Evaluation of Predictability for Vancomycin Dosage Regimens by the Bayesian Method with Japanese Population Pharmacokinetic Parameters

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The predictability of serum vancomycin (VCM) concentrations by means of the Bayesian method was evaluated to establish whether the method can be used to select safe and effective VCM treatment regimens for individual patients. Serum VCM concentrations at the trough and 2 h after the end of infusion (peak) were measured. Pharmacokinetic parameters were calculated for VCM dosage regimens based on a two-compartment model with the Bayesian method, using the Japanese population pharmacokinetic parameters estimated by Yasuhara *et al.* (1998). The predictive performance for serum VCM concentrations and the dosage regimens were analyzed using two points of serum VCM concentration in 41 patients whose serum creatinine and age were in the ranges of 0.4–4.6 mg/dl and 24–92 years, respectively. Although the predicted values for trough and peak VCM concentrations were slightly lower than measured VCM concentrations, the predictive performance was generally good. There were no differences among the groups classified by serum creatinine or age. An examination of predicted data that differed markedly from the measured serum VCM concentrations indicated that a larger difference in volume of distribution at the steady state (V_{dss}) calculated from serum VCM concentrations at the beginning and revision of dosage regimens resulted in a poorer correlation of predicted values and measured values. This finding indicates that therapeutic drug monitoring should be conducted frequently, and the dosage regimen revised accordingly, in the case of patients who may have a change of V_{dss} of VCM, for example, due to a complication such as heart failure or edema.

Key words vancomycin; MRSA; Bayesian method; dosage regimen; distribution volume

Vancomycin (VCM) is a glycopeptide antibiotic, isolated from *Streptomyces orientalis*, that is active against methicillin-resistant *Staphylococcus aureus* (MRSA). However, VCM has severe side effects, such as auditorotoxicity and nephrotoxicity,¹⁾ at dose levels only slightly higher than the effective treatment concentration. Therefore, therapeutic drug monitoring (TDM) is important to administer VCM effectively and safely.²⁾

Usually serum VCM concentration is measured at the start of VCM administration and the dose is adjusted as necessary. The Bayesian method can be used to predict serum VCM concentrations based on a few blood sampling times, and the dose can be adjusted according to the patient's individual pharmacokinetic parameters.^{3–5)} Application of the Bayesian method for VCM therapy has been evaluated from the viewpoints of using population pharmacokinetic parameters,^{6,7)} the influence of some coadministered drugs with important hemodynamic effects on VCM pharmacokinetics⁸⁾ and the difference between initial and steady state levels.⁹⁾ Because serum VCM concentrations, especially in geriatric patients, could not be predicted precisely, Sato *et al.* suggested that serum VCM concentration should be measured as soon as possible after starting dosage regimens and the dose should be adjusted on the basis of the measured concentrations.⁶⁾ In the present study, we attempted to evaluate the predictability of serum VCM concentrations according to the Bayesian method, based on the Japanese population pharmacokinetic parameters estimated by Yasuhara *et al.*¹⁰⁾, with the largest group of patients so far examined, classified according to renal function or age.

MATERIALS AND METHODS

Patients Data were collected for 41 hospitalized patients (24 males, 17 females) infected with MRSA, treated with VCM from May 1998 to April 2001. The mean age was 66.9 ± 9.1 years (range, 24 to 92 years). The mean body weight was 52.4 ± 11.7 kg (range, 30 to 70 kg). The mean serum creatinine (Scr) was 0.8 ± 0.7 mg/dl (range, 0.4 to 4.6 mg/dl), and the mean creatinine clearance (CLCr) calculated from Scr was 89.6 ± 51.0 ml/min (range, 15.8 to 150.1 ml/min). The following Cockcroft–Gault equation¹¹⁾ was used to estimate CLCr:

$$\text{CLCr (ml/min)}^{\text{male}} = (140 - \text{Age}) \times \text{BW (kg)} / 72 \times \text{Scr (mg/dl)}$$

$$\text{CLCr (ml/min)}^{\text{female}} = \text{CLCr}^{\text{male}} \times 0.85$$

in which Age is the patient's age and BW is the actual body weight (kg). Sixty-six serum samples for the trough or peak levels were used to predict or evaluate the present dosage regimens, respectively.

VCM Dosage and Concentrations VCM (500–1000 mg/dosage) was administered by intravenous infusion over 1 h and the dosing intervals were from 12 to 48 h. Serum VCM concentrations at the trough and 2 h after the end of infusion (peak) were measured more than four days after the start of dosing (assumed to be at the steady state). Serum concentrations of VCM were measured by means of the fluorescence polarization immunoassay (FPIA) method using the TDx system (Dinabot Co., Ltd., Tokyo) in the laboratory of our hospital.

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Bayesian¹²⁾ Pharmacokinetic Study 1) Pharmacokinetic Parameters: The individual VCM pharmacokinetic parameters were calculated by the Bayesian method, using Yasuhara's population pharmacokinetic parameters¹⁰⁾ (Table 1), based on a two-compartment model. The collected serum concentration data were analyzed by VCM-TDM Ver. 2 software.¹³⁾

2) Dosage Regimens: VCM (500—1000 mg/dose; empiric dosage used by physicians) was administered by intravenous infusion over 1 h and the dosing intervals were from 12 to 48 h. Serum samples to measure VCM concentrations at the trough and peak were collected at 4 d or more after initiation of administration. Then, we revised the VCM dosage regimens based on the pharmacokinetic parameters estimated by the Bayesian method. The analysis was based on two points of measured serum VCM concentration, within the goal of peak levels in the range of 20 to 40 $\mu\text{g/ml}$ and trough levels of 15 $\mu\text{g/ml}$ or less.^{14,15)} The number of data in the set was 66.

3) Predictive Performance: We predicted serum VCM concentrations using the Bayesian method. We applied a linear regression analysis between measured trough and peak levels and predicted serum VCM concentration at the steady state (after the fourth day). The predictive performance of the Bayesian method was determined by the method of Sheiner and Beal.¹⁶⁾ Prediction accuracy (bias) and precision were evaluated by calculating the mean prediction error (ME), the mean absolute error (MAE), and the root mean squared prediction error (RMSE), using the following expressions:

$$\text{ME} = 1/n \sum_{i=1}^n (\text{Cpred} - \text{Cmeas}) \quad (1)$$

$$\text{MAE} = 1/n \sum_{i=1}^n |\text{Cpred} - \text{Cmeas}| \quad (2)$$

$$\text{RMSE} = [1/n \sum_{i=1}^n (\text{Cpred} - \text{Cmeas})^2]^{1/2} \quad (3)$$

where Cpred and Cmeas are the predicted and the measured serum concentrations in each patient, respectively, and their difference (Cpred—Cmeas) is the error in the prediction. To check whether predictions were biased, their confidence intervals were calculated by means of Student's *t*-distribution. The predictions were considered not to differ significantly from the actual values if the 95% confidence interval (95% C.I.) of the ME included zero. Measured and predicted vancomycin concentrations were compared by using a paired Student's *t*-test whether ME was significantly different from zero or not. *p* values of less than 0.05 were considered to be significantly different.

4) Evaluation of the Dosage Regimens Calculated from Ordinary Linear Pharmacokinetics: The revised dosages were calculated with the Bayesian method and also from ordinary linear pharmacokinetics, using the following equation: revised dosage = initial dosage $\times$ (goal trough level / present trough level). Accuracy (bias) and precision were evaluated by calculating ME, MAE, RMSE.

Clinical Efficacy We examined the clinical efficacy by using the criteria of Matsuno *et al.*¹⁷⁾ If MRSA was not detected in sputum culture of a patient at 3 successive inspec-

Table 1. Pharmacokinetic Models and Parameters for VCM Dosage Regimens

1. Population mean
CL (l/h) = 0.0478 $\times$ CLcr (0.0425—0.0531) (CLcr < 85 ml/min)
CL (l/h) = 3.51 (3.09—3.93) (CLcr > 85 ml/min)
K ₁₂ (h ⁻¹) = 0.525 (0.452—0.598)
K ₂₁ (h ⁻¹) = 0.213 (0.174—0.252)
V _{ss} (l) = 60.7 (53.9—67.5)
2. Interindividual variability
ω_{CL} = 38.5 (%) (30.6—45.0)
ω_{K12} = — ^{a)}
ω_{K21} = 28.6 (%) (— ^{b)} —40.9)
ω_{Vss} = 25.4 (%) (19.7—30.0)
3. Intraindividual, residual variability
σ = 23.7 (%) (21.4—25.8)

Values in parentheses are the 95% confidence intervals.¹⁰⁾ a) Not estimated. b) Not obtained. CLcr, ml/min.

tions, we judged that MRSA had been eradicated. If C-reactive protein (CRP) fell by 50% or more, we determined that the inflammation had recovered. We defined eradication of MRSA and recovery of the inflammation as high clinical efficacy, and eradication of MRSA or recovery of the inflammation as clinical efficacy; these categories were both judged as clinically effective. The absence of either was judged as clinically ineffective. The ratio of inflammation recovery was calculated as the number of patients showing decreased CRP, divided by the total number of patients. The ratio of clinical efficacy was calculated as the number of patients showing clinical effective or better, divided by the total number of patients.

RESULTS

Predictive Performance Using the Bayesian Method

Figure 1 shows the relationship between the measured (trough and peak) concentrations and the predicted (trough and peak) values. The regression equation describing the relationship between the measured (*x*) and predicted (*y*) values was $y = 0.834x + 1.340$ ($r^2 = 0.858$, $n = 132$). To test for bias, the errors of the prediction were compared with zero (Table 2). The ME (95% C.I.) for trough and peak were -1.05 ($p < 0.05$, range, -1.59 to -0.51) $\mu\text{g/ml}$ and -2.08 ($p < 0.05$, range, -3.04 to -1.12) $\mu\text{g/ml}$, respectively. The predicted values for trough and peak VCM concentrations were slightly lower than the measured VCM concentrations. The MAE (95% C.I.) for trough and peak were 1.95 (range, 1.59 to 2.31) $\mu\text{g/ml}$ and 3.36 (range, 2.66 to 4.06) $\mu\text{g/ml}$, respectively. The RMSE (95% C.I.) for trough and peak were 2.42 (range, 1.99 to 2.77) $\mu\text{g/ml}$ and 4.39 (range, 3.38 to 5.20) $\mu\text{g/ml}$, respectively.

The predictability of serum VCM concentrations was examined in relation to CLcr and age. We evaluated the predictive performance of the Bayesian method for trough and peak serum VCM concentrations, stratified according to CLcr or age. The study population was classified into 3 CLcr groups and 2 age groups: CLcr (80 ml/min or more, 40 to < 80 ml/min, less than 40 ml/min), age (up to 80 or over 80 years). In each group, the predicted values for trough and peak VCM concentrations were slightly lower than measured VCM concentrations. No significant difference was observed

Fig. 1. Correlation between Measured and Predicted VCM Concentrations Obtained Using the Bayesian Method Based on Japanese Population Pharmacokinetic Parameters

The difference between V_{dss} at the start and end of VCM treatment was categorized into 3 groups: group I (■): 0 to 0.05, group II (●): >0.05 to 0.1, group III (▲): >0.1. The regression lines for the three groups are shown (---, --- and, respectively). The bold solid line represents the regression line for all patients.

Table 2. Predictive Performance of the Bayesian Forecasting Technique Based on Japanese Population Pharmacokinetic Data for Serum VCM Concentrations in All Patients

Sampling point	Measured concentration Mean ($\pm$ S.D.) (μ g/ml)	Predicted concentration Mean ($\pm$ S.D.) (μ g/ml)	<i>t</i> -test ^{a)}	ME Mean (95% C.I.) (μ g/ml)	MAE Mean (95% C.I.) (μ g/ml)	RMSE Mean (95% C.I.) (μ g/ml)
Trough concentration (<i>n</i> =66)	10.52 ($\pm$ 3.29)	9.47 ($\pm$ 2.55)	<i>p</i> <0.05	-1.05 (-1.59, -0.51)	1.95 (1.59, 2.31)	2.42 (1.99, 2.77)
Peak concentration (<i>n</i> =66)	24.61 ($\pm$ 5.69)	22.52 ($\pm$ 4.87)	<i>p</i> <0.05	-2.08 (-3.04, -1.12)	3.36 (2.66, 4.06)	4.39 (3.38, 5.20)

ME: mean prediction error (a measure of bias), MAE: mean absolute prediction error (a measure of accuracy), RMSE: root mean squared prediction error (a measure of precision). 95% C.I.: 95% confidence interval. ^{a)} Measured and predicted VCM concentrations were compared by using a paired Student's *t*-test to determine whether ME was significantly different from zero or not. *p* values of less than 0.05 were considered to be significant.

Table 3. Comparison of the Dosages of True, Ordinary Linear Pharmacokinetics Method, and the Bayesian Method

		Early dosage Mean ($\pm$ S.D.) (mg/h)	True dosage Mean ($\pm$ S.D.) (mg/h)	ME Mean (95% C.I.) (mg/h)	MAE Mean (95% C.I.) (mg/h)	RMSE Mean (95% C.I.) (mg/h)
Revised dosage (mg/time)	Bayesian method	49.98 ($\pm$ 24.17)	54.47 ($\pm$ 24.5)	4.49 (2.53, 6.45)	6.47 (4.89, 8.04)	9.08 (8.74, 9.41)
	Linear pharmacokinetics method	63.59 ($\pm$ 59.85)		-9.12 (-20.44, 2.20)	28.35 (19.18, 35.52)	46.63 (45.67, 47.56)
				<i>p</i> <0.05 ^{a)}	<i>p</i> <0.0001 ^{a)}	<i>p</i> <0.01 ^{a)}

The revised dosages were calculated with the Bayesian method from trough and peak level, or ordinary linear pharmacokinetics method from trough level. Furthermore, the true dosage was calculated with the Bayesian method from trough and peak level, which we used to evaluate the Bayesian method. ME, MAE, RMSE and 95% C.I. are defined in Table 2. ^{a)} The Bayesian method and ordinary linear pharmacokinetics method were compared by using a paired Student's *t*-test to determine whether each of ME, MAE and RMSE was significantly different from zero or not.

in predicted or measured concentrations according to CL_{cr} or age (data not shown).

On the other hand, the results of the ordinary linear pharmacokinetics method were biased and less accurate than those of the Bayesian approach (Table 3). Therefore, it is considered meaningful to individualize VCM dosing regimens with the Bayesian method.

Clinical Efficacy The mean initial VCM dosage was

17.59 $\pm$ 7.05 mg/kg/dose (range, 7.14 to 34.29 mg/kg/dose). The mean trough level was 11.23 $\pm$ 6.28 μ g/ml, and the mean peak level was 25.21 $\pm$ 10.39 μ g/ml. Serum VCM concentrations were within the therapeutic range at the trough and peak at 40 (60.6%) and 47 (71.2%) of 66 measured points, respectively. In the Bayesian revised regimen, the mean VCM dosage was 17.48 $\pm$ 5.83 mg/kg/dose (range, 8.31 to 33.33 mg/kg/dose). The mean trough levels were 10.52 $\pm$

Fig. 2. Comparison of Measured Serum VCM Concentrations at the Trough and Peak in the Initial Dose Setting (before: Circle) and the Bayesian Revised Regimen (after: Triangle)

In the initial dose setting, mean VCM dosage was 17.59 ± 7.05 (range, 7.14 to 34.29) mg/kg/dose. The mean trough level ($\circ$) was 11.23 ± 6.28 $\mu\text{g/ml}$, and the mean peak level ($\bullet$) was 25.21 ± 10.39 $\mu\text{g/ml}$. After the Bayesian revised regimen, the mean VCM dosage was 17.48 ± 5.83 (range, 8.31 to 33.33) mg/kg/dose. The mean trough level ($\triangle$) was 10.52 ± 3.29 $\mu\text{g/ml}$, and the mean peak level ($\blacktriangle$) was 24.61 ± 5.69 $\mu\text{g/ml}$.

Fig. 3. Correlation between Measured and Predicted VCM Concentrations by the Bayesian Revised Regimen in Heart Failure Patients

Group HF consists of patients who developed heart failure or edema, and group NHF consists of those who did not. The lines are the regression lines.

3.29 $\mu\text{g/ml}$, and the mean peak levels were 24.61 ± 5.69 $\mu\text{g/ml}$. Serum VCM concentrations were within the therapeutic range at the trough and peak at 57 (86.4%) and 52 (78.8%) of 66 measured points, respectively. The values of the Bayesian revised regimen were improved from those in the early dosing period (Fig. 2). The inflammation recover ratio was 73.2% (30/41), the disappearance ratio of MRSA was 70.7% (29/41), and the ratio of clinical efficacy was 78.0% (32/41). The numbers in parenthesis represent recovered or effective patients in total patients. No patient developed renal failure due to VCM treatment.

DISCUSSION

In this study, we examined the predictability for VCM dosage regimens by the Bayesian method using Japanese population pharmacokinetic parameters. Serum VCM concentrations were analyzed by the Bayesian method using two points of serum VCM concentration, based on a two-compartment model. A good correlation was found (Fig. 1).

Furthermore, the Bayesian method seems to be better approach than the ordinary linear pharmacokinetics method (Table 3). But, some of the observed values were very differ-

Table 4. Comparison of Predicted and Measured Serum VCM Concentrations according to Absolute Difference of Vdss Estimated from Predicted and Measured Serum Concentrations

Sampling points Vdss difference* (l/kg)	Measured concentration Mean ($\pm$ S.D.) (μ g/ml)	Predicted concentration Mean ($\pm$ S.D.) (μ g/ml)	<i>t</i> -test ^{a)}	ME Mean (95% C.I.) (μ g/ml)	MAE Mean (95% C.I.) (μ g/ml)	RMSE Mean (95% C.I.) (μ g/ml)
Group I 0—0.05						
Trough concentration (<i>n</i> =30)	10.71 ($\pm$ 3.16)	10.22 ($\pm$ 2.78)	N.S.	-0.49 (-1.06, 0.08)	1.30 (0.95, 1.65)	1.59 (1.23, 1.88)
Peak concentration (<i>n</i> =30)	23.91 ($\pm$ 5.26)	23.13 ($\pm$ 4.98)	N.S.	-0.78 (-1.74, 0.18)	2.23 (1.70, 2.76)	2.63 (2.09, 3.08)
Group II >0.05—0.1						
Trough concentration (<i>n</i> =14)	10.92 ($\pm$ 3.69)	9.59 ($\pm$ 2.77)	<i>p</i> <0.05	-1.33 (-2.39, -0.27)	1.75 (0.93, 2.57)	2.21 (0.99, 2.96)
Peak concentration (<i>n</i> =14)	24.28 ($\pm$ 4.89)	21.78 ($\pm$ 5.34)	<i>p</i> <0.05	-2.50 (-3.84, -1.16)	2.89 (1.87, 3.91)	3.35 (2.24, 4.18)
Group III 0.1 <						
Trough concentration (<i>n</i> =22)	10.03 ($\pm$ 3.30)	8.37 ($\pm$ 1.62)	<i>p</i> <0.05	-1.65 (-2.96, -0.34)	2.96 (2.29, 3.63)	3.31 (2.58, 3.91)
Peak concentration (<i>n</i> =22)	25.77 ($\pm$ 6.71)	22.17 ($\pm$ 4.54)	<i>p</i> <0.05	-3.60 (-6.01, -1.19)	5.21 (3.50, 6.92)	6.42 (4.50, 7.88)

ME, MAE, RMSE and 95% C.I. are defined in Table 2. N.S.: not significantly different. *a*) Measured and predicted VCM concentrations were compared by using a paired Student's *t*-test to determine whether ME was significantly different from zero or not. *p* values of less than 0.05 were considered to be significant.

Table 5. Comparison of Predicted and Measured Serum VCM Concentrations in Groups with or without Heart Failure

Sampling points	Measured concentration Mean ($\pm$ S.D.) (μ g/ml)	Predicted concentration Mean ($\pm$ S.D.) (μ g/ml)	<i>t</i> -test ^{a)}	ME Mean (95% C.I.) (μ g/ml)	MAE Mean (95% C.I.) (μ g/ml)	RMSE Mean (95% C.I.) (μ g/ml)
Group HF						
Trough concentration (<i>n</i> =31)	10.52 ($\pm$ 3.61)	8.76 ($\pm$ 2.27)	<i>p</i> <0.05	-1.76 (-2.72, -0.80)	2.79 (2.24, 3.34)	3.15 (2.56, 3.64)
Peak concentration (<i>n</i> =31)	25.56 ($\pm$ 6.10)	21.92 ($\pm$ 4.60)	<i>p</i> <0.05	-3.63 (-5.33, -1.94)	4.78 (3.55, 6.01)	5.81 (4.30, 7.00)
Group I: <i>n</i> =0						
Group II: <i>n</i> =9						
Group III: <i>n</i> =22						
Group NHF						
Trough concentration (<i>n</i> =35)	10.53 ($\pm$ 0.51)	10.12 ($\pm$ 2.65)	N.S.	-0.43 (-0.94, 0.08)	1.20 (0.90, 1.50)	1.50 (1.16, 1.77)
Peak concentration (<i>n</i> =35)	23.77 ($\pm$ 5.25)	23.06 ($\pm$ 5.11)	N.S.	-0.71 (-1.56, 0.14)	2.11 (1.62, 2.60)	2.53 (2.03, 2.95)
Group I: <i>n</i> =30						
Group II: <i>n</i> =5						
Group III: <i>n</i> =0						

Group HF: patients with heart failure, Group NHF: without heart failure. ME, MAE, RMSE and 95% C.I. are defined in Table 2. N.S.: not significantly different. *a*) Measured and predicted VCM concentrations were compared by using a paired Student's *t*-test to determine whether ME was significantly different from zero or not. *p* values of less than 0.05 were considered to be significant.

ent from the predicted values. The predictability of serum VCM concentrations was examined according to age or CLcr, but no significant differences were found. There was also no significant difference between the calculated VCM clearance (CLpr) based on the initial VCM concentrations and that (CLaf) based on VCM concentrations in the Bayesian revised regimen. No significant difference was observed in individual values of Scr before and after the Bayesian revised regimen.

The mean value and standard deviation of the prediction of volume of distribution at the steady state (Vdss) and its difference were 1.14 ± 0.43 and 0.13 ± 0.23 (l/kg) respectively. Then, we considered the interindividual variability of Vdss concentrations to evaluate the Bayesian method. The value of D was classified in Table 4 as 0 to 0.05 (l/kg) (group I), >0.05 to 0.1 (l/kg) (group II), or more than 0.1 (l/kg) (group III). The regression equation describing the relationship between the measured (*x*) and predicted (*y*) values was; (group I) $y = 0.929x + 0.595$ ($r^2 = 0.930$, $n = 60$), (group II)

$y = 0.899x - 0.142$ ($r^2 = 0.930$, $n = 28$), and (group III) $y = 0.723x + 2.333$ ($r^2 = 0.790$, $n = 44$) (Fig. 1). Thus, the correlation between the predicted and measured values becomes poorer if a marked difference in Vdss appeared during VCM administration in a given patient. Table 4 shows the predictive performance of the Bayesian method for trough or peak serum VCM concentrations, for the three groups. In group II and group III, the predicted values for trough and peak VCM concentrations were slightly but significantly lower than the measured VCM concentrations (Table 4). No significant difference was observed in group I. The mean prediction error (ME, MAE, RMSE) of group I was smaller than that of group III. Therefore, the predictability of VCM concentration serums to be impaired by a marked change of Vdss during the administration of VCM. We previously described a patient, in whom infective endocarditis had developed, causing a large change in Vdss for gentamicin.¹⁸⁾ Further, Zaske reported that heart failure patients generally showed marked fluctuation of Vdss for aminoglycoside antibiotics.¹⁹⁾

Therefore, we divided our patients into groups with (group HF) or without (group NHF) heart failure or edema. The mean value and standard deviation of the predicted Vdss and its difference in heart failure patients were 1.12 ± 0.48 and 0.25 ± 0.30 (l/kg). The mean value and standard deviation of the predicted Vdss and its difference in non heart failure patients were 1.15 ± 0.39 and 0.03 ± 0.02 (l/kg). Regarding interindividual variability of estimated Vdss, the value of 22.32% for the HF group is larger than that of 2.61% for the NHF group. Accordingly, it appears that heart failure might influence the predictive ability of the Bayesian method. Furthermore, the regression equations describing the relationship between the measured (x) and predicted (y) values were: (group HF) $y = 0.757x + 1.693$ ($r^2 = 0.826$, $n = 62$), (group NHF) $y = 0.938x + 0.490$ ($r^2 = 0.935$, $n = 70$) (Fig. 3). The correlation between the predicted values and measured values was poorer in group HF. The mean prediction error (ME, MAE, RMSE) of group HF was also larger than that of group NHF (Table 5). The Vdss classification of group HF was group I (0 in $n = 30$), group II (9 in $n = 14$), and group III (22 in $n = 22$). This supports the idea that a disease state causing fluctuation in Vdss values decreases the predictability of VCM concentration by the Bayesian method. Therefore, patients with complications such as heart failure and edema require more frequent monitoring of VCM concentration, and, if necessary, modification of the administration dosage and schedule. There have been reports of problems regarding VCM administration to patients after cardiac surgery or with prosthetic cardiac valves,^{8,20)} and after aminoglycoside antibiotics administration to patients with heart failure.¹⁹⁾ However, this is the first report dealing with VCM administration to patients with heart failure.

In the Bayesian revised regimen based on the Bayesian method, the number of serum VCM concentration measurements within the desired therapeutic range at the trough and peak amounted to 78.8 to 86.4% (before the Bayesian dosage regimens, 60.6 to 71.2%). The recovery rate of inflammation was 73.2%, the disappearance rate of MRSA was 70.7%, and the overall rate of clinical efficacy was 78.0%. No patient developed renal failure due to VCM treatment.

If VCM concentration has reached the elimination phase, it is reasonable to estimate the pharmacokinetic parameters approximately by using VCM-TDM Ver. 2 software¹³⁾ in the case of a 2-compartment model, because all of the dosage intervals in this study were more than 6 h and serum VCM concentration had reached the steady state (more than 4 d after changing dosage). Although the error of the peak level was large, this might not seriously affect prediction of the

Vdss.

Because pharmacokinetic parameters such as Vdss may vary depending on the degree of illness in each patient, serum VCM concentrations should be measured frequently. It may be necessary to develop faster assay methods for serum VCM in order to conduct safer and more effective treatment with VCM. Nevertheless, our results suggest that individualized dosage regimens based on the Bayesian method are effective.

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