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Do antiepileptics have any potential to induce insulin resistance? A comparison between levetiracetam and valproic acid

Gökhan Özer

Department of Neurology, Sanko University School of Medicine, Gaziantep, Turkey

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ABSTRACT

Objective: To explore whether levetiracetam and valproic acid are associated with insulin resistance and to determine their effects on glucose and insulin levels among different age groups.

Methods: Demographic data were collected for epileptic patients from different age groups with a normal body mass index and no chronic endocrine disease who were on levetiracetam or valproic acid therapy. In addition to routine laboratory tests, fasting insulin level was checked and Homeostatic Model Assessment for insulin resistance calculated for all patients. Based on these measurements, the effects of levetiracetam and valproic acid on laboratory parameters were compared statistically.

Results: A total of 61 patients (30 males, 31 females) diagnosed with epilepsy were included in the study. Thirty-four (55.7%) the patients were less than 15 years of age and the others were older. Twenty-three (37.7%) patients were on valproic acid therapy and 38 (62.3%) patients were receiving levetiracetam. Thirty-two (52.5%) the patients tested positive for insulin resistance and others were insulin resistance-negative. Nine (28.1%) patients on valproic acid treatment and 71.9% (n = 23) of patients on levetiracetam treatment were insulin resistance-positive.

Conclusions: In the present study, contrary to the published literature, levetiracetam was found to be associated with further negative effects on insulin and blood glucose metabolism compared to valproic acid. We determined that levetiracetam had a distinct pharmacokinetic profile in pediatric patients as demonstrated by its effects on glucose and insulin metabolism.

Keywords: insulin resistance, levetiracetam, epilepsy, valproic asid

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Altered patterns of hormonal secretion due to direct action of epileptic discharges have been shown in humans and animals, but it is difficult to establish the underlying cause of untoward effects of antiepileptic medications which can be multifactorial in epileptic patients. Monotherapy should be preferred whenever possible to avoid occurrence of adverse effects and complicated problems [1-5].

However, prolonged use of antileptic drugs is known to be associated with adverse effects such as metabolic and organ toxicity, endocrine disturbance, negative cognitive effects, and psychiatric problems, particularly with alterations in thyroid function in patients withepilepsy. Some antileptic drugs are

Address for correspondence: *Gökhan Özer, MD., Assistant Professor, Sanko University School of Medicine, Department of Neurology, Gaziantep, Turkey*
E-mail: primernordr@gmail.com

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enzymes responsible for vitamin D metabolism to the inactive metabolites of 25 (OH) 2 D vitamin. 1.25 (OH) 2 D vitamine level Decreases the calcium absorption so the second hyperparathyroidism, increased bone resorption and bone loss it is developing [6-9].

Studies have clearly demonstrated the impact of antiepileptic drugs, on hormonal status including effects on fertility, sexual function, bone structure and thyroid hormone. While studies evaluating thyroid function status in epileptic patients suggest that thyroid hormone levels are not directly related to epilepsy, some changes in thyroid function tests could be associated with the prescribed antileptic drugs [10].

Levetiracetam is structurally unrelated to other antiepileptic drugs although its effect on CYP450 enzyme induction is not clear. Levetiracetam specifically binds to the synaptic vesicle protein (SV2A) which is commonly found in the central nervous system and endocrine tissues [11]. It was observed that levetiracetam induces secretion of testosterone and estrogen without stimulating release of gonadotropin from ovarian follicular cells. This observation suggests that endocrine functions are affected by levetiracetam particularly in women of childbearing age [12]. Previous studies have shown that thyroid functions are not significantly influenced by LEV in children and adults [13]. In case-control studies, valproic acid was shown to lower blood glucose concentration independent of weight gain and hyperinsulinemia [14]. There are no studies in literature on the impact of levetiracetam on serum insulin and/or glucose levels.

METHODS

Non-diabetic patients with epilepsy for at least one year, using epilepsy medication for at least a year and a normal body mass index who admitted to Gaziantep Sanko University School of Medicine in 2017 and were on monotherapy were included in the study after being examined by a neurologist. Ethical approval was obtained from the ethics committee of the same hospital. Patients were stratified into two groups using 15 years of age as a cut-off (Group 1, less than 15 y and Group 2, ≥ 15 y). Patients receiving levetiracetam were compared with those on valproic acid. Valproic acid was chosen for the study due to its potential to induce weight gain and hyperinsulinemia and known effects on endocrine metabolism. In addition to routine biochemistry panel, fasting insulin values were measured for all patients. Medical history, age, and gender data were recorded by specialist neurologist. Height and body weight were measured to obtain body mass index (kg/m2) and age- and sex-specific body mass index percentiles. Associations between average doses of study medications and blood glucose, insulin and HOMA-IR values were examined in relation to age and gender. Insulin resistance was calculated using the The homeostasis model assessment of insulin resistance (HOMA-IR) formula of fasting insulin (uU/mL) × fasting glucose (mmol/L) / 405 using a cut-off value of 2.5 [15]. HOMA-IR is a noninvasive and effective alternative method to evaluate insulin sensitivity based on the glucose level and the level of serum insulin measured in fasting conditions. HOMA-IR is considered a standard method of measuring insulin resistance in epidemiological studies [16].

Statistical Analysis

Normality assumption for numerical variables was checked using the Shapiro-Wilk normality test. Mann-Whitney U test was used to compare numerical variables between independent groups and chi-square test was applied to investigate the relationship between categorical variables. Statistical analyses were conducted in SPSS for Windows, version 24.0 and a p value less than 0.05 was considered statistically significant.

Table 1. Demographic characteristics of patients

Variables		n	%
Age (years)	<15	34	55.7
	≥15	27	44.3
Gender	Male	30	49.2
	Female	31	50.8
Medication	VPA	23	37.7
	LEV	38	62.3
HOMA-IR status	IR (+)	32	52.5
	IR (-)	29	47.5

HOMA-IR = Homeostatic model assessment for insulin resistance, IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients, VPA = valproic acid

RESULTS

A total of 61 patients were included in the study, of whom 30 (49.2%) were males. Thirty-four patients were less than 15 years of age and the others were older. Twenty-three (37.7%) patients were on valproic acid therapy and the remaining patients were on levetiracetam therapy. Thirty-two (52.5%) patients were tested positive for insulin resistance and other patients were insulin resistance-negative (Table 1). Mean glucose value was 92.2 mg/dL, mean insulin value was 26.2 µU/mL and mean HOMA-IR value was 5.94 among insulin resistance-positive patients receiving valproic acid (Table 2). Mean glucose value was 95.91 mg/dL, mean insulin value was 21.2 µU/mL and mean HOMA-IR value was 5.29 among insulin resistance-positive patients receiving levetiracetam (Table 3). Among patients less than 15 years of age, 46.9% insulin resistance-positive and in patients older than 15 years of age, 53.1% were insulin resistance-

Table 2. Relationship between valproic acid, glucose, insülin, HOMA-IR

VPA group	IR (+) (n = 9)	IR (-) (n = 14)	*p* value
Glucose (mg/dL)	92.22 ± 16.79	83.57 ± 9.43	0.305
Insulin (µU/mL)	26.26 ± 12.67	35.72 ± 116.39	**0.001**
HOMA-IR	5.94 ± 3.02	0.94 ± 0.65	**0.001**

HOMA-IR = Homeostatic model assessment for insulin resistance, IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, n = the number of patients, VPA = valproic acid

Table 3. Relationship between levetiracetam, glucose, insülin, HOMA-IR

LEV group	IR (+) (n = 23)	IR (-) (n = 15)	*p* value
Glucose (mg/dL)	95.91 ± 8.18	81.67 ± 24.42	**0.006**
Insulin (µU/mL)	21.8 ± 13.29	75.47 ± 173.69	**0.005**
HOMA-IR	5.29 ± 3.55	1.59 ± 1.61	**0.001**

HOMA-IR = Homeostatic model assessment for insulin resistance, IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients

Table 4. Relationship between age, gender, medication and insulin resistance.

Variables		IR (+)		IR (-)		*p value**
		n	%	n	%	
Age (years)	<15	15	46.9	19	65.5	0.143
	≥15	17	53.1	10	34.5	
Gender	Male	14	43.8	16	55.2	0.373
	Female	18	56.2	13	44.8	
Medication	VPA	9	28.1	14	48.3	0.105
	LEV	23	71.9	15	51.7	

IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients, VPA = valproic acid, *Chi-square test

Table 5. Comparison of total dose between IR (+) and IR (-) groups.

Variable	Medication	n	IR (+)	n	IR (-)	*p value*
Total dose (mg/day)	VPA	9	1922.22 ± 3068.7	14	489.29 ± 203.98	**0.016***
	LEV	23	860.87 ± 501.58	15	860 ± 636.73	0.768
	Overall	32	1686.35±507.52	29	681.03±507.52	**0.046***

IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients, VPA = valproic acid, *Mann-Whitney U test

Table 6. Relationship between medication use and IR for different age groups

Age (years)	Medication	IR (+)		IR (-)		*p value**
		n	%	n	%	
< 15	VPA	5	33.3	12	63.2	0.084
	LEV	10	66.7	7	36.8	
≥ 15	VPA	4	23.5	2	20.0	0.831
	LEV	13	76.5	8	80.0	

IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients, VPA = valproic acid, *Chi-square test

positive. Insulin resistance was detected in 56.2% of female patients. Twenty-three (71.9%) patients receiving levetiracetam treatment and 28.1% (n = 9) of patients receiving valproic acid treatment were insulin resistance-positive. No significant association was found between insulin resistance and pharmacological agents in question, age, and gender when analyzed by chi-square test (Table 4). Total dose was significantly higher in insulin resistance-positive patients for valproic acid (p = 0.016) and overall comparison (p = 0.046). However, no significant difference was detected for levetiracetam (p = 0.768) (Table 5). There was no statistically significant association between valproic acid or levetiracetam use and insulin resistance in different age groups (Table 6). Insulin resistance was more likely to develop with increased dose of medication, particularly among patients using valproic acid (Figure 1).

DISCUSSION

Insulin resistance is a pathogenic factor for type 2 diabetes mellitus [17]. Increased insulin secretion and chronic hyperinsulinemia can develop, when pancreatic beta cells can no longer compensate and maintain glucose homeostasis, leading to the development of type 2 diabetes mellitus [18]. In adults, a cut-off value of 2.5 is generally used for HOMA-IR but at present, there is not a well-established cut-off for HOMA-IR in children.

One study in obese prepubertal and pubertal

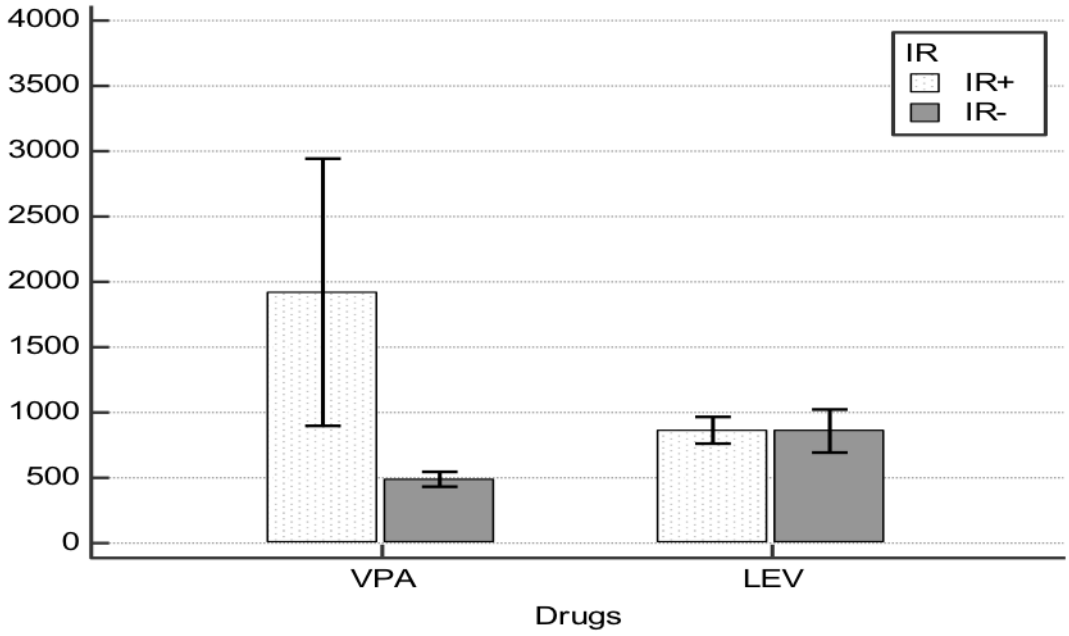

Figure 1. IR positivity increases with increased total dose of VPA. IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, VPA = valproic acid.

children and adolescents (aged 5-18 years) determined that HOMA-IR cut-off values ranged from 2.67 to 5.22 for boys and 2.22 to 3.82 for girls (19). Another study in 691 apparently healthy Indian adolescents (aged 10-17 years) established a HOMA-IR cut-off of 2.5 [20].

Notably, in the current study HOMA-IR values were higher than those previously reported in pediatric patients, with an average of 2.6 in normal weight children and 4.1 to 4.3 in overweight and obese children. In a prevalence study, insulin resistance was positive in 28.9% of females and 25.1% of males [21]. A pediatric study involving 42 children with a mean age of 10.3 years and normal body weight reported an average blood glucose of 86 mg/dL, an insulin value of 11.9 μU/mL and a HOMA-IR of 2.6 [22]. In our study, mean glucose values were 92.2 mg/dL and 95.9 mg/dL in insulin resistance-positive valproic acid and levetiracetam groups, respectively, which were greater than those found in patients with normal body weight.

In one study, on average, 25% of overweight individuals had insulin resistance; however, in the present study, 52.5% of the total study sample tested positive for insulin resistance although our patients had normal body weight [23]. As reported in literature, some children with normal body weight show a higher-than-average HOMA value and the underlying cause of this is not clear. It is possible that children in this age group (9-10 years) have higher HOMA-IR scores, perhaps due to the onset of puberty, where insulin levels have been reported to increase [24, 25]. However, as clearly shown by the current study, antiepileptic drugs have an impact on glucose and metabolism, at least to some extent.

Limitations

A limitation of the present study is the lack of comparison of data before and after initiation of the antiepileptic medication. Additionally, we did not evaluate other parameters that could influence insulin resistance such as diet, genetic and hormonal factors. Future studies might focus on these and other parameters.

CONCLUSION

Potential effects of antiepileptic drugs on glucose and insulin metabolism should be investigated in larger patient series and a wider range of antiepileptics. Patients may be screened for insulin resistance before starting antiepileptic treatment and care should be exercised when choosing an antiepileptic drug to avoid potential future development of diabetes mellitus in a susceptible patient. Patients at risk for diabetes mellitus should be educated about measures that help prevent insulin resistance including diet modification and physical activity and antiepileptics associated with development of insulin resistance should be avoided.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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