The Efficacy of Once-Daily Dose of Phenobarbital in Children with Generalized Tonic-Clonic Epilepsy

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ABSTRACT In spite of its long half life, phenobarbital is still given twice-daily in the treatment of generalized tonic-clonic epilepsy. This study aims to determine if daily dose of phenobarbital given once differs to that given twice daily. Subjects of this unblinded controlled clinical trial were generalized tonic-clonic epilepsy patients ranging in age from 1-15 years. There were 40 study cases and 42 controls. We gave phenobarbital 4-6 mg/kg/day once-daily for study group and twice-daily dose for control group. History, physical and EEG examination and phenobarbital plasma measurements were obtained at the beginning of the study and four weeks later. The ratio of the second to first phenobarbital plasma concentrations in the study group was 0.99 while in the control group it was 1.02. The proportion of seizure-free patients in the study group increased from 70% at the beginning to 85% at the end of study, and in the control group from 64.3% to 83.3%. Hyperactivity and irritability increased in both groups, and there were no significant differences in mean serum levels, seizures control, hyperactivity and irritability in both groups. Drowsiness was found in 50% of cases, but statistically significant decrease were found in study group. The compliance of the study group (92.5%) was significantly better than that of the control group (71.4%). **[Paediatr Indones 1995;35:172-179]**

Introduction

Epilepsy is a chronic condition characterized by repetitive seizures, without fever and with specific dysrhythmic electroencephalogram. The seizures consist of two episodes or more with the minimum interval of 24 hours.[1] The incidence rate of epilepsy is 50/100.000.[2]

In the treatment of the epilepsy, phenobarbital is effective, with minimal side effects, easily available, and inexpensive.[3,4] Unfortunately, the long-term treatment (at least three years seizure-free period) and twice-daily dose results in the decrease of patient's compliance. On the

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other hand, most studies indicate that the half-life of phenobarbital in pediatric patients is in the range of 37 to 133 hours.[5,6,12] Because of this long half-life, it seems reasonable to recommend once-daily dosing for children.[7,8] This unblinded controlled clinical trial was designed to test the validity of hypothesis that the daily dose of phenobarbital given once daily was as effective as if it was given twice-daily in treating generalized tonic-clonic seizures.

Methods

This unblinded controlled clinical trial was done at The Pediatric Neurology Clinic of Child Health Department, Cipto Mangunkusumo Hospital, Jakarta from March 1, 1989 till April 30, 1989. The study population was generalized tonic-clonic epilepsy patients ranging in age from 1 to 15 years. To be eligible to the study subjects had to have been treated with phenobarbital only, had never experienced adverse reaction to phenobarbital, had plasma phenobarbital level of 15-40 µg/ml, and had no other type of epilepsy. Subjects who received other antiepileptic drugs during the study and those who failed to undergo the second plasma level of phenobarbital were excluded.

The participants were randomly assigned into study group and control group by block randomization. Study patients were treated with 4-6 mg/kg/day of phenobarbital once-daily while controls received twice-daily of the same daily dose. History, physical examination, EEG examination and phenobarbital plasma concentration measurements in each patient were taken at the beginning of the study and four weeks later. In this study we classified epilepsy according to Commission on Classification and Terminology of the International League Against Epilepsy.[9]

Seizure control was based on Wada criteria,[10] i.e., complete control (no seizures), real effect (more than 90% seizures suppression), moderate effect (50-89% seizures suppression), minimal effect (10-49% seizures suppression) and no significant effect (seizure suppression less than 10%). Data was processed and appropriate statistical analysis was carried out.

Results

Group comparability

Eighty-two subjects satisfied the eligibility criteria, 45 (54.8%) of them were female. Table 1 shows the distribution of patients according to sex and treatment group; there was no significant gender difference between the groups.

Table 1. Distribution of patients according to sex and groups

Sex	Group		Total
	Study	Control	
Male	21 52.5%)	16 (38%)	37 (45.2%)
Female	19 47.5%)	26 (62%)	45 (54.8%)
Total	40 (100%)	42 (100%)	82 (100%)

$x^2 = 1.1844$ $p > 0.05$

Table 2 shows that 61 out of 82 cases

(74.4%) aged 1-9 years, and 21 cases (25.6%) aged 10-14 years. It shows that there was no significant age difference between the two groups.

Table 2. Distribution of patients according to age group

Age group	Groups		Total
	Study	Control	
1 - 4 years	14	16	30 (36.6%)
5 - 9 years	16	15	31 (37.8%)
10-14 years	10	11	21 (25.6%)
Total	40	42	82 (100.0%)

$z = 0.3111$ $p > 0.05$

Plasma phenobarbital concentration

Figure 1 showed that the mean of plasma phenobarbital concentration in the study group at the first examination was 22.57 (SD 5.74) μg/ml and the mean of the second examination was 22.52 (SD 7.27) μg/ml. The same parameter for control group were 22.95 μg/ml for the first examination and 23.53 μg/ml for the second. There were no significant differences between the means of the first and the second plasma phenobarbital concentrations of both intra- and between study groups.

Seizures and their changes

As shown in Table 3, 52 (63.4%) out of 82 cases were still free of seizures during the study, and the decrease of seizures were found in 22 cases (26.8%). The changes were not significantly different between the 2 groups.

Side effects

Drowsiness was one of the most common found side effects encountered in the treatment with phenobarbital. Table 4 shows the distribution of drowsiness in both groups before and after phenobarbital treatment in relation with plasma phenobarbital levels. It can be seen that 9 out of 11 cases with increased drowsiness had the plasma phenobarbital concentration in the therapeutic range. Twenty four cases (29.3%) had decreased drowsiness and 19 out of 24 cases (79.2%) reached no-drowsiness side effect.

Table 5 shows us that 47 (57.3%) out of 82 cases were continuously hyperactive and 10 cases (12.2%) with increased hyperactivity had the second plasma phenobarbital concentration in the therapeutic range.

As shown in Table 6, 37 (45.1%) out of our patients with persisted irritability and 12 cases (14.6%) with increased irritability also had the second plasma phenobarbital concentration within the therapeutic range. Furthermore, 3 (3.7%) out of 82 cases with persisted irritability and 4 cases (4.9%) with increased irritability had the second plasma phenobarbital concentration below the therapeutic range.

Patient's compliance

With regard to patient's treatment compliance, as can be seen in Table 7, 67 out of 82 cases (81.7%) has never missed to take the drug. The compliance of the study group was 92.5%, which was significantly better than that of the control group, which only reached 71.4% of compliance.

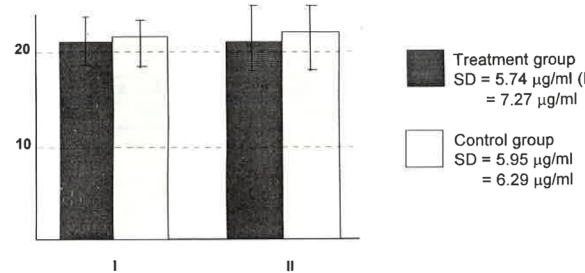

Figure 1. Means of the 1st and 2nd plasma phenobarbital concentration in the study and control groups.

Table 3. Relation of drug dosing and change of seizures

Groups	Change of seizure frequency								Total
	None	Decrease					No change	Increase	
		100%	>90%	50-89%	10-49%	<10%			
A	25	9	0	2	0	0	1	3	40
B	27	8	0	3	0	0	0	4	42
Total	52	17	0	5	0	0	1	7	82

A = study group B = control group K = 0.8729 p > 0.05

Table 4. Relation of second plasma phenobarbital level with drug dosing and change of drowsiness

Second plasma phenobarbital level	Groups*	Drowsiness					Total	Clearance
		None	Decrease		No change	Increase		
			100%	Partial				
>40 μg/ml	A	0	0	0	0	0	0	
	B	0	0	0	0	0	0	
15-40 μg/ml	A	9	14	1	6	5	35	K=1.1700 p<0.05
	B	12	3	3	17	4	39	
<15 μg/ml	A	1	2	0	1	1	5	K=0.8200 p>0.05
	B	0	0	1	1	1	3	
Total		22	19	5	25	11	82	

* A=study group B=control group

Table 5. Relation of the second plasma phenobarbital level with drug dosing and hyperactivity changes

Second plasma phenobarbital level	Groups	Hyperactivity					Total	p value
		Still no hyperactive	Decrease		Remained hyperactive	Increase		
			100%	Partial				
>40 μg/ml	A*	0	0	0	0	0	0	
	B*	0	0	0	0	0	0	
15-40 μg/ml	A*	2	0	9	20	4	35	K=0.6900
	B*	5	0	1	27	6	39	p>0.05
<15 μg/ml	A*	2	0	0	3	0	5	K=0.9100
	B*	0	0	0	1	2	3	p>0.05
Total		9	0	10	51	12	82	

* A=study group B=control group

Table 6. Relation of the second plasma phenobarbital level with drug dosing and irritability changes

2nd plasma phenobarbital level	Groups	Irritability					Total	p value
		Still no irritability	Decrease		Constant Irritability	Increase		
			100%	Partial				
>40 μg/ml	A*	0	0	0	0	0	0	
	B*	0	0	0	0	0	0	
15-40 μg/ml	A*	2	9	6	14	4	35	K=1.2100
	B*	6	0	2	23	8	39	p<0.05
<15 μg/ml	A*	1	0	0	2	2	5	K=0.3700
	B*	0	0	0	1	2	3	p>0.05
Total		9	9	8	40	16	82	

* A=study group B=control group

Table 7. Distribution of the patients according to groups and the compliance

Groups	Compliance		Total
	Good	Bad	
Study	37 (92.5%)	3 (7.5%)	40 (100%)
Control	30 (71.4%)	12 (28.6%)	42 (100%)
Total	67	15	82
$z = 2.4700$	$p < 0.05$		S

Discussion

In this study female patients outnumbered male; this was different with Shorvon's study[11] who found more boys than girls with epilepsy. Nevertheless, the two groups were comparable in terms of sex, age group, mother's education, history of epilepsy in the family, head circumference, socio-economical status, nutritional status, duration of the disease and phenobarbital treatment, seizures frequency and EEG. As shown in Figure 1, the mean of plasma phenobarbital level of the two groups were in the therapeutic range, and there were no significant differences of the first and the second plasma phenobarbital levels either within group or between the groups. Total body clearance of once-daily dose of phenobarbital in children is 0.0079 l/kg/ hour, two-folds of that in adults (0.004 l/kg/hour).[12] Nevertheless, the high clearance of phenobarbital does not make a variation in serum concentration. It can be caused by the lower glucuronidation of phenobarbital in children and neonates.[13] The ratio of the second to the first plasma phenobarbital level in the study group was 22.52/22.57=0.99, while in the control group it was 23.53/22.95=1.02. These data coincide with the study of Walson et al.[7] i.e. 0.81-1.11.

Table 3 shows us that free-seizures patients in the study group was 34 out of 40 cases (85%) , so there was an increase of 15%, while in the control group, there were 35 free-seizure cases (83.3%) , in the other words there was an increase of 19%. In fact, there were no statistically significant differences in increasing of free-seizure cases in either groups. These results also coincide with the study of Walson et al.[7] and that of Davis et al.[8]

Drowsiness is the most frequent side effect in the use of phenobarbital.[14] Nevertheless, this condition can be avoided by once-daily dose of phenobarbital in the evening, because phenobarbital has a long half-life and narrow plasma level fluctuation.[15] As shown in Table 4, drowsiness was significantly less in the study group than in the control group. This result has an important positive meaning because drowsiness in children could disturb the cognitive function in subtle condition and it will decrease the school performance.[14] In fact, the most frequently found side effect in our study was hyperacitivity (89%), followed by irritability (78%), while drowsiness was seen in only 50% of cases. This could be explained by the fact that drowsiness will be tolerated by the children faster than other side effects.[16] Table 4 also shows us that 9 out of 11 cases with increased drowsiness had the therapeutic level of second plasma phenobarbital. Furthermore, 2 out of 11 cases with increased drowsiness had the second plasma phenobarbital level lower than the therapeutic range.

This condition could occur because the appearance of side effects is not related to the high of plasma phenobarbital level.[17] As shown in Table 5, 4 out of 40 cases (10%) in the study group suffered from increased hyperactivity, but there were no significant difference with the control group. Similarly, Walson et al.[7] found 8% of increased hyperactivity in his study group.

As shown in Table 6, there were 6 (15%) out of 40 cases in the study group with increased irritability. In this relation, Davis et al.[8] only found 11% increase of irritability in his study group. We found an interesting finding in our study that patients with therapeutic plasma phenobarbital level had greater decrease of irritability in the study group compared with that in the control group.

Table 7 shows us that the compliance in the study group (92.5%) was significantly better than in the control group (71.4%). Davis et al.[8] also found the higher compliance in his study group (98%), although there was no significant difference in both groups. So, it was an evidence that we could not find the Hawthorn effect in this study. The effect means that both groups of patients will attempt to increase the compliance as good as they can because they know that we have a special attention to them.[18]

In developed countries, use of phenobarbital for generalized tonic-clonic epilepsy is decreased because of an assumption that it will disturb the cognitive function and behavior.[19] However, most authorities believe that phenobarbital is the mainstay of therapy in the management pediatric seizure disorders, primarily in developing countries.[4,8] Furthermore, this unblind-controlled clinical trial confirmed the hypothesis that once-daily dose of phenobarbital is as effective as twice-daily dose, and that once-daily dose of phenobarbital causes fewer side effects and better compliance. We suggest to give once daily dose of phenobarbital for generalized tonic-clonic epilepsy in children, primarily in our country and in other developing countries.

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