ORIGINAL RESEARCH ARTICLE

Diponegoro International Medical Journal 2022 July, Vol 3, No.1: 14 - 18
e-ISSN: 2745-5815

Association of Type of Antiepileptic Drugs and Serum Vitamin D Levels among People with Epilepsy

Adelia Putri Maharani[1], Hasna Syariva[1], Dwi Ngestiningsih[2], Arinta Puspita Wati[3], Santoso Jaeri[2*]

[1] Department of Medicine, Faculty of Medicine, Diponegoro University Semarang Indonesia
[2] Department of Medical Biology and Biochemistry, Faculty of Medicine, Diponegoro University Semarang Indonesia
[3] Department of Neurology, Faculty of Medicine, Diponegoro University Semarang Indonesia

Keywords:

Antiepileptic drugs (AEDs)
Phenytoin
Valproic acid
Vitamin D

*) Correspondence to:
jw.santoso@gmail.com

Article history:

Received 09 – 06 - 2022
Accepted 19 – 07 - 2022
Available online 31-07-2022

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, lipid profile changes, including vitamin D levels.
Objective: To determine the association of type of antiepileptic drugs and serum vitamin D levels among people with epilepsy
Methods: A cross-sectional study among 24 people with epilepsy obtained from outpatient clinic Diponegoro National Hospital Semarang. The subjects then classified based on the type of antiepileptic drugs into two groups. First group was subjects who using valproic acid (n=15) and second group was subjects who using phenytoin (n=9). The demographic and clinical data were collected, then the measurement of vitamin D levels was performed using ELISA. The two independent samples T-test were performed to determine the differences of serum vitamin D levels among people with epilepsy.
Results: The mean of serum vitamin D levels among 24 subjects were 17,32 + 6,37 ng/mL, and the mean of serum vitamin D levels based on the type of antiepileptic drugs were 16,92 + 4.27 ng/mL for the first group and 18 + 9.16 ng/mL for the second group. Furthermore, that there was no significant difference in the serum vitamin D levels in both groups (p=0,697).
Conclusion: There is no different effect of valproic acid and phyenitoin on the serum vitamin D levels among people with epilepsy

DIMJ, 2022, 3(1) 14-18, DOI: https://doi.org/10.14710/dimj.v3i1.14540

1. Introduction

Epilepsy is a brain disease characterized by recurrent unprovoked seizures as a result of paroxysmal neuronal detachment from abnormally excited neurons. [1] The primary management of epilepsy is the administration of antiepileptic drugs (AEDs). The long-term AEDs therapy is associated with metabolic abnormalities including the changes of lipid profile, cholesterol, and micronutrients such as vitamin D. [2.3] The use of CYP-450-induced AEDs such as phenytoin is considered one of the contributing factors for serum vitamin D reduction in epilepsy patients. [4] it is believed that phenytoin, through the activation of pregnane X receptor (PXR), lead to elevate the degradation of 25(OH)D and 1,25(OH)2D. In addition, phenytoin can accelerate vitamin D metabolism resulted in a decrease of vitamin D levels and abnormalities in bone mineral metabolism. [5]

Valproic acid is one of the CYP-450-inhibited AED. Previous study relevealed that valproic acid can reduce the plasma 25(OH)D levels. Another study demonstrated that valproic acid through a different metabolic pathway from phenytoin affects the vitamin D levels. Valproic acid enhances the activity of the CYP-24, a main enzyme in the catabolism of vitamin D3. Resulted in the alteration of the catabolism of 1,25(OH)2D which is supposed to bind with the core receptor of vitamin D. [6]

Due to the controversy over the results of previous studies regarding the effect of AEDs on vitamin D levels, we determine the effect of CYP450-inducing (phenytoin) and non-CYP450-inducing AEDs (valproic acid) on the serum vitamin D levels in order to get better understanding of effect of AEDs on the serum vitamin D levels

2. Methods

This study is an observational analytic study with a cross-sectional design among 20 patients with epilepsy obtained from outpatient clinic Diponegoro National Hospital who have met the inclusion such as aged 18 – 60 years old, using valproic acid or phenytoin and agreed to participate in this study and exclusion criteria such as taking vitamin D supplements and being diagnosed with parathyroid hormone disorders, dyslipidemia, and consuming lipid-lowering drugs.

The protocol of this study was approved by the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University, with the ethical clearance certificate number 201/EC/KEPK/FK-UNDIP/VI/2021.

The subjects who agreed to participate this study were signed the informed consent then the data of demographic and clinical were obtained using questioner. The venous blood was obtained from the median cubital vein by the laboratory staff of Diponegoro National Hospital Semarang. The examination of serum vitamin D levels was carried out in the Gangguan Akibat Kekurangan Yodium (GAKY) Laboratory Faculty of Medicine Diponegoro University Semarang using ELISA kit from Elabscience®. The protocol used in the examination of serum vitamin D levels is based on the manufacturer sheet.

The demographic characteristics and clinical data of subjects were classified based on the type of antiepileptic drugs and analysed using the two independent samples T-test for age, body weight, body height, and body mass index, furthermore for the duration of use of antiepileptic drugs was analysed using Mann Whitney U test because the distribution is not normal. The categorical data such as sex, history of alcohol consumption, smoking, diabetes mellitus and special diet were analysed using the Chi-square test and its alternative.

The primary outcome in this study-difference of serum vitamin D levels among two groups were analysed using the two independent samples T-test with the significance level p= 0,005.

3. Results

This study involved 24 subjects obtained from outpatients' clinic Diponegoro National Hospital Semarang period of August to September 2021. Subjects were divided into two groups; the first group was using valproic acid (n=15) and another group was using phenytoin (n=9). The mean age of subjects is 43,25 ± 19,58 years old, with the duration of use of AED is 82,87 ± 102,83 months or approximately 6-7 years. The characteristic of the subjects is depicted in table 1.

Table 1. Characteristics of research subjects

Characteristics	n (%), Mean ± SD
Sex	
Male	14 (58,3)
Female	10 (41,7)
Age (years)	43,25 ± 19,58
BMI (kg/m^2)	23.14 ± 4,11
History of Alcohol Consumption	
Yes	1 (4,2)
No	23 (95,8)
Smoking History	
Yes	2 (8,3)
No	22 (91,7)
History of Administration of Other Drugs	
Yes	18 (75)
No	6 (25)
History of Diabetes Mellitus	
Yes	2 (8,3)
No	22 (91,7)
Special Diet History	
Yes	1 (4,2)
No	23 (95,8)
Daily dose of antiepileptic drugs (AEDs)	
Phenytoin (mg/day)	211,11 ± 33,33
Valproic acid (mg/day)	566,67 ± 240,29

Table 1 depicted that there were more male than female subjects.

The body mass index (BMI) of the subjects was categorized as overweight, as stated in the World Health Organization (WHO) classification.[7] In addition, some subjects were detected to have a history of smoking (n=3), consuming alcoholic drinks (n=3), and using drugs other than the anti-epileptic drugs (AEDs). A small number of subjects were observed to have a history of diabetes mellitus, and special diets.

The characteristics of the study subjects grouped according to the types of their anti-epileptic drugs (AEDs) are listed in the Table 2. Table 2 revealed that the subjects in both groups shared relatively similar characteristics, where there was no difference in all of them (p>0.05), except for the gender.

Table 2. Characteristics of Research Subjects Based on Antiepileptic Drugs Group (N=24)

Characteristics	Group		p value
	Valproic Acid (n=15)	Phenytoin (n=9)	
Age (years)	40,00 ±19,30	48.67 ±19,93	0,304
Sex (n(%))			0,033
Male	6 (40)	8 (88,90)	
Female	9 (60)	1 (11,10)	
Body weight (Kg)	60,40 + 14,07	59,33 + 6,32	0,802
Body height (cm)	160,47 + 6,91	160,67 + 5,87	0,943
BMI (kg/m2)	23,34 ± 4,89	22,82 ± 2,60	0,773
History of Alcohol Consumption (n(%))			1,000
Yes	1 (6,67)	0 (0)	
No	14 (93,33)	9 (100)	
Smoking History (n(%))			1,000
Yes	1 (6,67)	1 (11,10)	
No	14 (93,33)	8 (88,90)	
History of Administration of Other Drugs (n(%))			0.635
Yes	12 (80)	6 (66,67)	
No	3 (20)	3 (33,33)	
History of Diabetes Mellitus (n(%))			1,000
Yes	1 (6,67)	1 (11,10)	
No	14 (93,33)	8 (88,90)	
Special Diet History			0.375
Yes	0 (0)	1 (11,10)	
No	15 (100)	8 (88,90)	
Duration of taking AEDs (months)	81,00 ± 96,35	86,00 ± 118,91	0,770

The mean of serum vitamin D levels among both groups were 17,32 $\pm$ 6,37 ng/mL. These levels were classified as deficiency. The results of statistical analyzes comparing serum vitamin D levels in the two groups of antiepileptic drugs are demonstrated in Table 3.

Table 3. Results of the Independent Samples t-Test Analysis of Serum Vitamin D Levels in Patients Using Valproic Acid with Phenytoin

	Group		p value
	Valproic Acid (n=15)	Phenytoin (n=9)	
Vitamin D Levels (Mean $\pm$ SD) ng/mL	16,92 $\pm$ 4,27	18,00 $\pm$ 9,16	0,697

The table indicated that there is no significant difference in serum vitamin D levels in the valproic acid group and the phenytoin group.

4. DISCUSSION

Vitamin D deficiency is one of the most common issues among people with epilepsy. Some literatures suggest that the use of AEDs also affects serum vitamin D levels in patients. The mechanisms of some AEDs affecting the vitamin D metabolisms are complex and heterogeneous.[8] Some evidence showed that CYP-450 enzymes-inducer AEDs such as phenytoin promote the catabolism of vitamin D in the body.[5,9,10] On the other hand, valproic acid, an inhibitor of the CYP-450 enzyme also affects the serum vitamin D levels through the increasing of the activity of the CYP-24 enzyme in the kidney, resulting in the increase of 24,25(OH)2D production and reducing the amount of 25(OH)D that will bind to 1-alpha-hydroxylase to carry out the second hydroxylase of vitamin D formation.[11]

This study determines whether there is different effect of both the CYP-450 enzyme-inducing AEDs (phenytoin) and the non-CYP-450 enzyme-induced AEDs (valproic acid) on the changes of the serum vitamin D levels. Our study demonstrated that there is no different effect of the CYP-450 enzyme-inducing AEDs (phenytoin) on the changes of the serum vitamin D levels compared to the non-CYP-450 enzyme-induced AEDs (valproic acid).

The results of this study are in line with a previous study of Ningsih et al. the study of Ningsih et al., among 59 subjects aged between 18 to 40 years with epilepsy taking the carbamazepine, phenytoin, phenobarbital, or valproic acid for at least six months revealed that there is a decrease in serum vitamin D levels in these subjects, but the changes in serum vitamin D levels were not related to the type of AEDs.[9]

In contrast, Teagarden et al. demonstrated that among 596 subjects aged 18 to 81 years with epilepsy have different serum vitamin D levels classified by the type of AEDs. Furthermore, this study also revealed that there are other factors that might have influenced the results of the study such as race, body mass index, gender, and season.[12] Unfortunately our study cannot determine these factors.

Our study also did not exclude subjects with polytherapy that might have effects on serum vitamin D levels. In addition, our study also did not assess other factors may affect patient's vitamin D levels, such as diet food, cholesterol levels as a precursor of vitamin D, and outdoor activities that contribute to the biosynthesis of vitamin D. [13,14] through the ultraviolet exposure in order to form the vitamin D. [9]

5. CONCLUSION

To sum up, our study suggests that there is a decrease in serum vitamin D levels among people with epilepsy, but there is no different effect of valproic acid and phyenitoin on the serum vitamin D levels among people with epilepsy.

Ethical Approval

The protocol of this study was approved by the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University, with the ethical clearance certificate number 201/EC/KEPK/FK-UNDIP/VI/2021.

Conflicts of Interest

There is no conflict of interest.

Funding

No specific funding was provided for this article.

Author Contributions

Conceptualization, APM and SJ; methodology, APM, SJ and DN; formal analysis, APM and SJ; investigation, APM and HS; resources, APM, HS, and SJ; data curation, APM, HS, and SJ; writing—original draft preparation, APM, SJ, DN, and APW; writing—review and editing, SJ, DN, and APW; visualization, APM, SJ, DN, and APW; supervision, SJ, DN, and APW; project administration, APM, HS.

Acknowledgments

The authors would like to thank Dr. Putri Rachmawati Dewi from the Department of Pulmonology and Cardiovascular, KRMT Wongsonegoro Hospital Semarang Indonesia for the editing a draft of this manuscript.

References

1. Rugg-Gunn F.J. Stapley H.B, Editors. Epilepsy 2021 From Bench to Bedside: A Practical Guide to Epilepsy: Proceeding of XVI ILAE SPR Teaching Weekend: 2017 September 23-24: University of Exford Mathematical Institute. England: Int Leag Against Epilepsy British Chapter. 2017.
2. Nanau RM, Neuman MG. Adverse Drug Reactions Induced by Valproic Acid. Clinical Biochemistry. 2013. DOI: 10.1016/j.clinbiochem.2013.06.012.
3. T Tunnicliff G. Basis of The Antiseizure

Action of Phenytoin. General Pharmacology. 1996. DOI: 10.1016/S0306-3623(96)00062-6.
4. He X, Jiang P, Zhu W, Xue Y, Li H, Dang R, et al. Effect of Antiepileptic Therapy on Serum 25(OH)D3 and 24,25(OH)2D3 Levels in Epileptic Children. Ann Nutr Metab. 2016;68(2):119–27. DOI: 10.1159/000443535.
5. Gröber U, Kisters K. Influence of Drugs on Vitamin D and Calcium Metabolism. Dermatoendocrinol [Internet]. 2012;4(2):158–66. DOI: 10.4161/derm.2073.
6. Vrzal R, Doricakova A, Novotna A, Bachleda P, Bitman M, Pavek P, et al. Valproic Acid Augments Vitamin D Receptor-mediated Induction of CYP24 by Vitamin D3: A Possible cause of valproic Acid-induced Osteomalacia? Toxicol Lett [Internet]. 2011;200(3):146–53. DOI: 10.1016/j.toxlet.2010.11.008.
7. WHO Expert Consultation. Appropriate Body-mass Index for Asian Populations and Its Implications for Policy and Intervention Strategies. Lancet (London, England). 2004 Jan;363(9403):157–63.
8. Nagarjunakonda S, Amalakanti S, Uppala V, Rajanala L, Athina S. Vitamin D in Epilepsy: Vitamin D Levels in Epilepsy Patients, Patients on Antiepileptic Drug Polytherapy and Drug-resistant Epilepsy Sufferers. Eur J Clin Nutr [Internet]. 2016;70(1):140–2. DOI: 10.1038/ejcn.2015.127.
9. Ningsih SU, Octaviana F, Soertidewi L, Budikayanti A, Prihartono J. Gambaran Kadar Vitamin D pada Penggunaan Obat Antiepilepsi Generasi Pertama. Neurona. 2013;30(4):1–4.
10. El-Hajj Fuleihan G, Dib L, Yamout B, Sawaya R, Mikati MA. Predictors of Bone Density in Ambulatory Patients on Antiepileptic Drugs. *Bone*. 2008 Jul;43(1):149–55. DOI:10.1016/j.bone.2008.03.002.
11. Christakos S, Ajibade D V., Dhawan P, Fechner AJ, Mady LJ. Vitamin D: Metabolism. Endocrinol Metab Clin North Am. 2010;39(2):243–53. DOI: 10.1016/j.ecl.2010.02.002.
12. Teagarden DL, Meador KJ, Loring DW. Low Vitamin D Levels Are Common in Patients with Epilepsy. Epilepsy Res. 2014 Oct;108(8):1352-6. DOI: 10.1016/j.eplepsyres.2014.06.008. Epub 2014 Jul 6. PMID: 25060996; PMCID: PMC4149948.
13. Kurniasih D. Hubungan Defisiensi vitamin D dengan Sindrom Metabolik Pada Anak Obes. 2017;20–7.
14. Filardi S, Guerreiro CAM, Magna LA, Neto JFM. Bone Mineral Density, Vitamin D and Anticonvulsant Therapy. Arq Neuropsiquiatr. 2000;58(3 A):616–20. DOI: 10.1590/s0004-282x2000000400003.