Paediatrica Indonesiana

VOLUME 48 January • 2008 NUMBER 1

Original Article

Comparison of monotherapy effect of phenytoin, carbamazapine and valproic acid in pediatric general tonic clonic and partial epilepsy

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Abstract

Background Problems on epilepsy do not only depend on the disease itself but also on management and drug regimens. Drug selection is very important to yield optimal treatment effect and to prevent side effects due to long-term therapy.

Objective To determine whether there are any different effects of monotherapy of phenytoin, carbamazapine, and valproic acid on pediatric general tonic clonic and partial epilepsy.

Methods We conducted a historical cohort study on one month until 18-years old children diagnosed as general tonic clonic or parsial epilepsy treated with phenytoin, carbamazapine, or valproic acid routinely for more than two years in Sardjito Hospital from January 2000 until May 2007. The sample size of each group was 41. The main outcome was the time of 12-month remission, whereas the secondary outcomes were withdrawal from treatment, time to remission, side effects and cure rates.

Results Valproic acid increased the possibility to achieve 12-month remission (RR 2.66; 95%CI 1.06;6.65) compared to phenytoin, whereas carbamazapine did not (RR 1.47; 95%CI 0.66;3.28). Survival analysis showed that valproic acid was better than carbamazapine (P=0.042) and phenytoin (P=0.007). There were no significant differences among groups in the result of withdrawal from treatment, time to remission, and cure variables. The side effects of valproic acid seemed less than those of others.

Conclusions Valproic acid increases the possibility of 12-month remission compared to carbamazapine and phenytoin as monotherapy in pediatric general tonic clonic and partial epilepsy without increasing side effects. Carbamazapine has similar effects of therapy to phenytoin. **[Paediatr Indones 2008;48:37-41]**.

Keywords: *epilepsy, child, monotherapy, effect*

Epilepsy is one of the most common neurological disorders in children.[1] The incidence is approximately 4.0-7.22 and the prevalence is 3.89-4.28 per 1000 children aged within 7-18 years old.[2] There are many etiologies of epilepsy, but only 25% of them have been identified.[2] Genetic factor contributes 40% of etiology in pediatric epilepsy.[3] There are over 50 million sufferers in the world today, 85% of them live in developing countries.[4] An estimation of 2.4 million new cases occurs each year globally. At least 50% of the cases begin at childhood or adolescence.[4] Epilepsy can cause a major impact on a child's development,[5,6] that is behavior and cognitive disorder[7] and can increase risk of death,[8] whether because of the disease itself or because of the long-term treatment and drug regimens. In many children, the seizures remit, but in others the disorder continues and may affect adult life.

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Immediate seizure controlling and drug selection is very important to yield optimal treatment effects and to prevent side effects due to long-term therapy. Phenytoin, carbamazapine and valproic acid are the first line drugs of anti-epilepsy that are commonly used worldwide for general tonic-clonic and parsial epilepsy. However, there are still many controversies to choose the best drug among them when the child is diagnosed as epilepsy for the first time.[9-13] Based on that, this study aimed to find the different effects of monotherapy of phenytoin, carbamazapine, and valproic acid on pediatric general tonic clonic and partial epilepsy.

Methods

We conducted a historical cohort study (**Figure 1**). The primary outcome was the time of 12-month remission from seizures and the secondary outcomes were the withdrawal from treatment, time to last seizure after treatment, side effects and cure rate. We recruited one month until 18-year old children diagnosed as general tonic clonic or parsial epilepsy (based on clinical sign and EEG examination) treated with phenytoin, carbamazapine, or valproic acid routinely for more than two years in Sardjito Hospital from January 2000 to May 2007. This study was done from June 2007 to August 2007 in Sardjito Hospital Yogyakarta. Time to 12-month remission, was defined as time needed to achieve 12 month free of seizure since the first treatment up to the 36 months of follow up. We defined treatment withdrawal as the discontinuity of the treatment because of side effects or uncontrolled seizure. Time to remission was the time needed to achieve the last seizure during treatment. Cured was the condition free from seizure without treatment after two years free from seizure with treatment. The inclusion criteria were children with general tonic clonic or parsial seizure, including secondary generalized seizure who routinely visited the pediatric neurology. Age was between 1 month and 18 years. The patients were treated with phenytoin, carbamazapine or valproic acid for two years or more. We excluded non convulsive epilepsy, children with severe neurological disorder (i.e. cerebral palsy, microcephaly and hydrocephalus), brain tumors, and severe epileptic syndrome (i.e. West syndrome, Lennox-Gestaut syndrome and Landau-Kleffner syndrome). We divided the research into three groups of treatment: phenytoin group, carbamazapine group and valproic acid group.

Our assumption was by follow up for about three years, 80% of patients with phenytoin, 67% patients with carbamazapine and 78% patients with valproic acid achieved 12-month experienced remission.[14] The power of the trial would exceed 80% (by the log-rank statistic at P=0.05, two-tailed) to detect improvements to 20% seizure free. We chose the higher samples among the three therapy above, so we found that the sample size of this study was 41 patients for each group

Chi-squared (X^2), t-test, ANOVA and survival analysis of Kaplan-Meier with log rank statistic were used to analyze the data.[15]

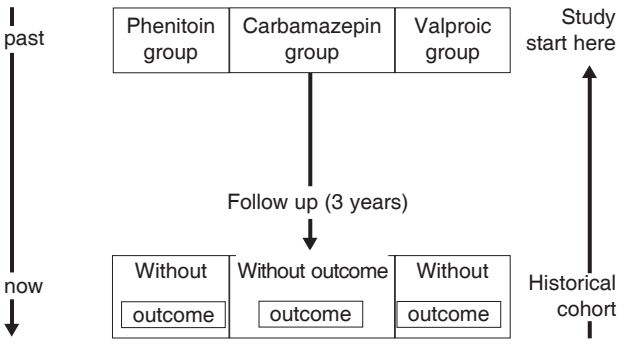

Figure 1. Study design of historical cohort

Results

Based on 399 medical records of epilepsy diagnosis during January 2000 up to May 2005, 273 medical records had diagnosis of general tonic clonic and parsial epilepsy, 175 had completed data that matched with the inclusion criteria, whereas 21 were excluded. Therefore, we had 154 medical records included in this study, that were 65 phenytoin group, 47 carbamazapine group and 42 valproic acid group. We collected all the data from 154 medical records, as the samples of this study.

Baseline characteristic data are shown in **Table 1**. The mean time of 12 month remissions were similar among groups, but if we compared one by one, there was significant difference between carbamazapine and

Table 1. Baseline characteristics data

Characteristic n=65 f (%)	Phenytoin n=47 f (%)	carbamazapine n=42 f (%)	Valproaic
Sex			
- Boys	42 (65)	28 (60)	25 (60)
- Girls	23 (35)	19 (40)	17 (40)
History of epilepsy in the Family			
- Yes	9 (14)	3 (6)	2 (5)
- No	56 (86)	44 (94)	40 (95)
Parent's education			
- Primary school	6 (9)	5 (11)	1 (2)
- Yunior high school	12 (19)	9 (19)	8 (19)
- Senior high school	38 (59)	28 (60)	20 (48)
- University	9 (14)	5 (10)	13 (31)
Parent occupation			
- Farmer	8 (12)	3 (6)	1 (2)
- Laborer	11 (17)	11 (24)	5 (12)
- Private	31 (48)	23 (49)	15 (36)
- Public of government/ soldier/ policeman	15 (23)	10 (21)	21 (50)
Age at first time seizure:			
- <2 year	36 (55)	16 (34)	20 (48)
- 2-5 year	11 (17)	11 (23)	13 (31)
- 6-10 year	12 (19)	17 (36)	8 (19)
- >10 year	6 (9)	3 (7)	1 (2)
Age at starting treatment:			
- <2 year	27 (42)	11 (23)	17 (40)
- 2-5 year	16 (25)	14 (30)	11 (26)
- 6-10 year	17 (26)	16 (34)	10 (24)
- >10 year	5 (7)	6 (13)	4 (10)
Number of seizures before treatment			
- 2	12 (19)	5 (11)	4 (10)
- >2-10	30 (46)	16 (34)	18 (43)
- 11-20	7 (11)	5 (10)	3 (7)
- >20	16 (24)	21 (45)	17 (40)
Developmental disorders	18 (28)	13 (29)	11 (26)
Drug doses:			
- Achieve 12 month remission (mg/kgBW/day)	6.3	10.8	15.3
- Not achieve 12 month remission (mg/kgBW/day)	7.7	16.8	26.7
Diagnosis:			
- General tonic clonic epilepsy	51 (79)	37 (82)	36 (86)
- Parsial epilepsy	14 (21)	10 (18)	6 (14)

valproic acid (P=0.031, 95%CI 0.28;5.66) (**Table 2**). Overall, 69.5% patients achieved 12-month remission in the 36 month of follow up and it was not different among groups (**Table 2**). Survival analysis showed that there were significant differences between phenytoin and valproic acid (P=0.007), carbamazapine and valproic acid (P=0.042), which was not found in phenytoin and carbamazapine (P=0.808) (**Figure 2**). From sub-analysis based on diagnosis, we found only phenytoin and valproic acid that have significant difference (P=0.016) in the general tonic clonic epilepsy. We found no difference among groups of partial epilepsy, although in week 28th all the patients in valproic acid group achieved 12-month remission.

There were adverse effects in the phenytoin and the carbamazapine groups (6.1% and 8.6%, respectively), and failure to control seizure occurred in 29.3% phenytoin group, 19.1% carbamazapine group and 19% valproic acid group (P=0.114). All of those required withdrawal and substitution of alternative drug. Time to last seizure after treatment were not different either, that was 6.2 month in the phenytoin group, 6.24 month in the carbamazapine group and 2.9 month in the valproic acid group (P=0.131). The side effects are presented in **Table 4**. Generally, all three drugs had good effect of treatment. Overall, 45.78% patients were cured and no significant difference among groups (P=0.40).

We calculated the relative risks with 95% confidence interval to compare the effect of treatment among the three drugs and phenytoin to be the control group. We found that valproic acid increased the

Table 2. Mean time of 12 month remission (in month)

Epilepsy	Phenytoin Mean (SD)	Carbamazapine Mean (SD)	Valproic acid Mean (SD)	P
- General tonic clonic	18.4 (10.56)	18.3 (6.92)	14.4 (3.36)	0.920
- Parsial	16.3 (6.46)	16.3 (4.63)	17.5 (7.15)	0.982
- Total	17.92 (9.75)	17.94 (6.55)	15.0 (4.29)	0.161

Table 3. Achieve 12 month remission in 36 months of follow up

Epilepsy	Phenytoin n=65 f (%)	Carbamazapine n=47 f (%)	Valproic acid n=42 f (%)	P
- General tonic clonic	31 (61)	27 (57)	28 (67)	0.202
- Parsial	9 (64)	6 (60)	6 (100)	0.085
- Total	40 (62)	33 (70)	34 (81)	0.095

Table 4. Number of patient with side effects

Side effect	Phenytoin n=65 f (%)	Carbamazapine n=47 f (%)	Valproic acid n=42 f (%)
Drowsiness	0 (0)	0 (0)	0 (0)
Skin rash	2 (3)	2 (4)	0 (0)
Hirsutism	0 (0)	0 (0)	0 (0)
Tremor	0 (0)	0 (0)	0 (0)
Ginggival hipertrophy	1 (2)	0 (0)	0 (0)
Intoxication	1 (2)	0 (0)	0 (0)
Stevens Johnson Syndrome	0 (0)	2 (4)	0 (0)
Total	4 (6)	4 (9)	0 (0)

possibility to achieve 12-month remission significantly when compared to phenytoin. The other variables were similar among groups (**Table 5**).

Discussion

There are several reviews represented the efficacy and tolerability of several antiepileptic drug,[9,16,17] but most of the studies were conducted in adults and only few studies in children. De Silva *et al*[14] and Verity *et al*[18]

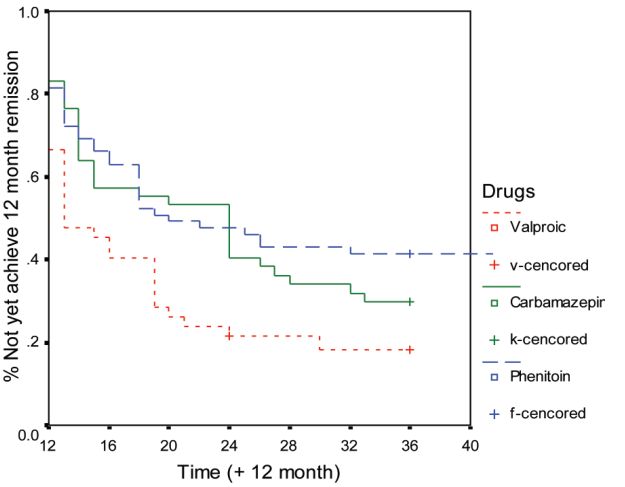

Figure 2. Survival analysis of 12 month remission

studies are two of few studies on childhood epilepsy investigated the efficacy of antiepileptic drug. They found that phenytoin, carbamazapine and valproate have similar efficacy and excellent controlling seizures.

Our study showed different results. We found that valproic acid is better than phenytoin and carbamazapine to achieve 12 months remission. We analyzed the data by relative risk and survival analysis and revealed that valproic acid was better than phenytoin and carbamazapine significantly. Although the number of side effects is small, valproic acid had fewer side effects than phenytoin and carbamazapine. Other secondary outcomes were similar among phenytoin, carbamazapine and valproic acid.

The baseline characteristics data were similar. Genetic factor that contributes approximately 40% of etiology of childhood epilepsy[3] was only 9% in this study. However, the investigation was only from the family epilepsy history. Camfield[19] described that onset of epilepsy is less than 12 years old and the number of seizure less than 21 times before treatment is the best

Table 5. Comparisson of treatment (phenytoin to be the control group)

Therapy	12 month remission	RR (95% CI) Withdrawal from treatment	Side effect	Cured
Carbamazapine	1.47 (0.66-3.28)	0.73 (0.33-1.62)	1.42 (0.34-1.52)	0.53 (0.19-1.48)
Valproic acid	2.66 (1.06-6.65)	0.40 (0.16-1.01)	NA	0.58 (0.16-2.01)

(NA = Not Available, because the side effect of valproic acid is 0%)

predictor to achieve remission. In this study, the two factors were similar. Each group had the same opportunity to get remission. The parental education and occupation were similar too. Therefore, they had the same chance to get medicines. Valproic acid was available since 2004. That is why many patients in valproic acid group had not finished the treatment yet. Treatment was withdrawn only if side effects were severe. No data about mild and moderate side effects. We did not analyze cognitive and behavior side effects in this study.

There are limitations in this study. This study was a historical cohort. Recall bias becomes a main problem in this study. Although we had a complete data from medical records, we were not able to control compliance of taking the medicine every day. We concluded that the patients have good compliance if they come for routinely check up to the pediatric neurology clinic. The diagnostic criteria that was based on clinical appearance and EEG results, sometime were not sufficient to create definitive diagnosis. Misdiagnosis is still possible with the consequence of wrong treatment. The doses of the drugs are within the range of therapeutic dose, but we do not have certain protocol yet when to increase the dose. It will influence the time to get the remission because of the lateness in increasing the dose.

In conclusion, valproic acid increases the possibility of 12-month remission compared to carbamazapine or phenytoin as monotherapy in pediatric general tonic clonic and partial epilepsy without increasing side effects. The therapy effect of carbamazapine is not different significantly from that of phenytoin.

References

1. Cowan LD, Bodensteiner JB, Leviton A, Doherty L. Prevalence of epilepsy in children and adolescent. Epilepsia 1998;30:94-106.
2. Kurtz Z, Tookey P, Ross E. Epilepsy in young people: 23 year follow up of British national child development study. BMJ 1998;316:339-42.
3. Annegers JF. The epidemiology of epilepsy. In: Wyllie E, ed. The Treatment of Epilepsy: Principles and Practice. 2nd ed. Baltimore, Md: Williams & Wilkins; 1996:165-172.
4. World Health Organization. Epilepsy: aetiology, epidemiology and prognosis. In WHO Fact sheet no.165. Geneva:2001.
5. Holdsworrth J, Whitmore K. A study of children with epilepsy attending normal schools. Dev Med Child Neurol 1974; 196:746-65.
6. Stores G. School children with epilepsy at risk for learning and behavioural problem. Dev Med Child Neurol 1978; 20:502-8.
7. Sadjimin T, Harjanto B, Sunartini, Indira LG. Frekwensi gangguan perilaku pada epilepsi anak di RSUP Dr. Sardjito Yogyakarta. Jurnal Epidemiologi Indonesia 1999;3:17-20.
8. Scambler G. Sosial aspects of epilepsy. In: Hopkins A, editor. Epilepsy. London: Chapman and Hall; 1987. p. 497-510.
9. Tudur S, Marson AG, Williamson PR. Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. The Cochrane Database of Systematic Reviews 2001, Issue 4.
10. Lazuardi S. Pengobatan epilepsy. In: Soetomenggolo, TS, Ismael, S, editors. Neurologi anak. 2nd ed. Jakarta: IDAI; 2000. p. 225-7.
11. Arzimanoglu A. Aicardi's epilepsy in children. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 363-86.
12. Ko DY. Tonic clonic seizure. Available from: url: http://www.emedicine.com.
13. Benbadis SR. Parsial epilepsy. Available from: url: http://www.emedicine.com.
14. De Silva M, MacArdle B, McGowan M, Hughes E, Stewart J, Neville BG, *et al*. Randomized comparative monotherapy trial of phenobarbitone, phenytoin, carbamazapinee, or sodium valproate for newly diagnosed childhood epilepsy. Lancet 1996;347:709-13.
15. Madiyono B, Moeslichan S, Sastroasmoro S, Budiman I, Purwanto SH. Perkiraan besar sampel. In: Sastroasmoro S, Ismael S, editors. Dasar-dasar Metodologi Penelitian Klinis. 2nd ed. Jakarta: Sagung Seto; 2000. p. 258-87.
16. Marson AG, Williamson PR, Hutton JL, Clough HE, Chadwick DW. Carbamazapinee versus valproate monotherapy for epilepsy. The Cochrane Database of Systematic Reviews 2000, Issue 3.
17. Tudur S, Marson AG, Clough HE, Williamson PR. Carbamazapinee versus phenytoin monotherapy for epilepsy. The Cochrane Database of Systematic Reviews 2002, Issue 2.
18. Verity CM, Hosking G, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazapinee in paediatric epilepsy. The Paediatric EPITEG Collaborative Group. Dev Med Child Neurol 1995;37:97-108.
19. Camfield C, Camfield P, Gordon K, Smith B, Dooley J. Outcome of Childhood Epilepsy: A Population-Based Study with A Simple Predictive Scoring System for Those Treated with Medication. J Pediatrics 1993;122:861-8.