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Relationship between CYP2C19 polymorphisms and weight gain in epilepsy patients treated with divalproex sodium: does gender matter?

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ABSTRACT

Introduction: Epilepsy is an unprovoked seizure caused by an abnormal paroxysmal neuronal release in the brain. One of epilepsy treatments is anti-epileptic drug divalproex sodium. It is often prescribed to control seizures but it increases body weight. Weight gain may decrease the effectiveness of epilepsy treatment and cause endocrine disorders. CYP2C19 polymorphism may help physicians map patients vulnerable to weight gain due to divalproex sodium. This study aimed to determine the relationship between CYP2C19 polymorphisms and the incidence of weight gain based on gender in epilepsy patients treated with divalproex sodium.
Methods: This cross-sectional study consisted of 17 male and 23 female patients. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to identify CYP2C19 polymorphism which was grouped into: extensive metabolizer, intermediate metabolizer and poor metabolizer. The results were analyzed using Chi-squared test to determine the relationship between CYP2C19 and each variable (gender, age, epilepsy types, valproic acid types, family history of obesity and presence of weight gain) based on of gender.
Results: The results showed that there was no statistically significant association between CYP2C19 polymorphisms and gender-based epilepsy patients groups ($p>0.05$). We found that most of the subjects in this study were women with an increase in body weight by 57.5%. There was no association of CYP2C19 polymorphism with type of divalproex sodium, dose of divalproex sodium, length of treatment, type of epilepsy and family history of obesity.
Conclusion: There is no significant association between CYP2C19 polymorphism and weight gain between genders in epilepsy patients.

Keywords: CYP2C19 polymorphism, epilepsy, divalproex sodium, body weight, gender.
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INTRODUCTION

Epilepsy is a cerebral disease due to abnormal paroxysmal neuronal release in the brain and one of the epilepsy therapies is using antiepileptic/anti-seizure drugs.[1-4] The most commonly prescribed anti-seizure is valproic acid (VPA). Since VPA has been known to cause a serious side effects, it is also available as the combination with sodium valproate to be divalproex sodium.[5,6] Both produce similar treatment results and can be used interchangeably under equivalent dose adjustment.[7] VPA or divalproex sodium has broad indications, besides seizures and epilepsy, such as bipolar psychiatric disorders, schizophrenia, borderline personality disorder, and migraine prophylaxis.[7,8] Despite having a broad spectrum, one of the most widely reported side effects of divalproex sodium is weight gain.[9] Weight gain is also at risk of decreasing patient adherence and discontinuing antiepileptic drugs. Drug-induced weight gain is also responsible for the incidence of endocrine disorders (menstrual disorders, polycystic ovaries, and hyperandrogenism).[8,10,11]

The frequency of weight gain occurrence after consuming divalproex sodium or VPA still varies. Two studies from Italy and Austria reported a significant increase in body weight (≥ 5 kg) occurred in 23.5% of men and 43.6% of women who were treated with VPA.[12,13] Other studies also showed an increase in body weight for 2 kg after 1 month of therapy.[12,14] Weight gain also occurred in 71% of VPA users and 58% in children and adolescents receiving VPA. This weight gain is more common in women than men.[8,15,16] A study in Japan showed that VPA increased serum testosterone levels in epilepsy patients, especially those who were treated with VPA since less than 20-year-old.[9] Testosterone positively correlates with orexigenic ghrelin level, conveying hunger signals to the brain.[17,18]

In clinical practice, not all patients experience weight gain despite taking VPA or divalproex sodium at high doses for a long period of time. This raises the suspicion of the influence of genetic variation on the incidence of weight gain due to VPA. Many studies have identified genes associated with VPA-induced

weight gain and have focused on factors influencing the molecular pathways involved in appetite stimulation and inhibition of food satisfaction.[10] CYP2C19 is one of the predominant enzymes in divalproex sodium metabolism. Three CYP2C19 genotypes were grouped in this study, namely the homozygous wild type/extensive metabolizer (EM) allele of CYP2C19*1/*1, the heterozygous intermediate metabolizer (IM) allele of CYP2C19*1/*2 or CYP2C19*1/*3 and the heterozygous poor metabolizer (PM) allele of CYP2C19*2/*3,

In the group of patients with an increased body weight, 70% had an EM genotype while the PM population was only 5%. However, in the normal or decreased weight group, the EM and PM populations were balanced (50%). In general, the frequency of PM in Asian population is 15-25%.[9] This finding was preceded by a study, by the same researchers, that demonstrated an association between CYP2C19 polymorphisms and weight gain in patients receiving VPA. It was concluded that in women receiving VPA, body mass index (p=0.002) and weight gain (p=0.032) were higher in patients with heterozygous EM and PM CYP2C19 polymorphisms than in homozygous EM. But, in the follow-up study, the higher BMI and weight gain were found in heterozygous EM.[9] Different results were also shown by a recent study that the risk of weight gain was three times higher in CYP2C19*1/*2 and CYP2C19*2/*2 than in CYP2C19*1/*1 of 108 VPA-treated epilepsy patients.[19]

The high incidence of weight gain after divalproex sodium or VPA treatment in female patients compared to male patients raises the suspicion of a different role of sex hormones in CYP2C19 gene polymorphisms and body weight by sex. Another study found an association of CYP2C19 polymorphisms with divalproex sodium, increased appetite and testosterone metabolism.[20] The differences in population, genotype, study methods and other factors might affect the study results obtained. This study was conducted to determine the relationship between CYP2C19 gene polymorphisms and weight gain associated with sex, based on divalproex sodium types, daily dosage, length of treatment, epilepsy types, family history of obesity, testosterone level and estrogen level.

METHODS

Study design and sample collection

This analytical cross-sectional study consisted of two sample groups and was compared simultaneously. The patients had been treated with divalproex sodium and divalproex sodium extended-release (ER) monotherapy at Airlangga University Hospital for 6 months. The subjects of this study were epilepsy patients who received valproic acid. They were selected using purposive consecutive sampling method based on inclusion and exclusion criteria. The inclusion criteria were 18-50 years old, with no history of impaired liver or kidney function, willing to participate and follow all study procedures. Specifically for the female patients, they had had regular menstrual cycles. The exclusion criteria were pregnant patients, who had a history of weight gain >2.5 kg in six months before being treated with divalproex sodium and divalproex sodium ER, used hormonal contraception, corticosteroid, or herbal medicine, and followed a weight gain or loss program. From the calculation of the sample size for two populations, the total sample size was 40 patients.

PCR-RFLP test

The materials for DNA isolation consisted of lysis buffer for cell membranes (CMLB), lysis buffer for nuclear membranes (NMLB), Tris-EDTA (TE) buffer (10 mM Tris HCl pH 7.4 and 0.1 mM Na2EDTA) and Tris-borate-EDTA (TBE) buffer 5x (54 g Trisbase, 27.5 g boric acid, 20 mL 0.5 M Na2EDTA pH 8). Primers used for polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) test was shown in Table 1.

Genotyping

The DNA was isolated from 3 ml EDTA-anticoagulated blood using an automatic gene extractor. CYP2C19 was genotyped using real-time PCR. Four reaction solutions were added to each sample according to the instruction. The internal reference probe was added to control the quality of the reaction. Each experiment was performed using a positive and a blank control. The PCR reaction consisted of a 30-minute hold at 37°C, a 15-minute hold at 95°C, followed by 30 cycles of 30 s at 95°C, 30 s at 56°C and 45 s at 65°C. The samples were amplified with GeneAmp PCR system 2400. When the amplification curve was obtained, the samples were analyzed using the cycle threshold value (CT-value). MyTaq HS Red Mix reagent, PCR Grade Water and primer were prepared at room temperature to amplify the genomic DNA. The remainder of the extracted DNA was stored at 2–8°C for 24 hours or -70°C for a longer period of storage. The CYP2C19 genotypes were identified with gel electrophoresis device and gel documentation XR. The results were categorized into three groups: patients with at least two *2 or *3 alleles (*2/*2, *2/*3, or *3/*3) as poor metabolizers (PM), those with one *2 or *3 allele (*1/*2 or *1/*3) as intermediate metabolizers (IM) and those without a *2 or *3 alleles (*1/*1) were classified as extensive metabolizers (EM).

Estrogen level examination

Blood sample was taken before 10 a.m. and processed to be separated from serum. It was stored at room temperature (20–25 °C). The blood containing precipitation was centrifuged at 10,000g for less than 2 hours to avoid evaporation. Before inserting the estradiol kit reagent into the apparatus of Electrochemiluminescence Immunoassay (ECLIA), the sample was inverted 30 times and gently shaken to suspend the blood sample. The complete suspension was confirmed visually, followed by the kit reagent removal. The sample was then stored at 2–9°C.

Free testosterone examination

The level of testosterone was analysed using enzyme immunoassay analysis (EIA). Blood sample was taken before 10 a.m. A total of 4–5 mL of each serum-free blood sample was stored in a centrifuge tube at 4°C for 24 hours or less than -10°C if it is analysed for more than 24 hours. Each calibrator, control, and specimen was pipetted 25 µL into the labelled wells. A total of 100 µL of conjugate working solution were added into each well and shaken for 10 seconds. The plate was incubated at 37°C for one hour. The wells

were washed three times with 350 µL of diluted wash buffer in each well and dried carefully with absorbent paper. As much as 150 µL of 3,3',5,5'-tetramethylbenzidine (TMB) substrate were pipetted into each well. The plate was incubated at 37°C for 10-15 minutes and pipetted 50 µL stopping solution into each well. The results were read in a microwell plate reader at 450 nm within 20 minutes.

Statistical analysis

The association between the CYP2C19 genotypes and patients based on divalproex sodium type, dosage, duration of therapy, epilepsy types, family history of obesity, free testosterone, estrogen level were analysed using Chi-squared test. The results were considered significant at $p<0.05$. All analyses were conducted using SPSS software (NY, USA).

RESULTS

There were 40 epilepsy patients included in this study. They were divided into two groups, patients with increased bodyweight and no increase in bodyweight group (Table 2).

The distribution of all three polymorphism groups were 60% (n=24) as EM, 37.5% (n=15) as IM and 2.5% (n=1) as PM. In male patients, the EM group was 11 (27.5%) and the IM group was 6 (15%). The EM group was 13 (32.5%) and the IM group was 9 (22.5%) in female patients. The IM and PM groups were mostly found in female group (Table 3).

The relationship analysis between CYP2C19 polymorphisms and sample variables (divalproex sodium types, dosage, length of treatment, epilepsy types, family history of obesity, free testosterone and estrogen level) is presented in Table 4. We found no significant relationship in CYP2C19 polymorphisms towards both of patients groups, in terms of divalproex sodium type (male vs. female, p=0.162 vs p=0.414), length of treatment (male vs. female, p=1.000 vs p=0.478) and family history of obesity (male vs. female, p=0.640 vs p=1.000).

Table 1. Primers used in PCR-RFLP test.

Genes	Primer	Sequence
CYP2C19*2	Forward	5'-CAGAGCTTGGCATATTGTATC
	Reverse	5'-GTAAACACAAAACTAGTCAATG
CYP2C10*3	Forward	5'AAATTGTTTCCAATCATTTAGCT
	Reverse	5'-ACTTCAGGGCTTGGTCAATA

Table 2. Demographic characteristics of the included patients.

Demographic characteristics	Total (n)	Percentage (%)
Gender		
Male	17	42.5
Female	23	57.5
Age (years)		
18-20 (inclusion criteria >18)	9	22.5
21-30	6	15.0
31-40	6	15.0
41-50	18	45.0
51-60	1	2.5
Epilepsy type		
General	19	47.5
Focal	20	50.0
Absence	1	2.5
Divalproex sodium type		
Divalproex sodium	20	50.0
Divalproex sodium ER (extended release)	20	50.0
Family history of obesity		
Yes	28	70.0
No	12	30.0
Weight gain		
Yes	20	50.0
No	20	50.0

Table 3. Distribution of CYP2C19 polymorphisms based on gender of the patients.

Gender	CYP2C19 polymorphism		
	*1/*1 (EM)	*1/*2 and *1/*3 (IM)	*2/*3 (PM)
Male	11 (27.5%)	6 (15%)	0 (0%)
Female	13 (32.5%)	9 (22.5%)	1 (2.5%)
Total	24 (60%)	15 (37.5%)	1 (2.5%)

DISCUSSION

There were 40 patients included in this study. Based on Table 2, the patients were mostly female (57.5%) with the age ranging between 41 and 50 years (45%). They were almost equally distributed to generalized epilepsy (47.5%) and focal epilepsy (50%). During divalproex sodium therapy, women with generalized epilepsy are vulnerable to anovulatory cycles, polycystic ovaries and obesity.[21] A significant rise of testosterone level is especially noticeable in women who begin treatment at less than 20 years, suggesting that young female epilepsy patients are at higher risk to the effects of divalproex sodium.[22]

Based on observations and interviews, 70% of the patients had a family history of obesity. It may cause other family members to be more likely to be obese and gain weight due to divalproex sodium consumption.[23,24] this study suggested no significant relationship between family history of obesity and the CYP2C19 in causing increased body weight of divalproex sodium-treated patients.

Reproductive hormones, like testosterone and estrogen, are important modulators of energy balance and food intake.[25] CYP2C19 has been linked to the metabolism of estrogen and testosterone. CYP2C19 is able to catalyze the oxidative catalysis of testosterone to produce 2b-, 6b-, 15b-, and 16b-hydroxytestosterone.[26]

Table 4. Relationship of CYP2C19 polymorphism and clinical parameters in epilepsy patients based on gender.

Parameter	Male				Female			
	EM (%)	IM (%)	PM (%)	*p*-value	EM (%)	IM (%)	PM (%)	*p*-value
Divalproex sodium type				0.162				0.414
Divalproex sodium ER	8 (80.0)	2 (20)	0 (0)		4 (40)	6 (60)	0 (0)	
Divalproex sodium	3 (42.9)	4 (57)	0 (0)		8 (60)	4 (33)	1 (7)	
Dosage (mg per day)				0.102				0.590
750–1500	5 (100)	0 (0)	0 (0)		1 (33.3)	1 (33.3)	1 (33.3)	
<750	(50)	6 (50)	0 (0)		11 (55)	9 (45)	0 (0)	
Length of treatment (month)	11 (64.7)	6 (35.3)	0 (0)	1.000	12 (52)	10 (43)	1 (3)	0.478
Epilepsy types								0.414
General	6 (75)	2 (25)	0 (0)	0.620	7 (64)	3 (27)	1 (9)	
Focal/Absence	5 (55.6)	4 (44.4)	0 (0)	0.620	5 (42)	7 (58)	0 (0)	
Family history of obesity				0.640				1.000
No	4 (57)	3 (42.9)	0 (0)		3 (60)	1 (20)	1 (20)	
Yes	7 (70)	3 (30)	0 (0)		9 (50)	9 (50)	0 (0)	
Free testosterone				0.644				1.000
Normal	7 (70)	3 (30)	0 (0)		11 (52)	9 (43)	1 (5)	
Increase	1 (100)	0 (0)	0 (0)		1 (100)	0 (0)	0 (0)	
Decrease	4 (66.1)	2 (33.9)	0 (0)		0 (0)	1 (100)	0 (0)	
Estrogen level				0.515				0.090
Normal	8 (57.1)	6 (42.9)	0 (0)		12 (6)	7 (35)	1 (5)	
Increase	2 (66.7)	1 (33.3)	0 (0)		0 (0)	2 (100)	0 (0)	
Decrease	0 (0)	0 (0)	0 (0)		0 (0)	1 (100)	0 (0)	

A high level of testosterone in women may cause insulin resistance and abdominal fat accumulation.[26] In men, the situation appears to be exactly the contrary, with more abdominal fat is associated with lower testosterone levels.[26] Estrogen may stimulate appetite and consequently cause weight gain. According to another study, CYP2C19 heterozygous EM and PM is associated with the increased level of testosterone and estrogen that induce weight gain, primarily on female epilepsy patients treated with divalproex sodium, though the actual mechanism remains unclear.[9] In this study, the three CYP2C19 genotypes were mostly distributed in female patients, where EM group was 13 (32.5%), IM group was 9 (22.5%) and PM group was 1 patient (2.5%) (Table 3). However, we found no significant relationship between the reproductive hormones (testosterone and estrogen) and CYP2C19 polymorphisms in inducing weight gain of divalproex sodium-treated patients, whether male or female.

Divalproex sodium inhibits the CYP2C19 to bind with a substrate which is needed to catalyze the conversion of androgens to estrogens. The inhibition of divalproex sodium works by binding to the enzyme's active site. Consequently, when the enzyme binds to a substrate (e.g., testosterone), the enzyme becomes inactive and the androgen conversion is disrupted.[27] In those with IM and PM polymorphisms, the divalproex sodium will cause a lower testosterone catalysis and increase the testosterone level. The excessive testosterone level may cause a rise of appetite and body weight.[26,28]

The average dose of divalproex sodium (mg/day) and the gender of the patients was not significantly associated. There is also no relationship between dose of divalproex sodium (mg/day) and CYP2C19 polymorphisms (Table 4). This result is different from a study in Japan that found a significant association between CYP2C19 cytochrome polymorphisms and weight gain, also a higher incidence of overweight was higher in women who lost one or two CYP2C19 alleles ($p<0.05$).[9]

Based on this study, there was no significant relationship between the CYP2C19 polymorphisms and gender-based bodyweight in epilepsy patients treated with divalproex sodium. This is similar to a previous finding that there was no significant relationship between gender of the patients and valproic acid in inducing weight gain ($p>0.05$).[9]

CONCLUSION

Our data suggest no association between CYP2C19 polymorphism and weight gain, in divalproex sodium-treated epilepsy patients. The result is not differed whether on male or female patients.

ETHICAL APPROVAL

The study protocol was approved by the ethical committee of Faculty of Medicine, Universitas Airlangga, Indonesia (No. 128/EC/KEPK/FKUA/2021).

COMPETING INTERESTS

The authors declare no conflict of interest.

GRANT INFORMATION

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AUTHOR CONTRIBUTION

All author had contributed in manuscript writing and agreed for the final version of the manuscript for publication.

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