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OTOLOGY

Acetazolamide in vestibular migraine prophylaxis: a retrospective study

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Abstract The aim of this study is to check the efficacy of acetazolamide in the prophylaxis of vestibular migraine (VM). Treatment options in VM are mainly based on migraine guidelines. We tried to assess the efficacy of acetazolamide in these patients depending on clinical similarities with episodic ataxia type 2 and familial hemiplegic migraine responding to the drug. This is a retrospective cohort study. Among 50 patients with VM and prescribed acetazolamide 500 mg/day, 39 patients were studied as five had been lost on follow-up and six had stopped taking the drug due to side effects. Vertigo and headache frequency determined by number of attacks per month, and the severity determined by visual analog scales measured in centimeters from 0 to 10 were collected from the records. Initial reported figures for frequency and severity were compared with the results gathered after 3 months of treatment. The results were compared. Acetazolamide was effective in reducing both the frequency and severity of vertigo and headache attacks and this effect was more prominent for vertigo frequency and severity.

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Introduction

Vertigo and headache are frequent symptoms in neurology clinics. After several studies in the field [1–6], vestibular migraine (VM) has been accepted as the term defining vestibular symptoms that are casually related to migraine and International Headache Society and Barany Society have created a consensus document with diagnostic criteria for this clinical entity [7]. The diagnosis was considered in the appendix of the new International Classification of Headache Disorders (ICHD)-3 beta version of headache classification [8].

VM is the most common cause for recurrent spontaneous vertigo with a lifetime prevalence of 1 %, and a 1-year prevalence of .9 % in the general population [9]. It can occur in any period of life [2–4]. Women are affected more frequently than men with a gender ratio between 1.5 and 5 [3–5]. Patients report spontaneous or positional vertigo attacks as well as imbalance [9]. The duration of attacks generally vary from minutes to a few days [1, 2, 4]. Auditory symptoms, including hearing loss, tinnitus, and aural pressure have been reported in up to 38 % of the patients [1, 3, 10]. However, hearing loss is usually mild.

During an attack and in-between attacks, the neuro-otological examination is generally normal. Mild central deficits such as persistent positional nystagmus [11] or peripheral deficits such as unilateral caloric hypoexcitability [12] have been reported.

Episodic ataxia type 2 (EA2) and familial hemiplegic migraine (FHM) are paroxysmal disorders going with vestibular symptoms and migraine headaches due to

alterations of the voltage-dependent calcium channel gene (CACNA1A) [13]. Depending on clinical similarities a genetic defect in the same region has been searched in patients with VM, but could not be identified [14, 15].

Various drugs have been used in the prophylactic treatment of VM. Apart from a recent randomized controlled trial with flunarizine [16], treatment options are mainly based on migraine guidelines.

The aim of this study was to assess the efficacy of acetazolamide on vertiginous attacks as well as headaches though it is not recommended in guidelines for migraine prophylaxis with the idea that it works in EA2 and FHM going with vestibular symptoms and migraine headaches.

Methods

The retrospective, single-center, open-label study was conducted in our tertiary care referral hospital after the approval of the study protocol by the ethics committee of Ege University Medical School between 2013 and 2015. Our patients with migraine, those both with vestibular features and just with headache are expected to keep a diary and to come to controls with their diaries indicating their attack days, the duration and severity of the attacks, the medications they took and how long it lasted before the symptoms had ceased after the medication. If they use a prophylactic medication, they are also expected to note the medication and the side effects. VM diagnosis was achieved by a special referral council that comprises specialists from otolaryngology, neurology, and physical medicine departments depending on the criteria of the Headache Classification Committee of the International Headache Society third edition (ICHD-3 beta version) [8]. Patients on follow-up for more than 6 months, experiencing two or more vertigo and/or headache attacks per month and on acetazolamide treatment for at least 3 months with vertigo and headache records clearly registered monthly were selected. Patients using other migraine-preventive or antihistamine drugs were excluded. The frequency of the vertigo and headache determined by attacks per month, and the severity determined by visual analog scales (VAS) measured in centimeters from 0 to 10 were collected from the records. The initiation of acetazolamide treatment was always with a 250 mg/day for the first week, raised to 500 mg/day in two divided doses afterwards. Adverse effects of medication were also searched. The baseline frequency and severity (mean severity determined by dividing the sum of severity values for each attack by the number of attacks) of vertigo and headache attacks were compared to those recorded at the end of the third month of therapy. Neither the physician nor the patients knew of the investigation during the initiation and follow-up of treatment.

Statistical analysis

IBM SPSS Statistics software, version 20.0, was used for data entry. Frequency values and descriptive were obtained. Since the data were obtained in ordinal scale, non-parametric statistical method "Wilcoxon Signed Ranks Test" for paired sample analysis was used. All statistical hypothesis testing were performed at $\alpha = .05$ significance level.

Results

Among 50 patients with VM who were on acetazolamide treatment 39 patients; 31 women and 8 men with a mean age of 46 (25–66) years were taken into consideration as 5 of the 50 had been lost on follow-up and 6 had stopped taking the drug within the first month because of side effects.

All patients were free for any neurological or otolaryngological signs in the examinations. Three patients had hypoexcitable caloric responses in one ear (hypoexcitability was described as the difference of Vmax for both ears >25 %), remaining 36 patients had normal caloric responses.

Vertigo and headache attack frequency and severity before treatment and at the end of the third month are given in Table 1. Mean frequency of vertigo attacks was 3.9 before treatment and 1.44 after treatment. Median values for vertigo frequency were 4 before treatment and 1 after treatment ($P < .01$). Mean and median values for vertigo severity on VAS were 5.62 and 5 cm before treatment and 2.28 and 2 cm after treatment, respectively ($P < .01$). Mean frequency of headache attacks was 4.31 before treatment and 2.85 after treatment. Median values for headache frequency were 4 before treatment and 3 after treatment ($P < .01$). Mean and median values for headache severity on VAS were 6.26 and 6 cm before treatment and 4.03 and 4 cm after treatment, respectively ($P < .01$). Ten patients were totally relieved from vertigo attacks at the end of the third month. Two patients reported no change in frequency or severity. One patient was free of headache attacks. Eight patients reported no change in frequency or severity and one patient reported a decrease in severity without a change in frequency. Frequency and severity of vertigo and headache attacks of the patients before and after treatment are shown in Figs. 1 and 2. When the reduction in frequency and severity of vertigo and headache attacks before and after treatment was compared a

Table 1 Frequency (number per month) and severity of vertigo and headache attacks before and after treatment

	Mean	Median	Min.	Max.
Pre-treatment vertigo frequency (attack number)	3.9	4	1	6
Post-treatment vertigo frequency (attack number)	1.44	1	0	6
Pre-treatment vertigo severity (cm)	5.62	5	2	10
Post-treatment vertigo severity (cm)	2.28	2	0	8
Pre-treatment headache frequency (attack number)	4.31	4	2	8
Post-treatment headache frequency (attack number)	2.85	3	0	6
Pre-treatment headache severity (cm)	6.26	6	3	10
Post-treatment headache severity (cm)	4.03	4	0	7

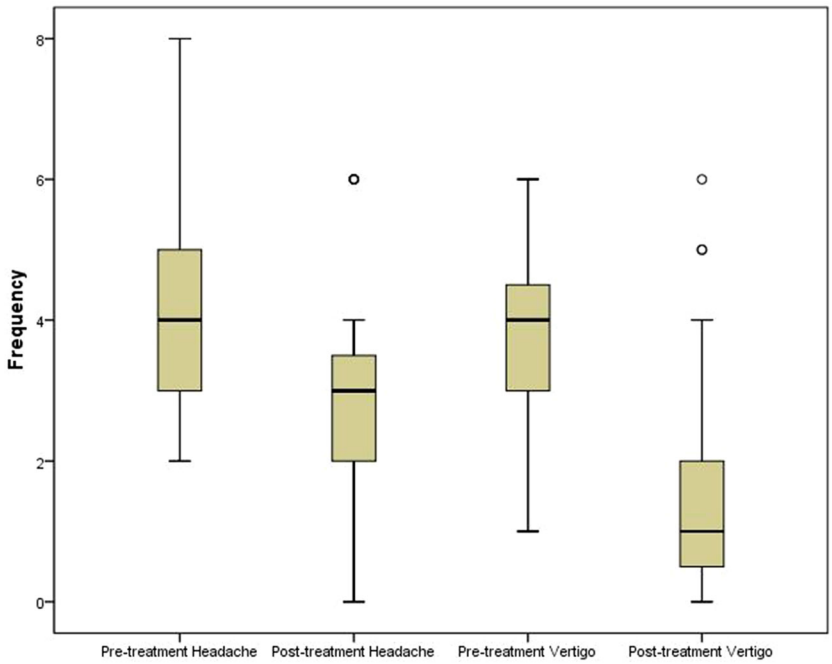

Fig. 1 Frequency of vertigo and headache attacks of the patients before and after treatment

significant decrease on behalf of vertigo attacks both in frequency and severity was found ($P < .01$).

Patients described adverse effects after drug administration within early days of treatment. In total, 34 out of 39 patients (87.2 %) described paresthesias, 26 (66.7 %) described change in taste, 19 (48.7 %) described fatigue and 4 (10.3 %) described nausea.

Discussion

Therapeutic studies on VM are few and they are mainly retrospective cohort studies and open-label trials.

In three retrospective cohort studies, beta-blockers, valproic acid, topiramate, lamotrigine, clonazepam, amitriptyline, and flunarizine have been shown to decrease the duration, intensity, and frequency of episodic vertigo and its associated features [17–19].

In a retrospective, open-label study lamotrigine has been used and was found to decrease the frequency of the vertiginous episodes without a statistically significant effect on headache frequency [20].

In a prospective, open-label study topiramate at 50 and 100 mg daily doses has been shown to reduce both the frequency and severity of vertigo and headache attacks [21]. Both doses of the drug were equally efficacious. However, 50 mg/day dose was advised as higher adverse effects were noted when 100 mg/day was used.

Cinnarizine has been studied in a retrospective, open-label study and the mean frequency of vertigo as well as the mean frequency, duration and intensity of migraine headaches have been found to decrease [22].

In the only randomized control trial with flunarizine the frequency and severity of the vertiginous episodes showed improvement whereas headache frequency and severity did not change [16].

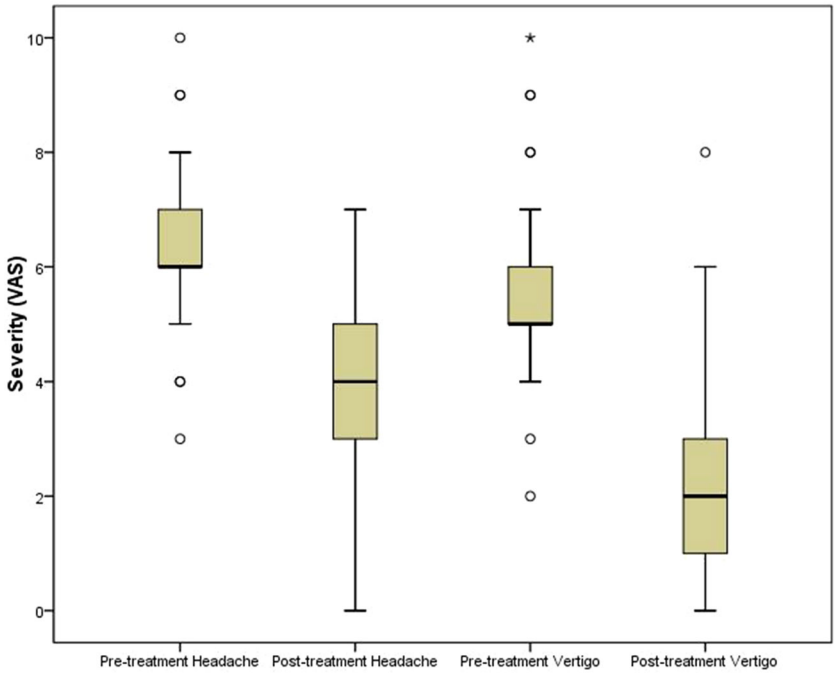

Fig. 2 Severity of vertigo and headache attacks of the patients before and after treatment

Acetazolamide is an unsubstituted sulphonamide. Its main biochemical action is the inhibition of carbonic anhydrase, an enzyme distributed widely in the brain and other tissues. Besides being a diuretic agent, it is used in diverse neurological disorders. Carbonic anhydrase is found in glial cells and myelin. Its inhibition in the brain causes a rise in total brain carbon dioxide concentrations [23] and also a blockade of chloride and bicarbonate membrane transport and increases the transmembrane chloride gradient. Perturbation of the CO_2 equilibrium and/or the inhibition of ion channels are the mechanisms of action in reducing seizures [24].

Conflicting results are present about the usage of acetazolamide in patients with migraine. In a clinical study investigating acetazolamide efficacy in sporadic migraine with and without aura, a reduction in the frequency of attacks in both migraine types has been reported and this effect was ascribed to the possible involvement of neuronal ion channels [25]. This last mechanism is the one thought to be responsible for the acetazolamide mechanism of action in familial ion channels disorders, such as FHM, hypokalemic periodic paralysis and EA2 [26–28].

On the other hand, in migraine sufferers Shirai et al. [29] found that acetazolamide by itself may induce headache.

When migraine treatment guidelines are taken into consideration one can see that it is not mentioned in the EFNS Guideline [30]. It is accepted as a level U drug according to the American Headache Treatment Guidelines which means that the data is insufficient to support or refute its usage [31]. Similarly, a Cochrane review accepted the data on acetazolamide as insufficient as there is only a single Class II study present which was stopped prematurely because of a high number of withdrawals due to side effects [32].

The efficacy of acetazolamide on VM has not been studied previously. There is just one family report with migraine headaches, episodic vertigo, and essential tremor showing improvement of all symptoms with the drug [33].

In our study, acetazolamide was effective in reducing both vertigo and headache attack frequency and severity and this effect was more prominent on vestibular features of VM. Though not yet identified, an ion channel deficit as it is the case in EA2 and FHM going with vestibular symptoms and migraine headaches can be the possible underlying mechanism in VM to explain the acetazolamide response. This needs to be clarified by further studies. Side effects seem to be the main restriction. Six of the fifty patients (12 %) stopped taking the drug in the first month and 87.2 % of the remaining 39 patients complained of disturbing paresthesias. Warning the patients about these side effects, acetazolamide can at least be initiated in cases with frequent and severe attacks restricting daily activities.

The retrospective design of our study, lacking a control group is the main limitation. Further randomized placebo-controlled trials are warranted to clarify the efficacy of the drug.

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