Optimal Sampling Strategy and Threshold of Serum Vancomycin Concentration in Elderly Japanese Patients undergoing High-flux Hemodialysis

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ABSTRACT

Background

The optimal sampling points and thresholds for initial serum vancomycin (VCM) concentrations have not been determined in hemodialysis (HD) patients. To clarify this, multiple blood tests were performed, and the correlations between VCM concentrations at several sampling points and the area under the concentration-time curve for 24 h (AUC_{24h}) were analyzed.

Methods

A single-center, prospective observational study was conducted. Patients with end-stage renal failure who received VCM treatment while undergoing chronic maintenance HD were enrolled in this study. HD was performed using a high-flux membrane as the dialyzer. After VCM administration, seven points were sampled between the 1st and 2nd HD. The AUC_{24h} after the end of the 1st HD ($AUC_{0–24}$) and that before the end of the 2nd HD ($AUC_{24–48}$) were calculated using the linear trapezoidal method. Correlation analysis and simple regression analysis between AUC_{24h} and serum concentrations were performed at each sampling point.

Results

Nine patients were evaluated. Strong correlations were found between $AUC_{24–48}$ and serum concentrations at 24 h after the initiation of VCM treatment following the 1st HD (C_{24h}, $R = 0.983$ and $P < 0.001$), between $AUC_{0–24}$ and C_{24h} ($R = 0.967$ and $P < 0.001$), and between $AUC_{24–48}$ and serum concentration just before the 2nd HD ($C_{pre(HD2)}$, $R = 0.965$ and $P < 0.001$). Regression equations with high coefficients of determination ($R^2 > 0.9$) were obtained, and a C_{24h} of ≥18.0 mg/L and a $C_{pre(HD2)}$ of ≥16.5 mg/L were required to achieve an $AUC_{24–48}$ value of ≥400 mg·h/L. In addition, a C_{24h} of ≤23.3 mg/L was estimated to satisfy the $AUC_{0–24}$ range of ≤600 mg·h/L.

Conclusion

C_{24h} and $C_{pre(HD2)}$ are optimal sampling points for predicting VCM-AUC_{24h} in HD patients.

KEYWORDS

Vancomycin, Hemodialysis, Therapeutic drug monitoring, AUC, Pharmacokinetics

BACKGROUND

Since hemodialysis (HD) patients are often older adults and immunocompromised hosts, the rate of mortality from infection among these patients is significantly higher than that in non-HD patients.[1] In particular, HD patients are more likely to be infected with *Staphylococcus* species through vascular access.[1, 2] Therefore, vancomycin (VCM), a standard anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drug, is empirically administered as a first-line treatment.[3, 4] To achieve the desired effects and prevent adverse effects and bacterial resistance, therapeutic drug monitoring (TDM) and use of an administration method based on the pharmacokinetics (PK)/pharmacodynamics (PD) theory are required for VCM therapy.[5, 6]

In non-HD patients, the area under the concentration-time curve for 24 h/minimum inhibitory concentration (AUC_{24h}/MIC) is the most useful PK/PD parameter in predicting the effectiveness of VCM.[7, 8] An AUC_{24h}/MIC of ≥400 mg·h/L is the recommended target value to achieve efficacy.[6, 9, 10] In recent years, an AUC_{24h} threshold value of 400–600 mg·h/L has been proposed for the non-HD population with severe MRSA infections.[11, 12] However, VCM AUC_{24h} is difficult to measure in daily practice, because multiple blood tests are required to calculate the VCM AUC_{24h}.[6, 13] The VCM trough concentration, which is highly correlated with AUC_{24h}, has traditionally been measured as surrogate markers for non-HD patients.[6, 14, 15] The target trough concentration range is 15–20 mg/L for serious MRSA infections.[16-18] In recent years, VCM TDM for serious MRSA infections in non-HD patients has helped determine the recommended doses based on the VCM AUC_{24h}, which is accurately estimated through minimal PK sampling using a Bayesian software or PK equations.[11]

Compared with non-HD patients, HD patients have different PK characteristics. The distribution of VCM is similar between HD patients and non-HD patients, but total clearance and protein binding

of VCM in HD patients are lower than those in non-HD patients.[13, 19] VCM is efficiently removed by high-flux dialysis membranes,[20-22] and a rebound effect in serum VCM concentration is observed immediately after the completion of HD.[23-25]; thus, HD patients require a different approach to managing VCM TDM in clinical practice. However, established guidelines on the timing and frequency of TDM in HD patients are limited.[11, 26] Currently, when performing VCM TDM for HD patients, the pre-HD serum VCM levels are often sampled instead of the trough levels.[11, 27, 28] However, it is unknown which pre-HD or other sampling points correlate best with AUC_{24h}. Furthermore, the optimal serum VCM concentration range for HD patients has not been clarified based on its correlation with AUC_{24h}.[13, 29]

In this study, to clarify the optimal sampling point and the optimal concentration range in HD patients, multiple blood tests were performed, and the correlation between VCM concentration at each sampling point and AUC_{24h} was analyzed.

METHODS

Study Design and Patients

This single-center, prospective observational study was conducted in Omihachiman Community Medical Center in Japan. It was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board at Omihachiman Community Medical Center (registration number: 23-6). Written informed consent was obtained from all patients prior to study entry. The recruitment period for this study was set between January 2012 and April 2013, and patients with end-stage renal failure who received VCM treatment while undergoing HD at our institution were enrolled. Meanwhile, patients (1) for whom VCM treatment was not performed in accordance with the administration protocol defined in our institution; (2) who experienced failures during blood sampling; (3) who underwent a different type of renal replacement therapy, such as continuous renal replacement

109 therapy, sustained low efficiency dialysis, or peritoneal dialysis (PD); (4) who had a daily urine volume
110 of >400 mL; and (5) whose interval between the 1st HD and 2nd HD was 72 h were excluded.

111 All patients underwent HD three times per week via vascular access. HD was performed using a
112 high-flux membrane, such as a polymethylmethacrylate or polysulfone membrane as the dialyzer.
113 Dialysis was performed using a TR-3000M® dialysis monitoring machine (Toray Co., Inc., Tokyo,
114 Japan). The following parameters were recorded: dialysis membrane area, dialysis time, blood flow
115 rate, dialysate flow rate, and total water removal.

116

117 **Administration of VCM**

118 VCM (vancomycin hydrochloride for intravenous infusion, 0.5 g [MEEK®], Meiji Seika Pharma
119 Co., Inc., Tokyo, Japan) was administered based on the administration protocol of Omihachiman
120 Community Medical Center. The loading doses were 1,000 mg on the first day (day 1) and 500 mg on
121 the second day (day 2), while the maintenance dose was 500 mg, which was administered immediately
122 after each HD session. The first HD day after the administration of the loading dose was set as the 1st
123 HD day. The next HD day after the 1st HD was set as the 2nd HD day. The duration of VCM
124 administration was 60 min.

125

126 **Data Collection**

127 As shown in Table 1, the serum VCM concentrations at seven points were collected from each
128 participant according to the planned sampling schedule. To measure serum VCM concentration,
129 approximately 3 mL of blood samples were collected in Venoject II® vacuum blood collection tubes
130 (Terumo Co., Inc., Tokyo, Japan). All blood samples were centrifuged at 2,250×*g* for 6 min. The serum
131 VCM concentrations were measured using a chemiluminescence immunoassay instrument (Architect®,

Abbott Japan Co., Inc., Tokyo, Japan; limit of quantification: 3.0 mg/L; coefficient of variation: ≤10%).

The apparent HD removal rate of the VCM was calculated based on the concentrations obtained immediately before and after HD:

$$\% \text{ removal} = [(C_{pre(HD)} - C_{end(HD)}) / C_{pre(HD)})] \times 100 \quad \text{(Eq. 1)}$$

where % removal is the apparent percent removal of VCM during the HD period, $C_{pre(HD)}$ is the serum VCM concentration obtained immediately before HD (mg/L), and $C_{end(HD)}$ is the serum VCM concentration obtained at the end of HD (mg/L). Here, since the enrollees were HD patients with oliguria and end-stage renal failure, the VCM removal rate due to the patient's residual renal function was smaller than that due to HD. The apparent removal rate during the HD period may be reflected by HD and residual renal clearance.

The half-lives and elimination constants during the non-HD period (i.e., the patient's own values, $T_{1/2(Pt)}$ and $k_{e(Pt)}$) and HD period ($T_{1/2(HD)}$ and $k_{e(HD)}$) were calculated as follows:

$$T_{1/2(HD)} = 0.693/k_{e(HD)} \quad \text{(Eq. 2)}$$

$$k_{e(HD)} = \ln (C_{pre(HD)} / C_{end(HD)})/T_{HD} \quad \text{(Eq. 3)}$$

$$T_{1/2(Pt)} = 0.693/k_{e(Pt)} \quad \text{(Eq. 4)}$$

$$k_{e(Pt)} = \ln (C_{peak} / C_{pre(HD)})/T_{Pt} \quad \text{(Eq. 5)}$$

where T_{HD} is the time (h) between the start and end of HD, C_{peak} is the serum VCM concentration (mg/L) obtained at 2 h after the end of VCM administration, and T_{Pt} is the time (h) between peak and pre-HD sampling.

The VCM AUC_{24h} was calculated using the linear trapezoidal method and defined as follows: $AUC_{0–24}$, AUC calculated for 24 h after the end of the 1st HD; $AUC_{24–48}$, AUC calculated for 24 h before the end of the 2nd HD.

154

155 **Statistical Analysis**

156 Correlation analyses between AUC_{24h} and each VCM dose, HD condition, and each sampling
157 point were performed. All correlation analyses were carried out using the Pearson product-moment
158 correlation coefficient test. A simple regression analysis between AUC_{24h} and each sampling point was
159 performed. From the obtained simple regression equation, the concentration range that satisfies an
160 AUC_{24h} of 400–600 mg·h/L was calculated at each sampling point, assuming an *S. aureus* infection
161 with an MIC of 1 mg/L.[11] A *P*-value of <0.05 was considered significant. All statistical analyses were
162 performed using IBM SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA).

163

164 **RESULTS**

165 **Patients' Characteristics and HD Conditions**

166 Twenty patients were enrolled in this study; among them, 11 were excluded. The reasons and
167 number of excluded patients were as follows: (1) VCM administration was different from the protocol
168 defined in our institution (n = 2); (2) experienced failures during blood sampling (n = 2); (3) underwent
169 renal replacement therapy other than HD, such as continuous renal replacement therapy, sustained low
170 efficiency dialysis, PD (n = 4); (4) the daily urine volume was >400 mL (n = 1); and (5) the interval
171 between the 1st and 2nd HD was 72 h (n = 2). A total of nine patients were evaluated, and their baseline
172 characteristics are summarized in Table 2. They were all older adults and low-weight patients.

173 The dialysis membrane area in each patient did not differ between the 1st and 2nd HD (median:
174 1.6 m^2). The average blood flow rate was less than 200 mL/min in all patients (median: 193.1 mL/min).
175 The dialysate flow rate was maintained at 500 mL/min in all patients. The median total water removal
176 rate was 1,800 mL per HD session.

177 The clinical outcomes and safety information are summarized in Supplemental Table S1. Among

the nine patients, three had poor clinical outcomes after VCM administration: died, clinical outcome remained unchanged, and experienced recurrence. All three patients showed abnormal laboratory values.

Serum VCM Concentration and Pharmacokinetic Parameters

The serum VCM concentrations at each sampling point are shown in Fig. 1. The $C_{pre(HD1)}$ exceeded 13.0 mg/L in all patients. The VCM concentration levels dropped sharply by approximately 30% after the 1st HD. After VCM maintenance dose administration and reaching C_{peak}, the VCM concentration levels gradually decreased until $C_{pre(HD2)}$. Approximately 20 h after the previous sampling, $C_{pre(HD2)}$ exceeded 15.0 mg/L in all patients. During the 2nd HD, the VCM was rapidly removed by approximately 30%. The PK parameters of the VCM are shown in Table 3. With regard to the $AUC_{0–24}$, all patients achieved an AUC of ≥400 mg·h/L (median: 556.4 mg·h/L, range: 425.5–644.5 mg·h/L). For the $AUC_{24–48}$, only 2 patients (Patient 3: 374.1 mg·h/L and Patient 6: 385.1 mg·h/L) achieved an AUC of <400 mg·h/L (median: 462.2 mg·h/L, range: 374.1–529.1 mg·h/L). The VCM $T_{1/2(HD)}$ was relatively short, whereas the $T_{1/2(Pt)}$ was extremely long (70–200 h).

Correlation Coefficients Between AUC and Each Variable

No significant correlations were found between AUC_{24h} and VCM dose (day 1, day 2, day 1 + day 2, and maintenance dose). In addition, no significant correlations were found between AUC_{24h} and HD conditions (dialysis membrane area, dialysis time, average blood flow rate, total water removal, and VCM removal rate) (Supplemental Table S2).

Supplemental Table S3 shows the correlation coefficients (*R*) and *P*-values between the AUC and serum VCM concentrations at each sampling point. Except for the $C_{end(HD)}$, the *R* values between each AUC and serum VCM concentration at each sampling point showed a significant correlation. With

regard to $AUC_{0–24}$ and $AUC_{24–48}$, the *R* values were higher in $C_{pre(HD2)}$ than in $C_{pre(HD1)}$. The *R* value obtained between $AUC_{24–48}$ and C_{24h} was the highest among all sampling points ($R = 0.983$, $P < 0.001$). All *R* values obtained between C_{24h} and $AUC_{0–24}$ and between C_{24h} and $AUC_{24–48}$ were also high (all $R \geq 0.95$). The *R* values between C_{peak} and AUC were high for $AUC_{0–24}$ ($R = 0.972$), but lower for $AUC_{24–48}$ ($R = 0.809$). By contrast, the *R* values between $C_{pre(HD2)}$ and AUC were lower for $AUC_{0–24}$ ($R = 0.806$), but higher for $AUC_{24–48}$ ($R = 0.965$).

Fig. 2 shows the scatter plots and simple regression lines between serum VCM concentration at each sampling point and $AUC_{0–24}$ or $AUC_{24–48}$. Simple regression lines with high adjusted coefficients of determination ($R^2 > 0.9$) were obtained between $AUC_{0–24}$ and C_{peak} (Fig. 2c), C_{24h} (Fig. 2d), $AUC_{24–48}$ and C_{24h} (Fig. 2k), and $C_{pre(HD2)}$ (Fig. 2l). At other sampling points, the R^2 of the regression lines was low. Based on the regression equations presented in Fig. 2k and 2l ($AUC_{24–48} = 19.3\ C_{24h} + 54.0$; $AUC_{24–48} = 24.0\ C_{pre(HD2)} + 4.9$), a C_{24h} of ≥18.0 mg/L or a $C_{pre(HD2)}$ of ≥16.5 mg/L was required to achieve an $AUC_{24–48}$ of ≥400 mg·h/L. Based on the regression equations in Fig. 2c and 2d ($AUC_{0–24} = 20.6\ C_{peak} + 15.6$; $AUC_{0–24} = 23.4\ C_{24h} + 56.8$), a C_{24h} of ≤23.3 mg/L and a C_{peak} of ≤28.3 mg/L were necessary to satisfy the $AUC_{0–24}$ of ≤600 mg·h/L.

DISCUSSION

The present study was conducted to determine the optimal sampling strategy and threshold for VCM in HD patients. Our study is the first to demonstrate that C_{24h} at the midpoint between the 1st and 2nd HD was highly correlated with both $AUC_{0–24}$ and $AUC_{24–48}$ for HD patients, and the C_{24h} target range was estimated to be 18.0–23.3 mg/L to satisfy the AUC_{24h} range of 400–600 mg·h/L in both periods. Blood sampling pre-HD serum VCM concentration is widely implemented, and our results suggest that $C_{pre(HD2)}$ is a reliable surrogate marker for AUC_{24h} immediately before the measurement date. In addition, a $C_{pre(HD2)}$ of ≥16.5 mg/L was required to achieve an $AUC_{24–48}$ of ≥400 mg·h/L.

The PK/PD parameter indicating the effectiveness of VCM is AUC_{24h}/MIC,[7,8] while an

227 AUC_{24h}/MIC of ≥400 mg·h/L has been recommended as a treatment target for MRSA infections.[6, 9, 10]
228 In recent years, an AUC_{24h} range of 400–600 mg·h/L has been proposed for the non-HD population
229 with severe MRSA infections.[11, 12] In the HD population, outcome studies validating the AUC_{24h} goal
230 have not been conducted, but this goal is being validated with the same AUC_{24h} target recommended
231 for the non-HD population (400–600 mg·h/L assuming an MIC of 1 mg/L).[11] In this study, we also
232 assumed an *S. aureus* infection with an MIC of 1 mg/L and calculated the concentration range that
233 satisfies the AUC_{24h} range of 400–600 mg·h/L at each sampling point from the simple regression
234 analysis results. Since the $AUC_{0–24}$ is always higher than the $AUC_{24–48}$, in the present study, the
235 threshold of $AUC_{0–24}$ was set as ≤600 mg·h/L to prevent adverse events, while the threshold of $AUC_{24–48}$ was set as ≥400 mg·h/L to achieve clinical effectiveness. Our results suggest that the target ranges
237 of C_{24h} and $C_{pre(HD2)}$ are 18.0–23.3 mg/L and ≥16.5 mg/L, respectively.

238 The extremely high correlations between C_{24h} and both $AUC_{0–24}$ and $AUC_{24–48}$ (Supplemental
239 Table S3) indicate that C_{24h} can estimate not only the $AUC_{0–24}$ before the C_{24h} sampling, but also the
240 $AUC_{24–48}$ after the C_{24h} sampling. As shown in the time-serum concentration profile (Fig. 1), serum
241 concentration near the C_{24h} at the midpoint between the 1st and 2nd HD was stable and independent of
242 the influence of HD. In addition, because the $T_{1/2(Pt)}$ values tended to be extremely high in HD patients
243 (Table 3), as reported in previous studies,[19, 26] the VCM concentration decreases slowly during the non-
244 HD period in HD patients. Therefore, the AUC_{24h} values just before and after C_{24h} sampling are thought
245 to correlate well with C_{24h}. In administering VCM for HD patients, the pre-HD serum concentrations
246 are often sampled instead of the AUC_{24h} values,[11, 27, 28] but C_{24h} can be a more optimal sampling time
247 in this study. Achieving the optimal serum concentration range early in the administration enhances
248 the effectiveness of VCM.[16, 30, 31] Thus, sampling at C_{24h} may be useful for healthcare professionals to
249 estimate the AUC_{24h} in HD patients.

250 In general, pre-HD blood sampling is recommended in chronic HD patients treated with VCM.[25,
251 27] The results of this study also showed that both $C_{pre(HD1)}$ and $C_{pre(HD2)}$ were strongly correlated with

252 $AUC_{0–24}$ and $AUC_{24–48}$, respectively. In the comparison between pre-HD concentrations in this study,
253 $C_{pre(HD2)}$ is more likely to be correlated with both $AUC_{0–24}$ and $AUC_{24–48}$ than $C_{pre(HD1)}$ (Supplemental
254 Table S3), indicating that $C_{pre(HD2)}$ is a better predictive marker for AUC_{24h} than $C_{pre(HD1)}$. Clark et al.
255 (2019) previously reported that VCM trough concentrations in non-HD patients were strongly
256 correlated with AUC_{24h} ($R = 0.731$, $P < 0.001$). As a result of this study, $C_{pre(HD2)}$ was even more highly
257 correlated with AUC_{24h} than the previously reported trough concentrations in non-HD patients.[15]
258 Therefore, similar to C_{24h}, $C_{pre(HD2)}$ can also be a surrogate marker and is highly correlated with AUC_{24h}
259 immediately before the measurement time.
260 In addition, VCM was administered immediately after the HD. Therefore, the actual VCM trough
261 concentration was at the end of the HD. However, the correlations between serum VCM concentrations
262 at the end of HD ($C_{end(HD1)}$ and $C_{end(HD2)}$) and AUC_{24h} were low among the sampling points
263 (Supplemental Table S3). The serum concentration immediately after the end of HD has a rebound
264 effect of 20%–40%; therefore, it does not accurately reflect the drug concentration in the body.[23, 24, 25]
265 The estimated thresholds of C_{24h} and $C_{pre(HD2)}$ were ≥18.0 and ≥16.5 mg/L, respectively, to achieve
266 an $AUC_{24–48}$ of ≥400 mg·h/L. In HD patients, the current target value of pre-HD serum VCM
267 concentration is 15–20 mg/L.[11, 26, 32] Fu et al. (2018) reported that a $C_{pre(HD)}$/MIC of ≥18.6 mg/L might
268 be associated with improved VCM treatment outcomes in MRSA bacteremia in HD patients.[33]
269 Although the threshold reported in this study was higher than that reported in our study, under the
270 assumption of an MIC of 1 mg/L, $C_{pre(HD)}$ needs to be slightly higher than 15 mg/L, which supports
271 our results.

272 The correlation between C_{peak} and AUC_{24h} was higher for $AUC_{0–24}$ than for $AUC_{24–48}$. C_{peak} tends
273 to depend on the dose and volume of the distribution rather than the individual patient clearance. C_{peak}
274 was unable to sufficiently reflect the subsequent elimination phase and had a relatively poor correlation
275 with $AUC_{24–48}$. In non-HD patients, routine peak measurements are not recommended because peak
276 serum VCM levels do not correlate with efficacy or toxicity.[34, 35] However, for HD patients in this

study, the correlation between the peak value, C_{peak}, and $AUC_{0–24}$ was as high as that between C_{24h} and $AUC_{0–24}$, and the peak level measurement may be suitable for estimating the $AUC_{0–24}$.

Only Patients 3 and 6 had an $AUC_{24–48}$ value of <400 mg·h/L (Table 3); Patient 3 died 14 days after the initiation of VCM treatment, while Patient 6 had an unchanged outcome according to the attending physician's judgment (Supplemental Table S1). Patient 3 also showed abnormal changes in the blood test values during the period of VCM treatment, which may be due to the patient's worsening condition. In Patient 9, the $AUC_{24–48}$ value was 526.8 mg·h/L; however, the clinical outcome remained unchanged, and MRSA infection recurred after 43 days. The $AUC_{0–24}$ value of Patient 9 exceeded 600 mg·h/L, and the AST levels significantly increased.

For HD patients, some studies reported that administration of a VCM loading dose of 20 mg/kg or more helped reach the target concentration early during the initial treatment period.[22, 32, 36] Because the patients had a lower weight and received a relatively high VCM dose per actual dry body weight (Table 2), all patients achieved an $AUC_{0–24}$ of ≥400 mg·h/L early during the dosing period. However, the correlation analysis showed no significant correlation between the VCM dose and AUC_{24h} (Supplemental Table S2). No significant correlations were also found between AUC_{24h} and HD conditions (Supplemental Table S2). VCM clearance by dialysis depends on several factors, including the type of dialysis membrane and filter, dialysis time, ultrafiltration rate, blood flow rate, and dialysate flow rate.[25, 27] On the contrary, body weight, duration of dialysis alone, blood flow rate, and dialysate flow rate were previously found not to be predictive of VCM removal in high-flux HD patients.[37] Even in HD patients with little residual renal function, the VCM clearance rates varied.[19, 26, 38] Our results suggest that it is difficult to estimate the VCM AUC_{24h} in HD patients based only on each HD condition.

HD patients still have the capacity for extrarenal or residual renal clearance of VCM in addition to HD clearance.[13, 27] In this study, the patients' own VCM elimination constants ($k_{e(Pt)}$) were smaller than that during the HD period ($k_{e(HD)}$), but a large interindividual variability in $k_{e(Pt)}$ was observed (Table 3). The interindividual variability was also observed in the difference between $AUC_{0–24}$ and

$AUC_{24–48}$ (Patient 4: 43.4 mg·h/L; Patient 8: 132.3 mg·h/L). The patient with a large difference between $AUC_{0–24}$ and $AUC_{24–48}$ values tended to have a large $k_{e(Pt)}$. Interindividual differences in AUC_{24h} values were considered to be caused by the patients' own clearance. In addition, the $AUC_{0–24}$ value was above 400 mg·h/L in all patients, while the $AUC_{24–48}$ was below 400 mg·h/L in two patients (Patient 3: 374.1 mg·h/L; Patient 6: 385.1 mg·h/L). As described above, no significant correlations were found between the $AUC_{24–48}$ value and VCM dose (Supplemental Table S2), suggesting that the low AUC_{24-48} values were due to the individual differences in extrarenal or residual renal clearance. Despite the wide individual differences, more than 75% of the study patients achieved an $AUC_{24–48}$ value of ≥400 mg·h/L after receiving the protocol-based VCM dose. However, a few patients did not achieve an $AUC_{24–48}$ of ≥400 mg·h/L. Therefore, TDM should be performed in patients undergoing HD.

This study has some limitations. First, it was a single-center study with a small sample size. Therefore, an unintended selection bias in patient selection might not have been completely excluded. In addition, since almost no patients had an AUC_{24h} value of <400 mg·h/L, it remains unclear whether these results could be directly applied to patients with lower AUC_{24h} values. Moreover, since the Omihachiman Community Medical Center is a community hospital, the possibility of intentional treatment and hospital bias exist. Second, because the early stages of VCM treatment was evaluated in actual clinical settings, the findings might not be sufficiently conclusive after completely entering the steady state. Finally, the calculated AUC_{24h} value may be overestimated using the linear trapezoidal method. A two-compartment model analysis is commonly used for the pharmacokinetic analysis of VCM. However, a two-compartment model analysis was not used in the present study due to the limited number of patients and sampling points. Therefore, our findings need to be validated in a larger prospective study.

CONCLUSION

The sampling serum VCM concentration at 24 h after the initiation of VCM treatment following HD can predict the AUC_{24h}, and the serum concentration at this point was thus considered to be an optimal surrogate marker for AUC_{24h}. In the current practice of measuring the pre-HD serum VCM concentration, sampling the serum concentration just before the 2nd HD may be useful as a surrogate marker for AUC_{24h}. Considering the results of the analysis based on the regression equation in this study, the optimal C_{24h} and $C_{pre(HD2)}$ values should be 18.0–23.3 mg/L and ≥16.5 mg/L, respectively.

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Table 1. Definition of serum VCM concentration and AUC

	Abbreviation	Definition
1.	$C_{pre(HD1)}$	Concentration immediately before the 1st HD after the initiation of VCM treatment
2.	$C_{end(HD1)}$	Concentration at the end of the 1st HD
3.	C_{peak}	Concentration at 2 h after the end of VCM administration at 1st HD
4.	C_{24h}	Concentration at 24 h after the initiation of VCM treatment at 1st HD
5.	$C_{pre(HD2)}$	Concentration immediately before the 2nd HD after the initiation of VCM treatment
6.	$C_{2h(HD2)}$	Concentration at 2 h after the start of the 2nd HD
7.	$C_{end(HD2)}$	Concentration at the end of the 2nd HD
8.	$AUC_{0–24}$	AUC calculated for 24 h after the end of the 1st HD
9.	$AUC_{24–48}$	AUC calculated for 24 h before the end of the 2nd HD

VCM, vancomycin; AUC, area under the concentration-time curve; HD, hemodialysis

Table 2. Patients' characteristics

	No. of patients
Total number	9
Male/female	5/4
Wound infections (including vascular access infections)	6
Bloodstream infections	2
Urinary tract infections	1
	Median (range)
Age (years)	70.0 (63.0–84.0)
Actual dry body weight (kg)	43.0 (33.8–50.7)
Serum albumin (g/dL)	2.6 (2.3–3.3)
Blood urea nitrogen (mg/dL)	44.3 (28.6–77.4)
Serum creatinine (mg/dL)	6.6 (2.3–12.0)
Day 1 dose of VCM (mg/kg)	23.3 (19.7–29.6)
Day 2 dose of VCM (mg/kg)	12.2 (9.9–14.8)
Maintenance dose of VCM (mg/kg)	11.6 (9.9–14.8)

VCM, vancomycin; Day 1, the first day of VCM administration; Day 2, the second day of VCM administration

460 **Table 3. VCM PK parameters of each patient**

Patient no.	VCM removal rate at 1st HD (%)	$k_{e(HD1)}$ (h^{-1})	$T_{1/2(HD1)}$ (h)	VCM removal rate at 2nd HD (%)	$k_{e(HD2)}$ (h^{-1})	$T_{1/2(HD2)}$ (h)	$k_{e(Pt)}$ (h^{-1})	$T_{1/2(Pt)}$ (h)	$AUC_{0–24}$ (mg·h/L)	$AUC_{24–48}$ (mg·h/L)
1	28.1	0.078	8.9	36.9	0.113	6.1	0.006	123.6	609.6	529.1
2	30.2	0.107	6.5	17.1	0.062	11.2	0.008	82.2	560.9	462.2
3	25.9	0.074	9.4	27.1	0.073	9.6	0.006	120.6	425.5	374.1
4	28.5	0.083	8.3	34.2	0.131	5.3	0.003	206.4	556.4	513.0
5	55.2	0.188	3.7	55.2	0.186	3.7	0.005	130.9	475.5	411.0
6	27.1	0.075	9.3	17.1	0.045	15.4	0.010	69.9	478.7	385.1
7	27.2	0.114	6.1	32.5	0.097	7.2	0.010	69.3	542.9	429.2
8	43.4	0.141	4.9	32.6	0.098	7.0	0.011	64.9	630.5	498.2
9	38.0	0.120	5.8	37.9	0.115	6.0	0.009	79.9	644.5	526.8
Median	30.2	0.107	6.5	32.5	0.098	7.0	0.008	82.2	556.4	462.2

461 VCM, vancomycin; PK, pharmacokinetics; HD, hemodialysis; Pt, patient own values; $T_{1/2}$, half-life; k_e, elimination constants; $AUC_{0–24}$, AUC
462 calculated for 24 h after the end of the 1st HD; $AUC_{24–48}$, AUC calculated for 24 h before the end of the 2nd HD

List of Supplemental Digital Contents

Supplemental Table S1. Clinical outcomes and safety after VCM administration in each patient

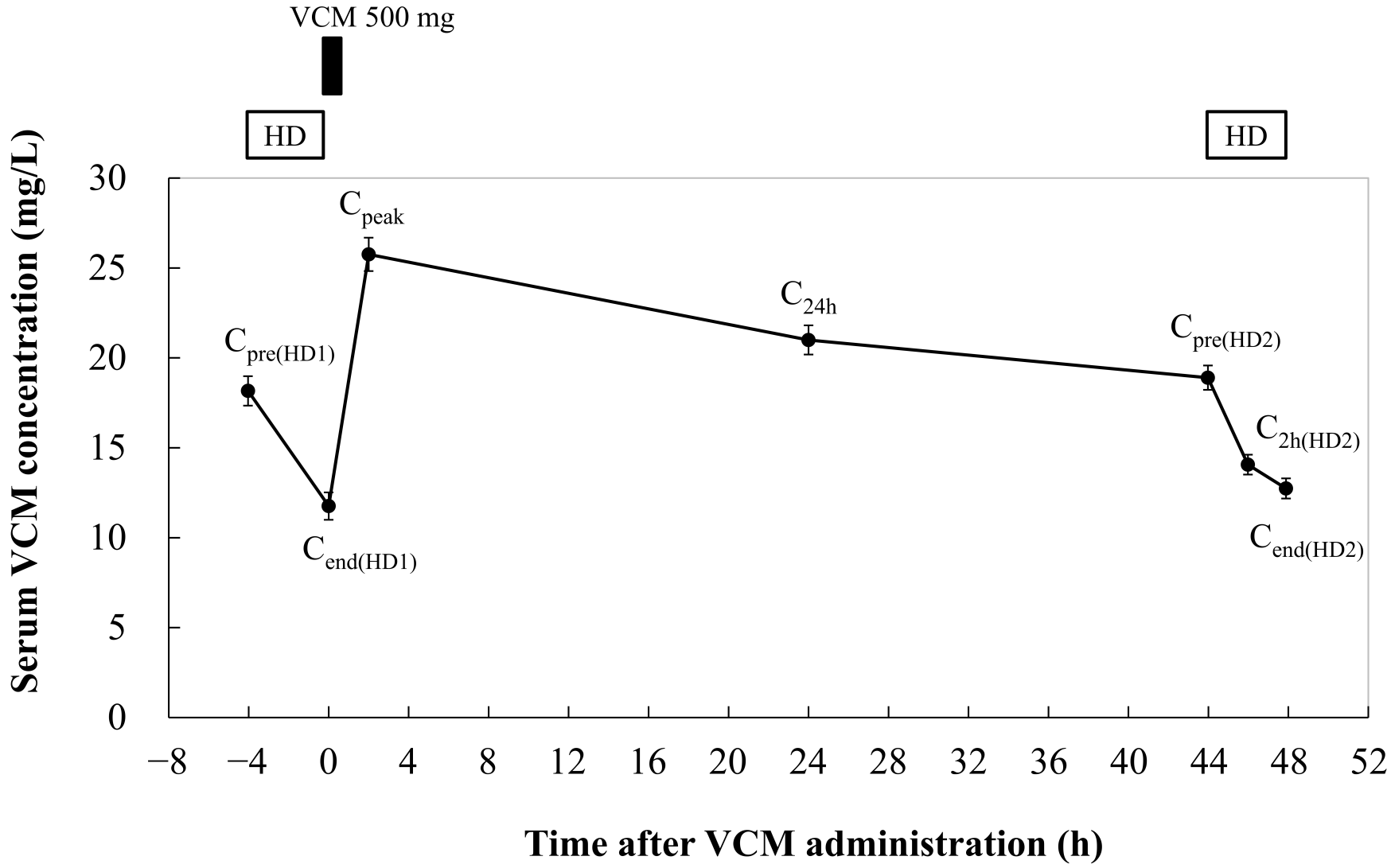
Supplemental Table S2. Correlation coefficients between AUC_{24h} and VCM dose or HD conditions

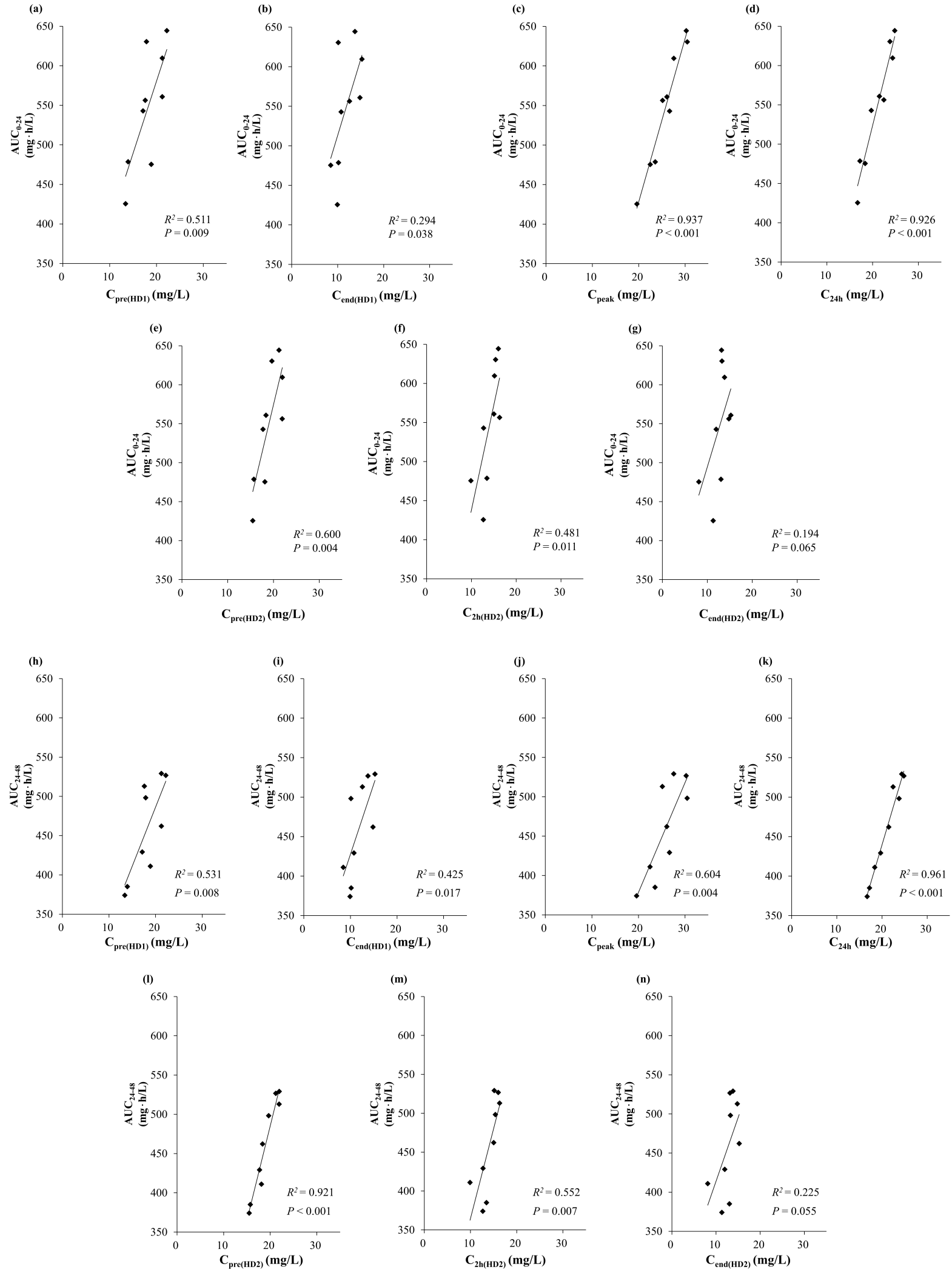
Supplemental Table S3. Correlation coefficients between AUC_{24h} and serum VCM concentrations at each sampling point

Figure legends

Fig. 1. Time-serum concentration profile after the administration of vancomycin (VCM) maintenance dose. The error-bars represent the standard error of the mean serum VCM concentration of nine patients. Squares labeled HD indicate the hemodialysis (HD) implementation period. The interval between the 1st HD and 2nd HD was 48 h. Black box indicates the VCM maintenance dose (500 mg), and the administration time was set to 0.

Fig. 2. Scatter plots and regression lines between serum vancomycin (VCM) concentrations and area under the concentration-time curve (AUC) for 24 h. The relationships of AUC calculated for 24 h after the end of the 1st HD ($AUC_{0\text{-}24}$) with $C_{pre(HD1)}$ (a), $C_{end(HD1)}$ (b), C_{peak} (c), C_{24h} (d), $C_{pre(HD2)}$ (e), $C_{2h(HD2)}$ (f), and $C_{end(HD2)}$ (g). The relationships of AUC calculated for 24 h before the end of the 2nd HD ($AUC_{24–48}$) with $C_{pre(HD1)}$ (h), $C_{end(HD1)}$ (i), C_{peak} (j), C_{24h} (k), $C_{pre(HD2)}$ (l), $C_{2h(HD2)}$ (m), and $C_{end(HD2)}$ (n). R^2, adjusted coefficient of determination


VCM 500 mg
HD
HD
30
25
20
15
10
5
0
Serum VCM concentration (mg/L)
C peak
C pre(HD1)
C end(HD1)
C 24h
C pre(HD2)
C 2h(HD2)
C end(HD2)
−8
−4
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Time after VCM administration (h)


(a)
AUC0-24 (mg·h/L)
Cpre(HD1) (mg/L)
R2 = 0.511
P = 0.009
(b)
AUC0-24 (mg·h/L)
Cend(HD1) (mg/L)
R2 = 0.294
P = 0.038
(c)
AUC0-24 (mg·h/L)
Cpeak (mg/L)
R2 = 0.937
P < 0.001
(d)
AUC0-24 (mg·h/L)
C24h (mg/L)
R2 = 0.926
P < 0.001
(e)
AUC0-24 (mg·h/L)
Cpre(HD2) (mg/L)
R2 = 0.600
P = 0.004
(f)
AUC0-24 (mg·h/L)
C2h(HD2) (mg/L)
R2 = 0.481
P = 0.011
(g)
AUC0-24 (mg·h/L)
Cend(HD2) (mg/L)
R2 = 0.194
P = 0.065
(h)
AUC24-48 (mg·h/L)
Cpre(HD1) (mg/L)
R2 = 0.531
P = 0.008
(i)
AUC24-48 (mg·h/L)
Cend(HD1) (mg/L)
R2 = 0.425
P = 0.017
(j)
AUC24-48 (mg·h/L)
Cpeak (mg/L)
R2 = 0.604
P = 0.004
(k)
AUC24-48 (mg·h/L)
C24h (mg/L)
R2 = 0.961
P < 0.001
(l)
AUC24-48 (mg·h/L)
Cpre(HD2) (mg/L)
R2 = 0.921
P < 0.001
(m)
AUC24-48 (mg·h/L)
C2h(HD2) (mg/L)
R2 = 0.552
P = 0.007
(n)
AUC24-48 (mg·h/L)
Cend(HD2) (mg/L)
R2 = 0.225
P = 0.055