—Regular Articles—

Effects of Concomitant Antiepileptic Drugs on Serum Carbamazepine Concentration in Epileptic Patients: Quantitative Analysis Based on Extracellular Water Volume as a Transforming Factor

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The effects of concomitant antiepileptic drugs on the serum carbamazepine concentration (C_t) were analyzed quantitatively. Primidone (PRM), phenobarbital (PB), phenytoin (PHT), valproic acid (VPA), zonisamide (ZNS), clonazepam (CZP), and ethosuximide (ETS) were coadministered with carbamazepine (CBZ). Routine therapeutic drug monitoring data, obtained from epileptic patients who were treated with the repetitive oral administration of CBZ fine granules/tablets, were used for the analysis. A total of 119 patients were administered CBZ alone, and 91, 39, 19, and 6 patients were coadministered one, two, three, and more than four different antiepileptic drugs, respectively. Using the data obtained from the patients administered CBZ alone, C_t could be expressed approximately as a function of the daily dose per extracellular water volume (D/V_{ECW}) as $C_t = A(D/V_{ECW})^B$ (A, B: parameter). By comparing the regression line on log C_t vs. log (D/V_{ECW}) for CBZ alone with that for CBZ plus another concomitant drug, C_t was thus found to be affected at each definite ratio by PB and PHT, but not by VPA and ZNS. We postulated a model showing that C_t is affected by each concomitant antiepileptic drug i at each definite ratio. We defined the parameter R_i ($i=1, 2, \cdots, 7$) representing the effect of each concomitant antiepileptic drug on C_t. A linear polynomial expression, in which both members of this model are converted into common logarithms, was used for a multiple regression analysis. The analysis clarified that PB and PHT lowered C_t to 0.770 and 0.710 the value of CBZ alone, respectively. On the other hand, VPA and ZNS did not affect C_t. The number of patients coadministered PRM, CZP, and/or ETS was not sufficient to detect the effect on C_t based on a test of significance. In the case of the addition or discontinuation of concomitant antiepileptic drugs in the same patient, the estimated C_t values were calculated using the value of each R_i and compared with the measured C_t values. Both values were in good agreement, and thus our results appear valid.

Key words——carbamazepine; serum concentration; concomitant therapy; antiepileptic drug; alteration ratio

INTRODUCTION

Carbamazepine (CBZ) is widely used for the treatment of epilepsy. Many reports have referred to the changes in CBZ disposition caused by other concomitant antiepileptic drugs.[1—3] In those reports, when the serum CBZ concentration (C_t) was compared with the daily dose per body weight (D/W), C_t was affected by confounding factors such as age and sex.[4,5] A significant positive correlation was also observed between age and the level-dose (LD) ratio $C_t/(D/W)$.[6,7] The relationship between C_t and the daily dose has not been assessed directly. The regression line for C_t against D/W, which does not intersect the origin, was used for the analysis. Concerning the effects of concomitant antiepileptic drugs on C_t, LD ratios were merely compared[8,9] and the effects were not evaluated quantitatively.

In our previous paper,[10] multiple regression analysis confirmed that C_t could only be correlated with the daily dose per extracellular water volume. In this study, we assumed that C_t was expressed as a power function of the daily dose per extracellular water volume and investigated which concomitant antiepileptic drugs affected C_t using a power function, in the same way as we investigated for valproic acid (VPA).[11,12] We showed the effects of concomitant antiepileptic drugs on C_t quantitatively, making it possible to estimate the changes in C_t values without grouping by other factors when the concomitant antiepileptic drugs are changed.

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METHOD

We collected data from epileptic patients who were chronically treated with repetitive oral administration of CBZ (Tegretol® granules/tablets, Novartis Pharma, Tokyo, Japan) at both Kagawa Medical University Hospital and Kurashiki Central Hospital from April 1996 to March 1997. Patients with abnormal findings on hepatic and renal function tests were excluded. All patients had been administered CBZ for more than 3 months. Blood samples were drawn 2 to 3 h after the last dosing in outpatients and 2 to 15 h after the last dosing in inpatients. When there were plural measurements for C_t in one patient with the same prescribed drugs during the study period, the mean value of C_t was used as the representative one. The age, body weight, height, and daily CBZ dose were also treated in the same manner. When there were several varieties of prescribed drugs in one patient, the count was taken as the number of patients. C_t was measured in duplicate using the FPIA method (TDX® or FLX® system, DAINABOT, Tokyo, Japan) and employed the mean value.

Data analysis was performed utilizing the statistical package NAP (ver.4).[13]

RESULTS

1. Patient Characteristics Table 1 shows the characteristics of the patients administered CBZ in each hospital. Age and C_t were significantly different and the effect of both variables on the analysis are uncertain, but we assembled the data to elevate the potential of detection in the analysis.

2. Effects of Concomitant Antiepileptic Drugs on C_t

(1) C_t for CBZ Alone In the previous paper,[10] we investigated the most suitable transforming factor to relate the daily CBZ dose (D) with the C_t for CBZ alone. Four types of transforming factor corresponding to clearance, *i.e.*, body weight, total body water volume, body surface area, and extracellular water volume (V_{ECW}) were used. Multiple regression analysis confirmed that C_t was only dependent on D/V_{ECW}. V_{ECW} was estimated by the following empirical formula[14]: $V_{ECW}[l] = 0.068 \times \text{body weight}\ [kg]^{0.400} \times \text{height}\ [cm]^{0.633}$.

In Fig. 1, the plots show the relationship between D/V_{ECW} and C_t for CBZ alone. It appears that the increment in C_t decreases gradually with the increase in

Table 1. Patient Characteristics

	Total or Mean±SD			t or χ^2 test
	Kagawa Medical University Hospital	Kurashiki Central Hospital	Both hospitals	
Total no. of patients	99	175	274	—
Sex: *SEX* Male	50	96	146	NS
Female	40	79	128	
Age: *AGE* [years]	26.2±18.9	33.5±20.7	30.9±20.4 (1～82)	$p<0.01$
Body weight: W [kg]	48.5±18.6	51.0±15.9	50.1±16.9 (11.0～96.0)	NS
Height: H [cm]	150.5±20.1	153.8±21.4	152.6±21.0 (80.0～182.5)	NS
Daily CBZ dose: D [mg/day]	462±198	481±270	474±246 (100～120)	NS
Serum CBZ concentration: C_t [μg/ml]	7.00±2.51	6.35±2.41	6.59±2.46 (1.30～14.50)	$p<0.05$
CBZ therapy Momo	40	79	119	NS
Concomitant	59	96	155	
No. of drugs Coadministered 1	40	51	91	$p<0.05$
2	16	23	39	
3	1	18	19	
>4	2	4	6	

t, χ^2 test: comparison between both hospitals. Values in parentheses indicate the range. NS: not significant.

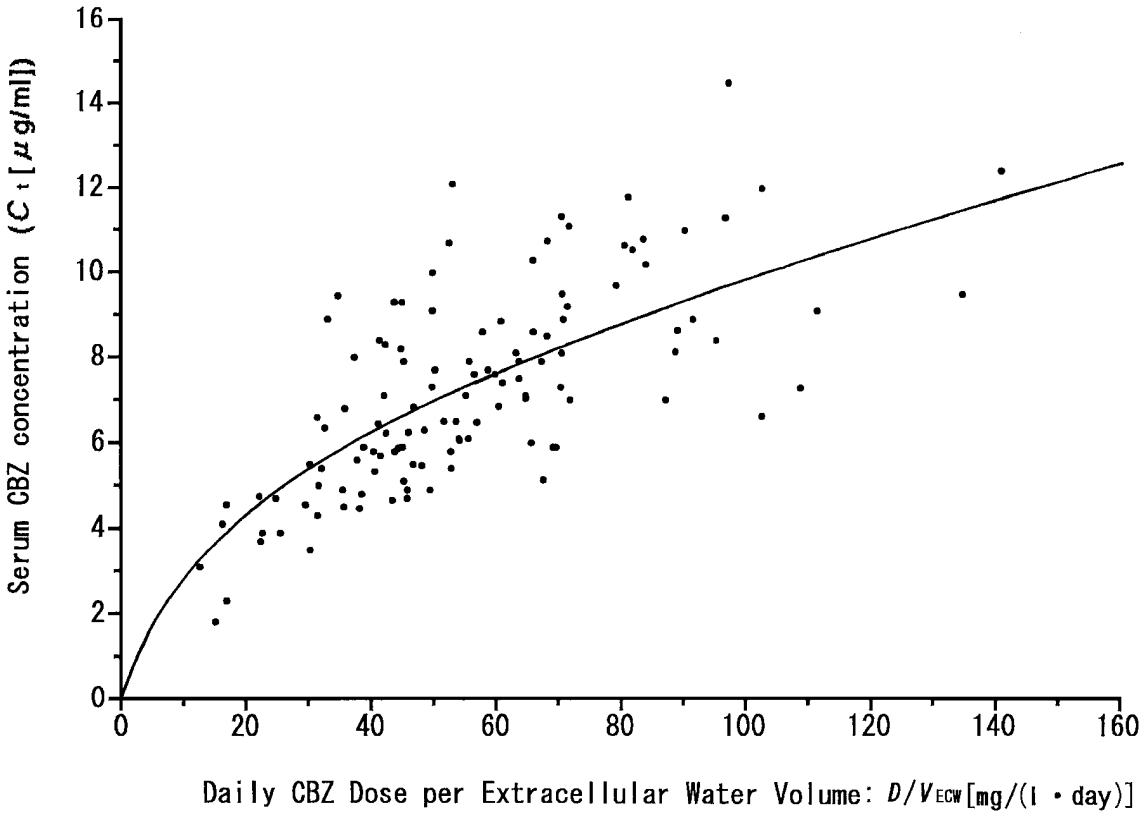

Fig. 1. Relation between the Daily CBZ Dose per Extracellular Water Volume (D/V_{ECW}) and the Serum CBZ Concentration (C_t)
Solid curve represents the regression curve calculated from Eq. (1).

Table 2. Comparison of Regression Line of C_t for CBZ Alone with Those for Another Concomitant Antiepileptic Drug with CBZ

Drug coadministered	No. of data (n) points	Regression line	S_y	Comparison of slope	Comparison of elevation
Phenobarbital	7	$y=0.596x-0.371$	0.208	NS ($p=0.948$)	$p<0.001$
Phenytoin	33	$y=0.800x-0.720$	0.164	NS ($p=0.069$)	$p<0.001$
Valproic acid	39	$y=0.420x+0.091$	0.102	NS ($p=0.061$)	NS ($p=0.106$)
Zonisamide	10	$y=0.504x-0.068$	0.096	NS ($p=0.657$)	NS ($p=0.081$)
Clonazepam	1	—	—	—	—
Ethosuximide	1	—	—	—	—
Carbamazepine alone	119	$y=0.586x-0.163$	0.099		

S_y: Sample standard deviation from regression line: $S_y=\sqrt{\left\{\sum_{j=1}^{n}(y_j-\hat{y}_j)^2\right\}/(n-2)}$ NS: not significant.

D/V_{ECW}. We postulated the convenient Eq. (1), in which C_t is proportional to the power function of D/V_{ECW}. Using a nonlinear least-squares method, parameters A and B were estimated to be 0.928 and 0.517, respectively.

$$C_t=A(D/V_{ECW})^B \quad (1)$$

(2) C_t for CBZ Plus Another Antiepileptic Drug The effects of concomitant antiepileptic drugs on the C_t of CBZ were investigated. Ninety-one patients were coadministered one of six antiepileptics drug with CBZ, *i.e.*, phenobarbital (PB), phenytoin (PHT), VPA, zonisamide (ZNS), clonazepam (CZP), and ethosuximide (ETS) were coadministered (Table 2).

We assumed that Eq. (1) could be adapted to express C_t in the coadministration of another antiepileptic drug with CBZ. Both members of Eq. (1) were converted into common logarithms,

$$y=a+bx \quad (2)$$

where $y=\log C_t$, $x=\log(D/V_{ECW})$, $a=\log A$, and $b=B$. The dose of concomitant antiepileptic drugs was not considered in this assumption. For simple regression analysis, y and x were assigned to be a criterion variable and an explanatory one, respectively. Then a and b were estimated.

Figure 2 shows the plots and regression lines of log C_t against $\log(D/V_{ECW})$ for CBZ alone and for the concomitant use of PB, PHT, VPA, and ZNS. The regression lines and the sample standard deviations from the regression lines (S_y) are shown in Table 2. The number of patients coadministered PRM, CZP, or ETS with CBZ was not sufficient to calculate the regression line.

A statistical method[15] was used to compare the regression line 0 for CBZ alone with line I (I=2, 3, 4, 5). The results are shown in Table 2. For the slope, no significant difference was detected between line 0 and other lines I. The slope of each line I was not different from that of line 0, and thus all the lines may be parallel. On the other hand, for the elevation, significant differences were detected for PB and PHT, but not for VPA and ZNS. These results indicate that C_t is affected at each definite ratio by PB and PHT, but not by VPA and ZNS.

(3) Model Representing the Effects of Concomitant Antiepileptic Drugs From the results mentioned above, we postulated Eq. (3) to analyze their ratios quantitatively.

$$C_t=A(D/V_{ECW})^B\cdot\prod_{i=1}^{7}R_i^{Z_i} \quad (3)$$

where R_i is a parameter representing the effect of each concomitant antiepileptic drug on C_t with CBZ alone, i.e., $A(D/V_{ECW})^B$. Hereafter, R_i is referred to as an alteration ratio. The subscript i represents the concomitant drug, and $i=1, 2, \cdots, 7$ corresponds to primidone (PRM), PB, PHT, VPA, ZNS, CZP, and ETS, respectively. z_i is 1 or 0 when drug i is coadministered or not. The doses of concomitant antiepileptic drugs were not considered in this model.

In Eq. (3), C_t is expressed under the assumption that the effects of concomitant antiepileptic drugs on C_t are independent from one another and multiplicative.

When both members of Eq. (3) are converted into

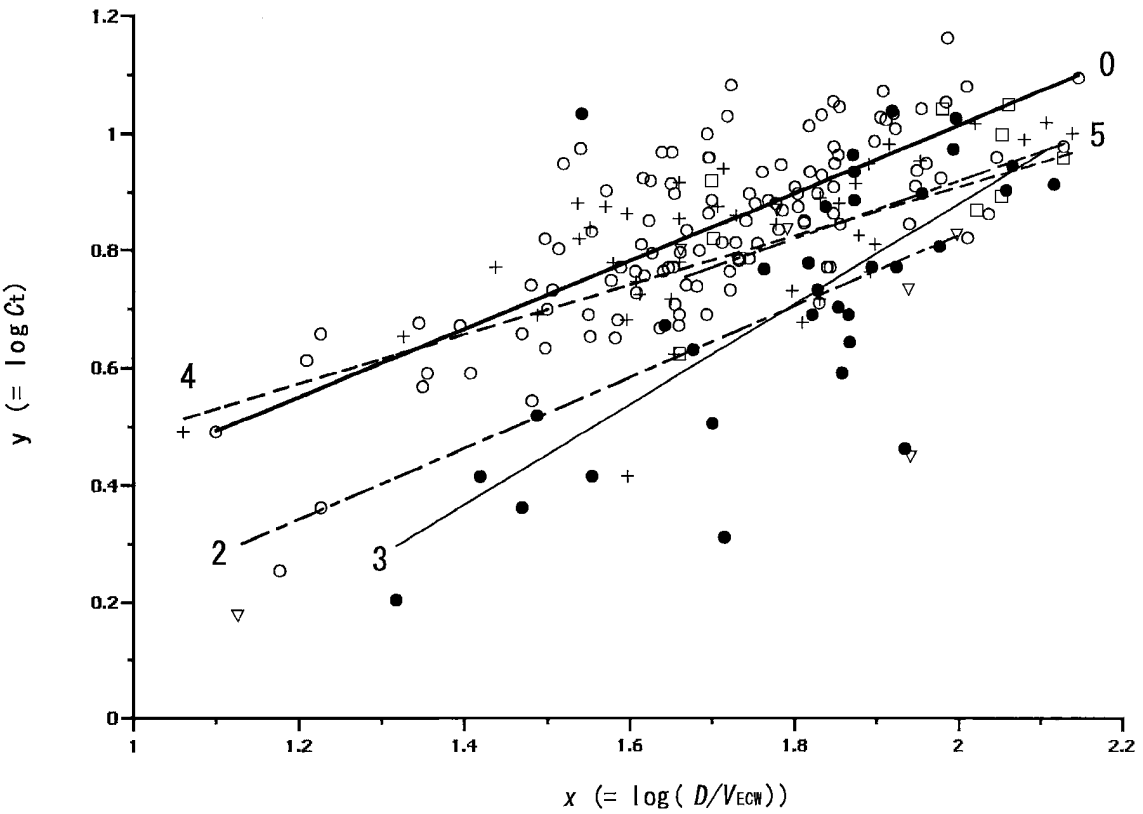

Fig. 2. Converted Plots and Regression Lines for CBZ Alone and CBZ Plus Another Antiepileptic Drug
CBZ alone (0), ○ ——; +PB (2), ▽ -·-·-; +PHT (3), ● ——; +VPA (4), + - - - -; +ZNS (5), □ -···-.

common logarithms,

$$y=a+bx+\sum_{i=1}^{7} r_i Z_i \qquad (4)$$

where $y=\log C_t$, $a=\log A$, $b=B$, $x=\log(D/V_{ECW})$, and $r_i=\log R_i$. For multiple regression analysis, y and x were assigned to be a criterion variable and an explanatory one, respectively. Then a, b, and r_i were estimated. The level of significance discriminating the addition and/or elimination of a variable using the F-test was taken as 0.05.

A total of 119 patients was administered CBZ alone, while 91, 39, 19, and 6 patients were coadministered one, two, three, and more than four different antiepileptic drugs (Table 1). A total of 274 cases was analyzed using Eq. (4) for multiple regression analysis. The results are shown in Table 3.

In the multiple regression analysis, the forward selection method was used to select the variables influencing C_t. PB and PHT were selected as the antiepileptic drugs influencing C_t (to be more precise, they influenced $y(=\log C_t)$). These drugs lower C_t to 0.770 and 0.710 the value for CBZ alone in concomitant use, respectively.

Multiple regression analysis with no variable selection method estimated r_5 for ZNS as -0.027, and the value is 0.941 for R. The standard deviation of r_5 was 0.023 and nearly equal to those of PB, PHT, and VPA. Thus ZNS can be said to have no effect on C_t. PRM, CZP, and ETS altered C_t to 0.932, 0.912, and 0.681, respectively, compared with the value for CBZ alone. However, multiple regression analysis using the variable selection method did not select them as drugs influencing C_t. Because the number of the patients administered these drugs was not sufficient and the data were scattered widely, their effects on C_t were not detected.

DISCUSSION

Major determinant factors of CBZ disposition are autoinduction and concomitant therapy.[16] In our patients, autoinduction could be neglected because of the sufficiently long administration periods.[17] Numerous reports have mentioned the effects of concomitant antiepileptic drugs on C_t, but no attention has been paid to the effects of confounding factors, such as age and sex. We conducted a study to clarify the effects of concomitant antiepileptic drugs on C_t, without being affected by confounding factors.

When C_t is not directly proportional to D/V_{ECW}, if the power function of D/V_{ECW} could be substituted for a regression curve, the curve could be converted into a straight line by taking logarithms of both members. Then the effects of concomitant antiepileptic drugs on C_t could be investigated by comparing the regression line on $\log C_t$ vs. $\log(D/V_{ECW})$ for CBZ alone with that for CBZ plus another concomitant drug. Eq. (1) proposed in this paper represents the $C_t-(D/V_{ECW})$ relation fairly well (Fig. 1). Each distribution of residuals from Eq. (1) and Eq. (2) for CBZ alone and for CBZ+PHT approximated a nor-

Table 3. Parameter Values Estimated by Multiple Regression Analysis

Parameter, r_i: drug coadministered	No. of cases $\sum_{j=1}^{274} Z_{ij}$	Estimated value ± SE	
		Variable selection method	No Variable selection method
r_1: PRM	9	—	-0.030 ± 0.045 (0.932)
r_2: PB	45	-0.113 ± 0.021 (0.770)	-0.109 ± 0.023 (0.779)
r_3: PHT	70	-0.149 ± 0.018 (0.710)	-0.150 ± 0.018 (0.708)
r_4: VPA	84	—	0.004 ± 0.017 (1.009)
r_5: ZNS	31	—	-0.027 ± 0.023 (0.941)
r_6: CZP	12	—	-0.040 ± 0.036 (0.912)
r_7: ETS	1	—	-0.167 ± 0.119 (0.681)
a: CBZ	274	-0.119 ± 0.060 (0.760)	-0.136 ± 0.062 (0.732)
b: CBZ		0.552 ± 0.035	$0.564+0.035$
Sample standard deviation from regression equation, S_y		0.119	0.119
Multiple correlation coefficient		0.773	0.778

Values in parentheses represent R_i ($R_i=10^{r_i}$) and A ($A=10^a$) calculated from estimated values r_i and a.

mal distribution. Eq. (1) detected the effects of concomitant antiepileptic drugs on C_t.

Parameters A and B in Eq. (1) are closely linked with the ratio of the bioavailability to the elimination rate constant, and the curvature of the fitting curve of CBZ binding to plasma protein,[10] respectively. The effects of concomitant antiepileptic drugs result in differences in the slope or elevation in Eq. (2), respectively. The slopes of all lines did not differ, but neither of the elevations for PB and PHT were equal to that of CBZ alone (Fig. 2, Table 2). The former result agreed with the reports that PHT, VPA,[18] and ZNS[19] did not affect the plasma protein binding of CBZ. The latter result indicated that A in Eq. (1) was altered by concomitant drugs. Thus C_t is affected at each definite ratio by these antiepileptic drugs. Because the bioavailability is considered to be almost constant, the change in the elimination rate would be reflected in each R_i value.

Eq. (3) was postulated for a detailed investigation of the interactions among antiepileptic drugs. The S_y value for CBZ alone in the simple regression analysis was 0.099 (Table 2), and S_y for all cases including one to more than four concomitant antiepileptic drugs was 0.119 (Table 3, using the variable selection method). Since there is little difference between both S_y values, Eq. (3) is considered useful. As this model can analyze all cases inclusively, the reliability of the estimated parameters is increased.

Multiple regression analysis revealed that PB and PHT lowered C_t to 0.770 and 0.710, respectively (Table 3). Our results agreed with the reports that PB and PHT lowered C_t with concomitant use.[2] The result that $R<1$ indicates that PB and PHT mainly increase the value of the elimination rate constant. These findings are due to the inducing actions of drug-metabolizing enzymes in these antiepileptic drugs.[9,20] On the contrary, VPA[21] and ZNS[22] were not reported to affect C_t, in agreement with our results. Although it was not clarified whether PRM affected C_t, PRM is anticipated to lower C_t due to the metabolization of PB.

When the concomitant use of PB or PHT is changed in a patient, the alteration in C_t can be estimated from Eq. (3) by using the values of R_2 and R_3 (Table 3).

When $C_{t(2,3)}$ represents C_t during concomitant therapy with PB, PHT, and CBZ and $C_{t(3)}$ represents C_t during therapy with PHT and CBZ, $C_{t(2,3)}$ and $C_{t(3)}$ can be written as

$$C_{t(2,3)} = AX_{(0)}^{B} \times R_2 \times R_3 \quad (5)$$

$$C_{t(3)} = AX_{(0)}^{B} \times R_3 \quad (6)$$

where $X_{(0)}$ is the daily CBZ dose (D) per extracellular water volume (V_{ECW}). From Eqs. (5) and (6):

$$\begin{aligned} C_{t(3)} &= C_{t(2,3)} \times 1/R_2 \\ &= C_{t(2,3)} \times 1/0.770 \\ &= C_{t(2,3)} \times 1.30 \end{aligned}$$

Thus C_t is expected to increase to 1.30 upon discontinuation of PB.

To maintain C_t, the daily CBZ dose can be estimated by setting $C_{t(2,3)} = C_{t(3)}$. Then

$$AX_{(0)}^{B} \times R_2 \times R_3 = AX_{(3)}^{B} \times R_3$$

where $X_{(3)}$ is $D_{(3)}/V_{ECW}$ and $D(3)$ is the daily CBZ dose after discontinuation of PB. Substituting $D_{(0)}/V_{ECW}$ and $D_{(3)}/V_{ECW}$ in $X_{(0)}$ and $X_{(3)}$, respectively, and rearranging:

$$\begin{aligned} D_{(3)} &= R_2^{(1/B)} \times D_{(0)} \\ &= 0.770^{(1/0.517)} \times D_{(0)} \\ &= 0.603 \times D_{(0)} \end{aligned}$$

As $D_{(0)}$ is the daily CBZ dose before discontinuation of PB, the daily CBZ dose after discontinuation should be decreased to 0.603 to maintain the same level of C_t.

To evaluate the value of each R_i obtained in this study, the measured and estimated values of C_t were compared between the cases where the prescribed drugs were changed in the same patient. For PB and PHT, the value of each R_i was obtained by multiple regression analysis using the variable selection method (Table 3). For PRM, VPA, ZNS, CZP, and ETS, the value of each R_i was postulated to be 1. Figure 3 shows the plots of estimated C_t versus measured C_t values. Both values appear to be in good agreement. The mean absolute error (MAE) was calculated to be 18.7% using the following equation.

$$\begin{aligned} \mathrm{MAE}(\%) = \Sigma\{(&|\text{measured value-estimated value}| \\ &/\text{measured value})/n\} \times 100 \end{aligned}$$

(n: number of sets compared)

Each regression line for the relationship between D/W and C_t for CBZ alone, CBZ+PHT, and CBZ+PB was reported.[9] The MAE calculated in the same manner was 23.1%. This value shows that better results were obtained in the present study.

Although our study was a retrospective one and our clinical data were scattered widely, we feel confident of the results. Each alteration ratio of R_i in our study population could be adapted to the patients without being grouped by other confounding factors. This

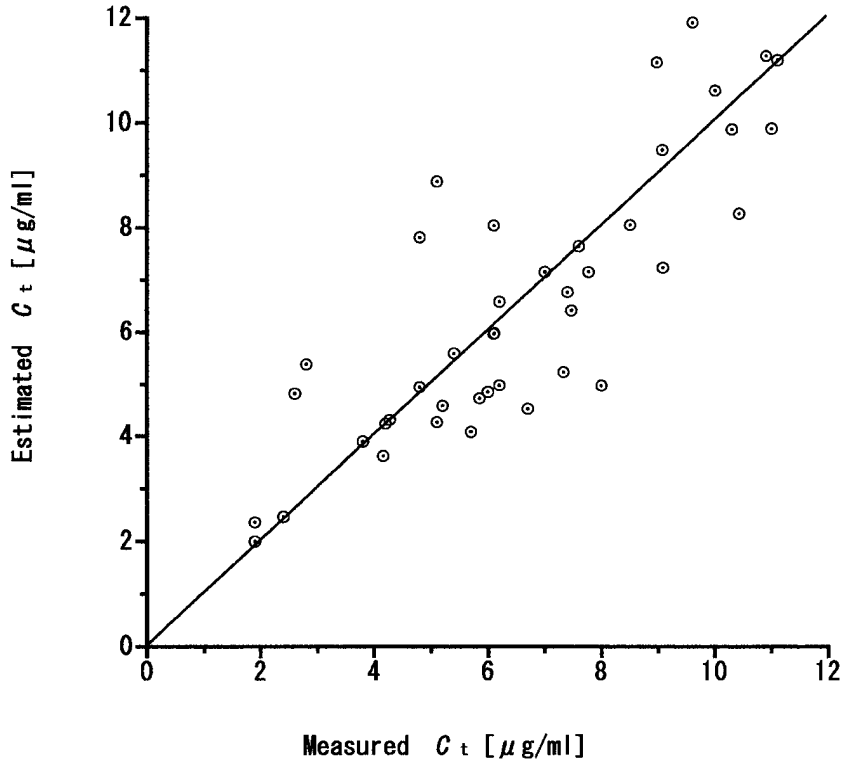

Fig. 3. Relation between the Measured and Estimated Values of C_t When the Prescribed Drugs Are Changed in the Same Patient

makes it easy to estimate C_t correctly with the addition or discontinuation of concomitant antiepileptic drugs during CBZ treatment of epileptic patients.

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