Original Research Article

Effectiveness and safety of betahistine in treatment naïve acute peripheral vertigo patients

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ABSTRACT

Background: The objective of the study was to assess the effectiveness and safety of oral betahistine in treatment naïve patients with acute peripheral vertigo, administered over 21 days.

Methods: Treatment naïve patients with confirmed peripheral vertigo, based on clinical diagnosis, were enrolled in this open-label, single-arm, interventional study. Patients received 48 mg betahistine (16 mg, TDS) for 21 days, and were followed up on day 1, 3, 7 and 21. Safety and effectiveness were assessed based on clinical response (scale for vestibular vertigo severity level and clinical response evaluation (SVVSLCRE)); frequency and severity of peripheral vertigo (videonystagmography (VNG)) and dizziness handicap inventory (DHI).

Results: Overall, 53 (70.67%) out of 75 enrolled patients completed 21 days of treatment and were included in the study. No significant improvement in SVVSLCRE score was noted from baseline to day 1 (p=0.0572), but significant reduction was seen from day 3 onwards and continued till day 21 (p<0.0001). Level wise severity analysis showed that patients with ‘moderate to severe’ category at baseline reported ‘mild’ severity on day 7. A significant reduction in mean change of DHI scale was observed from baseline to day 3, day 7 and day 21 (p<0.0001). No major therapy related serious adverse events were reported. Headache (4.0%) and nausea (2.6%) were the commonly reported adverse events, which were mild in nature.

Conclusions: Findings suggest that 48 mg betahistine (16 mg, TID) therapy is effective in treatment naïve patients with acute peripheral vertigo. Reduction in vertigo symptoms score was significant from day 3 to day 21. Betahistine was found to be safe and easily tolerated in these patients.

Keywords: Betahistine, Vertigo, Naive patients, Dizziness, Videonystagmography, Dizziness handicap inventory

INTRODUCTION

Vertigo is the most common presentation of dizziness, defined as an illusory sensation of motion of either the self or the surroundings in the absence of true motion. Understanding of prevalence of vertigo is important to improve clinical support, but epidemiological data on vertigo is limited in the literature. As per the statistics, dizziness, including vertigo, affects about 15% to 20% of adults yearly, with a lifetime prevalence of 2.9%. Disorders or diseases like benign paroxysmal positioning vertigo (BPPV), Meniere’s disease, ischemic attack, cerebellum damage, vestibular neuritis, labyrinthitis, etc. with vertigo as the main symptom is often reported.

Vertigo significantly impacts the general health status and quality of life of patients with vestibular disorders. Because of large number of causes for vertigo, a correct diagnosis is difficult. Many diagnostic methods for vertigo are currently available among which videonystagmography (VNG) testing is often recommended. If a patient has complaints of dizziness,
including vertigo (spinning sensation), imbalance, unsteadiness, and/or light headedness, VNG testing is preferred. VNG test is performed to determine if the vestibular portion of the inner ear, which is responsible for carrying balance signals to the brain, may be the cause of dizziness symptoms. VNG is one of the only tests capable of determining if a vestibular problem is localized to one or both sides of the balance system.\(^6\) Other diagnostic tests include otoscopy and examination of the presence of nystagmus, neurological examinations such as cerebellar tests - the finger-to-nose test, the rapid alternating-movements tests for dystaxia and dysmetria (dysdiadochokinesia) and static and dynamic tests to assess the efficiency of posture and gait (Romberg’s test, Unterberger’s stepping test). In order to differentiate between peripheral and central vertigo Hallpike’s maneuver is performed.\(^5\)

The treatment for peripheral vertigo includes medical intervention, physical therapy, and psychotherapy; a few limited cases may also require surgical treatment. Medical interventions administered for vestibular vertigo vary depending on aetiology.

Betahistine is commonly used in the management of vestibular disorders. Betahistine is approved in >115 countries for the treatment of Meniere’s disease and the symptoms of vertigo. Betahistine is a structural analogue of histamine, and a partial or weak agonist for histamine H\(_1\) receptors and a strong antagonist for H3 receptors.\(^7,8\) It has been observed that Betahistine acts by increasing vestibulocochlear blood flow.\(^9\) Clinical trials have demonstrated that Betahistine is effective in reducing the frequency and severity of vertigo, and improving vertigo-associated symptoms, including nausea and vomiting.\(^9\) Another study evaluated the effects of Betahistine on dizziness, symptoms of anxiety and depression in patients with peripheral vertigo. The study showed that treatment with Betahistine is associated with improvements in objective measures of health-related quality of life, with satisfactory tolerability.\(^13\) In another clinical study, it was observed that betahistine is safe and well-tolerated as an anti-vertigo drug without any sedative effect in patients with Meniere’s disease.\(^14\)

However, most of the studies performed were conducted for more than 2 months. VIRTUOSO, a prospective, multinational, non-comparative, post-marketing observational programme conducted for 60 days per patient who were already diagnosed with vestibular vertigo suggested that betahistine therapy (48 mg/day) is effective in treating vertigo in routine clinical settings.\(^9\) Similar results were presented by another systematic review which considered studies conducted from 15 days to upto 1 year, with patients having symptom for at least 3 months.\(^15\)

Thus, betahistine is often used in clinical practice with longer treatment period. However, its effectiveness in acute vertigo is not explored much. Hence the present study was planned to study the effectiveness and safety of Betahistine in treatment naive acute peripheral vertigo patients from day 1 of the treatment.

**METHODS**

**Study design**

This was an investigator initiated, open label, non-comparative, single arm, interventional study conducted at Bosco ENT Nursing Home, Mumbai, India between July 2018 and January 2019.

**Participants**

The study was initiated after approval from the Bhatia Hospital Medical Research Society Ethics Committee and was conducted in accordance with the principles of declaration of Helsinki, international council on harmonization good clinical practice guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines). The investigator explained the details of the study to the interested patients and a voluntary informed consent was obtained from all patients. All the eligible patients were prescribed 48 mg per day of oral betahistine 48 mg (Vertin, Abbott India Ltd; 16 mg three times daily) for 21 days. The decision and initiation of treatment were based on the clinical judgement of the physician.

**Inclusion criteria**

Inclusion criteria were treatment naive patients (aged ≥18 years) with confirmed peripheral vertigo based on clinical diagnosis were included. Patients with middle or inner ear infection who required surgery, patients suffering from brain tumour, head trauma, epilepsy, multiple sclerosis and paralysis of eye muscles, patients with established psychiatric disorders, significant neurological disorder like Parkinson’s disease or spinal cord damage, patients with peptic ulcer, patients with pheochromocytoma, patients with bronchial asthma, pregnant and lactating women, patients receiving any other agents for peripheral vertigo, patients with known hypersensitivity/allergic reaction to Betahistine, participants in any clinical trial in past 30 days before enrollment, and patients who are regular users of excessive amount of drugs and alcohol were excluded from study.

**Effectiveness and safety variables**

The effectiveness of the treatment was evaluated with change in the scale of vestibular vertigo severity level and clinical response evaluation (SVVSLCRE) from baseline (day-0) to day-7 following betahistine treatment. Secondary variables were change in the score of VNG test from baseline (day-0) to day-21, change in the SVVSLS CRE from baseline (day-0) to day-1, day-3, and day-21 and change in the score of dizziness handicap.
inventory (DHI) scale from baseline (day-0), to day-1, day-3, day-7 and day-21 following betahistine therapy. Safety variables included incidence of adverse events (AEs) and serious AEs; AEs leading to discontinuation of betahistine therapy were recorded.

Laboratory investigations (mainly CBC), family history, and X-ray of temporal and sinus were performed at the baseline.

Follow-up and data collection

Follow-up was done if there was any previously reported ADR. The follow-up information described whether the event has resolved or continued, if and how it was treated; and whether the patient continued or withdrew from study participation.

Study evaluations

Appropriate permission was procured for using the following scales in this study.

SVVSLCRE\textsuperscript{16}

This scale assists the physician in evaluating each patients’ degree of vertigo condition.

**Figure 1: Scale for vestibular vertigo severity level.**

- Level I: Absent or very mild vertigo (0-2)
- Level II: Mild vertigo (>2-4)
- Level III: Moderate vertigo (>4-6)
- Level IV: Severe vertigo (>6-8)
- Level V: Very severe vertigo (>8-10).

DHI scale\textsuperscript{17}

DHI is a 25 items self-assessment inventory designed to evaluate the self-perceived handicapping effects imposed by dizziness. There are three main domains functional (9 questions, 36 points); emotional (9 questions, 36 points); physical (7 questions, 28 points). There is a maximum score of 100 (28 points for physical, 36 points for emotional and 36 points for functional) and a minimum score of 0 (zero). Higher the score, greater the perceived handicap due to dizziness.

VNG test\textsuperscript{18}

The VNG pre and post-test protocol includes tests of oculomotor function (with fixation), tests of gaze stabilization (with or without fixation, alertness level), tests for specific etiologies like Dix-Hallpike maneuver (dynamic positioning), caloric test (water) etc. VNG machine used was neuro equilibrium\textsuperscript{TM} diagnostic systems pvt ltd.

Statistical methods

Analysis set

The statistical analysis was performed on intention-to-treat (ITT) population, defined as all patients who were enrolled, assigned to the study drug and at least one post-dose observation was available. Safety population included the patients who were enrolled and received at least a single dose of study treatment.

Sample size calculation

Patients who had complaint of dizziness were screened and 75 patients who met eligibility criteria were enrolled for this study. No formal sample size calculation was performed.

Statistical analysis

Discrete data was summarized using numbers (n) and percentages (%) along with 95% confidence interval (CI) for percentages. Continuous data was summarized using: n, mean, median, range, standard deviation, minimum and maximum along with 95% confidence interval for the mean, wherever applicable. Scores were compared using paired T-test at 5% level of significance. Statistical analyses were performed using SAS\textsuperscript{8} version 9.4 (SAS institute Inc., USA).

RESULTS

Demographics and baseline characteristics

A total of 75 patients with mean age of 46.12±14.90 years and mean BMI of 25.79±4.85 kg/m\textsuperscript{2} were enrolled in the study. Out of 75 patients, 26 (34.67%) were male patients and 49 (65.33%) were female patients. Majority of patients (n=68, 90.67%) patients had no history of peripheral vertigo. Overall, 53 (70.67%) out of 75 enrolled patients completed the study (Table 1).

Diagnosis were confirmed on the basis of clinical evaluation and VNG test which revealed that majority of the patients were diagnosed with BPPV (n=47, 62.67%), followed by meniere's disease (n=13; 17.33%), functional (somatic vertigo) (n=7; 9.33%), vestibulopathy (n=3; 4%), mixed presentation (n=3; 4%), labyrinthitis (n=1; 1%) and neuritis (n=1; 1%).

SVVSLCRE score

No significant improvement in SVVSLCRE scores was noted from baseline (day-0) to day-1 (p=0.0572). But significant reduction was seen from day-3 onwards and continued till day-21 (p<0.0001) (Table 2).
Table 1: Patient demographics.

| Parameter     | Statistics      | Overall (n=75) |
|---------------|-----------------|---------------|
| Gender        |                 |               |
| Male          | N (%)           | 26 (34.67)    |
| Female        | N (%)           | 49 (65.33)    |
| Age (years)   |                 |               |
| N             | Mean (SD)       | 46.12 (14.90) |
|               | Median          | 45.00         |
|               | Range (min-max) | 18.00:78.00   |
| Height (cms)  | N               | 75            |
|               | Mean (SD)       | 157.61(11.00) |
|               | Median          | 156.00        |
|               | Range (min-max) | 131.00:186.00 |
| Weight (kgs)  | N               | 75            |
|               | Mean (SD)       | 64.43 (14.94) |
|               | Median          | 65.00         |
|               | Range (min-max) | 32.00:111.00  |
| BMI (kg/m²)   | N               | 75            |
|               | Mean (SD)       | 25.79 (4.85)  |
|               | Median          | 25.15         |
|               | Range (min-max) | 16.53:39.34   |

Note: percentage (%) was calculated from the overall counts.

Table 2: Change in the score of vestibular vertigo severity level and clinical response evaluation from baseline to day-1, day-1 to day-3, day-3 to day-7 and day-7 to day-21.

| Statistics | Visit 1/ baseline | Visit 2 (day-1) | Visit 3 (day-3) | Visit 4 (day-7) | Visit 5 (day-21) |
|------------|-------------------|-----------------|-----------------|-----------------|-----------------|
| N          | 75                | 73              | 70              | 64              | 53              |
| Mean (SD)  | 4.91 (1.23)       | 4.84 (1.17)     | 4.30 (1.05)     | 3.03 (1.19)     | 1.47 (1.14)     |
| Mean change| -                 | -0.08 (73)      | -0.59 (70)      | -1.27 (64)      | -1.53 (53)      |
| 95% CI of mean change | -     | (-0.17:0.00)    | (-0.73:-0.44)   | (-1.44:-1.09)   | (-1.82:-1.24)   |
| P value*   | -                 | 0.0572          | <0.0001         | <0.0001         | <0.0001         |

Note: p value was calculated using paired t test at 5% level of significance for difference from baseline to day-1, day-1 to day-3, day-3 to day-7 and day-7 to day-21.

Table 3: Summary of mean change in the score of DHI scale from baseline to day-1, day-1 to day-3, day-3 to day-7 and day-7 to day-21.

| Statistics | Visit 1/ baseline | Visit 2 (day-1) | Visit 3 (day-3) | Visit 4 (day-7) | Visit 5 (day-21) |
|------------|-------------------|-----------------|-----------------|-----------------|-----------------|
| N          | 75                | 73              | 70              | 64              | 53              |
| Mean (SD)  | 27.39 (16.19)     | 27.84 (16.17)   | 24.77 (15.01)   | 17.16 (13.31)   | 7.92 (8.10)     |
| 95% CI     | 23.66: 31.11      | 24.06: 31.61    | 21.19: 28.35    | 13.83: 20.48    | 5.69: 10.16     |
| Mean change| -                 | 0.11 (73)       | -3.40 (70)      | -7.53 (64)      | -8.26 (53)      |
| 95% CI of mean change | -     | (-0.55:0.77)    | (-4.88:-1.92)   | (-9.98:-5.09)   | (-11.04:-5.49)  |
| P value*   | -                 | 0.7431          | <0.0001         | <0.0001         | <0.0001         |

P value was calculated using paired t test at 5% level of significance for difference from baseline to day-1, day-1 to day-3, day-3 to day-7 and day-7 to day-21.

VNG score

Change in the score of VNG test result was analyzed from baseline to day-21. Approximately 93% had an abnormal caloric test pre-treatment. Post-treatment with betahistine, by day-21, number of subjects with abnormal caloric test reduced to approximately 63%. Valsalva maneuver test revealed significant decrease in number of patients with abnormality (p<0.0001) on day-21. Audiometry coincided with the improvement in the overall condition.

DHI scale

The mean (SD) change in DHI score was analyzed from baseline through day-21. Significant reduction in mean change DHI scale was observed from baseline to day-3, day-7 and day-21 (p<0.0001) (Table 3).

Safety

No serious adverse events were reported in the study. The most commonly reported AEs were headache (4.0%) and nausea (2.6%), which were mild in nature and resolved with treatment.
DISCUSSION

Betaistine is a partial histamine H1 receptor agonist and more potent histamine H3 receptor antagonist. Its efficacy can be explained by mechanisms targeting the histamine receptors (HRs) at three different levels: the vascular tree, with an increase of cochlear and vestibular blood flow involving the H1 receptor; the central nervous system, with an increase of histamine turnover implicating the H3 receptor, and the peripheral labyrinth, with a decrease of vestibular input implying the H3/H4 receptors.5

Benign paroxysmal positional vertigo is the most common form of peripheral vestibular vertigo. It is a condition that is associated with a considerable burden on health-related quality of life.5 Betaistine promotes and facilitates central vestibular compensation and accelerates the recovery process.19 There are different treatment policies for patients with recurrent vertigo, dizziness and instability of vestibular origin, but drugs acting on the histaminergic system are drugs of choice for the treatment of symptoms of vertigo.20 Before starting treatment of vertigo, early diagnosis can be of immense importance for insight on the treatment outcome. VNG test is an important tool to diagnose vertigo, which records and displays the eye movements directly by infra-red video goggles with minicamera.21

In the present study all treatment naive patients underwent VNG pre- and post-treatment with Betahistine, where approximately 30% patients showed decrease in abnormal caloric test. A study was conducted to assess value of diagnosis of vertigo between VNG and electronystagmography (ENG), which indicated that VNG test is more useful and reliable in diagnosing of vertigo than ENG.21 In the present study, betahistine was found to be effective at 16 mg TDS, given up to 21 days, by demonstrating a significant reduction in vertigo severity (p<0.0001), as assessed by changes in SVVSLS CRE level and improvement in DHI score.21

The clinical efficacy of betahistine in the treatment of vertigo was evidenced in many studies where most of them were focused on subjective scales with vertigo as the main symptom, and/or on questionnaires on self-evaluation of quality of life.22 Similar results were obtained by Parfenov et al in multi-national, observational review, where betahistine treatment was given at a dose of 48 mg/day, and a significant change in vertigo severity was noted (p<0.001).9 A double-blind, multicentre and parallel-group randomized study with 144 patients showed that Betahistine had a significant effect on frequency, intensity and duration of vertigo attacks.23 An open label trial reported a significant reduction in the number of attacks per month in a total population of 112 patients with meniere's disease.24 Similar results were reported in a randomized, open-label study of 120 patients with well-established meniere's disease, where the improvement was observed in the first 12 weeks of betahistine treatment.25 In the present study the effectiveness of Betahistine was established in 21 days; however, long-term and effective treatment with betahistine was also confirmed by few clinical trials.24-26

Dizziness causes substantial impairment, therefore decrease in mean total DHI score is the important criterion. In the present study, significant reduction in mean change DHI scale was noted (p<0.0001). Similar results were presented in a review where baseline total DHI score of Indian population was high and post-treatment with betahistine the total DHI score decreased significantly.19

Present study reported few AEs like headache and nausea of mild severity, but no serious AEs were reported. This indicate the easily tolerable safety profile of betahistine at 16 mg TDS. VIRTUOSO study also reported similar results with no serious AEs reported in 309 patients, at 48 mg/day.9 An Indian study supported the present study, that Betahistine has a well-established safety profile and is easily tolerated, where only one suspected adverse drug reaction (mild gastritis) was reported in a patient receiving betahistine 16 mg TDS.19 Few more studies supported results of current study that betahistine treatment has shown minimal side-effects and has a positive safety profile in patients with vertigo.23,12

Limitation

Limitation of this study was non-comparative, open-label study design. Further, no formal sample size calculation was done in this study.

CONCLUSION

Findings suggest that betahistine (16 mg, TID) therapy is effective in treatment naive patients with acute peripheral vertigo. Reduction in vertigo symptoms score was evident from day-3 to day-21. Betahistine was found to have a good safety profile and well tolerated in these patients. It can be concluded that betahistine therapy may be considered for the treatment of acute peripheral vertigo in the Indian population.

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