Case Report

Assessment of Renal Function and Simulation Using Serum Cystatin-C in an Elderly Patient with Uncontrollable Plasma Vancomycin Levels Due to Muscular Dystrophy: A Case Report

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Herein, we describe a case of an elderly patient with muscular dystrophy for whom control of the plasma vancomycin (VCM) concentration proved difficult when he developed a catheter-related bloodstream infection. The pharmacist initially carried out therapeutic drug monitoring using an estimate of the creatinine clearance (CLcr) level, which was based on the serum creatinine (SCr) and serum cystatin-C (CysC) levels, but was ultimately unable to control the plasma VCM concentration. Therefore, the plasma VCM concentration was predicted ex post facto using population pharmacokinetic parameters as a covariate; that is, directly including the glomerular filtration rate (GFRCysC) estimated from the CysC level, which is not affected by the muscle mass. As a result, the estimated VCM concentration was closer to the actual concentration than that predicted using CLcr. Furthermore, the results of examining the predictive accuracy according to the assessment of renal function at the time of initial VCM administration suggested that estimation of the trough concentration using GFRCysC might be useful in elderly patients with muscular dystrophy.

Key words—muscular dystrophy; vancomycin; serum cystatin-C; therapeutic drug monitoring

INTRODUCTION

Although vancomycin hydrochloride (VCM) is the first-line drug for treating methicillin-resistant Staphylococcus aureus (MRSA) infections, the careful management of its plasma concentration through therapeutic drug monitoring (TDM) is necessary owing to the prevalence of concentration-dependent renal disorders associated with its use, especially in patients with reduced renal function and elderly patients.¹)

We have experienced a case of a patient with muscular dystrophy for whom control of the plasma VCM concentration proved difficult when he developed a catheter-related bloodstream infection. Usually, TDM of VCM involves the evaluation of renal function and drug clearance through measurements of the serum creatinine (SCr) and creatinine clearance (CLcr) levels, followed by estimation of the plasma VCM concentration and determination of the treatment design. However, because the SCr level is affected by the skeletal muscle mass, its estimation is often difficult in elderly individuals who have a low muscle mass. As our patient was elderly and had muscular dystrophy, which is an incurable disease, he had a significantly reduced muscle mass. Therefore, despite the evaluation of his renal function using serum cystatin-C (CysC) levels, we were unable to control his plasma VCM concentration. In this case report, we will outline the VCM dosing design for this patient, as well as discuss population pharmacokinetic simulation including the evaluation of renal function in an elderly muscular dystrophy patient with a very low muscle mass.

CASE

Patient A male patient in his 70s, with a height of 162 cm, body weight of 64.1 kg (body mass index: 24.4), and body surface area of 1.68 m² (DuBois method).

Chief Complaint Dyspnea

History of Present Illness The patient experienced dyspnea from pneumonia while receiving treatment for muscular dystrophy in another hospital, and his condition deteriorated to the point of needing intubation and artificial ventilation at one point. Despite improvement of the pneumonia and removal of the tube following treatment with combined piperacillin/tazobactam, the patient needed continued ventilatory management with non-invasive

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positive pressure ventilation and was admitted to our hospital for close examination and treatment of the underlying disease.

**Name of Comorbidity**  
Limb-girdle muscular dystrophy

**Physical Findings and Laboratory Results at Admission**  
Body temperature of 35.9°C, heart rate of 90 bpm, blood pressure of 127/79 mmHg, white blood cell count of 9230/μL, neutrophil count of 8220/μL, hemoglobin level of 10.0 g/dL, platelet count of 375000/μL, total protein level of 5.4 g/dL, serum albumin level of 2.2 g/dL, aspartate aminotransferase level of 39 IU/L, alanine aminotransferase level of 59 IU/L, urea nitrogen level of 32.0 mg/dL, and SCr level of 0.42 mg/dL.

**Post-admission Clinical Course**  
The patient presented with difficulty swallowing from Day 1 of admission. He was started on central venous hyperalimentation. On Day 8 of admission, the patient developed a fever of approximately 38°C and underwent two sets of blood culture tests. The central venous catheter was removed following the suspicion of a central venous catheter infection. Gram-positive bacteria were detected in the blood cultures by Gram staining, and therefore, empirical treatment with VCM (500 mg, 3 times daily) was initiated (Fig. 1). The SCr level at the start of treatment was 0.44 mg/dL.

On Day 4 of the VCM treatments, the plasma trough concentration of the drug (28.7 μg/mL) was high, and the SCr level was 0.39 mg/dL. Through a TDM analysis, the pharmacist performed a Bayes estimation of the VCM pharmacokinetics. As the patient was older than 65 years of age (in his 70s) and his SCr level was below 0.6 mg/dL, the SCr level was corrected to 0.6 mg/dL for the analysis and the CLcr was calculated with the Cockcroft-Gault formula to be 92.0 mL/min. On the basis of this result, the pharmacist recommended to the physician to reduce the VCM dosage to 500 mg given twice daily (estimated trough concentration of 17.0 μg/mL) after a 32-h drug holiday (4 doses from the same afternoon). The blood culture test detected MRSA, and the minimum inhibitory concentration of VCM was 1 μg/mL.
On Day 8 of the VCM treatments, the plasma trough concentration of the drug had increased to 30.2 μg/mL. However, there were no significant changes in the SCr (0.44 mg/dL), urea nitrogen, and urea levels, and the CysC level was 1.9 mg/dL. The glomerular filtration rate (GFR\textsubscript{CysC}, uncorrected for body surface area), which had been estimated from the CysC amount using the Hoek equation, was 37.0 mL/min. This value was then converted to the Cl\textsubscript{cr}, resulting in a value of 46.9 mL/min (= 37.0/0.789).

As a result of this TDM based on the Cl\textsubscript{cr}, it was recommended that the VCM dosage be reduced to 500 mg given once daily (estimated trough concentration of 11.7 μg/mL) following a drug holiday of 48 h after the final dose.

On Day 12 of the VCM treatments, the plasma trough concentration of the drug remained above the target range (10–20 μg/mL) at 24.6 μg/mL. However, the VCM treatment was terminated because the patient’s condition had improved and the duration of treatment was long enough to treat even bacteremia.

The support tool SHIONOGI-VCM-TDM (S-edition Ver. 2014 for Windows) was used for the TDM analysis in the treatment process.

**Concomitant Medications**

Concomitant medications for this patient were as follows: levofloxacin hydrate 500 mg/d (Day 8–15 of admission), prednisolone 12 mg/d (during hospitalization), famotidine 20 mg/d (during hospitalization), eldecalcitol 0.75 μg/d (during hospitalization), teneligliptin hydrobromide hydrate 20 mg/d (during hospitalization), magnesium oxide 250 mg/d (during hospitalization), brotizolam 0.25 mg/d (during hospitalization) and electrolyte infusion 23.4 mL/kg/d.

**DISCUSSION**

Muscular dystrophy is a muscular disease in which the muscle mass decreases as a result of degeneration and necrosis. The disease is hereditary and currently still incurable. Although a dose adjustment was carried out for this patient on the basis of renal function evaluations and Bayes estimation after initiation of the VCM treatments, we were ultimately unable to control the trough concentration of the drug to remain within the target range. To our best knowledge, there are not many known cases of TDM performed for elderly patients with muscular dystrophy, and this is the first report that is specifically regarding VCM treatments.

First, we examined the cause of the difficulty in controlling the trough concentration of VCM by assessing the renal function of the patient and measuring the Bayes estimate in the following manner. The pharmacokinetic parameters of VCM in the Japanese population, as determined by Yasuhara et al.,\textsuperscript{2} were input to the TDM data analysis support tool used for the Bayes estimation, and the Cl\textsubscript{cr} was used for predicting the clearance of the drug. As measurement of the Cl\textsubscript{cr} requires 24-h urine collection, it is common to use the estimated Cl\textsubscript{cr} value in clinical practice, as was done for this patient. However, given that the measured SCr level was low on Day 4 of the VCM treatments, the estimation was performed after correcting the SCr value to 0.6 mg/dL by the round-up method.\textsuperscript{3} Furthermore, in the TDM on Day 8 of the VCM treatments, the GFRCysC value estimated from the CysC level was converted to the Cl\textsubscript{cr} by dividing the value by 0.789. In TDM, Bayesian estimation makes it possible to estimate patient-specific pharmacokinetic parameters as an \textit{ex post facto} distribution based on the measured drug concentration by using the inter-patient variation distribution of the pharmacokinetic parameters in the general population as the \textit{ex ante} distribution. However, the patient parameters are known to be close to the population parameters when the measured concentration data are few,\textsuperscript{4} and it may not be possible to adequately estimate the patient-specific parameters. Therefore, to find the cause of the large discrepancy between the measured trough concentration of VCM (Day 8 of VCM treatments: 30.2 μg/mL) and the estimated concentration based on the TDM in Day 4 of the VCM treatments, a Bayesian estimation was performed under the same conditions as those of this patient while fluctuating the Cl\textsubscript{cr} value between 10 and 130 mL/min. As a result, the estimated trough concentration of VCM was between 16.8 and 47.2 μg/mL, with a more than 2-fold difference between the upper and lower limits of the estimated value (Supplementary materials, Table S1). As indicated in Table S1, when the Cl\textsubscript{cr} values were 15 and 20 mL/min, the estimated trough concentrations were 31.1 and 25.3 μg/mL, respectively. As the trough concentration of VCM on Day 8 of the treatments was close to 30.2 μg/mL, the actual Cl\textsubscript{cr} was considered to be within 15–20 mL/min; that is, 16–22% of the estimated value of 92.0 mL/min. Despite there being no figure
to estimate the muscle mass, we surmise that the very fact that this was a patient with muscular dystrophy with an extremely low muscle mass (according to the physical findings) would make estimation of the CL\textsubscript{cr} using the SCr level (which is affected by the muscle mass) difficult. Additionally, even though the SCr value was corrected by the round-up method for this patient, previous reports have suggested that such correction can cause errors in the renal function assessment and treatment regimen design,\textsuperscript{5} which suggests that our approach in correcting the SCr value may be another reason for the incorrect renal function assessment. During the TDM on Day 8 of the VCM treatments, we determined the treatment design using the CL\textsubscript{cr} value of 46.9 mL/min (=37.0/0.789), which was converted from the GFRCysC value (uncorrected for body surface area) that was estimated from the CysC level, which is not affected by the muscle mass. Despite this, we failed to control the VCM concentration to within its target concentration range. Therefore, we used the Microsoft Excel with Visual Basic for Applications\textsuperscript{6} that we had previously created to perform \textit{ex post facto} simulations based on the population parameters as a covariate,\textsuperscript{7} directly including the GFRCysC value (uncorrected for body surface area). As a result, the estimated VCM concentration was 17.1 μg/mL, which was relatively closer to the measured concentration (Day 12 of the VCM treatments: 24.6 μg/mL) than the estimated trough concentration (11.7 μg/mL) by using CL\textsubscript{cr}. We surmised that in this case, it would be preferable to use the population pharmacokinetic parameters including GFRCysC as a covariate.

As the concomitant medications, prednisolone (12 mg/d), which has been reported to increase CysC levels,\textsuperscript{8} was administered, however, its influence is unlikely because the estimated trough concentration was lower than the measured concentration. Also, although infusion load (23.4 mL/kg/d) might increase the volume of distribution of VCM and make VCM concentration lower, it is considered to have little effect because the measured concentration was very high.

Next, the renal function assessment performed when estimating the trough concentration of VCM during its first dosage administration was verified \textit{ex post facto} in the following manner. We simulated the trough concentration of VCM during its initial dosage regimen (500 mg, 3 times daily), using the renal function parameters estimated from the SCr or CysC levels. There were three types of renal function assessments: (A) CL\textsubscript{cr} (125.5 mL/min), calculated using the Cockcroft-Gault formula with the SCr value measured before VCM treatment; (B) CL\textsubscript{cr} (92.0 mL/min), calculated by correcting the SCr value to 0.6 mg/dL; and (C) GFRCysC (37.0 mL/min, uncorrected for body surface area), based on the CysC level. (A) and (B) were simulated using SHIONOGI-VCM-TDM (S-edition Ver. 2014 for Windows), whereas (C) was simulated using the Microsoft Excel with Visual Basic for Applications.

The VCM clearance results estimated by each of the population pharmacokinetic parameters\textsuperscript{5,7} were (A) 6.0 ± 2.3 L/h, (B) 4.4 ± 1.4 L/h, and (C) 1.9 ± 0.4 L/h. The estimated trough concentration of VCM at the initial dosage (500 mg, 3 times daily) and the difference between the estimated and measured concentrations (Day 4 of VCM treatments: 28.7 μg/mL), respectively, were (A) 5.1 and 23.6 μg/mL, (B) 8.1 and 20.6 μg/mL, and (C) 28.9 and 0.2 μg/mL. This meant that the estimated concentration, in the assessment that used GFRCysC (simulation C), showed the result closest to the measured concentration of VCM in this patient. Furthermore, to verify the accuracy of the estimated values based on each form of renal function assessment, we generated a random number within the inter-patient distribution range of VCM clearance in each group, estimated the trough concentration from the profiles of the VCM concentration based on each VCM clearance result, and calculated the estimated range (95% confidence interval) (Supplementary materials, Table S2). The results showed that the measured concentration (28.7 μg/mL) was only within the estimated range of simulation C, the trough concentration of VCM estimated using the CysC level.

In conclusion, we have determined that for elderly patients with muscular dystrophy who are perceived to have a reduced muscle mass, like the patient in our case report, the assessment of renal function might be considered using CysC values. In particular, it may be useful to analyze using population pharmacokinetic parameters including GFRCysC as a covariate. Similar pathologies are also observed in long-term bed rest patients,\textsuperscript{9} so it may be preferable to use GFRCysC for population pharmacokinetic analysis in such cases.

\textbf{Conflict of Interest} The authors declare no con-
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Supplementary Materials  The online version of this article contains supplementary materials.

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