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Efficacy and Safety of a Combination of Cinnarizine and Dimenhydrinate in the Treatment of Vertigo

Dr. Mayuresh Kiran[*1], Mr. Lalit Pawaskar[2]

[1]Vice President, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.
[2]Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.

Abstract:

Introduction and Background: *Vertigo is a medical condition where a person feels as he/ she or the objects around them are moving when they are stable and not moving. Antihistamines, Calcium antagonists, histamine analogs (eg, betahistine derivatives), diuretics, neuroleptics as well as other psychotherapeutic drugs, corticosteroids agents and hemorheologics can be used for the treatment of Vertigo. Combination of Cinnarizine which is a selective calcium-channel blocker and Dimenhydrinate which is an H 1 antihistaminic drug can be used in combination for the treatment of vertigo. This clinical study was conducted to evaluate the efficacy and safety of combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg in patients of vertigo of age group 18 to 65 years.* ***Methodology:*** *Out of total 216 patients, 168 completed the study. Efficacy assessment was made by analysing the reduction in vertigo symptom score (VSS). Safety assessment was made by analysing the adverse events experienced by the patient or observed by the investigator during trial.* ***Results:*** *Reduction in VSS from 7.277 (baseline) to 3.975 (day 3) and 0.987 (day 5). At visit 2 and visit 3 there was reduction of 45.373 % and 86.426 % in mean VSS score.* ***Conclusion:*** *A combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg is safe and efficacious in the treatment of vertigo.*

Keywords: ***Cinnarizine, Dimenhydrinate, Vertigo.***

Introduction

Vertigo is a medical condition where a person feels as he/ she or the objects around them are moving when they are stable and not moving. Active sensorimotor control system is mandatory for maintaining the balance of human body and for keeping the human body inside its limit of physical stability. This is a complex physical task which is based on finely tuned brain processing of sensory inputs which is provided by the visual, proprioceptive, vestibular and cognitive system. Data mismatch brought by unusual and therefore unchanged stimulation of the intact sensory systems or pathological dysfunction of any of these afferent components or of brain centers integrating these signals may lead to the symptoms of vertigo. Diabetes, hypertension or coronary heart diseases also causes unsystematic balance disorders. Systematic vertigo is mostly caused by disorders of the vestibular system. Vertigo caused by acute vestibular loss is less more common than chronic. Acute unilateral vestibular loss can have great impact, because it instantaneously leads to spontaneous horizontal rotatory nystagmus, rotatory vertigo attack along with postural imbalance, vomiting and nausea. In addition in some of the cases tinnitus, aural fullness and sensorineural hearing loss may occur. The occurrence of chronic as well as acute vertigo increases with the increasing age and imposes great limitations on activities of daily living of the patient. Patients suffering from vertigo are prone to frequent falls which may result in injuries. Patients of vertigo feel insecure while standing because of the fear of imbalance usually it results in loosing of self-confidence of the patient. Vertigo can also cause to chronic immobilization to the patient. [1]

Antihistamines, Calcium antagonists, histamine analogs (eg, betahistine derivatives), diuretics, neuroleptics as well as other psychotherapeutic drugs, corticosteroids agents and hemorheologic can be used for the treatment of Vertigo. Combination of Cinnarizine which is a selective calcium-channel blocker and Dimenhydrinate which is an H 1 antihistaminic drug can be used in combination for the treatment of vertigo. Since many years it is used for the treatment of vertigo as this is approved combination for the treatment of vertigo approved by DCGI on the date of 3rd February 2010. This clinical study was conducted to evaluate the efficacy and safety for the combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg in patients of vertigo of age group 18 to 65 years.[1]

Cinnarizine acts as an inhibitor of vestibular excitability by suppressing calcium influx into vestibular sensory cells. Through its specific inhibition of calcium entry into arterial smooth muscle cells, Cinnarizine improves cerebral and cochlear perfusion. Dimenhydrinate exerts antivertiginous and antiemetic effects via its regulatory potential, affecting the vestibular nuclei and closely associated vegetative centers in the brainstem.[1]

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Cinnarizine modulates Ca^{2+} fluxes and attenuates vasoconstrictor action of many endogenous substances. Cinnarizine inhibits vestibular sensory nuclei in the inner ear, suppresses post rotatory labyrinthine reflexes, possibly by reducing stimulated influx of Ca^{2+} from endolymph into the vestibular sensory cells. Beneficial effects have been reported in Méniére's disease and other types of vertigo. The drug is safe to use in patients of vertigo as it has only minor adverse effects as mild GI upset and sedation.[2]

Dimenhydrinate diminishes vestibular stimulation and depress labyrinthine function. It also acts on trigger zone of medullary chemoreceptor which is involved in the antiemetic effect. Dimenhydrinate is a competitive antagonist at the histamine H1 receptor, which is widely distributed in the human brain. Dimenhydrinate's anti-emetic effect is probably due to H1 antagonism in the vestibular system in the brain.[2]

The rationale for using a fixed dose combination of an antihistamine (Dimenhydrinate) and a calcium channel blocker (cinnarizine) for symptomatic relief of vertigo is derived from their modes of action. Dimenhydrinate acts mainly on the central vestibular system through inhibition of histamine-receptor and cholinergic receptor functions in the vestibular nuclei and vomiting center. As Cinnarizine exerts its anti-vertigo effects primarily on the peripheral vestibular system t6q8 through inhibition of calcium influx into vestibular hair cells, hence regulating hair-cell afferent vestibular transmission.[3]

Materials and Methods

This was a Phase IV Clinical study conducted with 11 ENT speciality investigators all across the India from February 2017 to July 2017. Total 216 patients were recruited for the study out of which 168 patients completed and 48 patients were lost to follow-up.

Inclusion and exclusion criteria

Patients with confirmed diagnosis of Vertigo, patients of both the genders (male as well as female) of age 18 to 65 years, and finally the patients who were ready to strictly adhere to the protocol and sign informed consent form were recruited for the study.

Patients having hypersensitivity to any individual study drug of the combination or to any of the ingredient present in the dosage form, lactating or pregnant woman or the patients who cannot adhere to the Protocol were excluded.

Sample size

This being a non-comparative Phase IV study, hence a sample size was decided to keep more than 150 and kept 216. Out of total 216 patients 48 patients were left to follow up and finally the study was conducted on 168 patients.

Study Intervention

Study drug contains combination of Cinnarizine (20 mg) and Dimenhydrinate (40 mg) per tablet. The patient was advised to take 1 tablet thrice a day for the study period of 5 days and for that 15 tablets of the study drug combination were provided to each patient. Sample for the study drug combination was provided to the patient by the investigator.

Study procedure

The study was conducted for the duration of 5 days. Patients of vertigo who met with the decided exclusion and inclusion criteria were recruited for the clinical study. A detailed medical history was obtained from each patient and physical examination was conducted by the investigators. All the investigators conducted this PMS study were holding post-graduate degree in ENT. Patients were dispensed with 15 tablets of study drug combination by investigators and asked to consume 1 tablet thrice a day for a study period of 5 days. Patients were asked to maintain a diary to record any adverse events experienced during the conduction of clinical study. Three visits were planned for all the patients recruited in this study-the first visit was baseline visit (V1) on day 1 before treating patient with the study drug combination, the second visit was revaluation visit (V2) on day 3 and third visit was conclusion visit (V3) on day 5. Adverse events occurring and vertigo symptom score were noted during each visit along with the physical examination is recorded in the case report form. In case if any investigator observes any adverse event, the investigator needs to convey that information to the principle investigator within 48 hrs. And in case of any serious adverse event investigator was asked to discontinue the study drug.

Concomitant therapy

No Pharmacological intervention including other than study drug combination was allowed during study duration of 5 days.

Efficacy assessment

The primary efficacy assessment was done by analysing the reduction in vertigo symptom score (VSS) on vertigo symptom scale. Vertigo symptom scale is an 11 point scale where 0 means no symptom and 10 mean maximum tolerated symptoms.

On vertigo symptom scale 1 to 3 is considered as mild intensity vertigo symptoms, 4 to 6 is considered as moderate intensity vertigo symptoms and 7 to 10 is considered as severe symptoms of vertigo.

Safety assessment

During the clinical trial period of 5 days, all the patients were asked to maintain the diary to record adverse events (AE) experienced and in case of any serious adverse event the patients were asked to contact the investigator and stop the study drug combination immediately. In case if the

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information about any serious adverse event (SAE) is conveyed to the investigator then same will be conveyed to the principle investigator (PI) and PI will convey the information about the adverse event as well as the treatment of it to all the investigators. In case of adverse events or serious adverse event the information of it will be recorded in the case record form as well as in AE or SAE reporting form. Adverse event were classified as drug related or nondrug related adverse events by using Naranjo's scale of probability. In case of any adverse event or serious adverse event if any patient needs to be treated then the necessary treatment will be done by the investigators till their resolution.

Regulatory matters

The said combination is available in India and approved by DCGI. It is classified as schedule H drug which means it should be sold only in the presence of prescription of a registered medical practitioner. All the patients participated in the study have read and signed the ICF.

Results

Study was conducted at 12 centers and total 216 patients were recruited for the study out of which 168 patients completed and 48 patients were lost to follow-up.

Efficacy analysis

For the efficacy analysis of the study drug combination mean VSS was calculated at all the visits. At baseline mean VSS was 7.277 which was reduced to 3.975 at visit 2 and further reduced to 0.987 at visit 3 as shown in figure 1. So from visit 1 to visit 2 there was reduction of 45.373 % and from visit 2 to visit 3 there was reduction of 86.426 % in mean VSS as shown in figure 2.

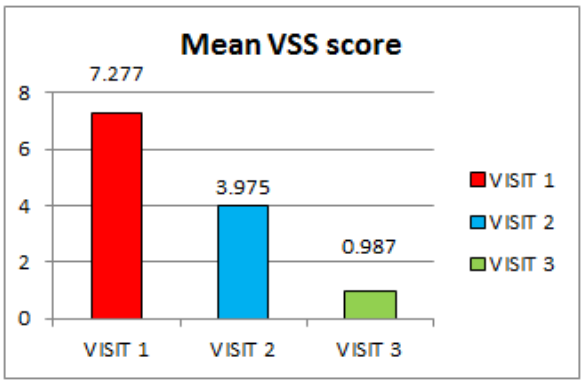

Figure 1: Reduction in mean VSS score at visit 1, 2 and 3

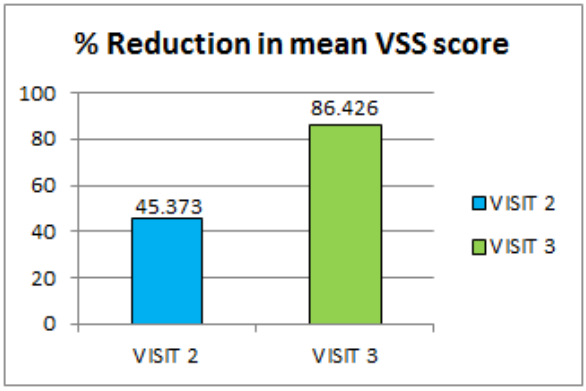

Figure 2: percent reduction in mean VSS score at visit 2 and 3 as compared to visit 1 (baseline)

In further analysis we have filtered patient's data into patients having mild, moderate and severe vertigo. Patients of VSS score 1 to 3, 4 to 6 and 7 to 10 were classified in patients having mild, moderate and severe symptoms or intensity of vertigo. Then the number and percentage of patients in each group were calculated as shown in table 1. As per the data shown in the table 2 the intensity of vertigo in the patients were decreased from baseline to visit 2 to visit 3.

Table 1 the number and percentage of patients having different intensity of vertigo symptoms at all the visits

VSS	Intensity of vertigo	VISIT 1		VISIT 2		VISIT 3	
		No. of patients	% of patients	No. of patients	% of patients	No. of patients	% of patients
0	NONE	0	0	3	1.785	53	31.547
1 to 3	MILD	12	7.142	53	31.547	112	66.666
4 to 6	MODERATE	35	20.833	111	66.071	3	1.785
7 to 10	SEVERE	121	72.023	1	0.595	0	0

Safety analysis

Out of total 168 patients 8 patients were reported 13 episodes of drowsiness which is a non-serious adverse event.

Discussion

Because of the diversity and complexity of pathogenic mechanisms of vertigo, which frequently involves both peripheral and central components of the vestibular system, adequate treatment of it is often difficult. The fixed dose of combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg has been used in the treatment of vertigo in Germany for more than 20 years and in India the same combination is approved by DCGI on 3rd February 2010. The present study was conducted to prove the safety as well as efficacy of the combination therapy of low dose combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg in the Indian patients and for that this study was conducted by the investigators all over the India.

At baseline mean VSS was 7.277 which was decreased by 45.373 % at visit 2 on day 3 and mean VSS was 3.975 and then it was decreased by 86.426 % at day 5 and mean VSS

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was 0.987. So in 5 days there was reduction of 86.426 % in all the symptoms of vertigo.

The patients having VSS score of 0, 1 to 3, 4 to 6 and 7 to 10 are considered as none, mild, moderate and severe symptoms of vertigo respectively. At baseline 72.023 %, 20.833 % and 7.142 % patients were having severe, moderate and mild symptoms of vertigo respectively. Majority of the patients at baseline were of severe vertigo symptoms. At visit 2, 0.595 %, 66.071 %, 31.547 % and 1.785 % of patients were having severe, moderate, mild and no symptoms. So at day 3 (visit 2) only 1 patient (0.595 %) patient was having severe symptom of vertigo, majority of the patients having severe symptoms of vertigo were shifted to moderate symptoms. At visit 3, no patient was having severe symptoms of vertigo; only 3 patients (1.785 %) were having moderate symptoms of vertigo; 66.66 % patients were having mild symptoms of vertigo and 31.547 % of patients were completely cured and was not having any symptom of vertigo.

Arne W. Scholtz *at al* conducted single-centered, randomized, double-blind, randomized, parallel-group clinical study for the comparison of clinical efficacy and tolerability of a fixed combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg versus monotherapy with respective components of the combination for the treatment of acute vertigo symptoms due to acute unilateral vestibular loss. The purpose of this study was to compare the clinical efficacy and tolerability of a fixed combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg and monotherapy with its respective components in the treatment of acute vertigo symptoms due to acute unilateral vestibular loss. The study was conducted on 50 patients with acute vestibular vertigo for the study duration of 4 weeks and each patient was asked to take 1 tablet thrice a day in all the cases. As a part of standard therapy all the patients were received 15 % mannitol infusion during first 6 days of treatment. Efficacy assessment was done by evaluating vertigo symptoms after 1 and 4 weeks of treatment using a verbal rating scale (vertigo score) and by vestibulo-ocular and vestibulospinal tests. After 1 week of treatment, the combination therapy was more efficacious than 20 mg Cinnarizine ($P < 0.001$) or 40 mg Dimenhydrinate ($P < 0.01$). After 4 weeks, the fixed combination was still significantly more efficient than Cinnarizine in reducing vertigo symptoms ($P < 0.01$) and significantly more efficient than Dimenhydrinate in improving the patients' balance while standing ($P < 0.05$). The combination therapy was found to be efficacious in 100 % patients, monotherapy of Cinnarizine was efficacious in 82.4 % of patients and Dimenhydrinate was efficacious in 94.4 % of patients. There was no serious adverse effect observed in any of the patient. So Arne W. Scholtz *et al* concluded that combination therapy was more efficacious for the treatment of Vertigo as compared to the monotherapy.[1]

Joseph Pytel et al conducted a 4 week, prospective, randomized, multicentered, double-blind, active- and placebo-controlled, parallel-group, outpatient study in men and women of age more than 30 years with central, peripheral or combined central or peripheral vestibular vertigo. The study was conducted to compare the efficacy and safety of the combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg and the monotherapy of Cinnarizine 50 mg and Dimenhydrinate 100 mg and placebo. Efficacy assessment was done by using 5 point visual analogue scale (VAS) from 0 to 4, where 0 means no symptom and 4 means maximum symptoms. Only patients recruited for the study having VAS score of more than 1 and having abnormal vestibulospinal moments pattern on craniocorpography were eligible for the study. Efficacy assessment on VAS scale was done by using 6 symptoms of vertigo. The study was done on 239 Hungarian patients for the duration of 4 weeks. The patients who were treated with combination therapy of Cinnarizine 20 mg and Dimenhydrinate 40 mg the VAS score was reduced from 1.85 to 0.45 by the change of 1.37. In the monotherapy of Cinnarizine 50 mg the VAS score was reduced from 1.72 to 0.81 by the change of 0.87. In the monotherapy of Dimenhydrinate 100 mg VAS score was decreased from 1.69 to 0.87 by the difference of 0.83. The patients took placebo showed decrease of 1.74 to 1.01 with the difference of 0.76. Joseph Pytel *et al* concluded that low-dose combination of cinnarizine 20 mg + dimenhydrinate 40 mg was significantly more effective than the higher doses of its single active components typically used as monotherapy. [4]

Miroslav Novotny *et al* conducted a randomized, double-blind, parallel group clinical study for the combination therapy of Cinnarizine 20 mg and Dimenhydrinate 40 mg and a monotherapy of Betahistine Dimesylate 12 mg on 82 patients suffering from Meniere's disease and having symptoms such as cochlear hearing loss, paroxysmal vertigo attacks or tinnitus for at least 3 months. Patients were asked to take the combination therapy or monotherapy 3 times a day for the study period of 12 weeks. The efficacy assessment was done by using 5 point visual analogue scale (VAS) from the possible rating between 0 to 4 where 0 means no symptoms and 4 means very strong symptoms. Rotary sensation was changed from 3.18 ± 0.55 by -2.63 ± 0.93 and from 3.15 ± 0.41 by -2.78 ± 0.73 in combination and monotherapy respectively. Tinnitus was changed from 3.29 ± 0.44 by 1.98 ± 1.04 and from 3.25 ± 0.48 by -1.86 ± 0.76 in combination and monotherapy respectively. Hearing loss was changed from 3.08 ± 0.64 by -1.88 ± 1.18 and from 3.05 ± 0.74 by -1.74 ± 0.93. Aural fullness was changed from 2.93 ± 0.58 by -2.21 ± 1.07 and from 2.78 ± 0.88 by -1.89 ± 1.02. However, no statistically significant difference

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was found between efficacy of combination or monotherapy. Miroslav Novotny concluded that the fixed dose combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg is safe and highly efficacious in the treatment of Meniere's disease. The combination therapy can be used in both the management of acute episodes and in long-term treatment. And reported that efficacy and safety of the combination therapy of Cinnarizine 20 mg and Dimenhydrinate 40 mg is equivalent to standard therapy of Betahistine in terms of safety and efficacy.[5]

Conclusion

Combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg per tablet was found to be safe as well as efficacious for the treatment of vertigo in Indian patients.

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Conflict of Interest - None

Disclosure

Dr. Mayuresh Kiran, Study Director and Mr. Lalit Pawaskar, Research Associate for this study are employees of Centaur Pharmaceuticals Pvt. Ltd. This study was conducted as a part of Pharmacovigilance activity for Vertidiz Tablets marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

References

[1] Arne W. Scholtz, Mario Schwarz, Wolfgang Baumann, Dieter Kleinfeldt, Heinz-Joachim Schohz. Treatment of Vertigo Due to Acute Unilateral Vestibular Loss with a Fixed Combination of Cinnarizine and Dimenhydrinate: A Double-Blind, Randomized, Parallel-Group Clinical Study. clinical therapeutics. 2004;26(6):866-877.

[2] Tripathi KD. Essentials of medical pharmacology. JP Medical Ltd; 2013 Sep 30.

[3] Perin P, Soto E, Vega R, Botta L, Masetto S, Zucca G, Valli P. Calcium channels functional roles in the frog semicircular canal. NeuroReport. 2000;11(2):417-20.

[4] Joseph Pytel, Gyorgy Nagy, Agnes Toth, Seindor Spellenberg, Mario Schwarz and Gabor Repassy. Efficacy and Tolerability of a Fixed Low-Dose Combination of Cinnarizine and Dimenhydrinate in the Treatment of Vertigo: A 4-Week, Randomized, Double-Blind, Active and Placebo-Controlled, Parallel-Group, Outpatient Study. Clinical Therapeutics 2007;29(1):84-98.

[5] Miroslav Novotny and Rom Kostfica. Fixed Combination of Cinnarizine and Dimenhydrinate Versus Betahistine Dimesylate in the Treatment of Meniere's Disease: A Randomized, Double-Blind, Parallel Group Clinical Study. International Tinnitus Journal. 2002; 8(2):115-123.

***Corresponding Author** -

Dr. Mayuresh Kiran
Centaur Pharmaceuticals Pvt. Ltd.,
Centaur House, Near Grand Hyatt, Vakola, Santacruz (East),
Mumbai - 400055
Mob. No. : +91 9820068567
Email: mayuresh_kiran@rediffmail.com

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