Factors Influencing the Serum Concentration of Antiepileptic Drugs
—Effects of Concomitant Antiepileptic Drugs on the Serum Valproic Acid Concentration in Epileptic Patients—

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(Received September 24, 1997)  (Accepted June 11, 1998)

The effects of concomitant antiepileptic drugs on the serum valproic acid concentration (Cs) were investigated. Primidone (PRM), phenobarbital (PB), carbamazepine (CBZ), phenytoin (PHT), zonisamide (ZNS), clonazepam (CZP) and ethosuximide (ETS) were coadministered with valproic acid (VPA).

The routine therapeutic drug monitoring data, obtained from epileptic patients who were treated with the repetitive oral administration of the sustained-release preparations of VPA (VPA-R), were used for the analysis. A total of 233 patients were administrated VPA-R alone, and 87, 21 and 6 patients were coadministered one, two and three different antiepileptic drugs, respectively.

Using the data obtained from the patients administrated VPA-R alone, Cs could be expressed conveniently as a function of X as Cs = AX. (X: VPA daily dose per modified body weight. A, B: parameter)

By comparing the regression line on logCs vs. logX for VPA-R alone with that for VPA-R plus one concomitant drug, Cs was thus found to be affected at each definite ratio by PB, CBZ, PHT, but not by ZNS.

Next, we defined the parameter Ri (i=1, 2,…,7) as a coefficient representing the effect of each concomitant antiepileptic drug on Cs. All data were analyzed to estimate Ri, using a model based on the assumption that each Ri was independent from one another and multiplicative. The analysis clarified that PB, CBZ and PHT lowered Cs to 0.879, 0.812 and 0.833 times, respectively. On the other hand, ZNS did not affect Cs. The number of patients coadministered PRM, CZP and/or ETS was not sufficient to detect the effect on Cs based on a test of significance.

Key words — valproic acid, serum concentration, concomitant therapy, antiepileptic drug, alteration ratio

Introduction

Monotherapy is recommended in the treatment of epilepsy by the reasons of preventing the
unpredictable adverse reactions and interactions caused by using more than two sorts of antiepileptic drugs, and of being capable to evaluate the effectiveness of an antiepileptic drug simply\(^1,2\). On the other hand, in the case of refractory seizures for which a monotherapy is not effective, it often requires a concomitant use of more than one antiepileptic drug\(^3,4\).

Valproic acid (VPA) has been found to be effective when used by adding other antiepileptic drugs or used as monotherapy\(^5,6\). Therefore, concomitant therapy is often changed to VPA monotherapy, and other antiepileptic drugs are often added to VPA monotherapy.

The serum VPA concentration (\(C_v\)) has been reported to be altered by the concomitant antiepileptic drugs\(^7,8\) . Thus, it is anxious for the occurrences of adverse reaction caused by the increased \(C_v\), and for the reduction of main reaction caused by the decreased \(C_v\). Therefore, evaluating the effects of concomitant antiepileptic drugs on \(C_v\) is important to use the VPA preparations properly, so that many papers have been referred to this point. However, in most of papers, the \(C_v\) measurements were obtained from the patients administrated the conventional preparations of VPA whose absorption rates were relatively rapid\(^9,10\) and the number of measurements in each patient was different\(^12\). Accordingly, the \(C_v\) values would vary greatly and, consequently, there seemed to be little consistency in the effects of concomitant antiepileptic drugs on \(C_v\). On the contrary, the sustained-release preparations of VPA (VPA-R) show a narrow \(C_v\) range in the oral administration once or twice a day\(^13\). Therefore, we collected the data from the epileptic patients administrated VPA-R and studied to obtain a quantitative expression which could provide the alteration of \(C_v\) in changing the combination of concomitant antiepileptic drugs with VPA-R.

**Method**

Data were collected from the epileptic patients, who were treated with repetitive oral administration of VPA-R (Selenica-R\(^6\) granules, Nikken Chemicals Co., LTD. Tokyo Japan, Depakene-R\(^5\) tablets, Kyowa Hakko Kogyo, Tokyo, Japan) at both Kagawa Medical University Hospital and Kurashiki Central Hospital from April 1995 to September 1996. The patients of abnormal findings on hepatic and renal functions were excluded. Blood samples were obtained 2 to 3 hours after last dosing in outpatients and 2 to 15 hours in inpatients. \(C_v\) was measured in duplicate by FPIA method (TDX\(^5\) or FLX\(^5\) system, DAINABOT, Tokyo Japan) in both hospitals.

When there were several measurements for \(C_v\) in one patient at the same prescribed drugs during the investigation period, the average value was used as a representative one. The age, body weight, height and the VPA daily dose were treated similarly. When there were several varieties of prescribed drugs in one patient, the count was taken as the number of patients.

The total numbers of patients administrated VPA-R alone and coadministered other antiepileptic drugs with VPA-R were 233 and 114, respectively. The total of 347 cases were used for analysis.

Data analysis was performed by utilizing the statistical packages, NAP (ver.4)\(^4\).

**Results**

1. Characteristics of the Patients

Table 1 shows the characteristics of the patients administrated VPA-R in each hospital. Kagawa Medical University Hospital abounded in pediatric patients and in the patients coadministered other antiepileptic drugs with VPA-R. Accordingly, significant differences in the age (AGE), body
weight (W), height (H) and the VPA-R therapy were observed between two hospitals. On the other hand, no significant differences in C, the VPA daily dose (D) and the number of drugs coadministered were observed.

By assembling the data of two hospitals together, we could collect many data in a wide range of age.

2. Effects of Concomitant Antiepileptic Drugs on C_i

(1) C_i for VPA-R Alone

In previous paper we reported that C_i could be satisfactorily correlated to only one variable of the VPA daily dose per modified body weight, and could be expressed as eq. (1) at steady-state by using a model where the VPA binding to plasma protein was considered.

\[ C_i = \alpha X \left( 1 + K_i C_m + K_i X \right) / (1 + \alpha K_i X) \]  \hspace{1cm} (1)

where, \( C_i \) is the serum VPA concentration [\( \mu g/mL \)], and X is the VPA daily dose per modified body weight (\( = D/W_s \)) [mg/(kg·day)]. \( \alpha \) is a parameter [day] which is proportional to the ratio of the bioavailability \( [-] \) to the elimination rate constant \( [1/day] \). \( K_i \) and \( C_m \) are the binding equilibrium constant to plasma protein [mL/\( \mu g \)] and the bound-VPA concentration in plasma in saturation [\( \mu g/mL \)], respectively. These parameter values were estimated by using a nonlinear least squares method. Employing the estimated parameter values, the plasma protein binding ratio of VPA had a good agreement with those reported previously.

Nevertheless, eq.(1) consists of many parameters and the calculation is complicated. Thus, we postulated a convenient equation, eq.(2), in which \( C_i \) is proportional to the power function of X. Parameters A and B were estimated by using a nonlinear least squares method.

\[ C_i = AX^n \]  \hspace{1cm} (2)

In Fig. 1, solid curve 1 and broken curve 2 represent the regression curves calculated from eq. (1) and eq.(2), respectively. Both curves were in fair agreement with each other in the extent of adopted X values. Namely, the sample standard deviations from regression curves were calculated
Fig. 1. Relationship between the VPA Daily Dose per Modified Body Weight ($D/W_m (=X)$) and the Serum VPA Concentration ($C_t$).

Fig. 2. Comparison of Regression Lines for VPA-R Alone and Coadministered PB, CBZ, PHT and ZNS. Each regression line represents for VPA-R alone; -- 0, coadministration of PB; --- 2, CBZ; ---- 3, PHT; ----- 4, ZNS; --- 5, respectively.
as 16.28(μg/mL) for eq.(1) and 16.33(μg/mL) for eq.(2), respectively, and both values were nearly equal. Accordingly, we investigated the effects of concomitant antiepileptic drugs on C₁ using the convenient eq.(2), hereafter.

(2) C₁ for Coadministration of Another Antiepileptic Drug

The 87 patients coadministered another antiepileptic drug with VPA-R. Seven sorts of antiepileptic drugs such as primidone (PRM), phenobarbital (PB), carbamazepine (CBZ), phenytoin (PHT), zonisamide (ZNS), clonazepam (CZP) and ethosuximide (ETS) were coadministered.

We assumed that eq.(2) could be adapted to express C₁ for the case of coadministration of another antiepileptic drug with VPA-R. Converting both members of eq.(2) into common logarithms,

\[ y = a + bx \]

where, \( y = \log C₁, x = \log X, a = \log A \) and \( b = B \). We paid no regard to the dose of concomitant antiepileptic drug in this assumption.

Fig. 2 shows the regression lines with respect to \( \log C₁ \) vs. \( \log X \) for VPA-R alone and for another concomitant antiepileptic drug, such as PB, CBZ, PHT and ZNS, with VPA-R. The regression line and the sample standard deviation from regression line (\( S_y \)) are shown in Table 2. The number of patients coadministered PRM, CZP or ETS with VPA-R was not enough to calculate the regression line.

As shown in Fig. 2, line 3 for CBZ+(VPA-R) locates lower extent of \( y \) than line 0 for VPA-R alone and both lines are almost parallel. The slope and height (\( y \) value) of both line 2 line for PB+(VPA-R) and line 4 for PHT+(VPA-R) are somewhat lower than those of line 0. Line 5 for ZNS+(VPA-R) seems to be in fair agreement with line 0.

Because the plots scattered widely (see \( S_y \) values in Table 2), a statistical method was employed to compare the regression line for VPA-R alone with another. The results are shown in Table 2.

<table>
<thead>
<tr>
<th>Drug Coadministered</th>
<th>Number of Data (n)</th>
<th>Regression Line</th>
<th>( S_y )</th>
<th>Comparison of Slope</th>
<th>Comparison of Height (( y ) Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primidone (PRM)</td>
<td>2</td>
<td>( y=1.006+0.548x )</td>
<td>0.131</td>
<td>n.s. (p=0.379)</td>
<td>** (p=0.004)</td>
</tr>
<tr>
<td>Phenobarbital (PB)</td>
<td>22</td>
<td>( y=0.629+0.844x )</td>
<td>0.146</td>
<td>n.s. (p=0.495)</td>
<td>** (p=0.001)</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>23</td>
<td>( y=1.173+0.427x )</td>
<td>0.115</td>
<td>n.s. (p=0.067)</td>
<td>** (p=0.005)</td>
</tr>
<tr>
<td>Phenytoin (PHT)</td>
<td>22</td>
<td>( y=0.984+0.655x )</td>
<td>0.136</td>
<td>n.s. (p=0.565)</td>
<td>n.s. (p=0.390)</td>
</tr>
<tr>
<td>Zonisamide (ZNS)</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam (CZP)</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide (ETS)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid (VPA-R alone)</td>
<td>233</td>
<td>( y=0.835+0.761x )</td>
<td>0.139</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( S_y \): Sample Standard Deviation from Regression Line

\( s_y = \sqrt{\frac{1}{n-2} \sum (y_i - \hat{y}_i)^2} \)

n.s.: not significant, **: p<0.01
ble 2. About the slope, significant difference was not detected between VPA-R alone and another concomitant antiepileptic drug with VPA-R. In other words, the compared two slopes are not different, and, consequently, all slopes are equal. On the contrary, about the height, significant differences were detected for PB, CBZ and PHT, but not for ZNS. These results indicate that $G$ is affected at each definite ratio by PB, CBZ and PHT, and not by ZNS.

(3) A Model Representing the Effects of Concomitant Antiepileptic Drugs

From the results mentioned above, we postulated eq.(4) as a model representing the effects of concomitant antiepileptic drugs.

$$C_i = AX^a \cdot \prod_{i=1}^{7} R_i^{z_i} \tag{4}$$

where $R_i$ is a coefficient representing the effect of each concomitant antiepileptic drug on $C_i$ at VPA-R alone, i.e., $AX^a$. Hereinafter, $R_i$ is called an alteration ratio. The subscript $i$ represents the concomitant drug, and $i=1, 2, \ldots, 7$ corresponds to PRM, PB, CBZ, PHT, ZNS, CZP, ETS, respectively. $z_i$ is 1 or 0 when drug $i$ is coadministered or not.

In eq.(4), $C_i$ is expressed with the assumption that the effects of concomitant antiepileptic drugs on $C_i$ are independent and multiplicative with each other. And no regard was paid to the doses of concomitant antiepileptic drugs in this model.

Converting both members of eq.(4) into common logarithms,

$$y = a + bx + \sum_{i=1}^{7} r_i z_i \tag{5}$$

where, $y = \log C_i$, $a = \log A$, $b = B$, $x = \log X$, $r_i = \log R_i$.

The 233 patients were administrated VPA-R alone. The 87, 21 and 6 patients were coadministered one, two and three different antiepileptic drugs, respectively (Table 1). The total of 347 cases were used in eq.(5) for a multiple regression analysis. Table 3 shows the results. There were 3 pa-

<table>
<thead>
<tr>
<th>Parameter, $r_i$</th>
<th>Number of Cases</th>
<th>Estimated Value $\pm$ S.E.</th>
<th>Variable Selection Method Employed</th>
<th>Variable Selection Method Not Employed</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_1$ : PRM</td>
<td>5</td>
<td>0.056 ± 0.068 (1.138)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$r_2$ : PB</td>
<td>35</td>
<td>-0.057 ± 0.024 (0.879)</td>
<td>-0.064 ± 0.026 (0.863)</td>
<td></td>
</tr>
<tr>
<td>$r_3$ : CBZ</td>
<td>36</td>
<td>-0.091 ± 0.024 (0.812)</td>
<td>-0.089 ± 0.024 (0.814)</td>
<td></td>
</tr>
<tr>
<td>$r_4$ : PHT</td>
<td>36</td>
<td>-0.079 ± 0.024 (0.833)</td>
<td>-0.080 ± 0.025 (0.831)</td>
<td></td>
</tr>
<tr>
<td>$r_5$ : ZNS</td>
<td>25</td>
<td>0.008 ± 0.029 (1.019)</td>
<td></td>
<td>0.021 ± 0.044 (0.852)</td>
</tr>
<tr>
<td>$r_6$ : CZP</td>
<td>11</td>
<td></td>
<td>0.021 ± 0.097 (1.050)</td>
<td></td>
</tr>
<tr>
<td>$r_7$ : ETS</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$y$ : VPA-R

The total of 347 cases were used in eq.(5) for a multiple regression analysis. Table 3 shows the results. There were 3 pa-

H

Values in Parentheses Represent $R_i (R_i=10^{r_i})$ and $A(A=10^{a})$ Calculated from Estimated Values $r_i$ and $A$. 

tients coadministered PRM without PB. As PRM is metabolized to PB within the body, 3 was added to the number of cases for PB. Therefore, the sum of the cases coadministered each drug, \( \sum_{i=1}^{7} \sum_{j=1}^{11} Z_{ij} \), becomes 150, though it can be calculated as 147 (=87+2X21+3X6) from the number of drugs coadministered (Table 1).

In the multiple regression analysis, the forward selection method was used to select the variables influencing \( C \). The level of significance discriminating the addition and/or elimination of variable by F-test was taken as 0.05. PB, CBZ and PHT were selected as the antiepileptic drugs influencing \( C \). (Strictly speaking, they influence \( y(=\log C) \).) These drugs would lower \( C \) to 0.879, 0.812 and 0.833 times, respectively.

The multiple regression analysis without variable selection estimated \( r_5 \) for ZNS at 0.008. This value comes to 1.019 in \( R \). The standard deviation of \( r_5 \) was 0.029 and practically equal to those of PB, CBZ and PHT. Thus, ZNS would be said to have no effect on \( C \). PRM, CZP, ETS altered \( C \) to 1.138, 0.952 and 1.050 times, respectively. Nevertheless, the multiple regression analysis with variable selection did not select them as the influencing drug on \( C \). Because the number of the patients administrated these drugs was not enough and the data scattered widely, their effects on \( C \) were considered not to be detected.

**Discussion**

To investigate the effects of concomitant antiepileptic drugs on \( C \), it is preferred to clarify the relationship between the daily dose and \( C \) for the patients administrated VPA-R alone. Some papers mentioned the nonlinearity between the daily dose and \( C \)(19,20). Eq.(1), proposed in our previous paper, represented this relationship fairly(15). As shown in Fig. 1, the convenient eq.(2) could also represent this relationship.

\( \alpha \) in eq.(1) is not equal to \( A \) in eq.(2), but nearly corresponds to \( A \). The remaining portion except \( \alpha \) in eq.(1) relates to the curvature of fitting curve led by the VPA binding to plasma protein. This portion is not equal to \( X^a \) in eq.(2), but nearly corresponds to \( X^a \). Eq.(1) should be used primarily for the analysis of the effects of concomitant antiepileptic drugs on \( C \). But the standard deviations of the estimated parameter values in eq.(1) even for VPA-alone group(15) were too large. In concomitant therapy, the deviations would be more large and the confidence of parameters would be lost.

Then, eq.(2) expressed by two parameters was used for the analysis.

Eq.(2) was transformed as a linear eq.(3) by converting both members into common logarithms. By comparing the regression line for VPA-R alone with that for another concomitant antiepileptic drugs such as PB, CBZ, PHT and ZNS, it was revealed that the slopes of all lines were not different, but neither of the heights for PB, CBZ and PHT were not equal to the height for VPA-R alone (Fig. 2, Table 2). The former result agreed with the reports that these drugs did not affect the plasma protein binding of VPA(21,22). The latter one indicated that \( A \) in eq.(2) was altered by such concomitant drugs. Thus, \( C \) would be affected at each definite ratio by these antiepileptic drugs and the alteration of elimination rate and bioavailability would reflect on \( R \) value.

It was postulated that, when more than two sorts of antiepileptic drugs were coadministered, the effects of these drugs on \( C \) were independent with each other. More precise and great many pa-
tients data may be needed to do a detail investigation about the interactions between antiepileptic drugs. S, for VPA-R alone in the simple regression analysis was 0.139 (Table 2), and S, for all cases including one to three concomitant antiepileptic drugs was 0.135 (Table 3, with variable selection). There is little difference between both S, values. This finding leads the propriety of eq.(4). As this model can analyze all cases inclusively, the reliabilities of parameters estimated will be increased.

The multiple regression analysis revealed that PB, CBZ and PHT lowered C, to 0.879, 0.812 and 0.833 times, respectively (Table 3). Our results agreed with the reports that PB, CBZ and PHT lowered C, in a concomitant use7-11. On the contrary, ZNS did not affect C,. The results of R < 1 indicates that the concomitant antiepileptic drugs raises mainly the value of elimination rate constant. These findings would be led by the inducing actions of drug-metabolizing enzymes possessed in these antiepileptic drugs23-25. On the other hand, it is suggested that ZNS has little effect on C, because of its little inducing and inhibitory effect on the enzymes26. Additionally, C, was reported not to be affected by ZNS27. Thus, our results coincided with those reported by previous investigators.

PRM, CZP and ETS could not be clarified whether they affected C, or not, because the number of patients coadministrated were not enough and the data were scattered. Nevertheless, PRM is anticipated to lower C, by its metabolized PB.

When the concomitant antiepileptic drugs such as PB, CBZ, and PHT are changed in the same patient, the alteration of C, can be estimated from eq.(4) by using the values of R2, R3 and R4 (Table 3). An example will be shown below.

Ex. In the case of discontinuation of CBZ from the concomitant therapy of CBZ and PHT with VPA-R.

When C(3,4) means C, at the concomitant therapy of CBZ and PHT with VPA-R and C(4) means C, at PHT with VPA-R, C(3,4) and C(4) can be written as,

\[ C_{(3,4)} = AX^{0.8} \times R_2 \times R_4 \]
\[ C_{(4)} = AX^{0.8} \times R_4 \]

where X is the VPA daily dose (D) per modified body weight (Wm). From eqs.(6) and (7),

\[ C_{(4)} = C_{(3,4)} \times 1/R_3 \]
\[ = C_{(3,4)} \times 1/0.812 \]
\[ = C_{(3,4)} \times 1.23 \]

Thus, C, is expected to be increased to 1.23 times by discontinuation of CBZ.

The VPA daily dose to maintain C, can be estimated by putting C(3,4) = C(4). Then,

\[ AX^{0.8} \times R_2 \times R_4 = AX_{(4)}^{0.8} \times R_4 \]

where X(4) is D(4)/Wm and D(4) is the VPA daily dose after discontinuation of CBZ. Substituting D/Wm and D(4)/Wm in X and X(4) respectively, and rearranging,

\[ D_{(4)} = R_3^{(1/0.812)} \times D_{(3,4)} = 0.751 \times D_{(3,4)} \]

As D(3,4) is the VPA-R daily dose before discontinuation of CBZ, the VPA daily dose after discontinuation should be decreased to 0.75 times to maintain the same level of C,.

To evaluate the values of R obtained in this study, the measured and estimated values of C, were compared between the cases where the prescribed drugs were changed in the same patient. For PB,
Fig. 3. Relationship between the Measured and Estimated Values of $C_v$ in the Cases of Changing the Prescribed Drugs in the Same Patient

CBZ and PHT, the values of $R$ obtained by the multiple regression analysis with variable selection were used (Table 3). For PRM, ZNS, CZP and ETS, $R$ was postulated to be 1. Fig. 3 shows the plots of estimated $C_v$ versus measured $C_v$. Both values seem to be in good agreement. The mean absolute error (MAE) was calculated as 23.0\%, by the following equation.

$$\text{MAE (%) = } \frac{\sum |\text{measured value} - \text{estimated value}|}{\text{measured value}} \times 100 \quad (n: \text{number of sets compared})$$

In the VPA therapy, the therapeutic drug monitoring will be more worthy because VPA-R became available in clinical use. Therefore, the increase in the patient is expected, who alters his treatment of VPA-R to mono/concomitant therapy to each other. Our alteration ratios presented in this study will be useful indicators for the estimation of $C_v$ in the case of addition or discontinuation of concomitant antiepileptic drugs and for the advices in the treatment of VPA-R for epileptic patients.

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