Evaluation of Bayesian Predictability of Vancomycin Concentration in Patients with Various Degrees of Renal Function

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To assess the usefulness of the population pharmacokinetic parameters of vancomycin (VCM) based on a two-compartment model in Japanese adult patients, predictability by a Bayesian method was evaluated using a concentration time course after single dosing to 22 patients with various degrees of renal function. Using one or two points from the observed data for each patient, the concentrations predicted by a Bayesian method were compared with the observed data for each sampling time. The patients were separated into five groups based on their renal functions indicated by creatinine clearance, and the mean prediction error (MPE) and root mean squared error (RMSE) were calculated for each group as measures of accuracy and precision, respectively. In both one- and two-point methods, the absolute MPE values at each sampling time in the elimination phase were less than 2.5 μg/ml, and the RMSE values were also small. No clear differences were found in MPE and RMSE among the groups. In the distribution phase, the MPE and RMSE were somewhat greater, and RMSE in some groups was around 15 μg/ml when trough data was used to predict the peak concentration. Also, the theoretical RMSE using this population parameter setting could well explain the observed RMSE. These results confirmed this population parameter setting is useful for at least predicting concentration in the elimination phase after single dosing, and the predictability was independent of renal function.

Key words vancomycin; Bayesian method; predictability; population pharmacokinetic parameter; Japanese adult patient

Vancomycin (VCM) is an effective glycopeptide antibiotic against gram-positive infections and has been widely used to treat patients with methicillin-resistant Staphylococcus aureus (MRSA).1—3) VCM has a recommended therapeutic window of serum concentration less than 25—40 μg/ml at 1 or 2 h after the end of infusion and less than 10 μg/ml as a trough concentration.4) Nephrotoxicity5) due to high trough concentration and less frequently, ototoxicity6) due to high peak concentration have been reported as side effects of this drug. VCM is mainly eliminated via the kidney by glomerular filtration,7) and insufficient renal function in a patient leads to long elimination half-life and a high serum level of VCM. In order to avoid such side effects, optimal dosage regimens according to the degree of renal function of each individual should be considered by way of therapeutic drug monitoring (TDM).8)

In TDM, only a few measurements of drug concentration are usually obtained from a patient and to overcome such a practical limitation, a Bayesian method9) has been applied as a pharmacokinetic analysis tool in combination with population pharmacokinetics (PPK)10,11) for theoretical prediction of the drug concentration profile for each individual. A Bayesian method requires complicated computation, i.e. the Bayesian least squares method, and several computer programs have been developed for this purpose.12,13) We have also developed and published computer software14) to support clinicians and pharmacists using the Bayesian method for TDM of VCM.

The serum concentration profile of VCM is well described by a two-compartment model,7) and we have already published the PPK parameters of VCM in Japanese adult patients based on a two-compartment model.15) Other PPK parameters of VCM by Rodvold et al.16,17) based on the same model have been also widely used in TDM. However, a two-compartment model may be complicated for Bayesian forecasting with sparse data, and a one-compartment model is sometimes preferred because it is less complicated and is easy to handle in TDM. The predictability of a Bayesian method depends on the number of compartments18) and also it depends on PPK parameters values and the sampling time.19—21)

As no precise evaluation of the PPK parameters of Japanese adult patients22) from the viewpoint of its predictive performance has been performed, we evaluated the predictive performance of a Bayesian method using the PPK parameter setting for patients with various degrees of renal function. The effect of sampling time of the data used for a Bayesian method on the predictability of VCM concentration was also examined. The theoretically computed root mean squared error (RMSE) was compared with the observed RMSE to check the results obtained.

MATERIALS AND METHODS

VCM Serum Concentration Data This study was carried out using serum concentration data from 22 adult patients (15 males and 7 females) with various degrees of renal function obtained in a previous study.22) Table 1 shows the characteristics of the 22 patients. To all patients, VCM was administered by intravenous infusion for 1 h at dose of 500 mg and blood samples were collected at 1, 1.5, 2, 3, 5, 7, 12 and 24 h after the start of the infusion. The serum concentrations of VCM were measured by a fluorescence polarization immunoassay (FPIA) method. Creatinine clearance (CLcr) was measured for all patients using serum and creatinine levels in urine collected for 24 h, and this value was used for a Bayesian prediction as a covariate in the PPK parameters.

Population Parameters and Pharmacokinetic Analysis PPK parameters reported by Yasuhara et al.15) were used for a Bayesian method based on a two-compartment model: population mean, CL (ml/min)=0.797×CLcr (ml/min), Vss (l)=60.7, K12 (h⁻¹)=0.525, K21 (h⁻¹)=0.213; inter-individual
variability (given as C.V.) CL: 38.5%, Vss: 25.4%, K_{21}: 28.6%. The inter-individual variability for K_{12} was arbitrary set at 50% (C.V.), although this could not be obtained in the PPK analysis. The intra-individual variability was 23.7% as C.V. The parameter CLcr is the creatinine clearance value measured for each individual.

Using this PPK parameter setting, one or two points of VCM concentration data were chosen from the observed data set for each patient and were used for a Bayesian prediction. A computer program for nonlinear mixed effect modeling, NONMEM Version V23) with posthoc option, was used for a Bayesian prediction with a FORTRAN 77 compiler (Sun-Pro) with a UNIX operating system (Sun Microsystems).

**Evaluation of Predicted Performance**

The predictive performance of VCM serum concentration by a Bayesian method was evaluated based on two indices, mean prediction error (MPE) as a measure of accuracy (bias) and root mean squared error (RMSE) as a measure of precision. MPE and RMSE at the $i$th sampling time used for a Bayesian method can be computed by Eqs. 1 and 2, respectively:

$$MPE_i = \frac{1}{N} \sum_{k=1}^{N} (C_{obs,k} - C_{pred,k})$$

(1)

$$RMSE_i = \sqrt{\frac{1}{N} \sum_{k=1}^{N} (C_{obs,k} - C_{pred,k})^2}$$

(2)

where $C_{obs,k,i}$ is the observed data at the $j$th sampling time for the $k$th individual, $C_{pred,k,i}$ is the predicted concentration at the $j$th sampling time by a Bayesian method using the $i$th sampling data for the $k$th individual, and $N$ is the number of patients. Absolute smaller MPE and smaller RMSE indicate better prediction. In order to evaluate the effect of different degrees of renal function on predictive performance, the patients were separated into five groups according to their CLcr values as shown in Table 1, and MPE and RMSE were computed separately for each group.

**Comparison of RMSE with Theoretical Estimates**

The RMSE in predicting serum concentration can be approximately obtained by taking the square root of Eq. 3:

$$\text{Var}(\hat{C}) = \sum_{i=1}^{n} \left( \frac{\partial f}{\partial P_k} \right)^2 \text{Var}(P_k)$$

(3)

where Var($\hat{C}$) is a variance of prediction error, $f$ is a function of a corresponding PK model (i.e., a two-compartment infusion model), $P_k$ is the $k$th pharmacokinetic parameter (population mean), and $m$ is the number of parameters. Var($P_k$) is the variance of the $k$th parameter estimate approximately given by Eq. 4:

$$\text{Var}(P_k) = \sum_{j=1}^{n} \left( \frac{\partial f}{\partial P_j} \right)^2 \text{Var}(P_j) + \frac{1}{\sigma^2}$$

(4)

where $\omega^2$ and $\sigma^2$ are the population variances for inter- and intra-individual variations, respectively, and $n$ is the number of observed data items used for a Bayesian prediction. The square root of Eq. 3 gives the theoretical standard deviation in the predicted concentration. In this report, the theoretical standard deviation is referred to as the ‘theoretical RMSE.’ The PPK parameters by a two-compartment model were applied to Eqs. 3 and 4, and the theoretical RMSE were compared with the observed RMSE by a Bayesian method. A typical CLcr value was required for computing Eq. 4 for clearance, and the middle values of the CLcr range in each group (e.g., 60 ml/min for A group, 40 ml/min for B group) were used as a typical value for the group. A typical value for the normal group was set at 100 ml/min by considering the normal range of CLcr as 70—130 ml/min. For comparison with the theoretical RMSE, the effect of the degree of renal function was not considered, and the averaged value of each of the typical CLcr values in all groups was actually used.

**RESULTS**

Figure 1 shows the serum concentration profiles of VCM in each group. The time course profiles clearly show a bi-exponential pattern that is usual for VCM.7)
Method

Figures 2 and 3 show the MPE and RMSE of the predicted serum concentration in each group by a one-point Bayesian method, where the observed data at 1, 3, 12, or 24 h were used for the prediction. MPE was generally small in the range of $\pm 2.5 \mu g/ml$ in the elimination phase, and was independent of the degree of renal function. MPE in the distribution phase tended to become worse when the data at a later sampling time was used, while MPE in the elimination phase seemed to be independent of the sampling time of the data used for prediction. The MPE at 1 h (i.e. the peak) was greater, especially when the data at 12 or 24 h were used for the normal group and D group, which suggested that the peak concentration might not be accurately predictable using the trough data alone. VCM concentration in the distribution phase tended to be underestimated in the normal group.

RMSE was generally small in the elimination phase, and was also less than $5 \mu g/ml$ in the distribution phase except for the normal group. RMSE at 1 h was much greater, especially in the normal group and D group, than in any of the other groups. RMSE in the distribution phase in the normal group was greater than in the other groups when 24 h data was used. However, in general, RMSE seemed to be independent of the degree of renal function.

Figures 4 and 5 show MPE and RMSE by the two-point Bayesian method. Sampling times (h) of the two data items used for the prediction were chosen for the four combinations of (1, 12 h), (3, 12 h), (1, 24 h), and (3, 24 h). Data at 1 and 3 h were regarded as a peak measurement and data at 12 and 24 h were regarded as a trough measurement. Compared with the results from the one-point Bayesian method using only 12 or 24 h data (Figs. 2, 3), MPE and RMSE at 1 h (at the peak) seemed to be improved when the data for prediction included 1 h data, however MPE and RMSE at other combinations were not. From these results it was found that MPE and RMSE in the elimination phase were almost independent of the sampling time, and also independent of the degree of renal function in the two-point Bayesian method.

Comparison of RMSE with Theoretical Estimates

Based on the above results, the predictive performance of a Bayesian method using the PPK parameter setting is independent of the degree of renal function. Therefore the renal function was not taken into consideration here, and RMSE values estimated for all patients were compared with the theoretical RMSE.

In Fig. 6, the observed RMSE for all patients by one- and two-point Bayesian methods were compared with the theoretical RMSE obtained from the square root of Eq. 3. Theoretical RMSE can explain the observed RMSE rather well except for the peak concentration when data for time other than 1 h were used. Even by the two-point Bayesian method, it seemed theoretically difficult to predict peak concentration.
DISCUSSION

The predictive performance of a Bayesian method using PPK parameter setting of VCM in Japanese adult patients based on a two-compartment model was evaluated for patients with various degrees of renal function. Two indices, MPE and RMSE, in the elimination phase seemed to be small, irrespective of renal function, for both one-point and two-point Bayesian methods. The MPE and RMSE at 1 h especially in the normal group and D group were somewhat greater than those at other prediction times when the data at the elimination phase were used for prediction. One possible reason is the difference in the backgrounds between the patients in this study and those participating in the PPK analysis. The PPK parameter setting was obtained mainly from the elderly patients, while the subjects in the normal group were relatively young (age: 28.0 ± 2.16 (years), mean ± S.D.). For D group, the CLcr values in subjects in this group were at the lower extremes for the original population. Moreover, the peak concentration is mainly affected by the distribution process of a drug and is usually difficult to predict from only data for the elimination phase.

In this study, it was shown that VCM concentration is well predicted in patients with various degrees of renal function by using a Bayesian method. Some nomograms are often used for the prediction, however, inter-individual variability is not considered in nomograms and predictability of VCM concentration by a nomogram is generally lower than by a Bayesian method.

Considering that the purpose of a Bayesian method is to predict a time course profile of a drug in each individual, the evaluation of the reliability of the predicted curve will be very important. The predicted time course curve is a mode of the posterior distribution of the predicted concentration given by the PPK parameters (prior distribution) and the observed data. Therefore the reliability as well as the accuracy (MPE) and precision (RMSE) may have to be considered to evaluate the predictive performance of the Bayesian method in the future. The method proposed by Yafune to simulate not only the predicted time course profile (mode) but also its confidence interval should be useful.

In conclusion, the present results suggest that our PPK parameters based on a two-compartment model are useful for predicting VCM concentration especially in the elimination phase for a wide range of renal function levels. It is also suggested that predictability was independent of the sampling time. Therefore it is concluded that the good predictability will be obtained by using the data at 1 or 2 h after the end of infusion or trough data as recommended in the guideline for TDM of VCM. These results contribute to clinical VCM therapy from a viewpoint of TDM. Although the complex computation of the two-compartment model in TDM of
VCM may be troublesome to clinicians and pharmacists, so sophisticated pharmacokinetic analysis software are available to resolve such issues.14)

REFERENCE


Fig. 6. Comparison of Observed RMSE with Theoretical RMSE from a One- (Upper Panels) and Two- (Middle and Lower Panels) Point Bayesian Methods
Values on the X-axis represent the time at which drug concentration was predicted, and the times given at the top right in each panel are the sampling time of the data for Bayesian prediction. ○, observed RMSE; —, theoretical RMSE.