ORIGINAL ARTICLE

Association of Duration of Valproic Acid Treatment and Glycemic Indexes among Adult

Santoso Jaeri[1], Kurnia Kusumastuti[2]

[1] Department of Medical Biology dan Biochemistry, Faculty of Medicine, Universitas Diponegoro, Kota Semarang, Jawa Tengah 50275, Indonesia
[2] Department of Neurology, Faculty of Medicine, Universitas Airlangga, Surabaya, Jawa Timur 60132, Indonesia

ABSTRACT

Introduction: Valproic acid (VA) is one of the commonly used for epilepsy, psychiatric problems, and recurrent migraine medication. Long-term use of VA maybe affects the metabolic processes, resulting in the gain of weight and disturbance of glycemic indexes which play an important role in cardiovascular consequences. Unfortunately, these impacts have not been fully understood. The study investigates the long-term impact of VA on the level of fasting blood sugar, 2-hour after-meal blood sugar and HbA1C among adults. **Methods:** An observational study with the cross-sectional study approach among forty participants (n=21, with less than 1-year medication, and n=19, with the 1 year or more medication) who fulfill the inclusion and exclusion criteria. The level of fasting blood sugar, 2 hours after-meal blood sugar, and HbA1C levels were examined. The two-independent T-test was performed to determine the statistical differences of the level of the fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C from both groups. **Results:** There are no significant differences in most of the demographic and clinical characteristics of participants except for age, and there are no significant differences in the level of fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C among both groups. **Conclusion:** There is no significant impact of long-term VA treatment on the homeostatis of blood sugar among adults measured by the level of fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C.

Keywords: Blood sugar level, Valproic acid, HbA1C, Adverse effects

Corresponding Author:
Santoso Jaeri, M.Si.Med., Neurologist
Email: jw.santoso@gmail.com
Tel: +62-821-33010-495

INTRODUCTION

Valproic acid (VA) is a branched and short-chain fatty acid, extracted from Valeriana officinalis (1, 2). VA is commonly used as an anti-epileptic, prophylaxis of migraine prophylaxis, and anti-bipolar disorder and anxiety agents (3-7). Chronic use of VA is correlated with metabolic disturbances such as an increase of insulin, leptin, insulin resistance, and leptin resistance which lead to gain of weight, dyslipidemia, and other metabolic disturbances (8, 9). Other side effects of VA are varied such as fatigue, sedation, tremor, and gastrointestinal complaints (1, 10).

Diabetes mellitus (DM) has a role in the pathogenesis of atherosclerosis. DM has an important contribution in the pathway of atherosclerosis by elevating permeability of endothelial, lipoprotein clearance from the vessel, inflammation, and foam cell formation (8, 11).

The effect of VA on glycemic indexes still in debate (8). Some pieces of evidence have found that VA affects the model of homeostatic assessment-insulin resistance (HOMA-IR) index that reflected hyperinsulinemia resulted lower fasting blood glucose levels (8, 12, 13), which is valproic acid has the potency for treatment of DM, while other studies failed to demonstrated that effects (8, 13-15). The mechanisms of changes in the glycemic indexes resulted from VA medication are remained unknown. Some evidence suggested that VA increases the level of insulin through several mechanistic hypotheses. For example, VA influences the first-pass metabolisms of insulin in the liver resulting in a high level of insulin in the peripheral tissues. Another hypothesis is that VA stimulates directly pancreatic insulin secretion due to its GABA-ergic ability (16). There is no literature discussing the association of the dose of VA medication and the homeostasis of glucose, despite the fact that there is proof of the effects of VA treatment and weight gain, and other metabolic parameters such as total cholesterol (17). Because of these circumstances, herewith we report the long-term impact of VA treatment on the level of fasting blood sugar, 2-hours after-meal blood sugar, and HbA1C among adults, to get more details of the

potential impact of VA on the management of DM.

MATERIALS AND METHODS

Samples

An observational analytic study with a cross-sectional approach was conducted in an adult who used VA for at least 1 month and visited the outpatient clinic department of Neurology Dr. Soetomo Hospital Surabaya Indonesia period July - October 2018.

The subjects were obtained by consecutive admission sampling method, with inclusion criteria: 18 years of age or more, and willing to take the study, and exclusion criteria: taking phenytoin and or carbamazepine, oral hypoglycemic agents, and have a history of DM before using VA.

A total of 40 subjects who met the inclusion and exclusion criteria was recorded their identities and demographic characteristics, asked for fasting for at least 8 hours for the examination of fasting blood sugar, and HbA1C levels then took a meal. Two hours after a meal, the venous blood was collected to examine the 2-hour postprandial blood sugar levels. We did not screen for impaired fasting glucose and impaired glucose tolerance.

Examination of the Level of Fasting Blood Sugar, 2-hours After-Meal Blood Sugar, and HbA1C

Level of fasting blood sugar and 2-hours after-meal blood sugar were examined in the Clinical Pathology Laboratory Dr. Soetomo Hospital Surabaya Indonesia with the enzymatic GOD-PAP method, and for HbA1C level use Glycated Hemoglobin A1C (HbA1C), ELISA Kit.

Statistic Analysis

Demographic and clinical data including age, sex, weight, height, body mass index (BMI), history of smoking, other drug use, a combination of anti-epileptic drugs, and the dose of VA were classified based on the duration of VA treatment into two groups: 1) less than 1 year, and 2) 1 year or more, then analyzed using SPSS software version 17.0 for Windows.

Categorical scale data such as gender, history of smoking, history of other drug use, and anti-epileptic drug combination were cross-tabulated using the Chi-square test. While for numerical scale data such as weight, height, BMI, and doses of VA were analyzed using a two-independent sample T-test because the data distribution is normal, furthermore, for age, and a dose of VA was analyzed using Mann Whitney U Test because the distribution is not normal.

The statistical difference in the level of fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C was analyzed using the two-independent sample T-test.

Ethical Approval

This study was agreed by the Local Committee of Research Ethics with ethical clearance certificate number 0347/KEPK /VI/2018.

RESULTS

Demographic and clinical characteristics of subjects including age, sex, weight, height, BMI, history of smoking, other medications, a combination of other anti-epileptic drugs, and doses of VA can be seen in Table I.

Table I: Demographic Characteristics of Subject

Variables	Duration of Valproic Acid Treatment		p	OR (95%CI)
	1 year or more (n=19) Mean ± SD, n (%)	Less than 1 year (n=21) Mean ± SD, n (%)		
Gender				
Men	7 (36,8)	10 (47,6)	0,491	0,642 (0,181-2,275)
Women	12 (63,2)	11 (52,4)		
Age (Year old)	34,16 ± 15,89	43,14 ± 13,83	0,041*	
Body weight (Kg)	61,53 ± 12,31	60,95 ± 12,80	0,886	
Body height (cm)	158,89 ± 8,82	160,57 ± 8,72	0,550	
Body mass index (Kg/m^2)	24,33 ± 4,52	23,57 ± 4,23	0,585	
History of other medication				
Yes	2 (10,5)	1 (4,8)	0,596	2,353 (0,196-28,226)
No	17 (89,5)	20 (95,2)		
Smoking				
Yes	1 (5,3)	3 (14,3)	0,607	0,333 (0,032-3,515)
No	18 (94,7)	18 (85,7)		
Anti-epileptic drugs combination				
Yes	2 (10,5)	2 (9,5)	1,000	1,118 (0,142-8,824)
No	17 (89,5)	19 (90,5)		
Daily dosage of vaproic acid (mg/KgBW)	12,28 ± 7,83	12,98 ± 4,11	0,270	

*p < 0,05, OR: Odd ratio, CI: Confidence interval, SD: Standard deviation, Kg: Kilograms, cm: Centimeters, m^2: meter cubic, mg: Milligrams, BW: Body weight

In this study, 40 subjects did not have a history of alcohol use and special diet history. A total of 3 subjects (7.5%) used other drugs: ranitidine, and amlodipine. Ten percent of subjects in this study used other anti-epileptic drugs in the form of clobazam 2 (0.05%), phenobarbital 1 (0.025%), and levetiracetam 1 (0.025%). The level of fasting blood sugar, 2-hours after-meal blood sugar and HbA1C in the first group was 84,47+10,60 mg/dL, 101,71+17.03 mg/dL and 5,47+0,40% respectively and 86,68+8,99 mg/dL. 99,31+16,78mg/dL and 5,21+0,40% for the second group.

The results of the crosstabulation analysis for the association between confounding variables and the duration of VA treatment showed that there was no significant association for gender, weight, height, BMI, history of other medication, diabetes mellitus, smoking, and the dose of VA ($p = 0.491$ for sex, 0.886 for weight, 0,550 for height, 0.585 for BMI, 0.596 for the history of other medication, 0.607 for smoking and 0.270 for the dose of VA used), but a significant association was found between the age and duration of VA treatment ($p = 0.041$).

At present, no study shows a cutoff point of time, related to the association of the duration of VA treatment and glycemic indexes, so we identified its cutoff points using the curve of Receiver Operating Characteristic (ROC). Our results proved that the cutoff points of time of 12 months are the ideal cutoff point (sensitivity of 50%, and specificity of 50%).

Data analysis was then continued to determine the difference of the level of fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C which are classified based on this cutoff point. The result of the analysis is in Table II and it shows that there is no difference in the level of fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C levels between the group which is treated with VA 1 year or less compared with the group which is treated with VA more than 1 year ($p = 0.484$ for fasting blood sugar, 0,657 for 2-hours after-meal blood sugar, and 0,053 for HbA1C).

Table II: The difference of Serum Fasting Blood Sugar, 2-hours Postprandial Blood Sugar, and HbA1C Levels based on Duration of Valproic Acid Treatment

	Duration of Valproic Acid Treatment		p
	1 year or more (n=19) Mean ± SD	Less than 1 year (n=21) Mean ± SD	
Fasting Blood Sugar (mg/dL)	86.68 ± 8.99	84.47 ± 10.60	0.484
2-hours Postprandial Blood Sugar (mg/dL)	99.31 ± 16.78	101.71 ± 17.03	0.657
HbA1C (%)	5.21 ± 0.40	5.47 ± 0.40	0.053

SD: Standard deviation, mg: Milligrams, dL: Deciliters

DISCUSSION

The results of the analysis for the comparison of confounding variables between two groups indicate that there were no significant differences or proportions for variables of sex, weight, height, BMI, history of other medication, smoking, a combination of other antiepileptic drugs, and the dose of VA, but there was a significant difference in the age between two groups of VA treatment.

Recently there is a controversy regarding the effect of VA and glucose metabolisms. Some studies suggest that VA interferes directly with pancreatic beta cells with a consequence of increase in insulin. In contrast, Yedulla et al., demonstrated that 5 hours of exposure to VA alters the pancreatic beta-cell secretion of insulin, stimulated by glucose (8).

No literature discusses the association of the duration and dose of VA medication and the homeostasis of glucose, despite there is proof of the effects of the duration of VA treatment and weight gain. VA increases body weight starting in the third month and reaches its peak after 6 months of use (8). To determine these associations of the duration of VA treatment and the level of fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C in this study, we use the cut-off point of a year obtained from ROC analysis.

At the cut-off point of a year VA treatment, it was found that there was no significant difference in the level of fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C in the group of people who treated with VA for less than 1 year compared to a group of people who treated with VA for 1 year or more.

Our results are contrasted with those of Nisha et al., 2018 that suggests that the fasting blood glucose level is significantly less on the people who use VA more than 1 year compared with newly diagnosed people with epilepsy, (19) Khan et al., 2016 that proved that VA treatment significantly reduced the level of plasma glucose but no effect on HbA1C level (20) and Rakitin et al., 2015 that proved that VA modulates glucose metabolism but no influence on insulin and C-peptide levels in people with epilepsy after first exposure, however, the two these studies do not depict the impact of long term use of VA on homeostatic of glucose metabolism (21).

The difference in the results of this study compared with Nisha et al., 2018 is we use respondents aged 34,16 + 15,89 for a group who treated for 1 year or more and 43,14 + 13,83 for the group who treated for less than 1 year. It differs from Nisha et al. They use people aged 27+7 years old for a patient newly diagnosed with epilepsy and 28+7 years old for a patient who has used

VA more than 1 year and may be due to differences in the study population which can be explained by the influence of genetic factors.

The result of this study depicted that there is no significant difference in the level of fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C between the group which is treated with VA 1 year or less compared with a group which is treated with VA more than 1 year, even though there are several confounding factors might have and influence for these results, such as age and other medication. Previous studies reported that calcium-channel blockers such as amlodipine, benzodiazepine, and levetiracetam have a protective effect on glycemic indexes.

The effects of VA on the homeostatis of glucose metabolism, might be bidirectional. At the first exposure, there is a modulating effect on glucose metabolism, so we can find a decrease in blood glucose level (21). Quan et al. 2018 reported that VA induces the incidence of acute pancreatitis in patients with bipolar disorder who are given VA therapy for 6 days, resulted in insulin hypersecretion with consequences increase of lipogenesis and reduce triglyceride and cholesterol clearance which can ultimately increase the serum total cholesterol levels (22). Further, the VA affects glucose homeostasis by elevating the proliferation and function of beta cells, reducing apoptosis of beta cells via histone deacetylases (HDACs) block. HDAC is crucial for the control of pancreatic islet cell lineage (21). This bidirectional effect suggests that VA has potency as an adjuvant treatment in diabetic patients.

CONCLUSION

In summary, our study depicted that there is no significant impact of long-term VA treatment on the homeostatis of blood sugar among adults measured by the level of fasting blood sugar, 2-hour after-meal blood sugar, and HbA1C. Further, study is needed to determine the pathway of the effect of VA on glucose metabolism, including the genomic effect on glucose metabolism.

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REFERENCES

1. Tomson T, Battino D, Perucca E. Valproic Acid After Five Decades of Use in epilepsy: Time to Reconsider the Indication of Time-honoured Drug. Lancet Neurol. 2015; 15: 1-9.
2. Fan H-C, Lee H-S, Chang K-P. The Impact of Anti-Epileptic Drugs on Growth and Bone Metabolism. Internat Journal of Molecular Sciences. 2016; 17: 1-22.
3. Ghodke-Puranik Y, Thorn CF, Lamba JK. Valproic Acid Pathway: Pharmacokinetics and Pharmacodynamics. Pharmacogenet Genomics. 2013; 23: 236-41.
4. Terbach N, Williams RSB. Structure-function Studies for The Panace, Valproic Acid. Biochemical Society Transaction. 2009; 37: 1126-32.
5. Tseng J-H, Chen C-Y, Chen P-C, Hsiao S-H, Fan C-C, Liang Y-C, Chen C-P. Valproic Acid Inhibits Glioblastoma Multiforme Cell Growth Via Paraoxonase 2 Expression. Oncotarget. 2017; 8(9): 14666-14679.
6. Coppola G, Piccorossi A, Operto FF, Verroti A. Anticonvulsant Drugs for generalized Tonic-Clonic Epilepsy. Expert Opinion on Pharmacotherapy. 2017.
7. Li H, Wang X, Zhou Y. Association of LEPR and ANKK1 Gene Polymorphisms with Weight Gain in Epilepsy Patients Receiving Valproic Acid. Internat Journal of Neuropsychopharmacology. 2015: 1-7.
8. Belcastro V, D'Egidio C, Striano P, Verrotti A. Metabolic, and Endocrine Effects of valproic Acid Chronic Treatment. Epilepsy Research. 2013; 8: 1-23.
9. Abaci A, Saygi M, Yis U, Demir K, Dirik E, Bober E. Metabolic Alterations During valproic Acid Treatment: A Prospective Study. Pediatr Neurol. 2009; 41: 435-9.
10. Chen S, Wu H, Klebe D, Hong Y, Zhang J. Valproic Acid: A New Candidate of Therapeutic Application for the Acute Central Nervous System Injuries. Neurochem Res. 2014.
11. Sakakura K, Nakano M, Otsuka F. Pathophysiology of Atherosclerosis Plaque Progression. Heart, Lung, and Circulation. 2013; 22: 399-411.
12. Plonka-Poltorak E, Zagrodzki P, Kryczyk-Koziol J. Does Valproate Therapy in Epileptic Patients Contribute to Changing Atherosclerosis Risk Factors? The Role of Lipids and Free Fatty Acids. Pharmacological Reports. 2016; 68: 1339-44.
13. Luo X, Zhang M, Deng L, Zhao J. Effects of Valproate on The Carotid Artery Intima-Media Thickness in Epileptics. Indian Journal of Pharmacology. 2015; 47: 45-8.
14. Erdemir A, Cullu N, Yis U. Evaluation of Serum Lipids and Carotid Artery Intima Media Thickness in Epileptic Children Treated with Valproic Acid. Brain & Development. 2009; 31: 713-6.
15. Auley MTM, Mooney KM. Computationally Modelling Lipid Metabolism and Aging: A Mini-review. Computational and Structural Biotechnology Journal. 2015; 13: 38-46.
16. Rakitin A. Does Valproic Acid Have Potential in the Treatment of Diabetes Mellitus? Front Endocrinol

(Lausanne). 2017; 8(147):1-3.
17. Kusumastuti K, Jaeri S. The Effect of Long-term Valproic Acid Treatment in the Level of Total Cholesterol among Adult. Indian J Pharmacol. 2020;52(2):134-137.
18. Yedulla NR, Naik AR, Kokotovich KM, Yu W, Greenberg ML, Jena BP. Valproate Inhibits Glucose-Stimulated Insulin Secretion in Beta Cells. Histochemistry and Cell Biology. 2018; 150: 395-401.
19. Nisha Y, Bobby Z, Wadwekar V. Biochemical Derangements related to Metabolic Syndrome in Epileptic Patients on Treatment with valproic Acid. Seizure: European Journal of Epilepsy. 2018; 60: 57-60.
20. Khan S, Jena G. Valproic Acid Improves Glucose Homeostasis by Increasing Beta-Cell Proliferation, Function, and Reducing its Apoptosis through HDAC Inhibition in Juvenile Diabetic Rat. J Biochem Molecular Toxicology. 2016; 30: 438-46.
21. Rakitin A, Koks S, Haldre S. Valproate Modulates Glucose Metabolism in Patients with Epilepsy After First Exposure. Epilepsia. 2015; 56: e172-e5.
22. Quan W, Shao Q, Zhang H, Liu FH, Zhang XH. Acute Pancreatitis Associated with Valproate Treatment. Chin Med J (Engl). 2018; 131: 1889-90.