

Development of Insulin Resistance in Patients with Epilepsy During Valproate and Carbamazepine Monotherapy



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Epilepsi Hastalarında Valproat ve Karbamazepin Tedavisi Sırasında İnsülin Direnci Gelişimi

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Summary

Objectives: This study investigated the development of insulin resistance (IR) secondary to the use of valproic acid (VPA) and carbamazepine (CBZ), which are highly effective and frequently used antiepileptic drugs.

Methods: This cross-sectional prospective cohort study included 111 participants aged 15 to 64 years. Patients diagnosed with epilepsy were divided into 2 groups: those using VPA (n=45) and those using CBZ (n=35). Those groups were compared to healthy control group (n=31). Preprandial blood glucose, insulin, C-peptide levels were examined, and IR was calculated. Anthropometric measurements were taken.

Results: A significant relationship was identified between VPA or CBZ use and development of IR (p<0.05). C-peptide level was significantly higher in patients who used antiepileptic drugs than in control group (p<0.05). Average body mass index (BMI) was not different between groups.

Conclusion: In patients under antiepileptic treatment, neuroendocrine dysfunction, such as insulin metabolism disorders, can develop in addition to common side effects. Thus, symptoms should be followed up carefully and patients should be evaluated in terms of side effects both before starting and during treatment.

Keywords: C-peptide; carbamazepine; insulin resistance; valproic acid.

Özet

Amaç: Bu çalışmanın amacı oldukça etkili ve sık kullanılan iki antiepileptik olan valproat (VPA) ve karbamazepin (KBZ) tedavisi sırasında insülin direnci (IR) gelişiminin araştırılmasıdır.

Gereç ve Yöntem: Bu kesitsel ileriye yönelik kohort çalışmasına yaşları 15–64 arasında değişen 111 kişi dahil edildi. Epilepsi hastaları VPA kullanan (n=45) ve KBZ kullanan (n=35) olmak üzere iki gruba ayrıldı ve sağlıklı kontrol grubu (n=31) ile karşılaştırıldı. Açlık kan şekeri, insülin, c-peptid düzeyleri ölçüldü ve IR hesaplandı. Antropometrik ölçümler yapıldı.

Bulgular: Valproat ya da KBZ kullananlarda IR kontrol grubuna göre daha yüksek bulundu (p<0.05). C-peptid düzeyleri antiepileptik ilaç kullananlarda kontrol grubuna göre anlamlı derecede yüksek saptandı (p<0.05). Ortalama vücut kitle indeksleri gruplar arasında farklılık göstermedi.

Sonuç: Antiepileptik tedavi altındaki hastalarda sık görülen yan etkilerin yanı sıra insülin metabolizmasına ait nöroendokrin bozukluklar görülebilir. Bu nedenle belirtiler dikkatle sorgulanmalıdır. Hastalar tedaviye başlamadan önce ve tedavi süresince bu açıdan takip edilmelidir.

Anahtar sözcükler: Karbamazepin; c-peptid; insülin direnci; valproik asit.

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Introduction

The purpose of treatment with antiepileptic drugs (AEDs) is to control and decrease the number of epileptic seizures. Many factors are taken into consideration when deciding to start treatment with AEDs and determining the optimal drug. A cost-efficient treatment plan should be established with consideration of pre-existing comorbid conditions, drug interactions, and side effects. A treatment to which the patient can adjust and that is associated with few side effects will improve the patient's quality of life as well as control the epileptic seizures.

Carbamazepine (CBZ) and valproic acid (VPA), two conventional AEDs, are among the most common drugs used for epileptic seizures. Drug activities and side effect profiles of CBZ and VPA have been thoroughly clinically tested. Both CBZ and VPA have well-defined side effects associated with the central nervous system, bone marrow, connective tissue, gastrointestinal system, and endocrine system. Practicing neurologists who treat patients with epilepsy regularly monitor these side effects.

Insulin resistance (IR) is a condition characterized by the failure of cells to respond to circulating insulin. Thus, the blood glucose level increases, stimulating further insulin secretion. The most common feature of IR is the combination of hyperglycemia and hyperinsulinemia. The entrance of insulin into the liver is resisted, and the resultant effects of insulin stimulation on muscle and fatty tissue induce the development of many diseases.

Many drugs, AEDs or not, may cause IR or endocrinological side effects.^[1-3] Many epilepsy patients want to know whole outcomes for their illness and treatment consequences.

The present study calculated IR in patients with epilepsy using AEDs such as VPA or CBZ; we also compared these patients with an age- and sex-matched healthy control group, and examined the relationship between the use of AEDs and metabolic syndrome.

In recent studies, VPA-induced obesity and insulin metabolism disorders have been well established,^[4-6] but there is a little knowledge about effect of CBZ on insulin metabolism. In the present study, IR was studied to clarify the subject with patients using AEDs. The present findings may add

valuable information to the literature in order to understand the side effects of AEDs and encourage new studies to investigate the mechanism of diabetic tendency in this group.

Materials and Methods

Case selection

Eighty consecutive outpatients (35 males, 45 females) who had been diagnosed with epilepsy ≥ 1 year previously and who were being treated with VPA or CBZ without any dosage changes at least for 1 year were examined in the Neurology Clinic of Diskapi Yildirim Beyazit Training and Research Hospital. The control group comprised 31 healthy individuals whose age and sex distribution were similar to those of the patient population. Results of systematic and neurological examinations of patients were retrospectively obtained from medical records. Institutional review board approved the trial. Written informed consent was obtained from all patients.

Exclusion criteria

The following exclusion criteria were enforced for the patients and controls because of potential to affect plasma insulin, blood glucose, and IR levels: diagnosis of epilepsy < 1 year previously, polytherapy, hypertension or diabetes mellitus, atherosclerotic vascular disease (cerebrovascular disease, transient ischemic attack, or myocardial infarction), autoimmune disease, medications such as steroids or growth hormones, androgyny, endocrine disease, and pregnancy.

Anthropometric measurements

The patients and controls were weighed in kilograms using an electronic scale. They were asked to remove their shoes, and height was measured with a fixed-length standard meter while standing. Body mass index (BMI) was calculated as weight (kg) / height squared (m^2).

Blood sample collection and processing

The fasting plasma glucose (FPG) and fasting insulin levels of all patients and controls were examined. Blood samples were taken between 8:30 and 9:00 am following a fast of ≥ 12 hours. Patients took the last dose of drugs the previous night, at least 12 hours before taking blood sample. The samples were sent to a laboratory for immediate analysis. Tests were performed using fully automated instruments in the biochemistry laboratory of Diskapi Yildirim Beyazit Training and Research Hospital in Ankara, Turkey. FPG was

examined using photometric method with Roche commercial autoanalyzer and Biosystems commercial kits and presented as mg/dL. Fasting insulin level was measured with spectrophotometric methods using a Siemens commercial autoanalyzer and Biosystems commercial kits and presented as mg/dL.

IR calculation

IR was measured using the fasting insulin level and FPG level as follows: Homeostatic model assessment (HOMA)-IR = fasting plasma insulin (U/mL) × FPG (mg/dL) / 405.

Statistical analysis

The data were analyzed using statistical software (SPSS for Windows version 17.0; SPSS, Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) test was used for comparison of groups. A p value of <0.05 was considered to indicate statistical significance. For variables with p value of <0.05, Tukey's honest significant difference (HSD) test was used to determine of which groups were significant. Results are presented as mean±SD.

Results

All 111 participants were separated into three groups. The first group comprised epileptic patients being treated with VPA (n=45; 27 females; mean age: 30 years; age range: 14-64 years; mean duration of epilepsy: 11 years; range of epilepsy: 1-45 years). The second group comprised epileptic patients being treated with CBZ (n=35; 18 females; mean age: 36 years; age range: 18-60 years; mean duration of epilepsy: 16 years; range of epilepsy: 2-43 years). The healthy control group comprised 31 volunteers (18 females; mean age: 34 years; age range: 17-58 years).

Mean duration of drug usage was 6.3 years for VPA group and 10.1 years for CBZ group (Table 1). The average dose of VPA was 950±380 mg (range: 250–2000 mg), and the average dose of CBZ was 660±200 mg (range: 300–1200 mg) (Table 1).

The average BMI in the VPA, CBZ and control group was 24.6 (range: 15–34), 25 (range: 18–33), and 25 (range: 18–32), re-

Table 1. Participants' demographic and clinical characteristics

Characteristic	VPA users		CBZ users		Controls	
	n	Mean±SD	n	Mean±SD	n	Mean±SD
Age (years)	–	30.6±13.3	–	36.7±13.2	–	34.3±9.7
Sex (n)	45	–	35	–	31	–
Male (n)	18	–	17	–	13	–
Female (n)	27	–	18	–	18	–
Duration of epilepsy (years)	–	11.3±10.5	–	16.2±10.7	–	–
Duration of drug use (years)	–	6.32±6.70	–	10.1±8.2	–	–
Daily drug dose (mg)	–	950±380	–	660±200	–	–
Drug blood levels (mg/dL)	–	67.4±27.5	–	8.0±2.8	–	–

CBZ: Carbamazepine; VPA: Valproic acid; SD: Standard deviation.

Table 2. General laboratory data

Features	Valproic acid users	Carbamazepine users	Controls	p
Body mass index (kg/m ²)	24.6±4.4	25.0±4.0	25.9±3.6	0.736
Fasting plasma glucose (mg/dL)	83 (62–108)	94 (69–191)	101 (74–149)	<0.001*
Insulin (mg/dL)	10 (2.5–47.7)	10.7 (1.3–37.5)	7.2 (3.4–20.6)	0.082
C-peptide	2.7 (0.9–8.7)	2.3 (0.9–7.5)	1.3 (0.7–2.5)	<0.001**
Insulin resistance	2.12±0.4	2.5±1.2	1.74±0.2	0.035***

Groups were compared with one-way ANOVA; p value of <0.05 was considered to indicate statistical significance.

*FPG is lower in VPA group than CMZ group and control group.

**C-peptide levels of the VPA and CMZ groups are significantly higher than that of the control group.

***IR of the patients is significantly higher than that of controls.

spectively. There were no statistically significant differences between the groups (Table 2).

The insulin level in the VPA, CBZ and control group was 10, 10.7, and 7.2U/mL, respectively, with no statistically significant differences. Average FPG level in the VPA group was significantly lower than that of control group ($p < 0.001$) (Table 2).

Although there were no significant differences in C-peptide level between VPA and CBZ groups, C-peptide level of VPA and CBZ groups was significantly higher than that of control group (Table 2).

IR calculated according to the HOMA-IR formula in VPA, CBZ and control group was 2.12 ± 0.4 , 2.5 ± 1.2 , and 1.74 ± 0.2 , respectively (Table 2). There was no statistically significant difference in the IR between VPA and CBZ groups. However, IR was significantly higher in the epilepsy patients than controls. Although FPG level was lower in VPA group, IR value in the VPA and CBZ groups was higher than that of control group (Table 2).

Discussion

VPA and CBZ are two very effective medications for epilepsy, but their side effects should be taken into consideration. Apart from common side effects of these two medications, hormonal changes can also occur.^[7–10] The use of AEDs has increased both the importance of side effects that appear with use of these drugs, and the number of scientific studies on AEDs.

In many patients, epilepsy causes a neuroendocrine functional disorder.^[11] Seizures may destroy the cortical organization of the structures that release hormones from the hypothalamus, leading to deterioration of the hypothalamo–hypophyseal axis.^[11–13] AEDs may directly affect the metabolism and concentrations of these hormones as well as function of the hypothalamo–hypophyseal axis, which is responsible for the organization of these hormones.^[9,14] Gamma-Aminobutyric acid (GABA), glutamate, serotonin, and interaction with endogenous opioids are related to the development of neuroendocrine functional deterioration.^[11,15–17]

VPA is known to cause increases in body weight.^[11,18,19] The incidence of this side effect ranges from 14% to 71% in var-

ious studies.^[4,20,21] Other studies have reported increases in the body weight of children and adults receiving long-term VPA treatment and have found that VPA was the primary causative agent for increases in BMI among all AEDs studied.^[4,5,11,22] Additionally, one study reported that females receiving VPA are more prone to weight gain than females taking other AEDs.^[20] Various mechanisms are responsible for weight gain, including increased insulin and proinsulin secretion caused by VPA, an increased appetite for carbohydrates, restricted energy expenditure, decreased beta oxidation of leptin level and oil acids due to carnitine deficiency.^[4,14] In the present cohort, we found no significant difference in obesity between the controls and patients. Generally, the lack of a significant relationship regarding obesity between the groups may be due to the small number of patients in the study, lack of data on the weight of patients before starting the AEDs, and differences among patients' nutritional characteristics. Average IR among patients in VPA group with BMI of ≥ 30 was 2.7; these patients had the highest IR. This finding is similar to that in the

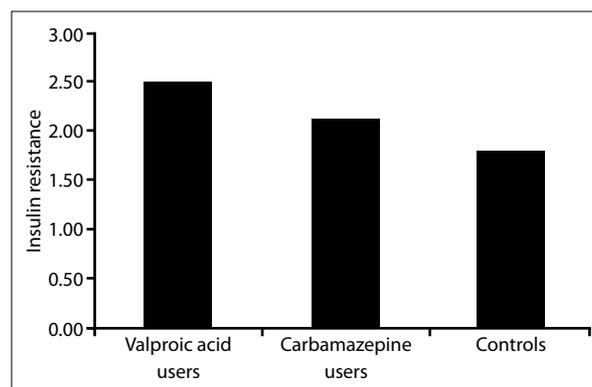


Fig. 1. The average IR in the VPA and in the CBZ group was higher than in the control group.

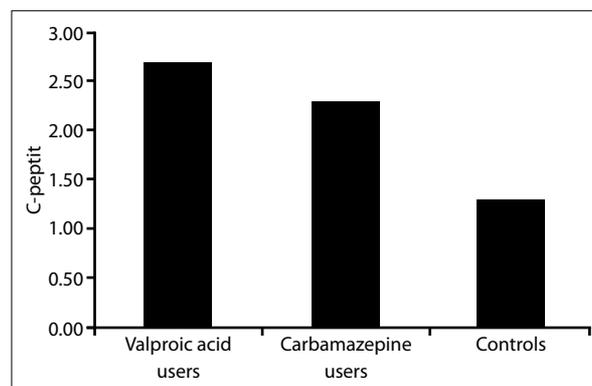


Fig. 2. The c-peptide levels in both the VPA and CBZ groups were higher than those in the control group.

study by Plyvanen et al.,^[23] who evaluated 81 patients and concluded that IR was very high in those who developed obesity during VPA use. The same researchers asserted that obesity was not the cause, but the result of IR when they later studied 96 patients in 2006.^[24] In the present study, although there was no difference in obesity between the groups, differences in IR were observed. Therefore, it could be alleged that during VPA use, IR develops first, followed by obesity.

The hyperinsulinemic-euglycemic clamp test is the optimal method of IR measurement. However, application of this test is difficult because it is time-consuming and costly. Therefore, HOMA-IR was calculated in the present study because it is easy to apply and correlates highly with the hyperinsulinemic-euglycemic clamp test.^[25] Using the HOMA-IR formula, the average IR in the VPA and in the CBZ group was higher than in the control group (Figure 1). Elevated IR may cause tendency for diabetes. One study suggested that the use of VPA or CBZ affects serum C-peptide level, while other reports have stated that no such change occurs.^[26-28] In the present study, C-peptide levels in both VPA and CBZ groups were significantly higher than those in the control group (Figure 2).

The underlying mechanism of IR in patients who use AEDs is still unknown. But it has been speculated that intrahepatic fat accumulation and impairment of mitochondrial beta-oxidation of fatty acids may cause IR.^[29] Nevertheless, this mechanism may be an issue to investigate in future studies. Various liver abnormalities result in the development of endocrine disorders.^[29] Moreover, HOMA-IR index is calculated using fasting insulin and glucose levels, which are associated with hepatic glucose secretion and insulin sensitivity.^[24,28] Like VPA, CBZ can also cause IR in this way.

IR is a condition in which cells fail to respond to the normal actions of the hormone insulin. Despite the presence of insulin, the cells are not adequately stimulated to take in glucose. The body attempts to compensate for this dysfunction with various metabolic processes that increase the amount of insulin. Insulin secretion is increased in beta cells and hepatic degradation is decreased to avoid hyperglycemia. As a result, the insulin level increases in the face of normoglycemia. IR is frequently diagnosed in patients with obesity and those with type 2 diabetes, but it is also diagnosed in non-obese patients and normoglycemics.^[25] Hence, IR is a

very common phenomenon in the general population. The use of VPA and CBZ has the potential to cause IR.

Consequently, the present study found that long-term treatment with VPA or CBZ could cause IR. Therefore, regular follow-up and monitoring during the treatment process is required.

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