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Original Article

The Effects of Betahistine and Dimenhydrinate on Caloric Test Parameters; Slow-Phase Velocity of Nystagmus

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OBJECTIVE: The aim of this study is to determine the effects of betahistine and dimenhydrinate on the slow phase velocity.

MATERIALS and METHODS: Forty patients with complaints of vertigo and dizziness volunteered to be included in the study. All patients who were included the study were treated at the other medical centers. The patients were divided into two Groups. Patients in the first Group were given betahistine 24 mg three times per day. During this treatment, caloric testing was performed, and the dose was increased to 48 mg three times a day due to ongoing complaints. The test was then repeated four weeks after using this higher dosage. Patients in the second Group had caloric testing while using and four weeks after stopping dimenhydrinate.

RESULTS: The study Group was comprised of 40 patients; 20 patients (13 female, 7 male, 18-68 years, median age 46) in the betahistine Group and 20 patients (14 female, 6 male, 24-74 years, median age 44.5) in the dimenhydrinate Group. The average slow phase maximum velocity in the first Group of patients was 18 -/+ 8.2 and 21.1 -/+ 10.8 deg/s at 24 mg betahistine three times a day and 48 mg three times a day, respectively. In the second Group of patients, the average slow phase velocity was 13.4 -/+ 5.1 and 18.2 -/+ 7.5 deg/s during and after stopping the treatment of dimenhydrinate, respectively. The caloric test-induced slow-phase velocity was decreased with dimenhydrinate and increased with the higher dosage of betahistine.

CONCLUSION: To our knowledge, this is the first study to demonstrate that betahistine increases caloric-induced slow-phase velocity in humans. Dimenhydrinate and betahistine should not be used together because of their opposite effects on the vestibular system. Dimenhydrinate can be used to treat acute episodes of vertigo, whereas betahistine should not be used during the episode but may be used in the period between the attacks to stimulate the vestibular system.

KEY WORDS: Vertigo, nystagmus, dimenhydrinate, betahistine

INTRODUCTION

Nystagmus is the only objective finding of vertigo that is a subjective symptom. The caloric test is a useful vestibular test for the evaluation of vertigo. Slow-phase maximum velocity (SPV) is currently thought to be the most reliable parameter in evaluating nystagmus [1]. It is considered that higher SPV levels indicate higher stimulation of the labyrinth [2].

The cause of vertigo is often difficult to establish. Unfortunately, before being diagnosed definitely, various medications are prescribed for patients for symptomatic relief. Betahistine and dimenhydrinate are drugs commonly used in the treatment of vertigo. Dimenhydrinate is an H_1 receptor antagonist. Betahistine's mechanism of effect is still not clear. Although it is commonly used in Europe, the efficacy of this drug Group has not been proven, and it has not been approved by the US Food and Drug Administration (FDA) [3]. In the central histaminergic system, betahistine is a weak postsynaptic H_1 receptor agonist and an effective presynaptic H_3 receptor antagonist. Moreover, it also has minimal H_2 receptor activity [4, 5].

The usage of antihistaminergic drugs, such as dimenhydrinate (H_1 receptor antagonist), together with histaminergic drugs, such as betahistine (H_1 receptor agonist), leads to a contradiction in the treatment of vertigo. The effects of betahistine and dimenhydrinate on the parameters of caloric testing are evaluated in this study.

MATERIALS and METHODS

A total of 40 volunteer patients who applied to the Otorhinolaryngology Department of Çukurova University Medical Faculty with complaints of vertigo and dizziness while taking betahistine and dimenhydrinate between December 2009 and January 2012 were included in this study. All patients who were included the study were treated at the other medical centers. All of

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the patients were already using betahistine and dimenhydrinate recommended by different centers for at least for 2 weeks. Twenty patients taking dimenhydrinate were advised to stop the drug immediately, as they did not have an attack of vertigo. These patients accepted having a caloric test done immediately with the added hope of less vestibular discomfort due to the test. The patients were informed that caloric tests measure the imbalance between the two inner ears and that testing while taking the drug may alter the results; all patients were informed about the details of the study and signed a voluntary certification form. The study was approved by our local ethics committee. The date of board decision was 03.12.2009 and the number was 5/2.

Twenty patients taking 24 mg of betahistine three times daily who had not recovered from vertigo attacks (14) or dizziness following a vertigo attack (6) had undergone caloric tests, and the dosage was increased to 48 mg three times daily. All patients were retested 4 weeks after discontinuing the dimenhydrinate or doubling the betahistine dosage.

Caloric Test and VNG Procedure

Micromedical Technologies, Inc (Chatham/USA) Visual Eyes 4 Channel Videonystagmography (VNG) equipment and a Chartr ICS NCI-480 (Minnesota/USA) caloric stimulator were used for the caloric testing. All patients received an otoscopic examination to rule out tympanic membrane perforation or impacted cerumen. All impacted cerumen was removed before caloric testing. Routinely, 250 cc of cold and hot water (30 and 44°C) was used for irrigation for 30 seconds, and the resultant nystagmus was recorded. All tests were carried out by the same person. Nystagmus was recorded for at least 90 seconds.

Measurement of SPV of Nystagmus with VNG

Slow-phase maximum velocity of nystagmus was measured automatically by the computer in terms of degrees/second (deg/s). This measurement was calculated automatically by the computer by averaging 10-second periods in which SPV achieved maximum value after water irrigation. This 10-second period is seen between 60-70 seconds (cumulation period). If the computer calculated an artifact instead of a nystagmus, the 10-second period was chosen manually.

Statistical Analysis

SPSS 18.0 package program was applied in the statistical analysis of the data. Categorical measurement was summarized as number and percentage; digital measurements were summarized as average and standard deviation. For comparison of categorical measurements in and between treatment Groups, the chi-square test statistic was applied. For comparison of digital measurements between treatment Groups, the T test was applied in independent Groups. In the event that the hypothesis was provided in the comparison of dependent digital measurements, the T test was applied, and in the event that the hypothesis was not provided, the Wilcoxon signed rank test was applied. In all tests, the statistical significance level was 0.05.

RESULTS

The study Group was comprised of 40 patients: 20 patients (13 female, 7 male, 18-68 years, median age 46) in the betahistine Group and 20 patients (14 female, 6 male, 24-74 years, median age 44.5) in the dimenhydrinate Group (Table 1).

In the betahistine Group, 12 patients had Meniere's syndrome, 5 patients had psychogenic dizziness and Meniere's syndrome, and 3 patients had compensation problems after vestibular neuritis.

In the dimenhydrinate Group, 10 patients had Meniere's syndrome, 4 patients had psychogenic dizziness, and 6 patients had vestibular neuritis.

In the dimenhydrinate Group, the average SPV in 4 measurements was 13.4 -/+ 5.1 deg/s while using the drug. The average SPV measured by the caloric test, carried out after stopping the drug, was 18.2 -/+ 7.5 deg/s. This increase was statistically significant ($p<0.001$) (Table 2).

When the patients in the betahistine Group were considered, during the usage of 24 mg three times daily, the average SPV in 4 measurements was 19.3 -/+ 8.2 deg/s. After increasing the drug dose to 48 mg three times daily, the average SPV increased to 23.2 -/+ 10.8 deg/s. This increase was found to be statistically significant ($p<0.001$) (Table 3).

DISCUSSION

The caloric test is a useful clinical test for the evaluation of vertigo. It is accepted that the most commonly used and the safest parameter in evaluating nystagmus is slow-phase maximum velocity [2, 7-9]. It is considered that higher SPV values are associated with higher labyrinth stimulation. While evaluating the sensitivity of the vestibular system, the addition of two PCNs (with 30°C and 40°C stimuli) of the ear is considered to be that ear's "stimulation value" [2]. Dimenhydrinate is a vestibulosuppressant drug that prevents vertigo by suppressing the vestibular system [10]. It has an antagonist effect on central histamin-

Table 1. Age, sex and gender distribution of patients

	Group		
Measurements	**Betahistine**	**Dimenhydrinate**	**p**
Gender			
Man	7 (%35)	6 (%30)	
Woman	13 (%65)	14 (%70)	0.736
Age	47.5 (18-68)	45 (24-74)	0.657

Table 2. Slow phase velocity of dimenhydrinate group and grade values

	Dimenhidrinate		
Measurements	**With dimenhydrinate SPV**	**Without dimenhydrinate SPV**	**p**
R-cold	12.2±5.2 9 (7-22)	16.8±9 14.5 (9-44)	0.003
R-warm	14.2±5 13 (5-25)	19.4±8.4 16 (10-44)	<0.001
L-cold	14±6.4 12.5 (6-30)	18±8.7 16.5 (5-38)	<0.001
L-warm	13.3±6.7 11 (6-28)	18.5±9.1 14.5 (8-42)	<0.001
Average	13.4±5.1 11.4 (7.2-23.5)	18.2±7.5 15 (9.2-33)	<0.001

SPV: slow-phase maximum velocity

Table 3. Slow phase velocity of betahistine group and grade values

	Dimenhidrinate		
Measurements	**3x1**	**3x2**	**p**
R-cold	19±9.8 16 (7-47)	22.4±12.6 17.5 (8-56)	0.015
R-warm	21.2±10.1 19 (10-50)	25.3±13.6 22.5 (8-71)	0.004
L-cold	17.6±7.3 16 (6-32)	20.6±8.7 20 (9-38)	0.015
L-warm	19.4±9 15 (5-38)	24.4±11.8 22.5 (9-55)	0.008
Average	19.3±8.2 18.2 (9-41.5)	23.2±10.8 21.1 (10-53.5)	<0.001

ergic H_1 receptors; accordingly, it suppresses SPV [11]. In our study, we saw that dimenhydrinate suppressed the SPV significantly. While the average SPV during caloric testing in patients taking dimenhydrinate was 13.45, the average of the repeated caloric test after stopping the drug was 18.175. The decrease in the average SPV in patients taking dimenhydrinate was statistically significant. ($p<0.001$) The number of studies showing the effect of dimenhydrinate on SPV is limited. Holtman et al. compared dimenhydrinate, ginger, and placebo, and the SPV was shown to be decreased significantly in patients using dimenhydrinate. The use of such vestibulosuppressant drugs can cause a delay in recovery by inhibiting vestibular compensation [10, 12, 13]. Thus, dimenhydrinate should be used only in the acute period and should be discontinued as soon as possible.

Antihistaminics suppress the vestibular system and cause delay in compensation period; accordingly, histaminic drugs can have an opposite effect. As a matter of fact, there are some studies proving that betahistine accelerates vestibular compensation in people and animals [14, 15]. In parallel with this mechanism, betahistine can increase SPV in humans.

Betahistine dihydrochloride is a drug commonly used in treating vertigo, particularly in Meniere's disease, and decreases frequency of the attacks [16, 17]. There have been various opinions on the mechanism of effect of betahistine in the literature [9, 18-20], however, the mechanism is not clear yet. Betahistine is a structural histamine analog. It is a weak postsynaptic H_1 receptor agonist in the central histaminergic system and an effective presynaptic H_3 receptor antagonist. Moreover, it also has little H_2 receptor activity [21]. The H_3 autoreceptor is an inhibitory autoreceptor, and it decreases histamine levels with an automatic feedback mechanism. Betahistine's histaminergic effect is mostly by an antagonistic effect, especially on presynaptic H_3 receptors [22]. Betahistine increases cerebral and vestibular system blood supply [21, 23]. Furthermore, there have been studies considering that it is effective on brain stem vestibular nuclei. Most of these studies indicate that betahistine has a suppressing effect on vestibular nuclei [17, 20, 22, 24]. On the contrary, Serafin et al. [2] reported that histamine increased the spontaneous arousal on vestibuler nuclei in an animal study.

To the best of our knowledge, our study is unique, indicating that betahistine increases SPV in humans. Betahistine is commonly used in European countries; however, the FDA in the United States has not approved the use of betahistine in the treatment of vertigo, because the mechanism of effect of betahistine is not clear. Moreover, they support the fact that evaluation of drug activity is very difficult in a disease characterized by spontaneous remission, such as Meniere's syndrome [3]. Also, the use of both histaminics and antihistaminics in the same disease was questioned in the FDA's web page. Antihistaminics and histaminics should not be used in the treatment of acute attack. The use of an antihistaminic during acute attacks and the use of histaminics between attacks, thus using different treatments in different phases of the disease, seem more logical.

There have been other studies that compared betahistine and dimenhydrinate. For instance, there is a study in which one Group of patients was given low-dose betahistine (12 mg) and the other Group was given a combination of cinnarizine (20 mg) and dimenhydrinate (40 mg) three times a day. The patients were assessed clinically [25, 26] and the combination of dimenhydrinate and cinnarizine, compared to betahistine, provided better control of acute vertigo treatment and vegetative symptoms. Dimenhydrinate and cinnarizine, which is a vestibulosuppressant combination, had better control of episodes of vertigo in this study. This finding supports our study; however, we recommend that betahistine should not be used in the acute episode, as it may increase vertigo and vegetative symptoms. We also demonstrated that there are only a few changes in caloric test-induced SPV between patients using betahistine and the combination treatment. The explanation for this may be the fact that betahistine was given in low doses. In another study that compared betahistine and the dimenhydrinate-cinnarizine combination, nystagmus frequency decreased during treatment in both Groups, contrary to our findings [27]. The decrease of nystagmus frequency in this study is probably not because of the drug effect but may be due to the subsiding of acute episodes.

The results of the study that was carried out with high-dose betahistine by Strupp et al. may support our study [28]. Strupp's study proposed that the frequency and severity of the vertigo episodes decrease in parallel with the increase in the dose of betahistine. In this study, only the subjective symptoms of the patients were evaluated, in contrast to our study, in which we evaluated the objective finding of vertigo (SPV). It can be argued that test-retest properties of the caloric test may be misleading, but the statistical analysis demonstrated that these findings are statistically important. Though SPV may change in different caloric test sessions in the same patient on repetitive examinations, statistical analysis shows that our findings are not coincidental.

Some of the patients in this study did not have a real vertigo attack. But, these patients had already been prescribed the mentioned drugs by other doctors, and all patients approved to be tested while using the drug. The only data used in this study were the slow-phase velocity of nystagmus with and without drug, and the diagnosis of the patients is beyond the subject of this manuscript.

In conclusion, contrary to dimenhydrinate, betahistine increases SPV, and this effect become clear with the increase in dosage. Thus, while dimenhydrinate suppresses the vestibular system, betahistine activates the vestibular system. Although they show opposite effects, both drugs are used in the treatment of vertigo. It may be considered

a paradox, but it is also because of the different progress on vertigo in the attack periods and non-attack periods. While dimenhydrinate suppresses the vestibular system in the acute period and prevents vertigo by sedation, betahistine stimulates the vestibular system between attack periods, and it may increase vigilance and attention and also may accelerate central and vestibular compensation.

Ethics Committe Approval: Ethics committee approval was received for this study from the ethics committee of Çukurova University Faculty of Medicine (03.12.2009/5-2).

Informed Consent: Informed Consent: Written informed consent was obtained from patients who participated in this study.

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