Risk factors associated with unexpectedly high trough concentration and the occurrence of nephrotoxicity in patients with vancomycin treatment

Yoshiko Takahashi[1,*], Sumiyo Tatsumi[1,*], Shingo Takubo[1], Takeshi Kimura[1] and Yoshio Takesue[2]

[1] Department of Pharmacy, Hospital of Hyogo College of Medicine
[2] Department of Infection Prevention and Control, Hyogo College of Medicine

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Objectives: The purpose of this study was to identify clinically important risk factors that may predispose patients with appropriate vancomycin dosing to an unexpectedly-high trough concentration (C_{min}) and the occurrence of nephrotoxicity.

Methods: Patients treated with vancomycin and who were performed therapeutic drug monitoring were included in the study. Nephrotoxicity was defined as an increase of >0.5 mg/dL or a 50% increase in serum creatinine over the baseline. Multivariate analysis was performed to identify independent risk factors for C_{min} of $\geq 20\,\mu$g/mL and deterioration of renal function.

Results: One hundred and ninety-seven patients were analyzed. Nephrotoxicity occurred in 16.8% of patients during vancomycin therapy. C_{min} of $\geq 20\,\mu$g/mL was demonstrated in 17.8% of patients. Twenty-five of 35 patients demonstrated a C_{min} of $\geq 20\,\mu$g/mL at multiple TDM. C_{min} of $\geq 20\,\mu$g/mL and deterioration of renal function were closely correlated with one another. Additionally, an independent risk factor identified to be associated with C_{min} of $\geq 20\,\mu$g/mL was the administration of diuretics [odds ratio (OR) 3.21, 95% confidence interval (CI) 1.30–7.90]. Use of non-steroidal anti-inflammatory drugs (NSAIDs) (OR 3.22, 95% CI 1.09–9.57) and management with total parenteral nutrition (OR 3.64, 95% CI 1.33–10.00) were independent factors associated with nephrotoxicity during vancomycin therapy.

Conclusions: NSAIDs, diuretic drug use and total parenteral nutrition (TPN) were independent risk factors for a high C_{min} or nephrotoxicity. Limited use of these drugs is preferable to prevent adverse events during vancomycin therapy.

*: Equal contribution

1. Introduction

Many studies have demonstrated a positive association between the risk of nephrotoxicity and higher vancomycin doses, ranging from 12 to 42.7% of patients[1–4]. The risk increases with higher vancomycin maximum trough levels, longer duration of vancomycin use, and concomitant use of other nephrotoxic agents as well as in patients who are critically ill or have previously compromised renal function[5]. The occurrence of nephrotoxicity significantly increased as the initial trough concentration (C_{min}) increased. Several reports have shown that C_{min} of ≥20 μg/mL had a significantly higher incidence of nephrotoxicity than those of <20 μg/mL[3,4,6].

Because vancomycin is mainly eliminated by glomerular filtration, a decrease in renal function, whatever the cause, will increase the vancomycin concentration. As the elevated concentrations of vancomycin may represent an effect, rather than a cause, of nephrotoxicity, the association between maximum C_{min} during vancomycin therapy and the occurrence of nephrotoxicity should be assessed with caution. Although several studies aimed to identify the risk factors for nephrotoxicity in patients receiving vancomycin therapy, to our knowledge, no study has definitively determined the risk factors causing unexpectedly high vancomycin concentration, such as trough levels of ≥20 μg/mL. If such risk factors are identified, they will have important implication for clinical practice. Alternative antimicrobial agents should be considered not only in patients with risk factors for nephrotoxicity, but also in patients who have factors that may cause a trough level of ≥20 μg/mL to prevent the occurrence of vancomycin-induced nephrotoxicity. The primary endpoint of the study was to identify the risk factors causing a trough level of ≥20 μg/mL during vancomycin therapy, which was managed by a certified pharmacist, and the secondary endpoint was to determine the risk factors associated with vancomycin-induced nephrotoxicity.

2. Material and Methods

A retrospective study was conducted among patients who received vancomycin for suspected or diagnosed Gram-positive infection between January 2011 and December 2011 in the Hyogo College of Medicine hospital (1,006 beds). This study was approved by the institutional review board at Hyogo College of Medicine. Patients who were treated with a certified pharmacist in the Department of Infection Control and Prevention were included in the analysis if they (i) were >17 years old, (ii) received vancomycin for at least 72 h (iii) had a vancomycin trough level measurement within 96 h after starting administration, and at least once every week thereafter. Exclusion criteria consisted of patients with hemodialysis, vasopressor support during therapy, concomitant administration of aminoglycosides or amphotericin B, use of contrast media during therapy, and a history of receiving vancomycin for at least 72 h in the 14 days prior to inclusion.

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 the creatinine clearance (which was calculated by the Cockcroft-Gault formula based on serum creatinine, age, and body weight) in patients with decreased renal function using a nomogram. Vancomycin concentration was measured using a commercial reagent kit (Vanc Flex; Siemens Healthcare Diagnostics Inc., Tokyo, Japan). This is a particle-enhanced turbidimetric inhibition immunoassay (PETINIA), which uses a Dimension Xpand analyzer. Predicted C_{min} value was calculated using analysis-supporting simulation software (VCM-TDM on EXCEL Ver.2.01, Shionogi & Co., LTD.). Targeted C_{min} was 10–15 μg/mL during the study period.

Deterioration of renal function (nephrotoxicity) was defined as an increase in serum creatinine of 0.5 mg/dL, or a ≥50% increase from the baseline serum creatinine level before start of vancomycin. A certified pharmacist ordered therapeutic drug monitoring (TDM) during the course of vancomycin therapy, and the vancomycin dosage was adjusted according to the C_{min}. Initial and maximum C_{min} during vancomycin therapy were used in the analysis of the association between vancomycin concentration and occurrence of nephrotoxicity.

Twenty-one variables were analyzed as possible risk factors associated with a C_{min} of ≥20 μg/mL and nephrotoxicity: age ≥65 years, sex (male), body weight <50 kg, comorbid disease (diabetes mellitus, liver cirrhosis/chronic hepatitis, chronic renal failure, cardiac disease, hypertension, carcinoma, or inflammatory bowel disease), surgery within 1 month, administration of concomitant drugs (diuretic drug, non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressive agents, or steroids), laboratory data (albumin <2.5 g/dL or serum creatinine ≥1.0 mg/dL) at the start of vancomycin treatment, and prolonged duration of vancomycin therapy (longer than the median value). Additionally, because the elevated concentrations of vancomycin may represent not only an effect, but also a cause of nephrotoxicity, deterioration of renal function was included in the analysis of risk factors for a trough level of ≥20 μg/mL, and a trough level of ≥20 μg/mL was analyzed as a possible risk factor for nephrotoxicity.

The variables selected by univariate analysis ($P<0.2$) were subjected to multivariate analysis. Statistical analysis was performed as follows: categorical variables were compared by the χ^2 test with Yates's correction or Fisher's exact probability test when necessary (chi-square procedures by Yates's correction can be legitimately applied only if all values are ≥5), using Microsoft Excel 2003. To calculate the correlation between each category of C_{min} (<20, 20–25, and ≥25 μg/mL) and the incidence of nephrotoxicity, the Cochran-Armitage test was used. The level of statistical significance was set at $P<0.05$. SPSS ver. 16 (SPSS Inc., Chicago, IL, USA) was used to perform these analyses.

3. Results

During the study period, vancomycin was administered to 225 patients, and 197 patients were evaluable. Clinical characteristics were demonstrated in Table 1. Of the 197 evaluable patients, 71 were deemed to have documented methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Initial and maximal trough concentrations were demonstrated in Table 2. Thirty-three patients (16.8%) met the definition of nephrotoxicity. All cases of nephrotoxicity were reversible, with short-term dialysis required in five patients. Incidence of nephrotoxicity was 7.4% (12/162 patients) in patients consistently with a maximum trough level of $<20\mu$g/mL, 44.4% (8/18

Table 1. Clinical characteristic in patients who received vancomycin for suspected or diagnosed Gram-positive infection

Characteristic	Mean ± deviation or No. of patients (%)
Age (years)	63.7 ± 15.5
Gender: male	121 (61.4%)
Body weight (kg)	55.6 ± 11.0
BMI (kg/m^2)	21.5 ± 3.8
Serum creatinine (mg/dL)	0.64 ± 0.22
Serum albumin (g/dL)	3.00 ± 0.63
Infection (No. of patients)	
pneumonia	42 (21.3%)
bacteremia	37 (18.8%)
skin/soft tissue infections	30 (15.2%)
osteomyelitis or arthritis	23 (11.7%)
urinary tract	4 (2.0%)
others	23 (11.7%)
not determined (empirical therapy)	38 (19.3%)

BMI: body mass index

Table 2. Trough level in patients who received vancomycin

Trough level (μg/mL)	Mean ± deviation or No. of patients (%)
Mean initial trough level (μg/mL)	9.56 ± 5.87
Maximum trough level during therapy	
Mean (μg/mL)	15.14 ± 8.89
No. of patients with C_{min} of ≥ 20 μg/mL (%)	35/197 (17.8%)
20-25 μg/mL	18
≥ 25 μg/mL	17

C_{min}: trough concentration

Table 3. Comparison of trough level, renal function, and dosing and duration of vancomycin therapy between patients demonstrating a trough level of ≥20 μg/mL and those consistently <20 μg/mL

	Patients demonstrating a C_{min} of ≥ 20 μg/mL (n=35)	Patients consistently demonstrating a C_{min} of < 20 μg/mL (n=162)	P-value
Observed C_{min} at the time of demonstrating a C_{min} of ≥ 20 μg/mL, or maximum C_{min} in patients consistently demonstrating a C_{min} of < 20 μg/mL	29.09 ±10.67 μg/mL	12.14 ±4.40 μg/mL	<0.001
Estimated C_{min} at the TDM prior to demonstrating a C_{min} of ≥ 20 μg/mL, or estimated maximum C_{min} in patients consistently demonstrating a C_{min} of < 20 μg/mL	10.82±4.52 μg/mL	11.00 ±5.79 μg/mL	0.719
Duration of vancomycin therapy until demonstrating a C_{min} of ≥ 20 μg/mL, or maximum C_{min} in patients consistently demonstrating a C_{min} of < 20 μg/mL	8.60±6.82 days	7.60±6.23 days	0.501
Daily dose of vancomycin at the TDM prior to demonstrating a C_{min} of ≥ 20 μg/mL, or maximum C_{min} in patients consistently demonstrating a C_{min} of < 20 μg/mL	1.72±0.56 g/day	1.65 ±0.53 g/day	0.096
Serum creatinine at the start of vancomycin (mg/dL)	0.60±0.28 mg/dL	0.65±0.21 mg/dL	0.082
Serum creatinine at the TDM prior to demonstrating a C_{min} of ≥ 20 μg/mL, or maximum C_{min} in patients consistently demonstrating a C_{min} of < 20 μg/mL	0.63 ±0.23 mg/dL	0.66 ±0.33 mg/dL	0.831

C_{min}: trough concentration, TDM: therapeutic drug monitoring

Table 4. Risk factors associated with a trough level of ≥20 μg/mL (univariate analysis)

Risk factors	No. of patients demonstrating a C_{min} ≥ 20 μg/mL (%)				Odds ratio	P-value
	Positive for factor		Negative for factor			
Male	18/121	(14.9)	17/76	(22.4)	0.809	0.180
Body weight < 50 kg	7/64	(10.9)	28/133	(21.1)	0.568	0.123
Age ≥ 65 years	18/110	(16.4)	17/87	(19.5)	0.906	0.562
Heart disease	10/44	(22.7)	25/153	(16.3)	1.361	0.329
Hypertension	20/74	(27.0)	15/123	(12.2)	1.714	0.008
Chronic hepatic disease	2/22	(9.1)	33/175	(18.9)	0.463	0.404
Chronic renal disease	0/1	(-)	35/196	(17.9)	0.000	0.398
Malignant tumor	16/80	(20.0)	19/117	(16.2)	1.157	0.498
Inflammatory bowel disease	3/17	(17.6)	32/180	(17.8)	0.992	0.750
Diabetes mellitus	10/53	(18.9)	25/144	(17.4)	1.076	0.806
Serum creatinine ≥ 1.0 mg/dL at the start of vancomycin	2/12	(16.7)	33/185	(17.8)	0.926	0.774
Serum albumin < 2.5 g/dL	6/36	(16.7)	29/161	(18.0)	0.926	0.960
Diuretic drug	19/56	(33.9)	16/141	(11.3)	2.377	0.001
NSAIDs	8/43	(18.6)	27/154	(17.5)	1.058	0.950
Anticancer therapy	1/17	(5.9)	34/180	(18.9)	0.289	0.313
Steroid use	8/39	(20.5)	27/158	(17.1)	1.194	0.789
Surgery	19/125	(15.2)	16/72	(22.2)	0.830	0.214
Enteral nutrition	12/61	(19.7)	23/136	(16.9)	1.134	0.639
Total parenteral nutrition	12/47	(25.5)	23/150	(15.3)	1.587	0.110
Duration of vancomycin therapy (> 75th percentile,13 days)	11/52	(21.2)	24/145	(16.6)	1.242	0.456
Deterioration of renal function during vancomycin therapy	21/33	(63.6)	14/164	(8.5)	8.100	<0.001

NSAIDs: non-steroidal anti-inflammatory drugs, C_{min}: trough concentration

Table 5. Risk factors associated with deterioration of renal function during vancomycin therapy (univariate analysis)

Risk factors	No. of patients with deterioration of renal function during vancomycin therapy (%)				Odds ratio	P-value
	Positive for factor		Negative for factor			
Male	18/121	(14.9)	15/76	(19.7)	0.868	0.374
Body weight < 50 kg	10/64	(15.6)	23/133	(17.3)	0.920	0.769
Age ≥ 65 years	19/110	(17.3)	14/87	(16.1)	1.038	0.826
Heart disease	8/44	(18.2)	25/153	(16.3)	1.104	0.953
Hypertension	16/74	(21.6)	17/123	(13.8)	1.371	0.156
Chronic hepatic disease	3/22	(13.6)	30/175	(17.1)	0.785	0.911
Chronic renal disease	0/1	(-)	33/196	(16.8)	0.000	0.372
Malignant tumor	15/80	(18.8)	18/117	(15.4)	1.147	0.534
Inflammatory bowel disease	2/17	(11.8)	31/180	(17.2)	0.663	0.813
Diabetes mellitus	8/53	(15.1)	25/144	(17.4)	0.884	0.871
Serum creatinine ≥ 1.0 mg/dL at the start of vancomycin	1/12	(8.3)	32/185	(17.3)	0.452	0.684
Serum albumin < 2.5 g/dL	9/36	(25.0)	24/161	(14.9)	1.657	0.223
Diuretic drug	16/56	(28.6)	17/141	(12.1)	1.988	0.005
NSAIDs	10/43	(23.2)	23/154	(14.9)	1.506	0.196
Anticancer therapy	1/17	(5.9)	32/180	(17.8)	0.311	0.360
Steroid use	7/39	(17.9)	26/158	(16.5)	1.087	0.987
Surgery	17/125	(13.6)	16/72	(22.2)	0.782	0.119
Enteral nutrition	14/61	(23.0)	19/136	(14.0)	1.480	0.119
Total parenteral nutrition	15/47	(31.9)	18/150	(12.0)	2.330	0.001
Duration of vancomycin therapy (> 75th percentile,13 days)	8/52	(15.4)	25/145	(17.2)	0.904	0.758
C_{min} ≥ 20 μg/mL	21/35	(60.0)	12/162	(7.4)	7.455	<0.001

NSAIDs: non-steroidal anti-inflammatory drugs, C_{min}: trough concentration

patients) in those demonstrating a maximum trough level of 20–25 μg/mL, and 76.5% (13/17 patients) in those with ≥25 μg/mL.

C_{min}, renal function and vancomycin therapy in patients demonstrating a C_{min} of ≥20 μg/mL and those consistently with <20 μg/mL (Table 3). There was no significant difference in serum creatinine at the start of vancomycin therapy between these two groups. Creatinine at the time of TDM prior to the TDM demonstrating a C_{min} of ≥20 μg/mL was 0.63±0.23 mg/dL. On average, a C_{min} of ≥20 μg/mL was first observed after 3.2±2.5 performances of TDM. Twenty-five of 35 patients demonstrated a C_{min} of ≥20 μg/mL at multiple TDM performances. The average C_{min} measured at the TDM prior to the one demonstrating the maximum C_{min} ≥20 μg/mL was 13.8±4.6 μg/mL, and a dose increase was performed in 2 of the 25 patients according to the C_{min} of the TDM prior to the TDM demonstrating the maximum C_{min} ≥20 μg/mL. The vancomycin daily dosage was 1.72±0.56 g, and the predicted C_{min} value was 10.82±4.52 μg/mL at the TDM prior to demonstrating a C_{min} of ≥20 μg/mL. The actual C_{min} was 29.09±10.67 μg/mL.

Univariate analysis of risk factors associated with a C_{min} of ≥20 μg/mL and those associated with deterioration of renal function during vancomycin therapy are shown in Tables 4 and 5, respectively. Diuretic drug use, deterioration of renal function during vancomycin therapy, total parenteral nutrition and male were selected for multivariate analysis of the risk factors for a C_{min} of ≥20 μg/mL, and NSAIDs, management of total parenteral nutrition, C_{min} of ≥20 μg/mL, surgery, enteral nutrition and diuretic drug use were selected for multivariate analysis of the risk factors for deterioration of renal function.

In multiple logistic regression analysis, diuretics use (adjusted odds ratio (OR): 3.21, 95% confidence interval (CI): 1.30–7.91) and deterioration of renal function during vancomycin therapy (adjusted OR: 16.39, 95% CI: 6.24–43.07) were found to be significantly associated with a maximum C_{min} of ≥20 μg/mL (Table 6). In addition, a C_{min} of ≥20 μg/mL (adjusted OR: 17.95,

Table 6. Independent risk factors associated with a trough level of ≥20 μg/mL (multivariate analysis)

Risk factors	Adjusted odds ratio (95% confidence interval)	P-value
Diuretic drug	3.211 (1.304-7.906)	0.011
Deterioration of renal function during vancomycin therapy	16.394 (6.240-43.068)	<0.001
Total parenteral nutrition	1.018 (0.368-2.813)	0.973
Male	0.633 (0.256-1.564)	0.322

Table 7. Independent risk factors associated with deterioration of renal function during vancomycin therapy (multivariate analysis)

Risk factors	Adjusted odds ratio (95% confidence interval)	P-value
NSAIDs	3.222 (1.085-9.568)	0.035
Total parenteral nutrition	3.642 (1.327-9.995)	0.012
C_{min} ≥ 20 μg/mL	17.953 (6.668-48.335)	＜0.001
Surgery	0.592 (0.229-1.527)	0.278
Enteral nutrition	1.747 (0.640-4.765)	0.276
Diuretic drug	1.781 (0.668-4.749)	0.249

NSAIDs: non-steroidal anti-inflammatory drugs, C_{min}: trough concentration

95% CI: 6.67–48.33), NSAIDs (adjusted OR: 3.22, 95% CI: 1.09–9.57), and total parenteral nutrition (TPN) (adjusted OR: 3.64, 95% CI: 1.33–10.00) were found to be independent risk factors associated with the occurrence of nephrotoxicity (Table 7).

4. Discussion

The associations between vancomycin exposure and nephrotoxicity were largely attributed to baseline differences in disease severity and concomitant nephrotoxin. In patients with elevated baseline risk of nephrotoxicity independent of vancomycin exposure, the risk is amplified substantially by the addition of vancomycin therapy. Induction of mild renal dysfunction prior to elevation of vancomycin concentration, and the resulting high serum concentration of vancomycin due to decrease of renal clearance may further cause deterioration of renal function (Lodise *et al.*[5]).

However, in the present study, baseline serum creatinine and serum creatinine prior to the TDM that demonstrated a high trough level did not differ between patients who experienced a C_{min} of ≥20 μg/mL and those consistently with a C_{min} of ＜20 μg/mL. The daily dose of vancomycin at the time of TDM prior to the TDM demonstrating a C_{min} of ≥20 μg/mL was 1.72 g, and there was no significant difference compared with that at the time of the TDM demonstrating the maximum C_{min} in patients with a C_{min} consistently ＜20 μg/mL. Duration of vancomycin therapy was 8.6 days in patients with C_{min} of ≥20 μg/mL and 7.6 days in patients with C_{min} of ＜20 μg/mL. Hence, neither overdosing, longer duration of vancomycin therapy, nor low renal

function should have caused a high C_{min} in patients with a C_{min} of ≥20 μg/mL. Similarly, Hidayat *et al.*[7] demonstrated that duration of vancomycin therapy and baseline serum creatinine values did not differ between those who attained high (15–20 μg/mL) vs low trough levels (<15 μg/mL).

Anticipation of high trough level or deterioration of renal function during vancomycin therapy is important to prevent the occurrence of adverse events due to vancomycin. As mentioned above, deterioration of renal function and a C_{min} of ≥20 μg/mL occurred simultaneously. Excluding these, independent risk factors for C_{min} of ≥20 μg/mL was diuretic drug use, and independent risk factors for deterioration of renal function during vancomycin therapy were NSAIDs and TPN. Risk factors associated with nephrotoxicity, other than vancomycin exposure, have been demonstrated by several authors[8]. Elyasi *et al.*[9] reported that there are a number of different risk factors which could accelerate or potentiate the occurrence of vancomycin-induced nephrotoxicity, with the most documented risk factors being high trough vancomycin level (especially ≥20 μg/mL) or dose (>4 g/day), concomitant treatment with nephrotoxic agents, prolonged therapy (even more than 7 days), and admittance to an intensive care unit (especially prolonged stay).

Concomitant nephrotoxic agents can increase the incidence of vancomycin-associated nephrotoxicity by up to 35%[10]. Most patients with drug-induced nephrotoxicity received amphotericin B, tobramycin or tacrolimus with vancomycin[7,11,12]. Concomitant vasopressor and intravenous contrast media agents were also reported as risk factors of vancomycin-induced nephrotoxicity[5,13]. Hidayat *et al.*[7] also reported that concomitant nephrotoxic agents remain the most significant predictor of the development of nephrotoxicity by multivariate analysis. Possible nephrotoxic agents were radiopaque dye, aminoglycosides, amphotericin B, cyclosporine A, tacrolimus, angiotensin-converting enzyme inhibitors and angiotensin receptor blocking agents and NSAIDs and COX-2 inhibitors are known to raise serum creatinine. To prevent the impact of these apparent risk factors for nephrotoxicity, we excluded patients with hemodialysis, vasopressor support during therapy, concomitant administration of aminoglycosides or amphotericin B, and use of contrast media during therapy. However, due to the frequent use, we included patients who were concomitantly administered NSAIDs.

Malnourished patients may represent a subgroup of critically ill patients for whom the clinician may consider initiating TPN. TPN is indicated for patients in whom enteral nutrition or oral intake are not feasible. The administration of oral or enteral nutrition in patients with sepsis has potential physiologic advantages related to the maintenance of gut integrity and prevention of intestinal permeability, dampening of the inflammatory response, and modulation of metabolic responses[14]. These might cause deterioration of renal function in patients with TPN during vancomycin therapy.

In our study, diuretic drug use were selected for multivariate analysis of the risk factors for a C_{min} of ≥20 μg/mL. McKamy *et al.*[15] reported that nephrotoxicity occurred in patients with targeted troughs of ≥15 μg/mL, in the intensive care unit, and receiving furosemide. Furosemide is

not a direct nephrotoxin, but its use may cause dehydration, in which the addition of vancomycin may further increase developing nephrotoxicity. Jeffres *et al.*[6] reported that a loop diuretic was present in 63% of adult patients who had nephrotoxicity during vancomycin therapy. Cappelletty *et al.*[16] reported that furosemide use, hypertension, and vancomycin C_{min} ≥16.2 μg/mL were each associated with nephrotoxicity during vancomycin therapy. Ingram *et al.*[17] reported that use of aminoglycosides or loop diuretics, and vancomycin C_{min} of ≥28 μg/mL were independent risk factors. From these, we hypothesized that concomitant use of nephrotoxic agents such as NSAIDs and dehydration caused by a diuretic drug induces mild renal dysfunction prior to elevation of vancomycin concentration, and the high serum concentration of vancomycin occurring as a result of decreased renal clearance causes further deterioration of renal function.

Our analyses have some limitations. First, degree of severity of infection was not assessed. Hemodynamic instability might cause renal dysfunction during vancomycin therapy, and enlargement of volume of distribution caused by extravasation have an impact on the serum vancomycin concentration[18]. Second, recent guidelines recommend C_{min} of 15–20 μg/mL in serious infection[19]. However initial C_{min} remaied 9.56±5.87 μg/mL in our study. Third, although we investigated the risk factors for deterioration of renal function and a C_{min} of ≥20 μg/mL individually, it is difficult to determine which occurred first and caused the other.

In conclusion, considerably high incidence of nephrotoxicity and high C_{min} was observed, even in patients receiving treatment with adequate dosing of vancomycin, and in those without lower renal function at baseline. NSAIDs, diuretic drug use, and TPN were independent risk factors for high C_{min} or nephrotoxicity. Limited use of these drugs is preferable to prevent adverse events during vancomycin therapy.

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Conflict of interest

Yoshio Takesue has received support grant from Shionogi & Co., Ltd. and Meiji Seika Pharma Co., Ltd. and payment for lectures from Pfizer Japan Inc., MSD K.K., Astellas Pharma Inc., Dainippon Sumitomo Pharma, Meiji Seika Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co., Asahi Kasei Pharma Co., Ltd. and the Japanese Association for Infectious Diseases. All other authors: none to declare.

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