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ORIGINAL ARTICLE

Preferable timing of therapeutic drug monitoring in patients with impaired renal function treated with once-daily administration of vancomycin

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Abstract The aim of this study was to investigate the timing of therapeutic drug monitoring (TDM) in patients with impaired renal function treated with once-daily administration of vancomycin (VCM). Once-daily administration was selected for patients whose creatinine clearance (C_{cr}) was <80 ml/min. TDM was conducted on day 3 or on day 4. Adult patients whose VCM dosage was not altered according to initial C_{min} and for whom subsequent follow-up TDM was performed within 1 week were entered into the study. Patients whose renal function deteriorated at follow-up TDM were excluded. One hundred sixty-five patients were eligible for analysis. Among patients with once-daily dosing, relative increases of C_{min} at follow-up TDM compared with initial TDM were 34.5 ± 39.2 % in TDM on day 3 and 16.6 ± 20.6 % in TDM on day 4 ($P = 0.016$). In contrast, there was no significant difference in the relative increase of C_{min} between TDM on days 3 and 4 (26.1 ± 39.6 vs. 18.4 ± 25.6 %, $P = 0.551$) in the twice-daily regimen. On multivariate analysis, TDM on day 3 alone (odds ratio, 4.93; 95 % confidence interval, 1.71–14.2) was selected as an independent risk factor associated with a relative increase of C_{min} by >30 % in the once-daily regimen. Steady-state VCM serum concentration was not achieved on day 3 in the once-daily regimen in patients with impaired renal function, and TDM on day 3 caused underestimation of C_{min}.

Keywords Vancomycin (VCM) · Therapeutic drug monitoring (TDM) · Trough concentration · Methicillin-resistant *Staphylococcus aureus* (MRSA) · Impaired renal function

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of serious hospital- and community-acquired infections [1–3]. Although newer agents with proven efficacy against MRSA infections are now available, vancomycin hydrochloride has been accepted as the standard therapy for MRSA infections. Clinical practice guidelines by the Infectious Disease Society of America for the treatment of MRSA infections in adults and children [4] recommend a vancomycin target trough concentration of 15–20 μg/ml for serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe skin and soft tissue infections caused by MRSA.

The introduction of higher-intensity dosing treatment aiming at trough concentrations of 15–20 μg/ml has increased the need for TDM practices for vancomycin [5, 6]. Prompt amendment of the dosing regimen based on the trough concentration is mandatory not only to prevent adverse events but also to attain the targeted therapeutic level at an early date. Serum trough concentrations (C_{min}) should be obtained just before the next dose under steady-

state conditions [4, 7]. At steady state, the rate of drug administration is equal to the rate of drug elimination, and the drug concentration remains constant.

In general, it is recommended that the initial trough sample is obtained before the fourth or fifth doses [4]; however, the achievement of a steady state is variable and depends on multiple factors. The time required for a drug concentration to reach steady state is theoretically determined by the drug's half-life [8, 9]. There is, however, no recommendation available about the timing of TDM of vancomycin in patients with renal dysfunction in whom the half-life of vancomycin is prolonged. In addition, several nomograms [10–12] have indicated once-daily administration of vancomycin in patients with renal insufficiency.

The aim of this study was to investigate the appropriate timing of TDM in patients with impaired renal function treated with once-daily administration of vancomycin and to clarify the policy regarding dosage adjustments based on initial C_{min} measured at a standard timing of TDM (on day 3).

Patients and methods

A prospective study was conducted in patients treated with vancomycin in the hospital of Hyogo College of Medicine in Japan (1,006 beds) between January 2008 and December 2011. This study was approved by the institutional review board at Hyogo College of Medicine. Patients who were treated by the Department of Infection Control and Prevention were included in the analysis if (1) they were >17 years old, (2) vancomycin was used for a suspected or proven gram-positive infection with once- or twice-daily administration, (3) C_{min} was measured on day 3 or 4 after starting vancomycin, and (4) follow-up TDM was subsequently performed within 1 week after initial TDM. Patients receiving hemodialysis, those whose renal function deteriorated at follow-up TDM compared with renal function at the initial TDM (creatinine increase: >50 %, +0.5 mg/dl), and those whose vancomycin dosage was altered according to the initial C_{min} were excluded from the study.

Vancomycin was administered at a dose of 15–20 mg/kg every 12 h to patients with normal renal function, and the dosing regimen was adjusted based on creatinine clearance (which was calculated by the Cockcroft–Gault formula based on serum creatinine, age, body weight, and gender) in patients with decreased renal function using a nomogram. In the 12-h vancomycin dosing regimen, an initial trough sample was obtained before the fifth dose in patients with TDM on day 3 and before the seventh dose in patients with TDM on day 4. If vancomycin was administered every 24 h, the initial trough sample was obtained before the third dose in patients with TDM on day 3 and before the fourth dose in patients with TDM on day 4. Vancomycin concentration was measured using a commercial reagent kit (Vanc Flex; Siemens Healthcare Diagnostics, Tokyo, Japan); this is a particle-enhanced turbidimetric inhibition immunoassay (PETINIA) that uses a Dimension Xpand analyzer.

Changes in C_{min} between initial and follow-up TDM were evaluated to determine whether initial C_{min} was regarded as a steady-state concentration. If a greater increase of C_{min} at follow-up TDM is observed, the initial C_{min} is assessed as the concentration before the achievement of the steady state (plateau). Twenty-four variables were analyzed as risk factors associated with a relative increase of >30 % in C_{min} at follow-up TDM: age ≥65 years, sex (male), body weight <50 kg, comorbid disease (diabetes mellitus, liver cirrhosis/chronic hepatitis, chronic renal failure, cardiac disease, hypertension, carcinoma, and inflammatory bowel disease), administration of concomitant drugs (diuretic drug, nonsteroidal antiinflammatory drugs, immunosuppressive agents, steroid, and narcotic drugs), surgery within 1 month, laboratory data at the start of vancomycin treatment (albumin <2.5 g/dl, total bilirubin ≥2.0 mg/dl, serum creatinine ≥1.0 mg/dl), diarrhea during vancomycin treatment that may cause dehydration (defined as bowel movements three times or more daily or more than 200 ml daily evacuation), creatinine ≥1.0 mg/dl and creatinine clearance <50 ml/min at the follow-up TDM, and blood urea nitrogen/serum creatine >20 at the follow-up.

The variables selected by univariate analysis ($P < 0.1$) were subjected to multivariate analysis. Statistical analysis was performed as follows: categorical variables were compared by the χ^2 test with Yate's correction or Fisher's exact probability test when necessary (chi-square procedures by Yate's correction can be legitimately applied only if all values are ≥5), using Microsoft Excel 2003. The level of statistical significance was set at $P < 0.05$. SPSS ver. 16 (SPSS, Chicago, IL, USA) was used to perform these analyses.

Results

During the study period, vancomycin was given to 624 patients, except those on hemodialysis. In the analysis of patients with an alteration of vancomycin dosing based on initial C_{min}, a significantly higher rate of dose increase and lower rate of dose decrease were observed in the once-daily vancomycin administration regimen compared with the twice-daily regimen (increase, 36.2 % vs. 21.0 %, $P < 0.001$; decrease, 4.9 % vs. 10.5 %, $P = 0.001$). In the comparison between patients whose TDM was performed on day 3 and 4, the rate of dose increase was significantly