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Review Article

Peripheral vertigo and appropriate use of Betahistine to improve outcomes

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ABSTRACT

Vertigo, characterized by a spinning or whirling sensation, is a common condition with a prevalence of 4.9% in the general population. It is caused by dysfunction in the vestibular system and can be classified as peripheral or central. Common causes of peripheral vertigo include benign paroxysmal positional vertigo (BPPV), Meniere's disease, and vestibular neuritis. Betahistine hydrochloride, a structural analog of histamine, is a commonly used treatment for peripheral vertigo. It acts as both a histamine H1 antagonist and a partial inverse agonist, improving cochlear blood flow and inhibiting vestibular neuronal firing. Betahistine has been shown to be effective in controlling symptoms, reducing frequency and intensity of vertigo attacks, and improving quality of life

Keywords: Betahistine, Peripheral vertigo, Histaminergic system

INTRODUCTION

Vertigo is a common clinical presentation in the outpatient department. Vertigo has an annual prevalence of 4.9% in the general population, and a lifetime prevalence of 20–30%.[1] Vertigo is commonly described by patients as spinning or whirling or rotator motion.[2] Vertigo is attributed to dysfunction at some level of the vestibular system. It is classified based on its origin as peripheral or central.[2] The common causes of peripheral vertigo include Benign paroxysmal positional vertigo (BPPV), Meniere's disease, and vestibular neuritis.[2] Vertigo markedly limits the daily activities of patients in almost 86% of patients with BPPV

In younger patients, BPPV significantly affects work-related activities, while older patients with BPPV have a greater incidence of falls, depression, and impairments to their daily activities.[3,4] The treatment of vertigo requires a multi-modal approach.[2] Current data implicates the central histaminergic system in the regulation of vestibular function.[5] The histaminergic system also affects behavioral recovery after unilateral damage of the peripheral vestibular system.[6] Drugs acting on the histaminergic system are could help relieve the symptoms of vertigo.[6] Antihistamine drugs are often used to treat vertigo but they are associated with sedation. They also adversely affect the recovery process.[6] But betahistine hydrochloride which is a structural analog of histamine has no sedative effects. Betahistine is used to treat peripheral vertigo.[7,8]

Betahistine is a partial histamineH1 Rs agonist and more potent histamine H3R antagonist. betahistine also functions as a partial inverse agonist and enhances histamine neuron activity.[6] Preclinical studies have demonstrated that betahistine has a triple pronged action at 3 distinct levels at the histamine receptors : At the vascular level , betahistine acts at the H1R and increases the cochlear and vestibular blood flow at the level of the central nervous system, betahistine acts at the H3R in increases histamine turnover, and at the level of the

peripheral labyrinth , betahistine decreases the vestibular output by modulating the H3R/H4R.[6] Betahistine improves cochlear blood flow by causing vasodilatation of inferior cerebellar artery.[6] Betahistine has a dose-dependent n time dependent inhibiting effect on vestibular neuronal firing (Figure 1).[2]

According to most clinical studies, 48 mg daily during 3 months seems to be the most successful therapeutic scheme for Meniere's disease and other types of peripheral vertigo. This dosage has been shown to be useful to control symptoms of vertigo, reduce frequency and intensity of attacks, facilitate vestibular compensation, improve quality-of-life, and prevent new episodes. Currently there are 4 important issues faced in the real world setting namely, the challenge of differentiating recurrence of vertigo from residual dizziness. The role of betahistine in prevention of recurrence and residual dizziness and whether the use of 48 mg per day of betahistine is the most appropriate dose in patients with vertigo, and the duration of the use of betahistine for best results.

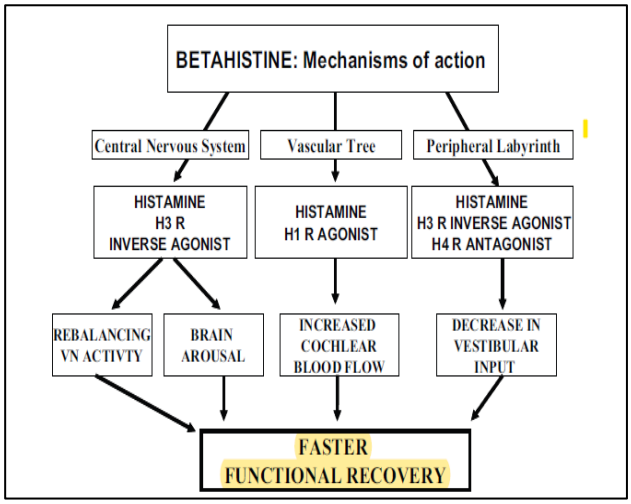

Figure 1: Mechanism of action of Betahistine.

Aims of the study was to differentiate between recurrent vertigo and residual dizziness in patients with BPPV. To evaluate the role of betahistine in prevention of recurrent vertigo and prevention of residual dizziness in patients with BPPV. To ascertain whether 48 mg per day of betahistine is the most appropriate dose of positive outcomes in patients with peripheral vertigo due to BPPV or Meniere's disease. To understand from the experts the appropriate duration of therapy of betahistine used in the real world setting for best results in patients with peripheral vertigo.

METHODS

A panel Ear, note throat (ENT) specialists or otolaryngologists from diverse regions across India who were treating patients with peripheral vertigo were invited to participate in a discussion of their approach to treating peripheral vertigo in the real-world setting. Prior to the meeting, a literature review was done using the Medline database. The key words used for the search were betahistine, peripheral vertigo, BPPV, Meniere's disease. The findings of the literature review were presented during the meeting of the expert ENT specialists. The chairperson spearheaded the discussion of vertigo management in the real-world setting. The discussion and debate regarding the approach of the expert ENT surgeons toperipheral vertigo, their experience with the use of betahistine in peripheral vertigo for positive outcomes was discussed. Insights from the discussion were chronicled and a manuscript of the real-world approach to the management of vertigo was written.

OBSERVATIONS DURING THE DISCUSSION OF EXPERTS PANEL MEETINGS

Discussion question 1

What is the clinically observed difference between recurrence and residual dizziness?

Current evidence

The recurrence rates of BPPV are estimated to be about 15–20% per year.[9] Repositioning maneuvers (RPM) are the gold standard treatment for management for vertigo in patients with PBBV. RPM like Epley or Semont maneuvers are used to remove the otolith from the semicircular canal for posterior canal BPPV.[3,10-12] But, about 30% to 50% patients have recurrence of vertigo by 3 years after treatment. The recurrence is caused by vascular disorders. In BPPV otoconia may be detached and released.[13]

Residual dizziness (RD) is defined as a sensation of non-specific dizziness in the absence of positional vertigo and typical nystagmus in patients upon resolution of BPPV. About 31–61% of patients, with symptoms lasting from a few days to several weeks. The risk factors for RD after successful CRM in BPPV patients include elderly, female gender, comorbidities, low vitamin D levels and long duration of BPPV before treatment.[13,14]

Expert opinion

Recurrence and residual dizziness are distinct entities. In patients with recurrence spinning are reported by the patients and it is primarily positional in nature. Recurrence is usually seen within the first year of the first attack of vertigo. In recurrence, there is also a previous intervening symptom free period. Residual dizziness is defined by the presence of remnant dizziness where the patient complains of dizziness inspite of a slight betterment post maneuver. After maneuvers, the persistent dizziness is not a true vertigo and it may be caused by labyrinthine dysfunction. Mild dizziness due to old age, peripheral neuropathy, cerebellar degeneration,

anxiety due to fear of fall could be defined as residual dizziness. In BPPV, repositioning maneuvers is the first line of treatment but 20-70% patients do not recover fully after the maneuvers who suffer from residual dizziness, which is a 'fogginess or lightheadedness' feeling for the patient, where the rotatory component is absent, but the sense of imbalance persists. Residual dizziness persists from 1 month to 3 months,

Discussion question 2

What isthe role of betahistine in prevention of recurrent vertigo and prevention of residual dizziness in patients with BPPV?

The evidence

In 31–61% of patients, with symptoms of residual dizziness last from a few days to several weeks.

Betahistine was registered in Europe in the 1970s and approved in more than 80 countries as a first-line treatment for Menière's disease.1It has been administered to more than 150 million patients. Betahistine reduces symptoms of residual dizziness by improving the static components by rebalancing of the vestibular nuclei neurons, reducing the spontaneous resting activity imbalance between the bilateral vestibular nuclei complexes through actions on the histamine H1, H2, and H3 receptors.[5,6,15] Betahistine also improves labyrinthine microcirculation and increases local vestibular blood flow by relaxation of the pre-capillary sphincters of the microcirculation in the inner ear.[2]

Another mechanism postulated for improved recovery after betahistine treatment is brain arousal.This is a crucial factor for functional recovery/behavioral adaptation, through general upregulation of histamine.[5,6,15] Betahistine increases histamine turnover and release, and modulation of release of other neurotransmitters, particularly GABA and thus helps late-stage vestibular compensation . Betahistine also enhances the rebalancing of the neuronal activity of the vestibular nuclei complexes on both sides. Oral betahistine accelerates functional recovery in patients with vertigo due to BPPV.[2]

The efficacy of betahistine in Ménière's disease may be due to its ability to modify the circulation of the inner ear or due to a direct effect on neurons of the vestibular nuclei.[2]

Expert opinion

Betahistine helps to reduce frequency and severity of recurrence. Betahistine helps in reducing recurrence and residual dizziness due to its mechanism of action-H1 agonism and H3 antagonism. It thus helps correct vestibular compensation by increasing the histamine levels. by H1 agonism and H3 antagonistic action, Betahistine increases blood flow to inner ear. In addition, it also activates afferent neurons in semicircular canals which help stabilize intracellular calcium ion concentration. This causes vasodilatation only in the inner ear. Thus, betahistine is selective and does not cause vasodilation elsewhere in the body. Hence Betahistine does not cause syncopal events or orthostatic drop in blood pressure even in elderly. This is an added advantage of betahistine.

Betahistine has multiple roles to play for preventing residual dizziness in patients with BPPV. Betahistine improves microcirculation and improves clearance of otoconia in patients with BPPV. Betahistine helps in rebalancing of vestibular nuclei and minimizes otoconial detachment. Long term administration of betahistine improves postural stability in patients with BPPV who undergo Epleys' maneuver.[16]

Discussion question 3

Is the dose of 48 mg per day of betahistine appropriate for management of patients with peripheral vertigo in the real-world setting?

Current evidence

The effectiveness of betahistine is dose-dependent and time-dependent. Several studies have demonstrated 48 mg per day of betahistine to be effective for treating peripheral vertigo due to BPPV and Meniere's disease. This dose of 48 mg per day is useful to control symptoms, reduce frequency and intensity of attacks, facilitate vestibular compensation, improve quality-of-life, and prevent new episodes of vertigo.[2]

In the post-marketing observational study by Zamergrad MV et al, the efficacy of betahistine dihydrochloride at the dose of 48 mg/day was evaluated in patients with paroxysmal vertigo of varied etiology.[17] About 74.1% of the patients rated the clinical response as good, very good or excellent over a period of 1 to 2 months ($p<0.001$). Treatment with betahistine decreased the monthly vertigo attack frequency from 8.0 to 3.0 ($p<0.001$). No serious adverse effects of betahistine were reported.[17]

Expert opinion

Residual dizziness persists from 1 month to 3 months, in which case, Betahistine in dose of 48 mg/day for long term that is approximately 3 months helps treat the residual dizziness and relapses of vertigo. Betahistine is a vestibular stimulant and hence, 48 mg/day is the optimal dose for treating patients with BPPV, recurrence and residual dizziness.

Similarly in vertigo due to Meniere's disease, Betahistine 48 mg per day is an effective and safe maintenance therapy.

Discussion question 4

What is the most appropriate duration of use of 48 mg per day of Betahistine in patients with peripheral vertigo? Several clinical studies have indicated that betahistine 48 mg daily administered during 3 months is an effective and safe option for the treatment of peripheral vertigo. In more than 40 years of clinical use, betahistine has shown an excellent safety profile with the usual dose range up to 48 mg daily.[2]

Expert opinion

At least 3 months of Betahistine in the dose of 48 mg/day is essential to ensure vestibular compensation, reduce recurrence and residual dizziness in a case of BPPV. For Meniere's disease, betahistine is required to be given lifelong.

Key messages from the expert panel

BPPV is the most common type of peripheral vertigo encountered in clinical practice. Recurrence of vertigo is characterized by presence of the spinning/ rotatory component in the patient complaints. Residual dizziness post repositioning maneuvers is the dizziness/sensation of imbalance without the spinning. Both recurrence and residual vertigo are reduced by Betahistine when used in the right dose (at least 48 mg/day) and for a long duration (at least 3 months).

At least 3 months of Betahistine in the dose of 48 mg/day is essential to ensure vestibular compensation, reduce recurrence and residual dizziness in a case of BPPV. For MD, it is required to be given lifelong. Betahistine is selective in its action of increasing vestibular and cerebral blood flow-it does not cause side-effects like syncope or orthostatic dizziness etc. due to its selective action.

CONCLUSION

Recurrence of vertigo is characterized by presence of the spinning/rotatory component in the patient complaints. Residual dizziness post repositioning maneuvers is the dizziness/sensation of imbalance without the spinning. At least 3 months of Betahistine in the dose of 48 mg/day is essential to ensure vestibular compensation, reduce recurrence and residual dizziness in a case of BPPV. For Meniere's disease, Betahistine is required to be given lifelong. Betahistine at the dose of 48 mg per day is effective and well tolerated for the management of peripheral vertigo.

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