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Long-term effects of levetiracetam and valproic acid on laboratory parameters in childhood epilepsy

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Abstract

Epilepsy is the most common neurological disorder in childhood which often requires long-term or sometimes lifelong treatment. In this study, we aimed to evaluate the change in hematological and biochemical laboratory parameters at the 24th month compared to the treatment baseline values in pediatric epilepsy patients receiving levetiracetam (LEV) and valproic acid (VPA) monotherapy. Complete blood count panel, biochemical and hormonal parameters were investigated retrospectively at baseline and at 24 months in patients diagnosed with epilepsy at the Balıkesir University Medical Faculty pediatric neurology clinic, Türkiye, and started on LEV and VPA monotherapy between 01.08.2019 and 01.08.2022. Forty-nine patients were using LEV and 14 VPA. A statistically significant difference in terms of the complete blood count parameters mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) was observed in the cases using LEV between baseline and the 24th month of treatment (p=0.006, p=0.004). Among the cases using VPA, significant differences between baseline and the 24th month of treatment were determined in the complete blood count parameters red blood cell (RBC), MCV, and monocyte (MON)% values (p=0.004, p=0.022, and p=0.01). In conclusion, epilepsy treatment is a lengthy process in pediatric patients, and patients need to be monitored using hematological and biochemical parameters at specific intervals in terms of potential seizure drug side effects.

Keywords: Levetirasetam, valproic acid, epilepsy, side effects

Introduction

Epilepsy is a predisposition to recurrent seizures; epilepsy is defined as at least two seizures occurring without a demonstrable cause and recurring for more than 24 hours; reflex seizures are included in this definition. Epilepsy can also be diagnosed with a single seizure (or reflex seizure) without a stimulus, in which case the risk of recurrence in the next 10 years after a single seizure is the same as the risk of recurrence after two seizures (60%). A single seizure is still considered sufficient for the diagnosis of epilepsy if it fits a specific epilepsy syndrome [1].

Epilepsy is the most common neurological disorder in childhood, and frequently requires long-term or even lifelong treatment. Approximately 70-80% of epileptic seizures can be brought under control through the use of seizure drugs at effective doses and for appropriate periods [2]. The remaining 20-30% exhibit resistance to treatment despite effective and tolerable novel seizure drugs [3]. Neurological, psychiatric, and dermatological side-effects can develop in association with long-term seizure drugs use. Hematological side-effects such as thrombocytopenia, pancytopenia, and hypogammaglobulinemia can also occur, albeit rarely [4].

Levetiracetam (LEV) is a new generation seizure drugs that is highly effective in the treatment of focal and generalized epilepsy, that is relatively safe in terms of side-effects, and that is well tolerated by patients. It is used in both combination and monotherapy in childhood epilepsies [5].

Valproic acid (VPA) is another frequently employed seizure drugs that is effective in several types of seizure [6]. Due to the need for

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long-term use, seizure drugs must be closely monitored in terms of side-effects and toxicity. Monitoring hematological laboratory parameters is important in that context. The number of studies investigating long-term changes in hematological parameters in epilepsy patients receiving LEV therapy is quite small [7,8]. The purpose of this study was to evaluate changes in hematological and biochemical parameters at 24 months of treatment compared to baseline in pediatric epilepsy patients receiving LEV and VPA monotherapy.

Material and Methods

Complete blood count panel, biochemical and hormonal parameters were investigated retrospectively by accessing patient records through hospital information systems at baseline and at 24 months in patients diagnosed with epilepsy at the Balıkesir University Medical Faculty pediatric neurology clinic, Türkiye, and started on LEV and VPA monotherapy between 01.08.2019 and 01.08.2022. Before the study, local ethics committee approval was obtained (decision no. 2022/96). Our study was conducted in accordance with the Declaration of Helsinki patient rights regulations.

Seizure classification was made according to the International League Against Epilepsy (ILAE) Diagnostic Manual. EEG was performed on all patients. Patients who were not receiving vitamin D, calcium, vitamin B12, folate supplements, and thyroid drugs included in the study.

Patients with deficient file data, another chronic disease (chronic liver, kidney, hematological, or immunological disease), with a history of any other drug use, with a history of febrile disease or infection during blood tests, or with malnutrition (celiac disease, hypothyroidism, or vitamin B12, folic acid, and other vitamin deficiencies) were excluded from the study.

Statistical analysis

Study data were summarized as mean, minimum and maximum values. Comparisons between groups were made using the Paired Sample T test method. Complementary statistical methods were used. P values less than 0.05 were considered significant in all tests. Analyzes were performed with IBM SPSS Statistics version 26.0 software.

Ethical approval

Approval for the study was granted by the Balıkesir University ethical committee (permission no: 2022/96, 07.09.2022).

Results

Sixty-three patients from the 350 started on treatment with diagnoses of epilepsy in our clinic and meeting the study criteria were included in the research. Forty-nine patients were using LEV and 14 VPA. Girls represented 59.2% (n=29) of the patients using LEV and boys 57.1% (n=8) of those using VPA. Mean ages were 10.33±4.56 (3-18) years in the LEV group and 8.93±4.21 (4-16) years in the patients using VPA. The clinical characteristics of the LEV and VPA groups are shown in Table 1.

A statistically significant difference in terms of the complete blood count parameters mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) was observed in the cases using LEV between baseline and the 24th month of treatment (p=0.006 and p=0.004, respectively). Only values for the biochemical parameters aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and the hormonal parameter vitamin B12 differed significantly (p=0.03, p=0.03, and p=0.02, respectively). Complete blood count, biochemical, and hormonal parameters before LEV therapy and at the 24th month of treatment are shown in Table 2 and Table 3.

Table 1. The general characteristics of cases using levetiracetam and valproic acid

	Levetiracetam	Valproic acid
Age [mean±SD (min-max)]	10.33±4.56 (3-18) years	8.93±4.21 (4-16) years
Gendern (n, %)		
Female	29 (59.2)	6 (42.9)
Male	20 (40.8)	8 (57.1)
Cranial MRI (n, %)		
Abnormal	10 (20.4)	-
Type of epilepsy (n, %)		
Focal	8 (16.3)	6 (42.9)
Generalized	11 (22.4)	5 (35.7)
Unknown	30 (61.2)	3 (21.4)
EEG (n, %)		
Epileptiform	25 (51)	5 (51)
Normal	12 (24.5)	4 (24.5)
Abnormal	12 (24.5)	5 (24.5)

MRI: magnetic resonance imaging, EEG: electroencephalography, SD: standard deviation, min: minimum, max: maximum

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Table 2. A comparison of hemogram subtypes before and at the 24th month of treatment in patients using levetiracetam and valproic acid

Parameter	Levetiracetam			Valproic acid		
	Pre-treatment mean±SD (min-max)	24th month of treatment mean±SD (min-max)	P	Pre-treatment mean±SD (min-max)	24th month of treatment mean±SD (min-max)	P
WBC (×10³/µL)	7.82±2.45 (4.1-15.8)	7.63±2.27 (4.5-17.7)	0.60	7.12±1.35 (4.8-9.2)	7.72±2.52 (4.3-13.6)	0.4
RBC (×10⁴/µL)	4.75±0.39 (4.07-5.93)	4.69±0.28 (4.1-5.3)	0.19	4.67±0.45 (3.9-5.55)	4.38±0.47 (3.7-5.4)	**0.004**
HGB (g/dL)	12.68±1.04 (10.4-16.1)	12.85±1.04 (9.8-15)	0.20	12.50±0.9 (11.4-14.3)	12.04±1.22 (10.3-14.6)	0.13
HCT (%)	38.19±2.86 (32.1-46.8)	38.46±2.80 (31-45.6)	0.48	37.25±2.93 (33-42)	36.1±3.55 (31.3-43.4)	0.15
PLT (×10⁴/µL)	339.61±86.24 (220-598)	325.86±107.28 (168-733)	0.38	308.71±68.99 (210-412)	300.29±81.39 (171-431)	0.66
MCV (fL)	80.51±6.27 (62.3-98.5)	82.26±6.07 (62.6-96)	**0.006**	80.17±6.43 (69-90)	82.71±5.13 (72.2-91.7)	**0.022**
MCH (pg)	26.75±2.37 (19.7-31.4)	27.5±2.39 (19.4-33.1)	**0.004**	27.03±2.27 (22.6-30.3)	27.6±1.82 (23.8-30.1)	0.27
MCHC (g/dL)	33.20±0.93 (30.2-34.7)	33.41±1 (31-36)	0.23	33.73±1.03 (31.9-35.8)	33.38±0.92 (32-35)	0.46
RDW (fL)	14.35±3.69 (12.3-38.6)	13.86±1.17 (12.3-17.9)	0.63	13.51±1.49 (12-17.6)	14±1.39 (12-17.4)	0.44
NEU# (10³/uL)	3.62±1.31 (1.7-7.1)	3.67±1.32 (1.6-6.7)	0.83	2.95±1.02 (1.6-4.8)	3.29±1.5 (1.8-6)	0.47
LYM# (10³/uL)	3.32±1.90 (1.1-9.7)	3.04±1.85 (0.9-13.6)	0.32	3.4±0.90 (2.5-5.9)	3.4±1.02 (2-5.6)	0.99
MON# (10³/uL)	0.56±0.2 (0.3-1.1)	0.66±0.43 (0.3-3.1)	0.09	0.57±0.15 (0.4-0.9)	0.8±0.43 (0.3-1.8)	0.08
EOS# (10³/uL)	0.21±0.2 (0-0.8)	0.22±0.27 (0-1.4)	0.89	0.2±0.1 (0.1-0.4)	0.2±0.09 (0-0.3)	0.81
BAS# (10³/uL)	0.02±0.04 (0-0.1)	0.03±0.09 (0-1)	0.35	0.20±0.04 (0-0.1)	0.01±0.04 (0-0.1)	0.67
NEU (%)	47.93±12.65 (17.6-70.6)	48.64±12.9 (9.6-78.7)	0.99	40.26±9.57 (22.9-54.8)	41.58±8.77 (24-56.4)	0.88
LYM (%)	41.18±12.84 (18-74.7)	39.14±12.57 (9.9-76.8)	0.32	47.57±8.32 (34.8-64.2)	45.2±9.48 (30.4-63.1)	0.48
MON (%)	7.34±1.75 (5-12.9)	8.71±4.82 (5.2-38.9)	0.07	8.15±1.67 (5-11.7)	10.05±2.52 (7-15)	**0.01**
EOS (%)	2.70±2.52 (0.4-10.5)	2.89±3.01 (0.3-14.4)	0.68	2.70±1.59 (0.8-5.9)	2.62±1.17 (0.3-4.4)	0.77
BAS (%)	0.54±0.23 (0-1)	0.59±0.49 (0-3)	0.51	0.59±0.19 (0.2-1)	0.51±0.3 (0-1)	0.37

WBC: white blood cell, RBC: red blood cell, Hg: hemoglobin, Hct: hematocrit, PLT: platelet, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, NEU: neutrophil, LYM: lymphocyte, MON: monocyte, EOS: eosinophile, BAS: basophile

Table 3. A comparison of hormonal and biochemical parameters before and at the 24 th month of treatment in patients using levetiracetam and valproic acid

Parameter	Levetiracetam			Valproic acid		
	Pre-treatment mean±SD (min-max)	24 th month of treatment mean±SD (min-max)	P	Pre-treatment mean±SD (min-max)	24 th month of treatment mean±SD (min-max)	P
AST (U/L)	30.46±26.75 (11-203)	26.12±13.55 (13-107)	**0.03**	28.69±7.88 (20-44)	24.21±6.99 (14-35)	**0.02**
ALT (U/L)	30.46±26.75 (9-211)	18.02±23.16 (1.7-174.2)	**0.03**	15.08±4.53 (10-23)	11.5±3.7 (6-19)	**0.03**
BUN (mg/dL)	23.1±7.41 (12-50)	21.85±5.84 (8-36)	0.27	23.69±10.43 (12-46)	26.29±10.82 (13-49)	0.69
CRE (mg/dL)	0.57±0.11 (0.4-0.9)	0.55±0.13 (0.3-0.8)	0.14	0.54±0.09 (0.39-0.73)	0.46±0.13 (0.2-0.8)	0.10
Na (mg/dL)	136.71±2.46 (132-145)	137.06±1.69 (130-141)	0.21	137±1.35 (134-139)	136.57±2.02 (133-140)	0.58
Ca (mg/dL)	9.88±0.46 (9.2-11.3)	9.79±0.4 (9-10.7)	0.27	9.70±0.27 (9.4-10.3)	9.63±0.45 (9-10.4)	0.19
Ferritin (ng/L)	22.69±28.07 (2.6-170.6)	21.35±24.35 (1.7-174.2)	0.53	26.75±14.13 (8.8-55.59)	23.75±17 (2.5-74.5)	0.56
Vitamin B12 (pg/mL)	246.51±99.26 (107-475)	351.61±224. 6 (147-1048)	**0.02**	346.42±171.81 (156-589)	485.9±189.66(301-847)	0.14
25 OH D vitamin (ng/mL)	22.63±13.24 (2.44-65.06)	22.43±10.78 (8.7-49.3)	0.85	19.40±9.74 (7.35-41.79)	23.4±6.33 (10.9-31.8)	0.28
Free T4 (ng/dL)	0.89±0.13 (0.63-1.16)	1.43±3.73 (0.61-26.5)	0.33	0.93±0.10 (0.74-1.09)	0.93±0.16 (0.55-1.15)	0.77
TSH (mIU/mL)	2.33±1.13 (0.61-5.86)	2.41±1.38 (0.75-9.02)	0.55	3.41±2.33 (0.85-9.68)	3.27±2.49 (0.4-9.18)	0.90

AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, CRE: creatinine, Na: sodium, Ca: calcium, TSH: tiroit stimulating hormone

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Among the cases using VPA, significant differences between baseline and the 24th month of treatment were determined in the complete blood count parameters red blood cell (RBC), MCV, and monocyte (MON)% values (p=0.004, p=0.022, and p=0.01, respectively), and the biochemical parameters AST and ALT (p=0.02 and p=0.03, respectively). Complete blood count, biochemical, and hormonal parameters before VPA therapy and at the 24th month of treatment are shown in Table 2 and Table 3.

Discussion

The treatment of epilepsy patients is generally long-term and may require gradual drug dosage increases and combined therapy. The principal adverse effects of long-term seizure drugs use include hepatotoxicity and behavioral and memory disorders. The hematological and endocrine systems, bone density, and lipid profiles can also be affected [9]. Patients using seizure drugs must therefore be closely monitored. LEV exhibits very low interaction with other drugs and antiepileptics. Due to its low side-effect profile it is suitable for use in pediatric and adolescent patients. The side-effects of LEV include numerous psychiatric behavioral problems (such as aggressive behavior, agitation, anger, and anxiety), central nervous system depression (somnolence, asthenia, fatigue, and vertigo), and hypersensitivity reactions such as maculopapular rash and Stevens-Johnson Syndrome [3,10]. Side-effects widely observed in association with LEV use are reported to occur in the first five months of treatment in 17.2-51.3% of patients [11-13]. Various hematological side-effects, including cytopenia, have also been reported with LEV use [14]. Dilber et al. observed no statistically significant difference in AST, ALT, GGT, albumin, or creatinine values between the pre-LEV therapy period and the first and third years of treatment in 114 cases aged 8-18 years, but reported significant variations in Hb, Hct, monocyte, MCV, ALS, and ANS values [15]. Attilakos et al. reported a significant decrease in patients' lymphocyte and platelet counts and an increase in neutrophil counts following 12-month LEV therapy [7]. A comparison of complete blood count panels before and at the 24th month of treatment in patients using LEV in the present study revealed significant differences in MCV and MCH values (p=0.006 and p=0.004, respectively).

Liver function tests are highly important in terms of the evaluation of side-effects and drug selection in patients receiving LEV therapy [16]. Several studies have investigated the effects of LEV on hepatic functions [17-20]. French et al. reported an increase in hepatic enzyme levels in 4.6% of patients receiving LEV therapy compared to a control group, although all other parameters were within normal limits. LEV use was also shown to be associated with fulminant hepatitis in a limited number of patients [19]. However, Dilber et al. reported no significant alteration in liver function tests during three-year follow-up of 114 patients using LEV significantly low AST and ALT values were determined ın the present study.

LEV is usually expelled by the kidneys without alteration [21-23]. While some studies have reported that LEV use can lead to interstitial nephritis and kidney failure [22], others have concluded that it causes no renal side-effects and is therefore relatively safe [15]. We observed no LEV use-associated change in kidney function tests in the present study.

VPA is an effective seizure drugs widely used in various types of seizure. However, hematological and non-hematological side-effects can be seen during VPA therapy. Hematological side-effects associated with VPA use seen at varying frequencies in previous studies include thrombocytopenia, leukopenia, anemia, bone marrow suppression, macrocytosis, platelet dysfunction, prolonged bleeding times, hypofibrinogenemia, Factor 13 deficiency, myelodysplastic syndrome, and HbF level elevation [14,24,25]. The most common of these side-effects is thrombocytopenia, which is generally dose-dependent and transient. Leukopenia is also transient, and can be seen in 15-26% of cases. Macrocytosis is a side-effect that can be seen during VPA therapy and that is not thought to be dose-dependent [26,27]. In the present study, no statistically significant difference was observed in the complete blood count parameters RBC, MCV, and MON% between pre-treatment and the 24th month of treatment in patients using VPA (p=0.004, p=0.022, and p=0.01, respectively).

Studies have reported that the use of VPA leads to a transient, 10-15% increase in aminotransferases, and that these changes are the most widespread side-effect associated with VPA use [28,29]. Although some studies have reported that long-term VPA use can lead to liver damage [30], others have observed no association between hepatotoxicity and VPA therapy in children [31]. However, Kayış et al. observed a significant decrease in AST values at the end of one- and two-year treatment compared to the start of treatment [32]. Consistent with that research, AST and ALT values at the 24th month of treatment in the present study were significantly lower than those at the start of treatment (p=0.02 and p=0.03, respectively). The biochemical parameters AST and ALT and the hormonal parameter vitamin B12 were significantly different between baseline and the 24th month of treatment in patients on LEV (p=0.03, p=0.03 and p=0.02, respectively). From a clinical perspective, it is significant that ALT and AST values are lower than at baseline.

The limitations of this study include the low number of patients taking part due to difficulties in patient compliance with treatment and an inability to perform polyclinic checks for a lengthy period due to the COVID-19 pandemic and its attendant restrictions.

Conclusion

In conclusion, epilepsy treatment is a lengthy process in pediatric patients, and it is important for patients to be monitored using hematological and biochemical parameters at specific intervals in terms of potential seizure drugs side-effects.

Further multicenter studies involving larger case numbers evaluating hematological and biochemical laboratory parameters in patients receiving LEV and VPA monotherapies for the same length of time or longer are now needed.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Before the study, ethical approval was obtained from the Balıkesir University Ethics Committee For Clinical Research (No: 2022/07.09/96).

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