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Factors associated with serum concentrations of vancomycin crystalline degradation product (CDP-1) among patients with chronic kidney disease

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Abstract

Background The aim of this study was to identify the clinical factors associated with serum trough concentrations of vancomycin crystalline degradation product (CDP-1) and to determine the impact of CDP-1 on chemiluminescence microparticle immunoassay (CMIA) results among patients with chronic kidney disease (CKD).

Methods In this retrospective observational study, patients with CKD who were receiving vancomycin intravenously were included if steady-state serum trough levels of vancomycin were available. Patients were allocated to three groups on the basis of their estimated creatinine clearance (eCrCl) on the day of trough level monitoring: G1 ($60 < eCrCl \leq 90$ mL/min), G2 ($30 < eCrCl \leq 60$ mL/min), and G3 ($eCrCl \leq 30$ mL/min). CDP-1 serum concentrations were determined via ultra-high performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS). Vancomycin serum concentrations measured via CMIA were compared with those measured via UPLC–MS/MS. Multiple linear regression analyses were performed to identify factors associated with the CDP-1 concentration and the ratio of vancomycin concentration determined via CMIA to vancomycin concentration via UPLC–MS/MS ($V_{CMIA}/V_{UPLC\text{-}MS/MS}$).

Results Among the 167 patients included, 49 (29.34%), 69 (41.32%), and 49 (29.34%) were allocated to G1, G2, and G3, respectively. There were significant differences in the CDP-1 trough concentrations and $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratios between the three groups. In the multivariate analysis, eCrCl levels ($P < 0.001$), the time interval from the initial dose to the trough level ($P < 0.001$), and vancomycin dose ($P < 0.001$) were associated with CDP-1 trough concentrations. The CDP-1 trough concentration was positively associated with the $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio ($P = 0.002$).

Conclusions Delayed timing of trough level sampling could contribute to increased CDP-1 levels and the overestimation of vancomycin levels, especially in patients with severe deterioration in renal function. It may be necessary to increase the frequency of TDM and select quantitative methods to measure vancomycin serum levels without interfering with CDP-1.

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Keywords Crystalline degradation product, Chronic kidney disease, Chemiluminescence microparticle immunoassay, Vancomycin, Therapeutic drug monitoring

Background

Chronic kidney disease (CKD) is recognized as a worldwide public health burden, with an estimated prevalence of 13.4% [1]. CKD patients are more vulnerable to infections due to their immune system alterations [2, 3]. Accordingly, infection is a leading cause of death among patients with CKD [4, 5]. Individuals with CKD are at increased risk of experiencing severe symptoms related to infectious diseases, thus contributing to a high incidence of mortality [6, 7].

Vancomycin, a glycopeptide antibiotic, is widely used for severe infections caused by multidrug-resistant gram-positive bacteria. Considering the considerable individual variability and narrow therapeutic window of vancomycin, therapeutic drug monitoring (TDM) has been advocated and routinely performed in clinical practice, especially for patients with CKD [8, 9]. The 2020 therapeutic monitoring consensus guidelines established area under the concentration–time curve (AUC)-guided dosing as the optimal strategy for severe methicillin-resistant *Staphylococcus aureus* infections to optimize therapeutic efficacy and minimize toxicity. Current evidence supports a pharmacokinetic/pharmacodynamic (PK/PD) target of AUC-to-minimum inhibitory concentration (AUC/MIC) ratio of 400–600 mg·h/L in adult patients for dose optimization. This approach requires the measurement of two steady-state serum vancomycin concentrations (including at least one trough concentration) to estimate the AUC for vancomycin through either first-order PK equations or Bayesian modeling with population model priors [10].

Commercially available automated immunoassays have been widely applied to quantify concentrations of vancomycin in clinical laboratories [11, 12]. However, compared with high-performance liquid chromatography (HPLC), the polyclonal antibody fluorescence polarization immunoassay (FPIA) has demonstrated overestimation of vancomycin serum concentrations exceeding 50% in dialysis patients [13–16]. These results prompted an attempt to improve the quality of immunoassays. At present, chemiluminescent microparticle immunoassay (CMIA) is one of the most routinely utilized methods in TDM [17]. Fan et al. reported a CMIA/ultra-performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS) concentration ratio of 1.24 ± 0.53 in hemodialysis patients [18]. In another study, vancomycin concentrations measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS) were 2.64% higher than those measured via CMIA (ranging from –57.88% to 39.48%) [19].

Investigators have suggested that the accumulation of vancomycin crystalline degradation product (CDP-1) may lead to the overestimation of vancomycin concentrations in patients with impaired renal function [13–15, 20]. CDP-1 contains two isomers: CDP-1-m (the minor isomer) and CDP-1-M (the major isomer) [21]. Given that both of these products lack antibacterial activity, the accumulation of these products in the human body may contribute to treatment failure or the development of drug resistance [22]. Notably, CDP-1 interference with immunoassays could introduce inaccuracies in vancomycin concentration measurements, leading to biased AUC estimations and potential effects on dose optimization strategies on the basis of pharmacokinetic modeling.

Backes et al. detected a mean CDP-1 concentration of 4.50 μg/mL (range: 1.00–10.20 μg/mL) in 76 hemodialysis patients via HPLC [20]. In another study, trough concentrations of CDP-1-m and CDP-1-M were found to be 0.69 ± 0.46 μg/mL and 0.94 ± 0.50 μg/mL, respectively, in 12 serum samples collected from patients with renal insufficiency (mean creatinine clearance: 8.3 ± 4.6 mL/min) [23]. However, the determinants of CDP-1 variability remain unclear, as CDP-1 concentrations and details regarding the clinical characteristics of patients have not been fully reported in prior studies.

The aim of this study was to identify the clinical determinants of serum CDP-1 concentrations while evaluating the effects of CDP-1 on CMIA for vancomycin determination in CKD patients.

Methods

Study population

This single-center retrospective observational study was performed at our hospital from July 2022 to July 2024. The inclusion criteria were as follows: (1) hospitalized patients with a discharge diagnosis of CKD; (2) aged ≥ 18 years; and (3) whose trough levels of vancomycin were monitored during intravenous vancomycin therapy. Patients were excluded if the vancomycin trough level was not obtained at steady state. Patients eligible for inclusion in the study were allocated to three groups on the basis of their estimated creatinine clearance (eCrCl) on the day of trough level monitoring: G1 (60 < eCrCl ≤ 90 mL/min), G2 (30 < eCrCl ≤ 60 mL/min), and G3 (eCrCl ≤30 mL/min).

Data collection

The following data were extracted from electronic medical records: patient demographics, comorbidities, infectious diagnosis, vancomycin dose, time interval from the

initial dose to the trough level, concomitant nephrotoxic agents while receiving vancomycin, and renal replacement therapy (RRT). Body temperatures during the period between administration of the initial dose and collection of the trough level sample were also recorded. Aminoglycosides, amphotericin B, colistin, piperacillin–tazobactam, loop diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and vasopressors are regarded as nephrotoxic agents. Other clinical data, including serum creatinine (Scr), albumin (ALB), urea, and total carbon dioxide (tCO_2) concentrations at baseline and during vancomycin therapy, were extracted from the laboratory database. eCrCl was calculated via the Cockcroft–Gault equation.

Trough concentration assessment of vancomycin and CDP-1

Steady-state trough level samples were obtained within 1 h prior to the fifth scheduled vancomycin dose. A previously published and validated UPLC–MS/MS method by Fan et al. was used to measure trough concentrations of vancomycin, CDP-1-m and CDP-1-M [23]. The method demonstrated linear dynamic ranges of 1.057–105.7 μg/mL for vancomycin, 0.144–14.4 μg/mL for CDP-1-m, and 0.254–25.4 μg/mL for CDP-1-M, with precision metrics showing intra-assay coefficients of variation (CV) of 1.8–8.1% (CDP-1-m), 2.1–4.6% (vancomycin), and 1.0–5.9% (CDP-1-M), and inter-assay CVs of 2.7–6.2%, 2.9–4.1%, and 2.5–6.9% respectively. Extraction recoveries averaged 99.5–106.2% for CDP-1-m, 94.8–101.8% for vancomycin, and 90.1–107.1% for CDP-1-M, while matrix effects in normal human serum ranged from 86.8–98.7% (CDP-1-m), 89.3–98.7% (vancomycin), to 91.0–99.4% (CDP-1-M).

The CMIA method was also applied to determine vancomycin concentrations in samples for comparison with the UPLC–MS/MS method. CMIA was run on an Architect I1000sr (Abbott Laboratories, USA) according to the manufacturer's instructions. The CMIA had declared parameters as follows: intra-assay CV 1.6–2.9%, inter-assay CV 3.1–6.2% and recovery 94.2–108.3% [24].

Statistical analyses

Statistical analyses were performed via JMP Pro software (version 13.0; SAS Institute Inc., Cary, USA). Descriptive statistics of all the variables were calculated. The Kolmogorov–Smirnov test was used to check the normal distribution of the data. The means ± standard deviations (SDs) were calculated for normally distributed quantitative variables. The median and interquartile range (IQR) were calculated for nonnormally distributed quantitative variables. Dichotomous variables are expressed as counts (percentages). One-way analysis of variance (ANOVA) was used to compare normally distributed continuous variables, and the Kruskal–Wallis test was used to compare nonnormally distributed continuous variables. The chi-square test was used to compare categorical variables.

Multiple linear regression analyses were performed to identify factors associated with the CDP-1 concentration and the ratio of vancomycin concentration determined via CMIA to vancomycin concentrations via UPLC–MS/MS ($V_{CMIA}/V_{UPLC\text{-}MS/MS}$). Variables with a p value of <0.1 in univariate analyses were subsequently included in the multiple linear regression model, and only variables that were statistically significant were retained in the final model. P values of less than 0.05 were considered statistically significant.

Results

Baseline characteristics

The final cohort included 167 patients stratified into renal function subgroups (Fig. 1): G1 (n = 49, 29.34%), G2 (n = 69, 41.32%), and G3 (n = 49, 29.34%). The mean eCrCl was 45.50 ± 21.41 mL/min. Table 1 shows the baseline characteristics used for the comparison. There were significant differences in the proportions of patients with diabetes, heart failure, sepsis, RRT, and concomitant use of vasopressors between the three groups. Additionally, the vancomycin dose and tCO_2 value significantly differed between the groups.

Trough concentrations of vancomycin and CDP-1

Table 2 shows the trough concentrations of vancomycin and CDP-1 in the three groups. The $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio was calculated to express the discrepancy in vancomycin concentrations determined by CMIA in comparison to those determined by UPLC-MS/MS. The ratio of the CDP-1 trough concentration to the vancomycin trough concentration via UPLC–MS/MS ($C/V_{UPLC\text{-}MS/MS}$) was calculated to describe the degradation of vancomycin. The average trough concentrations of CDP-1 in G1, G2, and G3 were 0.83 ± 0.78 μg/mL, 1.29 ± 0.92 μg/mL, and 2.67 ± 2.73 μg/mL, respectively. There were significant differences in vancomycin concentrations, CDP-1 concentrations, $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratios and $C/V_{UPLC\text{-}MS/MS}$ ratios among the three groups.

Factors influencing the CDP-1 concentration and $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio

Factors affecting the CDP-1 concentration were further investigated. In univariate analyses, diabetes (P = 0.016), sepsis (P = 0.043), RRT (P < 0.001), concomitant use of nephrotoxic agents (amphotericin B, colistin, or vasopressors) (P = 0.011, P = 0.012, and P < 0.001, respectively), vancomycin dose (P < 0.001), time interval from the initial dose to the trough level (P < 0.001), eCrCl levels (P < 0.001), and tCO_2 levels (P = 0.019) were associated

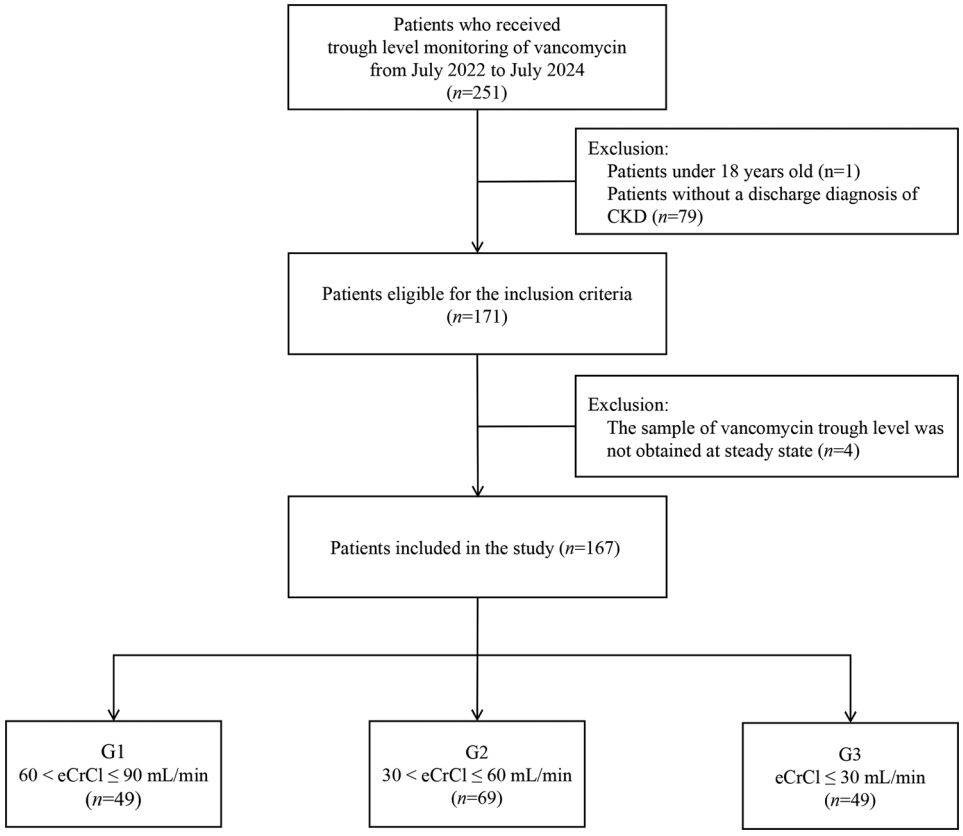

Fig. 1 Flowchart of patient selection and stratification process

with CDP-1 concentrations (Table 3). Multivariate analysis revealed a statistically significant relationship between the CDP-1 concentration and eCrCl level ($P < 0.001$), the time interval from the initial dose to the trough level ($P < 0.001$), and the vancomycin dose ($P < 0.001$, Table 3).

Table 4 displays the results of the linear regression analyses of the $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio. There were significant associations between the $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio and the CDP-1 concentration ($P < 0.001$), incidence of sepsis ($P = 0.008$), vancomycin dose ($P = 0.007$), time interval from the initial dose to the trough level ($P = 0.009$), concomitant use of vasopressors ($P = 0.033$), and eCrCl level ($P < 0.001$). Multivariate analyses revealed that a higher $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio was associated with increased CDP-1 concentrations ($P = 0.002$, Table 4).

Discussion

Our study mainly aimed to determine the value of serum CDP-1 concentrations among CKD patients with different levels of renal function and to identify the clinical factors associated with CDP-1 concentrations, which have not been well described in the existing literature.

Significant cross-reactivity of CDP-1 in the quantification of vancomycin was first reported by Morse et al. [13]. Overestimations of vancomycin in previous reports were mainly observed for the polyclonal antibody FPIA [13–16]. In the present study, the CMIA method was used to detect vancomycin concentrations. UPLC-MS/MS was applied as a reference method for determining vancomycin concentrations and detecting CDP-1 concentrations in CKD patients. We found that a higher $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio was correlated with an increased CDP-1 level. The average $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio in the G3 group was 1.12 ± 0.12, which was slightly lower than the value reported by Fan et al. (1.24 ± 0.53) in dialysis patients owing to the higher value of baseline eCrCl in our study [18].

Our results revealed that the average trough concentrations of CDP-1 in G1, G2, and G3 were 0.83 ± 0.78 μg/mL, 1.29 ± 0.92 μg/mL, and 2.67 ± 2.73 μg/mL, respectively. Subsequently, clinical variables that affect CDP-1 concentrations in patients with CKD were further explored. eCrCl showed the strongest negative association with the trough concentration of CDP-1. To our knowledge, the accumulation of CDP-1 in patients with renal impairment is thought to be caused by prolonged exposure of vancomycin to body temperature. The half-life of vancomycin increases as glomerular filtration decreases [25]. Compared with other CKD patients, patients with severe renal impairment, especially those with end-stage kidney disease, have a longer half-life of vancomycin, resulting in a higher level of CDP-1 and overestimation of CMIA.

Table 1 Baseline Characteristics of patients

Variables	Total	G1	G2	G3	*P*
	(*n* = *167*)	(*n* = *49*)	(*n* = *69*)	(*n* = *49*)	
Age, years	80 (70.00, 87.00)	77 (66.50, 83.50)	82 (72.00, 87.50)	81 (69.50, 89.50)	0.052
Sex, *n* (%)					
Male	111 (66.47)	32 (65.31)	51 (73.91)	28 (57.14)	0.160
Female	56 (33.53)	17 (34.69)	18 (26.09)	21 (42.86)	
Body weight, kg	62.33 ± 8.19	62.32 ± 8.38	62.89 ± 8.30	61.79 ± 7.90	0.770
Comorbidities, *n* (%)					
Diabetes	82 (49.10)	19 (38.78)	32 (46.38)	31 (63.27)	0.044
COPD	68 (40.72)	20 (40.82)	26 (37.68)	22 (44.90)	0.734
Heart failure	114 (68.26)	24 (48.98)	51 (73.91)	39 (79.59)	0.002
Hepatic dysfunction	105 (62.87)	32 (65.31)	46 (66.67)	27 (55.10)	0.403
Malignant solid tumor	39 (23.35)	15 (30.61)	18 (26.09)	6 (12.24)	0.078
Infectious diagnosis, *n* (%)					
Pneumonia	142 (85.03)	39 (79.59)	62 (89.86)	41 (83.67)	0.285
Catheter associated blood-stream Infection	8 (4.79)	2 (4.08)	1 (1.45)	5 (10.20)	0.092
Endocarditis	6 (3.59)	1 (2.04)	2 (2.90)	3 (6.12)	0.533
Intraabdominal Infection	10 (5.98)	5 (10.20)	1 (1.45)	4 (8.16)	0.106
Sepsis, *n* (%)	87 (52.09)	15 (30.61)	43 (62.32)	29 (59.18)	0.001
RRT, *n* (%)	46 (27.54)	3 (6.12)	18 (26.09)	25 (51.02)	<0.001
Vancomycin therapy					
Vancomycin dose,g/d	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)	1.00 (1.00, 2.00)	0.027
Time interval from the initial dose to trough level, days	3.00 (2.00, 4.00)	4.00 (3.00, 5.00)	3.00 (2.00, 4.50)	3.00 (2.00, 5.50)	0.079
Concomitant nephrotoxic agents, *n* (%)					
Aminoglycosides	31 (18.56)	5 (10.20)	12 (17.39)	14 (28.57)	0.061
Amphotericin B	10 (5.99)	1 (2.04)	4 (5.80)	5 (10.20)	0.233
Colistin	24 (14.37)	3 (6.12)	13 (18.84)	8 (16.33)	0.137
Piperacillin-Tazobactam	32 (19.16)	12 (24.49)	10 (14.49)	10 (20.41)	0.383
Loop diuretics	93 (55.69)	23 (46.94)	46 (66.67)	24 (48.98)	0.056
NSAIDs	41 (24.55)	15 (30.61)	15 (21.74)	11 (22.45)	0.501
Vasopressors	57 (34.13)	6 (12.24)	28 (40.58)	23 (46.94)	<0.001
Body temperature, ℃	37.00 (36.60, 37.80)	36.90 (36.60, 37.65)	37.00 (36.60, 38.00)	37.10 (36.80, 37.95)	0.345
ALB, g/L	29.69 ± 4.09	29.64 ± 3.72	30.15 ± 4.40	29.16 ± 3.93	0.431
tCO_2, mmol/L	24.15 (22.10, 28.07)	25.57 (24.55, 29.00)	24.80 (22.35, 25.74)	23.00 (20.95, 25.74)	<0.001

COPD: Chronic obstructive pulmonary disease, RRT: Renal replacement therapy, NSAIDs: Non-steroidal anti-inflammatory drugs, ALB: Albumin, tCO_2:Total carbon dioxide

Table 2 Trough concentrations of vancomycin and CDP-1 in serum

Variables	Total (*n* = *167*)	G1 (*n* = *49*)	G2 (*n* = *69*)	G3 (*n* = *49*)	*P*
CDP-1, μg/mL	1.56 ± 1.80	0.83 ± 0.78	1.29 ± 0.92	2.67 ± 2.73	<0.001
CDP-1-m, μg/mL	0.64 ± 0.64	0.38 ± 0.08	0.54 ± 0.07	1.01 ± 0.08	<0.001
CDP-1-M, μg/mL	0.93 ± 1.18	0.45 ± 0.15	0.74 ± 0.13	1.66 ± 1.36	<0.001
Vancomycin (UPLC-MS/MS), μg/mL	24.87 ± 16.06	18.48 ± 10.94	23.66 ± 11.95	32.63 ± 21.69	<0.001
Vancomycin (CMIA), μg/mL	27.80 ± 20.48	20.24 ± 12.97	25.63 ± 13.98	38.08 ± 28.63	<0.001
$V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio	1.09 ± 0.10	1.06 ± 0.08	1.08 ± 0.09	1.12 ± 0.12	0.008
$C/V_{UPLC\text{-}MS/MS}$ ratio, %	5.65 ± 2.50	4.18 ± 1.40	5.12 ± 1.46	7.88 ± 3.10	<0.001

CDP-1: Crystalline degradation product, CDP-1-m: Crystalline degradation product the minor isomer. CDP-1-M: Crystalline degradation product the major isomer, UPLC–MS/MS: Ultra-high performance liquid chromatography tandem mass, $V_{CMIA}/V_{UPLC\text{-}MS/MS}$: The ratio of vancomycin concentration by chemiluminescence microparticle immunoassay to vancomycin concentration by ultra high liquid chromatography–tandem mass spectrometry, $C/V_{UPLC\text{-}MS/MS}$: The ratio of crystalline degradation products trough concentration to vancomycin trough concentration by ultra-high performance liquid chromatography–tandem mass spectrometry

Table 3 Linear regression analyses of factors associated with CDP-1 trough concentration (n = 167)

Variables	Univariate				Multivariate				
	B	SE	t	*P*	B	SE	t	*P*	Adjusted-R^2
eCrCl	−0.015	0.001	−8.772	<0.001	−0.016	0.002	−0.587	<0.001	0.537
Time interval from the initial dose to the trough level	0.051	0.011	4.486	<0.001	0.052	0.008	0.335	<0.001	
vancomycin dose	0.238	0.082	2.896	<0.001	0.360	0.060	0.332	<0.001	
Diabetes	−0.109	0.045	−2.426	0.016					
Sepsis	−0.092	0.045	−2.033	0.043					
RRT	−0.183	0.049	−3.706	<0.001					
amphotericin B	−0.242	0.094	−2.555	0.011					
Colistin	−0.163	0.064	−2.549	0.012					
Vasopressors	−0.169	0.046	−3.649	<0.001					
tCO_2	−0.024	0.010	−2.373	0.019					

Adjusted for diabetes, sepsis, RRT, amphotericin B, colistin, vasopressors, tCO_2, CDP-1: Crystalline degradation product, eCrCl: Estimated creatinine clearance, RRT: Renal replacement therapy, tCO_2: Total carbon dioxide

Table 4 Linear regression analyses of factors associated with $V_{CMIA}/V_{UPLC\text{-}MS/MS}$ ratio (n = 167)

Variables	Univariate				Multivariate				
	B	SE	t	*P*	B	SE	t	*P*	Adjusted-R^2
CDP-1	0.074	0.011	6.603	<0.001	0.051	0.016	0.318	0.002	0.223
Sepsis	−0.019	0.007	−2.667	0.008					
vancomycin dose	0.035	0.013	2.736	0.007					
Time interval from the initial dose to the trough level	0.005	0.002	2.658	0.009					
Vasopressors	−0.161	0.007	−2.148	0.033					
eCrCl	−0.001	0.001	−3.514	<0.001					

Adjusted for sepsis, vancomycin dose, time interval from the initial dose to trough level, eCrCl, vasopressors, $V_{CMIA}/V_{UPLC\text{-}MS/MS}$: The ratio of vancomycin concentration by chemiluminescence microparticle immunoassay to vancomycin concentration by ultra high liquid chromatography–tandem mass spectrometry, CDP-1: Crystalline degradation product, eCrCl: Estimated creatinine clearance

Nonetheless, the overestimation by CMIA in our study was lower than that by the polyclonal antibody FPIA [13–16].

The G3 group demonstrated the highest mean trough CDP-1 concentration among all study groups. We hypothesize that this phenomenon may be attributable not only to prolonged vancomycin exposure but also to elevated serum vancomycin concentrations (mean 32.63 μg/mL) observed in the G3 group. However, it should be noted that the mean trough vancomycin concentration in the G3 group was nearly twice as high as the previously recommended trough range of 10–20 μg/mL [9]. These results suggest that increasing the monitoring frequency of vancomycin may be beneficial for achieving optimal vancomycin exposure. If vancomycin exposure is managed early within an appropriate range, the effect of CDP-1 could be negligible in clinical decision-making regardless of renal function.

The time interval from the initial dose to the trough level was also selected as a significant factor associated with the CDP-1 concentration. On the basis of this result, we assumed that the time interval would account for the difference in overestimation observed in previous studies. For patients with CKD, the initial vancomycin trough level is recommended to be started after 72 hours of vancomycin therapy since the time to achieve a steady-state trough level is delayed compared with that in patients with normal renal function [26]. On the other hand, the delayed timing of trough level sampling could contribute to increased CDP-1 levels and overestimation of vancomycin levels. Therefore, developing a precise strategy for the timing of vancomycin TDM in patients with CKD is necessary.

According to the in vitro evidence, temperature and pH appear to play roles in the degradation of vancomycin into CDP-1 [21]. Therefore, we explored the effects of body temperature and tCO_2 on the level of CDP-1, but no significant correlation was found.

There are limitations in our study. First, our study may be limited by its single-center, retrospective study design, which may contribute to confounding and information bias. Although multivariate analysis was performed to decrease bias from confounding variables, unanticipated variables existed and may have impacted our findings. Additionally, since the details within the medical records were not sufficient for evaluation, patients with CKD were identified according to their diagnosis at discharge in our study. This may have led to selection bias.

In conclusion, the eCrCl level, time interval from the initial dose to the trough level, and vancomycin dose were associated with the CDP-1 concentration. A greater degree of overestimation of serum vancomycin

concentrations by CMIA was correlated with elevated serum CDP-1 concentrations in patients with CKD. Nevertheless, in patients with CKD who have mild to moderate deterioration in renal function, overestimation may not have an important effect on clinical decisions or the outcomes of vancomycin therapy. For patients with severe deterioration in renal function, we recommend increasing the frequency of TDM and selecting quantitative methods to determine vancomycin serum concentrations without interfering with CDP-1 if necessary.

Abbreviations

CDP-1	Crystalline degradation product
CMIA	Chemiluminescence microparticle immunoassay
CKD	Chronic kidney disease
eCrCl	Estimated creatinine clearance
UPLC-MS/MS	Ultra-high performance liquid chromatography–tandem mass spectrometry
$V_{CMIA}/V_{UPLC-MS/MS}$	The ratio of vancomycin concentration determined via chemiluminescence microparticle immunoassay to vancomycin concentration via ultra-high liquid chromatography–tandem mass spectrometry
PK/PD	Pharmacokinetic/pharmacodynamic
AUC	Area under the concentration-time curve
AUC/MIC	The ratio of area under the concentration-time curve to the minimum inhibitory concentration
HPLC	High-performance liquid chromatography
FPIA	Fluorescence polarization immunoassay
LC-MS/MS	Liquid chromatography–tandem mass spectrometry
CDP-1-m	Crystalline degradation product the minor isomer
CDP-1-M	Crystalline degradation product the major isomer
NSAIDs	Non-steroidal anti-inflammatory drugs
RRT	Renal replacement therapy
Scr	Serum creatinine
ALB	Albumin
tCO_2	Total carbon dioxide
CV	Coefficients of variation
SD	Standard deviation
IQR	Interquartile range
ANOVA	Analysis of variance
COPD	Chronic obstructive pulmonary disease
$C/V_{UPLC-MS/MS}$	The ratio of the crystalline degradation products trough concentration to the vancomycin trough concentration via ultra-high performance liquid chromatography–tandem mass spectrometry

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Not Applicable

Author contributions
XX was involved in the study design, data collection, sample assessment, data interpretation and manuscript writing. CY, JL and LB helped assessing trough concentrations of vancomycin and CDP-1 in serum samples. ZS was involved in the study design and data interpretation. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics committee approval for the study was obtained from Scientific Ethics Committee of Capital Medical University Affiliated Beijing Shijitan Hospital (No. sjtkyll-lx-2022(131)). All procedures adhered to the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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