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Clinical Utility of a New and Simple Technique for Individualizing Phenytoin Dosage

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Wagner proposed a new and simple method to predict dosage of drugs obeying simple Michaelis-Menten elimination kinetics. From his theory the following equation, $D_n = D_o + \ln (C_d/C_o)/S$ can be derived, which forms the basis of predicting the required dosage (D_n) to obtain a desired steady-state concentration (C_d), using initial steady-state concentration (C_o), obtained with initial dose (D_o) and a population value of S for the drug.

We retrospectively investigated the value of S for phenytoin (PHT) in a population of 55 outpatients who had three or more reliable measurements of the steady-state concentration of PHT in serum, measured while they were taking different daily doses. The value of S for PHT was estimated to be 0.0122759 in Japanese patients.

The predictive performance of this equation was compared with Bayesian feedback method (B) using retrospective data from 220 outpatients. This equation yielded mean error (ME) of 0.0, mean absolute error (MAE) of 30.7 and root mean squared error (RMSE) of 40.9 mg/d compared to ME of −2.5, MAE of 30.3 and RMSE of 40.1 mg/d for B method, These results indicate that this equation may be a useful adjunct for prediction of PHT dosage as well as B method. Moreover, the simplicity of the equation allows calculation on a hand-held calculator.

Keywords — dose prediction; Michaelis-Menten; pharmacokinetics; phenytoin; Wagner equation

Introduction

Phenytoin (PHT) is one of the most widely used anticonvulsive drugs in clinical medicine. It is now clear that PHT follows Michaelis-Menten kinetics in human[1] with an optimal therapeutic range of 10—20 μg/ml.[2] Because of this narrow therapeutic range and the wide inter-individual variation of PHT pharmacokinetic parameters, measurement of serum concentration has been advocated to improve PHT therapy.[3] However, it is often difficult to adjust PHT dosage at therapeutic drug concentration even if measured serum concentration values are available. Many methods using measured serum drug concentrations have therefore been developed to optimize PHT dosing, including nomograms,[4-7] pharmacokinetic equations,[8-13] and Bayesian feedback method.[14]

More recently, Wagner proposed a new and simple equation to predict dosage of drugs obeying simple Michaelis-Menten elimination kinetics.[13] We have previously evaluated the various single dose-steady-state serum concentration (C_{ss}) feedback methods in Japanese populations.[15,16] In our results, the method proposed by Wagner showed poor predictive performances. This was the result of the parameter value used in this method being unsuitable for Japanese patients.[17] We expected that the predictive performance would be better if a parameter more suitable for Japanese patients was used.

Accordingly, we retrospectively investigated the suitable parameter in a population of Japanese patients taking PHT. The predictive ability of this method was compared with both original Wagner method and Bayesian feedback method.

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 for whom concurrent therapy was altered during the period of concentration measurement were excluded from the study. We collected 55 patients (29 males and 26 females) who had three

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TABLE I. Details of 55 Patients

Variables	Adults		Children		All patients	
	Mean±S.D. [a]	Range	Mean±S.D.	Range	Mean±S.D.	Range
Number of patients	30 [b,c]		25 [d,e]		55	
Number of observations	93		79		172	
Proportion of data from males	0.43		0.64		0.53	
Age (years)	29.8±12.0	16.4±66.7	10.8±3.3	4.2—15.9	21.1±13.1	4.2—66.7
Body weight (kg)	54.5±7.9	30.0±70.0	35.4±15.4	11.0—58.0	45.7±15.3	11.0—70.0
Daily dose (mg)	247.7±78.5	100.0±500.0	189.3±88.5	60.0—500.0	220.9±88.0	60.0—500.0
Serum concentration (μg/ml)	10.87±8.62	1.90±48.60	7.85±7.09	1.80—48.00	9.48±8.08	1.80—48.60

a) Standard deviation. *b)* Monotherapy in 8 patients, polytherapy in 22 patients (polytherapy comprised phenytoin plus phenobarbital, carbamazepine or valproate sodium). *c)* 15 patients were prescribed a powder of phenytoin. *d)* Monotherapy in 4 patients, polytherapy in 21 patients. *e)* 18 patients were prescribed a powder of phenytoin.

or more reliable measurements of the steady-state concentration of PHT in serum, measured while they were taking different daily doses. Patients aged from 4.2 to 66.7 years and weighed from 11 to 70 kg (Table I). All patients had normal renal and hepatic functions, and were given PHT acid. PHT was prescribed two to three times a day in tablet or powder form. The concentration was determined at least three weeks after any change in dosage. This time interval between changes in dosage was considered adequate to reach a new steady-state concentration in serum. All blood samples were drawn approximately 2 to 4 h after administration of a dose. The PHT concentration was routinely measured by enzyme multiplied immunoassay technique (EMIT) method. The coefficient of variation of this assay was less than 10%.

Wagner Method — Wagner[13] proposed a new and simple method to predict dosage of drugs obeying simple Michaelis-Menten elimination kinetics. He observed that a semilogarithmic plot of the steady-state serum concentration (C_{ss}) *versus* the daily dose (D) is linear with intercept (I) and slope (S) for a drug whose elimination obeys Michaelis-Menten pharmacokinetics. This linear equation has the form;

$$\ln C_{ss} = I + S \cdot D \tag{1}$$

From the above equation the following one can be derived to predict the daily dose of a specific drug required to produce a desired steady-state drug concentration;

$$D_n = D_o + \ln (C_d / C_o) / S \tag{2}$$

where D_n is the new dose, D_o is the initial dose, C_o is the initial steady-state serum concentration, and C_d is the desired steady-state serum concentration.

TABLE II. Details of the Patients in Predictive Performance of Phenytoin Dosage

Variables	Mean±S.D. [a]	Range
Number of patients	220	
Number of observations	505	
Proportion of data from males	0.55	
Age (years)	22.4±14.0	2.7—71.1
Body weight (kg)	47.5±16.1	10.0—115.0
Daily dose (mg)	217.5±77.7	40.0—500.0
Serum concentration (μg/ml)	8.97±7.09	1.00—48.60

a) Standard deviation.

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Fitting of Real Data — The dose D_n required to produce a steady-state concentration C_d is estimated by Eq. 2 using the initial concentration C_o obtained with initial dose D_o and the population value of S. Wagner proposed the S value of 0.007772 using the PHT data of Murphy *et al.*[18]

Individual PHT data of 55 patients, where three to four steady-state concentration were measured, were fitted in Eq. 1 to determine the suitable population value of S.

Prediction of PHT Dosage — The predictive performance of this equation using the new value of S was compared with the results of the Bayesian feedback method and the original Wagner method using retrospective data from 220 outpatients (Table II).

The microcomputer program (PEDA)[19] for the Bayesian feedback method[14] was written by one of the authors in BASIC programming language and was executed on a Casio FP-6000 microcomputer.

The values of the population mean parameters and the standard deviations for the population distributions have been set at:

$K_m = 2.2$ mg/l; <15 years
$K_m = 3.8$ mg/l; >15 years
$V_m = [415 \cdot (\text{weight}/70)^{0.6}]$ mg/d
$\sigma_V = 0.11\ (V_m)$; $\sigma_K = 0.56\ (K_m)$;
$\sigma_D = 0.12\ (D)$

as proposed by Grasela *et al.*[20]

Statistical Analysis — According to Sheiner and Beal,[21] the predictive performance of this method was evaluated using mean prediction error (ME), mean absolute prediction error (MAE) and root mean squared error (RMSE). The ME, which describes the bias that may be present, is determined by calculating the difference between the predicted and actual values for each subject. The MAE is a measure of precision and the RMSE is a composite measure of bias and precision; the smaller the MAE and RMSE, the greater the precision of the prediction. The ME, MAE and RMSE were calculated as follows:

$$\text{ME} = (1/n) \sum_{i=1}^{n} (\text{predicted dose} - \text{actual dose})$$

$$\text{MEA} = (1/n) \sum_{i=1}^{n} |\text{predicted dose} - \text{actual dose}|$$

$$\text{RMSE} = \sqrt{(1/n) \sum_{i=1}^{n} (\text{predicted dose} - \text{actual dose})^2}$$

where n is the number of predictions. Comparison of the relative predictive performance was evaluated by comparing 95% confidence intervals.

Results

Fitting of Real Data

The relationship between ln C_{ss} and D was subsequently evaluated for each patient. Table III gives the results of fitting the PHT data of 55 patients. The coefficients of variation of parameters I and S in Table III indicate that intersub-

TABLE III. Fitting of Patient Data to the Logarithmic Growth Function

Study group		Slope (S)	Intercept (I)	Correlation coefficient
Adults	Mean	0.0121507	−0.94826	0.9774
	S.D. a)	0.0070109	2.06941	0.0306
	CV (%) b)	57.7	218.2	3.1
Children	Mean	0.0124261	−0.45158	0.9644
	S.D.	0.0049279	1.00662	0.0424
	CV (%)	39.7	222.9	4.4
All patients	Mean	0.0122759	−0.72250	0.9714
	S.D.	0.0060999	1.67704	0.0367
	CV (%)	49.7	232.1	3.8

a) Standard deviation. b) Coefficient of variation.

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TABLE IV. Summary of Predictive Performance

Methods [a]	n	Correlation [b] coefficient (r)	ME (95% c.i.) [c] (mg/d)	MAE (95% c.i.) (mg/d)	RMSE (95% c.i.) (mg/d)
1	716	0.871	−2.5 (−5.5 to 0.4)	30.3 (28.3 to 32.2)	40.1 (37.5 to 42.5)
2	716	0.829	0.0 (−4.8 to 4.8)	51.4 (48.4 to 54.3)	65.4 (61.6 to 68.9)
3	716	0.878	0.0 (−3.0 to 3.0)	30.7 (28.7 to 32.7)	40.9 (38.1 to 43.5)

a) 1: Bayesian feedback method, 2: original Wagner equation (S= 0.007772), 3: modified Wagner equation (S= 0.0122759). *b)* Correlation coefficient between actual and predicted dose. *c)* 95% confidence interval of the mean.

TABLE V. Percentage of Predictions with Errors > 50 mg/d

	Bayesian feedback method	Original Wagner method	Modified Wagner method
n	716	716	716
Overprediction	8.1	20.7	10.1
Underprediction	11.2	20.7	10.1
Total	19.3	41.4	20.2

ject variation of I is much greater than variation of S. The mean S values for children and adults were 0.0124261 and 0.0121507, respectively. Significant difference was not observed between the two S values. Accordingly, the total mean value of S for PHT was estimated to be 0.0122759 in Japanese patients. This value was 58% higher than that originally reported by Wagner.

Prediction of PHT Dosage

The correlation coefficients, ME, MAE, RMSE and their respective 95% confidence limits for predicted PHT doses are shown in Table IV.

The modified Wagner equation yielded ME of 0.0, MAE of 30.7 and RMSE of 40.9 mg/d. The precision of the modified Wagner method was significantly better than that with the original Wagner method (MAE=51.4 mg/d; RMSE=65.4 mg/d), and was equivalent to that obtained with the Bayesian feedback method (MAE=30.3 mg/d; RMSE=40.1 mg/d).

Percentage of Predictions with Errors > 50 mg/d

Table V summarizes the percentage of predictions that had an absolute prediction error > 50 mg/d for each method. Figure 1 shows the scatter diagrams of dosage prediction errors *versus* initial steady-state serum concentration used in making the predication for each method.

The total error percentage (20.2%) of the modified Wagner method was significantly lower than that with the original Wagner method (41.4%), and was similar to that obtained with the Bayesian feedback method (19.3%).

Discussion

Many techniques have been advocated to aid in dosage adjustments based on a single-point PHT concentration determined at steady state. But it is important to use the most accurate dosing method to achieve the desired response and also to avoid toxicity. We have previously evaluated the various single dose-C_{ss} feedback methods in Japanese patients. The predictive performance of the Bayesian feedback method was superior to other methods and that proposed by Wagner indicated poor predictive performances. The original S value in this method was considered unsuitable for Japanese patients. The main purposes of this study were to estimate the S value for PHT in Japanese patients and to evaluate this method of predicting PHT dosage.

Wagner proposed the S value of 0.007772

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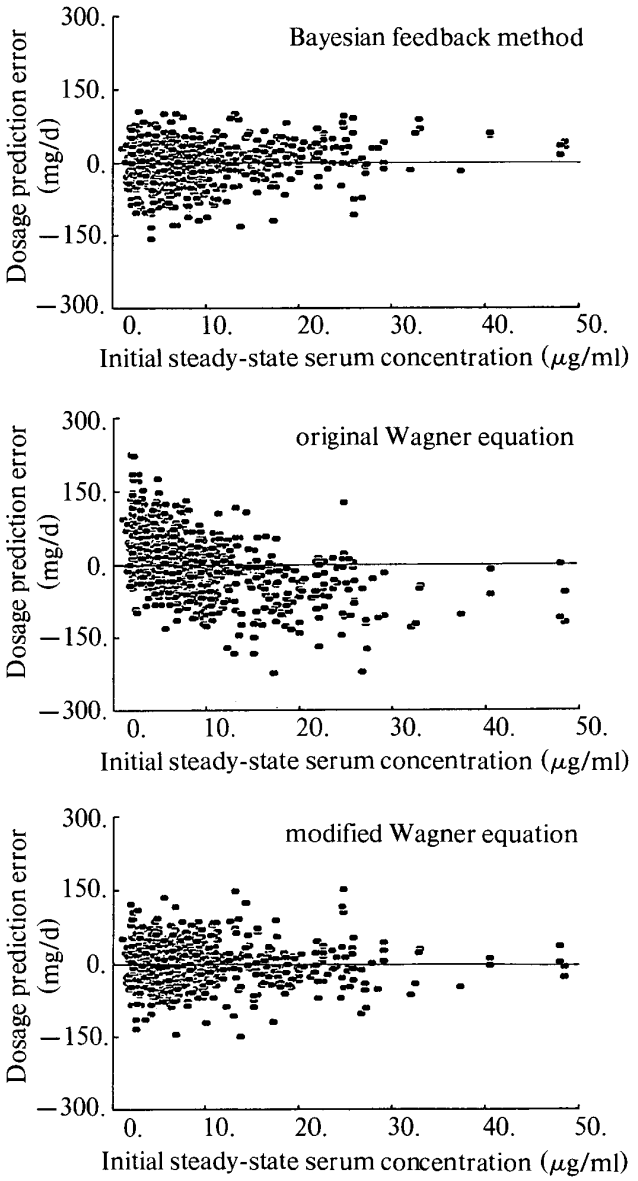

Fig. 1. Scatter Diagrams of Dosage Prediction Error *versus* Initial Steady-State Serum Concentration Used to Make the Prediction for the Bayesian Feedback Method, the Original Wagner Equation, and the Modified Wagner Equation

using PHT data of patients treated with PHT sodium. Similar research was performed with individual subject PHT data of 55 patients treated with PHT acid, where three to four steady-state concentrations were measured. The mean value of S for PHT was estimated to be 0.0122759 in Japanese patients. This value was found to be 58% higher than that originally reported by Wagner. This implies that toxic serum concentrations could be achieved at lower doses for this population group than for other population groups, and the group would also be more sensitive to dosage adjustment.

This finding is similar to that recently reported by Bryson *et al.*[22] in patients treated with PHT sodium. They found that the slope of the relationship between $\ln C_{ss}$ and D was 54% higher than the original value proposed by Wagner ($S=0.0120$). We have no clear reason for this similarity with our result at present.

The predictive performance of this equation using the new value of $S=0.0122759$ was compared with the result of the Bayesian feedback method using retrospective data from 220 outpatients. The precisions of the modified Wagner method was significantly better than that with the original Wagner method ($p < 0.05$), and was equivalent to that obtained with the Bayesian feedback method.

These results conclude that this equation may be a useful adjunct for prediction of PHT dosage as well as Bayesian feedback method. Moreover, the simplicity of this equation allows calculation on a hand-held calculator.

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