Evaluation of Single-Point Phenyltoin Dosage Prediction Methods in Pediatric Patients

Eiji YUKAWA, Shun HIGUCHI, and Toshinobu AOYAMA

Department of Hospital Pharmacy, Faculty of Medicine, Kyushu University, 3-1-1, Maidashi, Higashi-Ku, Fukuoka, 812, Japan

(Received May 2, 1988)

Phenytoin (PHT) dosage adjustment in a clinical situation is difficult because of the nonlinear metabolism of the drug. Therefore, many techniques have been advocated to aid in dosage adjustments based on single-point PHT concentration determined at steady-state (SS). We retrospectively investigated seven methods in a population of 90 outpatients treated with PHT. The dose needed to achieve a desired PHT concentration at SS was calculated based on an observed SS dose-concentration pair using the Richens and Dunlop nomogram (RD), the Rambeck nomogram, the Martin nomogram, the Chiba nomogram, a population clearance method, the Wagner dosing equation and the Bayesian feedback method (B).

Mean prediction error, mean absolute error (MAE), and root mean squared error (RMSE) were separately calculated for each method, and served as a measure of prediction bias and precision. The MAE and RMSE were lowest for method B (MAE = 28.7 mg/d, RMSE = 36.8 mg/d), followed by method RD (MAE = 30.3 mg/d, RMSE = 40.8 mg/d).

Therefore, we recommend the use of method B to make routine PHT dosage adjustments in pediatric patients when only one dose and one concentration are available.

Keywords — phenytoin; dosage adjustment method; Bayesian feedback method; pharmacokinetics; Michaelis-Menten

Introduction

Phenytoin (PHT) is commonly used in children and adults, but it is often difficult to adjust the dosage to attain therapeutic drug concentrations (10—20 μg/ml) due to the non-linear nature of PHT metabolism. This task is made notably more difficult by the considerable uncertainty concerning the clinical pharmacokinetics of the drug in children. Therefore, many techniques have been advocated to aid in dosage adjustments based on single-point PHT concentration determined at steady-state, including population-based algorithms and nomograms, pharmacokinetic equations, and Bayesian feedback method. However, it is important to use the most accurate dosing method to achieve the desired response and also to avoid toxicity.

Recently, it has been shown that systems utilizing the Bayesian feedback method perform better than all methods previously reported in drug dosage adjustments on an individual basis. But as far as we are aware, no simultaneous evaluation of PHT dosing methods based on only one dose—steady-state concentration (Css) pair has been undertaken in a large group of pediatric patients. Also, the evaluative studies done to date have compared no more than four different methods. In the previous study, we retrospectively investigated the predictive abilities of six methods in a population of 130 adult patients taking PHT without and with other anticonvulsants.

The purpose of this study was to determine which of seven different dosing methods most accurately predicts PHT dosage in a large group of pediatric patients taking PHT with and without other anticonvulsants.

Materials and Methods

Eligibility of Patients Participating in the Study — From many medical charts we selected 90 patients (51 males and 39 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. Patients who were judged to be non-compliant as defined by a ±20% variation of steady-state concentration determination for a
Phenytoin Dosage Prediction Methods

TABLE I. Medications

<table>
<thead>
<tr>
<th>Combined drugs</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT only</td>
<td>15</td>
</tr>
<tr>
<td>PHT + PB</td>
<td>7</td>
</tr>
<tr>
<td>PHT + CBZ</td>
<td>7</td>
</tr>
<tr>
<td>PHT + VPA</td>
<td>2</td>
</tr>
<tr>
<td>PHT + PB + CBZ</td>
<td>16</td>
</tr>
<tr>
<td>PHT + PB + VPA</td>
<td>8</td>
</tr>
<tr>
<td>PHT + CBZ + VPA</td>
<td>4</td>
</tr>
<tr>
<td>PHT + other drugs</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
</tr>
</tbody>
</table>

PB = phenobarbital, CBZ = carbamazepine, VPA = valproate sodium, other drugs = primidone, clonazepam, sulfonamide, ethosuximide, acetazolamide, diazepam.

given dose, or in whom concurrent therapy was altered, were excluded from the study. They were taking PHT alone or PHT combined with other anticonvulsants (Table I). Their ages ranged from 2.7 to 18.2 years (mean ± S.D.; 11.2 ± 3.5 yr) and their weights ranged from 10 to 71 kg (mean ± S.D.; 35.7 ± 15.3 kg). The details of these outpatients are shown in Table II. The frequency distribution within the patients' data set of demographic factors (age, weight, daily dose and serum concentration) are displayed in Fig. 1. 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

TABLE II. Details of the Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± S.D. $a$</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>No. of observations</td>
<td>211</td>
<td></td>
</tr>
<tr>
<td>Proportion of data from males</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.2 ± 3.5</td>
<td>2.7 - 18.2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>35.7 ± 15.3</td>
<td>10.0 - 71.0</td>
</tr>
<tr>
<td>Daily dose (mg/kg)</td>
<td>5.75 ± 2.24</td>
<td>1.07 - 13.3</td>
</tr>
<tr>
<td>Serum concentration (µg/ml)</td>
<td>8.02 ± 6.50</td>
<td>1.40 - 48.00</td>
</tr>
</tbody>
</table>

$a$) Standard deviation.

Fig. 1. Frequency Distribution of Age, Weight, Daily Dose and Serum Concentration within the Data Set of Patients Treated with Phenytoin
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 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%.

Description of the Prediction Method —

PHT doses were predicted by seven techniques requiring a single dose-concentration pair. The single-point PHT dosage prediction techniques consisted of a Bayesian feedback method, an nomogram developed by Richens and Dunlop, a nomogram developed by Rambeck et al., a nomogram developed by Martin et al., a nomogram developed by Chiba et al., a population clearance method of Graves et al., and a dosing equation developed by Wagner. The appendix provides a detailed review of the algorithms involved in the seven dosage prediction methods.

Statistical Analysis — The predictive performance of each method was evaluated, as was presented by Sheiner and Beal, 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:

\[
\text{ME} = \frac{1}{n} \sum_{i=1}^{n} (\text{predicted dose} - \text{actual dose})
\]

\[
\text{MAE} = \frac{1}{n} \sum_{i=1}^{n} |\text{predicted dose} - \text{actual dose}|
\]

\[
\text{RMSE} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (\text{predicted dose} - \text{actual dose})^2}
\]

where \( n \) is the number of dosage pairs. Comparison of the relative performance was evaluated by comparing 95% confidence intervals.

Results

Table III summarizes the precision and bias of the different prediction methods for all patients. The Rambeck nomogram was significantly biased, showing a bias to overpredict PHT doses \( (i.e., \text{the 95\% confidence interval of ME did not include zero}) \). For other methods, MEs were similar in magnitude, and the confidence intervals all included zero and overlapped with each other. The MAEs and RMSEs for each method were also similar in magnitude and overlapped with each other. The correlation between actual and predicted values was highest with the Bayesian feedback method \( (r=0.895) \). In terms of precision, the order of preference of PHT dosing methods was the Bayesian feedback method \( (\text{MAE} = 28.7 \text{ mg/d; RMSE} = 36.8 \text{ mg/d}) \), the Richens and Dunlop nomogram \( (\text{MAE} = 30.3 \text{ mg/d; RMSE} = 40.8 \text{ mg/d}) \), the Chiba nomogram \( (\text{MAE} = 31.5 \text{ mg/d; RMSE} = 40.8 \text{ mg/d}) \), the population clearance method

<table>
<thead>
<tr>
<th>Methods ( a) )</th>
<th>( n )</th>
<th>Correlation coefficient ( b) )</th>
<th>ME (95% c.i.) ( c) ) (mg/d)</th>
<th>MAE (95% c.i.) (mg/d)</th>
<th>RMSE (95% c.i.) (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>314</td>
<td>0.892</td>
<td>2.4 (2.1 to 6.9)</td>
<td>30.3 (27.2 to 33.3)</td>
<td>40.8 (35.7 to 45.4)</td>
</tr>
<tr>
<td>2</td>
<td>314</td>
<td>0.869</td>
<td>7.2 (1.4 to 12.9)</td>
<td>36.8 (32.7 to 41.0)</td>
<td>52.6 (44.3 to 59.7)</td>
</tr>
<tr>
<td>3</td>
<td>313</td>
<td>0.858</td>
<td>4.0 (1.6 to 9.6)</td>
<td>37.2 (33.4 to 41.0)</td>
<td>50.3 (43.5 to 56.3)</td>
</tr>
<tr>
<td>4</td>
<td>210</td>
<td>0.876</td>
<td>-2.9 (0.5 to 2.6)</td>
<td>31.5 (28.0 to 35.0)</td>
<td>40.8 (36.2 to 45.0)</td>
</tr>
<tr>
<td>5</td>
<td>314</td>
<td>0.834</td>
<td>-1.7 (0.6 to 3.4)</td>
<td>37.2 (34.2 to 40.2)</td>
<td>46.1 (41.2 to 49.7)</td>
</tr>
<tr>
<td>6</td>
<td>314</td>
<td>0.847</td>
<td>0.0 (0.6 to 8.3)</td>
<td>48.4 (44.1 to 52.6)</td>
<td>61.6 (56.4 to 66.4)</td>
</tr>
<tr>
<td>7</td>
<td>314</td>
<td>0.895</td>
<td>-0.4 (0.5 to 1.4)</td>
<td>28.7 (26.1 to 31.3)</td>
<td>36.8 (33.3 to 40.0)</td>
</tr>
</tbody>
</table>

\( a) 1: \text{Richens and Dunlop nomogram, 2: Rambeck nomogram, 3: Martin nomogram, 4: Chiba nomogram, 5: population clearance method, 6: Wagner equation (} S = 0.007772 \text{), 7: Bayesian feedback method. \( b) \text{Correlation coefficient between the actual and predicted dose. } c) \text{95\% confidence intervals of the mean.} \)
Phenytoin Dosage Prediction Methods

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

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overprediction</td>
<td>21.4</td>
<td>24.2</td>
<td>24.6</td>
<td>19.5</td>
<td>28.7</td>
<td>29.0</td>
<td>18.2</td>
</tr>
<tr>
<td>Underprediction</td>
<td>19.4</td>
<td>21.0</td>
<td>22.4</td>
<td>24.3</td>
<td>27.7</td>
<td>29.0</td>
<td>22.6</td>
</tr>
<tr>
<td>Total</td>
<td>40.8</td>
<td>45.2</td>
<td>47.0</td>
<td>43.8</td>
<td>56.4</td>
<td>58.0</td>
<td>40.8</td>
</tr>
</tbody>
</table>

1: Richens and Dunlop nomogram, 2: Rambeck nomogram, 3: Martin nomogram, 4: Chiba nomogram, 5: population clearance method, 6: Wagner equation ($S = 0.007772$), 7: Bayesian feedback method.

(MAE = 37.2 mg/d; RMSE = 46.1 mg/d), the Martin nomogram (MAE = 37.2 mg/d; RMSE = 50.3 mg/d), the Rambeck nomogram (MAE = 36.8 mg/d; RMSE = 52.6 mg/d), and the Wagner equation (MAE = 48.4 mg/d; RMSE = 61.6 mg/d). The Bayesian feedback method was superior in precision to all other methods evaluated, followed by the Richens and Dunlop nomogram.

Table IV summarizes for each method the percentage of predictions that had an absolute prediction error > 30 mg/d. Figures 2—8 show the scatter diagrams of dosage prediction error versus initial steady-state serum concentration used in making the prediction for each method. Comparison of Figs. 2—8 shows that the Bayesian feedback method yields fewest extreme errors among the methods for predictions of PHT dosage needed to achieve a desired $C_{ss}$ in the subset of subjects with initial $C_{ss}$ less than 5 µg/ml. The Bayesian feedback method and the Richens and Dunlop nomogram had the lowest percentage of total errors > 30 mg/d in relative magnitude. Further, the Bayesian feedback method had the lowest percentage of overprediction, 18.2%. The Wagner equation had the largest percentage of total errors > 30 mg/d, 29.0% overprediction and 29.0% underprediction.

Fig. 3. Scatter Diagram of Dosage Prediction Error versus Initial Steady-State Serum Concentration Used in Making the Prediction for the Rambeck Nomogram

Fig. 4. Scatter Diagram of Dosage Prediction Error versus Initial Steady-State Serum Concentration Used in Making the Prediction for the Martin Nomogram
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 each individual patient may often require several dosage adjustments.

For a drug such as PHT, which exhibits Michaelis-Menten kinetics, a small increase in dosage can cause a much larger increase in the resulting steady-state concentration. Thus, there has been considerable interest in the accurate prediction of PHT dosing rates to achieve therapeutic or non-toxic concentrations. We have attempted to evaluate the accuracy of seven methods in adjusting PHT dosages of pediatric patients.

The four nomogram methods reported in the literature were designed to allow prediction after administration of one dosage regimen and measurement of the corresponding steady-state concentration. The Rambeck nomogram is rated highly in Europe and America. However, data from this study demonstrate that the predictive performance of the Richens and Dunlop nomogram (MAE = 30.3 mg/d; RMSE = 40.8 mg/d) is superior to that of other nomograms (Table III).

Furthermore, the three newest single-point dosage adjustment methods that have been reported in the literature, have been evaluated with respect to the nomogram methods. The Wagner equation or the population clearance
method showed poor predictive performance as compared with nomogram methods. This is because the parameter values are unsuitable for Japanese children. We believe that the predictive performance would be better, if suitable parameters for Japanese children were employed. Overall, the MAE and RMSE were lowest in the Bayesian feedback method (MAE = 28.7 mg/d, RMSE = 36.8 mg/d), followed by the Richens and Dunlop nomogram. This result is similar to the precision of PHT dosage adjustments reported previously in a population of adult patients.\(^{15}\)

The results of the current study suggest that the Bayesian feedback method is most accurate in terms of the ability to predict a PHT dosing adjustment on the basis of percentage of significant over- or underprediction (± > 30 mg/d) and measures of precision. These findings are similar to those reported by previous investigators. Toscano and Jameson\(^{14}\) have evaluated the usefulness of the Bayesian feedback 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, the Rambeek nomogram and the population clearance method. Vozeh et al.\(^{10}\) and Yuen et al.\(^{13}\) also obtained similar results when comparing the Bayesian feedback method with nomogram methods. Therefore, if there is a question concerning patient compliance or other factors, Bayesian feedback methods would be preferred.

In conclusion, we recommend the use of the Bayesian feedback method to make routine PHT dosage adjustments in pediatric patients when only one dose and one concentration are available.

Appendix

Algorithms for Seven Single-Point Phenytoin Dosage Prediction Methods

i) The Richens and Dunlop Nomogram — This method is equivalent to setting the subject’s \(K_m\) value at the mean population value (3.8 mg/l), solving the Michaelis-Menten equation for \(V_{\text{max}}\) using the dose and measured steady-state concentration, and using \(K_m\) and \(V_{\text{max}}\) to determine a new dosage. The method may be represented algebraically as follows:

\[
D_n = D_o \times \frac{C_d \times (3.8 + C_o)}{[C_o \times (3.8 + C_d)]}
\]

where \(D_n\) is the new dose, \(D_o\) is the original dose, \(C_d\) is the desired steady-state serum concentration, and \(C_o\) is the observed steady-state serum concentration produced by \(D_o\).

ii) The Rambeek Nomogram — This method is a revised version of the Richens and Dunlop nomogram and the subject’s \(K_m\) value was set equal to 6.0 mg/l based upon PHT dose-concentration data from 127 patients. The method may be represented algebraically as follows:

\[
D_n = D_o \times \frac{C_d \times (6.0 + C_o)}{[C_o \times (6.0 + C_d)]}
\]

where \(D_n\) is the new dose, \(D_o\) is the original dose, \(C_d\) is the desired steady-state serum concentration, and \(C_o\) is the observed steady-state serum concentration produced by \(D_o\).

iii) The Martin Nomogram — This method uses the ratio of the observed serum PHT concentration to the predicted serum PHT concentration based upon the mean population value (\(K_m\): 11.54 mg/l; \(V_{\text{max}}\): 10.3 mg/kg/d) to estimate a new dose to achieve a new steady-state serum PHT concentration.

iv) The Chiba Nomogram — This method uses a steady value for \(V_{\text{max}}\) in different individuals in a given age group, solving the Michaelis-Menten equation for \(K_m\) using the dose and measured steady-state concentration, and using \(K_m\) and \(V_{\text{max}}\) to determine a new dosage.

0.5–3 years \(V_{\text{max}} = 13.8\) mg/kg/d

4–6 years \(V_{\text{max}} = 11.2\) mg/kg/d

7–9 years \(V_{\text{max}} = 9.5\) mg/kg/d

10–16 years \(V_{\text{max}} = 8.0\) mg/kg/d

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

\[ D_n = (D_o/C_o) \times C_d^{0.199} \times C_o^{0.804} \]

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.

vi) The Wagner Equation — Wagner proposed a new and simple method to predict dosage of drugs obeying simple Michaelis-Menten elimination kinetics. This method is based on the observation of a linear relationship between PHT dose and logarithm of steady-state concentration in Murphy’s study subjects.\(^ {17} \) A new dose is calculated using the following equation:

\[ D_n = D_o + \ln \left( \frac{C_d}{C_o} \right) / 0.007772 \]

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.

vii) The Bayesian Feedback Method — The theoretical basis of the Bayesian forecasting technique has been discussed in detail by Sheiner et al.\(^ {18, 19} \) This method makes 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 pharmacokinetics parameters to obtain the individual estimates:

\[ \text{OBJ}_{\text{Bayes}} = \left( \frac{V_{\text{max}} - V_{\text{max}}'}{\sigma_V} \right)^2 + \left( \frac{K_m - K_m'}{\sigma_K} \right)^2 + \left( \frac{D - D'}{\sigma_D} \right)^2 \]

where \( V_{\text{max}} \) and \( K_m \) are the population mean values; \( V_{\text{max}}' \) 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 \( V_{\text{max}}' \) and \( K_m' \) and initial measured \( C_{ss} \) in the Michaelis-Menten equation; \( D \) is the actual dosage given; \( \sigma_V \) and \( \sigma_K \) are interindividual standard deviations for \( V_{\text{max}} \) and \( K_m \), respectively; and \( \sigma_D \) 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:

\[ K_m = 2.2 \text{ mg/l}; \quad < 15 \text{ years} \]
\[ K_m = 3.8 \text{ mg/l}; \quad > 15 \text{ years} \]
\[ V_{\text{max}} = \left[ 415 \cdot \text{(weight/70)}^{0.6} \right] \text{ mg/d} \]
\[ \sigma_V = 0.20 \left( V_{\text{max}} \right); \quad \sigma_K = 0.50 \left( K_m \right); \quad \sigma_D = 0.086 \left( D \right) \]

as proposed by Kelman et al.\(^ {20} \) and by Grasela et al.\(^ {21} \)

The microcomputer program (PEDA)\(^ {22} \) 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.

References


6) E. Martin, T. N. Tozer, L. B. Sheiner and S. Riegelman: The clinical pharmacokinetics of phenytoin, \textit{J. Pharma-
Phenytoin Dosage Prediction Methods


