Original Article

Probable Toxic Effect of Sodium Valproate on Retina Using Electroretinogram

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Abstract

Background: The FDA approved drug Sodium Valproate (SV) is an anticonvulsant that is used for epilepsy and bipolar disorders. Also, neuropathic pains and migraine prophylaxis have been the target for SV. Its side effects have been reported in the literature. SV can have side effects on different organs. This report aims to explore the side effects of SV on the retina by using the Electroretinography (ERG) technique.

Material and Methods: To understand the side effects of SV, 25 patients who had used SV for more than 3 years were chosen. Flash Electroretinography was performed on these patients, and latency (msec) and amplitude (μV) of ERG of these patients were measured, then mean and standard deviations of these measurements were calculated. 25 non-SV takers were chosen as a control group, and the exact measurements and calculations were obtained.

Using SPSS (v13), these findings were compared for any differences.

Results: The mean latencies/S.D. and amplitude s/SD were 90.7 ± 9.39 and 114.94 ± 8.28 in patient and healthy groups, respectively. The difference in amplitude between the two groups was statistically significant, whereas the difference in latency was not statistically significant.

Conclusion: Based on findings of this work, it is evident that the retina is affected in SV consuming patients after three years of usage which will be discussed in full detail.

Keywords: Valproic Acid; Retina; Electroretinography.

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Introduction

SV (SV) is prescribed to treat epilepsy and bipolar disorder. It is also used to prevent migraine headaches [1]. But SV has specific side effects, which may be listed as follow. One of SV's common adverse side effects, especially at the beginning of therapy, is on the gastrointestinal. Side effects like pancreatitis, gaining weight, and sedation have been observed. Fetal side effects have been observed in SV usage during pregnancy [2]. SV also may have adverse side effects on the visual system. These side effects might be because of extended treatments or extended dosage. Adverse effects like diplopia, nystagmus, and blurry vision have been reported [3]. During treatment with SV, the retina is the tissue that might be affected by SV side effects. Electrophysiological techniqes i.e., visual evoked potential (VEP), electrooculography (EOG) and electroretinography (ERG) are among the techniques to survey different visual system disturbances [4-7].

Totan et al. investigated the side effects of Valproic acid (VPA) in retinitis pigmentosa (RP) patients. 48 eyes of these long-term VPA users were tested. No positive effects were observed in BCVA (best correction visual acuity) and VFA (visual field analysis) indices of these patients after 9 months. Also, a decrease in mfERG (multifocal electroretinogram) parameter was observed. Eventually, Totan suggested that VPA prescription for RP patients must be suspended until more thorough investigations on the safety and efficiency of VPA were done [8].

Aktas et al. investigated the toxic effects of VPA and Oxcarbazepine (OB) on Retinal ganglion cells (RGC) in rats. Their findings indicate that the number of RGC was lower in rats that have been treated with OB and VPA compared to the control group. Also, they found that usage of VPA had no meaningful effect, as the number of RGC of both groups was not so different, and there was no critical difference [9].

The contradictory result in these findings is so broad that we decided to study the probable toxic effect of valproate sodium on the retina of a human being using electroretinography which will be considered in brief in this paper.

Material and Methods

For the ERG test, the device (BIOMEDICA MANGONI SNC, Italy) with 3 electrodes connected to the patients. The active electrode was connected to the cornea, the reference electrode was connected to the ear lobe, and the earth electrode was connected to the forehead. The active electrode was a hard contact lens. Detection and electrical response from the retina and transfer of these signals were made by thread-shaped cotton soaked in saline. Electrophysiological conductive paste connected the reference, and earth electrodes were connected to the skin by electrophysiological conductive paste.

Before connecting electrodes, standard dilating eye drops were applied to patients' eyes, and then the anesthetic drop was applied to numb their eyes. Then the electrodes were placed.

Stimulation occurred by a standardized flash of light. The produced ERG signal is a wave, a combination of a and b waves. In this study, latency (m sec), amplitude (μV), and b wave were recorded for each eye. Then, using these entries, the mean and standard deviation of data of each group were calculated. The final data of the two groups were compared with each other.

The mean and standard deviation values were used to present our data and the Kolmogorov-

Table 1: Demographic findings of participants in the control and case Groups

Variable		n per groups	Group		P value
			Control	Case	
Age		50	30 ± 5.4	29.9 ± 5.23	0.86*
Sex	Male	50	23	26	0.54**
	Female		27	27	
VA (LogMAR)		50	0 ± 0	0.044 ± 0.06	0*

*Mann-Whitney Test

** Chi-Square Test

Smirnov test to evaluate the normality of distribution for all variables. We used T-test for normal variables, Mann-Whitney for variables that are not normal, and Chi-square for categorical variables to describe differences between study groups. We performed the statistical analysis using SPSS software version 22 (IBM, Armonk, NY, USA). P values less than 0.05 were considered significant. The power of the study was > 99 %, with alpha level 0.05 based on web-based sample size calculator analysis. This study has been accepted by the Ethical Committee of Tehran Islamic Azad University of Medical Sciences; ethical code: IR.IAU.TMU.REC.1399.179

Results

Table 1 shows the age, sex, and visual acuity. The difference between the two groups is not statistically significant. Table 2 shows the mean latency (m sec)/SD and amplitude (μV) SD of ERG, b wave in the case of patients (case) and healthy population (control)groups. Analyzing the results obtained, the differences between the two groups are statistically significant as far as the amplitude of ERG b wave is concerned.

Discussion

SV is a helpful drug to treat patients suffering from bipolar and seizure, but while useful for some causes, it may have specific side effects on the retina. In the present study, it is observed that the patients under SV treatment have abnormal electroretinography, which was noticeable in the amplitude of the b wave. It is already mentioned that ERG, b wave is originated from bipolar and Muller cells in the retina [10], so these are the layers that may be affected in these patients.

Table 2: Measurements of the mean latency and amplitude of ERG in the control and case groups

Variable	Group		P value*
	Control	Case	
Amplitude (μv)	114.94 ± 8.28	90.7 ± 9.39	0.000
Latency (m sec)	44.36 ± 1.49	44.44 ± 1.52	0.85

*Mann-Whitney Test

Some research documents are in contradiction with the findings of this work.

M et al. and in 2019 worked on probable adverse effects of VPA on the retina using the ERG technique. They concluded that SV does not affect the retina. It should be mentioned that they checked the patients after 2 years, whereas we selected the patients after 3 years of treatment [11].

Finally, Naser M et al. 2014 worked on the possible effect of SV on the retina of the patients. The patients were treated for 1 year, and they could not find retinal disturbances in those patients [12].

Another supporting research work was done by Farabiy et al. in 2019. They worked on 27 patients with epilepsy following SV treatment for at least one year. They tested the visual evoked potential technique and found abnormal VEP tests in the patients, indicating visual pathway disorders [13]. It is a fact that the visual pathway starts from the retina to the visual cortex [14]. So, it contributes from the retina; thereby, abnormal VEP may also produce pathological changes in the retina.

In another report, Verrotti et al. in 2003 worked on color vision deficit in epileptic adolescents the following mono with VPA and carbamazepine (CBZ). The result of their work confirms that epileptic patients treated with VPA and CBZ can show color vision deficits. These abnormalities are presented not only in the foveal area but also in the peripheral area, which is parts of the retina [15].

The report mentioned above, to some extent, supports the result of the present work.

Conclusion

The findings of this study show that SV may affect the retina in patients using the medication at least for three years.

Ethical approval

This study has been accepted by the Ethical Committee of Tehran Islamic Azad University of Medical Sciences; ethical code: IR.IAU.TMU.REC.1399.179.

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Footnotes and Financial Disclosures

Conflict of interest

The authors have no conflict of interest with the subject matter of the present manuscript.