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Bayesian Prediction of Serum Phenytoin Concentration in a Simulation Study[1)]

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The predictive performance of the Bayesian weighted least-squares method (BWLS), *viz.*, the Bayesian method, was evaluated and compared with that of the ordinary weighted nonlinear least-squares method (OWLS) in a simulation study. Phenytoin was selected as a model drug for a one-compartment nonlinear model (Michaelis–Menten model). The patient population for the phenytoin study (K_m: $3.9 \pm 2.1\,\mu g/ml$, V_{max}: $6.78 \pm 1.27\,mg/kg/d$) was generated by using a random number generator.

When estimating the parameters by the Bayesian method, the V_{max} estimate was more precise than the K_m: V_{max} could be estimated with a 15% and 10% prediction error with one and two observations, respectively, as opposed to 30% and 20% for K_m. It was also inferred that the predictive performance of the one- and two-observation BWLSs was a slightly better than or equal to that of the three-observation OWLS but did not approach that of the four-observation OWLS.

The present simulation study indicated that the Bayesian method could provide reliable estimations of Michaelis–Menten parameters such as K_m and V_{max} and clinically acceptable predictions for the steady-state serum concentration with at least one observation (the root mean squared error, $3.4\,\mu g/ml$; 95% confidence interval, 1.4—$4.6\,\mu g/ml$), if appropriate population pharmacokinetic parameters (*i.e.*, means and variances) were available.

Keywords——Bayesian method; prediction; simulation; blood level; population pharmacokinetics; methodology; Michaelis–Menten model; phenytoin; PEDA; microcomputer

Introduction

Difficulty in selecting an appropriate phenytoin (PHT) dosage has been experienced because of the nonlinear relationship between the steady-state serum concentration (Cp_{ss}) and the total daily dosage and the narrow therapeutic range of the Cp_{ss} (10—$20\,\mu g/ml$). Several reliable methods exist for estimating the Michaelis–Menten parameters when two or more Cp_{ss} at different dosages are available.[2,3)] However, these methods require a relatively long time, sometimes more than two weeks, to achieve the therapeutic range. Methods for making an appropriate dosage adjustment based on a single dose–Cp_{ss} pair have thus been sought in clinical practice, and various methods have been proposed to accomplish this.

The authors have previously evaluated the various single dose–Cp_{ss} feedback methods,[4)] including the Richens and Dunlop method,[5)] the nomograms of Rambeck *et al.*[6)] and Martin *et al.*,[7)] the population clearance method,[8)] the method proposed by Wagner[9)] and the Bayesian feedback method,[10)] in Japanese adult population. The Bayesian feedback method was considered to be the most precise and useful method among them.

Toscano and Jameson[11)] have evaluated the Bayesian method by a simulation study for predicting the daily PHT dosage required to achieve the therapeutic range, and compared the results with the linearized version of the Bayesian method,[12)] the Rambeck method and the population clearance method. So far, however, there has been little critical study on the theoretical results, especially on the precision of Michaelis–Menten parameter estimates

derived from the Bayesian method.

The purposes of the present study were to assess the precision of the Michaelis–Menten parameter estimates and the prediction error of Cp_{ss} by the Bayesian weighted least-squares method (BWLS), on a theoretical basis, and to compare the predictive performance of BWLS with that of the ordinary nonlinear least-squares method (OWLS) as a reference method.

Methods

Generation of Simulated Data——The patient population for the PHT study was generated from a normal distribution (mean and standard deviations) of K_m and V_{max} using a random number generator. The resultant individual parameters (the number of parameter sets was 20) were defined as the true parameter values. The population mean values in the generated population were as follows: K_m, 3.9 ± 2.1 μg/ml (C.V. = 55.4%); V_{max}, 305 ± 57 mg/d/45 kg (C.V. = 18.7%).

Dose–Cp_{ss} pairs were generated by using Eq. 1, given each individual patient's kinetic parameters ($K_{m(i)}$ and $V_{max(i)}$) and the daily dose from 20 to 400 mg. Simulated concentrations of more than 50 μg/ml or the negative value were excluded from the subsequent prediction study. The simulated Cp_{ss} was defined as the exact Cp_{ss}.

$$Cp_{ss} = \frac{K_m \cdot \text{dose}}{V_{max} - \text{dose}} \tag{1}$$

Prediction Study——One or two of the exact Cp_{ss} for the BWLS (designated as 1-point BWLS and 2-point BWLS) and three or four for the OWLS (3-point OWLS and 4-point OWLS) were selected at random, and subsequently noisy actual Cp_{ss}s were obtained by adding the normally distributed random error (15% as C.V.).

After parameter optimization, predictions by revised parameters were performed for another true Cp_{ss}. This was repeated 60 times over the population randomly.

The BWLS was carried out on a microcomputer program PEDA which had been developed by one of us previously,[13] and the OWLS was performed with a slight modification of PEDA.

Objective Functions——The BWLSs in our study minimize Eq. 2, while the OWLSs minimize Eq. 3:

$$O_{BWLS} = \sum_{i=1}^{n} \frac{(Cp_{ss(i)} - \widehat{Cp_{ss(i)}})^2}{\sigma_{Cp_{ss(i)}}^2} + \frac{(K_m - \widehat{K_m})^2}{\sigma_{K_m}^2} + \frac{(V_{max} - \widehat{V_{max}})^2}{\sigma_{V_{max}}^2} \tag{2}$$

$$O_{OWLS} = \sum_{i=1}^{n} \frac{(Cp_{ss(i)} - \widehat{Cp_{ss(i)}})^2}{\sigma_{Cp_{ss(i)}}^2} \tag{3}$$

where $\widehat{K_m}$ and $\widehat{V_{max}}$ are the population mean values, and K_m and V_{max} are the individual parameter estimates. $Cp_{ss(i)}$ is the steady-state drug concentration measurement, $\widehat{Cp_{ss(i)}}$ is the predicted drug concentration for the i-th observation and n is the total number of measurements. $\sigma_{K_m}^2$ and $\sigma_{V_{max}}^2$ are the prior, interindividual variance for the K_m and V_{max}, respectively, and $\sigma_{Cp_{ss(i)}}^2$ is the residual error variance of the $Cp_{ss(i)}$ attributable to both assay error and intraindividual variability.

For the BWLS, instead of the actual S.D., σ_{K_m} and $\sigma_{V_{max}}$ in the objective function were set at 50 and 20% of the K_m and V_{max} values, respectively, according to those of Kelman *et al.* and Peck *et al.*[14] The 15% C. V. was used for weighting of the serum concentrations in both the BWLS and OWLS methods. The population mean values used were those of the simulated population.

Statistical Methods——The predictive ability of the methods was evaluated from the mean prediction error (ME) as a measure of the bias and the root mean squared error (RMSE) as a measure of the precision[15]:

$$ME = \frac{1}{n} \sum_{i=1}^{n} Pe \tag{4}$$

$$RMSE = \left\{ \frac{1}{n} \sum_{i=1}^{n} Pe^2 \right\}^{1/2} \tag{5}$$

where Pe is the prediction error (prediction minus true value) and n is the number of pairs of predictions. A probability level of less than 0.05 was considered to be significant. Comparison of the relative predictive performance was evaluated by comparing the 95% confidence intervals (C.I.s) with each other.

Results

Estimating K_m and V_{max} Values by the Bayesian and Ordinary Weighted Least-Squares Methods

The predictive performances of BWLSs and OWLSs for K_m and V_{max} estimation are

TABLE I. Predictive Performance of the Bayesian and Ordinary Weighted Least-Squares Methods for Estimating Michaelis–Menten Parameters

Parameter	Method[a]	n[b]	r[c]	ME (95% C.I.)	RMSE (95% C.I.[d])[e]
K_m (μg/ml)	1p-BWLS	60	0.663	−0.384 (−0.788, 0.021)	1.599 (1.218, 1.906)
	2p-BWLS	60	0.886	−0.428 (−0.679, 0.176)	1.057 (0.859, 1.223)
	3p-OWLS	57[f]	0.837	−0.198 (−0.535, 0.140)	1.278 (0.971, 1.525)
	4p-OWLS	54[f]	0.979	0.001 (−0.080, 0.081)	0.294 (0.196, 0.366)[h]
V_{max} (mg/d)[g]	1p-BWLS	60	0.666	−12.35 (−23.43, −1.264)[j]	44.31 (37.36, 50.31)
	2p-BWLS	60	0.585	−5.03 (−17.0, 6.945)	46.26 (29.13, 58.57)
	3p-OWLS	57[f]	0.372	−13.92 (−36.2, 8.404)	84.66 (55.66, 106.0)[i]
	4p-OWLS	54[f]	0.868	−1.25 (−4.354, 1.855)	11.37 (8.525, 13.64)[h]

a) 1p- and 2p-BWLS, the Bayesian method with 1 and 2 observations; 3p- and 4p-OWLS, the ordinary weighted least-squares method with 3 and 4 observations. *b*) n indicates the number of predictions. *c*) r, correlation coefficient between the predicted and true values. *d*) Values in parentheses indicate the lower and upper 95% confidence intervals. *e*) ME, mean prediction error (prediction minus true value); RMSE, root mean squared error. *f*) Generation of negative values: 3p-OWLS, 3; 4p-OWLS, 6. *g*) Values are presented on the basis of 45 kg body weight. *h, i*) Significant differences were observed in precision: 4p-OWLS *vs.* other three methods; 1p-BWLS *vs.* 3p-OWLS. *j*) Significantly underpredicted true V_{max}.

shown in Table I.

The 4-point OWLS gave the most precise estimates of the K_m values (*i.e.*, the least RMSE; 7.5% of the true value), as compared to the other three methods ($p<0.05$). For all methods except the 4-point OWLS, the precisions were similar in magnitude in terms of the %RMSE: 3-point OWLS = 31.4%; 1-point BWLS = 35.4%; 2-point BWLS = 27.4%.

Although no method gave a significant bias (*i.e.*, each ME included zero in its 95% C.I.), both the 1-point and the 2-point BWLSs showed higher negative values of ME (−12% of the true value) than the OWLSs: 3-point OWLS = −3.4%; 4-point OWLS = −1.7%. It seems likely therefore that the BWLS underpredicts the true K_m value. The BWLS was considered to be less precise than the 4-point OWLS and comparable to the 3-point OWLS for estimating the K_m value.

Concerning the bias in V_{max} estimates, the 1-point BWLS significantly underpredicted the true V_{max} by −12.3 mg/d ($p<0.05$). However, there was no significant bias in all the other methods.

The 1-point and 2-point BWLSs gave RMSEs of 44.3 mg/d (16.2% of the true value) and 46.3 mg/d (14.3%), respectively, and showed no significant difference in precision with respect to the number of Cp_{ss} measurements used to estimate the parameter. The 4-point OWLS gave the most precise estimates of V_{max} (RMSE = 11.4 mg/d), while the 3-point OWLS gave a relatively high prediction error (RMSE = 84.7 mg/d) and was significantly less precise than the BWLSs for V_{max} estimation.

Prediction of the Steady-State Serum Concentration by the Bayesian and Ordinary Weighted Least-Squares Methods

Table II shows the predictive performances of BWLSs and OWLSs for predicting Cp_{ss}.

None of the methods showed any bias in the prediction of Cp_{ss}. The 4-point OWLS gave the least ME and RMSE among the methods (%ME = 0.2%, %RMSE = 3.4%). For all methods except the 4-point OWLS, there was no significant difference in the magnitude of ME: 1-point BWLS = 0.34 μg/ml; 2-point BWLS = −0.38 μg/ml; 3-point OWLS = 0.54 μg/ml. This tendency was the same as that observed in the K_m estimation.

As regards the precision, the 1-point BWLS gave 3.4 μg/ml as the RMSE and the 2-point BWLS, 2.7 μg/ml. The precision by the 2-point BWLS was thus a little higher than that by the 1-point BWLS, but only by 0.7 μg/ml, showing no significant difference in precision between the two BWLSs. The prediction error of the BWLS was therefore considered to be

TABLE II. Predictive Performance of the Bayesian and Ordinary Weighted Least-Squares Methods for Prediction of Serum Concentrations

Method[a)]	n[b)]	r[c)]	ME (95% C.I.) unit: μg/ml	RMSE (95% C.I.[d)])[e)] unit: μg/ml
1p-BWLS	60	0.856	0.340 (−0.481, 1.161)	3.377 (1.391, 4.570)
2p-BWLS	60	0.873	−0.376 (−1.011, 0.259)	2.722 (1.191, 4.174)
3p-OWLS	57[f)]	0.834	0.538 (−0.407, 1.483)	3.545 (1.157, 4.878)
4p-OWLS	54[f)]	0.999	0.012 (−0.050, 0.075)	0.259 (0.176, 0.321)[g)]

a—f) See footnotes to Table I. *g*) Significant differences were observed in precision: 4p-OWLS *vs.* other three methods.

approximately 3.0 μg/ml (95% C.I.; 1.4—4.6 μg/ml), regardless of the number of observations used for predicting Cp_{ss}. Moreover, the precision obtained from the BWLSs was comparable to that of the 3-point OWLS.

Discussion

Figure 1 shows the absolute prediction error of K_m and V_{max} estimates as a percent of the true values.

K_m could be estimated with less than 30% prediction error: 1-point BWLS, 30%; 2-point BWLS, 20%; 3-point OWLS, 25%; 4-point OWLS, 5%. For V_{max}, the predictive ability of each method was approximately two-fold higher than for K_m: 1-point BWLS, 15%; 2-point BWLS, 10%; 3-point OWLS, 20%; 4-point OWLS, 2%. The difference in precision between the K_m and V_{max} estimates seem to be related to the determinate error existing in the Michaelis–Menten model itself (the relative error in K_m or V_{max} estimates can be approximated theoretically by a linear expansion[16] of Eq. 1; details not shown).

For the prediction of Cp_{ss}, the 4-point OWLS provided the most precise estimates among the methods evaluated, and the other three methods showed no significant difference in relative bias and precision between each other (Table II).

On the whole, the BWLS with as few as one or two observations was concluded to be comparable to the 3-point OWLS in precision, but significantly less precise than the 4-point OWLS. However, it is important to note that these results were obtained after excluding unreasonable predictions of negative or of very large values: the OWLS applied to the Michaelis–Menten model gave such predictions even with more than three observations (3 of 60 in 1-point OWLS, 7 of 60 in 2-point OWLS), whereas the BWLS did not. In other words, the BWLSs are considered to be constrained by the population parameter values, the mean and variance, in the optimizing process, so that we found no such predictions as observed in the OWLSs. This is one of the advantages of the Bayesian method in clinical practice.

As regards the number of observations to predict further Cp_{ss} of PHT, there is no difference in both bias and precision between the 1-point and the 2-point BWLSs. This tendency is partly in agreement with those obrained from actual patient data. In the reports of Vozeh *et al.*[12] and Yuen *et al.*,[17] although both evaluated the linearized Bayesian method for predicting the total daily dosage as a target value, no difference was found in both the bias and precision of the daily dosage prediction between one and two observations. On the other hand, this trend is inconsistent with results obtained previously in simulation studies of a drug with a one-compartment open linear model,[18,19] where a significant decrease of bias or an increase of precision was found with increase in the number of observations from one to two. This model-dependent difference in bias with number of observations cannot be clearly explained at present.

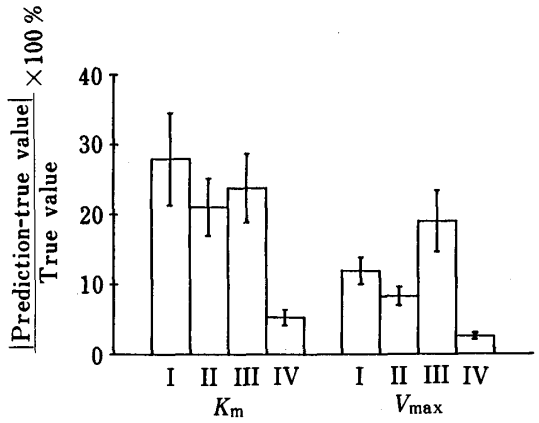

Fig. 1. Percent Absolute Error of Estimated Parameters in the Bayesian and Ordinary Weighted Least-Squares Methods

The vertical lines indicate ± S.E.M. I, 1-point BWLS; II, 2-point BWLS; III, 3-point OWLS; IV, 4-point OWLS.

Our simulation study revealed that the upper value of the 95% confidence interval of RMSE is near to 4.6 μg/ml, indicating a clinically acceptable prediction error, given an appropriate population mean and variance; *i.e.*, the serum concentration in 95% of the general population would fall within the therapeutic range of 10—20 μg/ml using the Bayesian method with at least one observation, if the desired concentration was targeted at 15 μg/ml, the midpoint of the range. In another study by us on Japanese children taking PHT,[20] the RMSE obtained from actual patient data was approximately 6.6 μg/ml ($n=67$, 95% C.I.; 3.1—8.7 μg/ml), showing a reduced applicability in clinical practice. The difference in magnitude of the prediction error between the simulated and actual patients might be accounted for by inappropriate selection of the population parameters (*i.e.*, lack of available information) in the actual patient population. This suggests that if appropriate population parameter means and variances are provided in a specified patient population, the actual prediction error should approach the value obtained from the simulation study.

References and Notes

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