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CASE REPORT

Therapeutic drug monitoring of vancomycin in a patient with Duchenne muscular dystrophy (DMD): A case report

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Vancomycin is a widely used glycopeptide antibiotic that requires therapeutic drug monitoring (TDM) owing to its narrow therapeutic window. It is primarily eliminated by renal excretion; thus, estimating the renal function of a patient is vital in the TDM of vancomycin. In patients with Duchenne muscular dystrophy (DMD), it is difficult to estimate the glomerular filtration rate using the serum creatinine level owing to the pathophysiological nature of the disease. Here, we report a case of a patient in whom TDM of vancomycin was performed, and explore the appropriate methods for evaluating renal function in patients with DMD based on serum levels of creatinine and cystatin C.

Vancomycin, a glycopeptide antibiotic, is one of the most widely used antibiotics in the treatment of gram-positive infections including methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[1] It has a narrow therapeutic index with potential risks of nephrotoxicity and ototoxicity; therefore, therapeutic drug monitoring (TDM) is vital in clinical applications. Since vancomycin is known to be eliminated primarily via renal excretion, estimating the renal function of a patient as well as the serum vancomycin concentration is considered essential.[2]

Creatinine is produced constantly by the skeletal muscles, and is mainly eliminated via glomerular filtration and not reabsorbed or secreted. Therefore, the serum creatinine level (SCr) is widely used as an indicator of glomerular filtration rate (GFR), which is an index of renal function in clinical practice. However, the estimation of GFR using SCr in patients with muscle disease has limitations owing to the reduced mass of skeletal muscles.[3]

Duchenne muscular dystrophy (DMD) is an X-linked disease that leads to an absence of or defect in the protein dystrophin, resulting in progressive muscle degeneration.[4] In DMD patients, reduced muscle mass lowers serum creatinine level, which can cause overestimation of the GFR. This makes it difficult to predict the concentrations of drugs that are primarily eliminated via the renal route.[5]

Here, we report a case of a patient in whom TDM of vancomycin was performed, and determine the appropriate methods for estimating the renal function in DMD patients for TDM of vancomycin.

Case report

A 25-year-old male patient (height: 176 cm, body weight: 42 kg, body surface area (BSA): 1.43 m^2) with a 5-day history of fever, sputum, and chest pain was admitted to Seoul National University Hospital (SNUH) for suspected ventilator-associated pneumonia (VAP).

A diagnosis of DMD was made in 2003, and the patient also had dilated cardiomyopathy. On admission, it was noted that he had been receiving enalapril, digoxin, carvedilol, and sildenafil.

On physical examination, the patient was found to have a fever (temperature of 38.1°C [100.6°F]), decreased lung sounds in the right lower lung field, and crackles in dependent lungs. Initial clinical laboratory tests results were as follows: WBC count, 8.67 × 10^3/μL (77.4% neutrophils, 12.8% lymphocytes, and 0.6% eosinophils); blood urea nitrogen level, 7 mg/dL; serum creatinine level, 0.18 mg/dL; serum high-sensitive C-reactive protein level, 8.73 mg/dL; and serum albumin level, 3.3 g/dL. The results of

the urine and stool cultures were negative. The clinician began the treatment with vancomycin 630 mg IV q6h and meropenem 800 mg IV q8h for VAP in the intensive care unit.

To prevent toxicity caused by vancomycin, TDM was conducted. For TDM, a blood sample was obtained to measure the serum vancomycin concentration just before the 5th dosing. The observed serum vancomycin concentration was 20.4 μg/mL. The estimated GFR calculated using the Cockroft-Gault equation based on the initial serum creatinine level of the patient (0.18 mg/dL) was 372.7 mL/min.[11] Based on this GFR, the predicted trough serum vancomycin concentration at steady state was 16.7 μg/mL, which was significantly lower than the corresponding observed value. Owing to this discrepancy, an inverse calculation was performed using the observed serum vancomycin concentration value, and the calculated GFR value was approximately 70 mL/min. Assuming that this inversely calculated GFR was similar to the actual GFR of the patient, to achieve a trough serum vancomycin concentration of 15.0 μg/mL at steady state, the dosing regimen was adjusted to vancomycin 630 mg IV q8h. The vancomycin treatment was stopped two days after the TDM, and the patient was discharged because of general condition recovery; hence, no further TDM was conducted.

Pharmacokinetic calculations were conducted using the ABBOTTBASE® Pharmacokinetic Systems software (version 1.10, Abbott Laboratories, Abbott Park, IL, USA).

Discussion

The estimated GFR of the DMD patient based on the serum creatinine level was overestimated, and this overestimation resulted in a significantly lower predicted serum vancomycin concentration compared to the observed serum vancomycin concentration. This case indicates that the adjustment of the vancomycin dose according to the estimated GFR using the serum creatinine level may not be appropriate in DMD patients.

The ideal endogenous marker of GFR should be produced at a constant rate, and be primarily eliminated by glomerular filtration and not reabsorbed or secreted.[3,6] Cystatin C has been recognized as a promising endogenous marker of GFR. Cystatin C is a non-glycated basic protein, which is produced by all nucleated cells at a constant rate. It is freely filtered in the glomerulus, and does not undergo tubular secretion and undergoes only limited extra-renal elimination.[7]

The equations most widely used to estimate the GFR using the

Table 1. Appropriateness of the various renal function estimation methods for TDM of vancomycin in a DMD patient (age: 25 years, height: 176 cm, body weight: 42 kg, body surface area: 1.43 m^2, serum creatinine: 0.18 mg/dL, serum cystatin C: 1.0 mg/L)

Equation		GFR (mL/min)	Serum vancomycin concentration	
			Predicted (μg/mL)	Observed (μg/mL)
Cockroft-Gault equation[11]	$\frac{(140 - age[years]) \times body\ weight[kg] (\times 0.85\ if\ female)}{72 \times serum\ creatinine[mg/dL]}$	372.7	16.7	20.4
Schwartz equation [12]	$\frac{k^{1)} \times body\ height[cm]}{Serum\ creatinine[mg/dL]}$	684.4$^{2)}$	16.1	
Simplified MDRD equation[13]	$186.3 \times \text{serum creatinine}[mg/dL]^{-1.154} \times age[years]^{-0.203}$	701.2$^{2)}$	16.0	
CKD-EPI creatinine equation[14]	$141 \times (serum\ creatinin[mg/dL]/0.9)^{-0.411} \times 0.993^{age[years]}$	229.2$^{2)}$	17.8	
Larsson et al.[8]	$77.239 \times \text{cystatin C}[mg/L]^{-1.2623}$	77.24	20.0	
Tan et al.[10]	$\frac{87.1}{cystatin\ C[mg/L]} - 6.87$	80.23	19.8	
Grubb A et al.[9]	$87.62 \times \text{cystatin C}[mg/L]^{-1.693}$	87.62	19.6	
CKD-EPI cystatin C equation[14]	$133 \times (cystatin\ C[mg/L]/0.8)^{-1.328} \times 0.996^{age[years]}$	89.5$^{2)}$	20.1	

*GFR: Glomerular Filtration Rate, DMD: Duchenne Muscular Dystrophy. $^{1)}$k = 0.33 if infant (low birth weight <1 year), 0.45 if (term <1 year), 0.55 if child or adolescent girl, and 0.70 if adolescent boy; 0.70 was used in this case. $^{2)}$Unit: mL/min/1.73 m^2.

serum creatinine level are the Cockcroft-Gault equation, the Schwartz equation, the simplified Modification of Diet in Renal Disease Study (MDRD) equation, and the Chronic Kidney Disease Epidemiology (CKD-EPI) creatinine equation.[11-14] Further, cystatin C-based equations have been applied to estimate GFR, such as those published by Larsson A et al., Grubb A et al., and Inker LA et al.[6,8-10,14] To determine appropriate methods for estimating renal function, GFRs were calculated using various equations by applying the initial serum creatinine level (0.18 mg/dL) and the latest measured serum cystatin C level (1.0 mg/L) of the patient. The corresponding predicted serum vancomycin concentrations of each estimated GFRs were compared with the observed serum vancomycin concentration (Table 1). All of the creatinine-based equations overestimated the patient's renal function. On the other hand, the cystatin C-based equations allowed relatively closer prediction of the GFR compared to the corresponding values from the serum creatinine-based equations (Table 1).

In DMD patients, estimating the GFR using the serum creatinine level may be difficult owing to the muscle degenerative nature of the disease.[4] To conduct effective TDM of vancomycin in DMD patients, cystatin C can be considered as an alternative endogenous marker of renal function. It should be noted that our attempt to find an appropriate method to estimate the renal function of DMD patients, by comparing creatinine-based equations and cystatin C-based equations, was based on one patient. Further cases should be investigated to determine whether cystatin C-based equations are more appropriate in estimating renal function of DMD patients. Moreover, the use of cystatin C as an alternative endogenous marker of renal function in DMD patients should be investigated with other drugs that are also primarily eliminated via the renal route.

Conflict of interest

The that there is no conflict of interest regarding the publication of this paper.

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