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Lipid Profile Between Epileptic Patients With Cyp-450 Enzyme Inducer Versus Cyp-450 Enzyme Inhibitor As A Monotherapy Anti Epileptic Drug: A Comparative Study

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Abstract

Treatment of epilepsy is often a lifetime. Several studies report the effect of anti epileptic drug (AED) to lipid profile. This study aims to assess the differences of lipid profile of epileptic patients receiving CYP-450 enzyme inducer and inhibitor monotherapy AED.

This study was conducted in cross-sectional terms with consecutive sampling, from June-October 2019, at Wahidin Sudirohusodo Regional Hospital, Hasanuddin University Hospital, and private practice. The independent variable were AEDs, consist of phenytoin, phenobarbital, carbamazepine, or valproic acid, while the dependent one was the lipid profile. Thirty-five samples were obtained using CYP-450 enzyme inducer AED, consisted of 11 samples using phenytoin, 11 samples using phenobarbital, 13 samples using carbamazepine, and 16 samples using CYP-450 enzyme inhibitor AED (valproic acid).

The results showed higher level of total cholesterol, Low Density Lipoprotein (LDL), and High Density Lipoprotein (HDL) in the CYP-450 enzyme inducer AED group than the CYP-450 inhibitor one; there was no difference of triglyceride (TG) level, while higher level was shown in the CYP-450 enzyme inducer AED group.

Keywords: anti epileptic drug, CYP-450 enzyme, lipid profile

1. INTRODUCTION

Epilepsy is a disease characterized by clinical seizures due to electrical disruption in the brain, which can be idiopathic or symptomatic. According to the World Health Organization (WHO), more than 50 million people worldwide suffer from epilepsy. The Epilepsy Study Group of the Indonesian Neurological Association conducted a study in 18 hospitals in 15 cities in 2013 for 6 months, found that 2288 epileptic patients consisted of 487 new cases and 1801 old ones. Some developing countries report a peak incidence of epilepsy in young adulthood, the prevalence is higher in the first to second decade age than in old age. [1–3]

Treatment of epilepsy is often a lifetime. Anti epileptic drug (AED) can be divided into two groups in general, namely drugs that affect cytochrome P-450 (CYP-450) such as carbamazepine, phenytoin, primidone, and valproic acid, and those that do not affect CYP-450 such as gabapentin, vigabatrin, levetiracetam, oxcarbazepine, and topiramate. [2,4] Anti epileptic drug which induces enzymes (phenytoin, phenobarbital, carbamazepine, and

primidone) increase the activity of the CYP-450 system, which is involved in the synthesis of serum cholesterol, so it can be increased. On the other hand, valproic acid is the inhibitor one, so it can decrease the serum cholesterol. [5] An increased levels of Total Cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-C), Triglyceride (TG), and decreased levels of High Density Lipoprotein Cholesterol (HDL-C) contribute to cardio-cerebrovascular diseases. [2]

Some epidemiologic studies have demonstrated a positive correlation between epilepsy and comorbidity of vascular diseases; and there are very limited data about the effect of AED to them, at least in South Sulawesi, Indonesia. Therefore, this study is done to see how important is the evaluation of lipid profile in epileptic patients, which is indirectly associated with an increased risk of cardio-cerebrovascular diseases.

2. METHODS

Study design and patients

The cross-sectional study consisted of 51 consecutive epileptic patients, did a regular medical check up at Wahidin Sudirohusodo Hospital, Hasanuddin University Hospital, and private practice, between June-October 2019. The exclusion criterias were patients using drugs that affect CYP-450 enzyme, patients with cardiovascular and cerebrovascular comorbidities. The epileptic patients were classified as patients using CYP-450 inducer, consist of phenytoin, phenobarbital, carbamazepine, and CYP-450 inhibitor, consist of valproic acid. All participants signed a written consent form, and the study procedures were approved by the Human Research Ethics Committee of the Medical Faculty of Hasanuddin University, South Sulawesi, Indonesia.

Measurement of lipid profile

Blood sample was collected from study subjects. Three milliliters (3mL) of venous blood was collected by researcher under sterile conditions using a disposable syringe, after 12 hours fasting, and the sample was sent to Clinical Pathology Laboratory of Hasanuddin University Hospital within 2 hours to check for TC, LDL-C, TG, and HDL-C. Laboratory reports of all study subjects were collected by researcher. Information regarding patients' age, sex, treatment duration, medication history, body height and weight, TC, LDL-C, TG, HDL-C levels were collected.

Statistical analysis

Collected data was entered in Microsoft Office Excel 2007 and analysed using SPSS (version 22) package for Windows. The significant difference of lipid profile between epileptic patients with CYP-450 enzyme inducer versus CYP-450 enzyme inhibitor was assessed using an independent t-test and Mann-Whitney; while the significant difference between each AED was assessed using One-way Anova and Kruskal Wallis test. A p-value <0.05 was considered to indicate statistical significance.

3. RESULTS

There were 51 patients each in phenytoin (n=11), phenobarbital (n=11), carbamazepine (n=13), and valproic acid (n=16) group; the mean age was 29.27, and the mean duration of treatment was 4.22 years.

We observed statistically significant high mean of TC, LDL-C, and HDL-C levels in the group receiving CYP-450 inducer AED when compared with CYP-450 inhibitor AED group; the highest mean of TC and LDL-C was found in the carbamazepine group, and the highest mean of HDL-C was found in the phenytoin group. The mean TC level of phenytoin, phenobarbital, carbamazepine, and valproic acid were 197.45±39.83 mg/dl, 197.45±48.84 mg/dl, 219.00±52.76 mg/dl, and 162.63±44.27 mg/dl respectively (Figure 1). The mean LDL-C level of phenytoin, phenobarbital, carbamazepine, and valproic acid were 125.00±37.54 mg/dl, 116.91±40.11 mg/dl, 147.08±34.75 mg/dl, and 98.54±39.96 mg/dl respectively (Figure 2). The mean HDL-C level of phenytoin, phenobarbital, carbamazepine, and valproic acid were 63.55±10.01 mg/dl, 51.09±11.11 mg/dl, 60.62±19.03 mg/dl, and 45.56±12.99 mg/dl respectively (Figure 3).

We did not observe any statistically significant difference of TG levels in CYP-450 inducer AED group when compared with CYP-450 inhibitor AED group, while higher level is shown in the CYP-450 enzyme inducer AED group (the highest one is in the phenobarbital group). The mean TG levels among patients receiving phenytoin, phenobarbital, carbamazepine, and valproic acid were 92.27±35.89 mg/dl, 148.82±93.24 mg/dl, 126.23±83.85 mg/dl, 90.31±46.04 mg/dl respectively (Figure 4).

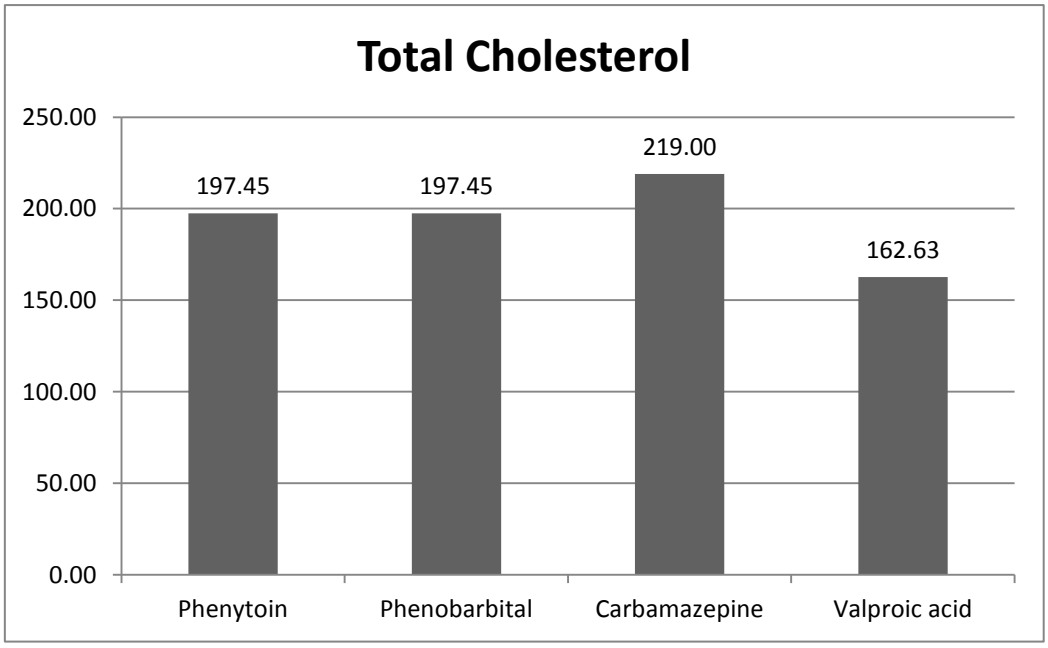

Figure 1. Comparison of mean Total Cholesterol (TC) levels in epileptic patients receiving phenytoin, phenobarbital, carbamazepine, and valproic acid

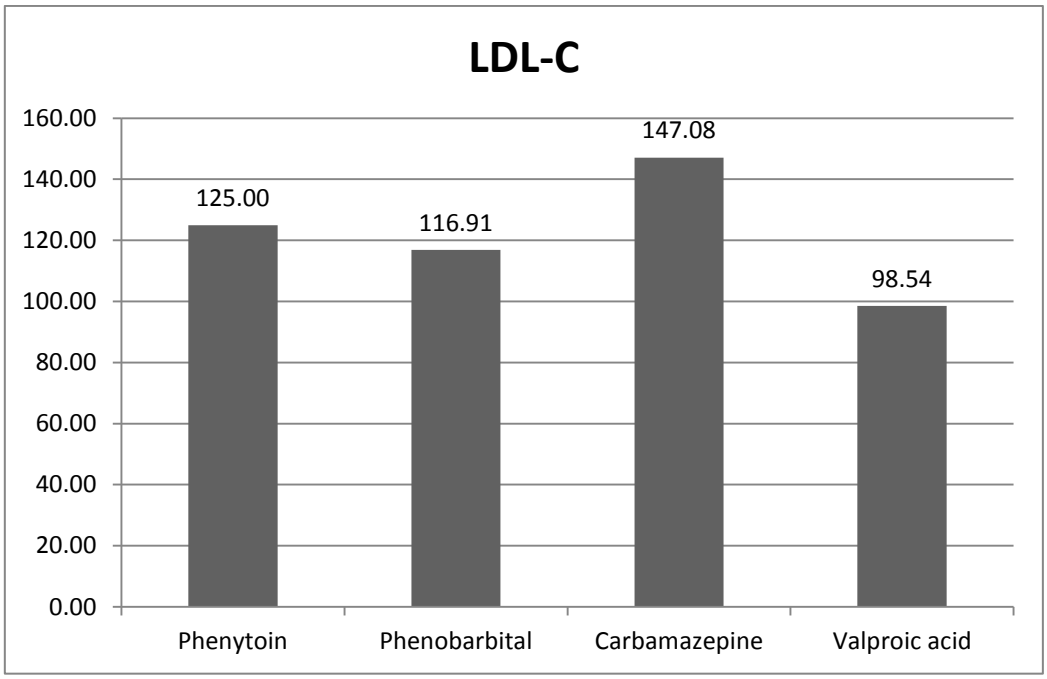

Figure 2. Comparison of mean LDL-C levels in epileptic patients receiving phenytoin, phenobarbital, carbamazepine, and valproic acid

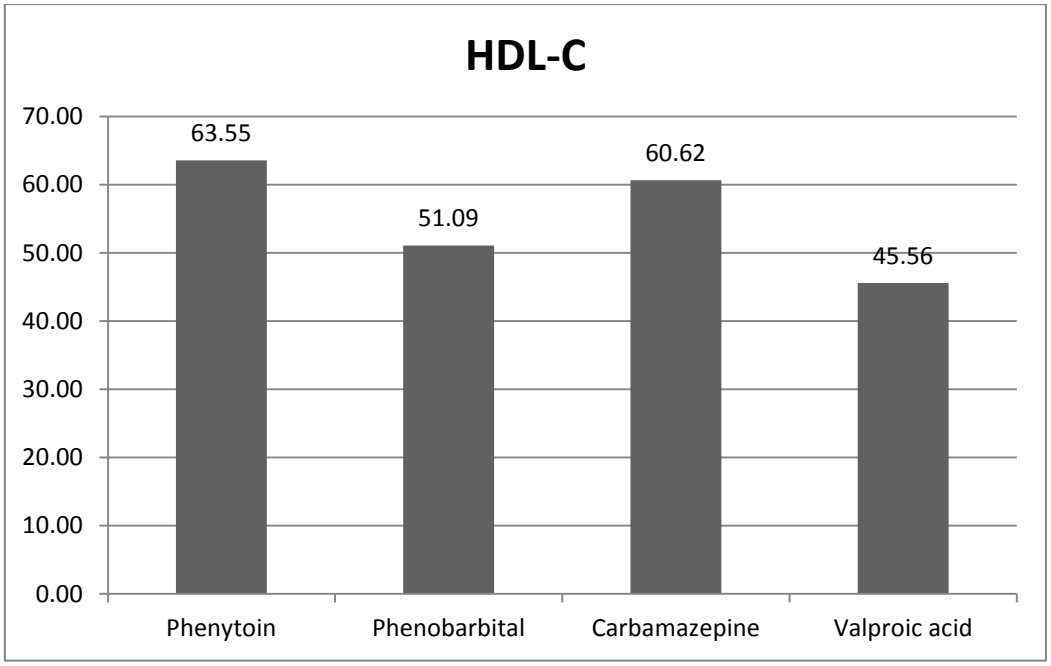

Figure 3. Comparison of mean HDL-C levels in epileptic patients receiving phenytoin, phenobarbital, carbamazepine, and valproic acid

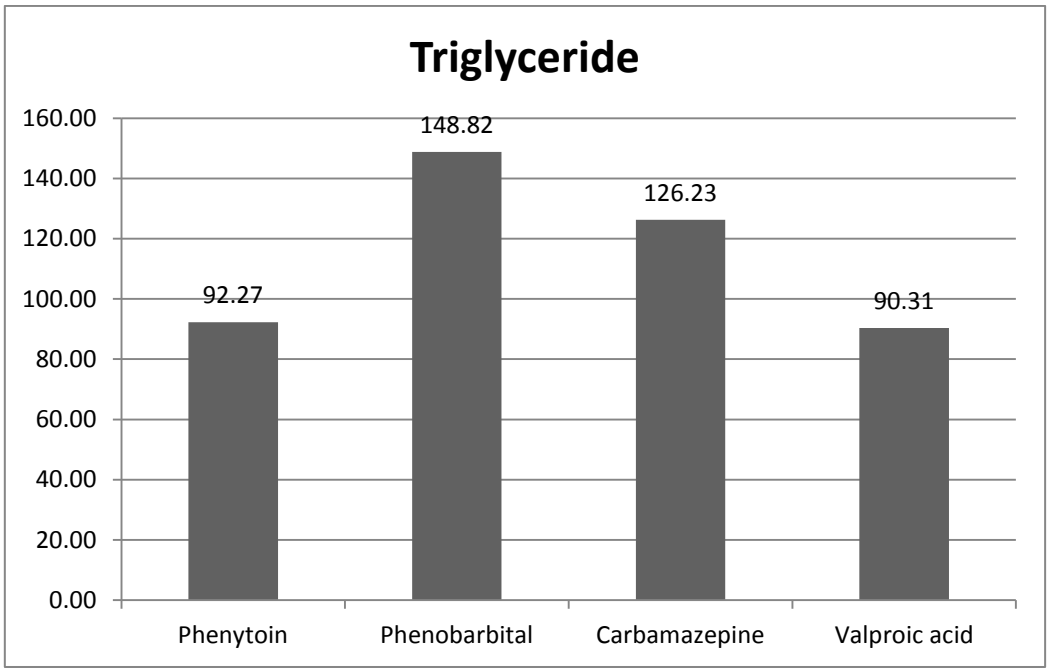

Figure 4. Comparison of mean Triglyceride (TG) levels in epileptic patients receiving phenytoin, phenobarbital, carbamazepine, and valproic acid

4. DISCUSSION

The present study was designed to investigate the differences of lipid profile of epileptic patients receiving CYP-450 enzyme inducer and inhibitor monotherapy AED.

We observed significant increase in mean TC, LDL-C, and HDL-C levels in epileptic patients receiving CYP-450 enzyme inducer AED group compared with CYP-450 inhibitor one. The results in our study findings are similar to other investigation done by Franzoni et al. He reported that there was a significant increase in total cholesterol in CYP-450 enzyme inducer AED group, like carbamazepine, phenobarbital, and phenytoin, while in CYP-450 enzyme inhibitor AED group, total cholesterol level was the same with control group. [6]

Study results conducted by Nikolaos T et al observed higher LDL-C in carbamazepine and phenytoin group. Salehiomran and Hosseini also wrote that total cholesterol and LDL-C had a significant increase after giving phenobarbital in epileptic children. [7,8] A significant increase of HDL in our study was also similar with study conducted by Nadkarni et al, Miller M et al, Nikolaos T, Yamamoto et al, and Salehiomran and Hosseini, mostly showed that HDL-C was significantly increased in epileptic patients giving carbamazepine, phenytoin, and phenobarbital. [7–11]

The differences of lipid profile between AED groups may be due to the difference of biotransformation pathway of these drugs; phenytoin, phenobarbital, and carbamazepine are CYP-450 enzyme inducer, while valproic acid is CYP-450 enzyme inhibitor. [6] Our study also found a highest level of TC and LDL-C in carbamazepine group, then followed by phenytoin and phenobarbital. It may be due to carbamazepine has an auto-induction effect, it can increase its metabolism three times, also it can stimulate the hepatic synthesis of cholesterols, increase the production of bile acids and the intestinal absorption of cholesterol. Several literatures show that phenytoin and phenobarbital are mild inducer, which is

compatible with in vitro studies showing that phenytoin has mild to moderate inductive effects only on the CYP2C subfamily. The literature does not show that phenobarbital causes auto-induction. [2,12]

We did not observe significant increase in mean TG level in epileptic patients receiving CYP-450 enzyme inducer AED group compared with CYP-450 inhibitor one, although we found that CYP-450 enzyme inducer AED group had a higher TG that CYP-450 inhibitor one. The result in our study findings are similar to other investigations done by Sareen et al and Nikolaus T, also reported same findings that there was a higher TG level in carbamazepine, phenytoin, and phenobarbital group but not significant if they were compared with control group. [7,13] It may be due to these AEDs can cause an increase level of TG with different mechanism. Phenytoin, phenobarbital, and carbamazepine increase TG level through hepatic enzyme induction, while valproic acid increase TG level through mechanism of carnitine depletion, so it will decrease fatty acid metabolism and cause free fatty acid accumulation. It may also increase TG level. [5]

Total cholesterol, LDL-C, TG, and HDL-C consistently had the lowest level in valproic acid group, according to its feature as a broad spectrum enzyme inhibitor. Several studies and reviews support that; Manimekala et al reported that epileptic patients receiving valproic acid did not experience significant changes in TC, LDL-C, TG, and HDL-C levels compared with the control group; review from Herink and Ito reported that consuming valproic acid had almost no effect on the lipid profile. [2,14] The results of the study that showed TC, LDL-C, TG, and HDL-C of valproic acid group had the lowest level compared with other CYP-450 enzyme inducer AEDs, which did not mean that valproic acid did not contribute to the atherosclerosis process. Luo et al reported the mean carotid artery intima-media thickness (CA-IMT) in epileptic patients receiving valproic acid was higher than in healthy people. [15,16] The mechanism is unclear. Possible mechanisms are due to insulin resistance and hyperinsulinemia, which cause lipid transport disorder and lipogenesis. [17] Another possible mechanism is valproic acid can interfere with intestinal absorption of the folic acid and modify lipid parameters that explain the relationshop of this drug with metabolic syndrome. [18] Vyas et al reported a systematical review about the use of AED in epileptic patients and its relationship with dyslipidemia, reviewing 31 studies with a total of 4.126 study subjects; carbamazepine, phenytoin, and valproic acid were the most studied AEDs and had an implication to lipid profile changes in epileptic patients. This systematical review stated that there was an increase in TC and LDL-C levels in epileptic patients using all three groups of AEDs; however, carbamazepine and phenytoin were also associated with high HDL-C level. Vyas et al could not specifically identify which AED was worse than the other one. [19]

This study had several limitations. First, this study was conducted with a cross-sectional design so that we cannot monitor lipid profile changes in study subjects. Second, this study did not consider the effect of dose and duration of AED treatment on lipid profile, and no observations were made on the eating patterns of the study subjects before examining the lipid profile.

In conclusion, in the present study, we compared the lipid profile between epileptic patients receiving CYP-450 enzyme inducer anti epileptic drug and CYP-450 enzyme inhibitor one. The results showed higher level of Total Cholesterol, Low Density Lipoprotein Cholesterol, and High Density Lipoprotein Cholesterol in the CYP-450 enzyme inducer AED group like phenytoin, phenobarbital, and carbamazepine than the CYP-450 inhibitor one like valproic acid; there was no difference of Triglyceride level, while higher level was shown in the CYP-450 enzyme inducer AED group.

DISCLOSURE

Declarations of interest: None

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