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The Difference of Malondialdehyde and Lipid Profile Level Between Pediatric Patients with Epilepsy Who Had Long Term Valproic Acid and Carbamazepine Therapy

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Abstract

Epilepsy is one of the most common neurological impairment in the world. Previous study have suggested that long term used of anti epileptic drugs in children might impair lipid metabolism and increase lipid peroxidation. The purpose of this study is to determine the long term impact of antiepileptic drugs (AED) such as valproic acid and carbamazepine, on malondialdehyde (MDA) and lipid profile (total cholesterol, high density lipoprotein, and low density lipoprotein) level of pediatric patients with epilepsy. It is a Cross-sectional study, performed from May to July 2016 in Neurology Pediatric Ward Dr.Hasan Sadikin Hospital Bandung. There were 61 children, aged 2-14 years who fulfilled the inclusion criteria. Blood sample was drawn to measure MDA and lipid profile (total cholesterol, HDL, and LDL) level in each subject. The study showed higher MDA levels in carbamazepine group and had significant difference ($p<0.05$) based on Mann-Whitney test on both groups. The lipid profiles, whether it were total cholesterol, LDL or HDL level, were also higher in carbamazepine group and showed significant difference of lipid components in both group ($p<0.05$) based on MANOVA test. As a conclusion, there is a consideration to observe lipid profile (total cholesterol, LDL, and HDL) level in children with epilepsy treated by long term carbamazepine.

Keywords: Epilepsy, children, lipid profile, malondialdehyde, anti-epileptic drug

1. Introduction

There were about 3,5 million new epilepsy cases globally, in which 40% of them occurred in children. (Camfield et al, 2006). There were at least 700,000–1,400,000 cases of epilepsy in Indonesia, 40–50% of which occurred in children (Harsono et al, 2006). The main management of epilepsy is administration of antiepileptic drugs (AED), which is frequently related with the long term used side effects, such as metabolic and endocrine disturbance, bone metabolism impairment, body weight increment, and drugs interaction (Conway JM in Swaiman KF, 2012. Nakken K, 2011). Valproic acid and carbamazepine are the most frequently used AED at daily practice. There were notions correlating the side effects of several AED with vascular risks (Jakubus et al, 2009). Increasing LDL accompanied with decreasing HDL level are the risk factors of atherosclerosis. In addition, lipid peroxidation also has a significant role in atherosclerosis formation due to LDL oxidation (Kutuk et al, 2003. Garelnabi et al, 2008. Stapran S et al, 2005. Surapaneni-Krishna M, 2010. Ritu S et al, 2006). Side effects of the long term use of AED such as increasing lipid peroxidation and increasing lipid profile is remain controversy (Mintzer S et al, 2009. Verotti et al, 2002. Yuksel et al, 2000. Belcastro et al, 2013). The aim of the study is to determine the differentiation of valproic acid and carbamazepine long term therapy, which towards to MDA and lipid profile (total cholesterol, HDL, and LDL) level.

2. Material and Methods

This study was held from May–July 2016 at Neurology Pediatric Ward Dr. Hasan Sadikin General Hospital Bandung. During the study, there were 61 patients included. One patient was excluded from carbamazepine group because the subject had a history consuming valproic acid before. The subjects were divided into two groups.

Inclusion criteria were children with epilepsy at age of 2–14 years who were already diagnosed as epilepsy through clinical and electroenchepalogram (EEG) examination, who had been treated with carbamazepine or valproic acid for at least 12 months, had a good nutritional status and or experienced obesity after valproic acid

administration, and voluntered to join this study. Children with epilepsy who had chronic diseases such as diabetes mellitus, hypertension, kidney impairment, liver disease, malignancy, and severe malnutrition were excluded from this study. Other exclusion criteria were patients who consumed antioxidant supplement one month prior to the study, consumed drugs that could disturb lipid profile such as statin, fibrate group, hormonal therapy, or any other drugs with similar effect, had experienced obesity before treated with valproic acid, and had family history of obesity, atherosclerosis, or other metabolic disturbance.

The sampling method used in this study was consecutive sampling. History taking, physical examination, measurements of body height and weight, and dietary recall were done to each subject. Blood sample was drawn once to measure routine blood examination, blood glucose serum, liver function, kidney function, lipid profiles (total cholesterol (TC), LDL, HDL) and MDA. Non fasting lipid profile blood sample was used in this study and were processed using direct or homogenous methods.

The comparation of MDA levels in each group were analyze with Mann-Whitney test. The data was normalized before we performed MANOVA test for analyze lipid profile on both groups. Data are evaluated with SPSS for windows version 15 statistical program. In this study we performed multivariate analysis to determine differentiation lipid profile on both groups.

This study had been approved by the Medical Research and Ethical Committee of Medical Faculty, Universitas Padjadjaran. And written consent was taken for each subject.

3. Results

There were 61 patients who were met inclusion criteria which consisted of 31 boys and 30 girls. The average age in valproic acid group was 96.0 (44.6) months and 70.7 (47.6) months in carbamazepine group. Characteristics of the subjects included hemoglobin and trombocyte level, liver function test, kidney function test, blood glucose serum, blood pressure, free seizure duration and epilepsy type. There were no abnormality laboratorium values on both groups. All patients had a normal blood pressure based on their age and the most epilepsy type on this study was a focal form (Table 1).

Table 1. Characteristic of the subjects

Variable	Subject's General Characteristic	
	Valproic acid (n=31)	Carbamazepine (n=30)
Age (month)	96.0 (44.6)	70.7 (47.6)
Hemoglobin (g/dL)	11.9 (1.1)	12.70 (0.90)
Trombocyte (mm^3)	253,709.6 (119,544.7)	342,064 (108,432.1)
SGOT (U/L)	26.5 (11.4)	27.61 (17.07)
SGPT (U/L)	11.6 (8.3)	15.84 (15.06)
Ureum (mg/dL)	21.8 (7.7)	17.7 (5.5)
Creatinine (mg/dL)	0.5 (0.1)	0.4 (0.1)
Blood glucose (mg/dL)	93.6 (14.4)	89.8 (10.2)
Blood pressure (mmHg)		
Systolic	100.9 (10.8)	94.3 (8.9)
Diastolic	67.6 (7.1)	63.7 (8.4)
Free seizure duration (month)	7.5	11
Epilepsy type		
Generalized	26	0
Focal	5	30

Table 2. Factors affecting malondialdehyde and lipid profiles level

Variable	Valproic acid (n=31)	Carbamazepin (n=30)	P value
Gender			
Boys	15	16	0.611**
Girls	16	14	
Nutritional status			
Good	31	29	0.313*
Moderate malnutrition	0	1	
Therapeutic duration (month)			
Median	15.0	16.0	0.340*
Range	12–36	12–60	
Dosage (mg/kgBW/day)			
High dose	8	6	0.589**
Non-high dose	23	24	

* Mann-whitney test; ** Chi square test

In this study, no patient experienced obesity in valproic acid group and most of the subjects on each group had a good nutritional state. Most of the subjects used the AED in non high dose range. Characteristic of the factors affecting MDA and lipid profile level were similar between the two groups as shown in Table 2.

Table 3. Differentiation of malondialdehyde level on valproic acid and carbamazepine group

Variable	Valproic acid (n=31)	Carbamazepin (n=30)	P value*
Malondialdehyde (ng/mL)			
Mean (SD)	57.0 (30.2)	125.8 (127.0)	<0.001
Median	53.8	80.3	
Range	20.7–155.1	24.1–707.9	

*mann-whitney test ($p<0.05$)

The MDA level in this study was founded higher in carbamazepine group. From the Mann-whitney test we found significant difference ($p<0.05$) of MDA level in both group (Table 3).

Table 4. Differentiation of total Cholesterol (TC), LDL, and HDL level on valproic acid and carbamazepine group

Variable	Valproic acid (n=31)	Carbamazepine (n=30)	P value*
Total cholesterol (mg/dL)			
Mean	136.0 (25.1)	175.8 (36.7)	<0.001
Range	91–206	112–268	
LDL (mg/dL)			
Mean	83.4 (20.4)	112.2 (29.4)	<0.001
Range	43–131	52–176	
HDL (mg/dL)			
Mean	39.1 (16.0)	49.5 (19.5)	0.034
Range	3–82	26–118	

F Hotteling's=483.114*MANOVA test ($p<0.05$)

The carbamazepine group had significantly higher TC and LDL, as well as HDL level compared to the valproic acid group. MANOVA test showed significant differences between the two groups in terms of TC ($p< 0.001$), LDL ($p<0.001$), and HDL ($p= 0.034$) levels (table 4).

4. Discussion

This cross-sectional study revealed that the average of malondialdehyde level in carbamazepine group was higher compared with valproic acid group. It showed that oxidative stress was found higher in epileptic patients who had carbamazepine therapy. It was in accordance with the research by Aycicek et al., (2007) Ono et al., (2000) Tutanc et al., (2015) Those studies concluded that carbamazepine administration could decrease antioxidants, and increase formation of free radical through unknown mechanism. The reason why MDA level is much lower in valproic acid group is also unknown. It is suspected that long term valproic acid administration could protect neuron cells through expression of endoplasmic reticulum protein GRP78 and anti-apoptotic factor bcl-2 at cerebral cortex. It is believed that the escalating of those two proteins may assist in stabilizing mitochondria trans-membrane potential, inhibiting release of cytochrome C and inhibiting radical oxygen particles accumulation, based on experimental study by Wang et al., (2003) under mice cerebral cortex which were incubated with ferrichloride oxidant ($FeCl_3$), and were given valproic acid in therapeutic range. On the other hand, antioxidant mechanism of valproic acid might increase glutation level, which were corresponded with the experimental study result done by Cui J et al., (2007).

Previous studies regarding lipid profile in epilepsy patients who had AED showed various results (Verotti A et al, 1997. Verotti A et al, 1998. Koantoush M et al, 1998. Isojarvi J et al, 1993. Nikolaos et al, 2004). In this study, authors found significant differences of total cholesterol serum, LDL, and HDL level in epilepsy patients who had carbamazepine compared to valproic acid group. It was reported from the previous descriptive study results concluded by Brown et al., (1992) Calandre et al., (1991) Verotti et al., (1997) Yalcin et al., (1997) and Tomoum et al (2008). It had been described previously, one of explained mechanism relationship between hypercholesterolemia and carbamazepine was the involvement of carbamazepine as a CYP450 inducer group which is involved in cholesterol synthesis (Verotti A et al, 1997. Verotti A et al, 1998. Koantoush M et al, 1998. Isojarvi J et al, 1993. Nikolaos et al, 2004. Sanders, 2016) by increasing the conversion of lanosterol and dihydrolanosterol into cholesterol (Gibbons G, 2002). Carbamazepine administration is believed could increase cholesterol production including low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride (Verotti A et al, 1998. Isojarvi J et al, 1993).

In this study, the median of total cholesterol, LDL and HDL levels in valproic acid group were found to be lower. The explanation was probably because of valproic acid was included in the inhibitor of several CYP enzyme drug group (Barry EG, 2004).

This study had several limitations. This study was a cross-sectional study that could only measure MDA and lipid serum level at a time. We did not have data about MDA and lipid serum level prior the treatment. Besides,

the evaluation of dietary intake in this study was done by using food frequency questionnaire, this method had several weakness such as the limitation of food types written in the questionnaire, incorrect prediction of the amount of food portion, and the probability of false report because of the retrospectively data (Waterterp KR et al, 2002). Authors also did not examine triglyceride serum level because the limitation and disapproval of subjects to do fasting for approximately 10 hours before blood sampling.

5. Conclusion

There is a consideration to observe lipid profile (total cholesterol, LDL, and HDL) level in children with epilepsy treated by long term carbamazepine periodically.

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