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DISTRIBUTION OF PLASMA DIPHENYLHYDANTOIN, PHENOBARBITAL AND PRIMIDONE CONCENTRATIONS IN EPILEPTIC CHILDREN WITH MENTAL RETARDATION

Shosuke WATANABE, Chie KUYAMA, Shigeo YOKOYAMA, Shinsuke KUBO and Hiroyuki IWAI

Department of Psychiatry, Kawasaki Medical School, Kurashiki, 701-01, Japan

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INTRODUCTION

As reported in our previous paper, the plasma levels of various antiepileptics were measured in adult epileptic patients, with relatively lower blood effective levels being noted in our patients rather than those reported for occidental patients in general, especially on the plasma diphenylhydantoin levels (DPH).[19,20,21]

We also reported that the daily dose, with respect to one drug, may be lower in comparison with those described in occidental literatures because a combined therapy with various antiepileptics is frequently employed in the drug treatment for epileptics in our country, and that the lower plasma DPH levels noted when the drug was combined with any of barbiturates may be presumed due to the interaction of the drugs.

The significance and/or importance of determining the plasma levels of antiepileptics, particularly in the case of epileptic children in whom the rate of drug metabolism is generally high and the individual difference may be greatly observed, has been suggested.[18] In this study, the plasma levels of DPH, phenobarbital (PB) and primidone were determined in epileptic children accompanied with mental retardation, and then the estimation of effective plasma concentrations, correlation between the dose and the plasma levels, distributions of plasma levels of these three drugs as well as factors influencing the plasma levels were studied. Concerning the clinical effects and the plasma concentrations of antiepileptics in children, Borofsky *et al.*,[1,2] Svensmark *et al.*,[18] Melchior *et al.*,[13] Dowson *et al.*,[5] Houghton *et al.*,[9] and Scherwin *et al.*,[17] reported about DPH, while the result on PB was reported by Faerφ,[6]

渡辺昌祐，久山千衣，横山茂生，久保信介，岩井隅之

Svensmark or Miyamoto *et al.*[15] and Miura *et al.*[14] in out country. Comparatively few results of the study are presented specially in our country, probably due to the difficulties in the method of determination. Enzyme immunoassay recently developed by Syva was confirmed to be simple to manipulate and highly accurate. Therefore, we began to use this method for the determination of the plasma levels of these three antiepileptics since July, 1976, with the result reported hereinafter.

SUBJECTS AND METHODS

Thirty-nine epileptic children accompanied with mental retardation, hospitalized in Asahikawa Jido-In without any change in prescription at least for the last one month were selected for our study. The age of patients, composed of 18 males and 21 females, ranged from 4 to 14 years old (average: 10.3=3.1). The average body weight was 23.5±8.0 kg (13.5 kg−45.0 kg).

According to the clinical episodes, epileptic patients were classified as follows: grand mal 14; hemispasm 3; salaam convulsion 4; Lennox-Gastaut syndrome 10; latent epilepsy 8.

The patients were simultaneously subdivided into 3 groups in accordance with the conditions of seizure control: the controlled group[22] in which no epileptic seizure during the last 6 months; the uncontrolled group[11] having one or more seizures during the last one month; partially controlled group[4] where one or more seizures were noted during the last six months. The numbers in the brackets indicate the number of patients included in each corresponding group. The patients in the controlled group were composed of grand mal 10, hemispasm 2, salaam convulsion 3 and latent epilepsy 8; namely, 23 cases in total, by the clinical diagnosis. While 4 cases of grand mal, one of hemispasm, 10 of Lennox-Gastaut syndrome and one of salaam convulsion were included in partially controlled+uncontrolled groups.

All patients had received as a rule 2 or more antiepileptics (average: 4 drugs, max 7 drugs).

None had concomitant hepatic and/or renal dysfunction. Blood samples for the determination of antiepileptics were taken immediately before the drug administration in the morning via cubitus vein. The plasma was removed as soon as possible and kept at 4°C to be used.

The plasma concentrations of DPH, PB, and primidone were determined by using enzymeimmunoassay (EMIT) previously mentioned.[19-21]

RESULTS

1. The dose of DPH, PB and primidone and average plasma concentrations (Table 1)

TABLE 1.

Dose and plasma concentration of diphenylhydantoin, phenobarbital and primidone

	diphenylhydantoin		phenobarbital		primidone	
	dose mg/kg/day (mg/day)	plasma concentration μg/ml	dose mg/kg/day (mg/day)	plasma concentration μg/ml	dose mg/kg/day (mg/day)	plasma concentration μg/ml
total	3.28±0.23 (74.2±5.3) N=37	1.22±0.45 N=37	2.43±0.14 (53.2±2.8) N=37	25.2±2.8 N=39	23.9±1.9 (560±69) N=15	6.49±1.24 N=15
controlled	2.68±0.27 (63.2±5.2) N=22	0.43±0.18	2.12±0.13 (48.6±3.6) N=22	16.9±2.8 N=23	21.6±3.3 (600±141) N=2	6.18±2.70 N=2
partially controlled+ uncontrolled	4.03±0.36 (90.3±9.1) N=15	2.38±1.00 N=15	2.89±0.22 (60.0±4.4) N=15	37.0±4.1 N=16	24.2±2.1 (554±77) N=13	6.54±1.37 N=13
statistic difference	$p<0.01$	$p<0.1$	$p<0.01$	$p<0.001$	N. S.	N. S.

mean ± S. E. M.

The average dose of DPH, administered to all patients, was 3.28 ± 0.23 mg/kg/day (74.2 ± 5.3 mg/day: max. 7.83 mg/kg/day, min. 0.78 mg/kg/day) and the plasma concentration was 1.22±0.45 μg/ml (max.: 1.53 μg/ml, min.: 0).

The dose of DPH and the plasma concentrations were compared between the controlled group (N=22) and partially controlled + uncontrolled group (N=15). In the controlled group, the dose of DPH and plasma concentration were 2.68±0.27 mg/kg/day and 0.43±0.18 μg/ml, respectively. While in the partially controlled+uncontrolled groups, a relatively higher dose as 4.03 ± 0.36 mg/kg/day was administered as compared with controlled group ($p < 0.01$). The plasma level of 2.38 ± 1.00 μg/ml was slightly greater than that of controlled groups, but no significant difference was detected between the two values ($p < 0.1$).

The dose of PB was 2.43±0.14 mg/kg/day or 53.2±2.8 mg/day, which was within the range commonly used for epileptic children in

our country. In contrast a significantly higher does of PB was administered to the patients in the partially controlled + uncontrolled groups ($p < 0.01$). Moreover, the plasma PB level was 25.2±2.8 μg/ml, with respect to all patients examined, on almost the same level as that obtained from adult epileptic patients (24.75±1.49 μg/ml).[20] It was 37.0±4.2 μg/ml in partially controlled+uncontrolled groups, which was significantly higher than the plasma PB level in controlled group.

As far as the dose of primidone is concerned, it was 23.9±1.9 mg/kg/day or 560±69 mg/day, in all the patients. The values were within

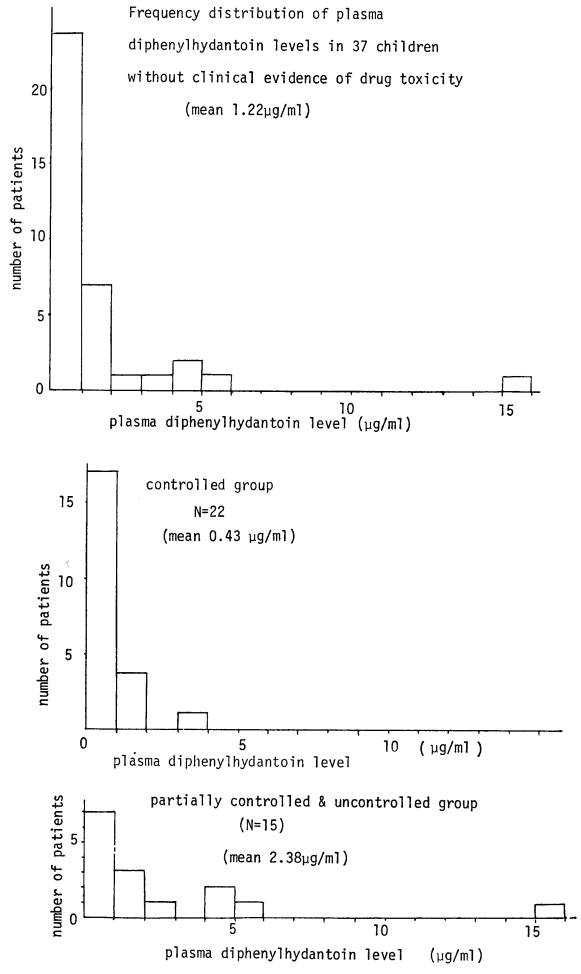
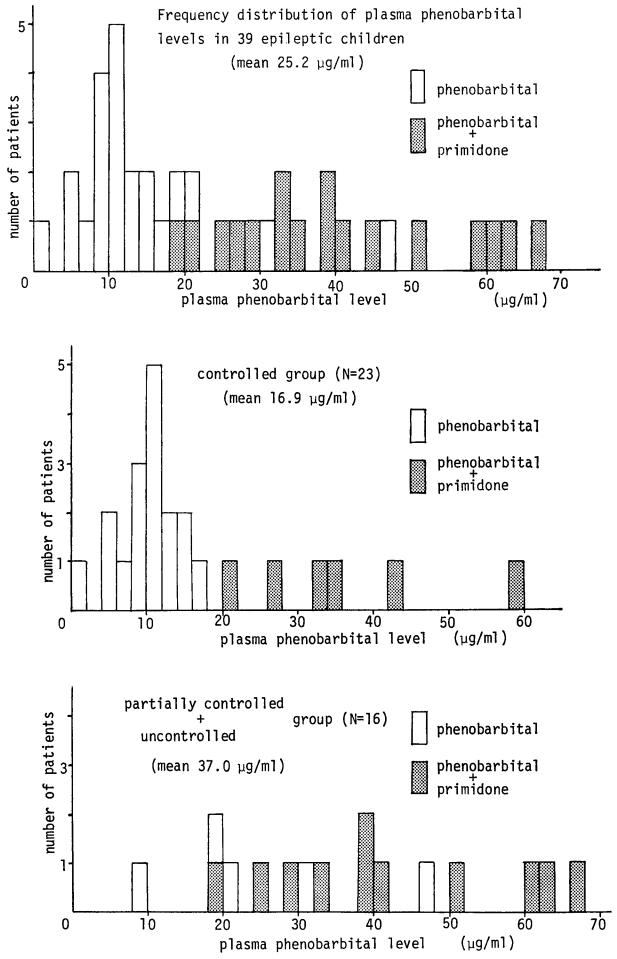


Fig. 1.

the range of dose commonly used for epileptic children in our country. No significant difference was noted in both of the dose of primidone and the plasma concentrations between the two groups, i. e., controlled and partially controlled + uncontrolled groups.

2. Frequency distribution of plasma DPH, PB and primidone levels. (Fig. 1, 2, 3)

The distribution of plasma DPH levels in all patients is shown in Fig. 1.



Fig, 2.

Twenty-four out of all children (64.9%) exhibited the levels of less than 1 μg/ml, and in 23 of them (62.2%), these levels were not detectable. Patients having the plasma levels of less than 2 μg/ml amounted to 31 in all these cases (83.3%) except for one case (15.3 μg/ml), the plasma DPH levels were less than 6 μg/ml.

The distribution of plasma concentrations in controlled or partially controlled+uncontrolled groups were separately described by middle or low figures in Fig. 1. In controlled group, the determinations could not be made in 17 out of 22 cases (85%). Moreover, 21 patients (95.5%) showed the plasma levels of less than 2 μg/ml, while the maximum value was 3 μg/ml. In contrast, less than 1 μg/ml of the plasma level were encountered in 7 cases (46.7%), and there were 4 patients with more than 4 μg/ml (26.7%) in partially controlled+uncontrolled groups. The maximum value in partially controlled+uncontrolled group was 15.3 μg/ml.

The plasma PB concentrations distributed from 1.36 to 66.0 μg/ml, with the most frequent value of 10-12 μg/ml being noted (Fig. 2). The range of this distribution was almost the same as that for adult epileptic patients in our country. The frequency distribution in patients receiving PB and primidone combined therapy is shown by the shaded portion in the middle figures in Fig. 2. To 81% out of the patients whose plasma PB levels were more than 18 μg/ml (N=21), primidone was concomitantly given. In addition an extremely high concentration of 47 μg/ml was noted in one case in the single PB group.

The distribution of plasma PB levels in controlled group or partially controlled+uncontrolled group is separately described by the middle figure in Fig. 2. In controlled group, the plasma PB levels distributed from 1.3 to 58.0 μg/ml, with the most frequent values being noted at 10-12 μg/ml. While, the patients receiving a combined therapy with barbital preps, except for PB, are shown by the shaded portion in the figure. All cases having the PB levels of more than 20 μg/ml were given two or more barbital preps., while all the cases having the PB levels of less than 20 μg/ml received a single PB administration.

In partially controlled+uncontrolled groups, the values were found to be scattered from 8.9 μg/ml at the lowest to 66.0 μg/ml at the highest. Eleven patients (69%) were combined with barbital preps, but for PB, and the maximum PB level in patients without combination therapy was 47 μg/ml.

The frequency distribution of plasma primidone levels in 15 epileptic

children is shown in Fig. 3. The values distributed from 2.0 at the lowest to 17.2 μg/ml, with the most frequent value being 2-3 μg/ml. As exception in two controlled patients, one exhibited the plasma primidone level of 2.35 μg/ml and the other showed 10.0 μg/ml. The maximum and minimum plasma primidone levels in partially controlled+uncontrolled groups were 2.0 μg/ml and 17.2 μg/ml, respectively.

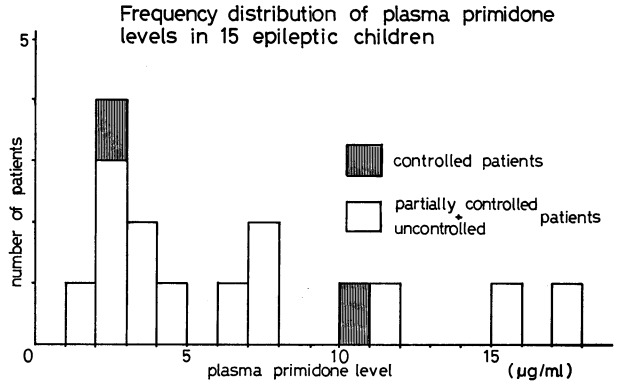


Fig. 3.

3. Correlation between the dose mg/kg/day of DPH, PB, and Primidone and the plasma levels (Figs. 4, 5, 6)

Correlation between the dose of DPH and the plasma levels is described in Fig. 4. The linear regression, $y=1.421x-3.442$, was obtained from the plotted values, with a direct correlation being noted between the dose (x) and the plasma levels (y) ($\gamma=0.744$, $p<0.001$). In Fig. 4, the linear regression derived from the plasma DPH dose and the dose for adult epileptic patients was simultaneously described. The plasma levels against the dose per kg of body weight were comparatively lower in the subjects for this study rather than in adult patients.

The correlation between the dose of PB (x) and the plasma levels (y) in 22 cases, where not any other barbital preps, except for PB were combined, was examined (Fig. 5). A direct correlation was noted between the two functions from the linear regression of $y=10.45x-8.90$ ($\gamma=0.665$, $p<0.001$). In the same figure, the linear regression in adult epileptic patients was also arranged. When the dose per kg of body weight was identical, with reference to epileptic children, the plasma PB levels exhibited a lower tendency in comparison with those of adult patients.

When the correlation between the dose (x) of primidone and the

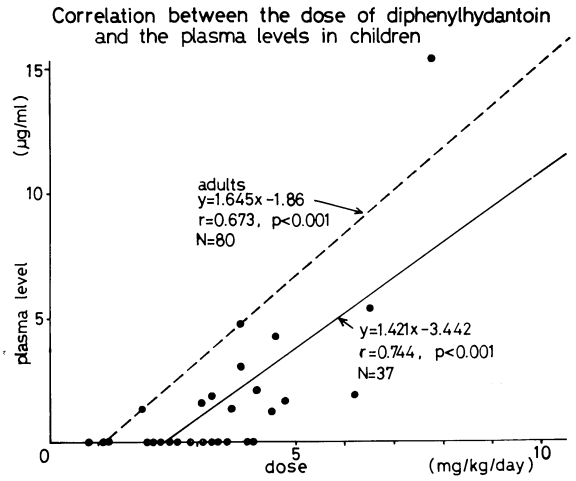

Correlation between the dose of diphenylhydantoin
and the plasma levels in children
plasma level (μg/ml)
15
10
5
0
adults
y=1.645x-1.86
r=0.673, p<0.001
N=80
y=1.421x-3.442
r=0.744, p<0.001
N=37
5
10
dose (mg/kg/day)

Fig. 4.

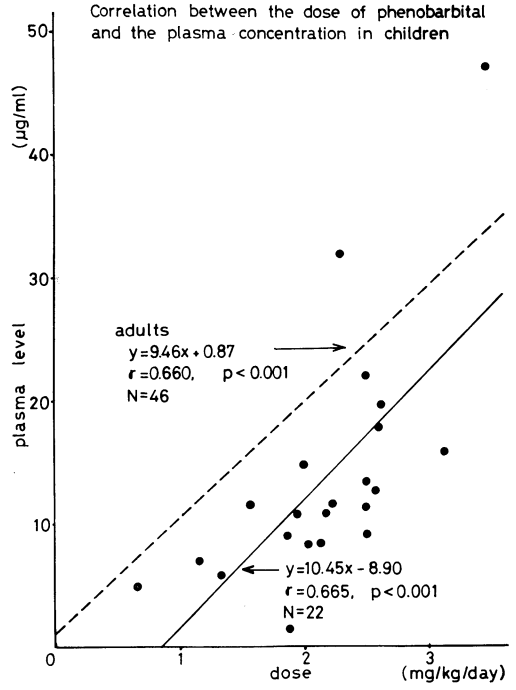

Correlation between the dose of phenobarbital
and the plasma concentration in children
plasma level (μg/ml)
50
40
30
20
10
0
adults
y=9.46x+0.87
r=0.660, p<0.001
N=46
y=10.45x-8.90
r=0.665, p<0.001
N=22
1
2
3
dose (mg/kg/day)

Fig. 5.

plasma levels (y) was examined (Fig. 6), a direct correlation was detected between the two functions ($y=0.384x-2.677$, $\gamma=0.586$, $p<0.05$). Besides, the linear regression derived from the dose of primidone and the plasma levels was also described in Fig. 6.

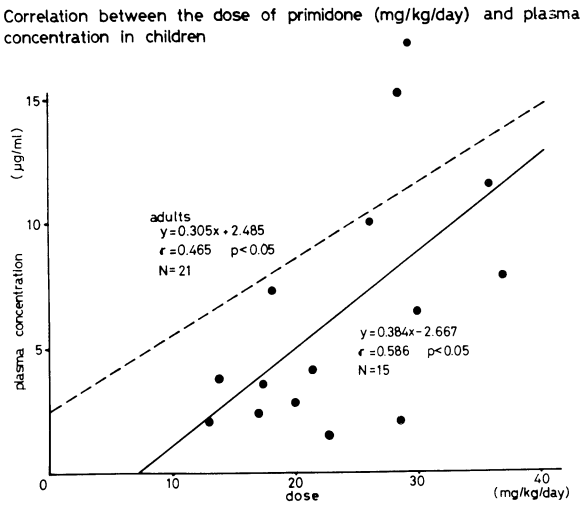
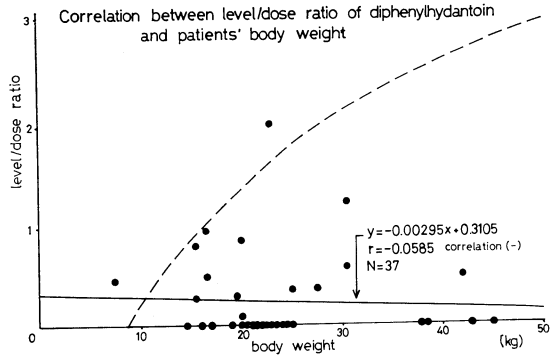


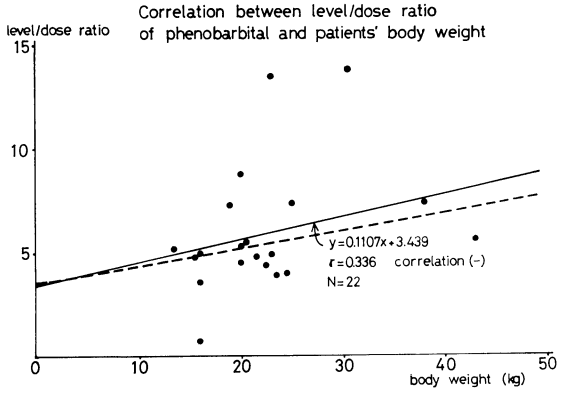
Fig. 6.

The lower trend was noted in epileptic children in comparison with adult patients, when the dose (mg/kg/day) of primidone was identical.

4. Correlation between level μg/ml/dose mg/kg weight ratio of DPH, PB, primidone and patient's body weight (Fig. 7)

The correlation between level/dose ratio of DPH (y) and patient's body weight is shown in Fig. 7. The linear regression, $y=-0.002957x+0.3105$, revealed no evidence of correlation between the two functions ($\gamma=0.0585$). In Fig. 7, an analogous regression curve proposed by Svensmark *et al.*[18] was also plotted. As for PB, no direct correlation was noted from the two regression ($y=0.1107x+3.429$, $\gamma=0.360$), but the lighter the body weight was, the lower the level/dose ratio became. Although an analogous regression curve in epileptic children proposed by Svensmark *et al.*[18] as shown by the interrupted line, it is well coincidental with ours. No correlation was also detected between the two functions, with respect to primidone. ($y=0.558x+0.1327$, $\gamma=0.246$). The level/dose ratio ranged between 0.1−0.5 when the body weight ranged between 10−40 kg.





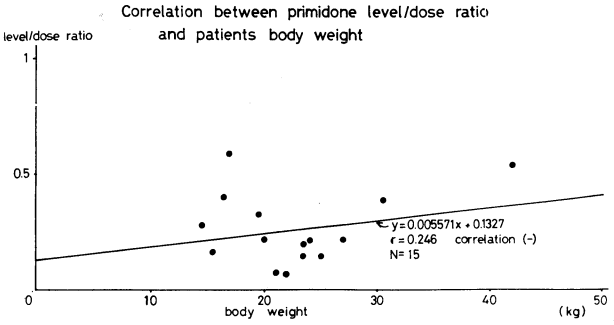


Fig. 7.

5. Plasma concentration ratio of PB and primidone in epileptic children receiving primidone not PB (Table 2)

TABLE 2.

Plasma concentration ratio of phenobarbital and primidone in epileptic children taken with primidone, not taken with phenobarbital

case number	dose mg/kg/day	plasma concentration μg/ml		phenobarbital (mole)
	primidone	primidone	phenobarbital	primidone (mole)
1. (10 y.o.)	21.3	4.1	26.5	6.0
2. (14 y.o.)	28.6	15.2	18.6	1.1

The ratio of the plasma primidone and PB levels were examined in 2 epileptic children receiving primidone, not any other barbital preps, selected from our subjects. Case No. 1 was a 10-year-old girl and the dose of primidone was 21.3 mg/kg/day. The plasma primidone level, PB level and the molar ratio (PB/primidone) in this case were 4.1 μg/ml, 26.5 μg/ml and 6.02, respectively, while these corresponding values were 15.2 μg/ml, 18.6 μg/ml and 1.14 in Case No. 2 of 14-year-old boy receiving the dose of 28.6 mg/kg/day.

DISCUSSION

The dose of DPH in our patients remained within the range of conventional dose in our country[7,10] and foreign countries, but 65% patients exhibited less than 1 μg/ml of the plasma DPH levels, and patients having less than 2 μg/ml occupied 84% of all the cases. Thus, marked low values were obtained in our patients in comparison with the therapeutic effective levels of DPH of 10-20 μg/ml in occidental epileptic children.[18]

From the standpoint of the condition of seizure control, the dose of DPH as well as the plasma level were relatively higher in uncontrolled group. Patients included in partially controlled+uncontrolled groups were diagnostically composed of 4 cases of grand mal, 1 of hemispasm, 1 of salaam convulsion and 9 of Lennox-Gastaut syndrome. In spite of the higher plasma DPH levels in this group as compared with those in controlled group, epileptic seizures were not well controlled, so that the disease itself may be considered to be intractable. The dose may be required to be further increased, considering the therapeutic levels of 10-20 μg/ml employed in occidental countries. Although several reasons why the plasma DPH levels were extremely low are discussed the combination use with other kind of antiepileptics is mainly proposed. All the

epileptic children subjected to this study usually had one or more other antiepileptics such as phenobarbital (PB), with 6 drugs at the maximum being combined. Many investigators[8,11,12,16] already demonstrated that the combination with barbital preps. promotes the metabolism of DPH. As shown in Fig. 4 of our patients, it is notable that the plasma DPH level was undetectable in all cases when the dose of DPH was less than 2.5 mg/kg/day. When such a low dose of DPH is combined with PB, for example, it is demonstrated that almost all drugs will be excreted and the plasma DPH will disappear after 16 hours of the completion of the drug administration three times a day. The further systematic investigation on DPH prescription for epileptic children seems to be necessary.

Although a direct correlation was noted between the dose of DPH and the plasma level in our patients as shown in Fig. 4, the plasma level/dose ratio vary with the growth in children, and Svensmark *et al.*[18] suggested this ratio will be lower in proportion to the younger age. For this reason, the metabolism of drugs will be more rapid in children rather than in adult. No direct correlation was detected between the plasma level/dose ratio and patient's body weight, as shown in Fig. 7. Simultaneously, the correlation between the two functions proposed by Svensmark *et al.*[18] was arranged in the middle figure of Fig. 3, thus a marked low plasma level/dose ratio was clearly observed in our patients.

Subjects participated in the study by Svensmark *et al.*[18] were composed of epileptic children in the age range of 1-14 years receiving a single DPH or combined with PB, but the blood sampling was performed on 2-3 hours after the last administration. Namely, it differs from our study in that the number of combined drugs was relatively small, and that the duration between the last administration and blood sampling was short, so that these different points may be understood to contribute to the higher plasma level/dose ratio. The PB dose was 2.43 ± 0.14 mg/kg/day or 53.2 ± 2.8 mg/day (Table 1), which is within the range of dose suggested by Ichihashi[10] and Hamamoto[7] *et al.* with respect to the dose for epileptic patients of 4-14 years old. The plasma PB level of 25.2 ± 28 μg/ml was similar to that for adult epileptic patients in our country.[19] In our study 43.6% of the subjects were given PB combined with primidone, so that the plasma PB level obviously included PB derived from primidone. In controlled group, the dose of PB was relatively low, and the plasma level decreased significantly. While in uncontrolled group, it is clearly observed that the clinical attacks were

not yet controlled in spite of the higher PB dose as well as the plasma level. Besides, the number of antiepileptic given to partially controlled +uncontrolled groups was 4.75±1.45 drugs, while this figure was 2.94 ±1.30 drugs in controlled group. In view of this, the fact that the seizures were not sufficiently controlled in spite of a relatively large number of drugs combined may reflect the disease itself to be intractable.

Miura *et al.*[14] and Faerϕ[5] suggested the therapeutic effective plasma PB level to be 16 μg/ml or more for febrile convulsions in children. Moreover, Buchanan *et al.* (1971) indicated the value to be 0-47.0 μg/ml, 10 μg/ml on average. It was impossible to determine the therapeutic effective level of PB due to a variety of pathogenesis existing in our patients.

As far as the correlation between the dose of PB and the plasma levels is concerned, the higher dose per kg of body weight seems to be required for epileptic children in comparison with the dose for adult patients.[1,2,3] In our patients (N=22), as shown in Fig. 6, the plasma level was distinctly lower in children than in adult, with respect to the same dose per kg of body weight. This result was well coincidental with the suggestion by Miura *et al.*[14] Besides, the plasma level/dose ratio in our subjects was well in agreement with those for occidentals (Fig. 7). Svensmark *et al.*[18] suggested the plasma level/dose ratio will be lower as the patient's body weight becomes less, but such a relationship was not noted in our patients (Fig. 7). The dose of primidone was 23.9±1.9 mg/kg/day or 560±69 mg/day (Table 1), which is within the range of therapeutic dose for epileptic children in our country. No intra-group difference (controlled and partially controlled+uncontrolled) was noted in the dose of primidone and the plasma levels (Table 1). Furthermore, in the frequency distribution of plasma primidone level, the most frequent value was 2-3 μg/ml, ranging from 2.0 μg/ml at the lowest to 17.2 μg/ml at the highest, so that the therapeutic concentration of primidone cannot be proposed in this study. Primidone may produce phenylethylmalonamide or PB as an intermediary metabolite, and the effectiveness of the drug will be attained by the maternal substance as well as its matabolites, so that the plasma effective concentration of primidone should be discussed when the plasma levels of such active metabolites are demonstrated.

Although a direct correlation was noted between the dose of primidone and the plasma levels, as shown in Fig. 6, the plasma level/dose per kg of body weight ratio in our patients exhibited a lower trend as compared with those for adult epileptic patients (Fig. 6), being similar

to the results with PB. In any event, the rate of drug metabolism in children will be more rapid than that in adults, and the plasma concentration will be variable by the metabolism even when the same prescription is continued for a certain duration. With the help of drug interaction, therefore, it is considered of a great importance that a clinical seizure should be controlled while referring to the plasma level of antiepileptics.

SUMMARY

The plasma diphenylhydantoin, phenobarbital and primidone levels were determined by using enzyme immunoassay in 35 epileptic children with mental retardation. All patients were administered with combination of 2-7 kinds of antiepileptics.

1) The dose of DPH and the plasma level were 3.28 ± 0.23 mg/kg/day and 1.22 ± 0.45 μg/ml, respectively, in all the children examined. These values were markedly low compared with the therapeutic effective concentration reported in other countries.

2) In partially controlled+uncontrolled groups when compared with controlled group, a relatively higher dose of DPH was given ($p < 0.01$) and the plasma DPH levels tended to be fairly high ($p < 0.1$).

3) The distribution of plasma DPH concentration ranged between 0 μg/ml at the lowest and 15.3 μg/ml at the highest. 23 subjects (62.2%) exhibited the plasma DPH level of 0, 24 (64.9%) exhibited 1 μg/ml or less and 31 (83.3%) showed less than 2 μg/ml of the plasma DPH concentration.

4) The plasma DPH concentration was 0 μg/ml in all cases when the daily dose of DPH was less than 50 mg or 2.5 mg/kg.

5) The dose of PB and the plasma level were 2.43 ± 0.14 mg/kg/day and 25.2 ± 2.8 μg/ml, respectively, while the corresponding values for primidone were 23.9 ± 1.9 mg/kg/day and 6.49 ± 1.24 μg/ml.

6) The distribution of plasma PB concentration ranged from 1.36 to 66.0 μg/ml, with the most frequent value at 10-12 μg/ml. The corresponding values, of primidone, were 2.0-17.2 μg/ml and 2-3 μg/ml.

7) In controlled group as compared with partially controlled$\pm$uncontrolled groups, the dose of PB was relatively low ($p < 0.01$) and the plasma level was also reduced ($p < 0.001$), so that the therapeutic effective concentration of PB was impossible to be decided. As to primidone, no significant difference in the dose and the plasma level was noted between the two groups.

8) The plasma PB level/dose ratio in our patients was well coincidental with that described in occidental literatures, which was lower than that for adult patients.

9) No evidence of correlation was noted between the plasma level/dose ratio and the patient's body weight.

10) A direct correlation was observed between the plasma primidone levels and the dose, and the plasma level/dose ratio tended to be lower than that for adult patients.

11) No correlation was detected between the plasma primidone level/dose ratio and the patient's body weight.

12) The plasma concentration ratio of phenobarbital and primidone in epileptic children taking primidone, but not taking phenobarbital, was 6.0 in Cases No. 1 and 1.1 in Case No. 2.

13) It is considered to be of great importance especially in children that the clinical attack should be controlled while with referring carefully to the plasma concentration of antiepileptics.

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