Phenytoin Dosage Adjustment Method Using Population Clearance

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Phenytoin (PHT) is a commonly used drug in children and adults, but it is often difficult to adjust the dosage to attain therapeutic drug concentrations due to the nonlinear nature of PHT metabolism. Therefore, many techniques have been proposed to aid dosage adjustment based on single-point PHT concentration determined at the steady state. We have derived a simple equation to predict PHT dosage in a patient in whom one steady-state serum concentration is known. This equation is based on a power relationship between PHT clearance (CL; l/d) and PHT concentration determined at the steady state (C_{ss}; μg/ml).

$$CL = D/C_{ss} = a \cdot C_{ss}^{\ b} \quad (1)$$

$$D_n = D_o \cdot C_o^{\ -(b+1)} \cdot C_d^{\ (b+1)} \quad (2)$$

where D is the PHT dose (mg/d), D_o is the original dose, D_n is the new dose, C_o is the original C_{ss}, and C_d is the desired C_{ss}.

We retrospectively investigated the values of a and b in a population of 40 outpatients who had three or more reliable measurements of C_{ss} in serum, measured while they were taking different daily doses. The a and b values were estimated to be 114.34 and −0.6786, respectively ($n = 126$; $r = 0.871$). Graves *et al.* have previously derived a similar equation based on an exponential relation between CL of PHT and C_{ss} in 59 patients ($a = 133.03$, $b = -0.804$). The predictive ability of this equation was compared with the results of Graves's method and the Bayesian feedback method using retrospective data from 70 patients. This equation allowed the prediction of a dose needed to produce a desired steady-state concentration with satisfactory error, being as effective as the Bayesian feedback method for therapeutic drug monitoring.

Keywords dose prediction; Michaelis–Menten; pharmacokinetics; phenytoin; clearance; anticonvulsant

Phenytoin (PHT) is an effective anticonvulsant which has been used for treatment of seizure disorders for many years. The usually accepted therapeutic range is 10—20 μg/ml.[1] In 1972, PHT was shown to obey Michaelis–Menten elimination kinetics.[2] The Michaelis–Menten equation can be written as

$$D = \frac{V_m \cdot C_{ss}}{K_m + C_{ss}} \quad (1)$$

where V_m is the maximum rate at which the drug can be metabolized, K_m is the serum concentration when half-V_m is achieved, D is the daily dose and C_{ss} is the steady-state serum concentration.

Clearance is the parameter that relates rate of elimination to the serum concentration. From Eq. 1, it can be seen that the clearance (CL) of PHT is a function of the serum concentration, that is

$$CL = \frac{V_m}{K_m + C_{ss}} = \frac{D}{C_{ss}} \quad (2)$$

Recently, Graves *et al.* have derived a simple equation to predict dosing requirement if one dose–C_{ss} pair relationship is known. This equation is based on an exponential relation between CL of PHT and C_{ss} in 59 patients.[3] The authors have derived a simple equation to predict PHT dosage in a patient in whom one steady-state concentration is known. This equation is based on a power relationship between CL of PHT and C_{ss} in a population of patients taking PHT. The predictive ability of this equation was compared with the results of the population clearance method proposed by Graves *et al.* and the Bayesian feedback method[4-6] in Japanese patients.

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 40 patients (19 males and 21 females) 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 patients were aged from 4.3 to 66.7 years and weighed from 11 to 70 kg. The details of these patients are shown in Table I. All patients had normal renal and hepatic functions, and were given PHT acid. PHT was prescribed two to three times a day as a tablet preparation or a powder preparation (Aleviatin® brand tablet and powder [Dainippon Pharmaceutical Co. Ltd., Osaka]). 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 a new steady-state concentration to be reached in serum. All blood samples were drawn at approximately 2 to 4 h after administration of a dose. The PHT concentration was routinely measured by the enzyme multiplied immunoassay technique (EMIT®) method. The coefficient of variation of this assay was less than 10%.

Equations The CL of a drug obeying Michaelis–Menten elimination kinetics gives a power relationship on graph paper when CL is plotted *versus* the corresponding C_{ss}. This power equation has the form

$$CL = D/C_{ss} = a \cdot C_{ss}^{\ b} \quad (3)$$

If a ratio is made of two equations like Eq. 3, with C_o corresponding to dose D_o, and C_d corresponding to D_n, with parameters a and b remaining constant, then a cancels out and the following equation is obtained:

$$\frac{D_n}{D_o} = \frac{C_d \cdot C_d^{\ b}}{C_o \cdot C_o^{\ b}} \quad (4)$$

Solving for D_n in Eq. 4 gives

$$D_n = D_o \cdot C_o^{\ -(b+1)} \cdot C_d^{\ (b+1)} \quad (5)$$

Hence, Eq. 5 provides a method of estimating the dose, D_n, necessary to give a desired steady-state concentration C_d if one knows a single steady-state concentration C_o corresponding to the maintenance dose D_o and if a population value of b is used.

Individual subject PHT data of 40 patients, where three to four steady-state concentrations were measured, were fitted to Eq. 3, and the population values of a and b were investigated. For the regression analysis, a computer program (STANDARD PAC) written in Basic was used on a

Hewlett–Packard 85 microcomputer.

Prediction of PHT Dosage The predictive ability of this equation was compared with the results of the population clearance method proposed by Graves *et al.* and the Bayesian feedback method using retrospective data from 70 patients not included in the calculation of these parameters. The details of these patients are shown in Table II. The PHT concentration was routinely measured by the fluorescence polarization immunoassay (FPIA) method. The coefficient of variation of this assay was less than 10%.

The Population Clearance Method: This method is based on the observation of an exponential relation between 177 pairs of PHT clearance and PHT concentration at the steady state as determined in 59 patients. A new dose is calculated using the following regression equation:

$$D_n = D_o \times C_d^{0.2} \times C_o^{-0.2}$$

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

The Bayesian Feedback Method: The theoretical basis of the Bayesian forecasting technique has been discussed in detail by Sheiner *et al.*.[7,8] 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 intraindividual standard deviations. The following objective function is minimized with respect to the pharmacokinetic parameters to obtain the individual estimates:

$$OBJ_{Bayes} = [V_m - V_m')/\omega_v]^2 + [(K_m - K_m')/\omega_k]^2 + [(D - D')/\sigma_D]^2$$

where V_m and K_m are the population mean values, V_m' and K_m' are the individual parameter estimates with respect to which the expression is to be minimized, D' is the dosage that would have been calculated using the current estimates of V_m' and K_m' and initial measured C_{ss} in the Michaelis–Menten equation, D is the actual dosage given, ω_v and ω_k are interindividual standard deviations for V_m and K_m, 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 have been set at:

$K_m = 3.08$ mg/l; <15 years

$K_m = 3.67$ mg/l; $\geqq 15$ years

$V_m/F = [369 \cdot (\text{weight}/60)^{0.55}]$ mg/d

$F = 1.0$ for tablet form; $F = 0.895$ for powder form

$\omega_v = 0.186$ (V_m); $\omega_K = 0.574$ (K_m); $\sigma_D = 0.114$ (D)

as proposed by the authors.[9]

The microcomputer program (PEDA)[10] 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.

Statistical Analysis According to Sheiner and Beal,[11] the predictive ability of this method was evaluated by 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:

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

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

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

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

TABLE I. Details of the 40 Patients

Variables	Mean ± S.D.[a]	Range
Number of patients	40[b]	
Number of observations	126[c,d]	
Proportion of data from males	0.48	
Age (years)	21.1 ± 13.1	4.2—66.7
Body weight (kg)	45.7 ± 15.3	11.0—70.0
Daily dose (mg)	220.9 ± 88.0	60.0—500.0
Serum concentration (μg/ml)	9.48 ± 8.08	1.80—48.60

a) Standard deviation. *b*) The number of patients treated with tablet form: 16. *c*) The number of levels from patients treated with tablet form: 51. *d*) Three $D - C_{ss}$ pairs, 34 patients; four $D - C_{ss}$ pairs, 6 patients.

TABLE II. Details of the Patients in the Prediction Study

Variables	Mean ± S.D.[a]	Range
Number of patients	70[b]	
Number of observations	149[c,d]	
Proportion of data from males	0.4	
Age (years)	28.7 ± 13.5	0.6—64.1
Body weight (kg)	52.6 ± 14.6	9.0—87.0
Daily dose (mg)	242.4 ± 62.7	90.0—375.0
Serum concentration (μg/ml)	12.22 ± 8.73	1.20—49.60

a) Standard deviation. *b*) The number of patients treated with tablet form: 46. *c*) The number of levels from patients treated with tablet form: 96. *d*) Two $D - C_{ss}$ pairs, 62 patients; three $D - C_{ss}$ pairs, 7 patients; four $D - C_{ss}$ pairs, one patient.

Results

Fitting of Real Data Figure 1 shows the scatter diagram of CL *versus* C_{ss} for all the PHT data of 40 patients. These data were fitted to Eq. 3, and the a and b values were estimated to be 114.34 and -0.6786, respectively ($n = 126$; $r = 0.871$).

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

The correlation between actual and predicted values was highest with the Bayesian feedback method (method 1: $r = 0.903$). For each method, MEs were similar in magnitude, and the confidence intervals all included zero and overlapped with each other. The modified population clearance method using $b = -0.6786$ (method 3) yielded MAE of 25.1 mg/d and RMSE of 34.3 mg/d. The precision of method 3 was better than that of the population clearance method proposed by Graves *et al.* (method 2: MAE = 29.3 mg/d; RMSE = 36.2 mg/d). Method 1 was superior in precision to other methods, but no significant difference was observed between methods 1 and 3.

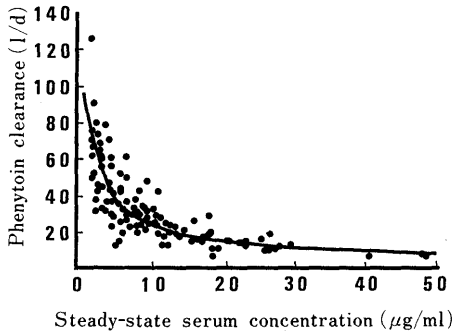

Fig. 1. Correlation of Phenytoin Clearance *versus* Steady-State Serum Concentration

$CL = 114.34 \cdot C_{SS}^{-0.6786}$; $r = 0.871$; $n = 126$.

TABLE III. Comparison of Predictive Ability

Methods[a]	n[b]	Correlation coefficient[c] (r)	ME (95% c.i.)[d] (mg/d)	MAE (95% c.i.)[d] (mg/d)	RMSE (95% c.i.)[d] (mg/d)
1	178	0.903	0.5 (−3.7 to 4.7)	22.6 (20.1 to 25.2)	28.4 (25.4 to 31.1)
2	178	0.840	−1.7 (−7.0 to 3.7)	29.3 (26.2 to 32.4)	36.2 (31.9 to 40.0)
3	178	0.880	0.6 (−4.5 to 5.6)	25.1 (21.7 to 28.5)	34.3 (28.6 to 39.1)

a) 1, Bayesian feedback method; 2, population clearance method proposed by Graves *et al.*; 3, modified population clearance method ($b = -0.6786$). *b*) $n = (62$ patients × 2 levels × 1 prediction) + (7 patients × 3 levels × 2 predictions) + (1 patient × 4 levels × 3 predictions). *c*) Correlation coefficient between actual and predicted dose. *d*) The 95% confidence interval of the mean.

TABLE IV. Percentage of Predictions with Errors >30 mg/d

	Methods[a] 1	2	3
n	178	178	178
Overprediction	15.2	19.7	13.5
Underprediction	13.5	23.6	12.4
Total	28.7	43.3	25.9

a) 1, Bayesian feedback method; 2, population clearance method proposed by Graves *et al.*; 3, modified population clearance method ($b = -0.6786$).

Table IV summarizes the percentage of predictions that had an absolute prediction error >30 mg/d for each method. The total error percentage (25.9%) of method 3 was lower than that of method 1 (28.7%). Further, it had the lowest percentage of overprediction (13.5%). Method 2 had the largest percentage of total errors >30 mg/d, 19.7% overprediction and 23.6% underprediction.

Discussion

The most appropriate PHT serum concentration may be different in individual patients depending on the type of seizure and other individual factors. Therefore, the search for the optimal PHT level for an individual patient may often require several dosage adjustments. To aid clinicians in making dosage adjustments, several methods have been proposed which use steady-state concentration data. Recently, it has been shown that systems utilizing Bayesian feedback techniques perform better than all methods previously reported in appropriate dosage adjustment.[5,6] However, this calculation is very difficult. The Bayesian feedback method is not suitable for use on a typical hand-held programmable calculator of current vintage.

We proposed a simple method to predict dosage of PHT obeying nonlinear pharmacokinetics. This equation is based on a power relationship between PHT clearance and C_{ss}. The use of a population value of the parameter b and one measured steady-state concentration allowed the prediction of a dose needed to produce a desired steady-state concentration. Graves *et al.* presented a population value of $b = -0.804$ determined in 59 American adults. In Japanese patients, the population value of parameter b was found to be 15.6% lower than that reported by Graves *et al.*. Estimates of the influence of age and dosage form on a population value of parameter b were not easy to make. The predictive ability of this modified population clearance method using $b = -0.6786$ was superior to that of Graves's method. The percentage of prediction that had an absolute prediction error >30 mg/d was lowest for the modified population clearance method, followed by the Bayesian feedback method. However, the percentage of predictions that had an absolute error >50 mg/d was lowest for the Bayesian feedback method (7.3%), followed by the modified population clearance method (13.5%). The predictive ability of the Bayesian feedback method was superior to that of the modified population clearance method.

These results indicate that this modified population clearance method may be a useful adjunct for prediction of PHT dosage as well as the Bayesian feedback method. Moreover, this method is easily executed on a hand-held programmable calculator. Its simplicity is attractive, but its inherent limitation of accuracy (using a constant value of parameter b) may call for careful adjustment of the parameters of the equation for different patient populations before this method is used in routine clinical practice.

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