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One-point Feedback Control Method for Phenytoin Dosage Adjustment

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Abstract—Routine clinical pharmacokinetic data collected from patients receiving phenytoin have been analysed to propose a new and simple equation to aid the dosage adjustment of this drug. The data were analysed using NONMEM, a computer program designed for population pharmacokinetic analysis that allows pooling of data. The rate equation for the elimination of phenytoin can be written as $D_o = kC_{ss}^n$, which fits the steady-state serum concentration (C_{ss}) and daily dose data (D_o). The parameter n is the kinetic order and the parameter k is an arbitrary rate constant. From the above equation, $D_2 = D_1C_1^{-n}C_2^n$ can be derived, which forms the basis of predicting the dosage, D_2, to obtain a desired C_{ss}, C_2, using one initial C_{ss}, C_1, obtained with an initial dose, D_1, and using a population value of n. The value of n for phenytoin was estimated to be 0·312 in this study. The predictive performance of this equation was compared with the Richens and Dunlop nomogram and Bayesian feedback method using two or more steady-state concentration/dose pairs from each of 78 outpatients. This equation allowed the prediction of a dose needed to produce a desired steady-state concentration with errors comparable with the Bayesian feedback method for therapeutic drug monitoring.

Phenytoin, an anticonvulsant, has a therapeutic range of 10–20 $\mu g\,mL^{-1}$ (Kutt & McDowall 1968), but some patients may require lower or higher concentrations. Achieving a therapeutic concentration is made more difficult because the drug obeys non-linear pharmacokinetics so that a dosage change does not produce a proportional change in steady-state concentration.

The difficulty with phenytoin disposition kinetics lies in the fact that it is neither first order nor zero order but somewhere in between. The rate equation for the elimination of phenytoin can be written:

$$\text{Rate} = kC^n \quad (1)$$

where n is the kinetic order (between 0 and 1), C is the serum concentration, and k is an arbitrary rate constant.

At steady state the rate of elimination is equal to the rate of drug input or the daily dose (D_o). Therefore,

$$D_o = kC_{ss}^n \quad (2)$$

where C_{ss} is the steady-state serum concentration.

This study has been conducted to determine the average values in the population of k and n. The purpose of this study was to propose a new and simple equation to aid the dosage adjustment of phenytoin, and to compare the accuracy of dosing predicted by this equation with the Richens and Dunlop nomogram (Richens & Dunlop 1975) and Bayesian feedback method (Sheiner et al 1972, 1979; Vozeh et al 1981).

Materials and Methods

Data sources

We studied 290 patients (148 males and 142 females) who had two or more reliable measurements of the steady-state concentration of phenytoin in serum while they were taking different daily doses. Patients for whom concurrent therapy was altered were excluded from the study. Eighty-two patients were taking phenytoin alone and 208 were taking the drug in combination with other anticonvulsants (Table 1). Their ages and weights ranged from 1·0 to 71·0 years (mean 23·8 years, s.d. 16·0 years) and 9·0 to 115·0 kg (mean 49·0 kg, s.d. 16·0 kg), respectively. Oral doses were from 40 to 500 mg day^{-1} (mean 223·1, s.d. 75·1 mg day^{-1}), and serum phenytoin concentrations were between 1·0 and 49·6 $\mu g\,mL^{-1}$ (mean 9·71, s.d. 7·61 $\mu g\,mL^{-1}$). Fig. 1 shows the frequency distribution within the patients data set of demographic factors (age, weight, daily dose and serum concentration). All patients had normal renal and hepatic function, and were given phenytoin acid (Aleviatin tablets and powders, Dainippon Pharmaceutical Co. Ltd, Osaka). Four steady-state serum concentrations at four different doses were determined in nine patients, three steady-state serum concentrations at three different doses were determined in 56 patients and two steady-state serum concentrations at different doses were determined in 225 patients (total number of observations:

Table 1. Drugs administered.

Combined drugs	Number of patients
PHT alone	82
PHT + PB	43
PHT + CBZ	25
PHT + VPA	9
PHT + PB + CBZ	29
PHT + PB + VPA	12
PHT + CBZ + VPA	9
PHT + PB + CBZ + VPA	23
PHT + PB,CBZ,VPA + other drugs	58
Total	290

PHT = phenytoin, PB = phenobarbitone, CBZ = carbamazepine, VPA = valproate sodium, other drugs = primidone, clonazepam, sultiame, ethotoin, ethosuximide, acetazolamide, diazepam.

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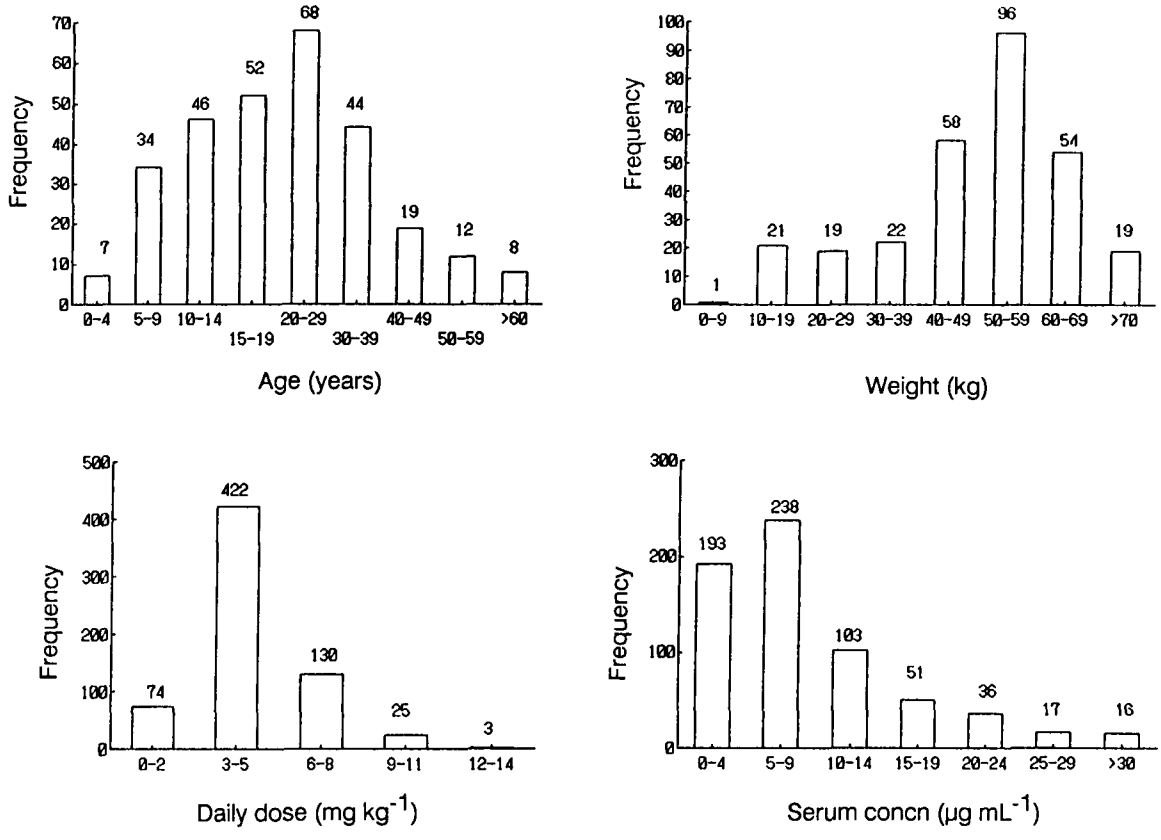

FIG. 1. Frequency distribution of the patients by age, weight, daily dose and serum concentration.

654). Phenytoin was prescribed two or three times a day either as a tablet or as a powder. The concentration of phenytoin was determined at least 30 days after any change in dosage, to give adequate time to reach a new steady-state concentration in serum. Blood samples were drawn 2–5 h after drug administration. The phenytoin concentration was routinely measured by immunoassay techniques (EMIT or FPIA). The coefficient of variation of this assay was less than 10%.

Population pharmacokinetics of phenytoin

Data analysis was performed with the NONMEM program (Sheiner et al 1977; Sheiner & Beal 1979, 1980) on the mainframe computer of Kyushu University (FACOM M-780). The statistical model used in this program is based on the premise that particular pharmacokinetic parameters of a population arise from a contribution which could be described by the population mean and inter-individual variation.

The data were fitted to the following model:

$$D_{ij} = k_j C_{ssij}^{nj} + \varepsilon_{ij} \quad (3)$$

where D_{ij} equals the observed dosage rate for the ith pair in the jth patient (mg day^{-1}); n_j is the theoretical kinetic order for the jth patient; k_j is the arbitrary rate constant for the jth patient; C_{ssij} is the steady-state serum concentration (μg mL^{-1}) measured in the jth patient whilst receiving the ith dosage; and ε_{ij} are independent identically distributed statistical errors with mean zero and variance σ_ε^2.

We examined the influence of age on the population mean values (n and k) for phenytoin using equations 4 and 5, and examined the influence of administering powder instead of a tablet on the population mean value for k of phenytoin using equation 5.

$$\hat{n}_j = nAn_j \quad (4)$$

$$\hat{k}_j = kAk_jF_j \quad (5)$$

$$An_j = \begin{cases} 1 & \text{if age} \geqq 12 \\ \theta_n & \text{if age} < 12 \end{cases} \qquad F_j = 1 \begin{cases} 1 & \text{for tablet} \\ \theta_F & \text{for powder} \end{cases}$$

$$Ak_j = \begin{cases} 1 & \text{if age} \geqq 12 \\ \theta_k & \text{if age} < 12 \end{cases}$$

where $\hat{n}_j$ and $\hat{k}_j$ are the predicted parameters for jth individual, respectively; n and k are the parameter values for the 'standard' patient (adult patient with phenytoin prescribed in tablet form); An_j or Ak_j is an indicator variable which has a value of unity if the jth patient is more than 12 years, and θ_n or θ_k otherwise; F_j is an indicator variable which has a value of unity if the phenytoin of the jth patient is prescribed as a tablet, and θ_F otherwise.

θ_n, θ_k and θ_F represent the fractional increase or decrease in the pharmacokinetic parameter associated with the presence of the corresponding indicator variable.

For inter-individual variation, we assume:

$$\ln(n_j) = \ln(\hat{n}_j) + \eta_{nj} \quad (6)$$

$$\ln(k_j) = \ln(\hat{k}_j) + \eta_{kj} \quad (7)$$

where n_j and k_j are from equations 4 and 5, η_{nj} and η_{kj} are independently distributed statistical errors with mean zero and variances ω_n^2 and ω_k^2.

To test the significance of various factors that influence n and k, we used the value of the objective function (the log likelihood) determined in the NONMEM fitting routine. The difference in objective function values (the log likelihood difference) obtained by comparing a restricted model in which a parameter's value is fixed with the null hypothesis value, and a non-restricted model in which the parameter's value is freely estimated, is asymptotically distributed as chi-square with one degree of freedom. In order to identify potentially significant factors, the log likelihood difference >7.9, associated with a P value of <0.005 was required.

Phenytoin dosage adjustment method

If a ratio is made of two equations such as equation 2, with C_1 corresponding to dose D_1, and C_2 corresponding to D_2, with a parameter n and k remaining constant, then k cancels out and the following equation is obtained:

$$\frac{D_2}{D_1}=\frac{C_2^n}{C_1^n} \quad (8)$$

Solving for D_2 in equation 8 gives

$$D_2=D_1C_1^{-n}C_2^n \quad (9)$$

Hence, equation 9 provides a method of estimating the dose, D_2, necessary to give a desired steady-state concentration C_2 if one knows a single steady-state concentration C_1 corresponding to the maintenance dose D_1 and if a population value of n is used.

Solving for C_2 in equation 8 gives

$$C_2=(D_2C_1^n/D_1)^{1/n} \quad (10)$$

This equation provides a method of estimating steady-state concentration C_2 corresponding to a second maintenance dose D_2.

To assess the utility of these equations, we compared the method with two other single feedback dosing methods using data from patients not included in the calculation of these parameters (Table 2).

The Richens and Dunlop nomogram. This method is equivalent to setting the subject's K_m value at the mean population value (4·0 μg mL^{-1}) solving the Michaelis-Menten equation for V_{max} using the dose and measured steady-state concentration, and using K_m and V_{max} to determine a new dosage or a new steady-state concentration.

The Bayesian feedback method. The theoretical basis of the Bayesian forecasting technique has been discussed previously (Sheiner et al 1972, 1979). This method minimizes the following objective function in the case of phenytoin:

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

where V_{max} and K_m are the population mean values, V_{max}' 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_{max}' 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_{max} and K_m, respectively, and σ_D is the standard deviation of the combined intra-individual and model misspecification errors.

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

$K_m=3.08$ μg mL^{-1}; <15 years
$K_m=3.67$ μg mL^{-1}; ≥ 15 years
$V_{max}/F=[369\cdot(\text{weight}/60)^{0.55}]$ mg day^{-1}
$F=1.0$ for tablet; $F=0.895$ for powder
$\omega_v=0.186(V_{max})$; $\omega_K=0.574(K_m)$; $\sigma_D=0.114(D)$

as proposed by us (Yukawa et al 1989).

The microcomputer program (PEDA) (Higuchi et al 1987) 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.

For each patient, the predicted dose or concentration values were compared with the actual values by calculating the prediction errors (predicted value − actual value), and the bias (mean prediction error; m.e.) and precision (mean absolute prediction error; m.a.e.) were determined (Sheiner & Beal 1981).

Table 2. Details of the patients in the prediction study.

Characteristic	
Number of patients[a]	78
Number of observations[b]	169
Means ± s.d.	
Age (years)	19·0 ± 14·2
Weight (kg)	42·3 ± 17·9
Daily dose, D (mg day^{-1})	186·7 ± 69·7
Steady-state concentration, C_{ss} (μg mL^{-1})	7·84 ± 5·81

[a] Males: 46 patients; females: 32 patients. [b] The number of observations on patients treated with the tablet form is 91.

Results

Population pharmacokinetic parameter estimates

We executed hypothesis tests of various factors that might influence parameters of our proposed phenytoin kinetic model. Table 3 lists the null hypothesis value for each parameter, the parameter estimate obtained by NONMEM, the log likelihood difference associated with the null hypothesis, and associated P value. The table indicates that the data do not support an influence of age on the mean kinetic order ($\theta_n \neq 1$, $P>0.05$). On the other hand, the mean arbitrary rate constant is significantly reduced in patients less than 12 years of age ($\theta_k \neq 1$, $P<0.005$) and in patients prescribed a powder ($\theta_F \neq 1$, $P<0.005$). The shift at 15 years provided a poorer fit than at 12 years in the analyses of these data. Moreover, we could not accept the influence of other factors (gender, concurrent anti-epileptic drugs etc.) on phenytoin kinetics.

The final pharmacokinetic parameter estimates using the simpler model $\theta_n=1$ and the standard errors for these parameters are summarized in Table 4. The small standard errors indicate a good fit with reliable parameter estimates.

Table 3. Influences of various factors.

Parameters	Hypothesized value[a]	NONMEM estimate[b]	Log likelihood difference	P value
θ_F	1	1·09	14·00	<0·005
θ_n	1	0·916	2·92	>0.05
θ_k	1	0·651	28·97	<0·005

[a] One of the parameters was constrained to be a hypothesized value. [b] All parameters were included and estimated.

Table 4. Final parameter estimates.

Parameter	Estimate (s.e.m.)
n	0·312 (0·012)
k	118 (4·00)
ω_n (%)	10·2[a] (2·1)[b]
ω_k (%)	30·3[a] (2·8)[b]
σ_E	25·8 (8·96)
θ_F	1·09 (0·026)
θ_k	0·731 (0·036)

[a] All estimates of the variance components are expressed as coefficients of variation. [b] S.e.m. of the variances (ω^2 or σ^2) are estimated by NONMEM. The s.e.m. of the standard deviation ($\sqrt{\omega^2}$ or $\sqrt{\sigma^2}$) was approximated by $\text{s.e.m.}_{SD} = \sqrt{\omega^2 + \text{s.e.m.}_{var.}} - \sqrt{\omega^2}$ or $\sqrt{\sigma^2 + \text{s.e.m.}_{var.}} - \sqrt{\sigma^2}$ and expressed in % of $\sqrt{\omega^2}$ or $\sqrt{\sigma^2}$.

Prediction of phenytoin dose or concentration

The m.e., m.a.e., and their respective 95% confidence limits for predicted phenytoin doses and C_{ss} are shown in Table 5. If there are two dose-C_{ss} pairs in the subject, the 1st pair is used and the 2nd C_{ss} is set as the "target" concentration and the dose required predicted. The 2nd pair and 1st C_{ss} is also used to predict the dose required to produce the 1st C_{ss}. In the same way, the prediction of the C_{ss} is performed.

For a drug such as phenytoin, which obeys non-linear pharmacokinetics, a small error in dosage can produce a much larger error in the resulting steady-state concentration in certain individuals. Table 6 summarizes the percentage of dose predictions that had an absolute prediction error >40 mg day^{-1} (twice average m.a.e. of each method).

Discussion

Phenytoin dosing can be viewed as three processes: (a) determination of the initial maintenance dose, (b) a first dosage adjustment following achievement of a steady-state condition where a single dose/steady-state serum concentration pair (single feedback) is available, and (c) dosage adjustments based on two or more dose-steady-state concentration pairs (multiple feedback). Phenytoin serum concentrations of 10–20 μg mL^{-1} are generally accepted to be therapeutic. However, it can be difficult to achieve this range with standard dosage regimens because of non-linearity of phenytoin pharmacokinetics and large intersubject differences in kinetic parameters. Although several reliable dosing methods based on individual pharmacokinetic parameters (Richens & Dunlop 1975; Ludden et al 1977; Mullen & Foster 1979; Rambeck et al 1979; Wagner 1985; Graves et al 1986) have been developed to facilitate attainment of an optimal phenytoin dosage, the clinician is often challenged to make an appropriate dosage adjustment based on only a single dose/steady-state concentration pair. Recently, it has been shown that systems utilizing Bayesian feedback techniques perform better than all single feedback methods previously reported for appropriate dosage adjustment (Vozeh et al 1981; Yuen et al 1983; Toscano & Jameson 1986; Yukawa et al 1988a, b). However, this calculation is very difficult. We have proposed a new and simple equation to allow the prediction of phenytoin dosage or steady-state concentration on a handheld calculator.

By the NONMEM analysis, the parameters n and k of the patient population studied were estimated to be 0·312 and 118, respectively. The coefficients of variation of parameters n and k in Table 4 indicate that intersubject variation of k is much greater than variation of n. The factors of age and dosage form have a statistically significant influence on k in our population, but not on n. Therefore, we constructed an equation that assumed a constant value for n in different individuals. The predictions based on equation 9 using the constant value of n had a m.a.e. of 20·7 mg day^{-1} for phenytoin dosage and 3·5 μg mL^{-1} for the C_{ss} of phenytoin. Using the proposed method, precision was better than that obtained with the Richens and Dunlop nomogram, and was similar to that obtained with the Bayesian feedback method.

Table 6. Percentage of predictions with errors >40 mg day^{-1}.

	Methods		
	Proposed method	Bayesian feedback	Richens and Dunlop nomogram
Overprediction	5·2	5·7	11·3
Underprediction	8·0	2·3	5·7
Total	13·2	8·0	17·0

Table 5. Prediction performance evaluation.

Method	Number of predictions[a]	Prediction of dose: Bias (m.e., mg day^{-1})	Prediction of dose: Precision (m.a.e., mg day^{-1})	Prediction of C_{ss}: Bias (m.e., μg mL^{-1})	Prediction of C_{ss}: Precision (m.a.e., μg mL^{-1})
Proposed method	212	−1·4 (−5·0, 2·1)[b]	20·7 (18·5, 22·9)	1·8 (0·9, 2·6)	3·5 (2·7, 4·2)
Bayesian feedback	212	1·7 (−1·6, 5·0)	18·8 (16·7, 20·9)	1·4 (0·3, 2·5)	3·6 (2·6, 4·6)
Richens and Dunlop nomogram	212	3·9 (−0·4, 8·3)	23·5 (20·4, 26·5)	1·1 (0·1, 2·1)	3·7 (2·8, 4·6)

[a] (67 patients × 2 levels × 1 prediction) + (9 patients × 3 levels × 2 predictions) + (2 patients × 4 levels × 3 predictions). [b] Parentheses are the 95% confidence intervals of the mean.

In conclusion, the use of a population value of parameter n and only one dose-measured steady-state concentration pair allows (a) the prediction of the maintenance dose needed to produce a desired steady-state concentration and (b) the prediction of the steady-state concentration as a function of maintenance dose with an acceptable error for therapeutic drug monitoring. However, the selection of appropriate population parameter n is important for the success of this technique.

References

Graves, N. M., Leppik, I. E., Termond, E., Taylor, J. W. (1986) Phenytoin clearances in a compliant population: description and application. Ther. Drug Monit. 8: 427–433

Higuchi, S., Aoyama, T., Horioka, M. (1987) PEDA: a microcomputer program for parameter estimation and dosage adjustment in clinical practice. J. Pharmacobio-Dyn. 10: 703–718

Kutt, H., McDowall, F. (1968) Management of epilepsy with diphenylhydantoin sodium. Dosage regulation for problem patients. J. Am. Med. Ass. 203: 969–972

Ludden, T. M., Allen, J. P., Valutsky, W. A., Vicuna, A. V., Nappi, J. M., Hoffman, S. F., Wallace, J. E., Lalka, D, McNay, J. L. (1977) Individualization of phenytoin dosage regimens. Clin. Pharmacol. Ther. 21: 287–293

Mullen, P. W., Foster, R. W. (1979) Comparative evaluation of six techniques for determining the Michaelis-Menten parameters relating phenytoin dose and steady-state serum concentrations. J. Pharm. Pharmacol. 31: 100–104

Richens, A., Dunlop, A. (1975) Serum-phenytoin levels in management of epilepsy. Lancet ii: 247–248

Rambeck, B., Boenigk, H., Dunlop, A., Mullen, P. W., Wadsworth, J., Richens, A. (1979) Predicting phenytoin dose—a revised nomogram. Ther. Drug Monit. 1: 325–333

Sheiner, L. B., Beal, S. L. (1979) NONMEM Users Guide. (Technical report) Division of Clinical Pharmacology, University of California, San Francisco

Sheiner, L. B., Beal, S. L. (1980) Evaluation of methods for estimating population pharmacokinetic parameters. I. Michaelis-Menten model: routine clinical pharmacokinetic data. J. Pharmacokinet. Biopharm. 6: 553–571

Sheiner, L. B., Beal, S.L. (1981) Some suggestions for measuring predictive performance. Ibid. 9: 503–512

Sheiner, L. B., Rosenberg, B., Marathe, V. V. (1977) Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. Ibid. 5: 445–479

Sheiner, L. B., Rosenberg, B., Melmon, K. L. (1972) Modeling of individual pharmacokinetics for computer aided drug dosage. Comput. Biomed. Res. 5: 441–449

Sheiner, L. B., Beal, S. L., Rosenberg, B., Marathe, V. V. (1979) Forecasting individual pharmacokinetics. Clin. Pharmacol. Ther. 26: 294– 305

Toscano, J. P., Jameson, J. P. (1986) Comparison of four single-point phenytoin dosage prediction techniques using computer-simulated pharmacokinetic values. Clin. Pharm. 5: 396–402

Vozeh, S., Muir, K. T., Sheiner, L. B., Follath, F. (1981) Predicting individual phenytoin dosage. J. Pharmacokinet. Biopharm. 9: 131–146

Wagner, J. G. (1985) New and simple method to predict dosage of drugs obeying simple Michaelis-Menten elimination kinetics and to distinguish such kinetics from simple first order and from parallel Michaelis-Menten and first order kinetics. Ther. Drug Monit. 7: 377–386

Yuen, G. J., Taylor, J. W., Ludden, T. M., Murphy, M. J. (1983) Predicting phenytoin dosage using Bayesian feedback. A comparison of other methods. Ibid. 5: 437–441

Yukawa, E., Higuchi, S., Aoyama, T. (1988a) Comparison of single-point phenytoin dosage prediction techniques. J. Clin. Pharm. Ther. 13: 293–305

Yukawa, E., Higuchi, S., Aoyama, T. (1988b) Evaluation of single-point phenytoin dosage prediction methods in pediatric patients. J. Pharmacobio-Dyn. 11: 738–743

Yukawa, E., Higuchi, S., Aoyama, T. (1989) Population pharmacokinetics of phenytoin from routine clinical data in Japan. J. Clin. Pharm. Ther. 14: 71–77