Clinical Evaluation of Population Pharmacokinetic Parameters in Phenytoin Dosage Adjustment

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We investigated the influence of the population pharmacokinetic parameters on the performance of the Bayesian feedback method in predicting the phenytoin (PHT) dosage needed to achieve a desired PHT serum concentration. Population pharmacokinetic parameters studied were taken from reports by Sheiner *et al.* (I), Grasela *et al.* (II), Miller *et al.* (III), and the authors (IV). The predictive abilities of the Bayesian feedback method were evaluated by using retrospective data from 70 patients. The mean prediction error, mean absolute prediction error (*MAE*), and root mean squared error (*RMSE*) served as measures of prediction bias and precision.

The precision of the initial estimates based on the population parameter set IV was superior to those of other initial estimates studied. The performance of the Bayesian feedback method to predict PHT dosage at the steady state was relatively insensitive to bias in the estimates of the population parameters. However, the revised estimates derived from the Bayesian feedback method using the population parameter set IV with one feedback gave the lowest *MAE* and *RMSE* in predicting PHT dosage.

Keywords phenytoin; Bayesian feedback method; prediction; population pharmacokinetic parameter; dose prediction; Michaelis–Menten

Phenytoin (PHT) is an effective anticonvulsant which has been used for treatment of seizure disorders for many years. Its pharmacology and pharmacokinetics make the determination of an appropriate maintenance dose difficult. It has been shown that the system utilizing the Bayesian feedback method performs better than all methods previously reported in PHT dosage adjustment on an individual basis.[1-4] A prerequisite of such methods is a good estimate of the population or subpopulation parameter distributions (means and variances). The greater the confidence in these distributions, the better will be the performance of the associated Bayesian feedback method.

More recently, an alternative approach to population pharmacokinetic data analysis has been implemented in the Nonlinear Mixed Effects Model (NONMEM) computer program.[5-7] It has been applied to the retrospective analysis of clinical data of PHT by Sheiner *et al.* (I),[8] Grasela *et al.* (II),[9] Miller *et al.* (III),[10] and the authors (IV).[11]

PHT dosing can be viewed as the following process: a) determination of initial maintenance dose (initial estimate), and b) a first dosage adjustment using Bayesian feedback based on one dose-steady-state concentration pair (Bayesian estimate). Accordingly, the population pharmacokinetic parameters for PHT were evaluated retrospectively to assess their effect on the determination of the initial maintenance dose and the predictive performance of the Bayesian feedback method based on one dose-steady-state concentration (*Css*) pair in the first dosage adjustment.

TABLE I. Details of the Patients

Variables	Adults[a]	Children[b]	All patients
Number of patients	58	12	70
Number of observations	123	26	149
Proportion of data from males	0.41	0.33	0.40
Age (years)	32.7±11.2[c]	10.0±4.9[c]	28.7±13.5[c]
Body weight (kg)	56.8±10.2[c]	32.6±15.8[c]	52.6±14.6[c]
Daily dose (mg)	250.8±57.1[c]	202.7±73.2[c]	242.4±62.7[c]
Serum concentration (μg/ml)	12.81±8.94[c]	9.41±7.12[c]	12.22±8.73[c]

a) ≧15 years. *b)* <15 years. *c)* Mean±standard deviation.

Patients and Methods

Patients The clinical data in this report were retrospectively obtained from epileptic children and adults receiving PHT alone or PHT combined with other anticonvulsants. Patients whose concurrent therapy was altered in a period of concentration measuring were excluded from the study. We collected 70 patients (28 males and 42 females) who had two or more reliable measurements of the steady-state concentration of PHT in serum, measured while they were taking different daily doses. The details of these patients are summarized in Table I. All patients had normal renal and hepatic function, and were given PHT acid. PHT was prescribed two to three times a day as a tablet preparation or a powder preparation. The concentration of PHT was determined at least 30 d after any change in dosage. This time interval between changes in dosage was considered adequate to allow establishment of the new steady-state concentration in serum. All blood samples were drawn at approximately two to four hours after administration of a dose. The PHT concentration was routinely measured by the fluorescence polarization immunoassay (FPIA) method. The coefficient of variation of this assay was less than 10%.

Pharmacokinetic Model The usual Michaelis–Menten model was used, *i.e.*:

$$D_{ij} = Vm_j Css_{ij}/(Km_j + Css_{ij})$$

where D_{ij} is the dosage of PHT in mg/d predicted to achieve the i-th *Css* in the j-th patient; Vm_j is the maximum elimination rate of the j-th patient in mg/d; and Km_j is the Michaelis–Menten constant (in mg/l of PHT) for the j-th patient. Bioavailability is assumed to be 100%; if not, Vm_j must be regarded as Vm_j/F_j, where F_j is the bioavailability of PHT in the j-th patient.

Bayesian Feedback Method The theoretical basis of the Bayesian forecasting technique has been discussed in detail by Sheiner *et al.*[12,13] This method makes the dosage predictions on the basis of the measured values of steady-state concentration and prior information about PHT kinetics. Prior information about PHT kinetics is necessary because the method requires knowledge of the 'average' values of the parameters that define PHT kinetics together with their inter- and intra-individual standard deviations. The following objective function is minimized with respect to the pharmacokinetics parameters to obtain the individual estimates:

$$OBJ_{\text{Bayes}} = [(Vm - Vm')/\omega_V]^2 + [(Km - Km')/\omega_K]^2 + [(D - D')/\sigma_D]^2$$

where *Vm* and *Km* are the population mean values, *Vm'* and *Km'* are the individual parameter estimates with respect to which the expression is to be minimized; and *D'* is the dosage that would have been calculated using the current estimates of *Vm'* and *Km'* and initial measured *Css* in the Michaelis–Menten equation; *D* is the actual dosage given; ω_V and ω_K are

interindividual standard deviations for Vm and Km, respectively; and σ_D is the standard deviation of the combined intraindividual and model misspecification errors.

The values of the population mean parameters and the standard deviations for the population distributions studied are given in the Appendix.

The microcomputer program (PEDA)[14] for the Bayesian feedback method was written by one of the authors in BASIC programming language and was executed on a Casio FP-6000 microcomputer.

Data Analysis The predictive performance of each method was evaluated, as was presented by Sheiner and Beal,[15] by calculating mean prediction error (*ME*), mean absolute prediction error (*MAE*) and root mean squared error (*RMSE*).

The *ME*, *MAE* and *RMSE* were calculated as follows:

$$ME=(1/n)\sum_{i=1}^{n}(Pe)$$

$$MAE=(1/n)\sum_{i=1}^{n}|Pe|$$

$$RMSE=\sqrt{(1/n)\sum_{i=1}^{n}(Pe)^2}$$

where Pe is the prediction error (predicted dose minus actual dose) and n is the number of predictions. The relative performance was evaluated by comparing 95% confidence intervals.

Results

We tested the propriety of our estimated population pharmacokinetic parameters in comparison with other reported values for predicting initial PHT maintenance dose in Japanese patients.

The correlation coefficients, *ME*, *MAE*, *RMSE* and their respective 95% confidence intervals for the predictions produced by the initial estimates with various population parameter sets are shown in Table II.

The initial estimates using the population parameter sets I and III significantly underpredicted the actual doses in children (*e.g.* the 95% confidence interval of the *ME* did not include zero). The initial estimates using the population parameter sets I, III and IV significantly overpredicted the actual doses in adults. The precision of the initial estimates using the population parameter set IV was superior to those of other initial estimates studied in adults and children.

Figure 1 illustrates the relationships between age and the prediction error produced from each parameter set. The parameter sets I and III underpredicted the actual doses in a population of less than 15 years old. These results indicate that the parameter set IV is the most suitable for predicting the initial PHT dosage of Japanese patients, followed by the parameter set II.

Table III shows the predictive performance of Bayesian estimates using various population parameter sets with one feedback in making PHT dosage adjustments of Japanese patients. For these methods, *MEs* were similar in magnitude, and the confidence intervals for each method included zero and overlapped with each other. The *MAEs* and *RMSEs* were also similar in magnitude and the confidence intervals overlapped with each other. In terms of precision, the order of preference of each method for PHT dosage prediction was method IV ($MAE=22.62$ mg/d; $RMSE=28.40$ mg/d), method II ($MAE=23.48$ mg/d; $RMSE=29.38$ mg/d), method I ($MAE=23.87$ mg/d; $RMSE=30.50$ mg/d), and method III ($MAE=31.22$ mg/d; $RMSE=$

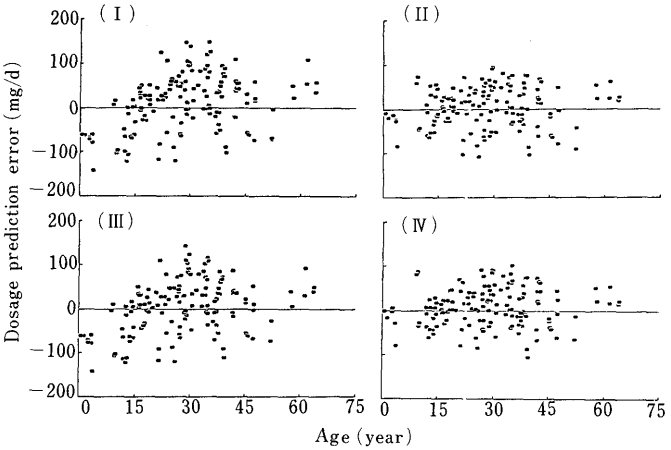

Fig. 1. Scatter Diagrams of Prediction Error *versus* Age Used in Making the Prediction of Initial Phenytoin Dosage for the Parameters of Sheiner *et al.* (I), Grasela *et al.* (II), Miller *et al.* (III), and Yukawa *et al.* (IV)

TABLE II. Predictive Performance of Initial Estimates in Predicting Phenytoin Dosage

Methods[a]	n	Correlation[b] coefficient (r)	*ME* (95% c.i.)[c] (mg/d)	*MAE* (95% c.i.)[c] (mg/d)	*RMSE* (95% c.i.)[c] (mg/d)
Adults					
I	123	0.618	25.78[d] (15.68 to 35.88)	51.21 (44.96 to 57.46)	61.96 (54.83 to 68.36)
II	123	0.636	6.99 (−1.39 to 15.37)	38.43 (33.50 to 43.36)	47.25 (42.02 to 51.95)
III	123	0.602	16.94[d] (7.41 to 26.47)	45.44 (39.64 to 51.24)	55.79 (49.13 to 61.73)
IV	123	0.685	11.05[d] (3.33 to 18.77)	36.04 (31.37 to 40.71)	44.46 (39.36 to 49.04)
Children					
I	26	0.820	−56.19[e] (−74.15 to −38.24)	59.94 (44.17 to 75.72)	71.17 (54.79 to 84.43)
II	26	0.820	−9.44 (−26.58 to 7.70)	36.88 (28.00 to 45.76)	42.74 (32.95 to 50.67)
III	26	0.813	−58.80[e] (−76.81 to −40.78)	61.66 (45.34 to 77.98)	73.33 (56.58 to 86.91)
IV	26	0.852	−9.82 (−25.31 to 5.67)	30.29 (20.23 to 40.35)	38.94 (25.38 to 48.87)
All patients					
I	149	0.685	11.48[d] (1.38 to 21.57)	52.73 (46.99 to 58.48)	63.67 (57.36 to 69.41)
II	149	0.715	4.12 (−3.34 to 11.59)	38.16 (33.88 to 42.44)	46.49 (41.97 to 50.62)
III	149	0.675	3.72 (−5.80 to 13.25)	48.27 (42.74 to 53.80)	59.22 (53.11 to 64.76)
IV	149	0.752	7.41[d] (0.49 to 14.32)	35.04 (30.87 to 39.20)	43.55 (38.97 to 47.70)

a) Population pharmacokinetic parameters studied (see Appendix) were taken from reports by Sheiner *et al.* (I), Grasela *et al.* (II), Miller *et al.* (III) and Yukawa *et al.* (IV). *b*) Correlation coefficient between the actual and predicted dose. *c*) The 95% confidence intervals of the mean. *d*) Significantly overpredicted the true dosage, $p<0.05$. *e*) Significantly underpredicted the true dosage, $p<0.05$.

TABLE III. Predictive Performance of Bayesian Estimates in Predicting Phenytoin Dosage

Methods[a]	n	Correlation[b] coefficient (r)	ME (95% c.i.)[c] (mg/d)	MAE (95% c.i.)[c] (mg/d)	RMSE (95% c.i.)[c] (mg/d)
Adults					
I	146	0.883	1.97 (−3.03 to 6.98)	24.56 (21.53 to 27.58)	30.79 (26.83 to 34.30)
II	146	0.882	2.14 (−2.52 to 6.81)	23.05 (20.25 to 25.84)	28.74 (25.44 to 31.69)
III	146	0.834	5.41 (−0.13 to 10.94)	27.72 (24.39 to 31.04)	34.43 (30.76 to 37.74)
IV	146	0.880	1.39 (−3.35 to 6.14)	23.53 (20.72 to 26.34)	29.18 (25.79 to 32.21)
Children					
I	30	0.920	−8.13 (−18.67 to 2.42)	20.50 (12.72 to 28.27)	29.00 (12.58 to 39.04)
II	32	0.904	−6.68 (−18.21 to 4.84)	25.44 (18.23 to 32.64)	32.15 (22.90 to 39.28)
III	32	0.829	−39.27[d] (−54.20 to −24.34)	47.21 (35.78 to 58.64)	56.59 (44.34 to 66.62)
IV	32	0.944	−3.78 (−12.66 to 5.10)	18.49 (12.58 to 24.39)	24.53 (17.09 to 30.19)
All patients					
I	176	0.896	0.25 (−4.27 to 4.77)	23.87 (21.05 to 26.68)	30.50 (26.67 to 33.90)
II	178	0.894	0.56 (−3.77 to 4.88)	23.48 (20.88 to 26.08)	29.38 (26.32 to 32.15)
III	178	0.828	−2.62 (−8.41 to 3.16)	31.22 (27.69 to 34.75)	39.34 (35.19 to 43.10)
IV	178	0.903	0.46 (−3.72 to 4.65)	22.62 (20.09 to 25.15)	28.40 (25.38 to 31.12)

a) Population pharmacokinetic parameters studied (see Appendix) were taken from reports by Sheiner *et al.* (I), Grasela *et al.* (II), Miller *et al.* (III) and Yukawa *et al.* (IV). *b*) Correlation coefficient between the actual and predicted dose. *c*) The 95% confidence intervals of the mean. *d*) Significantly underpredicted the true dosage, $p<0.05$.

39.34 mg/d). Method III gave not only a poor correlation ($r=0.828$) between actual and predicted values but also a large value of prediction error ($MAE=31.22$ mg/d). Method IV demonstrated the highest correlation between actual and predicted values ($r=0.903$), and it was superior to all other methods evaluated in accuracy and precision. Nevertheless, significant differences were not observed between methods IV and II or methods IV and I.

Discussion

The need to individualize PHT dosage is now widely acknowledged, and a number of population pharmacokinetic parameters and feedback control methods have been used for this purpose.

Our first objective was to compare the accuracy and precision of the 4 major population pharmacokinetic parameters of individualizing PHT initial dosage. Sheiner *et al.* reported the result of NONMEM analysis conducted on 124 dose-*Css* pairs from 49 adult epileptic patients. Miller *et al.* reported the result of NONMEM analysis conducted on 100 dose-*Css* pairs from 37 epileptic patients ranging in age from 11 years to 60 years. Consequently, the predicted PHT initial dosage using their parameters (initial estimates) underpredicted the actual dosage needed to achieve various serum concentrations in a population of less than 15 years old (Fig. 1).

Grasela *et al.* presented a more comprehensive analysis of PHT data collected from a number of different sources: Japan (104 patients, 236 dose-*Css* pairs), the United Kingdom (40 patients, 159 dose-*Css* pairs) and Germany (178 patients, 385 dose-*Css* pairs). The predictive ability of initial PHT dosage using their parameters in Japanese patients was superior to those of Sheiner *et al.* and Miller *et al.* The present study also demonstrates that population pharmacokinetic parameters that were determined previously by the authors can be used successfully for predicting initial PHT dosage in a different group of Japanese patients.

The Bayesian feedback method appears to be most accurate in predicting drug doses necessary to achieve a specific serum drug concentration. The Bayesian feedback algorithm requires the measured value(s) and adequate population pharmacokinetic parameters and their variances in individual drug dosage adjustment. It can be readily appreciated from the theoretical basis of the Bayesian feedback method that the predictive performance of the method is sensitive to population or subpopulation parameter values (means and variances).

Our second objective was to compare the accuracy and precision of the Bayesian feedback method using these population parameter sets in individual PHT dosage adjustment. In our PHT study with the four kinds of population parameter sets, no significant difference in predictive performance of the Bayesian feedback method was found in terms of both bias and precision. Therefore, the performance of the Bayesian feedback method with respect to point prediction at the steady state seems relatively insensitive to bias in the estimates of the population parameters. But, the Bayesian feedback method using the population parameter set IV with one feedback gave the lowest *MAE* and *RMSE*.

In conclusion, we recommend use of population parameter set IV for the determination of initial maintenance PHT dose and the first dosage adjustment using Bayesian feedback in Japanese patients.

Appendix

Various Population Parameter Sets

I: Sheiner *et al.*
$Vm=7.22$ mg/kg/d
$Km=4.44$ mg/l
$\omega_V=23.8\%$ (C.V.)
$\omega_K=54.1\%$ (C.V.)
$\sigma_D=0.25$ mg/kg/d

II: Grasela *et al.*
$Vm=[415\cdot(\text{weight}/70)^{0.6}]$ mg/d
$Km=3.8$ mg/l > 15 yr
2.2 mg/l < 15 yr
$\omega_V=11.0\%$ (C.V.)
$\omega_K=56.0\%$ (C.V.)
$\sigma_D=12.0\%$ (C.V.)

III: Miller *et al.*
$Vm=6.5$ mg/kg/d
$Km=3.4$ mg/l
$\omega_V=20.3\%$ (C.V.)
$\omega_K=73.0\%$ (C.V.)
$\sigma_D=28.0\%$ (C.V.)

IV: Yukawa *et al.*

$Vm = [369 \cdot (\text{weight}/60)^{0.55}]$ mg/d $\quad \omega_V = 18.6\%$ (C.V.)

$Km = 3.67$ mg/l $\geqq 15$ yr $\quad \omega_K = 57.4\%$ (C.V.)

3.08 mg/l < 15 yr $\quad \sigma_D = 11.4\%$ (C.V.)

$F = 1$ for tablet

0.895 for powder

C.V. = coefficient of variation

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