ORIGINAL ARTICLE

Study of the Amiodarone Toxic Effect on the Visual Pathway by Visual Evoked Potential Examination

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ABSTRACT

Background: Amiodarone is a third-class antiarrhythmic drug used to treat a number of heart conditions such as ventricular and supraventricular arrhythmias and atrial fibrillation. Like any other drug, it has side effects, the most important of which are ocular side effects such as inflammation of the optic nerve, impaired vision, the appearance of deposits on the corneal epithelium and visual loss.
Aim: To evaluate the amiodarone toxic effect on the visual pathway by visual evoked potential stimulation using checkerboard pattern.
Methods: In this study, 25 patients treated with amiodarone who had visual impairment (blurred vision, seeing a colored ring around the light) were referred to Basir Eye Clinic were randomly selected, p100 latency (in milliseconds) and amplitude (in microvolts) measured in them and compared with 25 patients as a control group from April 2019 to March 2020.
Results: The mean latency of p100 wave in the case group was 116.9 and in the control group was 99.7 which showed a statistically significant difference between the two groups (P <0.001). Also the mean amplitude recorded in case group was 2.2 and in the control group was 6.1 which showed a statistically significant difference between the two groups (P <0.001).
Conclusion: this is inferred that amiodarone has a significant effect on the optic nerve pathway, which is detected by the visual evoked potential based on the decreasing amplitude index and increasing p100 wave latency.
Keywords: visual evoked potential, amiodarone, checkerboard pattern.

INTRODUCTION

Amiodarone is a third-class antiarrhythmic drug used to block supraventricular and ventricular arrhythmias by blocking ion channels in the heart, including sodium, potassium, and calcium channels[1,2]. Systemic side effects of the drug include thyroid failure, pulmonary complications, drug interactions with other drugs such as digoxin and warfarin, peripheral neuropathy, ataxia, photosensitivity, and gastrointestinal side effects[3]. An important complication of amiodarone, which is associated with permanent vision loss, is optic neuropathy. It is clinically very similar to the Non-arterial anterior ischemic optic neuropathy (NAION) and presents bilaterally[4,5]. Although there are various methods (MRI, VEP, OCT, etc.) to examine the visual pathways abnormalities, VEP is one of the most common methods of examination[6]. Visual Evoked Potential (VEP) is a method of assessing the function of the visual pathways and visual cortex of the brain (cerebral occipital cortex) to diagnose pathological disorders in patients who do not show apparent signs of ocular or visual impairment (Visual loss without cause)[7].

Due to the proximity of the visual cortex to the surface of the skull, VEP is a relatively easy recording method of the reactions of this part of the cerebral cortex[8,9]. In addition, VEP is a non-invasive procedure that is not painful and does not require hospitalization[10]. The electrical potential of a visual stimulus affects the electrical activity of the brain and measured by the Electrodes located on the occipital skin[11]. According to studies, The most common stimulus used in VEP is a checkerboard pattern (due to pattern reversal). Although there is more inter-subject VEP reliability in the checkerboard pattern than other Stimuli (flash or pattern onset stimuli), each check size in the pattern and visual field size can affect the VEP. Most clinical laboratories use large check sizes because the referred patients have reduced visual acuity. The highest amplitude and fastest peak of the P100 wave in VEP are recorded when the smallest check size is used, be sharply visible for the subject[12]. In this regard, we aimed this study to investigate the clinical role of long-term usage of Amiodarone on the visual pathway by visual evoked potential experiment.

METHODS AND PATIENTS

In this Cross-sectional study, 25 patients treated with amiodarone with a dosage of at least 400mg/day who had visual impairment (blurred vision, seeing a colored ring around the light) were referred to Basir Eye Clinic, were randomly selected, p100 latency (in milliseconds) and amplitude (in microvolts) measured in them and compared with 25 patients as a control group from April 2019 to March 2020. Our inclusion criteria were: Does not have a migraine (does not have a migraine attack at least one month before the start of the study), Does not have multiple sclerosis, willingness to participate in the study, Does not take drugs that cause vision problems (such as chloroquines, ethambutol, chemotherapy drugs), and Taking amiodarone for at least 6 months. The exclusion criteria were: History of neurological diseases associated

with seizures, Optic neuritis, unwillingness to participate in the study.

During the experiment, patients were alert and comfortable and there was no noise in the test room, to prevent possible artifacts. The stimulus was clearly visible, and patients who wore glasses were allowed to use them during the experiment to optimize vision[13]. Also, no medication was used to dilate the pupil.

In the visual evoked potential test Oz (occipital lobe) was considered as the location of the active electrode, Fz (forehead) as the reference, and ground electrode was put at Cz (vertex), then Latency and amplitude were measured at P100 wave. The mean and standard deviation of the mentioned parameters were calculated in two groups (case and control).

The visual evoked potential test was performed by Micromed^{TM} evice monocularly for each eye. Checkerboard with 100% contrast and 5cpd (cycle per degree) spatial frequency were considered as visual stimuli.

A system for placing electrodes was the "10-20 International System." The surface impedance of the electrodes was less than 2 kΩ, and finally, the final signal was obtained by averaging 100 signals. The data were analyzed using SPSS version 26. The statistical test used was an independent t-test and to describe the information, we used descriptive statistics (mean, standard deviation, and frequency distribution). P<0.05 was considered statistically significant.

RESULTS

The age of patients in both groups was between 25 and 45 years and both groups included 12 men and 13 women. Patients were referred to the clinic when amiodarone caused vision problems. Table 1 shows the findings regarding the latency of P100 wave and amplitude in both amiodarone-treated or case and control groups. The mean latency of p100 wave in the case group was 116.9 msec with a standard deviation of 4.6 and in the control group was 99.7 msec with a standard deviation of 3.7, which showed a statistically significant difference between the two groups (P<0.001).

The mean amplitude recorded in the case group was 2.2 µV with a standard deviation of 0.9 and in the control group was 6.1µV with a standard deviation of 1.3, which showed a statistically significant difference between the two groups (P < 0.001).

Table 1- Frequency distribution of Latency and Amplitude indices recorded in VEP

	group	N	Mean	Std. Deviation
latency	control	25	99.7600	4.66619
	case	25	116.9600	3.79122
amplitude	control	25	6.1200	1.36382
	case	25	2.2000	.95743

Table 2.

	Group			statistic	Std. Error
latency	control	Mean		99.7600	.93
		95% Confidence Interval for Mean	lower Bound	97.8339	
			upper Bound	101.6861	
		Std. Deviation		4.66619	
		Minimum		88.00	
		Maximum		108.00	
	case	Mean		116.9600	.75
		95% Confidence Interval for Mean	lower Bound	115.3951	
			upper Bound	118.5249	
		Std. Deviation		3.79122	
		Minimum		110.00	
		Maximum		124.00	
amplitude	control	Mean		6.1200	.27
		95% Confidence Interval for Mean	lower Bound	5.5570	
			upper Bound	6.6830	
		Std. Deviation		1.36382	
		Minimum		4.00	
		Maximum		8.00	
	case	Mean		2.2000	.19
		95% Confidence Interval for Mean	Lower Bound	1.8048	
			Upper Bound	2.5952	
		Std. Deviation		.95743	
		Minimum		.00	
		Maximum		4.00	

According to the results of the research, the minimum level of amplitude (μV) in the case group is 0 and the maximum is four, the lowest level of amplitude in the control group is 4 and the highest is eight. Similarly, the minimum and maximum levels for the P100 wave latency in the case and control group are shown in detail in Table 2.

DISCUSSION

Researchers have long been aware of the ocular side effects of long-term use of amiodarone and have reviewed data on prevalence and prognostic factors. However, given these data and other research in the past, there are studies that have proven otherwise. Therefore, considering the importance of using amiodarone as a very useful drug in the control of cardiac arrhythmias, we decided to use the visual evoked potential, which is an accessible and non-invasive method, to evaluate the effect of this drug on the eye as a vital organ. Many studies have reported that Verticillate keratopathy has occurred in 70% to 100% of cases using high-dose of amiodarone[14], but in the current study, no cases were reported due to patients using low-dose amiodarone.

One of the largest studies conducted by Feiner et al. In 2004 on the effect of amiodarone on the optic nerve showed that 13 of the 447 participants in the study lost their vision. 5 out of 13 had diabetes and high blood pressure, in addition to heart disease, which is a risk factor for non-arterial ischemic anterior ischemic neuropathy (NAION). The researchers also looked at the prevalence of amiodarone-dependent optic neuropathy, which was 1.76 percent in people who had been taking amiodarone for more than a decade, compared with the same condition This rate was about 0.3% in people over 50 years old who didn't take amiodarone(15). In our study, all participants in the case group who took amiodarone for at least 6 months showed a significant delay of p100 wave. in order to avoid duplication of other factors involved in visual impairment, people with Migraine, multiple sclerosis, or even the use of drugs with induced visual impairments were not included in the study.

In a case study by Adhami et al. in 2017, A 39-year-old man who underwent eye surgery complained of seeing a colored ring around the lights after surgery. Fundoscopic examination of the eye was normal and fluorescein angiography did not show any abnormalities. There was no history of trauma to the eye and The VEP examination of the patient's eye showed a marked prolongation of the P100 wave and a decrease in amplitude. In the patient's history, it was found that the patient had been taking amiodarone for a while due to a heart problem, and for this reason, after contacting a cardiologist, he was allowed to stop taking amiodarone(16). In our study, optic neuritis caused by long-term use of amiodarone for heart problems is shown by increasing p100 wave latency and reducing amplitude in results.

In a 2014 study by Galazi et al. In Italy, two patients treated with amiodarone were respectively studied for 46 and 15 months, in both patients progressive lower extremity weakness, impaired perception, and decreased deep tendon reflex Showed. The Subsequent electrophysiological study showed sensory-motor neuropathy, which resulted from demyelination of peripheral nerves. Bilateral P100 wave latency increased In the visual evoked potential with no visual symptoms and normal MRI. The presence of previously known peripheral neuropathy was ruled out in specific laboratory studies. In the first case, neuropathy continued after 21 months of amiodarone discontinuation, while the P100 wave latency rate returned to normal, and the second patient returned to normal P100 wave latency rate after 7 months of discontinuation, while neuropathy continued until 2 years later[17]. In a study conducted by us, conditions such as impaired perception and evaluation of deep tendon reflexes were not investigated, and also patients' follow-up after discontinuation of the drug due to complications were not examined.

In this study, the most important limitations include:

1. A relatively small number of people can be examined
2. The unwillingness of some people to participate in the study
3. Impossibility of following up with patients after participating in the study

For this reason, more people were examined in Basir eye center but in the end, no one was obliged to take part in this study. Finally, it is recommended that more studies be performed to confirm the findings obtained in this study, with larger sample size and in a multicenter manner with more diverse target groups and compare their results. Studies that include following up with patients after discontinuation of the drug or reducing its dose to achieve the dose that gives the least side effects.

CONCLUSION

Based on the results of this study and their comparison with other studies, it is concluded that long-term use (at least six months) of amiodarone has an effect on the eye and optic nerve pathway and can cause impaired vision after inflammation of the optic nerve, observation of colored lights and even loss of vision. Visual complications following the use of amiodarone are influenced by factors such as the duration of drug use, dosage, association with other conditions such as diabetes, hypertension, neurological diseases (epilepsy, migraine. etc), and other conditions.

Abbreviations: NAION: Non-arterial anterior ischemic optic neuropathy; MRI: Magnetic resonance imaging; VEP: Visual Evoked Potential; OCT: Optical coherence tomography; cpd: cycle per degree.

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Competing interests: The authors declare that they have no competing interests.

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