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Evaluation of risk factors for nephrotoxicity associated with high-dose vancomycin in Japanese patients

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Introduction: Considering the physique of the Japanese population, the standard daily vancomycin dose of 2 g/day and doses ≥ 3 g/day are high in terms of dose per body weight. Studies have reported that administering high-dose vancomycin to achieve a high target trough concentration has been associated with nephrotoxicity. The risk of high-dose vancomycin-associated nephrotoxicity is believed to be exceptionally high for Japanese patients because of their relatively low body weights, but data on the population is lacking. In this retrospective study, we aimed to evaluate risk factors associated with nephrotoxicity in Japanese patients treated with vancomycin. *Methods:* We examined the medical records of 107 Japanese patients who received vancomycin (3 to 4 g/day). They were divided into two groups based on the presence or absence of nephrotoxicity, and their demographics and clinical characteristics were compared. *Results*: The incidence of nephrotoxicity in patients receiving high-dose vancomycin was 13%. Age (≥ 60 years) and concurrent use of piperacillin/tazobactam were independent risk factors for vancomycin-associated nephrotoxicity (P = 0.027 and 0.017, respectively). *Conclusions:* We conclude that the nephrotoxicity risk of high-dose vancomycin in Japanese patients is not excessively high when administered within the confines of a therapeutic drug-monitoring program. However, special care must be taken with patients who are older or on concurrent piperacillin/tazobactam therapy.

1. Introduction

Vancomycin (VCM) is a glycopeptide antibiotic used for the treatment of gram-positive infections including methicillin-resistant *Staphylococcus aureus* (MRSA). The ratio of the area under the curve over 24 h (AUC₂₄) to the minimum inhibitory concentration (MIC) is the pharmacokinetic/pharmacodynamic parameter of VCM and AUC₂₄/MIC ≥ 400 has been associated with improved clinical response and microbiologic eradication (Liu et al. 2011). To achieve AUC/MIC ≥ 400 for in patients with isolates with MIC ≤ 1, high target trough concentrations of 15 to 20 mg/L VCM are needed (Rybak et al. 2009). VCM is a nephrotoxic drug and dose escalation may increase the risk of developing nephrotoxicity. Lodise et al. (2008) reported that the incidence of nephrotoxicity was higher in patients who received ≥ 4 g VCM daily to attain high target trough concentrations than in those who received < 4 g daily. Furthermore, Lodise et al. (2009) showed that the VCM trough value was associated with nephrotoxicity. Although high blood trough levels may be associated with nephrotoxicity (Bosso et al. 2011; Cano et al. 2012; Horey et al. 2012; Chuma et al. 2018; Filippone et al. 2017), it is difficult to evaluate whether renal dysfunction occurs because of increased blood levels of VCM (Lodise et al. 2008, 2009; Filippone et al. 2017). Thus, caution is required when planning high-dose treatment to achieve high target trough concentrations of VCM.

In a survey of the Japan Ministry of Health, Labor and Welfare (2017), mean body weight in Japanese adult male and female individuals was reported to be 66.9 kg and 52.3 kg, respectively, indicating that the Japanese have lower body weights than Westerners. According to Japanese practice guidelines, the standard dose of VCM is 15–20 mg/kg every 12 h for patients with normal renal function (Matsumoto et al. 2013). Considering body weight, the standard daily dose of VCM for the Japanese population is 2 g/day and a 3 to 4 g daily dose is high in terms of dose per body weight. However, blood concentrations of VCM in some patients (e.g. young patients with a higher total body clearance of VCM than that of older patients or those with severe illness with increased volume of distribution or renal clearance (Guay et al. 1993; Roberts et al. 2014; Álvarez et al. 2017) who begin treatment at 2 g/day may not reach the target levels of 15–20 mg/L. Consequently, clinicians increase VCM to the higher dose based on therapeutic drug monitoring (TDM). High doses of VCM may affect renal function, but the relationship between a 3 or 4 g daily dose of VCM and nephrotoxicity has not been well documented in Japanese patients. In addition, little information is available on the risk factors of VCM-associated nephrotoxicity in the population. Thus, the objective of the present study was to investigate the occurrence of nephrotoxicity and the risk factors in patients receiving a 3 or 4 g daily dose of VCM based on TDM.

2. Investigations and results

2.1. Ethics approval

This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by the Institutional Review Board of the Faculty of Medical Sciences, University of Fukui. As this is a retrospective study, informed consent was waived by the review board.

2.2. Study design, setting, and patients

A retrospective cohort study was performed with patients who received VCM for a suspected or proven gram-positive infection between June 1, 2006, and July 31, 2017, at University of Fukui Hospital, a 600-bed secondary and tertiary care university hospital in Fukui, Japan. This protocol was conducted in accordance with

the Declaration of Helsinki. During the study survey period, 1979 patients received intravenous VCM. Patients who initially received intravenous VCM at 2 g/day or less, and then had the dose increased to 3 or 4 g/day based on TDM were included. Patients were excluded if they were aged < 18 years, had been administered 3 or 4 g/day for < 3 days, had received VCM within 1 month, or had no blood concentration data during treatment at 3 or 4 g/day.

2.3. Data collection

The following information was collected from patients' medical records: age, sex, actual body weight, height, serum creatinine (SCr), cancer chemotherapy (within 30 days before starting VCM), surgery (within 30 days before starting VCM), neutropenia (< 500/mm^3), intensive care unit (ICU) stay at the initiation of VCM, MRSA bacteremia, underlying disease, focus of infection, and concomitant use of other drugs. Twenty-four patients, who were not tested for neutrophils, were determined not to have neutropenia. Treatment data including the daily dose, blood concentration, and duration of VCM were collected. The duration from VCM start to occurrence of nephrotoxicity was documented. The illness severity at the start of VCM was assessed using the confusion, urea, respiratory rate, blood pressure plus age ≥ 65 years (CURB-65) pneumonia severity score. The score has been reported to be useful for evaluating severity of patients with conditions other than pneumonia (Howell et al. 2007; Armiñanzas et al. 2013; Marwick et al. 2014). Because a score of < 2 is considered a low risk of mortality, we set the score threshold to 2.

2.4. Definition of creatinine clearance (Ccr)

Creatinine clearance (Ccr) was calculated using the Cockcroft-Gault equation (Cockcroft and Gault 1976) and a value of 0.6 mg/dL was substituted for the SCr when it was < 0.6 mg/dL (Miyabe et al. 2011). In addition, the Ccr was calculated using ideal body weight (obtained by multiplying the height squared by 22) when the body mass index (BMI) exceeded 22. Because three patients without nephrotoxicity had no height data, the Ccr was calculated using actual body weight.

2.5. Definition of nephrotoxicity

Nephrotoxicity was defined as an absolute increase of > 0.5 mg/dL (or a ≥ 50% increase) in SCr over baseline values in consecutively obtained daily values, as described previously (Rybak et al. 2009).

2.6. Statistical analysis

Continuous variables of the two groups were compared using the Student's *t*- or Welch's *t*-test after performing Levene's test for homoscedasticity. Fisher's exact test was used to compare categorical variables of the two groups. A logistic regression analysis was used to control for confounding variables of independent risk factors for nephrotoxicity. Variables with P < 0.2 in the univariate analysis were considered for inclusion in the multivariate analysis, which did not use blood concentrations obtained following a dose of 3 or 4 g/day because the day nephrotoxicity occurred was close to the TDM day at this dose. Additionally, there was a high correlation between Ccr and age, so these data were not included in the multivariate analysis simultaneously. *P*-values < 0.05 were considered significant for the two-tailed tests. All calculations were performed using the Statistical Package for the Social Sciences (SPSS) software program version 17.0 for Windows (SPSS Japan, Inc., Tokyo, Japan).

2.7. Results

During the study period, 1979 patients receiving VCM were identified including 107 who met the inclusion criteria (Fig.), including 93 and 14 patients whose dose was increased to 3 and 4 g daily, respectively. Nephrotoxicity was observed in 13 patients under a 3 g daily dose and one under 4 g daily. The incidence of nephrotoxicity in all patients was 13%. Patient demographics and clinical characteristics are presented in Table 1. The underlying disease, focus of infection, and disease severity assessed using CURB-65 were similar in both groups.

Patients who developed nephrotoxicity were significantly older (67.1±8.9 vs. 56.4±13.9 years old, P = 0.006) and had a lower baseline Ccr (76.8±18.5 vs. 94.2±21.7 mL/min, P = 0.042) than patients who did not develop nephrotoxicity. Blood concentrations of VCM after doses of 3 or 4 g/day were significantly higher in the nephrotoxicity group than in the non-nephrotoxicity group (24.0±11.0 vs. 15.4±4.4 mg/L, P = 0.012). A significant difference in co-administration of piperacillin/tazobactam (PIPC/TAZ) (28.6% versus 5.4%, P = 0.016) was found between patients with and without nephrotoxicity.

The following variables (P < 0.2 in the univariate analysis) considered for the multivariate analysis were included: age ≥ 60 years, BMI ≤ 22, surgery (within 30 days before starting VCM), diabetes, concomitant use of liposomal-amphotericin B, co-administration of PIPC/TAZ, and daily dose corrected to actual body weight. In the multivariate analysis, age ≥ 60 (odds ratio [OR], 6.04; 95% confidence interval [CI], 1.23–29.7; P = 0.027), and co-administration of PIPC/TAZ (OR, 6.72; 95% CI, 1.40–32.4; P = 0.017), were

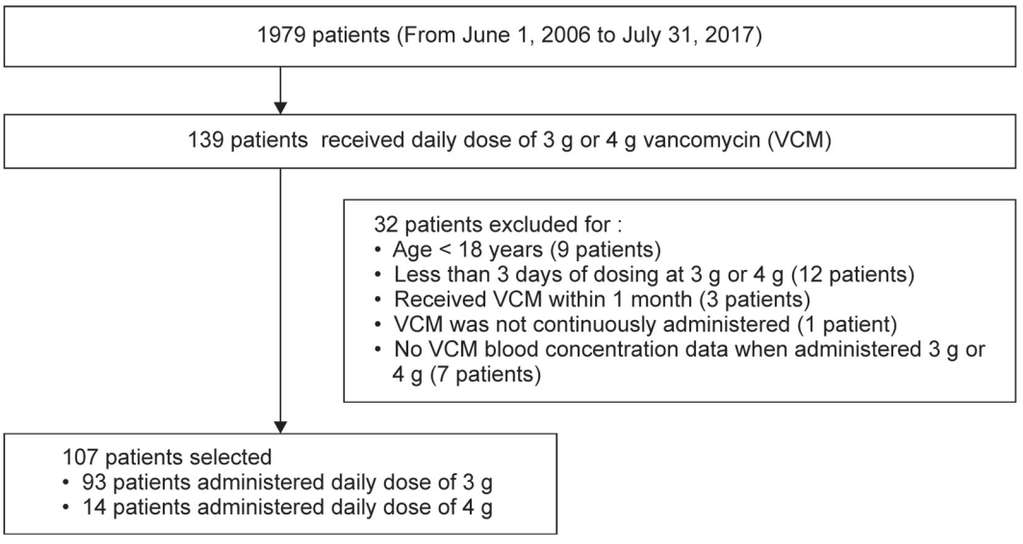

Fig.: Patient selection diagram

Table 1: Patient demographic and clinical characteristics

Characteristic	Patients with nephrotoxicity (n = 14)	Patients without nephrotoxicity (n = 93)	P- value
Age, years	67.1 ± 8.9	56.4 ± 13.9	0.006
Age ≥ 60 years	12 (85.7)	47 (50.5)	0.019
Male	9 (64.3)	65 (69.9)	0.758
Actual body weight, kg	64.8 ± 11.6	61.5 ± 12.2	0.355
Height*, m	1.65 ± 0.08	1.62 ± 0.07	0.135
Body mass index (BMI), kg/m^2	24.5 ± 5.1	22.6 ± 4.1	0.071
BMI > 30	1 (7)	4 (4)	0.511
25 < BMI ≤ 30	3 (21)	15 (16)	0.701
22 < BMI ≤ 25	7 (50)	30 (32)	0.233
BMI ≤ 22	3 (21)	41 (44)	0.145
Baseline SCr, mg/dL	0.63 ± 0.19	0.59 ± 0.17	0.484
SCr ≥ 0.6	6 (43)	47 (51)	0.776
0.5 ≤ SCr < 0.6	5 (36)	19 (20)	0.299
0.4 ≤ SCr < 0.5	2 (14)	14 (15)	1.000
SCr < 0.4	1 (7)	13 (14)	0.388
Baseline Ccr, mL/min	76.8 ± 18.5	94.2 ± 21.7	0.042
Cancer chemotherapy	4 (28.6)	19 (20.4)	0.494
Surgery	6 (42.9)	59 (63.4)	0.155
Neutropenia**	15 (16.1)	1 (7.1)	0.689
MRSA bacteremia	0(0)	6(6.5)	1.000
ICU stay at VCM initiation	0 (0)	3 (3.2)	1.000
CURB-65 score ≥ 2	5 (35.7)	24 (25.8)	0.521
Underlying disease			
Diabetes mellitus	5 (35.7)	17 (18.3)	0.158
Heart failure	0 (0)	4 (4.3)	1.000
Respiratory disease	0 (0)	3 (3.2)	1.000
Hepatic dysfunction	0 (0)	5 (5.4)	1.000
Decubitus ulcers	0 (0)	2 (2.2)	1.000
HIV infection	0 (0)	1 (1.1)	1.000
Focus of infection			
Intra-abdominal	1 (7.1)	9 (9.7)	1.000
Hepatobiliary	1 (7.1)	1 (1.1)	0.246
Urinary tract	0 (0)	2 (2.2)	1.000
Skin and soft tissue	2 (14.3)	10 (10.8)	0.656
Catheter related	1 (7.1)	12 (12.9)	1.000
Respiratory tract	3 (21.4)	12 (12.9)	0.411
Febrile neutropenia	0 (0)	11 (11.8)	0.352
Central nervous system	4 (28.6)	17 (18.3)	0.468
Infective endocarditis	0 (0)	5 (5.4)	1.000
Bone joint infection	0 (0)	3 (3.2)	1.000
Unknown	2 (14.3)	11 (11.8)	0.678
Concomitant drug use			
Vasopressor	0 (0)	7 (7.5)	0.591
Liposomal amphotericin B	2 (14.3)	4 (4.3)	0.176
Aminoglycoside	0 (0)	4 (4.3)	1.000
Cyclosporine or tacrolimus	0 (0)	1 (1.1)	1.000
Contrast media agents	8 (57.1)	41 (44.1)	0.400
Loop diuretics	2 (14.3)	11 (11.8)	0.678
PIPC/TAZ	4 (28.6)	5 (5.4)	0.016
Imipenem/cilastatin	1 (7.1)	5 (5.4)	0.578
NSAIDs	10 (71.4)	60 (64.5)	0.767

Characteristic	Patients with nephrotoxicity (n = 14)	Patients without nephrotoxicity (n = 93)	P- value
Initial VCM dose, g/day	1.9 ± 0.3	1.9 ± 0.3	0.801
Maintenance dose			
Daily dose, g/day	3.1 ± 0.3	3.1 ± 0.3	0.484
Daily dose corrected for actual body weight, mg/kg/day	48.6 ± 8.0	52.9 ± 11.2	0.165
First TDM to start VCM			
Blood concentration, mg/L	7.0 ± 2.3	7.1 ± 2.3	0.850
Number of days from start of VCM to TDM, days	3.1 ± 1.0	3.1 ± 1.5	0.912
TDM after increasing the amount of VCM to 3 or 4 g/day			
Blood concentration, mg/L	24.0 ± 11.0	15.4 ± 4.4	0.012
Number of days from start of VCM to TDM, days	7.6 ± 2.4	7.8 ± 3.3	0.878
Number of days from VCM start when nephrotoxicity occurred, days	-	11.9 ± 5.7	-
Total duration of VCM therapy, days	15.4 ± 9.4	15.1 ± 7.8	0.879

Data are means ± standard deviation or n (%)
HIV, human immunodeficiency virus; BMI, body mass index; Ccr, creatinine clearance; ICU, intensive care unit; MRSA, methicillin-resistant staphylococcus aureus; SCr, serum creatinine; TDM, therapeutic drug monitoring; VCM, vancomycin; PIPC/TAZ, piperacillin/tazobactam; NSAIDs, non-steroidal anti-inflammatory drugs; *Three patients without nephrotoxicity had no height data; **Twenty-four patients not tested for neutrophils were determined not to have decreased levels.

Table 2: Logistic regression model for the occurrence of nephrotoxicity

Parameter	Adjusted Odds ratio (95% CI)	P-value
Age ≥ 60 years	6.04 (1.23–29.7)	0.027
PIPC/TAZ	6.72 (1.40–32.4)	0.017

Logistic regression was performed using age ≥ 60 years, body mass index (BMI) ≤ 22, liposomal amphotericin B (L-AMB), tazobactam/piperacillin (TAZ/PIPC), surgery (within 30 days before starting VCM), diabetes, and daily dose corrected to actual body weight.

shown to be independent risk factors for nephrotoxicity associated with VCM (Table 2). Using Ccr instead of age in the analysis identified co-administration of PIPC/TAZ as an independent risk factor for nephrotoxicity, although Ccr was not.

3. Discussion

In the present study, we found that the prevalence of nephrotoxicity in patients administered VCM at a 3 or 4 g daily dose was 13% and age ≥ 60 years and co-administration of PIPC/TAZ were risk factors for nephrotoxicity associated with VCM. Lodise et al. (2008) had reported the occurrence of nephrotoxicity in 34.6% of patients who received ≥ 4 g VCM daily to rapidly reach a high target trough concentration. They also evaluated the relationship between the pharmacodynamic index, AUC or trough value, and nephrotoxicity in the same population from a previous study (Lodise et al. 2009). The blood concentration within 96 hours of initiation of VCM, but not the AUC, was independently associated with nephrotoxicity in the multivariate analysis.

Two studies by Lodise et al. (2008, 2009) indicated that an initial high dosing schedule for an initial high target trough concentration might be associated with nephrotoxicity. The mean actual weight of patients administered ≥ 4 g VCM daily was 86.9 kg (Lodise et al 2008), which greatly differs from that of Japanese individuals. The differences in physique between patients in the study of Lodise et al. (2008) and Japanese populations (Ministry of Health, Labor and Welfare 2020) allow the hypothesis that a < 4 g daily dose of VCM may increase the risk of nephrotoxicity in Japanese patients who have a lower average body weight. However, in the present study, nephrotoxicity was observed in 13% of patients who received a 3 or 4 g daily dose, which was similar to the percentage incidence (0-17%) previously reported for VCM monotherapy (Rybak et al. 2009). The results of the present study suggest that increasing the dose of VCM to 3 or 4 g based on TDM is likely to be a safe and practical method of enhancing the therapeutic effects in Japanese patients.

A relationship was previously reported between advanced age and nephrotoxicity, and Pauly et al. (1990) reported age as an independent risk factor for nephrotoxicity in patients administered VCM with an aminoglycoside in a logistic regression analysis. However, there are some conflicting results, such as that by Vance-Bryan et al. (1994), which reported a significant increase in the occurrence of nephrotoxicity with age ≥ 60 in patients, but age was not identified as a significant risk factor for nephrotoxicity in the multivariate models. Additionally, Carreno et al. (2013) reported that no differences were identified in the risk of acute kidney injury between younger and older adults.

The present study found that baseline Ccr in patients with nephrotoxicity was significantly lower in the univariate analysis than it was in those without nephrotoxicity. However, Ccr was not identified as a risk factor for nephrotoxicity in the multivariate analysis, although a high correlation was observed between age and Ccr. The Ccr was evaluated using the estimated Cockcroft-Gault equation and the prediction accuracy improved when the rounded SCr was used in patients with low SCr (Miyabe et al. 2011). However, several studies have investigated the phenomenon of underestimating Ccr by using rounded SCr in patients with low SCr (Smythe et al. 1994; Winter et al. 2012), and accurate Ccr calculation is difficult for all patients. In our study, a 3 or 4 g daily dose of VCM might have been excessive in some patients with decreased renal function who were of advanced age.

Thomson et al. (2009) evaluated new VCM dosage guidelines targeting VCM trough concentrations of 10 to 15 mg/L using a population pharmacokinetic model. In this study, a 1500 mg dose of VCM administered every 12 h was required to reach the target trough concentration in populations with Ccr > 110 mL/min, indicating the suitability of a 3 or 4 g daily dose in patients with renal function above 110 mL/min of Ccr. To the best of our knowledge, no prior study has investigated the association between advanced age or renal function and VCM-induced nephrotoxicity, as a risk factor.

Recently, it was reported that concomitant use of VCM and PIPC/TAZ is associated with acute kidney injury (Giuliano et al. 2016; Hammond et al. 2017); however, the mechanism behind this neph-

rotoxicity is not known. These findings are consistent with our results, so in patients receiving VCM who also require antimicrobial therapy against gram-negative pathogens, alternative regimens to PIPC/TAZ may need to be selected.

A few limitations to our study are worth mentioning. First, because the number of samples was small in the short-term survey, the survey period was long. During the study period, the therapeutic strategy of using VCM for gram-positive infections including MRSA did not change much, except that the target trough concentration of VCM for deep-seated infections shifted from 15 to 20 mg/L following MIC creep for MRSA. Second, although the survey was long-term, the number of samples was small, which may have affected the result of the multivariate analysis. In the analysis, age ≥ 60 years was shown to be an independent risk factor for nephrotoxicity associated with VCM, but the result was not consistent with those of previous studies (Vance-Bryan et al. 1994; Carreno et al. 2013). These results must be interpreted cautiously as there may be other factors associated with nephrotoxicity.

Third, this study had no control group and, therefore, the association between doses of up to 3 or 4 g daily on the occurrence of nephrotoxicity could not be assessed. However, the incidence of nephrotoxicity in the present study was within the range reported in a previous study that reported administration of VCM alone (Rybak et al. 2009). Fourth, the present study evaluated the risk factors for VCM-induced nephrotoxicity in a specific group. Risk factors for nephrotoxicity have been reported numerous times (Filippone et al 2017; Elyasi et al. 2012; Carreno et al. 2014), and these data are in accordance with those of the present study. Finally, this study did not assess the causal relationship between blood concentrations of VCM and nephrotoxicity. Nephrotoxicity has been associated with high VCM trough concentration, especially ≥ 15 mg/L (Bosso et al. 2011; Cano et al. 2012; Horey et al. 2012; Filippone et al. 2017).

In the present study, blood concentrations following a 3 or 4 g daily dose in patients with nephrotoxicity were higher than those of patients without nephrotoxicity. However, it would be difficult to identify a causal relationship between VCM blood concentration and nephrotoxicity because a decrease in renal function induced by any cause may increase blood concentrations (Lodise et al. 2008; 2009; Filippone et al. 2017). Indeed, we observed that TDM after a VCM dose increases to 3 or 4 g daily and the onset of nephrotoxicity occurred on the same day in 6 of 11 patients with nephrotoxicity whose blood concentration was ≥ 15 mg/L (data not shown).

In conclusion, setting the VCM dosage to 3 or 4 g daily based on TDM is a feasible therapy plan in Japanese patients. Furthermore, older patients should be evaluated to determine whether a high dose of 3 or 4 g daily is appropriate, including evaluation of renal function. Caution must also be exercised with the co-administration of PIPC/TAZ in patients on a 3 or 4 g daily dose. Further investigations are needed to elucidate the association between VCM blood concentrations and nephrotoxicity in patients who received high doses of VCM.

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