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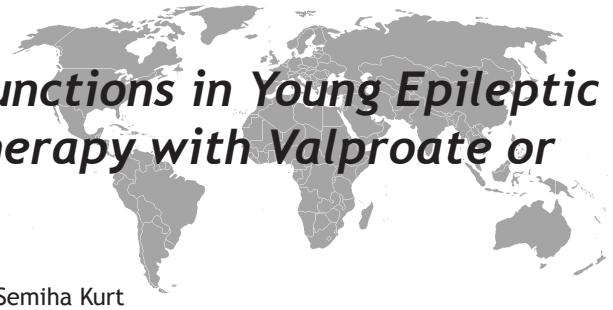

Serum Lipids and Thyroid Functions in Young Epileptic Patients Undergoing Monotherapy with Valproate or Levetiracetam

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ABSTRACT

The negative side effects of classic antiepileptics, such as Valproate (VPA), often cause patients to discontinue their use. While the negative effects of VPA on lipid profile and thyroid functions have been well published, data regarding the side effects of new antiepileptics, such as levetiracetam (LEV), are not as conclusive. In this study, we investigated the effects of a well-known antiepileptic, VPA, and a new antiepileptic, LEV, on serum lipid levels and thyroid functions in young epileptic patients. Our study included 79 epileptic patients aged between 18-40 years who were undergoing VPA (n=42) or LEV (n=37) monotherapy for at least two years and 58 healthy subjects. Patients with hypertension, diabetes mellitus, thyroid dysfunction, smoking or alcohol addiction, and those who were being treated with any other drugs were excluded from the study. Fasting total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels were measured for each patient and thyroid function tests were performed. The three groups were compared in terms of these aforementioned parameters. There were no statistical differences in the total cholesterol, LDL-cholesterol, HDL-cholesterol and free-T3 levels between the three groups. The triglyceride levels of the VPA group were significantly higher than those of the LEV and control groups (p=0.0001). While the free-T4 levels of the VPA group were significantly lower than those of the LEV and control groups (p=0.020), TSH levels were higher. The free-T4 and TSH levels did not differ significantly between the LEV and control groups. This study revealed that while the long term use of VPA negatively affected serum triglyceride levels and thyroid functions, LEV did not have any negative effects on these parameters.

Key words: *Antiepileptic treatment, valproate, levetiracetam, triglycerides, thyroid function tests*

Valproat ve Levetirasetam Monoterapisi alan Genç Epileptik Hastaların Serum Lipitleri ve Tiroit Fonksiyonları

ÖZET

Valproat (VPA) gibi klasik antiepileptikler, kimi zaman ilaç değiştirmeyi gerektirecek yan etki profiline sahiplerdir. VPA' nın lipit profili ve tiroit fonksiyonları üzerine olumsuz etkileri iyi araştırılmıştır, levetirasetam (LEV) gibi yeni antiepileptiklerin etkileri ile ilgili çelişkili yayınlar vardır. Bu çalışmada VPA gibi iyi bilinen bir antiepileptikle yeni kuşak antiepileptiklerden LEV' in serum lipit profili ve tiroit fonksiyon testleri üzerine olan etkilerini genç hastalar üzerinde araştırdık. En az iki yıldır VPA (n=42) veya LEV (n=37) monoterapisi alan, 18-40 yaşlar arasında 79 epileptik hasta ve 58 sağlıklı birey çalışmaya alındı. Hipertansiyon, diyabet, tiroit fonksiyon bozukluğu olanlar, başka bir ilaç alan, sigara, alkol kullananlar çalışmaya dahil edilmediler. Hastaların açlık total-kolesterol, LDL-kolesterol, HDL-kolesterol, trigliserit düzeyleri ve tiroit fonksiyon testleri ölçüldü. Gruplar tanımlanan parametreler açısından karşılaştırıldılar. VPA, LEV ve kontrol grupları arasında total-kolesterol, LDL-kolesterol, HDL-kolesterol, serbest-T3 değerleri açısından anlamlı bir fark olmamasına rağmen, trigliserit, tiroit-stimulan hormon (TSH) ve serbest-T4 değerleri açısından anlamlı fark vardı. VPA grubunun trigliserit düzeyleri LEV grubundan ve kontrol grubundan (p=0.0001) anlamlı şekilde yüksekti, LEV grubu ile kontrol grubu arasında anlamlı fark yoktu. VPA grubunun serbest-T4 değerleri LEV grubundan ve kontrol grubundan (p=0.020) anlamlı şekilde düşük, TSH değerleri ise anlamlı şekilde yüksekti. LEV ve kontrol grubu arasında serbest-T4 ve TSH açısından anlamlı fark saptanmadı. Bu çalışmada uzun dönem kullanımda VPA' nın serum trigliserit düzeyleri tiroit fonksiyonları açısından olumsuz etkisi gözlenmiş, LEV' in ise bu parametrelere olumsuz etkisinin olmadığı sonucuna ulaşılmıştır.

Anahtar Kelimeler: *Antiepileptik tedavi, valproat, levetirasetam, trigliserit, tiroit fonksiyon testleri*

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INTRODUCTION

Classic antiepileptic drugs (AEDs) such as carbamazepine, phenytoin, valproate (VPA) and phenobarbital have serious side effect profiles that may require their discontinuation (1). Carbamazepine, phenytoin, and phenobarbital have been implicated in the acceleration of atherosclerosis. They are potent inducers of the hepatic cytochrome P450 (CYP) system, which is extensively involved in the synthesis and metabolism of cholesterols (2-4). It has also been reported that VPA increases serum lipid levels. Obesity or metabolic syndromes caused by VPA have been reported to have possible effects on serum lipid levels (3,5). It has been proven that serum lipid levels are related with atherosclerosis and cardiovascular diseases. While the effects of classic antiepileptics on thyroid functions have been well established, there are few studies regarding the effects of new generation antiepileptics.

We have limited information on side effects of new epileptics, which were developed for good seizure control with minimal side effects. VPA (an old generation AED) and Levetiracetam (LEV) (a new generation AED) are used either separately or together in daily clinical practice. Therefore, the aim of this study was to investigate the effects of VPA and LEV on serum lipid levels and thyroid functions in young epileptic patients.

MATERIALS AND METHODS

Seventy-nine patients suffering from epilepsy with focal onset with or without secondarily generalized epilepsy who was living in Tokat city or neighboring provinces, aged between 18 and 40 years were included in our study. All of these patients were taking either VPA or LEV monotherapy for at least two years, and all of them were suitable in terms of age, body mass index (BMI), sex and duration of drug use. Patients with hypertension, diabetes mellitus, thyroid dysfunction, chronic renal and/or hepatic disease, smoking and/or alcohol addiction were excluded from the study, as were those who were on another drug therapy, those who experienced a seizure in the last week, those who were using drugs other than antiepileptics, and those who were using a combination of antiepileptics. All patients had regular follow-ups for up to 6 months for neurological examinations. Fifty-eight voluntary healthy subjects who were currently working in our hospital at the time were chosen for the control group. All control group participants were not on another kind of drug treatment and had the same inclusion criteria in terms of age and gender. Laboratory controls were performed in the morning after a 10-h overnight fasting period. Routine blood count, fasting total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride levels, free-triiodothyronine (f-T3), free-thyroxine (f-T4), and thyroid stimulating hormone (TSH) levels were measured for all of the participants. All three groups were compared in terms of these described parameters. The local ethics committees approved this study, and all participants gave written informed consent.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables. The analysis of variance (ANOVA) and Tukey test (a post hoc test) were used to compare continuous variables in terms of TC, LDL-C, HDL-C, triglyceride, fT3, fT4 and TSH levels in the three groups. A two independent samples t test was used to compare drug use periods and mean duration of epilepsy between the VPA and LEV groups. Continuous variables were described as means ± Standard deviation (SD). P values under 0.05 indicated a statistically significant difference. All analyses were performed using a statistics software program (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY).

RESULTS

There were no statistically significant differences between the VPA, LEV and control (n:58, 31 males, 27 females) groups in terms of age or gender. The mean drug use period in the VPA group was 4.2±2.9 years and was 3.8±0.8 years in the LEV group. All trough serum levels of VPA were within normal range in VPA group. Basic clinical characteristics in VPA and LEV groups were as show in Table 1. There were no statistically significant differences between the three groups in terms of mean LDL-C, HDL-C, total cholesterol and fT3 levels (Table 2), although triglyceride, TSH and fT4 levels differed significantly between groups (Table 2). According to the analyses performed with the Tukey test, the triglyceride levels of the VPA group were significantly higher than those of both the LEV (p=0.003) and control (p=0.0001) groups. There was no statistically significant difference between the triglyceride levels of the LEV group and the control group (p□0.05). According to the results of an ANOVA, fT4

***Table 1**. Basic clinical characteristics in valproate and levetiracetam groups.*

	Valproate Group	*Levetiracetam Group*	*P value*
Age (years)	*29,82±9,92*	*27.21±8.45*	*0.49*
Sex			
Female N (%)	*23 (54.7)*	*19 (51.4)*	*0.76*
Male N (%)	*19 (45.3)*	*18 (48.6)*	
Mean duration of epilepsy (year)	*4.8±3.6*	*4.6±6.5*	*0.84*
Time on medication (year)	*4.2±2.9*	*3.8±0.8*	*0.12*
Daily drug dose (mg/day)	*1033.32±325.50*	*1562.50±442.53*	*-*
Serum VPA concentration(µg/ml)	*82.6±11.25*	*-*	*-*

and TSH levels differed significantly between groups, and in the VPA group mean fT4 levels were significantly lower than both the LEV (p¤0.027) and control (p=0.020) groups. TSH levels were significantly higher in the VPA group than in the other two groups (for LEV group p¤0.012 and for control group p¤0.0001) (Table 2). The fT4 and TSH levels did not differ significantly between the LEV and control groups.

***Table 2**. Comparison of the mean age, plasma lipid profile and thyroid function tests in VPA, LEV and control groups (ANOVA test was used for comparisons of groups)*

	Group	*Mean*	*Std. Deviation*	*f*	*p value*
Age (year)					
	Valproate	*29.82*	*9.92*	*0.684*	*0.50*
	Levetiracetam	*27.21*	*8.45*		
	Control	*29.06*	*4.03*		
Triglycerides (mg/dl)					
	Valproate	*162.02*	*76.52*	*9.86*	*0.0001*
	Levetiracetam				
	Control	*109.31*	*107.86*	*73.12*	*27.58*
Total- cholesterol (mg/dl)					
	Valproate	*160.60*	*40.38*	*1.17*	*0.32*
	Levetiracetam	*162.37*	*52.06*		
	Control	*156.61*	*37.67*		
LDL- cholesterol (mg/dl)					
	Valproat	*113.90*	*44.14*	*0.76*	*0.46*
	Levetiracetam	*113.61*	*48.00*		
	Control	*104.73*	*28.86*		
HDL- cholesterol (mg/dl)					
	Valproate	*52.40*	*9.39*	*0.82*	*0.44*
	Levetiracetam	*59.01*	*3.60*		
	Control	*55.41*	*6.82*		
fT3 (picogram/ml)					
	Valproate	*3.26*	*0.85*	*0.67*	*0.87*
	Levetiracetam	*3.16*	*0.77*		
	Control	*3.21*	*0.63*		
fT4 (picogram/ml)					
	Valproat	*1.09*	*0.14*	*4.90*	*0.010*
	Levetirasetam	*1.24*	*0.22*		
	Control	*1.22*	*0.19*		
TSH (uIU/ml)					
	Valproate	*2.78*	*1.29*	*9.09*	*0.0001*
	Levetiracetam	*1.83*	*1.19*		
	Control	*1.67*	*1.04*		

DISCUSSION

Thus far, it has been shown that classical enzyme-inducing antiepileptics such as carbamazepine, phenobarbital, phenytoin and primidone increase serum triglyceride, total cholesterol and LDL-C levels (6-9).
Epidemiological, clinical and experimental studies have shown that serum lipids and lipoproteins are associated with atherogenesis (10,11). Increased atherosclerotic risks may account for the higher mortality and morbidity arising from cerebrovascular disease or atherosclerosis-related heart disease in patients with epilepsy who are undergoing prolonged AED therapy (1,4,12,13,14). It has been reported that serum triglyceride levels, along with the other atherosclerotic risk factors, increase in children who use VPA treatment for more than two years (15). A study conducted on a patient population suffering from bipolar disorder identified that serum triglyceride levels were higher and HDL levels were lower in patients using additional VPA treatment compared to those who were not (16). Another study demonstrated that serum triglyceride levels increased, while HDL-C levels decreased, in patients who were on VPA monotherapy compared to those who were not. Moreover, the same study also revealed that TSH levels increased in the VPA group, and this was attributed to the GABAergic activity of VPA affecting TSH secretion (17).

In our study, while serum total cholesterol, LDL-C and HDL-C levels did not differ significantly between groups, serum triglyceride levels were higher in the VPA group when compared to the control and LEV groups (p¤0001). It has been reported that VPA has either limited effects (18) or does not have negative effects (19,20,21,22) on serum lipid levels. Another study, which was conducted on new and old antiepileptic drugs, revealed that VPA caused an increase in homocysteine and some oxidative stress markers (1). Weight gain triggered by VPA was related with insulin resistance and metabolic syndrome, which was hypothesized to be a possible reason for the subsequent development of dyslipidemia (3,7,23,24,25). Give the relationship between hypothyroidism and dyslipidemia, and taking into account insulin resistance, thyroid dysfunction observed in our VPA group may associated with hypertriglyceridemia (26-28). A study conducted using the data of thousands of patients showed that risk of hypothyroidism significantly increased when VPA was used in combination with some other classic antiepileptics. This was attributed to the inhibition of histone deacetylase by VPA, which eventually suppressed hormone secretion (29). A recent study conducted by Yılmaz et al. demonstrated that TSH levels increased in children in the first month of treatment with VPA. However, fT4 and TSH levels did not change in the same patient population receiving LEV treatment (30). Another study conducted on children and adolescent epileptic patients receiving VPA treatment indicated that subclinical hypothyroidism developed more often in the treatment arm when compared to the control arm (31). Consistent with these results, we did not observe LEV to have any effects on thyroid functions.

According to our study, the long term use of LEV did not cause any significant effects on serum lipid levels and thyroid function tests, and therefore, it appears that LEV has more advantages than does VPA. However, Kim et al. conducted a study including 40 patients and showed that LDL-C levels significantly increased in patients receiving LEV treatment. LEV did not significantly affect total cholesterol, triglyceride, HDL-C, and vitamin B12 levels in the same study (14). In contrast, another study showed that switching patients with high lipid levels who were taking carbamazepine or phenytoin to LEV treatment significantly decreased their total cholesterol, LDL-C and triglyceride levels along with other vascular risk markers (6). In this study, we evaluated a young patient population who was using epileptic treatment for not so long period of time (mean 3 years) and who did not have additional metabolic disorders brought by aging. Consistent with previous studies, LEV seemed to have more advantages in terms of metabolic effects. Antiepileptic drug use is a long process that often begins in childhood and continues for years. Along with studies of drugs like VPA, which have well known side effects, further studies conducted to study the effects of new generation antiepileptic drugs, such as LEV, on metabolic balance with a larger number of patients are required to further this field.

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