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Correlation of Pharmacokinetic Parameters with Serum Vancomycin Concentration in Elderly Patients with Malignancies

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Vancomycin (VCM) is a glycopeptide antibiotic that is generally used to treat methicillin-resistant *Staphylococcus aureus* (MRSA). Recently, it has been reported that VCM clearance (CL) is significantly higher in elderly patients and infants and children with malignancies, compared with those without malignancies. We have treated many patients with a variety of malignant tumors in whom serum VCM concentrations were found to be moderately lower during therapeutic drug monitoring (TDM). The aim of this study was to determine whether the presence of malignant tumors influences trough concentrations of VCM and VCM pharmacokinetics in elderly patients during treatment for MRSA infection. Comparison of the clinical characteristics and VCM pharmacokinetic parameters between patients with and without malignancies was undertaken in 49 elderly Japanese patients infected with MRSA. The mean trough concentration of VCM in patients with malignancies was significantly lower than that in patients without malignancies. Our results showed significantly higher values of VCM CL and volume of distribution and a shorter elimination half-life in patients with malignancies. Univariate logistic regression analysis of the pharmacokinetic parameters indicated that VCM CL contributed as a significant factor independent of the relation to malignant tumor. In conclusion, it is suggested that the therapeutic effects and side effects of VCM should be actively monitored using TDM, because concentrations may decrease when CL increases in VCM therapy for elderly patients with malignant tumors.

Key words——vancomycin pharmacokinetics; malignancy; elderly patient; methicillin-resistant *Staphylococcus aureus*; therapeutic drug monitoring

INTRODUCTION

Vancomycin (VCM) is a glycopeptide antibiotic that is generally used for the treatment of gram-positive infections, particularly methicillin-resistant *Staphylococcus aureus* (MRSA).[1–4] VCM is mainly eliminated from the body *via* the kidney.[5] Therefore altered renal function is very important in modifying VCM pharmacokinetics.[6]

Therapeutic drug monitoring (TDM) is necessary to increase the efficacy of VCM in the treatment of MRSA infection. We generally plan VCM administration using the trough concentration as one measure. We have treated many patients with a variety of malignant tumors in whom the serum VCM concentrations were found to be moderately lower based on TDM data obtained in our hospital, despite the fact that this drug was administered in accordance with the package insert instructions or the dose was increased.

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The presence of malignancy in infants and children increases VCM clearance (CL), resulting in larger dosage requirements.[7,8] Similarly, the presence of hematologic malignancies in adults also increases CL rate and shortens the half-life ($t_{1/2}$) of the drug, compared with those in adults without malignancies.[9] Although similar reports have been published,[10,11] the mechanism of the pharmacophysiologic changes in VCM pharmacokinetics remains unclear. However, to date there have been no reports focusing on elderly patients with MRSA infection. The aim of this study was to determine whether the presence of malignant tumors influences trough concentrations of VCM and VCM pharmacokinetics in elderly patients during treatment for MRSA infection.

MATERIALS AND METHODS

Patients We studied 49 elderly Japanese patients infected with MRSA (37 men and 12 women) who received intravenous infusion of VCM (Shionogi & Co., Ltd., Osaka, Japan) from January 2003 to September 2007. Their age ranged from 65 to 92 years

(mean±S.D.: 79.25±7.87 years). These elderly patients treated with VCM were divided into subgroups according to the presence or absence of malignancies. Twenty-one patients had malignancies, including gastric cancer ($n=5$), colorectal cancer ($n=5$), esophageal cancer ($n=3$), lung cancer ($n=2$), bile duct carcinoma ($n=2$), gallbladder cancer ($n=1$), hepatocellular carcinoma ($n=1$), bladder cancer ($n=1$), and malignant lymphoma ($n=1$). The remaining patients ($n=28$) had no malignancy.

For each patient, the clinicopathologic parameters included gender; age; weight, serum creatinine (Scr); creatinine clearance (CrCL); trough concentration; daily VCM dosage; combination with furosemide; the presence or absence of edema, ascites, and pleural fluid; CL, volume of distribution (Vd); and elimination $t_{1/2}$. Individual pharmacokinetic parameters were calculated using the Bayesian estimation method,[12] and a two-compartment model was adopted using population pharmacokinetic parameters for Japanese adult patients.[13] CrCL was subsequently estimated using the Cockcroft-Gault equation,[14–16] which considered Scr, weight, age, and gender.

Administration and Measurement of VCM MRSA infection was treated with VCM at dosages of 1000 mg twice a day or once a day. Serum samples were collected after the steady state for VCM had been achieved (i.e., at least 72 h after the initiation of therapy). Samples for trough concentration were taken immediately prior to administration of the next scheduled dose. The serum concentration of VCM was measured using the fluorescence polarization immunoassay method (BML Inc., Tokyo, Japan).

Statistical Analysis All data are expressed as mean±S.D. The clinical characteristics and VCM pharmacokinetic values were compared between patients with and without malignancies using the Mann-Whitney *U*-test and univariate logistic regression analysis. As the target functions for logistic regression analysis, CL, $t_{1/2}$, and distribution volume were analyzed. The differences in gender, combination with furosemide, and the presence or absence of edema, ascites, and pleural fluid were assessed using the chi-square test. The SPSS 11.5 software package (SPSS Inc., Tokyo, Japan) was used for all statistical analyses. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Comparison of Clinical Characteristics between Patients with and without Malignancies The clinical characteristics of the elderly patients examined in this study are shown in Table 1. The Mann-Whitney *U*-test revealed that the mean trough concentration of VCM in patients with malignancies was significantly lower than that in patients without malignancies ($p=0.0012$). However, there were no significant differences in gender, age, weight, Scr, CrCL, VCM daily dosage, or combination with furosemide between patients with and without malignancies.

Comparison of VCM Pharmacokinetic Parameters between Patients with and without Malignancies The mean CL and Vd in patients with malignancies were increased significantly compared with those in patients without malignancies (Mann-Whitney *U*-test, $p=0.0213$ and $p=0.0374$, respectively). On the

Table 1. Comparison of the Clinical Characteristics between Patients with and without Malignancies

Characteristic	Patients		*p* value
	Malignancy ($n=21$)	Non malignancy ($n=28$)	
Gender (male/female)	18/3	19/9	0.1918**
Age (years)[a]	77.71±8.07	80.39±7.65	0.2884*
Body weight (kg)[a]	52.02±7.11	48.36±9.01	0.1620*
Scr (mg/dl)[a]	0.79±0.25	0.88±0.46	0.8875*
CrCL (ml/min)[a]	61.10±22.35	54.21±27.53	0.3850*
Trough concentration (μg/ml)[a]	10.72±5.37	19.39±9.48	0.0012*
VCM daily dosage (mg/kg/day)[a]	19.55±2.54	21.45±4.46	0.1633*
Combination with furosemide (yes/no)	9/12	5/23	0.1101**
Edema, ascites, pleural fluid (yes/no)	7/14	9/19	0.8260**

Scr, serum creatinine; CrCL, creatinine clearance; N.S., not significant. * Mann-Whitney *U*-test, ** chi-square test.
a) Mean±standard deviation.

Table 2. Comparison of VCM Pharmacokinetic Parameters between Patients with and without Malignancies

Pharmacokinetic parameter	Patients		p value*
	Malignancy ($n=21$)	Non malignancy ($n=28$)	
CL (ml/min/kg)[a]	0.85±0.31	0.62±0.28	0.0213
Vd (l)[a]	62.37±2.47	60.48±3.58	0.0374
$t_{1/2}$ (h)[a]	23.60±9.29	31.79±13.17	0.0423

CL, vancomycin clearance; Vd, volume of distribution; $t_{1/2}$, elimination half-life. * Mann-Whitney U-test. *a*) Mean±standard deviation.

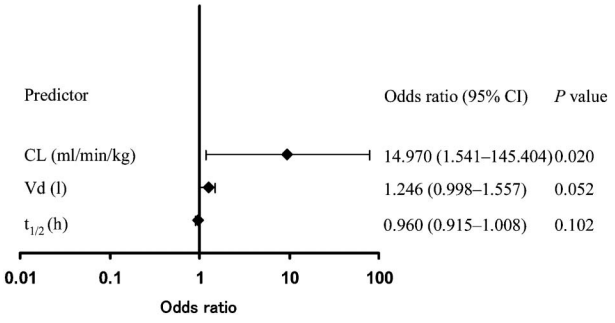

Fig. 1. Representative Forest Plot of Logistic Regression Analysis of the Pharmacokinetic Parameters for VCM

CL, vancomycin clearance; Vd, volume of distribution; $t_{1/2}$, elimination half-life; CI, confidence interval.

other hand, the mean $t_{1/2}$ in patients with malignancies was significantly lower than that in patients without malignancies ($p=0.0423$) (Table 2).

Independent Pharmacokinetic Parameters Related to Malignancies Univariate logistic regression analysis of three pharmacokinetic variables VCM clearance, Vd, and $t_{1/2}$ indicated that VCM clearance contributed as a significant factor independent of the relation to malignant tumor ($p=0.02$; odds ratio, 14.97; 95% confidence interval, 1.541–145.404) (Fig. 1).

DISCUSSION

The use of the trough concentration of VCM and data from TDM improves efficacy and safety outcomes. In particular, the trough concentration of VCM is usually recommended to be less than 10 μg/ml.[17] However, treatment with a dose of less than 10 μg/ml for MRSA infection sometimes leads to failure in many cases, so that a higher treatment concentration is necessary to ensure effectiveness,[18] i.e., in patients with malignant tumors[7–11] and endocarditis.[19] In the present study, our results support higher dosage requirements for MRSA infection in elderly patients with malignancies because of the lower trough concentrations of VCM. The data on the transition of VCM into peritoneal and pleural effusions is similar to that in blood (company data from Shionogi & Co., Ltd., Osaka, Japan). In addition, it is known that the Vd of VCM increases and the serum concentration decreases in edema and in peritoneal and pleural effusion in patients with malignant tumors. Therefore edema and peritoneal and pleural effusion were considered to increase the Vd and decrease the serum concentration. Therefore, we also further investigated patients with edema and peritoneal and pleural effusion, although, no significant differences were observed. These results indicate that edema or peritoneal or pleural effusion may have little impact on the alteration of CL in patients with malignant tumors who undergo VCM therapy. Further investigation, including basic experiments regarding the transition of the drug into each organ, will be essential to investigate the cause.

Furthermore, our results also indicated higher CL rates in elderly patients with malignancies, supporting the previous reports and justifying the need for higher concentrations for elderly patients with malignancies.[7–11] Since VCM is mainly metabolized and excreted in the kidney, various degrees of renal function can influence VCM pharmacokinetics.[6] In particular, the elderly generally exhibit renal hypofunction, and chemotherapy with anticancer drugs for malignancies induces various degrees of renal injury. However, there were no significant differences in Scr and CrCL between patients with and without malignancies in this study; although CrCL obtained based on the Cockcroft-Gault formula would be overestimated when calculated based on Scr in elderly patients.[20] In this study, although no significant differences were found in Scr and CrCL, the SD was large and the number of patients was insufficient. Since the possibility of second-class error was suspected, the examination was conducted with the level of statistical significance set at 10% as well as 5% and demonstrated no significant difference, even at $p<0.1$. Thus aging and the presence of malignancies may elevate CL independently, but not necessarily through changes in renal function. Since the CL of VCM is influenced by renal function, actual measurement values from pooled urine should be used to evaluate renal function precisely. However, the population

parameters of Yasuhara *et al*.[13] implemented in this study were estimated using the Cockcroft-Gault equation. Furthermore, the predictability of the serum concentration of VCM based on TDM estimated by the Cockcroft-Gault equation has been reported to be high in the elderly.[21] Thus, in this study, CrCL calculated with the Cockcroft-Gault equation was used as a substitute for the level of renal function.

Although the population parameters of Yasuhara *et al*.[13] target patients with MRSA infection, it is not clear whether the parameters include patients with malignant tumors. The population parameters of Yasuhara *et al*.[13] are cited in many reports of the TDM of VCM in Japan and the credibility is believed to be high, i.e., the parameters are considered adequate to determine differences between patients with malignancies and those without. Thus the need to establish population parameters for patients with malignant tumors based upon a larger number of cases was suggested.

When Vd decreases or CL increases, the $t_{1/2}$ is shortened. In this study, we observed significantly higher values of CL and Vd and shorter $t_{1/2}$ in patients with malignancies. It has been reported that the terminal elimination half-life of VCM is prolonged and CL is lower in the elderly, aged 60 to 95 years, compared with those in the younger age group of 18 to 59 years, because of the altered disposition of VCM in the elderly.[22] Meanwhile, there were no significant differences in VCM pharmacokinetic parameters between the elderly over 70 years of age (mean$\pm$S.D., 75.0$\pm$5.4 years) and the young.[23]

Several pathophysiologic factors related to malignancy, such as cancer type, high-dose antineoplastic therapy, advanced disease stage, hypoalbuminemia, fluid overload, and cachexia may affect aminoglycoside pharmacokinetics.[24–28] We consider that factors related to malignant tumors changed the VCM pharmacokinetic parameters. However, since the current study sample size was relatively small, it remains to be confirmed whether this finding is reproducible in larger samples.

In conclusion, it is suggested that the therapeutic effects and side effects of VCM should be actively monitored using TDM, because VCM concentrations may decrease when CL increases during the treatment of elderly patients with malignant tumors.

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