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Prediction of Serum Vancomycin Concentrations using One-, Two- and Three-compartment Models with Implemented Population Pharmacokinetic Parameters and with the Bayesian Method

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Abstract

Although previous studies have shown that vancomycin has a complicated pharmacokinetic profile requiring description using a two- or, better, three-compartment model, until recently predictions of serum vancomycin concentrations have been mainly based on one- or two-compartment models using computer software packages. In this study, we have predicted serum vancomycin concentrations in 59 patients using one-, two- and three-compartment models with implemented population pharmacokinetic parameters in the Abbott PKS program and by use of the Bayesian method.

The percentage errors of predictions made using the one-compartment model were smaller when either the Bayesian method or implemented population pharmacokinetic parameters were used (medians of −8·61% and −9·49%, respectively). Predictions using the one-compartment model with the Bayesian method were less biased (median of $-1{\cdot}52\,\mu g\,mL^{-1}$). The best predictions were those made using the three-compartment model with the Bayesian method—they were most accurate (median of $3{\cdot}40\,\mu g\,mL^{-1}$) and highly precise (median of $11{\cdot}53\,\mu g^2\,mL^{-1}$).

The results suggest that predictions made using the one-compartment model with implemented population pharmacokinetic parameters are preferable if no samples are available, otherwise predictions made using the three-compartment model with the Bayesian method are preferable. The results also supported our previous argument that the greater the number of compartments involved in individualization, the better the predictions obtained using the Bayesian method.

Several sophisticated computer software packages are currently used for clinical optimization of drug regimens and prediction of drug concentrations. One drug of interest, vancomycin, has a complicated pharmacokinetic profile requiring description using a two- or, better, a three-compartment model (Matzke et al 1986). Until recently predictions of serum vancomycin concentrations were mainly based on one- or two-compartment models using computer software packages (Pryka et al 1989; Rodvold et al 1995; Wu & Furlanut 1997) and results have shown that predictions made using the two-compartment model are not always better than those made using the one-compartment model (Pryka et al 1989; Rodvold et al 1995). Because of the complexity of the pharmacokinetics of vancomycin, it would be useful to predict serum vancomycin concentrations using the three-compartment model and to compare the results with predictions made using the one- and two-compartment models.

The Abbott PKS program, software widely used in clinical pharmacology (Buffington et al 1993), has been used to predict serum vancomycin concentrations in numerous studies (Pryka et al 1989; Rodvold et al 1995; Wu & Furlanut 1997). Because most predictions of serum vancomycin concentration have been obtained using the PKS program, it would be also important to use the PKS program to predict serum vancomycin concentrations using one-, two- and three-compartment models and to compare the predictions.

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Moreover, the implementation of the Bayesian method in most software packages plays an important role in individualization of implemented population pharmacokinetic parameters and in the prediction of the concentrations of various drugs (Wu et al 1998). It is also meaningful to compare the predictions obtained with implemented population pharmacokinetic parameters and by the Bayesian method.

The aim of this study was, therefore, to predict serum vancomycin concentrations using one-, two- and three-compartment models with implemented population pharmacokinetic parameters and by use of the Bayesian method.

Materials and Methods

Patients, vancomycin dosage and serum vancomycin concentrations

Data were collected during routine therapeutic drug monitoring in 59 patients (Table 1). All patients had stable renal function—fluctuation of serum creatinine was $< 0{\cdot}5\,gL^{-1}$ from the beginning of the therapy (Wu & Furlanut 1996). Each patient received 500mg vancomycin by continuous intravenous infusion for 1h with the patient-specified dosage; most had four administrations per day. Peak and trough blood samples were taken for determination of serum vancomycin concentrations by fluorescence-polarization immunoassay (TDx; Abbott Laboratories, Irving, TX; Schwenzer et al 1983). During therapeutic drug monitoring at least four blood samples were taken (two peaks and two troughs) from each patient before and after intravenous infusion. More than 30 blood samples were obtained from some patients on long-term therapy.

Predictive program and implemented population pharmacokinetic parameters

The PKS program (Abbottbase Pharmacokinetic System; Abbott Laboratories, Abbott Park, IL) was used to predict serum vancomycin concentrations. The implemented population pharmacokinetic parameters were: for the one-compartment model, volume of distribution (Vd) $0{\cdot}82\,Lkg^{-1}$, clearance (CL) $0{\cdot}003\,Lh^{-1}kg^{-1}$; for the two-compartment model Vd in the central compartment $0{\cdot}22\,Lkg^{-1}$, CL $0{\cdot}008\,Lh^{-1}kg^{-1}$, transfer rates ($k_{12}$ and k_{21}) $1{\cdot}03\,h^{-1}$ and $0{\cdot}41\,h^{-1}$; for the three-compartment model Vd in the central compartment $0{\cdot}153\,Lkg^{-1}$, CL $0{\cdot}067\,Lh^{-1}kg^{-1}$, transfer rates ($k_{12}$, k_{21}, k_{13}, k_{31}, and k_{10}) $0{\cdot}907\,h^{-1}$, $0{\cdot}504\,h^{-1}$, $0{\cdot}855\,h^{-1}$, $0{\cdot}952\,h^{-1}$ and $0{\cdot}399\,h^{-1}$, respectively. The coefficient of variance was 20% for all parameters.

Table 1. Patient demographics.

Age (years)	57 ± 16
Sex (female : male)	19 : 40
Weight (kg)	69 ± 11
Height (cm)	169 ± 8
Creatinine dose ($mgdL^{-1}$)	1·1 ± 0·8

Predictive methods

To predict patient drug concentrations patient demographic factors and dosage can be used in conjunction with implemented population pharmacokinetic parameters (Wu et al 1995a, c). Because demographic factors cannot account for all the possibilities such as inter- and intra-patient variability, etc., predictions using implemented population pharmacokinetic parameters might be less precise but such predictions can be used before the first dosage. Comparison of concentrations predicted using implemented population pharmacokinetic parameters with measured concentrations can be used to evaluate whether or not implemented population pharmacokinetic parameters in a software package are biased for a particular population of patients.

The Bayesian method can use previous information (i.e. from blood samples) obtained from a patient to individualize the implemented population pharmacokinetic parameters and further minimize intra-subject variability, etc. In these circumstances predictions obtained using the Bayesian method are better than those obtained using implemented population pharmacokinetic parameters. However, because blood samples are needed for the Bayesian method, it can be used only after dosing and obtaining blood samples. In this study we used one peak and one trough serum vancomycin concentrations for each patient for individualization using the Bayesian method, and then predicted other serum vancomycin concentrations.

Statistics

Data calculation. Measured and predicted vancomycin concentrations were used to calculate percentage prediction errors (Wu 1995b; Wu et al 1995b), i.e. percentage prediction error = ((predicted concentration − measured concentration)/measured concentration) × 100. Outliers (3 × s.d.) were detected by Healy's method (Healy 1979). Absolute and relative predictive performances were calculated by methods described elsewhere (Sheiner & Beal 1981; Wu 1995a). The absolute predictive performance includes: the mean or median prediction error as bias; the median absolute error as accuracy; and the mean- or median-squared prediction error as precision. The relative

predictive performance is the prediction difference among the one-, two- and three-compartment models with implemented population pharmacokinetic parameters and using the Bayesian method.

Data presentation. The Shapiro-Wilk's *W*-test was used to determine the distribution of the data. Normally distributed data are presented as means ± s.d. Non-normally distributed data are presented as medians with interquartile ranges.

Statistical inference. The paired Student *t*-test and the Mann-Whitney *U*-test were used, with $P < 0.05$ being regarded as indicative of statistical significance.

Results and Discussion

When the percentage prediction error is used to evaluate predictions (Table 2), the median of predictions of the one-compartment model using the Bayesian method is the smallest and the interquartile range of the three-compartment model using the Bayesian method is the narrowest. Among various comparisons, predictions made using the one-compartment model with either the Bayesian method or implemented population pharmacokinetic parameters are better than others, and the advantage of the Bayesian method is not evident because three groups of predictions using the Bayesian method are better than predictions made using implemented population pharmacokinetic parameters and another three groups of predictions using implemented population pharmacokinetic parameters are better than the predictions obtained by use of the Bayesian method.

When the prediction error (bias) is used to evaluate predictions, predictions made using the one-compartment model with the Bayesian method are less biased, with the smallest median, and the interquartile range of the three-compartment model with the Bayesian method is the narrowest. Among various comparisons, predictions made using the one-compartment model with either the Bayesian method or implemented population pharmacokinetic parameters are better than the others, although predictions made using the Bayesian method are better than predictions made using implemented population pharmacokinetic parameters (seven groups of predictions vs one group of predictions in Table 3).

When the absolute prediction error (accuracy) is used to evaluate the predictions (Table 4), predictions made using the three-compartment model with the Bayesian method are most accurate, i.e. the smallest median and narrowest interquartile range. Among various comparisons, predictions using the three-compartment model with the Bayesian method are the best and eleven groups of predictions using the Bayesian method are better than predictions made using implemented population pharmacokinetic parameters.

When the squared prediction error (precision) is used to evaluate the predictions (Table 5), predictions made using the three-compartment model with the Bayesian method are highly precise, i.e. the smallest median and narrowest interquartile range. Among various comparisons, predictions

Table 2. Prediction error (%) and comparison within and between structural models.

	Prediction error	BM-1	IPPP-2
IPPP-1	−9·49 (−39·45–22·59)	BM-1 = IPPP-1	IPPP-1 > IPPP-2***
BM-1	−8·61 (−39·43–22·34)		BM-1 > IPPP-2***
IPPP-2	−13·99 (−45·16–10·60)		
BM-2	−12·78 (−40·69–8·48)		
IPPP-3	−24·54 (−64·79–9·68)		
BM-3	−15·49 (−35·12–1·32)		
	BM-2	**IPPP-3**	**BM-3**
IPPP-1	IPPP-1 > BM-2***	IPPP-1 > IPPP-3***	IPPP-1 > BM-3***
BM-1	BM-1 > BM-2***	BM-1 > IPPP-3***	BM-1 > BM-3***
IPPP-2	BM-2 > IPPP-2*	IPPP-2 > IPPP-3***	IPPP-2 > BM-3*
BM-2		BM-2 > IPPP-3***	BM-2 > BM-2***
IPPP-3			BM-3 = IPPP-3
BM-3			

Data are presented as median with interquartile range. BM-1, BM-2 and BM-3 are the predictions made using the one-, two- and three-compartment models with the Bayesian method. IPPP-1, IPPP-2 and IPPP-3 are the predictions made using the one-, two- and three-compartment models with implemented population pharmacokinetic parameters. = indicates there was no statistically significant difference between the first and second predictions. > indicates that the first prediction was better than the second. *$P < 0.05$ and ***$P < 0.001$ (paired Student's *t*-test, n = 582).

Table 3. Prediction error ($\mu g\,mL^{-1}$) and comparison within and between structural models.

	Prediction error	BM-1	IPPP-2
IPPP-1	−1·56 (−6·98–2·78)	BM-1 > IPPP-1*	IPPP-1 > IPPP-2***
BM-1	−1·52 (−6·94–2·56)		BM-1 > IPPP-2***
IPPP-2	−2·38 (−8·04–1·53)		
BM-2	−2·29 (−7·71–1·33)		
IPPP-3	−4·07 (−10·01–1·36)		
BM-3	−2·42 (−6·00–0·14)		
	BM-2	**IPPP-3**	**BM-3**
IPPP-1	IPPP-1 > BM-2***	IPPP-1 > IPPP-3***	IPPP-1 = BM-3
BM-1	BM-1 > BM-2***	BM-1 > IPPP-3***	BM-1 = BM-3
IPPP-2	IPPP-2 = BM-2	IPPP-2 > IPPP-3***	BM-3 > IPPP-2*
BM-2		BM-2 > IPPP-3***	BM-2 = BM-3
IPPP-3			BM-3 > IPPP-3***
BM-3			

Data are presented as median with interquartile range. BM-1, BM-2 and BM-3 are the predictions made using the one-, two- and three-compartment models with the Bayesian method. IPPP-1, IPPP-2 and IPPP-3 are the predictions made using the one-, two- and three-compartment models with implemented population pharmacokinetic parameters. = indicates there was no statistically significant difference between the first and second predictions. > indicates that the first prediction was better than the second. *$P < 0.05$ and ***$P < 0.001$ (paired Student's t-test, n = 582).

made using the Bayesian method are the best, because five groups of predictions using the Bayesian method are better than the predictions made using implemented population pharmacokinetic parameters.

Figure 1 shows that predictions made using one-, two- and three-compartment models are stable over a period of time and we can thus exclude the possibility that the predictions might become worse in patients undergoing long-term therapy. Because we used two samples to individualize the implemented population pharmacokinetic parameters in each patient to enable prediction of other concentrations (from two predictions to approximately 30 predictions) with the Bayesian method, it would be interesting to know whether the predictions are similar when the first two predictions are compared with other predictions. Figure 1 also shows no

Table 4. Absolute prediction error ($\mu g\,mL^{-1}$) and comparison within and between structural models.

	Absolute prediction error	BM-1	IPPP-2
IPPP-1	5·22 (2·14–8·67)	BM-1 > IPPP-1***	IPPP-2 > IPPP-1**
BM-1	5·11 (2·17–8·59)		BM-1 = IPPP-2
IPPP-2	4·89 (2·01–8·62)		
BM-2	4·32 (1·86–8·56)		
IPPP-3	6·40 (3·12–10·47)		
BM-3	3·40 (1·49–6·94)		
	BM-2	**IPPP-3**	**BM-3**
IPPP-1	BM-2 > IPPP-1***	IPPP-1 > IPPP-3***	BM-3 > IPPP-1***
BM-1	BM-2 > BM-1***	BM-1 > IPPP-3***	BM-3 > BM-1***
IPPP-2	BM-2 > IPPP-2*	IPPP-2 > IPPP-3***	BM-3 > IPPP-2***
BM-2		BM-2 > IPPP-3***	BM-3 > BM-2**
IPPP-3			BM-3 > IPPP-3***
BM-3			

Data are presented as median with interquartile range. BM-1, BM-2 and BM-3 are the predictions made using the one-, two- and three-compartment models with the Bayesian method. IPPP-1, IPPP-2 and IPPP-3 are the predictions made using the one-, two- and three-compartment models with implemented population pharmacokinetic parameters. = indicates there was no statistically significant difference between the first and second predictions. > indicates that the first prediction was better than the second. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ (paired Student's t-test, n = 582).

Table 5. Squared prediction error ($\mu g^2 mL^{-2}$) and comparison within and between structural models.

	Squared prediction error	BM-1	IPPP-2
IPPP-1	27·25 (4·58–75·167)	BM-1 > IPPP-1**	IPPP-2 > IPPP-1**
BM-1	26·11 (4·71–73·79)		BM-1 = IPPP-2
IPPP-2	23·91 (4·04–74·30)		
BM-2	18·66 (3·44–73·24)		
IPPP-3	40·96 (9·73–106·62)		
BM-3	11·53 (2·22-48·16)		
	BM-2	IPPP-3	BM-3
IPPP-1	BM-2 > IPPP-1*	IPPP-1 > IPPP-3***	IPPP-1 = BM-3
BM-1	BM-1 = BM-2	BM-1 > IPPP-3***	BM-1 = BM-3
IPPP-2	BM-2 = IPPP-2	IPPP-2 > IPPP-3***	IPPP -2 = BM-3
BM-2		BM-2 > IPPP-3***	BM-2 = BM-3
IPPP-3			BM-3 > IPPP-3**
BM-3			

Data are presented as median with interquartile range. BM-1, BM-2 and BM-3 are the predictions made using the one-, two- and three-compartment models with the Bayesian method. IPPP-1, IPPP-2 and IPPP-3 are the predictions made using the one-, two- and three-compartment models with implemented population pharmacokinetic parameters. = indicates there was no statistically significant difference between the first and second predictions. > indicates that the first prediction was better than the second. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ (paired Student's t-test, n = 582).

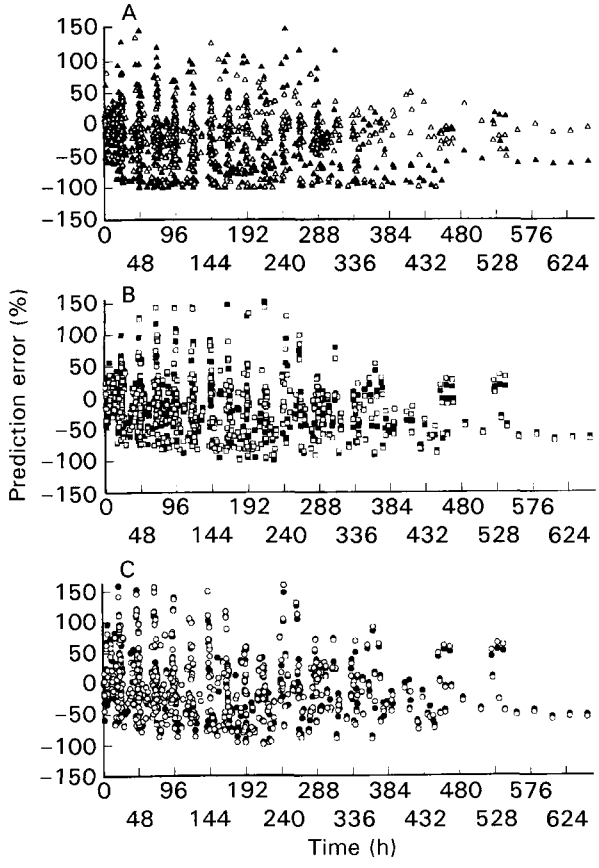

Figure 1. Percentage prediction errors with time. A, B and C are the predictions made using the one-, two- and three-compartment models, respectively. △, □, ○, Predictions made with implemented population pharmacokinetic parameters; ▲, ■, ●, predictions made using the Bayesian method.

difference between the first two predictions within 50h and other predictions beyond 50h (Mann-Whitney U-test).

Predicted differences among models and methods are mostly related to peak concentrations; this is important because the peak concentrations can be more closely related to therapeutic and adverse effects of vancomycin. The three-compartment model with the Bayesian method modifies both predicted peak and trough concentrations, and one- and two-compartment models with the Bayesian method mainly modify the predicted peak concentrations.

In this study predictions made using the three-compartment model with the Bayesian method are better than those made using the two- and one-compartment model with either implemented population pharmacokinetic parameters or the Bayesian method. This seems reasonable, because the three-compartment model has been reported as being the most suitable for vancomycin pharmacokinetics (Matzke et al 1986). These results support our observation that the greater the number of compartments involved in individualization the better the predictions obtained using the Bayesian method (Wu et al 1996).

That predictions made using the one-compartment model with implemented population pharmacokinetic parameters are better than those made using the two- and three-compartment models with implemented population pharmacokinetic parameters might be because the one-compartment model has so far been used in most pharmacokinetic studies of vancomycin because of the simplicity of computer operation, even though the

three-compartment model is more suitable for vancomycin pharmacokinetics. Because vancomycin pharmacokinetic parameters are not so readily obtained in the two- and three-compartment models, especially the three-compartment model, the population used to construct the one-compartment vancomycin pharmacokinetic parameters is much larger than those used to construct the two- and three-compartment vancomycin pharmacokinetic parameters and so the one-compartment vancomycin pharmacokinetic parameters are more applicable to other patients. Thus, predictions made using the one-compartment model with implemented population pharmacokinetic parameters are better than those obtained using the two- and three-compartment models with implemented population pharmacokinetic parameters.

The results reveal slight differences between the methods used for statistical evaluation, i.e. evaluation by use of percentage prediction error gives results slightly different from those obtained by use of absolute and relative prediction performance. This slight difference requires further study.

Our results suggest that in clinical management predictions made using the one-compartment model with implemented population pharmacokinetic parameters is preferable if no samples are available, otherwise predictions made using the three-compartment model with the Bayesian method are preferable.

In conclusion, the results suggest that the three-compartment model with the Bayesian method is most suitable for predicting serum vancomycin concentrations.

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