Acta Med. Okayama, 2020
Vol. 74, No. 4, pp. 365-370

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

Successful Vancomycin Dose Adjustment in a Sepsis patient with Bacterial Meningitis Using Cystatin C

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Cystatin C-guided vancomycin (VCM) dosing is useful in critically ill patients. Its usefulness in septic patients with bacterial meningitis remains unknown, as there are no published reports. In this study, we sought to clarify its benefit. Cystatin C was used to guide VCM dosing in a septic bacterial meningitis patient with normal kidney function, according to therapeutic drug monitoring (TDM). Using cystatin C, the Bayesian method-based TDM made optimal VCM dosing possible, and decreased the predicted error (4.85 mg/L) compared to serum creatinine (16.83 mg/L). We concluded TDM of VCM using cystatin C can be considered in sepsis patients with bacterial meningitis with normal kidney function.

Key words: vancomycin, therapeutic drug monitoring, cystatin C, bacterial meningitis, sepsis

Bacterial meningitis caused by *Streptococcus pneumoniae* has a high mortality rate and therefore requires appropriate and effective antimicrobial chemotherapy [1,2]. Vancomycin (VCM) is a recommended treatment. However, because VCM has a narrow therapeutic window, VCM dosing needs to be adjusted according to therapeutic drug monitoring (TDM) to maximize the therapeutic effect without toxicity, particularly nephrotoxicity [3]. VCM trough levels of 10-20 mg/L are recommended to improve the clinical outcome in methicillin-resistant *Staphylococcus aureus* (MRSA)-infected patients, and levels of 15-20 mg/L are recommended for bacterial meningitis patients [3]. VCM is excreted directly into urine, mainly by glomerular filtration, and the most important factors that determine its dosage are renal function and body weight. However, VCM clearance (CLvcm) in critically ill patients is influenced by pathophysiological factors such as acute kidney injury (AKI) or augmented renal clearance (ARC) [4]. It is therefore necessary to establish a VCM-dosing regimen that utilizes novel renal functions, because a standard indicator of glomerular filtration rate (GFR) such as creatinine clearance (CrCl) may not be accurate in critically ill patients [5].

Cystatin C provides a more precise GFR estimate compared to serum creatinine (SCr) [6]. Cystatin C is freely filtered through the glomerulus, is almost completely reabsorbed and catabolized by proximal tubular cells, and is an endogenous inhibitor of cysteine proteases, which are produced in all nucleated cells [7]. Cystatin C-guided VCM dosing has been reported use-

Received September 24, 2019; accepted April 8, 2020.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

ful in critically ill patients with various infections, including septic patients [8,9]. It was shown to enhance the GFR of critically ill patients with acute infectious meningitis [10]. The CLvcm of neurosurgical intensive care unit (ICU) patients was higher than that of non-ICU patients, suggesting that it is influenced by meningitis in critically ill patients [11]. However, the usefulness of cystatin C-guided VCM dosing in sepsis patients with bacterial meningitis remains unclear, because previous studies have excluded patients with high renal clearance, and have not specified whether bacterial meningitis patients were included [8,9]. Therefore, it is necessary to examine the usefulness of cystatin C-guided VCM dosing for septic patients with bacterial meningitis, because VCM concentration needs to be adjusted within a narrow therapeutic concentration window in such patients. In this study, we report a successful case of VCM dosing adjustment using cystatin C in a sepsis patient with bacterial meningitis.

Case Report

This case was part of a study to examine the relationship between CLvcm and cystatin C in critically ill patients under the approval of the Tokushima University Hospital's (Reference Number: 3285) Ethics Committee. The patient was a 38-year-old man with neuromyelitis optica, who was undergoing treatment with prednisolone 40 mg, and was transferred to the intensive care unit (ICU) because of consciousness disturbance. His diagnosis was sepsis, given that he had a sequential organ function assessment (SOFA) score of 8 (Table 1), coupled with acute infectious meningitis or suspected bacterial meningitis due to an increased cell count and protein level, decreased cerebrospinal fluid (CSF), and plasma glucose in CSF (Table 2).

At this point, treatment with VCM and meropenem (the empiric therapy for penicillin-resistant *Streptococcus pneumoniae*, the major cause of bacterial meningitis), and acyclovir (the empiric therapy for Herpes simplex virus) was commenced [1,2]. An SCr of 0.66 mg/dL and a urine output that did not reveal AKI indicated normal renal function (eGFR, 107.6 mL/min) [12]. AKI was defined according to the KDIGO clinical practice guidelines: (1) an increase in serum creatinine level by ≥ 0.3 mg/dL; (2) an increase in serum creatinine level by ≥ 1.5 times baseline occurring within the prior 7 days; or (3) urine volume < 0.5 ml/kg/h for 6 h [13]. The patient's mean urine output 6 h before VCM administration was 1.15 mL/kg/hr, approximately 75% of normal urine output. However, his predicted eGFR was approximately 80 mL/min ($107.6 \times 0.75 = 80.7$). His

Table 1 Baseline patient characteristics

Subject	
Gender	male
Height (cm)	174.1
Body weight (kg)	79.7
Age (years)	38
SCr (mg/dL)	0.66
Total bilirubin (mg/dL)	0.5
Serum albumin (g/dL)	2.6
White blood cell ($\times 10^3/\mu$L)	1.5
C- reactive protein (mg/dL)	3.56
Platelet ($\times 10^4/\mu$L)	389
SOFA score	8
APACHE II score	15
Renal parameters at 1st TDM (Day 5)	
CrCl (CG formula)	250.9
CrCl (Hoek formula)	91.5

SCr, serum creatinine; SOFA score, sequential organ function assessment score; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; TDM, therapeutic drug monitoring.

Table 2 Information of cerebrospinal fluid and inflammation

	CSF					
	Cell count (/mL)	Polymorphonuclear cells (%)	Glucose (mg/dL)	CSF/plasma glucose	Protein (mg/dL)	CRP (mg/dL)
Day1	28	13.3	67	0.33	134	3.56
Day2	37	10.9	63	0.41	120	12.37
Day8	13	2.6	83	0.29	75	6.08
Day15	11	3.1	128	0.51	67	1.55

CSF, cerebrospinal fluid; CRP, C-reaction protein.

initial VCM regimen of 1 g q12 h was decided based on his body weight (79.7 kg) and his estimated renal function (eGFR, 80.7 mL/min), according to recommended therapeutic drug monitoring (TDM) guidelines (12.5 mg/kg).

Since his urine output was changing within short periods of time, there was a concern of VCM overdose; therefore, he did not receive a loading dose [14]. At the 9th VCM dosing, his first trough concentration was 6.9 mg/L (Fig. 1), and because his SCr (0.44 mg/dL) was lower than the standard value on day 5, the assessment of his renal function based on cystatin C showed that his VCM trough concentration was still below the desired therapeutic range (10-20 mg/L). Using the pharmacokinetic (PPK) parameters of ICU patients documented by Revilla *et al.*, the predicted VCM concentrations were calculated by applying the Bayesian method [15], and because sepsis with bacterial meningitis is a critical illness, CrCl was calculated using the Hoek formula [16, 17] as follows:

$$\text{CrCl (mL/min)} = -4.32 + 80.35/\text{cystatin C} \times \text{BSA}/1.73\text{m}^2$$

These calculations were performed using TDM software (VCM-TDM Microsoft Excel, version 3.0; Shionogi and Co., Osaka, Japan). The PPK parameters and patient characteristics reported by Revilla *et al.*, which included age, sex, body weight, SCr 9 levels, and VCM dose, were used because the predicted concentration of 17.25 mg/L was obtained using the Bayesian method when VCM (2 g q12 h) was administered [15]. The second trough concentration at the 9th VCM dosing was found to be 22.1 mg/L with a prediction error of 4.85 mg/L. The formula used for calculating the prediction error is as follows (Table 3) [18]:

$$\text{MAE} = \frac{1}{n}\sum_{n=1}^{n}|\text{predicted concentration} - \text{observed concentration})|$$

Owing to clinical and cerebrospinal fluid symptom improvements, treatment with VCM was stopped on day 15, and the cerebrospinal fluid culture remained negative. Because of careful TDM using cystatin C, VCM-associated nephrotoxicity was not observed (SCr and urine output did not change during VCM treat-

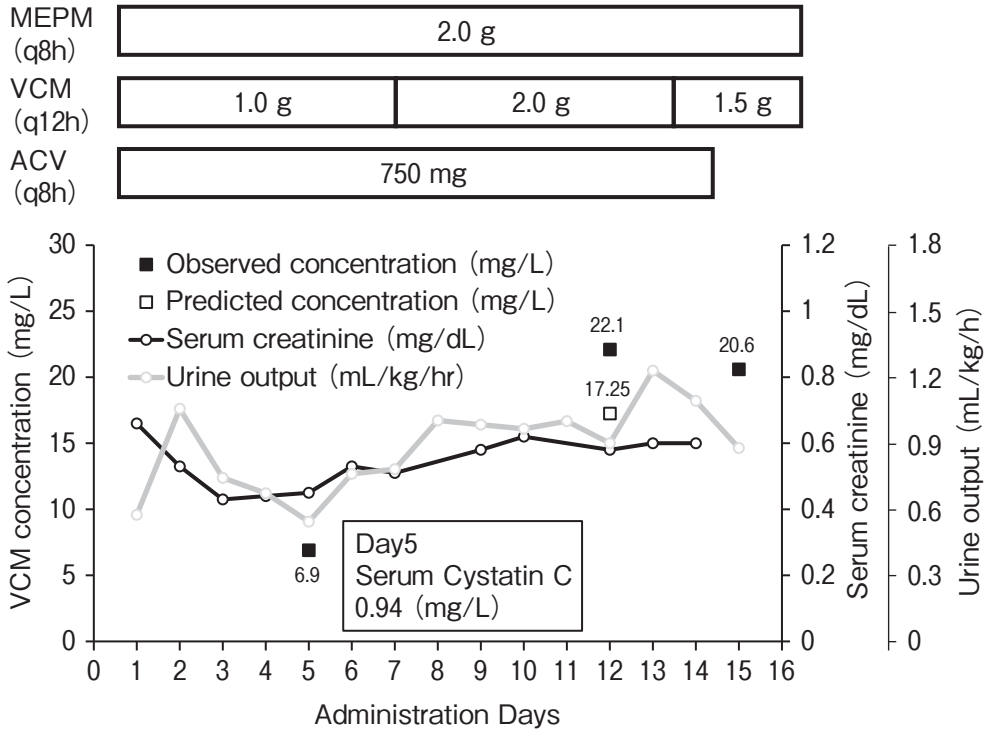

Fig. 1 Serum vancomycin trough concentration and renal function. Closed square, observed concentration; Open square, predicted concentration; Grey symbol and line, serum creatinine levels; and Black symbol and line, urine output. MEPM, meropenem; VCM, vancomycin; ACV, acyclovir.

ment), although VCM trough concentrations were almost 20 mg/L. The cerebrospinal fluid culture revealed no positive findings for bacteria.

Discussion

Vancomycin (VCM)-dosing adjustment via therapeutic drug monitoring (TDM) with cystatin C is useful for achieving the desired therapeutic range in critically ill patients. There are no reports on cystatin C-guided VCM dosing in septic patients with bacterial meningitis, even though it is necessary to accurately adjust VCM trough concentrations to fall within the recommended therapeutic range.

The present study revealed that carrying out TDM using cystatin C made it possible to adjust the dose of VCM a in septic patient with bacterial meningitis. The prediction errors obtained from the Bayesian method using the Cockcroft-Gault (CG) formula and the Hoek formula were then calculated and compared. Previous reports revealed that in the Japanese population, it is useful for a VCM-dosing regimen using cystatin C to utilize eGFR values derived from the Hoek formula [16, 19, 20]. Using the Hoek formula proposed by Kozono and a cystatin C value of 0.94 mg/L, an estimated CrCl value of 81.2 mL/min was obtained [17]. We calculated the CrCl using the Hoek formula because eGFR using the Hoek formula does not differ when using CrCl [17, 21].

CG formula: [22]

$\mathrm{CrCl\ (mL/min)^{male}} = ((140 - \mathrm{age}) \times \mathrm{body\ weight}) / (72 \times \mathrm{SCr\ (mg/dL)})$

$\mathrm{CrCl\ (mL/min)^{female}} = \mathrm{CrCl\ (mL/min)^{male}} \times 0.85$

The prediction error obtained using the Hoek formula was lower, indicating higher prediction accuracy (Table 3). Similarly, the prediction error obtained from the Hoek formula (6.88 mg/L) calculated using other pharmacokinetic (PPK) parameters [23] was lower than that obtained from the CG formula (8.65 mg/L). Furthermore, using the PPK parameters of hospitalized Japanese patients [20], the prediction error using the Hoek formula was 6.94 mg/L.

We reported that the calculated pharmacokinetics of VCM utilizing the PPK parameters reported by Revilla *et al.* [15] were similar to those calculated using the PPK parameters of Yasuhara *et al.*, which have been used for calculated pharmacokinetics of VCM in patients with various infections, including sepsis [24]. Previous reports have shown that the prediction errors in sepsis patients calculated using PPK parameters by Yasuhara *et al.* are 4.28-6.41 (mg/L) [18, 25]. The prediction error in this study, 4.85 (mg/L), is plausible because it is similar to that of previous reports [18, 25]. Therefore, the prediction accuracy was highest when the Hoek formula and the PPK parameters documented by Revilla *et al.* were used [15]. This suggests that the prediction error may differ depending on the indicator used, *i.e.*, GFR or PPK parameters.

Table 3 Prediction error by the Bayesian method using some population pharmacokinetics parameters

Population	Regression equation CL	Regression equation Vd	Residual variability	Predicted concentration (mg/L)	Prediction error (mg/L)	Ref
ICU patients	CL (mL/min/kg) = $0.67 \times \mathrm{CrCl} + \mathrm{Age}^{-0.24}$ ωCL = 30.13 ωCL (%) = 16.4	Vd (L/kg) = 0.82×2.49^{A} A = 0 or 1 if SCr ≤1 or SCr>1 ωVd = 22.83 ωVd (%) = 38.8	±4. 2mg/L CV (%) = 9.8	Hoek: 17.25 CG: 5.27	4.85 16.83	15
MRSA-infected patients	If CrCl <85 (mL/min) CL = 0.0487 × CrCl (mL/min) If CrCl ≥85 (mL/min) CL (L/hr) = 3.51 ωCL (%) = 38.5	Vd (L) = 60.71 ωVd (%) = 25.4	CV (%) = 23.7	Hoek: 15.22 CG: 13.45	6.88 8.65	23
Hospitalised patients	CL (L/hr) = 0.0525 × GFR (mL/min) ωCL (%) = 19.8	Vd (L/kg) = 0.864 ωVd (%) = 30.7	CV (%) = 12.7	Hoek: 15.16	6.94	20

The residual variability of parameters was expressed as coefficient of variation (CV, %). The predicted concentrations were calculated using the Bayesian method, using CrCl, according to the Hoek formula or Cockcroft formula. ICU, intensive care unit; CL, vancomycin clearance; Vd, volume of distribution; Predicted conc, predicted concentration; Ref, Reference; SCr, serum creatinine; ω, between subject variability; CG, Cockcroft-Gault.

Previous studies showed that prednisolone increased serum cystatin C concentration [26]. In addition, the accuracy of eGFRcys in patients taking prednisolone <10 mg was lower than in patients taking ≥ 10 mg prednisolone [27]. However, Kazama reported that steroids did not interfere with serum cystatin C concentration [28]. Thus, the influence of steroids on cystatin C is controversial. Assessment using other markers in addition to cystatin C for renal function should be considered for dose adjustment of VCM using cystatin C taking steroids, as in this case.

To conclude, the TDM of VCM using cystatin C may be considered in bacterial meningitis sepsis patients with normal kidney function. However, given that this study is a case report of a single patient with normal renal function, further studies are necessary to better clarify the usefulness of this method in treating a larger population of septic patients with bacterial meningitis, including those with abnormal renal function.

Acknowledgments. This study was supported by JSPS KAKENHI [grant number 19K16448].

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