Single-point phenytoin dosage predictions in Singapore Chinese

E. Chan PhD
Department of Pharmacy, National University of Singapore, Singapore

SUMMARY
Phenytoin dosing is often difficult in a clinical situation because of the non-linear nature of phenytoin metabolism at therapeutic plasma concentrations. This study was performed to examine retrospectively five pharmacokinetic methods of adjusting phenytoin dosage based on a single steady-state plasma phenytoin concentration–dose pair in 66 epileptic Chinese children and adults. The methods compared included four fixed-parameter(s) methods (1 = the fixed \( K_m \) (Michaelis–Menten constant) method; 2 = the fixed \( V_m \) (maximum rate of elimination) method; 3 = the fixed \( V_{\text{max}}/K_m \) method; 4 = the fixed \( S \) (slope of logarithmic growth model) method) and a Bayesian feedback method (method 5). Measures of bias or accuracy (mean error, percentage dose) and precision (root mean squared error, percentage dose) were 20·1/88·0, -1·85/21·5, 2·14/21·9, -1·07/21·1 and -1·98/22·2, respectively. Method 1 was significantly inferior to methods 2–5 with respect to accuracy and precision. The correlation between the predicted and observed doses was higher with methods 2–5 \((r=0·862, 0·855, 0·866 \text{ and } 0·841, \text{ respectively})\) when compared to method 1 \((r=0·539)\). All methods had a sizeable number of poor predictions (range: 21·2% for method 4 to 37·9% for method 1), i.e. predictions with an error of greater than 20% of the dose. With respect to the frequency of poor versus good predictions, comparisons of all methods showed no significant differences.

INTRODUCTION
Phenytoin is one of the most frequently used anticonvulsant drugs for the treatment of grand mal and focal seizures. Difficulties often arise in attempting to determine an appropriate phenytoin dosage regimen for a particular patient because of the non-linear nature of phenytoin metabolism at the therapeutic concentration range 10–20 mg/litre (1). To aid clinicians in making adjustments to individualized doses, several methods have been proposed using one steady-state phenytoin concentration–dose pair in the individual patient and prior information about the population pharmacokinetic parameter(s) of the drug (2–6). These methods have been applied to Caucasian and Japanese patients, whereas their clinical utilization in Chinese patients has not been investigated (7–8). Recent studies have demonstrated ethnic differences in phenytoin pharmacokinetics (9). Thus, a method which is proved useful in one ethnic patient population may be less applicable in another ethnic patient population. It is desirable under such circumstances to select a method that gives more accurate and precise dosage adjustment for the particular patient population. The objective of the present study was to compare the applicability of five established pharmacokinetic methods using a single steady-state concentration–dose pair to predict subsequent phenytoin dosage in Chinese epileptic patients in Singapore.

METHODS
Drug monitoring profiles were retrospectively reviewed from epileptic Chinese patients at the Neurology Clinic of the Paediatric Department and the Outpatient Clinic of the hospital. Sixty-six patients were selected on the basis that they had two reliable steady-state plasma phenytoin concentration measurements at different daily doses on different occasions. They were also not suspected to be non-compliant, although strict tests of compliance were not performed. Patients who received any concurrent medication known to displace phenytoin from plasma protein binding sites were excluded from the study.
Patients with concurrent medications (primarily other anticonvulsants) were included in the study if the dosages of these medications remained unaltered during the period of concentration measurements. Twenty-two patients (33%) were female and 44 (67%) male. Forty-three (65%) patients were over 15 years of age. Age and body weight ranged from 2 to 76 years and 12 to 82 kg, respectively.

The following methods utilized the most recent steady-state phenytoin concentration–dose pair to predict the subsequent dosage for a given steady-state plasma concentration. The population pharmacokinetic parameters of phenytoin used were derived from the Chinese population instead of those derived from the other ethnic patient populations (Japanese and caucasians). The mean population parameters and their intra- and inter-individual variability, necessary for the Bayesian feedback prediction method, were previously estimated, using the population error model (9).

**Method 1**

This method utilizes the procedure proposed by Richens and Dunlop (2), described by equation 1.

\[
D_n = D_o \times \left( \frac{C_{o(ss)} + K_m}{C_{d(ss)} + K_m} \right) \times C_{o(ss)} \]

where \(D_n\) is the new daily dose, \(D_o\) is the initial daily dose, \(C_{o(ss)}\) is the initial steady-state plasma concentration, \(C_{d(ss)}\) is the desired steady-state plasma concentration and \(K_m\) is the Michaelis–Menten constant. This method assumes that \(K_m\) is constant and that the maximum rate of elimination (\(V_m\)) varies within the patient population. \(K_m\) is set to the population mean value (2·18 mg/litre) (Table 1).

**Method 2**

The second method utilizes the procedure proposed by Chiba et al. (4), described by equation 2.

\[
D_n = V_m \times C_{d(ss)} / C_{o(ss)} \times (V_m / D_o - 1) + C_{d(ss)} \]

This method assumes that \(V_m\) is constant and \(K_m\) varies within the patient population. \(V_m\) is set to an age-adjusted population mean value (10·9 mg/kg/day for < 15 years, 8·05 mg/kg/day for > 15 years) (Table 1).

**Method 3**

This method utilizes the procedure proposed by Martin et al. (3), described by equation 3.

\[
D_n = V_m / K_m / (R / C_{d(ss)} + 1 / K_m) \]

where \(R\) is the ratio of the observed initial steady-state plasma concentration \((C_{o(ss)})\) to the expected initial steady-state plasma concentration \((C_{e(ss)})\), and \(C_{e(ss)} = D_o \times K_m / (V_m - D_o)\. K_m\) is set to the population mean value while \(V_m\) is set to an age-adjusted population mean value (Table 1).

**Method 4**

The fourth method utilizes the procedure proposed by Wagner (6), described by equation 4.

\[
D_n = D_o + \ln(C_{d(ss)} / C_{o(ss)}) / S \]

where \(S\) is the slope parameter of the logarithmic growth model. The slope of the least squares regression line from a plot of \(\ln C_{ss}\) versus daily dose gives an estimate of \(S\). \(S\) is set to the population mean value of 0·648 days × mg/kg. The \(S\)-values were derived from the current study population. No statistically significant difference in \(S\) was found between children (0·593 ± 0·389 days × mg/kg) and adults (0·676 ± 0·478 days × mg/kg) when the \(S\)-values were estimated from the plots of \(\ln C_{ss}\) versus weight-adjusted daily dose (mg/kg/day).

**Method 5**

The fifth method utilizes the general Bayesian feedback method proposed for dosage prediction by Sheiner and Beal (5). This method minimizes the following objective function (OBJ) in the case of one feedback prediction.
\[
OBJ = \frac{1}{2} \left( \frac{V_m - V_{m(i)}}{\sigma_{vm}} \right)^2 + \frac{1}{2} \left( \frac{K_m - K_{m(i)}}{\sigma_{km}} \right)^2 + \frac{1}{2} \left( \frac{D_o - D}{\sigma_{d}} \right)^2 \tag{5}
\]

where \( V_m \) and \( K_m \) are the population mean values, \( V_{m(i)} \) and \( K_{m(i)} \) are the individual parameter estimates with respect to which the function is to be minimized, \( \sigma_{vm} \) and \( \sigma_{km} \) are the inter-individual standard deviations for \( V_m \) and \( K_m \) respectively, \( \sigma_d \) is the residual error standard deviation (between predicted and observed dosage) which accounts for all uncertainties caused by intra-individual time variation in \( V_m \) and \( K_m \), and sampling errors, and model misspecification; and \( D = V_{m(i)} \times C_{o(ss)} / (K_{m(i)} + C_{o(ss)}) \), where \( C_{o(ss)} \) is the observed steady-state plasma concentration associated with \( D_o \). With the current estimates of \( V_{m(i)} \) and \( K_{m(i)} \), the individual new daily dose required to achieve a desired steady-state plasma concentration \( (C_{d(ss)}) \) can then be predicted using equation 6.

\[
D_n = V_{m(i)} \times C_{d(ss)} / (K_{m(i)} + C_{d(ss)}) \tag{6}
\]

Table 1 lists the population mean values and the intra- and inter-individual standard deviation values used. The non-linear multiple regression program MULT12(BAYES), based on Bayesian algorithm for microcomputer, was employed in this feedback prediction (10).

The predictive performance of each method was measured in terms of mean prediction error (ME) and square root of mean squared prediction error (RMSE) (11). The former is a measure of bias (or accuracy) whereas the latter is a measure of precision. Poor predictions, those that yielded absolute errors greater than 20% of observed doses, were also tabulated for comparison between methods—the chi-squared test for a contingency table was performed on the tabulated data of poor versus good predictions. The assessment of bias for each method was performed using the one-sample t-test. The strength of association between the predicted and observed daily doses was measured using Pearson’s correlation coefficient \( r \). Direct comparison between methods for ME and RMSE was performed using the Friedman test, a non-parametric one-factor repeated measures analysis of variance. Statistical significance was defined as \( P<0.05 \).

RESULTS

Figure 1 presents the scatter diagrams of predicted versus observed daily dose for each method. Only 63 of the 66 cases are shown for method 1, because the three extreme cases excluded (predicted doses of 1353, 1635 and 1862 mg/day were at least four times the observed doses) were far from the cluster of the majority of data. The correlation between the predicted and observed values was found to be higher with methods 2–5 \( (r=0.862, 0.855, 0.866 \text{ and } 0.841, \text{ respectively}) \) when compared to method 1 \( (r=0.539 \text{ for all cases or } 0.632 \text{ for 63 cases}) \).

The measures of bias and precision for all the prediction methods are summarized in Table 2. Method 4 appeared to be the least biased (ME = −1.07% of the dose) and the most precise (RMSE = 21.1% of the dose), whereas method 1 was the most biased (ME = 20.1% of the dose for all cases or 3.01% of the dose for 63 cases) and the least precise (RMSE = 88.0% of the dose for all cases or 74.4% of the dose for 63 cases). When all cases were taken into account, method 1 was significantly different from methods 2–5 with respect to predictive performance in terms of bias and precision. Methods 2–5 tended to have similar precision and accuracy (see Table 2) and to have no bias—the 95% confidence intervals contained zero and the ME values were not significantly different from zero.

Table 3 summarizes the number of poor predictions for each method. Method 4 had fewer poor predictions (21.2%) when compared to other methods. Method 1 had the highest number of poor predictions (37.9%), most of which were over-predictions. Method 5 had the next highest number of poor predictions (33.3%), most of which were under-predictions. Methods 2–4 tended to be unbiased for poor predictions; the number of over-predictions was equal to that of under-predictions. With respect to the frequency of poor versus good predictions, comparisons of all methods showed no significant differences.

DISCUSSION

The wide inter-individual variability in both \( V_m \) and \( K_m \) for phenytoin and its narrow therapeutic index have created a demand for its routine use in therapeutic drug monitoring during antiepileptic treatment. It is important to do this in the most cost-effective manner possible. With the limited number of plasma data normally available in therapeutic monitoring, considerable efforts have been devoted to devising and testing methods to individualize phenytoin dose
Fig. 1. Predicted versus observed phenytoin dosage for each method.

based on a single-point phenytoin plasma concentration determined at steady-state. Such a dosing method (dosage optimization) should be without bias, have good precision and be as simple as possible to apply.

The present study examined five dosing methods using a single steady-state plasma concentration–dose pair to predict subsequent phenytoin dosage in Singapore Chinese patients with epilepsy. The predictive performance of method 1 (the fixed $K_m$ method) appeared to be inferior to the other four methods with respect to bias (or accuracy) and precision. Previous studies have demonstrated that variability in $K_m$ is the main factor causing inter-individual differences in the dosage and steady-state plasma concentration relationship (9). Substantial deviations of individual $K_{m(i)}$ from the population mean value might at least in part, if not completely, account for the three cases of extremely large over-predictions and the relatively poor predictive performance of the fixed $K_m$ method.

The correlation coefficients (0·866 and 0·841 for methods 4 and 5, respectively) obtained in this study are similar to those (0·878 and 0·871, respectively) reported by Yukawa et al. (7) who demonstrated the comparable predictive performance between methods 4 and 5 in Japanese patients. The predictive performance of methods 2–5 appeared to be similar in terms of bias and precision. However, when the frequency of poor predictions were also taken into account, method 4 (the fixed $S$ method) tended to be more robust than the other methods, method 2 (the fixed $V_m$ method) tended to outmatch both method 3 (the fixed $V_m/K_m$ method) and method 5 (the Bayesian feedback method), while method 1 (the fixed $K_m$ method) appeared to be the least promising prediction method.

A trend was also demonstrated between method 2 and method 5 when Yuen et al. (8) examined the predictive performance between these two methods in US paediatric patients, although they found the latter tended to have less poor predictions than the former. It is worthwhile to note that method 4 tended to have the same number of under-predictions and over-predictions, whereas for method 5 most of the poor predictions were under-predictions. A similar finding was reported in Japanese patients by Yukawa et al. (7).

Under-predictions may minimize the risk of potentially toxic dosages. This view may put method 5 in some sort of advantageous position over method 4. However, subtherapeutic doses may leave epileptic patients without adequate control of fits, which may in turn increase the risk of permanent brain damage. Method 4 offers additional advantage over method 5, because for the application of the latter, software on Bayesian algorithm for microcomputer is required, whereas the simplicity of the former allows dosage predictions using a pocket calculator. As previously noted (9), there are differences in both $V_m$ and $K_m$ (based on the traditional Michaelis–Menten model) among different ethnic patient population groups. On the basis of the logarithmic growth model, the $S$ estimates (from the plots of ln $C_{ss}$ versus daily dose) obtained in the present Chinese population (0·0216 ± 0·0134 days/mg and 0·0127 ± 0·0108 days/mg for 31·0 ± 15·8 kg children and 57·1 ± 12·3 kg adults, respectively) were higher than those reported in Japanese patients.

Table 2. Comparison of single-point dosage prediction methods

<table>
<thead>
<tr>
<th>Method*</th>
<th>Patients n</th>
<th>Bias, percentage dose (ME, 95% CI)</th>
<th>Precision, percentage dose (RMSE, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63†</td>
<td>3·01 (-5·95, 12·0)</td>
<td>74·4 (38·0, 53·3)‡</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>-1·85 (-7·11, 3·41)</td>
<td>21·5 (13·3, 27·2)</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>2·14 (-0·07, 3·35)</td>
<td>21·9 (15·9, 26·8)</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>-1·079 (-6·27, 4·12)</td>
<td>21·1 (14·4, 26·2)</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>-1·98 (-7·69, 3·73)</td>
<td>22·2 (11·6, 29·3)</td>
</tr>
</tbody>
</table>

Table 3. Percentage of predictions with errors >20% of observed daily doses

<table>
<thead>
<tr>
<th>Method</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Over-prediction</td>
<td>22·7</td>
<td>13·6</td>
<td>15·2</td>
<td>10·6</td>
</tr>
<tr>
<td></td>
<td>Under-prediction</td>
<td>15·2</td>
<td>13·6</td>
<td>15·2</td>
<td>10·6</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>37·9</td>
<td>27·2</td>
<td>30·4</td>
<td>21·2</td>
</tr>
</tbody>
</table>

ME=mean error, RMSE=root mean squared error, CI=confidence interval.
*Sources of methods: 1=Richens and Dunlop, 2=Chiba et al., 3=Martin et al., 4=Wagner, 5=Bayesian feedback.
†Three extreme cases excluded.
‡Significantly different from methods 2–5 ($P<0·0001$).
(0·0124 ± 0·0049 days/mg and 0·0121 ± 0·0070 days/mg for 35·4 ± 15·4 kg children and 54·5 ± 7·9 kg adults, respectively), indicating that toxic plasma levels could be achieved at lower phenytoin doses in our ethnic population group. Clearly, method 4 fulfilled the criteria for a dosing method and the selection of appropriate population parameter value is important for the success of its application.

The overall results obtained in the present study point to the usefulness of a single-point approach to phenytoin dosage prediction. The Bayesian method with one feedback (method 5) fails to display any advantage when compared to other methods, in particular methods 2, 3 and 4, that require only part of prior information about the population pharmacokinetic parameters of phenytoin. In view of the large number of predictions with an error of greater than 20% of a dose, whichever method is employed to aid phenytoin dosage adjustments in epileptic patients, some individuals may still receive an inappropriate dosage regimen. It is therefore important that patients receive both phenytoin concentration monitoring and clinical status examination at appropriate intervals after dosage adjustments.

REFERENCES