were divided into those with or without changes in renal function, which is often unstable in critically ill patients. The patients were further classified based on the presence or absence of ARC. In particular, patients with a change in CrCl > 30 mL/min during the start of VCM administration to the initial TDM were defined as the renal function change group, and the rest were defined as the renal function non-change group. This criterion was based on the renal function classification of the US Food and Drug Administration (FDA) guidance [33]. Moreover, patients with CrCl > 130 mL/min on the first day of VCM administration were defined as the ARC group, and the rest were defined as the Non-ARC group. The sample size required for the correlation analysis was determined based on previous studies on critically ill patients. In these previous studies, the correlation between CrCl and VCM plasma concentrations was r = -0.53 [34] and -0.57 [35]. From these results, we calculated the effect size as 0.55, α error 0.05, β error 0.2, with the required sample size being n = 16 in G*power [36].

The difference in VCM C/D ratio between ARC and Non-ARC patients was assessed as the secondary outcome. Patients were classified into the following three groups: patients with CrCl > 130 mL/min during the start of VCM administration to the initial

TDM (Actual ARC group), patients with CrCl > 130 mL/min on the first day of VCM administration and CrCl < 130 mL/min thereafter (Borderline ARC group), and patients with CrCl < 130 mL/min during the start of VCM administration to the initial TDM (Non-ARC group). In each group, other patient data, such as estimated renal function, trough plasma concentration of VCM, and maintenance daily dose of VCM, were also compared.

Statistical analysis

Continuous data were presented as the mean (standard deviation). If the continuous data were non-normally distributed, data were presented as the median (interquartile range, IQR). Categorical data were presented as counts (%). Paired *t*-test was used to analyze the correspondence of continuous data. In the non-correspondence analysis of continuous data, which had non-normal distribution, Steel–Dwass test was used for multi-group comparisons. Significance was set at $P < 0.05$. The correlation between two variables was established using Spearman's correlation coefficient by rank test, and *P*-values < 0.05 were considered to indicate correlation. All statistical analyses were performed using the Excel add-in software Statcel ver.3 (OMS Publishing, Japan).

Ethics

We carried out this study in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study was approved by the Ethics Committee of Hokkaido University Hospital (No. 020–0002). Since this was a retrospective study, informed consent from the subjects was not mandated. An opt-out approach was used with the disclosure form available at https://www.huhp.hokudai.ac.jp/wp-content/uploads/2020/09/020-0002.pdf.

Results

Patient characteristics

During the study period, 202 patients were included in the study. Of these, a total of 137 patients were excluded for the following reasons (some patients have duplication): aged younger than 18 years (n = 26), received renal replacement therapy (n = 83), and changed the VCM maintenance dose from the start of VCM administration to the initial TDM (n = 93). Finally, 65 patients were enrolled for the analysis. The characteristics of the patients are shown in Table 1. Among these patients, 16 were classified into the renal function change group and 49 to the renal function non-change group. The median (IQR) CrCl in all patients was 92.9 mL/min (63.7-138 mL/min). The median (IQR) trough

plasma concentration of VCM in all patients was 11.6 μg/mL (8.6-15.4 μg/mL).

Correlation of estimated renal function and VCM C/D ratio

The correlation between estimated renal function and VCM C/D ratio in three formulas (CrCl, $eCrCl_{C\text{-}G}$, and KeGFR) is shown in Fig. 2. Usually, high renal function is associated with a low C/D ratio; thus, the correlation coefficient is negative. Accordingly, the correlation coefficient between CrCl and VCM C/D ratio in all patients was -0.598. In all groups except the Non-ARC patients in the renal function change group, CrCl tended to show a stronger negative correlation with VCM C/D ratio than $eCrCl_{C\text{-}G}$ and KeGFR (Fig. 2, i–v). In patients without ARC, the correlation between estimated renal function and VCM C/D ratio tended to be weaker in the renal function change group than in the renal function non-change group (Fig. 2, iii, v). In addition, in the Non-ARC patients in the renal function change group, there was no correlation between all estimated renal functions and VCM C/D ratio (Fig. 2, iii). In patients with ARC, regardless of the presence or absence of renal function changes, CrCl tended to show a stronger negative correlation with VCM C/D ratio than $eCrCl_{C\text{-}G}$ and KeGFR. Moreover, they showed no correlation between $eCrCl_{C\text{-}G}$ or KeGFR and VCM C/D ratio (Fig. 2, ii, iv).

Comparison of VCM C/D ratio between ARC and Non-ARC patients

As shown in Table 2, the Actual ARC group tended to have a significantly lower VCM C/D ratio than the Non-ARC group (0.24 versus 0.52 kg/L). There were no significant differences between the Actual ARC group and the Borderline ARC group or between the Borderline ARC group and the Non-ARC group. The median (IQR) CrCl was 171.6 mL/min (157.5-203.0 mL/min), 137.2 mL/min (135.2-139.3 mL/min), and 72.5 mL/min (55.4-92.7 mL/min) in each group (the Actual ARC, Borderline ARC, and Non-ARC groups); these values were significantly different. Of the 65 patients analyzed, 22 were ARC patients with CrCl > 130 mL/min. However, only 5 and 7 patients were determined to have ARC using $eCrCl_{C\text{-}G}$ and KeGFR, respectively.

Discussion

The purpose of this study was to evaluate the clinical applicability of CrCl for the initial dosing design of VCM in critically ill patients. We evaluated its usefulness by comparing the correlation between estimated renal function and VCM C/D ratio using three formulas. In addition, continuous monitoring of CrCl in patients with ARC was used to assess whether the VCM C/D ratio differed between ARC and Non-ARC patients.

As shown in Fig. 2, in all groups except the Non-ARC patients in the renal function change group, CrCl tended to show a stronger negative correlation with VCM C/D ratio than $eCrCl_{C\text{-}G}$ and KeGFR, indicating that CrCl is useful as a renal function assessment formula in determining the initial dose of VCM. In critically ill patients, $eCrCl_{C\text{-}G}$ is not able to provide correct judgment because this formula is based on the kidney status of a healthy individual, and sCr takes longer to detect changes in renal function. Moreover, the recently proposed KeGFR incorporating the rate of change of sCr was also examined and found to be inappropriate as well as $eCrCl_{C\text{-}G}$.

On the other hand, there was no correlation between all estimated renal function indicators, including CrCl and VCM C/D ratio, in the Non-ARC patients in the renal function change group. The reason for this is that the patients in this study were on a fixed maintenance dose of VCM and their CrCl increased or decreased above 30 mL/min after day 2, and thus the C/D ratios of day 1 CrCl and VCM in that group did not correlate. The usefulness of continuously measuring CrCl and adjusting the dosage of VCM in critically ill patients with changing renal function needs to be clarified in the future. In many cases, $eCrCl_{C\text{-}G}$ is used to assess renal function instead of the more laborious CrCl. However, in a 24 h monitoring situation, such as an intensive care unit, evaluation by CrCl is considered necessary owing to its usefulness. It is also possible to save labor by using 8 h of CrCl instead of 24 h of CrCl [37–39]. A recent study suggested that creatinine-based equations have a lower performance in predicting GFR in critically ill patients than cystatin C-based equations [40]. However, it is difficult to continuously estimate renal function because cystatin C measurement can only be claimed for medical expenses once every 3 months in Japan. In general, as CrCl is the result of both glomerular filtration and tubular excretion, this overestimation error is inherent to this method [41]. Considering this error, CrCl has shown reasonable performance and may be a cheaper alternative to cystatin C-based equations [8].

In patients with ARC, regardless of the presence or absence of renal function changes, only CrCl showed a significant negative correlation with VCM C/D ratio (renal function change group: -0.525, renal function non-change group: -0.489). This may be due to a higher basic renal function and a small rate of change in renal function, and thus only CrCl, which can discriminate ARC, was correlated with the C/D ratio of VCM. There is a report from Japan that renal function in patients with ARC can be adequately assessed by $eCrCl_{C\text{-}G}$ [42]. However, many reports argue that CrCl should be used [22, 23, 25, 43]. Specifically, among the 22 patients with ARC judged by CrCl, only 5 and 7 patients were judged by $eCrCl_{C\text{-}G}$ and KeGFR, respectively. In this study, the majority of patients with ARC judged by CrCl could not be judged by $eCrCl_{C\text{-}G}$ and KeGFR.

Herein, a significantly lower VCM C/D ratio was observed in patients with persistent ARC than in Non-ARC patients (0.24 versus 0.52 kg/L). This is generally consistent with previous reports on burns in ARC patients [44] and suggested that a high VCM dose is required in patients with persistent ARC. In general, in patients with ARC, the decision to switch from first-line VCM to other anti-MRSA agents is rarely based on advanced renal function alone on the first day, and switching to other anti-MRSA agents is usually considered after the initial TDM confirms low trough plasma concentrations. On the other hand, in critically ill patients, underdosing should be avoided even for short periods of time because of the high risk of treatment failure. Moreover, other anti-MRSA drugs as well as VCM have been reported to have a risk of decreased plasma concentrations in patients with ARC [45, 46]. Therefore, in some cases, a monitorable VCM is preferable. We believe that this study provides information on the need for early VCM-TDM to avoid under-dosing of VCM in patients with ARC.

This study had some limitations. First, this study was conducted at a single center. Second, the number of cases was low and there were groups that did not meet the sample size (n = 16) set for correlation analysis. It is necessary to conduct further studies with a higher number of cases and verify whether same results can be obtained in multiple institutions. Third, in the current VCM-TDM guidelines, AUC-guided TDM only, and not trough-guided TDM, is recommended for VCM [14]. In the future, it is necessary to validate the clinical applicability of CrCl under AUC-guided TDM in critically ill patients.

Conclusions

We revealed the clinical applicability of CrCl in determining the initial dose of VCM for critically ill patients. Furthermore, our results indicate that patients with persistent ARC require a higher VCM dose than Non-ARC patients. We consider it necessary to continuously monitor renal function using CrCl and comprehensive evaluation including disease because the renal function of critically ill patients often changes on a daily basis. Although our findings are limited, they have a value for further verification.

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None.

Conflict of interest

The authors declare no potential conflicts of interest.

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Figure legends

Fig. 1 The procedure for VCM dosing design and CrCl collection.

Abbreviation: VCM, vancomycin; VCM-TDM, therapeutic drug monitoring for vancomycin; CrCl, urinary creatinine clearance.

Fig. 2 Linear correlation between estimated renal function and VCM C/D ratio.

The correlation between the two variables was established using Spearman's correlation coefficient by rank test (Rs). A *P* value of < 0.05 was considered significant.

Abbreviation: ARC, augmented renal clearance; CrCl, urinary creatinine clearance; $eCrCl_{C\text{-}G}$, Cockcroft-Gault equation; KeGFR, KineticGFR equation; VCM, vancomycin; VCM C/D ratio, vancomycin trough plasma concentration/maintenance daily dose (C/D) ratio.

Tables

Table 1. Patient characteristics

	All	Renal function change group		Renal function non-change group	
		ARC	Non-ARC	ARC	Non-ARC
N	65	9	7	13	36
Age, years*	69 (50-73)	48 (39-71)	64 (54-70)	50 (41-56)	71 (67-78)
Male/Female, n	45/20	6/3	3/4	11/2	27/12
Height, cm*	164 (156-171)	172 (160-175)	153 (151-164)	168 (162-172)	162 (156-170)
Weight, kg*	62 (54-71)	62 (58-74)	54 (51-66)	67 (55-72)	62 (53-68)
BMI, kg/m^2*	23.3 (20.7-26.0)	23.7 (20.4-26.0)	24.3 (20.5-25.9)	23.1 (20.4-26.7)	23.0 (20.7-25.6)
BSA, m^2*	1.68 (1.53-1.82)	1.76 (1.62-1.85)	1.53 (1.46-1.68)	1.75 (1.65-1.87)	1.63 (1.52-1.79)
Serum albumin, g/dL*	2.5 (2.1-3.0)	2.6 (2.5-2.8)	3.2 (2.5-3.3)	2.5 (2.2-2.8)	2.4 (1.9-2.8)
Serum creatinine, mg/dL*	0.80 (0.57-0.94)	0.63 (0.50-0.88)	0.85 (0.77-0.99)	0.64 (0.48-0.79)	0.82 (0.60-1.04)
Estimated renal function*					
Day1 CrCl, mL/min	92.9 (63.7-138)	140 (136-205)	65.3 (46.8-85.5)	156 (142-170)	73.3 (55.8-94.1)
Day2 CrCl, mL/min	95.2 (65.3-135)	139 (65.4-181)	94.1 (75.3-110)	167 (141-175)	76.4 (56.4-98.2)
Day3 CrCl, mL/min	89.6 (65.2-134)	158 (123-233)	78.3 (59.6-94.6)	140 (128-195)	73.5 (52.0-90.4)
Day1 $eCrCl_{C\text{-}G}$, mL/min	81.6 (57.7-113)	117 (104-126)	55.2 (49.1-74.0)	113 (98.2-137)	67.7 (46.6-90.4)
Day2 $eCrCl_{C\text{-}G}$, mL/min	84.9 (60.1-108)	108 (77.3-118)	68.4 (44.7-87.9)	106 (92.0-147)	69.9 (55.1-92.4)
Day3 $eCrCl_{C\text{-}G}$, mL/min	81.0 (60.1-108)	118 (104-123)	69.5 (51.7-87.4)	113 (92.0-138)	72.3 (49.6-91.4)
Day1 KeGFR, mL/min	76.2 (44.3-97.2)	107 (86.1-121)	51.6 (33.5-69.0)	100 (94-123)	65.2 (31.1-90.0)

Day2 KeGFR, mL/min	80.5 (44.5-101)	104 (77.3-108)	42.5 (35.6-82.8)	97.2 (88.7-138)	64.1 (34.6-88.7)
Day3 KeGFR, mL/min	80.1 (49.0-102)	108 (98.8-118)	50.0 (38.6-83.8)	98.2 (85.0-126)	66.1 (37.4-88.2)
VCM trough plasma concentration, μg/mL*	11.6 (8.6-15.4)	7.3 (4.8-13.4)	8.6 (6.75-11.5)	10.8 (8-13.8)	13 (10.25-16.2)
Time interval between VCM administration and VCM trough plasma concentration measured, h*	59.5 (42.5-61.5)	59.5 (47.5-79.5)	58.5 (51-60.5)	47.5 (39.5-59.5)	58.5 (40.5-62.0)
Loading dose †	16 (25)	0 (0)	2 (28.6)	1 (7.7)	13 (36)
Daily maintenance dose, mg/kg/day*	29.8 (19.5-34.1)	28.2 (18.7-42.9)	26.3 (16.7-30.6)	39.7 (30.3-44.9)	29.5 (18.7-32.4)
VCM C/D ratio, kg/L*	0.42 (0.28-0.64)	0.27 (0.23-0.32)	0.42 (0.29-0.53)	0.25 (0.19-0.42)	0.52 (0.36-0.72)
APACHE II score*	24 (21-26)	24 (22-26)	23 (22-25)	20 (19-25)	25 (22-28)
Admission diagnosis †					
Cardiovascular diseases	26 (40)	4 (44)	5 (71)	3 (23)	14 (39)
Respiratory failure	7 (11)	0 (0)	0 (0)	1 (8)	6 (17)
Central nervous system diseases	6 (9)	3 (33)	0 (0)	1 (8)	2 (6)
Digestive diseases	6 (9)	0 (0)	1 (14)	2 (15)	3 (8)
Trauma	13 (20)	1 (11)	1 (14)	6 (46)	5 (14)
Sepsis	7 (11)	1 (11)	0 (0)	0 (0)	6 (17)

*median (IQR), †n (%).

Abbreviation: APACHE II score, Acute Physiology and Chronic Health Evaluation II score; ARC, augmented renal clearance; BMI, body mass index; BSA, body surface area; CrCl, urinary creatinine clearance; $eCrCl_{C\text{-}G}$, Cockcroft-Gault equation; KeGFR, KineticGFR equation; VCM, vancomycin; VCM C/D ratio, vancomycin trough plasma concentration/maintenance daily dose ratio.

Table 2. Data in the ARC and control groups

	Actual ARC (n = 14)	Borderline ARC (n = 8)	Non-ARC (n = 43)
CrCl, mL/min*	171.6 (157.5-203.0)	137.2 (135.2-139.3)	72.5 (55.4-92.7)‡
$eCrCl_{C-G}$, mL/min*	124.3 (104.6-135.4)	102.1 (92.5-114.1)	66.4 (47.0-90.0)¶,‖
KeGFR, mL/min*	119.3 (102.5-133.8)	107.1 (94.7-137.2)	64.9 (31.3-84.4)¶,**
Serum creatinine, mg/dL*	0.63 (0.49-0.81)	0.65 (0.48-0.76)	0.85 (0.64-1.05)§
$eCrCl_{C-G}$ > 130 mL/min†	4 (28.6)	1 (12.5)	0 (0)
KeGFR > 130 mL/min†	4 (28.6)	3 (37.5)	1 (1.5)
Serum creatinine < 0.6 mg/dL†	6 (42.9)	3 (37.5)	9 (13.8)
VCM trough plasma concentration, μg/mL*	9.4 (5.9-11.9)	13.7 (9.3-18.5)	12.3 (9.9-16.2)§
Daily maintenance dose, mg/kg/day*	34.2 (28.3-42.1)	42.3 (18.2-57.3)	29.4 (17.9-32.0)§
VCM C/D ratio, kg/L*	0.24 (0.17-0.29)	0.32 (0.25-0.48)	0.52 (0.36-0.69)¶

*median (IQR), †n (%), ‡P-values < 0.01 between all groups was considered significant by Steel-Dwass test, §P-values < 0.05 for Actual ARC versus Non-ARC was considered significant by Steel-Dwass test, ¶P-values < 0.01 for Actual ARC versus Non-ARC was considered significant by Steel-Dwass test, ‖P-values < 0.05 for Borderline ARC versus Non-ARC was considered significant by Steel-Dwass test, **P-values < 0.01 for Borderline ARC versus Non-ARC was considered significant by Steel-Dwass test.

Abbreviation: ARC, augmented renal clearance; CrCl, urinary creatinine clearance; eCrClC-G, Cockcroft-Gault equation; KeGFR, KineticGFR equation; VCM, vancomycin; VCM C/D ratio, vancomycin trough plasma concentration/maintenance daily dose ratio.

Figure 1.

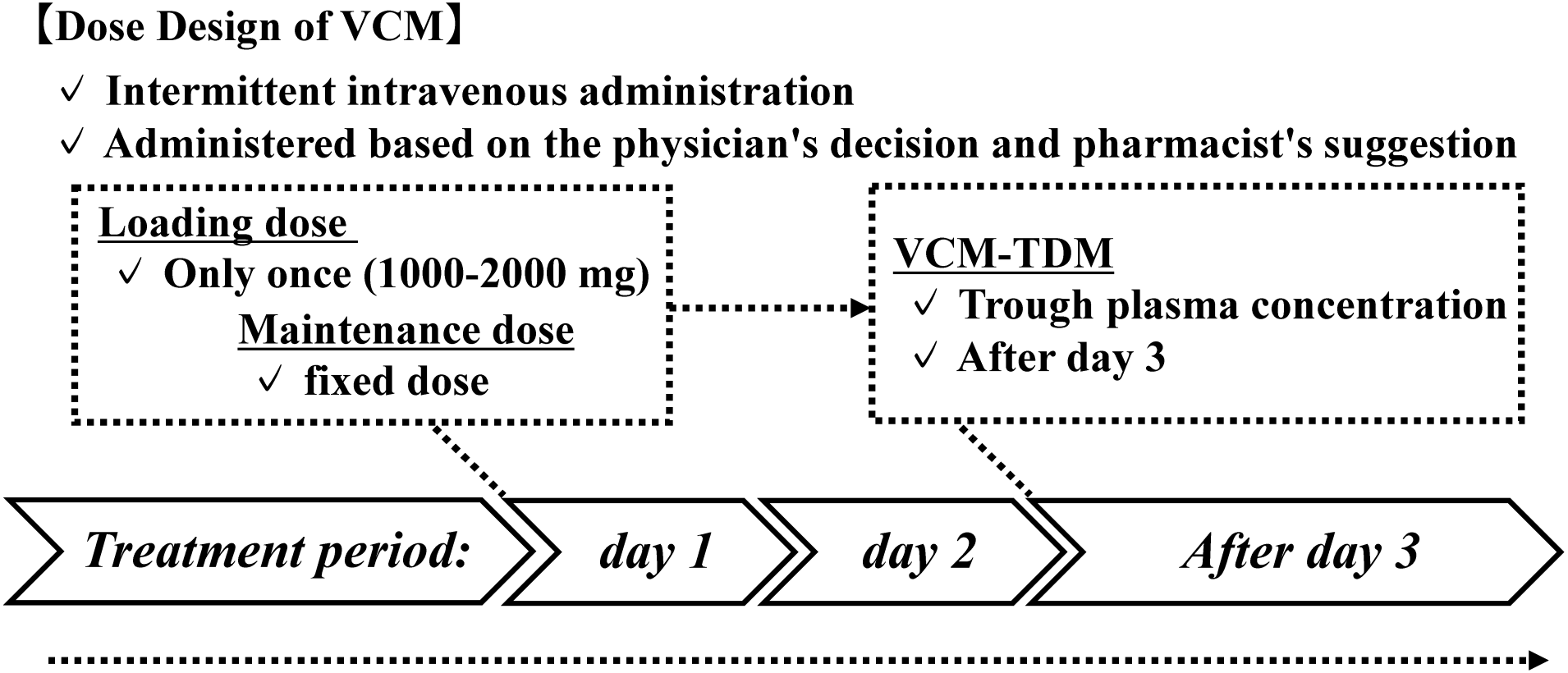
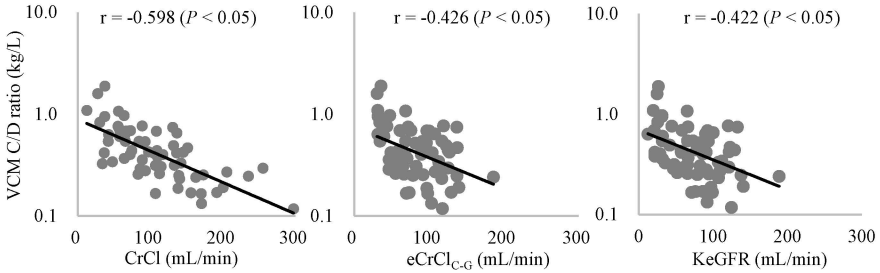
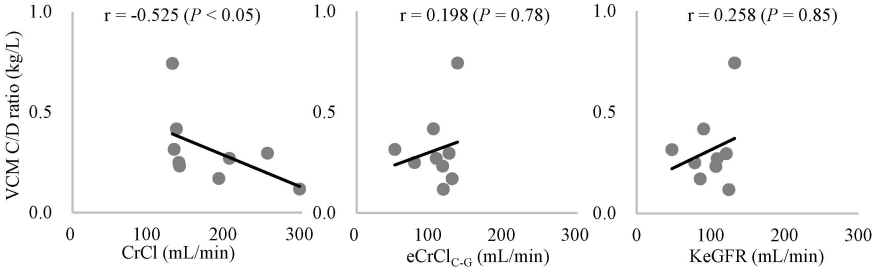

【Dose Design of VCM】
✓ Intermittent intravenous administration
✓ Administered based on the physician's decision and pharmacist's suggestion
Loading dose
✓ Only once (1000-2000 mg)
Maintenance dose
✓ fixed dose
VCM-TDM
✓ Trough plasma concentration
✓ After day 3
Treatment period:
day 1
day 2
After day 3
【Monitoring of CrCl】
✓ Daily CrCl monitoring
✓ CrCl was calculated from an 8 h (22:00-6:00) urine collection
✓ Urine volume was monitored by nurses 24 h a day

Figure 2.

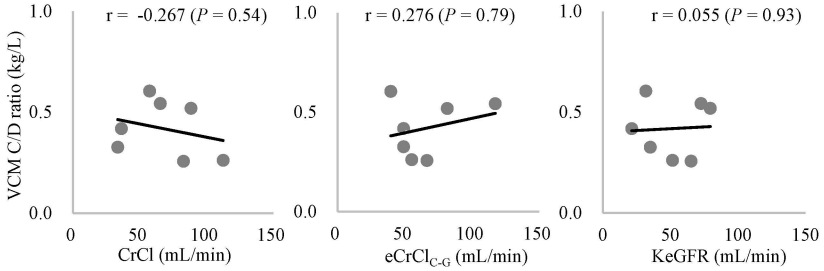
i. All



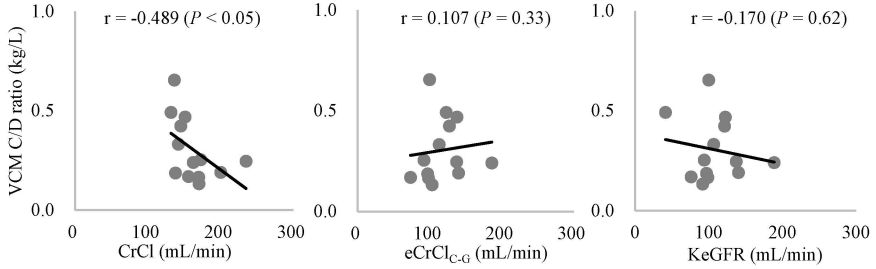
ii. ARC patients in the renal function change group



iii. Non-ARC patients in the renal function change group



iv. ARC patients in the renal function non-change group



v. Non-ARC patients in the renal function non-change group

