The Effect of Valproic Acid on Fetal Hemoglobin Synthesis in Children with Epilepsy

Valproik Asitin Epileptik Çocuklarda Fetal Hemoglobin Sentezi Üzerine Etkileri

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Abstract: Valproic acid has been used to treat epilepsy in children. The most common side effects are hepatotoxicity, anemia and thrombocytopenia. However the effect of valproic acid on fetal hemoglobin levels has not been revealed adequately. In this study it was aimed to search the effect of valproic acid on hemoglobin levels in children receiving valproic acid. In the present cross sectional study the research group consisted of children with epilepsy who had been receiving valproic acid monotherapy for at least six months. The control group contained children without epilepsy or valproic acid medication. The data from 44 patients and 57 controls were analyzed. The mean percentage of HbF of the study group and control group were 0.48 ±0.96 (%) and 0.25 ±0.61 (%) respectively, and there was no statistical difference between groups. There was a positive relation between blood valproic acid level and HbF levels. The present research showed that valproic acid has no effect on HbF levels. For children on valproic acid therapy, the detection of increased fetal hemoglobin levels must be evaluated carefully.
Key Words: epilepsy, valproic acid, children

Carman KB, Ozdemir ZC, Duzenli Kar Y, Gunduz E, Uskudar Teke H, Sivrikaya C, Arslantas D, Yarar C, Bor O. 2018, The Effect of Valproic Acid on Fetal Hemoglobin Synthesis in Children with Epilepsy, *Osmangazi Tıp Dergisi*, 40(3): 8-12

Doi: 10.20515/otd.411757

Özet: Valproik asit çocuklarda epilepsi tedavisinde kullanılmaktadır. En sık görülen yan etkileri hepatotoksisite, anemi ve trombositopenidir. Valproik asit bazı hematolojik hastalıklarda tedavi amacıyla kullanılmaktadır. Epileptik hastalarda fetal hemoglobin üzerine olan etkileri tam olarak araştırılmamıştır. Bu vaka kontrol çalışmasında en az altı aydır valproik asit tedavisi alan epilepsi hastası çocuklar ve sağlıklı gönüllüler dahil edilmiştir. Fetal hemoglobin değerleri, ilaç kan düzeyleri araştırılmıştır. Kırk dört epilepsi hastası çocuk ve 57 sağlıklı çocuk araştırmaya dahil edildi. Ortalama fetal hemoglobin (HbF) yüzdesi epilepsi hastalarında ve kontrol grubunda sırasıyla 0.48 ±0.96 (%) ve 0.25 ±0.61 (%) saptandı. Kan valproik asit düzeyi ile HbF düzeyi arasında anlamlı bir ilişki belirlendi. Çalışmamız valproik asit tedavisinin HbF düzeyini etkilemediğini gösterdi. Epileptik hastalarda HbF yüksekliği belirlenmesi durumunda dikkatli bir araştırma gerekmektedir.
Anahtar Kelimeler: epilepsi, çocuk, valproik asit, fetal hemoglobin

Çarman KB, Özdemir ZC , Düzenli Kar Y, Gündüz E, Üsküdar Teke H, Sivrikaya C, Arslantaş D, Yarar C, Bör Ö. 2018, Valproik Asitin Epileptik Çocuklarda Fetal Hemoglobin Üzerine Etkileri, *Osmangazi Journal of Medicine*, 40(3): 8-12
Doi: 10.20515/otd.411757

Geliş Tarihi / Received
02.04.2018

Kabul Tarihi / Accepted:
16.04.2018

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1. Introduction

Fetal hemoglobin (HbF) is the predominant hemoglobin at 24-week gestation, it constitutes 90% of the total hemoglobin. During the 3rd trimester, a gradual decline occurs, and at birth HbF averages 70% of the total hemoglobin. Synthesis of HbF decreases rapidly postnatally, and by 6-12 months of age only a trace is present [1]. Some medications might induce the synthesis of HbF. This induction might provide a new opportunity to treat some hematological disorders, such as Diamond Blackfan Anemia, via increasing HbF level [2, 3].

Valproic acid, also known as n-dipropylacetic acid or 2-propylpentaoic acid, has been used in the treatment of different types of epilepsy. It has adverse effects on different organ systems or tissues including blood, such as thrombocytopenia, and leukopenia [4]. Although anemia is another adverse effect related to valproic acid treatment, it might induce fetal hemoglobin synthesis. Fetal hemoglobin levels might be increased in epileptic patients treated with valproic acid and could be misinterpreted as hemoglobinopathy [5].

The present study aimed to search the effect of valproic acid treatment on HbF level in children with epilepsy.

2. Materials and Methods

This study was conducted at a university hospital in Turkey. The research group consisted of children with epilepsy who have been receiving valproic acid monotherapy for at least six months. The control group contained children without epilepsy or valproic acid medication. Children suffering from hemoglobinopathies and children treated with multiple anti-epileptic drugs (AEDs) were excluded.

Serum valproic acid levels were measured by enzyme immunoassay method (Olympus AU400 Chemistry Analyzer).

Samples for complete blood count were collected in K3EDTA tubes and analyzed with an automated hematology analyzer, COULTER LH750 Analyzer (Beckman Coulter, Florida, USA). Serum samples for hemoglobin electrophoresis were analyzed with a capillary electrophoresis system, Minicap Flex Piercing (Sebia, Lisses, France).

This research was approved by local ethical committee (Number: 7, Date: 26.01.2017).

Informed consents were obtained from parents of all participitants. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, Ill., USA). Student t test (Student's t test) and Pearson correlation analysis were used to for compare mean values and correlation respectively. $p \leq 0.05$ was considered statistically significant.

3. Results

The study group consisted of 44 children and the mean age was calculated as 8.75 ± 5.12 years old. In the control group, the mean age was 8.12 ± 5.56 years old and there were fifty-seven children. There was no statistical difference between the study and control groups ($p > 0.05$).(Table 1).

The results of hematologic evaluations of the study and control group revealed that complete blood counts were similar in the two groups. The mean percentage of HbF in the study group and control group were 0.48 ± 0.96 (%) and 0.25 ± 0.61 (%) respectively, and there was no statistical difference between groups (Table 2).

Table 1.
Demographic characteristics of children

	Study group	**Control group**
Sex	44	57
Female	21	27
Male	23	30
Mean age (Years)	8.75 ± 5.12	8.12 ± 5.56

Table 2.
The hematological parameters of children.

	Study group	Control group	p value
Mean hemoglobin (Hb) g/dL	12.86 ± 1.39	13.30 ± 1.29	0.10
Mean platelet count	277250 ± 63668	302.210 ± 82618	0.09
Mean HbF (%)	0.48 ± 0.96	0.25 ± 0.61	0.17
Mean HbA (%)	96.87 ± 0.96	97.24 ± 0.77	**0.03**
Mean HbA2 (%)	2.58 ± 0.23	2.49 ± 0.58	0.28
MCV (fL)	79.00 ± 4.34	77.32 ± 4.88	0.76
PLT	277250 ± 63668	302210 ± 82618	0.10

HbF: fetal hemoglobin, HbA: hemoglobin A

There was no significant difference in hematological parameters in both sexes, including HbF values (p> 0.05). The valproic acid levels ranged from 22.38 to 143.39 µg/mL with a mean 73.17 µg/Ml, and there was correlation between serum valproic acid level and HbF value (Figure1).

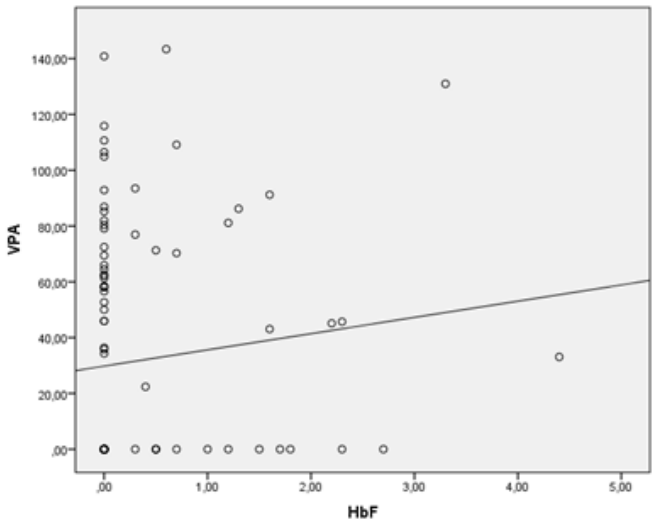

Figure 1. *Relation between blood valproic acid and HbF levels*.

4. Discussion

Valproic acid has been used for treating epilepsy in children worldwide. One of the major side effects of valproic acid is on the hematological system, such as anemia, thrombocytopenia, and neutropenia [6]. On the other hand valproic acid has effect on fetal hemoglobin synthesis [3]. It is structurally related to butyric acid analogs which has been shown to increase HbF. It acts via cellular signal pathways, inhibits the ERK (external-regulated kinase) and activates the p38 pathways, which results in increased HbF synthesis [7].

This affect might be seen in patients receiving valproic acid for epilepsy treatment [8]. The effect of valproic acid on fetal hemoglobin levels in children with epilepsy have been searched rarely. Kieslich et al [5] researched the HbF levels in children treated with valproic acid for at least three months. They reported that fetal hemoglobin levels of epileptic children were higher than controls, and found a positive correlation between HbF and serum valproic acid levels. Unlike previous researches, the present study revealed no effect of valproic acid treatment on HbF synthesis. Although the molecular mechanism is well understood, clinical practice is quite complicated. Selby R et al [9] searched the effect of valproic acid HbF levels in individuals with and without sickle cell disease (SCD) and reported increased HbF levels only present in SCD patients. These contradictory results were also observed in between β-Thalassemia and SCD. It was shown that exposure to butyric acid provides less clinical improvement in β-Thalassemia cases than SCD patients. Fathalllah H et al [10] reported that butyric acid exposure result in increase of γ-globin mRNA levels in both SDC and β-Thalassemia cases. Interestingly butyric acid also decreases α-globin mRNA levels in SCD patients. They claimed that these different clinical responses of cases might be due to effect of butyric acid on other globin genes.

Their hypothesis might be the reason why the present research revealed no increase in HbF levels and no correlation between HbF and valproic acid levels in patients. Different laboratory methods used in previous studies might be another factor effecting the results of researches done in patients with epilepsy.

The results of the present study showed no difference in the hematological parameter and HbF values in both sex. Contrary to these results, a study conducted with psychiatric patients receiving valproate for the treatment of bipolar disorder showed a positive correlation between serum valproic acid levels and mean corpuscular volume (MCV) in females [11].

This study is a cross sectional research has limitations. We believe that in a prospective study, the measurement of basal HbF levels at the start of valproic acid therapy might provide valuable information.

In conclusion, the present research showed that valproic acid, which is widely used, has no effect on HbF levels. For children on valproic acid therapy, the detection of increased fetal hemoglobin levels must be evaluated carefully.

Funding

This study was financially supported by Turkish Pediatric Association (Turk Pediatri Kurumu).

Conflict of interest

The authors declare no conflict of interest statement at the end of the manuscript

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