Influence of Coadministered Antiepileptic Drugs on Serum Phenobarbital Concentrations in Epileptic Patients: Quantitative Analysis Based on a Suitable Transforming Factor

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This study investigated most suitable transforming factor related to the daily Phenobarbital dose (D) providing a steady-state serum concentration (C) and analyzed the influences of concomitant antiepileptic drugs on C, quantitatively. Data obtained by routine therapeutic drug monitoring from a total of 326 epileptic patients treated with multiple oral administrations of phenobarbital (PB) as a powder, were used for the analysis. A total of 156 patients were administered PB alone, and 92, 57, and 21 patients were coadministered one, two, and three different antiepileptic drugs, respectively. Valproic acid (VPA), carbamazepine (CBZ), phenytoin (PHT), zonisamide (ZNS), clonazepam, and ethosuximide were coadministered with PB. For administration of PB alone, four types of transforming factor corresponding to clearance, i.e., total body weight, total body water volume, body surface area and extracellular water volume (VECW) were proposed. With VECW as a transforming factor, the level/dose (L/D) ratio ([C/((D/VECW))] was independent of the patient's age and gender. C was dependent on only one variable regarding D/VECW and expressed as C=0.989×(D/VECW). The coadministration of one drug caused a difference in the gradient of the regression line of PB alone, and the influence of each drug was detected by dividing each mean L/D ratio of PB plus another one drug by that of PB alone. VPA, CBZ, and PHT significantly increased (p<0.01) the L/D ratio to 1.48, 1.35, and 1.23 of the value for PB alone, respectively. With coadministration of multiple drugs, the L/D ratio rose significantly (p<0.05) as the number (i.e., 2) of drugs coadministered increased regardless of the type, and also increased with the concomitant use of 3 drugs compared with 2 drugs. For a more detailed analysis, we defined the parameter R, representing the influence of each antiepileptic drug on the L/D ratio of PB alone. A model based on the assumption that each coadministered drug competitively inhibited PB-metabolizing enzyme, was adopted. The analysis clarified that VPA, CBZ, and PHT significantly increased (p<0.05) the L/D ratio of PB to 1.466, 1.177, and 1.186, respectively. In the case of the addition or discontinuance of concomitant treatment with antiepileptic drugs in the same patient, the estimated L/D ratios were calculated using the value of each R, and compared with the measured value. The mean of prediction error was calculated as 23.1%. Our results appear valid and R should be available for clinical use.

Key words phenobarbital; transforming factor; level/dose ratio; extracellular water volume; concomitant therapy; alteration ratio

Phenobarbital (PB) is used to treat generalized tonic-clonic seizures, complex partial seizures and febrile convulsions, being effective at a serum concentration of 15—40 μg/ml.1) Although monotherapy for seizures is preferable, improved control is sometimes achieved with concomitant therapy. The measurement of serum PB concentrations can be of value in individualizing dosage. It is clinically important to clarify the influences of antiepileptic drugs on the serum PB concentration in a steady-state (Ct).

When Ct is related to the daily dose (Dt), the latter is often transformed to a variable (transformed daily dose: D’t) being divided by an individual factor (transforming factor) such as total body weight (W) or body surface area, Ct and Dt are expressed as a function of clearance, the transforming factor is thus used as a substitute for clearance. Then the influences of the coadministered antiepileptic drugs on PB disposition were evaluated by Ct/D’t (level/dose (L/D) ratio).

For PB, with W as a transforming factor, the L/D ratio (Ct/(D/W); Ct/Dw) was found to be dependent on age.2) Many reports have referred to changes in the Ct/Dw ratio caused by other coadministered antiepileptic drugs, but there has been no regard paid to the influences of age. These results based on Ct/Dw are misleading because patients might not be grouped by the age. For these reasons, if D’t, which was related to Ct without being affected by confounding factors such as age and gender, could be determined, it would be worth evaluating for clinical use. And it is preferable to clarify the relation between D and Ct in the administration of PB alone. Then, the influence of concomitant drug use on the serum concentration could be evaluated in all the patients without grouping them by other confounding factors.

In this paper, the authors searched for suitable transforming factor affecting the L/D ratio of PB independent of confounding factors in the administration of PB alone, then clarified the relation between the daily PB dose and Ct. In patients receiving concomitant therapy, the authors detected the drug affect on L/D ratio and investigated its influence quantitatively.

MATERIALS AND METHODS

We collected data from epileptic patients, who were chronically treated with multiple oral administrations of PB (Phenobar® powders, Sankyo Co., Osaka, Japan) at Kagawa Medical University Hospital between November 1996 and October 1997 and at Kurashiki Central Hospital between April...
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Total or mean±S.D.</th>
<th>Kagawa Medical University Hospital</th>
<th>Kurashiki Central Hospital</th>
<th>Both Hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>116</td>
<td>210</td>
<td>326</td>
</tr>
<tr>
<td>Gender: GENDER</td>
<td>Male</td>
<td>52</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>64</td>
<td>85</td>
</tr>
<tr>
<td>Age: AGE [years]</td>
<td>18.3±18.9</td>
<td>23.4±21.7</td>
<td>21.6±20.9 (0—90)</td>
</tr>
<tr>
<td>Body weight: W [kg]</td>
<td>38.3±24.1</td>
<td>41.2±21.4</td>
<td>40.1±22.4 (1.4—112.0)</td>
</tr>
<tr>
<td>Height: H [cm]</td>
<td>130±37</td>
<td>138±32</td>
<td>135±34 (38—178)</td>
</tr>
<tr>
<td>Daily PB dose: D [mg/d]</td>
<td>85±51</td>
<td>70±39</td>
<td>75±44 (3—346)</td>
</tr>
<tr>
<td>Serum PB concentration: C1 [μg/ml]</td>
<td>16.4±5.8</td>
<td>13.1±6.3</td>
<td>14.3±6.3 (1.3—40.8)</td>
</tr>
<tr>
<td>PB therapy</td>
<td>Alone</td>
<td>70</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Concomitant</td>
<td>46</td>
<td>124</td>
</tr>
<tr>
<td>No. of drugs coadministered</td>
<td>1</td>
<td>27</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>16</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>18</td>
</tr>
</tbody>
</table>

Values in parentheses indicate the range.

Table 2. Gender and Age Differences in L/D Ratio for Each Transforming Factor

<table>
<thead>
<tr>
<th>Transforming factor</th>
<th>W</th>
<th>VTBW</th>
<th>BSA</th>
<th>VECW</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/D ratio</td>
<td>C1/DW</td>
<td>C1/D'TBW</td>
<td>C1/D'BSA</td>
<td>C1/D'ECW</td>
</tr>
<tr>
<td>GENDER</td>
<td>Male (83)</td>
<td>4.78±2.18</td>
<td>2.86±1.12</td>
<td>0.179±0.06</td>
</tr>
<tr>
<td></td>
<td>Female (73)</td>
<td>5.23±2.22</td>
<td>3.08±1.11</td>
<td>0.182±0.06</td>
</tr>
<tr>
<td>AGE</td>
<td>&lt;15 (128)</td>
<td>4.50±1.81</td>
<td>2.76±0.95</td>
<td>0.178±0.05</td>
</tr>
<tr>
<td></td>
<td>≥15 (28)</td>
<td>7.25±2.50</td>
<td>3.91±1.86</td>
<td>0.211±0.07</td>
</tr>
</tbody>
</table>

NS: Not significant. **p<0.01, *p<0.05. (): number of patients.

1995 and March 1996. The total number of patients administered PB was 326. Patients with abnormal findings on hepatic and renal function tests were excluded. Blood samples were drawn 2 to 3 h after the last dosing in outpatients and 2 to 15 h in inpatients. The fluctuations of C1 at different sampling times were considered to be negligible because of PB’s long elimination half-life.39

When there were multiple measurements for C1 in one patient with the same prescribed drugs during the study period, the average value was used. The age, total body weight, height and daily PB dose were treated in the same manner. When several varieties of drugs were prescribed in one patient, the count was taken as the number of patients. In both hospitals, C1 was measured in duplicate by the FPIA method (TDX® or FLX® system, DAINABOT, Tokyo Japan) and the average value employed.

Data analysis was performed by utilizing a statistical package, NAP (ver.4).41

RESULTS

Patient Characteristics Table 1 shows the characteristics of the study populations administered PB in each hospital. We combined the data from the two hospitals to elevate the power of tests in the analysis and to obtain various combinations of concomitant therapy.

PB Alone

Correlation of L/D Ratio with GENDER and AGE: Empirical formulas (1), (2), and (3) have been reported for total body water volume (VTBW),5) body surface area (BSA),5) and extracellular water volume (VECW),5) respectively.

\[
V_{\text{TBW}}[1]=0.135\times H^{0.466}\times W^{0.535} \tag{1}
\]

\[
\text{BSA} [m^2]=0.007246\times W^{0.425}\times H^{0.725} \tag{2}
\]

\[
V_{\text{ECW}} [1]=0.068\times H^{0.666}\times W^{0.613} \tag{3}
\]

(W: total body weight [kg], H: height [cm])

The following transformed daily doses, DW (=DW), DTBW (=D/VTBW), DBSA (=D/BSA), and DECW (=D/VECW), were proposed. The correlation of age with the L/D ratio was investigated for two groups, AGE<15 and AGE ≥15. C1/DW, C1/D'TBW, and C1/D'BSA showed a significant difference between the two groups, but C1/D'ECW did not. In contrast, the L/D ratios showed no significant difference between genders (Table 2).

For example, C1/DW and C1/D'ECW in relation to AGE are compared in Fig. 1. The C1/DW ratio showed a positive correlation with AGE for the groups of AGE<15 and all AGE (a). No significant correlation was found between C1/D'ECW and
AGE in any group, that is, the \( C_i/D_{ECW} \) ratio was independent of \( AGE \) (b).

Factors Influencing \( C_i \): The data from the 326 patients were used for multiple regression analysis, with \( C_i \) assigned as the criterion variable and \( D_W, D_{TBW}, D_{BSA}, \) or \( D_{ECW} \) as the main-explanatory variable. \( W, D, AGE, \) and \( GENDER \) were assigned as the sub-explanatory variables. The forward selection method was used to select the variables influencing \( C_i \).

The level of significance, which prescribed the addition of \( C_i \) as the criterion variable and \( D_{ECW} \) as the sub-explanatory variable. The difference between \( r_{mi}^2 \) and \( r_s^2 \) indicates the contribution of the sub-explanatory variable to \( C_i \). In contrast, only the main-explanatory variable was selected in \( V_{ECW} \). That is, \( C_i \) could be related only with the variable \( D'_{ECW} \).

Figure 2 shows the relationship between \( C_i \) and \( D'_{ECW} \). Both variables were significantly correlated and could be expressed approximately as line 1: \( C_i=0.989 \times D'_{ECW} \).

Concomitant Therapy

Influence of One Drug on \( C_i \): It is comprehensible to investigate the influence of concomitant drug use by first examining the effect of one drug. Ninety-one patients were coadministered one antiepileptic drug such as valproic acid (VPA), carbamazepine (CBZ), phenytoin (PHT), or zonisamide (ZNS) (Table 4). As shown in Fig. 2, the correlation

and/or elimination of a variable using the \( F \)-test, was taken as 0.05.

In Table 3, the standard partial regression coefficients of the selected explanatory variables, namely the factors influencing \( C_i \), the simple correlation coefficient \( (r_c) \) between the main-explanatory variable and \( C_i \), and the multiple correlation coefficient \( (r_m) \) between all selected explanatory variables and \( C_i \) are shown. In the transforming factor of \( W, V_{TBW} \) and \( BSA, D \) or \( H \) was selected as the sub-explanatory variable, respectively. The difference between \( r_{mi}^2 \) and \( r_s^2 \) indicates the contribution of the sub-explanatory variable to \( C_i \).
Table 4. L/D Ratio and Alteration Ratio on Coadministration of One Drug

<table>
<thead>
<tr>
<th>Drug coadministered</th>
<th>No. of patients</th>
<th>C/D&lt;sub&gt;ECW&lt;/sub&gt; ratio (mean±S.D.)</th>
<th>Alteration ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid (VPA)</td>
<td>156</td>
<td>1.032±0.324</td>
<td>—</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>33</td>
<td>1.531±0.485</td>
<td>1.48**</td>
</tr>
<tr>
<td>Phenytoin (PHT)</td>
<td>42</td>
<td>1.395±0.340</td>
<td>1.35**</td>
</tr>
<tr>
<td>Zonisamide (ZNS)</td>
<td>8</td>
<td>1.727±0.406</td>
<td>1.23**</td>
</tr>
</tbody>
</table>

**p<0.01, NS: not significant.

![Fig. 3. Influence on L/D Ratio of Number of Antiepileptic Drugs Coadministered](image)

Values in parentheses indicate the number of patients. *p<0.05, **p<0.01, NS: not significant.

of C<sub>e</sub> versus D<sub>ECW</sub> was expressed approximately as the line 2 which intersected the origin for PB+PHT. The same results were obtained with each of the other antiepileptic drugs (data not shown). From these results (Fig. 2), the influence of the coadministered drug was evident from the change in the gradient of the regression line. We could thus compare each L/D ratio to detect the influence of another antiepileptic drug.

In Table 4, each alteration ratio is shown as the ratio of the L/D ratio of PB plus one drug to that of PB alone. The L/D ratio of PB alone was significantly increased by VP A, CBZ, and PHT (p<0.01). However, ZNS did not have an effect.

**Influence of Antiepileptic Drugs on C<sub>e</sub>/D<sub>ECW</sub>:**

The L/D ratio rose significantly (p<0.05) as the number (±2) of drugs coadministered increased regardless of their type. The L/D ratio also increased with the concomitant use of 3 drugs as compared with 2 drugs (Fig. 3).

**DISCUSSION**

There are reports that C<sub>e</sub>/(D/W) was increased significantly in children up to 15 years old. Before investing the influences of coadministered antiepileptic drugs on C<sub>e</sub>, it is preferable to clarify the relationship between the daily dose and C<sub>e</sub> for PB alone. Any confounding factors in this relationship should be excluded to evaluate the influences of antiepileptic drugs on C<sub>e</sub>. No gender-based differences were found at any L/D ratio. As a transforming factor was substituted for the clearance, gender differences were not found for clearance as observed for VPA. On the other hand, when the L/D ratio was significantly different between two groups (AGE<15 and AGE≥15), the age-dependent change in the transforming factor except for V<sub>ECW</sub> was not closely correlated with that in clearance. In our study population, the number of patients 15 years old or younger was sufficient and the ratio of C<sub>e</sub>/(D/V<sub>ECW</sub>) was independent throughout the AGE (Fig. 1(b)).

BSA is recommended as a transforming factor because of its close correlation with a number of age-dependent physiological parameters influencing the disposition of a drug such as renal blood flow and hepatic weight. V<sub>ECW</sub> is also closely correlated to these parameters. V<sub>ECW</sub> is a more suitable transforming factor for PB than W or BSA (Table 3). Since most drugs distribute through the extracellular water space in order to reach their receptors, V<sub>ECW</sub> is more suitable for the ultimate drug level than BSA. For these reasons, we selected V<sub>ECW</sub> as a transforming factor.

In the present study, a significant linear relationship was found between C<sub>e</sub> and D<sub>ECW</sub>, and concomitant therapy changed only the gradient of the regression line (Fig. 2). The L/D ratio was increased because the coadministered drug raised the gradient for PB alone. VPA, CBZ, and PHT were found to raise the L/D ratio of PB (p<0.01) when they alone were coadministered (Table 4). However, the number of patients coadministered one drug was not sufficient to detect any influence of the coadministered drugs, precisely.

Metabolism is the most important mechanism of elimination and accounts for drug interactions. The cytochrome P450 (CYP) system is the most important system for antiepileptic drugs. The main metabolic pathway of PB is p-hydroxylation by CYP isoenzymes, possibly CYP2C19 and another important metabolic pathway is N-glucosidation. VPA inhibits both PB pathways and significantly reduces its metabolic clearance.

CBZ is an inducer of CYP2C9, but may be an inhibitor of CYP2C19 and other metabolic pathways. CBZ may also slightly inhibit PM-metabolizing enzyme. PB and PHT are metabolized by the same enzyme system, they may each inhibit metabolism of the other by a competitive mechanism, decreasing their metabolic clearance. ZNS does not affect CYP systems for PB metabolism.

Though significant differences were not observed, the L/D ratio of PB alone was slightly increased by ZNS.

The influences of these drugs on the L/D ratio as observed in Fig. 3, were not additive and/or multiplicative. From these results of an increased L/D ratio and the competitive inhibition mechanism of these drugs between PB and its metabolizing enzyme, which was previously reported, we postulated that each coadministered drug competitively inhibits the PB-metabolizing enzyme.

\[ E + \frac{k}{k + \theta} EI \rightarrow EI \]

Where E is the PB-metabolizing enzyme, I is the coadministered drug, k<sub>q</sub> is the binding rate constant, and k<sub>-q</sub> is the dissociation rate constant. The deactivation ratio of the PB-metabolizing enzyme is postulated to be θ on the left, and the residual activation ratio of the enzyme is 1−θ on the right. Then, the total enzyme activation is written as E<sub>t</sub>, and the following equations can be expressed from these concentrations.

\[ k_{q} [E][I]=k_{-q}[EI], [E]+[EI]=[E_{t}], [EI]/[E]=\theta \]

The apparent equilibrium constant (η) can be written as

\[ \eta=k_{q}[I]/k_{-q}=\theta (1-\theta) \]
then, the residual activation ratio \((1 - \theta)\) can be written as 
\[
1/(1 + \eta).
\]

Next, in the case of two drugs coadministered, both drugs are distinguished by the subscript 1 and 2. The enzyme reactions are as follows.

\[
\begin{align*}
E + L \overset{k}{\underset{k_t}{\rightleftharpoons}} El_1 \\
E + L \overset{k}{\underset{k_t}{\rightleftharpoons}} El_2
\end{align*}
\]

Both coadministered drugs deactivate the PB-metabolizing enzyme competitively. The enzyme deactivation ratio is \((1 - \theta_1 - \theta_2)\) on the left of each equation and is \(\theta_1\) and \(\theta_2\) on the right. The residual enzyme activation ratio can be written as \(1/(1 - \theta_1 - \theta_2)\), the same as when one drug is coadministered. Then, \(\eta_1\) and \(\eta_2\) can be written as \(\theta_1/(1 - \theta_1 - \theta_2)\) and \(\theta_2/(1 - \theta_1 - \theta_2)\), respectively.

Similarly, in the case where multiple drugs are coadministered, the residual enzyme activation ratio can be written as
\[
1/\left(1 - \theta_1 - \theta_2 - \cdots - \theta_n \right) = 1/(1 + \eta_1 + \eta_2 + \cdots + \eta_n)
\]
where \(\eta_i\) is written as \(\theta_i/(1 - \theta_1 - \theta_2 - \cdots - \theta_i)\) \((n: \text{number of coadministered drugs}, i = 1, 2, \ldots, n)\). The elimination rate constant of PB is proportional to the residual enzyme activity, and is given as
\[
(k_{el,i})_{p} = (k_{el})_{i} 	imes \left(1/(1 + \sum \eta_i z_i)\right)
\]
where \((k_{el})_{i}\) and \((k_{el})_{p}\) is the elimination rate constant with concomitant therapy and PB alone, respectively. The subscript \(i\) represents the drug coadministered, and \(i = 1\) to 6 corresponds to VPA, CBZ, PHT, ZNS, clonazepam (CZP), and ethosuximide (ETS), respectively. \(z_i\) is 1 or 0 when drug \(i\) is or is not coadministered.

In the repetitive administrations, few errors would be caused by assuming that the daily amount of PB administered is equal to that eliminated. At a steady-state, the mass balance equation for PB in plasma can be expressed as Eq. 5.

\[
D \times F \cdot k_d \times C_i \times V_{al}\left(D \times F \cdot k_d\right) \text{ (5) then, } 1/k_d = C_i/(D \times F \cdot k_d)
\]

where \(D\) is the daily PB dose [mg/d], \(F\) is the bioavailability \([-\]\), \(C_i\) is the free-PB concentration in plasma [\(\mu g/ml\)], and \(V_{al}\) is the distribution volume of free-PB \([1]\).

As \(C_i\) and \(V_{al}\) would be proportional to \(C_i\) and \(V_{ECW}\), Eq. 6 can be written as

\[
1/k_d = \alpha \cdot C_i/(D \times V_{ECW})
\]

In Eq. 7, \(\alpha\) is the constant \([-\]\) and \(C_i/(D \times V_{ECW})\) is the \(L/D\) ratio. Equations 5 and 7 give \(C_i/(D \times V_{ECW})\) as

\[
C_i/(D \times V_{ECW}) = (C_i/(D \times V_{ECW}))_o \times \left(1 + \sum \eta_i z_i\right)
\]

We established Eq. 8 to elevate the power of the test and to better estimate the precise influence of each drug, quantitatively.

\[
L/D(\text{meas}) = L/D(0) \times (1 + \sum \eta_i z_i) + \epsilon
\]

where \(L/D(\text{meas})\) is the measured \(L/D\) ratio and \(L/D(0)\) is the \(L/D\) ratio of PB alone. \((1 + \sum \eta_i z_i)\) is a parameter representing the influence of each antiepileptic drug on the \(L/D\) ratio of PB alone. Hereafter, it is called the alteration ratio \((R)\). \(\epsilon\) is an error term. No regard was paid to the dose or serum concentration of the antiepileptic drugs in this model.

<table>
<thead>
<tr>
<th>Table 5. Estimated Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug coadministered</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>1 VPA</td>
</tr>
<tr>
<td>2 CBZ</td>
</tr>
<tr>
<td>3 PHT</td>
</tr>
<tr>
<td>4 ZNS</td>
</tr>
<tr>
<td>5 CZP</td>
</tr>
<tr>
<td>6 ETS</td>
</tr>
</tbody>
</table>

\(R = 1 + (\sum \eta_i z_i)\).

Multiple regression analysis revealed the drugs influencing the \(L/D\) ratio \((p<0.05)\) and their estimated \(R\) values (Table 5). VPA, CBZ, and PHT were selected and would increase the \(L/D\) ratio to 1.466, 1.177, and 1.186 times the value for PB alone, respectively.

To evaluate each \(\eta_i\) obtained in this study, measured and estimated concentrations were compared in cases where the drugs prescribed to the patient were changed. Both concentrations seem to be accurate (Fig. 4). The mean prediction error (MPE) was calculated as 23.1% from the following equation.

\[
\text{MPE} = \left(\frac{1}{n} \sum \left| \frac{\text{measured value} - \text{estimated value}}{\text{measured value}} \right| \right) \times 100
\]

\((n): \text{number of sets compared}\). By elevating the power of the test and from the raised \(L/D\) ratio with the increase in the number of drugs coadministered (Fig. 3), the authors postulated \(\eta_i\). As this model (Eq. 8) could analyze all cases inclusively, the reliability of the estimated values would be improved. As a result, VPA, CBZ, and PHT were found to raise the \(L/D\) ratio significantly. Even with an increase in patient number, ZNS was not found to influence the \(L/D\) ratio of PB. As shown in Tables 4 and 5, estimated values closely corresponded to each other. These findings thus supported a competitive inhibition of these drugs for PB-metabolizing enzymes.

Our results were consistent with the reports that VPA,[16] and PHT[17] raised the \(L/D\) ratio on concomitant use. CBZ was reported to show a slight decrease in clearance[14] or no alterations[15] for PB. Though not clarified in our study, these
evaluations might be affected the confounding factors. The result $R > 1$ indicates that the coadministered antiepileptic drugs mainly lower the value of the elimination rate constant. These findings would also be due to the inhibition by these antiepileptic drugs. It could not be clarified whether CZP and ETS had an effect or not because of an insufficient number of patients.

When the antiepileptic drugs administered to a patient are changed, the change in the $L/D$ ratio can be estimated from Eq. 8 using the value of $\eta_i$ (Table 5). In the case where the administration of VPA is added during therapy using PHT with PB, each $L/D$ ratio is calculated as follows.

$$L/D_{(0)}=L/D_{(0)} \times (1 + \eta_i) = L/D_{(0)} \times (1 + 0.186)$$  \hspace{1cm} (9)

$$L/D_{(1,3)}=L/D_{(0)} \times (1 + \eta_i + \eta_3) = L/D_{(0)} \times (1 + 0.186 + 0.466)$$  \hspace{1cm} (10)

Where $L/D_{(0)}$ is the $L/D$ ratio of PB alone, $L/D_{(1)}$ and $L/D_{(1,3)}$ mean the concomitant use of PHT and of VPA+PHT, respectively.

From Eqs. 9 and 10, the alteration ratio of $C_i$ is given as the ratio of $L/D_{(1,3)}$ to $L/D_{(3)}$.

$$\left( L/D_{(1,3)} \right) / \left( L/D_{(3)} \right) = (L/D_{(0)} \times 1.652) / (L/D_{(0)} \times 1.186) = 1.393$$

thus, $C_i$ is expected to increase to 1.39 upon addition of VPA. The daily PB dose should be reduced to 0.72 (=1/1.39) to maintain the same level of $C_i$.

Although the present study was retrospective and the clinical data were from a number of sources, we feel confident of the results (Fig. 4). Many patients switch from PB treatment to mono/concomitant therapy. Each alteration ratio of $R_i$, in our study population, could be adapted to all the patients without them being grouped by other confounding factors. This will make it easy to estimate $C_i$ correctly on the addition or discontinuance of co-treatment with antiepileptic drugs in PB therapy.

REFERENCES