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The Effects of Short- and Long-Term Therapy on Laboratory Parameters Among Pediatric Patients with Epilepsy Receiving Antiepileptic Drug Monotherapy

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Abstract

Objective: To evaluate the effect of short- and long-term treatment on laboratory parameters in patients diagnosed with epilepsy in childhood and receiving monotherapy (carbamazepine, valproic acid, phenobarbital, levetiracetam).

Methods: This study included a total of 258 patients who were admitted to Adiyaman University pediatric neurology clinic between 1 October 2017 and 1 June 2019, diagnosed with epilepsy, and received monotherapy. Hematological, biochemical, and hormonal profiles were compared in the third and nine months following the initiation of monotherapy.

Results: Of the patients, 115 (44.57%) were female and 143 (55.43%) were male. The mean age was 8.33 ± 3.51 (0-17) years. Examination of biochemical parameters showed that there was a statistically significant difference in creatinine levels in patients using levetiracetam and phenobarbital ($p = 0.009$, $p = 0.031$); calcium levels in patients using valproic acid ($p = 0.002$); and alanine aminotransferase levels in patients using carbamazepine ($p = 0.045$). Considering hematological parameters, a statistically significant difference was observed in white blood cell count levels in patients receiving valproic acid ($p = 0.005$); hemoglobin and hematocrit levels in those receiving carbamazepine ($p = 0.010$, $p = 0.042$); and platelet levels in patients receiving phenobarbital ($p = 0.037$). In all patients receiving monotherapy, there was no statistically significant difference between hormonal parameters (folate, 25-OH D3, vitamin B12, free t4, and TSH) measured in the third and ninth months.

Conclusions: We recommend that AED therapy should be checked routinely to investigate the effects of treatment on hormonal, biochemical, and hematological parameters.

Keywords: Antiepileptic drug, children, epilepsy, monotheraphy

INTRODUCTION

Epilepsy is one of the most common disorders encountered in pediatric neurology practice with an estimated prevalence of 1% and requires long-term treatment.[1] Adverse effects that may occur due to anti-epileptic drugs (AEDs) are important for the follow-up of patients. Seizures can be controlled in 60%-70% of patients with the use of appropriate pharmacological treatment.[2] More adverse effects may be seen in patients with epilepsy using multiple AEDs, and monotherapy is, therefore, considered the gold standard. Known adverse effects of AEDs include drowsiness, dizziness, weight changes, nausea, memory problems, skin rash, tremors, impaired liver function tests, gastrointestinal symptoms, osteoporosis, and depression.[3] This study aimed to evaluate the effect of short- and long-term treatment on laboratory parameters among pediatric patients, who were diagnosed with epilepsy and receiving monotherapy (carbamazepine [CBZ], valproic acid [VPA], phenobarbital [PB], and levetiracetam [LEV]).

METHODS

This study included a total of 258 patients, who were admitted to Adıyaman University pediatric neurology policlinic within the period from October 1, 2017, to June 1, 2019, diagnosed with epilepsy and received monotherapy (phenobarbital, valproic acid, levetiracetam, and carbamazepine) for at least 9 months. Before the study, local ethics committee approval was obtained (decision no. 2020/3-28).

Seizure classification was made according to the International League Against Epilepsy (ILAE) Diagnostic Manual. Hematological (white blood cell count [WBC], hemoglobin [Hb], hematocrit [Hct], platelet [PLT], and red blood cell count [RBC]), biochemical (urea [BUN], creatinine [Cr], alanine aminotransferase [ALT], aspartate aminotransferase [AST], sodium [Na], and calcium [Ca]), and hormonal profiles (free thyroxine [FT4], thyroid-stimulating hormone [TSH], folate, vitamin B12, and 25-hydroxy vitamin D3 [25-OH D3]) were compared in the third and ninth month following the initiation of monotherapy.

Patients who were not receiving vitamin D, calcium, vitamin B12, folate supplements, and thyroid drugs, those who were seizure-free for at least 9 months, and those whose drug levels were within normal ranges were included in the study.

Study exclusion criteria were as follows: receiving polytherapy; use of any drug affecting thyroid, liver, and kidney functions and the skeletal system 6 months ago; presence of any known thyroid, liver, kidney, bone, or any endocrine disease; abnormal neurological examination findings; presence of progressive neurodegenerative diseases; having a family history of endocrine, liver, and kidney disease; and plasma level of AEDs outside the normal range.

Valproic acid of 20-30 mg/kg/day, CBZ of 10-20 mg/kg/day, PB of 3-5 mg/kg/day, and LEV of 20-30 mg/kg/day were initiated in 2 divided doses. Hematological, biochemical, and hormonal parameters were measured in the third and ninth months following the initiation of antiepileptic therapy and were compared.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences Statistics for Windows, Version 23.0 (IBM Corporation, Armonk, NY, USA). Data measured in the third and ninth months were compared in each group. Kolmogorov–Smirnov test was used to determine whether the data followed a normal distribution. Data following normal distribution were evaluated with paired *t*-test. A *P* value of <.05 was considered statistically significant.

RESULTS

The study included a total of 258 epileptic patients receiving monotherapy (VPA, LEV, CBZ, and PB); 115 (44.57%) of the patients were females and 143 (55.43%) were males. The mean age was 8.33 ± 3.51 (0-17) years. Age and gender of patients receiving monotherapy are shown in Table 1.

Examination of biochemical parameters showed that there was a statistically significant lower difference in Cr levels in patients receiving LEV and PB (*P* = .009, *P* = .031); Ca levels in patients receiving VPA (*P* = .002); and ALT levels in patients receiving CBZ (*P* = .045). Considering hematological parameters, a statistically significant lower difference was observed in WBC levels in patients receiving VPA (*P* = .005); Hb and Hct levels in those receiving CBZ (*P* = .010, *P* = .042); and PLT levels in patients receiving PB (*P* = .037). A statistically significant difference was observed in the WBC and Ca values in the VPA group; PLT count and Cr level in the PB group; and Hb, Hct, and ALT levels in the CBZ group; Cr level in the LEV group; however, these levels were within normal limits

In all patients receiving monotherapy, there was no statistically significant difference between hormonal parameters (folate, 25-OH D3, vitamin B12, FT4, and TSH) measured in the third and ninth months (Tables 2, 3, 4, and 5).

Table 1. Age and Gender of Patients Receiving Monotherapy

	Gender, n (%)	Total, n (%)	Age, Mean ± SD	Drug Initiation Age, Mean ± SD
Levetiracetam	Girls n = 33 (45.8) Boys n = 39 (54.2)	72 (27.9)	9.33 ± 4.35 (0-17)	6.93 ± 4.73 (0-16)
Valproic acid	Girls n = 59 (49.6) Boys n = 60 (50.4)	119 (46.1)	10 ± 3.82 (2-17)	6.42 ± 4.44 (0-16)
Phenobarbital	Girls n = 15 (35.7) Boys n = 27 (64.3)	42 (16.3)	3.02 ± 2.55 (0-13)	0.42 ± 0.71 (0-2)
Carbamazepine	Girls n = 8 (32) Boys n = 17 (68)	25 (9.7)	10.96 ± 3.33 (2-16)	6.37 ± 3.91 (1-14)

SD, standard deviation.

DISCUSSION

This study compared the short- and long-term effects of commonly used AEDs in monotherapy (VPA, CBZ, LEV, and PB) on hematological, biochemical, and hormonal parameters and showed that short- and long-term monotherapy caused no significant change in hematological and hormonal parameters and in most of the biochemical parameters.

Phenytoin, PB, CBZ, VPA, and oxcarbazepine are AEDs causing abnormalities in thyroid hormones; however, such adverse effects have

Table 2. Characteristics of Laboratory Parameters of Patients Taking Levetiracetam

Parameters	Third Month of Treatment	Ninth Month of Treatment	*P*
WBC (×10³/μL)	9.27 ± 3.25	8.82 ± 3.77	.443
RBC (×10⁴/μL)	4.96 ± 0.38	5.04 ± 0.5	.7
Hb (g/dL)	13.09 ± 1.22	13.34 ± 1.23	.56
HCT (%)	39.78 ± 3.77	40.15 ± 3.88	.435
PLT (×10⁴/μL)	279.99 ± 81.18	281.53 ± 95.77	.842
AST (U/L)	27.35 ± 13.08	39.38 ± 96.45	.303
ALT (U/L)	19 ± 21.56	28.45 ± 80.43	.249
BUN (mg/dL)	23.46 ± 7.81	23.18 ± 7.48	.806
Cr (mg/dL)	**0.54 ± 0.90**	**0.57 ± 0.08**	**.009**
Na (mg/dL))	139.01 ± 2.57	138.56 ± 2.56	.327
Ca (mg/dL)	9.49 ± 0.85	9.69 ± 0.94	.309
Folate (ng/mL)	11.61 ± 3.21	9.69 ± 3.34	.199
Vitamin B12 (pg/mL)	261.07 ± 126.89	303.15 ± 135.33	.159
25 OH D vitamin (ng/mL)	13.90 ± 3.36	15.80 ± 6.05	.583
Free T4 (ng/dL)	0.94 ± 0.13	0.87 ± 0.13	.107
TSH (mIU/L)	2.09 ± 1.28	1.92 ± 1.01	.441

WBC, white blood cell; RBC, red blood cell; HCT, hematocrit; PLT, platelet; BUN, blood urea nitrogen, Cr, creatinine; ALT, alanine aminotransferase; Hb, hemoglobin; AST, aspartate aminotransferase; Na, sodium; Ca, calcium; FT4, free thyroxine; TSH, thyroid-stimulating hormone; 25 OH D vitamin, 25-hydroxy D vitamin.

MAIN POINTS

- The purpose of the antiepileptic drug treatment is to control the seizures without causing any side effects.
- The use of anti-epileptic drugs sometimes causes side effects.
- Anti-epileptic drug therapy should be checked routinely to investigate the effects of treatment on hormonal, biochemical, and hematological parameters.

Table 3. Characteristics of Laboratory Parameters of Patients Taking Valproic Acid

Parameter	Third Month of Treatment	Ninth Month of Treatment	*P*
WBC (×10³/µL)	**8.88 ± 3.11**	**7.94 ± 2.26**	**.005**
RBC (×10⁴/µL)	4.81 ± 0.43	4.78 ± 0.39	.402
HGB (g/dL)	13.10 ± 1.18	13.35 ± 3.10	.391
HCT (%)	39.39 ± 3.21	39.30 ± 3.12	.731
PLT (×10⁴/µL)	244.54 ± 64.35	253.81 ± 72.97	.175
AST (U/L)	24.76 ± 6.29	24.84 ± 7.46	.931
ALT (U/L)	14.01 ± 5.80	14.36 ± 6.12	.670
BUN (mg/dL)	24.41 ± 6.95	24.49 ± 8.77	.944
Cr (mg/dL)	0.54 ± 0.09	1.19 ± 5.84	.295
Na (mg/dL)	138.83 ± 2.71	137.82 ± 14.41	.520
Ca (mg/dL)	**9.38 ± 0.79**	**9.68 ± 0.40**	**.002**
Folate (ng/mL)	10.41 ± 3.47	10.32 ± 3.65	.877
Vitamin B12 (pg/mL)	327.95 ± 187.34	399.82 ± 194.56	.069
25 OH D vitamin (ng/mL)	18.01 ± 6.31	21.25 ± 8.70	.180
Free T4 (ng/dL)	0.90 ± 0.16	0.87 ± 0.14	.196
TSH (mIU/L)	2.75 ± 1.42	2.77 ± 1.10	.930

WBC, white blood cell; RBC, red blood cell; HCT, hematocrit; PLT, platelet; BUN, blood urea nitrogen, Cr, creatinine; ALT, alanine aminotransferase; Hb, hemoglobin; AST, aspartate aminotransferase; Na, sodium; Ca, calcium; FT4, free thyroxine; TSH, thyroid-stimulating hormone; 25-hydroxy D vitamin.

not been reported in lamotrigine, LEV, tiagabine, vigabatrin, and topiramate. The AEDs may affect thyroid hormone levels by increasing hepatic microsomal enzyme induction or by the effect of the hypothalamic–pituitary–adrenal axis.[4] Several studies have reported that VPA disrupts thyroid hormone balance, whereas there are also studies reporting that VPA does not affect thyroid hormone levels.[5,6] In the literature, VPA is highlighted to increase TSH levels due to its gamma-aminobutyric acid (GABA)-like effect since GABA suppresses somatostatin release and somatostatin inhibits TSH secretion.[7] Valproic acid binds to plasma proteins at a high rate, causing T4 to separate from where it binds.[8] The use of VPA monotherapy is further reported to increase TSH levels. Many studies involving both adults and children have shown that short- and long-term treatments with AEDs affect thyroid hormone levels.[9,10] On the other hand, there are also studies reporting no change in FT4 and TSH levels in epileptic patients receiving VPA monotherapy.[11,12] Carbamazepine has the potential to increase thyroid hormone metabolism by inducing the hepatic enzyme system.[13] This effect of CBZ therapy occurs in the initial months of therapy and continues throughout the therapy. Chronic exposure to PB has reported no changes in the TSH levels, whereas a significant decrease has been reported in the FT4 levels.[14] In another study, no significant difference has been observed between epileptic patients using PB and the control group in terms of FT4 and TSH levels.[15] In the study by Attilakosa et al[16] in 2019 reported no change in thyroid hormone levels in the 12th month of LEV monotherapy. Similarly, no significant change has been observed in thyroid hormone levels in the short- and long-term use of VPA, CBZ, PB, and LEV monotherapy in the present study.

Table 4. Characteristics of Laboratory Parameters of Patients Taking Carbamazepine

Parameter	Third Month of Treatment	Ninth Month of Treatment	*P*
WBC (×10³/µL)	7.04 ± 2.48	7.82 ± 4.16	.454
RBC (×10⁴/µL)	4.85 ± 0.39	4.95 ± 0.37	.188
HGB (g/dL)	**13.14 ± 1.04**	**13.69 ± 1.20**	**.010**
HCT (%)	**39.87 ± 3.03**	**41.02 ± 3.29**	**.042**
PLT (×10⁴/µL)	258.25 ± 73.87	288.80 ± 74.04	.088
AST (U/L)	26.93 ± 5.75	25.13 ± 3.73	.126
ALT (U/L)	**14.06 ± 4.66**	**15.81 ± 5.85**	**.045**
BUN (mg/dL)	27.62 ± 5.07	25.31 ± 9.00	.233
Cr (mg/dL)	0.56 ± 0.08	0.55 ± 0.10	.538
Na (mg/dL)	139.29 ± 2.68	139.58 ± 1.37	.689
Ca (mg/dL)	9.44 ± 0.34	9.57 ± 0.54	.381
Folate (ng/mL)	8.34 ± 3.74	7.63 ± 3.06	.606
Vitamin B12 (pg/mL)	308.87 ± 288.42	337.62 ± 175.51	.616
25 OH D vitamin (ng/mL)	22.71 ± 7.57	23.26 ± 8.91	.5
Free T4 (ng/dL)	0.75 ± 0.13	0.73 ± 0.17	.864
TSH (mIU/L)	1.82 ± 0.75	2.77 ± 1.81	.243

WBC, white blood cell; RBC, red blood cell; HCT, hematocrit; PLT, platelet; BUN, blood urea nitrogen, Cr, creatinine; ALT, alanine aminotransferase; Hb, hemoglobin; AST, aspartate aminotransferase; Na, sodium; Ca, calcium; FT4, free thyroxine; TSH, thyroid-stimulating hormone; 25 OH D vitamin, 25-hydroxy D vitamin.

Long-term use of AEDs is an important risk factor for vitamin D deficiency. Periodic monitoring of blood levels and the use of vitamin D supplements are recommended for children receiving long-term AED therapy. Seizures, neuromotor retardation, immobilization, polytherapy, and long-term therapy affect bone health and aggregate vitamin D deficiency.[17,18] Baek et al[19], reported that 25-OH D was significantly lower in patients receiving AED therapy for less or more than 2 years. In a study by Lee et al[20], basal vitamin D levels were found to be negatively affected in patients receiving AEDs for more than 2 years. In the present study, no significant change was observed in vitamin D levels in short- and long-term monotherapy.

Folic acid deficiency is known to develop in several epileptic patients receiving AEDs (e.g., VPA and CBZ). In a study by Karabiber et al[21], the serum folate level of the groups receiving VPA and CBZ was reported to be lower than the control group. Information about the B12 level of patients using AEDs is controversial. In the literature, B12 levels have been reported to be decreased, normal, or increased in patients with epilepsy.[21-23] Karabiber et al[21] found that serum B12 levels were significantly lower in the group receiving CBZ, whereas they did not observe any difference between the VPA group and the control group. In a study by Tamura et al[23], serum vitamin B12 concentrations were found to be significantly higher in patients receiving VPA compared to those receiving phenytoin, lamotrigine, or CBZ.[23] There is no consensus on the effect of long-term use of AEDs on folic acid and vitamin B12 metabolism. In the present study, there were no changes in folic acid and vitamin B12 levels in patients receiving short- and long-term monotherapy.

Most AEDs cause a varying range of hematological disorders, including thrombocytopenia, neutropenia, anemia, and bone marrow failure. Aplastic anemia and agranulocytosis are reported to be associated with the use of CBZ, whereas thrombocytopenia and leukopenia are some of the serious hematological adverse effects of VPA, CBZ, and LEV therapy cited in the literature.[24] Valproic acid has a wide range of hematological toxicity, including anemia, leukopenia, macrocytosis, and Pelger–Huët anomaly.[25] The hematological effects of LEV are controversial. Cases of neutropenia, lymphopenia, or thrombocytopenia resulting from the use of LEV are reported in the

Table 5. Characteristics of Laboratory Parameters of Patients Taking Phenobarbital

Parameter	Third Month of Treatment	Ninth Month of Treatment	*P*
WBC (×10³/µL)	10.47 ± 2.76	9.93 ± 3.25	.352
RBC (×10⁴/µL)	4.70 ± 0.54	4.84 ± 0.39	.124
HGB (g/dL)	11.93 ± 1.18	12.13 ± 1.02	.388
HCT (%)	36.09 ± 3.26	36.65 ± 2.59	.267
PLT (×10⁴/µL)	**349.75 ± 116.24**	**310.36 ± 114.67**	**.037**
AST (U/L)	34.06 ± 8.47	34.72 ± 9.00	.699
ALT (U/L)	20.59 ± 8.82	20.53 ± 9.05	.966
BUN (mg/dL)	23.17 ± 10.62	25.25 ± 15.35	.511
Cr (mg/dL)	**0.43 ± 0.03**	**0.46 ± 0.06**	**.031**
Na (mg/dL)	137.75 ± 2.91	138.63 ± 3.52	.272
Ca (mg/dL)	9.79 ± 0.51	9.65 ± 0.64	.217
Folate (ng/mL)	11.63 ± 7.83	12.20 ± 7.10	.814
Vitamin B12 (pg/mL)	468.81 ± 388.28	436.09 ± 239.13	.668
25 OH D vitamin (ng/mL)	20.87 ± 10.32	19.11 ± 5.01	.771
Free T4 (ng/dL)	0.94 ± 0.16	0.86 ± 0.17	.185
TSH (mIU/L)	2.12 ± 0.86	1.99 ± 1.04	.656

WBC, white blood cell; RBC, red blood cell; HCT, hematocrit; PLT, platelet; BUN, blood urea nitrogen, Cr, creatinine; ALT, alanine aminotransferase; Hb, hemoglobin; AST, aspartate aminotransferase; Na, sodium; Ca, calcium; FT4, free thyroxine; TSH, thyroid-stimulating hormone; 25 OH D vitamin, 25-hydroxy D vitamin.

literature.[26-28] Dinopoulos et al[29] evaluated the hematological parameters in 22 epileptic patients receiving LEV before the treatment and in the second and sixth months of treatment. The authors reported that lymphocyte count was significantly decreased in the sixth month of treatment and no significant change in the other parameters was observed in the second and sixth months of treatment. In a study by Evans et al[30], there was no significant change in the mean Hct and PLT levels in 176 epileptic patients receiving CBZ for 12 months, whereas there was a decrease in WBC and total neutrophil count at the first, eighth, and twelfth months of treatment; however, these differences were not statistically significant. Alsamman et al[31] reported that adolescents receiving CBZ monotherapy for at least 1 year had lower Hb and PLT levels compared to the control group; however, this difference was not statistically significant. Contrary to this, Evans et al[30] and Halikas et al[32] reported no significant change in PLT and WBC levels in epileptic patients receiving CBZ. In the present study, the statistically significance increase between the carbamazepine and Hb and Hct levels relationship may be affected by many parameters such as the patient's diet, age, and hemodilution. In fact, this increase is also within the normal limits. The liver is the main organ responsible for the metabolism and elimination of many AEDs. There is a wide range of reactions associated with AEDs, from mild and transient elevations of hepatic enzymes to fatal hepatic failure. Liver enzymes are important biomarkers of hepatoxicity. Clinical manifestations of hepatotoxicity are hepatocellular injury and elevated AST and ALT levels.[33] Several AEDs (e.g., CBZ, PB, and VPA) cause mild elevations of liver enzymes. These elevations are usually transitory or dose-related.[34] In a study by Sonmez et al[35] involving 64 epileptic patients aged 1-15 years receiving PB (n = 18.5 mg/kg/day), CBZ (n = 22, 10-15 mg/kg/day), and VPA (n = 24, 20 mg/kg/day), the AST, ALT, ALP, and GGT levels measured before treatment and at the third, sixth, and twelfth months of treatment were compared. The authors reported that AST, ALT, ALP, and GGT levels increased significantly at the third, sixth, and twelfth months of treatment in the PB group, whereas they observed no significant changes in liver enzymes in the group receiving CBZ and VPA.[35] Yoshimura et al[36] found no change in biochemical parameters in adults before VPA treatment and in the sixth month of treatment. Hauser et al[37] reported that they observed no significant elevation in AST, ALT, GGT, and ALP levels, but a significant decrease in ALT in the third and sixth months of VPA treatment. Although different results have been obtained in studies investigating the effect of AEDs on liver function, VPA has been reported as a potentially hepatotoxic drug as it elevates liver enzyme levels in 20% of epileptic patients.[33] Furthermore, CBZ therapy has been reported to be associated with lower rates of drug-induced hepatotoxicity compared to VPA and to elevate liver enzyme levels in 5%-10% of patients.[38] In the present study, while a statistically significant difference was found in ALT levels in patients receiving CBZ, no statistically significant change was observed in AST and ALT levels in patients receiving other AEDs.

Metabolic acidosis, hypoglycemia, hypophosphatemia, hypocalcemia, hypernatremia, and hyperammonemia are among the rare metabolic adverse effects of VPA.[39] In the present study, there was a statistically significant lower difference in Ca values in patients receiving VPA and their Ca levels were within the normal limits.

Levetiracetam is mostly excreted in the urine without causing any changes. Since it is primarily excreted in the urine, its dose should be adjusted according to Cr clearance.[40] In a large community-based label study on the safety and effectiveness of LEV, no kidney damage was observed in 1030 patients receiving treatment for partial-onset seizures.[41] In another multi-center study involving 99 patients with refractory partial-onset seizures receiving LEV of 1000-3000 mg/day, no change was reported in the blood urea and Cr values.[42] On the other hand, there are several studies reporting LEV-induced kidney damage.[43-45]

About 25% of PB is excreted unchanged by the kidneys. Its dose should be reduced in patients suffering from renal insufficiency.[46] In the present study, a statistically significant difference was found in patients using LEV and PB in terms of Cr; however, this increase was within the normal range for Cr, and none of our patients developed kidney damage.

Although there are studies evaluating hematological, hormonal, and biochemical parameters in the literature, the number of studies investigating the long-term effects of AEDs on these parameters is limited.[29,47-49]

Limitations

This study has several limitations. First, it is a retrospective study and homocysteine, ALP, and PTH values could not be compared due to its retrospective design.

CONCLUSION

As a result of our study, these AEDs, if used as monotherapy and in appropriate doses, do not cause serious side effects on biochemical and hormonal parameters and they are safe. There is a need for long-term and prospective studies in this regard.

Ethics Committee Approval: This study approved by the Non-invasive Clinical Research Ethics Committee at Adıyaman University (Date: April 21, 2020, Decision no2020/3-28).

Informed Consent: Patient informed consent could not be obtained because it was a retrospective study.

Peer-review: Externally peer-reviewed.

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