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Research

Vitamin D Status In Epileptic Adults With Valproic Acid Therapy At The Neurology Clinic, Diponegoro National Hospital, Semarang

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Abstract

Background Epilepsy is a brain disease characterized by repeated unprovoked seizures at least two times with an interval of more than 24 hours between the first seizure and subsequent seizures. Valproic acid is an anti-seizure drug. Long-term use of valproic acid may be associated with metabolic disorders such as weight gain, and lipid profile changes, including vitamin D levels.

Objectives To determine the correlation between the duration of valproic acid therapy and serum vitamin D levels in adults using valproic acid.

Methods An observational analytic study with a cross-sectional design. The demographic and duration of valproic acid use were determined using questioner, and the serum vitamin D levels were measured using the ELISA method. The normality test was carried out using the Shapiro-Wilk test and then continued with the Pearson test to determine the correlation between the duration of valproic acid therapy and serum vitamin D levels. The results showed significance if the p-value <0.05.

Results The mean serum vitamin D level among subjects was low (16.44+4,24 ng/mL), furthermore, there is no significant correlation between the duration of valproic acid therapy and serum vitamin D levels (p=0.956, r=-0,011).

Conclusion There is vitamin D deficiency among adults with epilepsy but, the duration of valproic acid therapy does not correlate with serum vitamin D levels.

Keywords: Epilepsy, antiepileptic, valproic acid, vitamin D

INTRODUCTION

Epilepsy is a brain disease characterized by recurrent unprovoked seizures, occurring at least twice in more than 24 hours between the first and subsequent seizures.[1] One approach to the management of epilepsy is by administering anti-seizure drugs to control epileptic seizures and improve the patient's quality of life.[2] Anti-seizure drugs are divided into two groups, namely the first-line group and the second-line group. Anti-seizure drugs, included in the first line group are carbamazepine, valproic acid, phenobarbital, and phenytoin, while drugs included in the second line are lamotrigine, levetiracetam, clobazam, and topiramate.[2]

Valproic acid is commonly used as an anti-seizure drug, psychiatric medication including bipolar disorder, schizophrenia, and personality disorders, and migraine prophylaxis.[3] Long-term use of valproic acid may be associated with metabolic abnormalities such as weight gain, and changes in lipid profiles, including vitamin D levels.[3,4] Vitamin D itself is a fat-soluble vitamin needed by the body for metabolic processes.[5] The impact of vitamin D deficiency is a lack of minerals in bone, which can cause rickets in children and osteomalacia in the elderly.[6] The effect of valproic acid on the vitamin D level may be through the increase of vitamin D-induced and basal cytochrome P24A (CYP24A) expression.[7] CYP24 is one of the CYP450 enzymes, that is important for hydroxylating the 25 hydroxyvitamin D3 (25(OH)D3) and 1,25 dihydroxy vitamin D3 (1,25(OH)2D3) to produce calcitroic acid. Valproic acid also reduces the 25(OH)D3 levels by creating 24,25 dihydroxy vitamin D3 (24,25(OH)2D3).[8] Furthermore, long-term use of valproic acid also decreases cholesterol levels as one of the precursors of vitamin D resulting in a low level of vitamin D.[9] There is little evidence demonstrating the association of duration of valproic acid therapy on the vitamin D level. This study is to determine the correlation between the duration of valproic acid therapy and serum vitamin D levels among people with epilepsy to get a better understanding of the effect of valproic acid on vitamin D levels.

METHODS

This study is an observational analytic study with a cross-sectional design among 29 subjects obtained from an outpatient clinic, Diponegoro National Hospital Semarang Indonesia, period of August to September 2021 who met the inclusion and exclusion criteria. Inclusion criteria in this study were patients aged between 18-60 years old, using valproic acid, and willing to participate in this study, and the exclusion criteria in this study were patients taking vitamin D, having parathyroid hormone abnormalities, determined from medical records, and confirmation to the subjects, history of dyslipidemia or using lipid-lowering drugs.

Subjects who agreed to participate in this study signed the informed consent then the demographic and clinical data were obtained using a questionnaire. The venous blood was obtained from the median cubital vein by the laboratory staff of Diponegoro National Hospital Semarang. Examination of serum vitamin D levels was carried out at the Gangguan Akibat Kekurangan Yodium (GAKY) Laboratory using ELISA methods. The protocol of examination was performed according to the manufactured sheet obtained from Elabscience®.

The demographic characteristics of subjects were presented in mean and standard deviation for numerical scale, and the proportion for the categorical data.

The primary outcome in this study-serum vitamin D level was tested for the normality distribution using the Shapiro-Wilk test, then continued with the correlation test using bivariate analysis. The correlation between the demographic and clinical data of subjects and the serum vitamin D levels was determined using the Spearman correlation test for the categorical data such as gender, history of alcohol consumption, smoking, use of other drugs, diabetes mellitus, special diet, and a daily dose of valproic acid. The Pearson test was used to determine the correlation between the duration of valproic acid therapy and serum vitamin D levels at the significance level of p= 0.005.

The protocol of this study was approved by the Local Health Research Ethics Commission from the Faculty of Medicine, Diponegoro University, with the number of ethical clearance 197/EC/KEPK/FK-UNDIP/VI/2021.

RESULTS

This study involved 29 subjects obtained from the out-patient clinic Diponegoro National Hospital Semarang period of August to September 2021. The mean age of subjects is 32,10±16,40 years old. The characteristic of the subjects is depicted in table 1.

Table 1. *The Demographic and Clinical Characteristics of Research Subjects*

Characteristic		n (%), Average ± SD	R	p-value
Gender			-0.357	0.058
	Man	10 (34,5)		
	Woman	19 (65,5)		
Age (year)		32,10±16,40	0.160	0.408
Body Mass Index (Kg/m2)		26,00±5,22	-0.001	0.997
History of alcohol consumption			-0.164	0.395
	Yes	5 (17,2)		
	No	24 (82,8)		
Smoking history			0.198	0.303
	Yes	7 (24,1)		
	No	22 (75,9)		
Other drugs history			0.159	0.411
	Yes	24 (82,8)		
	No	5 (17,2)		
Diabetes melitus history			-0.159	0.411
	Yes	1 (3,4)		
	No	28 (96,6)		
Special diet history			-0.159	0.251
	Yes	2 (6,9)		
	No	27 (93,1)		
Daily dose (mg)		491,37±205,75	-0.198	0.304

Table 1 depicted that there were more female than male subjects with the body mass index (BMI) of the subjects categorized as overweight, as stated in the World Health Organization (WHO) classification. In addition, some subjects were detected to have a history of smoking (n=7) and using drugs other than antiepileptic drugs (AEDs). A small number of subjects were observed to have a history of diabetes mellitus and special diets.

In this study, the mean duration of valproic acid used in the research subject was 50,58±76,51 months with the shortest duration being 2 months and the longest duration being 384 months.

The mean serum vitamin D level in our study is 16.44 ng/mL, where this value can be interpreted as a sign of vitamin D deficiency. Where the normal value of serum vitamin D is 20 – 50 ng/mL However, the bivariate analysis revealed that there is no correlation between the duration of valproic acid use with serum vitamin D levels with a p-value = 0.956.

DISCUSSION

Valproic acid is one of the drugs widely used as anti-seizure drugs, maintenance of bipolar disorder, schizophrenia, personality disorders, and migraine prophylaxis.[3] Long-term use of the drug valproic acid can be associated with several things, such as weight gain, changes in lipid profile, and changes in vitamin D levels.[14]

Prawitasari et al. showed that the duration of using valproic acid negatively correlated with serum calcium levels.[10] The mechanism of the effect of valproic acid on serum calcium levels hypothesizes in several ways, including through a decrease in intestinal calcium absorption mediated by calcitriol.[11] The meta-analysis showed that valproic acid reduces vitamin D levels in children with epilepsy patients demonstrated that extended use ofvalproic acid may lead to decreased levels of vitamin D.[12] In addition, Abdullah et al. observed the use of the drug valproic acid can reduce vitamin D levels compared to a group of healthy children.[13] However, the correlation of prolonged use of valproic acid with serum vitamin D levels is unclear. This study aimed to prove the correlation of the duration of valproic acid use with serum vitamin D levels. The results of this study indicated that serum vitamin D levels in subjects were less than normal. This is similar to several works of the literature that showed that valproic acid could reduce serum vitamin D levels. Unfortunately, our study showed no significant correlation between the duration of valproic acid use and serum vitamin D levels. These results were in contrast with the hypothesis of this study and other studies, which showed that the duration of antiepileptic drug use (AEDs) was associated with theserum vitamin D level, done by Abdullah et al. There is a different study by Abdullah et al and ours. Abdullah et al. used children as subjects, but our study used adults, which might affect the results.

The metabolism of vitamin D is affected by several factors such as exposure to ultraviolet light, food intake, and might be a precursor of vitamin D such as cholesterol. Our study did not examine directly related physical activity with exposure to ultraviolet light and food intake.[14,15] In addition, some patients did not use valproic acid as monotherapy (data is not shown), which may lead to biased resultsdue to the different mechanisms of action of the anti-epileptic drugs used. Furthermore, all subjects werenot tested for cholesterol before, so the authors did not know whether the cholesterol levels of the research subjects were within normal limits or not.

CONCLUSION

To sum up, our study suggests that there is a decrease in serum vitamin D levels among people with epilepsy, but the duration of therapy of valproic acid does not correlate with the serum vitamin D levels.

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CONFLICT OF INTEREST AND FUNDING RESOURCES

There is no conflict of interest

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