Study of Safety and Efficacy for the Combination of Chlorpheniramine maleate and Phenylephrine in Infants suffering from Allergic Rhinitis and Associated Symptoms

Mayuresh Kiran[1], Lalit Pawaskar[2]

ABSTRACT

Introduction: The epidemiological data suggest that there is alarming rise in the prevalence of allergic rhinitis. It often goes intractable in small children. A combination of nasal decongestant and antihistaminic drug is preferred over the various aetiologies associated with allergic rhinitis. Study objective was to evaluate the efficacy and safety for the combination of Chlorpheniramine maleate and Phenylephrine in patients of allergic rhinitis and associated symptoms.

Material and Methods: Total 215 patients were enrolled out of which 177 patients completed the study and efficacy assessment was made by reduction in TSS and four point Likert-Type scales. Safety assessment was made by analysing the adverse events during clinical trial.

Results: There was significant reduction in TSS from 5.677 (baseline) to 2.711 (day 3) and 0.542 (day 5). At day 3 and day 5 there was reduction of 52.23% and 90.44% as compared to baseline. Nearly all the patients had > 50% reduction in symptom score at all visits and majority of patients had complete relief from the symptom.

Conclusion: A combination of Phenylephrine and Chlorpheniramine maleate was found to be efficacious as well as safe in the treatment of allergic rhinitis.

Keywords: Phenylephrine, Chlorpheniramine Maleate, Allergic Rhinitis and Total Symptom Score (TSS)

INTRODUCTION

Allergic rhinitis (AR) is an IgE-mediated inflammation of the nasal mucosa induced after the exposure of allegens and presents with the 3 cardinal symptoms including sneezing, nasal obstruction, and rhinorrhea. AR is a global health problem that causes major illness and disability worldwide. It affects social life, sleep, school, and work.[1]

In allergic rhinitis, many inflammatory cells including CD4-positive T cells, mast cells, B cells, eosinophils and macrophages infiltrate the nasal lining upon exposure to an allergen. Cockroach residues, moulds, pollens, animal dander, cockroach residues or airborne dust mite fecal particles can act as an allergen. When any individual gets suffered from AR, cytokines (e.g., interleukin [IL]-3, IL-4, IL-5, and IL-13) gets released by the T cells which are predominantly T helper 2 (Th2) in nature. Cytokines promotes production of immunoglobulin E (IgE) by plasma cells. Crosslinking of IgE bound to mast cells by allergens, in turn, initiates the release of mediators, such as leukotrienes and histamines because of which increased vascular permeability, arteriolar dilation, rhinorrhea, itching, smooth muscle contraction and mucous secretion occurs in the lung. Primarily the cytokines and mediators gets released in the early phase of an immune response to an inciting allergen which triggers a further cellular inflammatory response over the next 4–8 h which is late-phase inflammatory response which results in recurrent symptoms including nasal congestion that often persists.[2]

AR is a common disorder that affects up to 40% of the worldwide population and the evidence shows that the prevalence of this disorder is increasing year by year. AR of severe intensity is also associated with major impairments in sleep, work performance and quality of life.[3] AR can be treated with the combination of antihistaminic agents to reduce the allergy and nasal decongestant to give the symptomatic relief from symptoms of AR. Chlorpheniramine maleate (CPM) is one of the most often recommended and used 1st generation antihistaminic agent and Phenylephrine is an systemic nasal decongestant. Combination of CPM and Phenylephrine can be used for the treatment of AR. Brief information about the CPM and Phenylephrine is provided below. This phase IV clinical trial was conducted to test the efficacy and safety for the fixed dose combination of Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml in the infant's population of age up to 1 year all across India.

Chlorpheniramine maleate (CPM) is one of the most often recommended and used 1st generation antihistaminic agents. The primary action of CPM is competitive binding to the H1 receptors of the vascular tunica medius in the nasal mucosa to prevent the histamine vasoreactive response. The anti-histaminic action of CPM is translated to its anti-allergic and anti-inflammatory action in the nasal mucosa. The additional anti-cholinergic action of CPM is responsible for decrease

[1]Vice-President – Medical Services and Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd., Centaur House, Near Grand Hyatt Vakola, Santacruz – East, Mumbai – 400 055, [2]Executive - Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd. Centaur House, Near Grand Hyatt Vakola, Santacruz – East, Mumbai – 400 055, Maharashtra, India

Corresponding author: Dr. Mayuresh Kiran, Centaur Pharmaceuticals Pvt. Ltd., Centaur House, Near Grand Hyatt Vakola, Santacruz – East, Mumbai – 400 055., Maharashtra, India

How to cite this article: Study of safety and efficacy for the combination of chlorpheniramine maleate and phenylephrine in infants suffering from allergic rhinitis and associated symptoms. International Journal of Contemporary Medical Research 2019;6(3):C1-C4.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.3.52

in the nasal discharge, which is infective. Thus CPM is useful to control the symptoms of AR like Running Nose and Sneezing.[4]

Phenylephrine is a sympathomimetic primarily used as a systemic nasal decongestant.[5] The mechanism by which decongestants bring off their action is by activation of postjunctional alpha-adrenergic receptors found on precapillary and post capillary blood vessels of the nasal mucosa. Activation of these receptors is by distinct binding of the sympathomimetic agent to the binding site of the receptor or by enhanced release of norepinephrine which leads to vasoconstriction. Such vasoconstriction leads to shrinkage of the tissue by decreasing blood flow through the nasal mucosa.[6]

MATERIAL AND METHODS

12 pediatric centers were selected all across the India for conducting this phase IV clinical trial. Total 215 patients were recruited, considering 150 patients will complete the clinical trial but 177 patients completed and 38 were lost to follow-up. This study was started on October 2016 and ended in January 2017.

Inclusion and Exclusion Criteria

The study included patients of both the genders and confirmed diagnosis of allergic rhinitis of age 1-12 months and body weight 2-12 kg were recruited in the study. Those patients whose guardians were ready to adhere to the protocol were included in the clinical trial. Patients known, or thought to be hypersensitivity to study drugs were excluded from the study. Patient's guardians unwilling to sign Informed Consent form were also excluded from this study.

Study Intervention

Study drug combination containing Phenylephrine 2.5 mg and Chlorpheniramine maleate 1 mg per ml of oral drops was provided by the sponsor at free of cost to the patients guardians recruited in the clinical trial. All the guardians were asked to give it to the patients at the dose of 0.2 ml td for the infants of age 1 – 6 months and of weight 2 to 9.7 kg and 0.4 ml td for the infants of age 7 – 12 months and weight 6.7 – 12 kg.

Study procedure

The study duration was kept 5 days. Patients of Allergic Rhinitis satisfying the inclusion and exclusion criteria were recruited for the phase IV clinical trial. An itemized medical history was taken and physical examination (including general and systemic examination and vital signs) was conducted by the investigators. Free samples for the patients were provided by the sponsor to the investigator and asked to provide it to the patients. All the guardians were asked to give it to the patient in the dose of 0.2 ml td for the patients of age 1 – 6 months and weight of 2 to 9.7 kg and 0.4 ml td for the patients of age 7 – 12 months and weight 6.7 – 12 kg. To monitor the adverse events experienced by the patients or observed by the guardians, all the guardians were asked to maintain a diary to record the adverse events occurring in the patient in the clinical trial duration. Three visits were outlined for the patients recruited in the clinical trial - V1 (baseline visit) on day 1, V2 (re-evaluation visit) on day 3 and V3 (conclusion visit) on day 5. Total symptom score and adverse events occurring were recorded at each visit along with medical history and physical examination. Investigators were asked to stop the study drug combination in case of severe adverse event.

Concomitant therapy

No Pharmacological intervention and medication including antibiotics, topical decongestants (sprays/ drops and aromatic oils), multi-vitamins and multi-minerals were allowed during the study duration, other than study drug. Non-Pharmacological interventions like steam inhalation and drinking of warm/hot water at regular intervals were allowed and encouraged during the study duration.

Efficacy assessment

The primary assessment was reduction in Total Symptom Score (TSS) which was a score of all the symptoms on an eleven-point scale (0 to 10) where 0 is no symptoms and 10 is maximum tolerated symptoms. The TSS was further extrapolated to the Likert-type symptom severity scale with 4 grades – no symptoms (0 on TSS), mild (1 – 4 on TSS), Moderate (5 – 7 on TSS) and Severe (8 – 10 on TSS). The secondary assessment was done by calculating the mean TSS and percent reduction in mean TSS at visit 2 and 3 as comparted to baseline.

Safety assessment

Patients were asked for any adverse event and the same if present was noted in the case record form during each post-dose visit. These adverse events were classified into serious adverse events and non-serious adverse events. Naranjo's scale of probability was used to classify the adverse event as drug related or nondrug related. Adverse events were followed up by the investigators till their resolution.

Regulatory and Ethical consideration

The study drug combination has been approved for manufacturing and marketing in 2005 by CDSCO. The said combination is available under various brands but is classified as schedule H drugs in India, i.e. to be sold in presence of prescription of a registered medical practitioners only. All the patient guardians participating in this study read and voluntarily signed the informed consent form.

RESULTS

Efficacy assessment

Mean of Total Symptom Score (TSS) was recorded at all the visits (V1, V2 and V3) and thus the reduction in mean TSS and percentage reduction at visit 2 and 3 as compared to baseline was calculated. The mean TSS at V1 or the baseline visit was 5.677, which was reduced to 2.711 at V2 or day 3 and further reduced to 0.542 on V3 or day 5. At V2 and V3 there was reduction of 52.23% and 90.44% as compared to baseline respectively. The reduction in TSS corresponded with the improvement in general and physical examination of the patients. Mean TSS at V1, V2 and V3 is graphically presented in the figure 1 and percentage reduction in mean

Adverse events	No. of episodes	No. of patients	Percentage of patients
Sedation and drowsiness	33	25	14.1%
Dryness and crusting of nasal cavity	6	4	2.2%
Total	39	27	15.25%

Table-1: Adverse events occurred during study

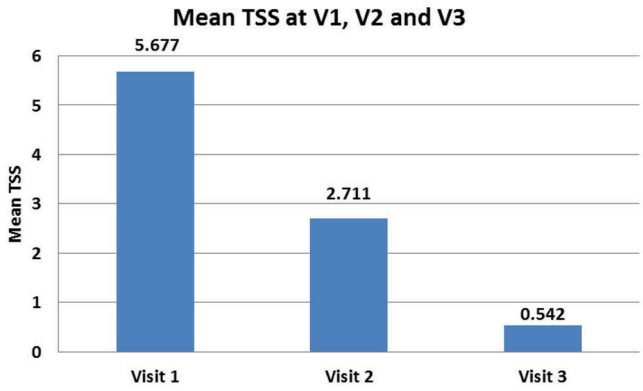

Figure-1: Mean TSS at Visit 1, Visit 2 and Visit 3

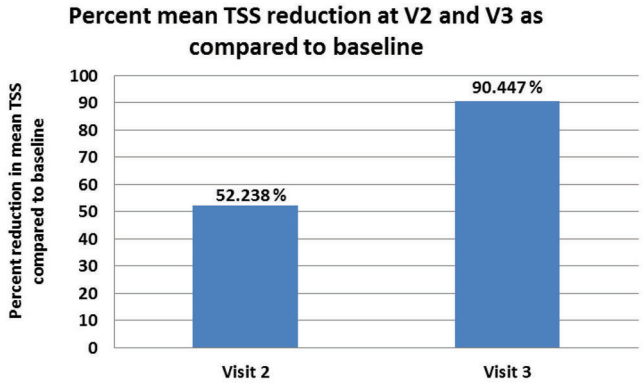

Figure-2: Percent reduction in mean TSS at visit 2 and visit 3 as compared to baseline

TSS at V2 and V3 compared to baseline is presented in the figure 2.

Safety assessment

There were no serious adverse events reported during the study. Total 39 episodes of adverse events were reported in total 27 patients. All the details regarding the adverse events are shown in the table 1.

DISCUSSION

Allergic rhinitis is the most common type of chronic rhinitis, affecting 10 to 20% of the population, and evidence suggests that the prevalence of the disorder is increasing. Severe allergic rhinitis has been associated with significant impairments in quality of life, sleep and work performance. This study was conducted to test the efficacy and safety for the combination of Phenylephrine 2.5 mg and Chlorpheniramine maleate 1 mg per ml of oral drops in infant patients of all across the India. The study was conducted on 177 patients and mean TSS at each visit and percentage reduction in mean TSS at visit 2 and 3 as compared to baseline is calculated. Mean TSS at visit 1 was 5.677 which was decreased to 2.711 at visit 2 i.e. at visit 2 it was decreased by 52.23%. At visit 3 mean TSS was further decreased to 0.542 i.e. as compared to baseline it was decreased by 90.44%. So at the end of the clinical trial there was total 90.44% of decrease in the mean TSS in just 5 days. So the study drug combination was efficacious in the treatment of AR.

Kiran M et al.[7] conducted a phase IV clinical trial for the combination of Chlorpheniramine Maleate, Phenylepherine and Paracetamol to test the safety and efficacy in the patients suffering from allergic rhinitis and common cold. The study was conducted in 187 patients for the clinical trial duration of 5 days and efficacy assessment was done by calculating the reduction in total symptom score (TSS) which was extrapolated to four point Likert-type scales. At baseline mean TSS was 6.58 (moderate) which was reduced to 3.76 (moderate) at day 3 and 1.78 (mild) at day 5. So at day 3 and day 5 there was reduction of 42.85% and 72.94% as compared to baseline. Safety assessment for the study drug was done by analyzing the adverse events observed or experienced by the patient. Study concluded that the combination of Chlorpheniramine maleate, Phenylepherine and Paracetamol is safe as well as effecacious in the treatment of Common Cold and AR.[7]

Kiran M et al.[8] conducted a phase IV clinical trial to test the efficacy and safety for the combination of Levocetrizine, Phenylepherine and Paracetamol for the treatment of AR and common cold. The study was conducted on 201 adult patients for the clinical trial duration of 5 days. Efficacy assessment was done by reduction in TSS score. Mean TSS score was reduced from 6.82 at baseline to 3.63 at day 3 and 1.14 at day 5. Safety assessment was made by analyzing the adverse events during the clinical trial and no serious adverse event was found. Thus the study concluded that combination of Paracetamol, Phenylepherine and Levocetrizine is safe and effective in the treatment of AR and Common Cold.[8]

Picon et al.[6] conducted a Phase III clinical study in Brazilian population with a consolidation of Paracetamol, Phenylephrine and Chlorpheniramine maleate (different strength capsule) in treatment of Common Cold, in Brazilian population. Efficacy and Safety of the combination were evaluated in 146 patients and were compared with placebo. The curtailment of symptom score in the combination (test) arm was from baseline score of 14.09 to 3.54 at the end of 10 days study period. At the end of 10 days the reduction in placebo arm was from a baseline score of 14.23 to 4.64. The distribution, type and number of adverse events were analogous in both the groups. The study ceased that the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate is better than placebo in the treatment of Common Cold and flulike syndrome in adults.[6]

A combination of Nasal Decongestants conjoined Anti-Histamines and NSAID is much celebrated in treatment of Common Cold and has ample clinical data including the

aforementioned studies.

Condition like allergic rhinitis is essentially afebrile and associated with less pain therefore does not warrant the use of NSAID. Furthermore, NSAID expedite adverse effects like gastritis, vomiting, nausea and rarely even hepatic failure.

CONCLUSION

The current study has drawn a statement that a combination of Phenylephrine 2.5 mg and Chlorpheniramine maleate 1 mg provides optimum symptomatic relief and is safe for the treatment of allergic rhinitis in infants. Importantly these drugs should be present at optimum dose based on the severity and duration of signs and symptoms.

Disclosure

This study was conducted as a part of Pharmacovigilance activity for Sinarest AF Drops marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 04-02-2019; **Accepted:** 16-03-2019; **Published:** 30-03-2019