The Real-World Safety and Effectiveness of Prochlorperazine in Indian Patients with Dizziness

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Abstract

Background: Considering the prevailing concerns about extrapyramidal symptoms (EPS) associated with oral prochlorperazine, this study was conducted to assess the safety of oral prochlorperazine (in recommended dose/duration) in the management of acute dizziness. Effectiveness was also assessed in the Indian real-world setting.

Methods: A prospective, multicentric, single-arm observational study was conducted across 20 centers in India. Data from 500 patients were analyzed. Patients presenting with a complaint of dizziness, receiving prochlorperazine (Stemetil® MD-5 mg, t.i.d.) as per the routine clinical practice were enrolled. Safety and effectiveness at Week-1, compared to baseline, were assessed.

Results: The mean (SD) age of the population was 43.3 (11.93) years with a marginally higher proportion of women (women: 52.2% Vs men 47.8%). The mean (SD) dose of prochlorperazine was 14.9 (0.24) mg/day. Only three patients (0.006%) reported adverse drug reactions (headache, asthenia, somnolence) during the conduct of the study, which were mild in severity and were completely resolved. Further, a significant reduction in the number of episodes of dizziness was noted at the end of Week-1 (p<.0001). Moreover, improvement in the number of episodes from baseline to Week-1 was significant for nausea, vomiting, lightheadedness, and headache.

Conclusion: Prochlorperazine was well-tolerated in the management of acute dizziness when administered at a mean dose of 14.9 mg/day, and mean duration of 7.2 days. Additionally, prochlorperazine was effective in providing significant symptomatic relief from dizziness and associated vomiting and nausea.

Introduction

Dizziness is an illusory sense of motion without any real movement in relation to gravity as defined by the American Academy of Otolaryngology and Head and Neck.¹ Reported literature has shown that dizziness is one of the most prevalent complaints in medicine, affecting approximately 20%-30% population worldwide.²⁻⁴ In the Indian context, a study reported that 5% of all patients visiting a general physician and about 10% of patients visiting neurologists and ENT specialists present with vertigo, a type of dizziness.⁵

Dizziness is classified into four main types: (1) vertigo, (2) presyncope, (3) disequilibrium, and (4) lightheadedness, based on the evaluation of the patients.⁶ The incidence of dizziness has been reported to be higher in the females and elderly population aged > 50 years.⁷ The primary cause of dizziness is reported to be peripheral vestibular disorders like Benign Paroxysmal Positioning Vertigo (BPPV).⁸ The clinical condition is often examined by recording the timing (onset, duration, and evolution of dizziness) and triggers (actions, movements, or situations) that provoke dizziness.⁹

Understanding the fundamental causes of dizziness and vertigo is necessary for choosing an appropriate management therapy.¹⁰ The patients suffering from dizziness and vertigo may often show an acute phase of dizziness. A comprehensive method for management is essential for faster relief, to avoid reoccurrence, management of associated conditions and treating anxiety to prevent delayed recovery.¹¹ Management of symptomatic relief for acute attacks of dizziness is effective with drug therapy. Two categories of drugs, vestibular suppressants, and antiemetics, are prescribed for the management of acute dizziness and associated symptoms.¹²

Prochlorperazine is an antiemetic with a vestibular suppressing effect. It has been approved by the FDA in 1956 and recommended for severe nausea and vomiting.¹³ It has a long history of being used in vertigo pharmacotherapy for dizziness. Earlier studies have demonstrated complete clearance of symptoms associated with vertigo on long term treatment without any safety concern in Indian patients. However, the sample size was small and is not the complete representation of the general population.¹⁴

Despite the clinical success, data on clinical safety and effectiveness of prochlorperazine is inconsistent and limited. The lack of consistency may be attributed to the clinical evidence from varying ethnic populations. In addition, the limited data from Indian milieu fails to provide real-time evidences of prochlorperazine as a treatment measure. Furthermore, extrapyramidal symptoms (EPS) due to antiemetics with central dopamine antagonist properties are well documented.¹⁵ Additionally, like other phenothiazines, the use of prochlorperazine can cause akathisia (motor restlessness/anxiety) and dystonia (muscle spasms). However, there is variation in the
reported incidences of EPS related to prochlorperazine from different regions. Therefore, a Pan India study evaluating the safety and effectiveness of prochlorperazine, with an adequate representation across geographical regions, with the correct sample size is vital.

In this light, the present study evaluated the safety of low dose prochlorperazine in terms of number and severity of adverse drug reactions (ADRs), the effectiveness with respect to improved dizziness symptoms and overall clinical response of patients prescribed with prochlorperazine.

**Methods**

**Study population**

This multicentric, single-arm, observational study was conducted between June 2018 to January 2019 across 20 centers in India (Maharashtra, Delhi, Madhya Pradesh, Karnataka, Rajasthan, Tamil Nadu, Gujarat, and West Bengal). A total of 500 patients (≥18 years) with dizziness (as per the investigator’s clinical judgment) completed the study. All study patients were prescribed with Stemetil® MD 5 mg tablets three times a day (as per the routine clinical practice and label). Pregnant or lactating women and patients requiring urgent treatment or hospitalization were excluded.

This study involved two visits at baseline (Visit 1) and at Week 1 (± 2 days; Visit 2). Patients with ongoing ADRs were contacted telephonically at Week 4 (± 2 days; Visit 3) for follow-up regarding ADR resolution status.

The primary endpoint of this study was the analysis of ADRs during the study period. The secondary endpoints were the change in the mean number of daily episodes and severity of dizziness from baseline to Week 1, change in the mean number of episodes and severity of symptoms associated with dizziness (nausea, vomiting, headache, and lightheadedness) from baseline to Week 1, the overall clinical response, and the percentage of patients receiving concomitant medications by type and frequency of medication.

At baseline, demographic and socioeconomic details, history of dizziness (as per Common Terminology Criteria for Adverse Events),10 history of symptoms associated with dizziness (nausea, vomiting, headache, lightheadedness), concomitant medications (type and frequency) and vital signs and physical examination details (based on the investigator’s discretion) were collected.

All enrolled patients were asked to return after 1 week within a window of ±2 days for following assessments: history of dizziness from baseline visit, history of symptoms associated with dizziness from baseline visit, number, frequency, severity of dizziness episodes at the end of treatment, concomitant medications, vital signs and physical examination details (based on the investigator’s discretion) and details of ADRs and treatment effectiveness.

This study was performed in conformity with the principles of the Declaration of Helsinki, International Council for Harmonization—Good Clinical Practices (ICH-GCP) guidelines, Indian Council of Medical Research, Indian GCP guidelines. The study protocol was approved by the independent ethics committees of all participating centers, and informed consent was obtained from all patients before data collection.

**Statistical analysis**

No formal sample size calculation was performed. Continuous variables such as change in mean number of symptoms associated with dizziness were summarized with the number of observations, mean, standard deviation (SD), median, minimum and maximum values, and 95% confidence interval (CI). The 95% CI for categorical variables was calculated by using the Clopper-Pearson Method for the exact confidence interval for a binomial proportion. The change in mean episodes was performed through paired t-test. All statistical tests were performed at a 2-sided 5% level of significance. The statistical analysis was done using Statistical Analysis System® version 9.4 software (SAS Institute Inc., Cary, NC). The Proc-t-test procedure of SAS was used to compare the change from baseline.

**Results**

**Baseline Characteristics - Demographic and clinical profile**

All 500 enrolled patients completed the study. The mean age (SD) of the patients was 43.3(11.93) years, with 261 females and 239 males. Most study patients were graduates (46.0%) and unemployed (24.2%) as shown in Table 1.

Out of 500, 45 (9%) patients reported at least one comorbid condition. The most commonly reported comorbidities were diabetes mellitus (n=8), dyslipidemia (n=3), and hypocalcemia (n=1).
Prior to being enrolled in the study, majority of the patients had history of dizziness with Grade 2 [278 (55.6%), Grade 1 [198 (39.6%)], and Grade 3 [24 (4.8%)] severity. The mean (SD) number of episodes of dizziness was 2.9 (1.83) per day (n=300), 2.6 (1.10) per week (n=177) and 1.6 (1.03) per month (n=23).

The vital signs and physical examination analysis are depicted in Table 2A and 2B. Vital sign analysis reported clinically significant abnormalities in body temperature in three patients and respiratory rate in one patient. Clinically significant abnormalities were reported in the respiratory system (n=1), abdominal (n=1) hematological (n=1), physiological (n=2) and psychological examinations (n=2) at baseline, and physiological (n=1) and psychological examinations (n=1) at Week 1.

Forty-nine patients received prochlorperazine ≤ five days and all other enrolled patients received treatment for > five days (N = 451).

### Safety outcomes

Only three patients (0.006%) reported ADRs (headache, asthenia, somnolence) during the conduct of the study, which were possibly related to prochlorperazine. All of these ADRs were mild in severity and were completely resolved. No serious ADR or ADR of special interest were reported in the present study.

### Effectiveness outcomes

#### Symptom reduction and recurrence

Reduction in symptoms and recurrence is depicted in Table 3A and 3B. Statistically significant change in the frequency of dizziness of episodes from baseline was reported at Week 1 [Baseline: 3.4 (2.77), Week 1: 1.8 (1.05)] after administration of Stemetil® MD 5 mg tablets three times a day. A total of 198 patients reported mild dizziness at baseline and remained in the same category at Week 1. Moderate dizziness was reported by 278 patients at baseline, of which 245 shifted to mild category, 32 remained moderate and one patient was restored to health at Week 1. Similarly, out of 24 patients with severe dizziness at baseline, 19 moved to mild category and 5 to moderate at Week 1.

Other associated symptoms with dizziness and treatment

A slight decline in the number of patients with dizziness associated nausea (28.4% Vs. 27.8%), vomiting (30.4% Vs. 28.8%) and headache (25.8% Vs. 24.0%) were reported after one week of treatment. Additionally, the severity of nausea, vomiting, headache, lightheadedness, and other symptoms reduced significantly after one week of treatment. Frequency of symptoms of nausea [142(28.4%)], vomiting [152(30.4%)], headache [129(25.8%)], lightheadedness [92(18.4%)] and others [16(3.2%)] improved at Week 1 in all enrolled patients who received treatment for > five days (N = 451).
Table 2B: Summary of physical examination

<table>
<thead>
<tr>
<th>Category, n (%) / Response</th>
<th>Baseline(N=500)</th>
<th>Visit 2 (week 1)(N=500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was Physical examination performed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>500(100.0%)</td>
<td>340(68.0%)</td>
</tr>
<tr>
<td>Not Done</td>
<td>0</td>
<td>160(32.0%)</td>
</tr>
<tr>
<td>Cardiovascular, [a]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>500(100.0%)</td>
<td>340(100.0%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>If Abnormal, [b]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NCS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory,[a]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>499(99.8%)</td>
<td>340(100.0%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>1(0.2%)</td>
<td>0</td>
</tr>
<tr>
<td>If Abnormal,[b]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>1(100.0%)</td>
<td>0</td>
</tr>
<tr>
<td>NCS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal,[2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>499(99.8%)</td>
<td>340(100.0%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>1(0.2%)</td>
<td>0</td>
</tr>
<tr>
<td>If Abnormal,[b]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>1(100.0%)</td>
<td>0</td>
</tr>
<tr>
<td>NCS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neurological,[a]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>500(100.0%)</td>
<td>340(100.0%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>If Abnormal,[b]</td>
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</tr>
<tr>
<td>CS</td>
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<td>0</td>
</tr>
<tr>
<td>NCS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other,[a]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Percentages were calculated by taking respective Done count as denominator. [b] Percentages were calculated by taking the Abnormal count as denominator.

treatment for > five days. However, in patients who received the study drug for ≤five days, the decrease in the mean number of symptoms of lightheadedness was not significant. The mean number of episodes of nausea, vomiting, headache, and lightheadedness were reduced from 2.4 to 1.4, 1.9 to 1.2, 2.4 to 1.5 and 2.3 to 1.7 per day, respectively (Figure 1).

Treatment response based on the Investigator’s assessment

A majority of the patients reported good [262(52.4%), followed by excellent [175(35.0%)], and fair [56(11.2%)] overall clinical response at Week 1 as per the investigator’s assessment.

Concomitant medications

The highest percentage of concomitant medications taken by patients were paracetamol (n=14), rabeprazole (n=13), ondansetron (n=8) and ranitidine hydrochloride (n=8) during the study period (Figure 2).

Discussion

Dizziness with associated nausea, vomiting, headache, and lightheadedness are common presentations impacting the general quality of life of the patient. As dizziness and vertigo are frequently associated with numerous symptoms, a comprehensive approach for effective treatment is imperative. Several pharmacological agents are used in the treatment of dizziness and vertigo. Prochlorperazine is found to be efficacious in providing relief from spinning sensation and associated vegetative symptoms, owing to its antidopaminergic and anticholinergic potential. It acts as an antiserotonergic and antidopaminergic agent, making it the drug of choice for symptomatic treatment of acute vertigo. Likewise, prochlorperazine is an ideal option for treating dizziness associated with nausea and/or vomiting in patients with vertiginous disorders. As anxiety is a common dizziness associated symptom, its management is exceedingly important. Prochlorperazine has shown to significantly counteract anxiety without any other side effects.

This study demonstrated the safety and effectiveness of prochlorperazine in the real world in the Indian population as a short-term therapy of one week. The study cohort comprised of 500 patients with a mean age of 43.3 (11.93) years, which was relatively lower as compared to the other reported studies. In concordance with the published data, female preponderance was noted in this study.

In the present study, the most commonly reported comorbidities were diabetes mellitus and dyslipidemia. However, the overall comorbidity percentage was lower in our study when compared to others. The most commonly reported symptoms of dizziness included nausea and vomiting, as also seen in our study.

Prochlorperazine has been reported to be effective in reducing the frequency of nausea, and severity of headache in adult patients when compared with ondansetron treatment in a randomized controlled trial. Similar favorable clinical outcomes of prochlorperazine were demonstrated in a 1-week
treatment study by 73% of the patients with new-onset vertigo (p<0.0001). In the present study also, a significant decline in the severity and duration of nausea, vomiting, headache, and lightheadedness was reported at Visit 2. The average dose of prochlorperazine was 14.9 mg/day; the duration of consumption was ≤5 days by 9.8% and >5 days by 90.2% of patients in the present study. The reported mean dose per day was slightly higher in the recently concluded study by Kameshwaran et al. The comparatively smaller duration of treatments in the present study may be the reason for the difference in dose range.

In this study, the use of concomitant medication was low, and the usage of antiemetics and antinauseants was limited to only 2% of patients. This
could be attributed to the multimodal mechanism of prochlorperazine, thereby limiting the concomitant use of antiepileptics and antinauseants. A decline in the mean duration of dizziness episodes from baseline was reported at Week 1. Moreover, in around one-tenth of patients who received prochlorperazine treatment for five days, a significant reduction in frequency was achieved in the majority of dizziness associated symptoms.

In this study, only three patients reported ADRs (headache, asthenia, somnolence), which was in concordance with the reported literature.25, 26

Our study has several strengths. Firstly, this is the first of its kind Pan India study with a representation of effectiveness across various Indian geographical locations and diverse age groups. Secondly, the observations are derived from the dizziness patients in the real-time setting. A few of the limitations of the study were the absence of control or comparator group for reducing bias, and lack of exact diagnosis.

Conclusion

Prochlorperazine was found to be well-tolerated and effective in Indian patients when administered at a mean dose of 14.9 mg/day, and a mean duration of 7.2 days. In the present study, the incidence of dizziness was found to be higher in females. Diabetes mellitus was the most common comorbidity reported. A significant decline in the frequency and duration of dizziness and associated symptoms was noted with prochlorperazine.

Expert comments

- The exact diagnosis of the causes of dizziness is mandatory and proper referral is imperative for appropriate disease management
- Identifying the red flags is of utmost importance and symptomatic treatment should be discouraged in such cases.
- A proper history and physical examination are of paramount importance for making a correct diagnosis in patients with dizziness.
- Consensus statements are warranted to optimize patient care and healthcare utilization for one of the most common symptom presentations in all the medicine.

Funding

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Conflict of Interest

All authors were investigators in the study. All authors were affiliated with Chord’s hospital during the conduct of the study, but is presently affiliated with Trustwell Hospitals Pvt. Ltd, Bengaluru.

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