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SAFETY AND EFFICACY FOR THE COMBINATION OF PARACETAMOL, PHENYLEPHRINE AND LEVOCETIRIZINE IN PATIENTS OF COMMON COLD AND ALLERGIC RHINITIS: POST MARKETING SURVEILLANCE STUDY

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ABSTRACT

Introduction: Common cold and allergic rhinitis are the most commonly encountered diseases in clinical practices. Though it is self-limiting in nature, it causes major loss of school and work days. Single drug therapy is considered to be ineffective to provide complete symptomatic relief so the multiple drug combinations are commonly considered for the treatment. A combination of Paracetamol (anti-inflammatory/ antipyeretic), Phenylephrine (nasal decongestant) and Levocetirizine (anti-histaminic) can be used for the treatment of common cold and allergic rhinitis. This post marketing surveillance study was conducted to evaluate the efficacy and safety for the combination of Paracetamol, Phenylephrine and Levocetirizine in treatment of common cold and allergic rhinitis. **Methodology:** Out of total 200 enrolled, 188 trial subjects completed the study. Efficacy assessment was done by reduction in total symptom score (TSS) which was extrapolated to four-point Likert type symptom severity scale. Safety assessment was made by analysing the reported adverse events during the study. **Results:** At baseline the mean TSS was 6.531 which was reduced to 3.345 by 48.778 % as compared to the baseline at day 3 and was further reduced to 0.935 by 85.672 % as compared to the baseline at day 5. In the population of recruited trial subjects, 22 adverse drug reactions (ADR) were reported by 17 trial subjects. All reported ADRs were of expected and non-serious nature. **Conclusion:** Combination of Paracetamol, Levocetirizine and Phenylephrine was found to be efficient and safe for the symptomatic treatment of common cold and allergic rhinitis.

KEYWORDS: Paracetamol, Levocetirizine, Phenylephrine, common cold and allergic rhinitis.

INTRODUCTION

Common cold is also known as acute coryza is recurrent and major cause of morbidity which affects not only adults but also children. During the routine clinical practises, common cold is the disease which is mostly encountered by the healthcare professionals. Adults can have around two to four episodes of common cold in a year whereas young children can have average six to eight episodes. Most commonly is considered to be caused by Rhinovirus and also other viruses can cause the same including but not limited to respiratory syncytial virus, adenovirus, coronavirus, parainfluenza and influenza viruses. Common cold generally is accompanied by the symptoms of fever (generally considered as major symptom), bodyache, headache, Sneezing and blocked or running nose.[1] As common cold is considered to be the self-limiting disease and only symptomatic treatment is considered to be required for the treatment. As per American Academy of Family Physicians, there are no effective antivirals to cure the common cold but there are few effective measures to prevent it including vaccines so ideally the treatment should focus on symptomatic relief.[2]

Allergic Rhinitis is a symptomatic disorder of the nose induced after exposure to allergens via IgE mediated hypersensitivity reactions, which are characterized by 4 cardinal symptoms of nasal obstruction, watery rhinorrhea, sneezing and nasal itching.[1] Though it is not frequently encountered in clinical practices as common cold, but it still accounts for a prevalence of 10-30% in adults and nearly 40% in children, in the US. Problems that one can face due to allergic rhinitis include but not limited to otitis media (serous type), sinusitis, tonsillitis and pharyngitis.[1] As a single drug can be ineffective to cure all the symptoms of the common cold or allergic rhinitis so various drug combinations are generally used for the symptomatic treatment.[3]

As per the guidelines of DPHHS, Cochrane review, Picon PD et al and Eccles R et al combination of analgesics, decongestants and antihistamine provides benefits for multi symptom relief in common cold.[4]

A Non-Steroidal Anti-Inflammatory drug, Paracetamol is an important key analgesic. It exhibits strong and immediate antipyretic action, does not depress breathing, alters the balance of the acid-base, or causes gastric irritation. Paracetamol can therefore be effective for the treatment of common cold symptoms such as fever, headache, and body ache.[5] Phenylephrine is an effective nasal decongestant. It is a selective agonist of the alpha 1 -adrenergic receptor. Phenylephrine induces vasoconstriction in the nasal mucosa at the therapeutic dose, alleviates the cause of nasal blockage due to inflammation. Phenylephrine is also effective for the symptomatic treatment of common cold symptoms including but not limited to blocked nose or nasal congestion etc.[6] Levocetirizine is one of the most commonly used 2nd generation antihistaminic drug. As a primary mechanism of action Levocetirizine competitively binds to H1 receptors of the vascular tunica medius present in the nasal mucosa and as a result prevents the histamine vasoreactive response. Due to its mechanism of action, Levocetirizine provides antiallergic as well as anti-inflammatory action in the nasal mucosa. Also as the Levocetirizine is a 2nd generation antihistaminic drug, it causes low intensity of sedation and drowsiness as adverse events as compared to other antihistaminic drugs of 1st generation.[1]

A combination of Paracetamol, Levocetirizine and Phenylephrine is often used to treat common cold and allergic rhinitis during daily practises of healthcare professionals. Also the above mentioned combinations are available in developed countries like US, New Zealand and Australia etc as OTC.[1] This Post marketing surveillance study was conducted to test the efficacy and safety for the fixed dose combinations of Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Levocetirizine hydrochloride 2.5 mg per tablet in the Indian patients of common cold and allergic rhinitis.

METHODOLOGY

Fourteen ENT specialty clinical trial sites were selected all across India to conduct this post marketing surveillance (PMS) study. Considering the 20% lost to follow-up, total 200 trial subjects were recruited for the PMS study out of which 188 trial subjects completed and others were lost to follow-up. In the study duration of 5 days, 3 visits were scheduled including visit 1 (baseline visit) on day 1, visit 2 (re-evaluation visit) on day 3 and visit 3 (conclusion visit) on day 5.

Inclusion and Exclusion Criteria

As per the inclusion criteria mentioned in the study protocol, patients of both the genders including male and female of age between 18 to 65 years with the confirmed diagnosis of common cold or allergic rhinitis were recruited for the PMS study. Patients with 4 out of 9 symptoms of common cold or allergic rhinitis including headache, fever, body ache, nasal congestion, rhinorrhoea, sneezing, sore throat, dysphonia and malaise were considered as common cold or allergic rhinitis patients. All the patients were asked to strictly adhere to the study procedure and only the patients who were ready to strictly adhere to the study procedures were recruited for the study.

Patients known to be hypersensitive to the investigational products or patients with hepatic or renal impairment were excluded from the post marketing surveillance study. Patients with hepatic or renal impairment were excluded from the post marketing surveillance study due to the presence of Paracetamol in the investigational product. Also, the pregnant and lactating woman were excluded from the post marketing surveillance study. Patients who cannot adhere to the study procedures including but not limited to mentally ill and patients with the psychological problems were also excluded from the study.

Study Intervention

Fixed dose combination of Paracetamol 500 mg, Phenylephrine 10 mg and Levocetirizine 2.5 mg per tablet was used as an investigational product for the PMS study. The investigational product was provided to the trial subjects at no cost by the Investigator and the investigational product was provided to the Investigator by the Sponsor at no cost.

Study design

Since this was a multicentric PMS study, this study was conducted at 14 clinical trial sites and was completed on 188 trial subjects. As the study design was of non-randomized, non-comparative and open label nature, no control medication was applicable to this study and all investigators, clinical research staff and trial subjects or any other people either from the side of investigator, trial subject or the sponsor were aware of the investigational product and its composition.

Study Procedure

Trial subjects were recruited for the study as per the above-mentioned inclusion and exclusion criteria by the investigator. At the baseline visit, day 1, detailed medical history was obtained from all enrolled trial subjects, which was followed by through clinical examination. Each trial subject was provided with 10 tablets of investigational product and was asked to take it in the dose of 1 tablet twice a day. All the trial subjects were asked to keep the diary for daily symptoms to detect the adverse events if any. In case of any safety related issues i.e. unexpected or serious adverse events, the investigator was authorised to withdraw the trial subject and treat according to severity of the symptoms. For trial subjects, three visits were planned for efficacy and safety assessment including baseline visit (visit 1) at day 1, before taking the investigational product, re-evaluation

visit (visit 2) on day 3 and conclusion visit (visit 3) at day 5. During each visit, the total symptom score and adverse events occurred along with medical history and physical examination, was recorded.

Concomitant therapy

In the study duration, no pharmacological intervention and medication, including antibiotics, topical decongestants (sprays/drops and aromatic oils), multi-vitamins and multi-minerals, other than investigational product were permitted. During the study period, non-pharmacological measures such as steam inhalation and drinking of warm water at regular intervals were permitted and encouraged.

Efficacy Assessment

In the study duration of 5 days, the efficacy assessment was done by calculating the decrease in the Total Symptom Score (TSS) for each trial subject. TSS scale was used as an eleven-point scale ranging from 0 to 10 where 0 was no symptom to 10 was the highest tolerated symptoms. The TSS was further extrapolated with 4 grades including no symptoms (0 on TSS scale), mild (1-3 on TSS scale), moderate (4-6 on TSS scale) and severe (7-10 on TSS scale) to the Likert-type symptom severity scale.

Safety assessment

Trial subjects were asked by the investigator to report the adverse event/s if any during each post-dose visit (i.e. at visit 2 and 3 on day 3 and 5 respectively). These adverse events were categorized into serious and non-serious adverse events and also causality assessment was done for the same.

Regulatory Matters

The investigational product was approved for manufacturing and marketing in India. In India the investigational product is categorised under the category of schedule H drug i.e., to be sold only in the presence of licensed medical practitioners' prescription. Also before recruiting the trial subject to the study, all trial subjects were well informed about the study procedures and the investigational product.

RESULTS

Fourteen ENT specialty clinical trial sites were selected all across the India to conduct PMS study. Considering the 20% lost to follow-up, total 200 trial subjects were recruited out of which 188 completed the study.

At baseline visit (day 1) the mean TSS was 6.531 which was further decreased to 3.345 at visit 2 (day 3), re-evaluation visit and was further decreased to 0.935 at visit 3 (day 5). Mean TSS score at visit 1, 2 and 3 is graphically presented below in fig. 1.

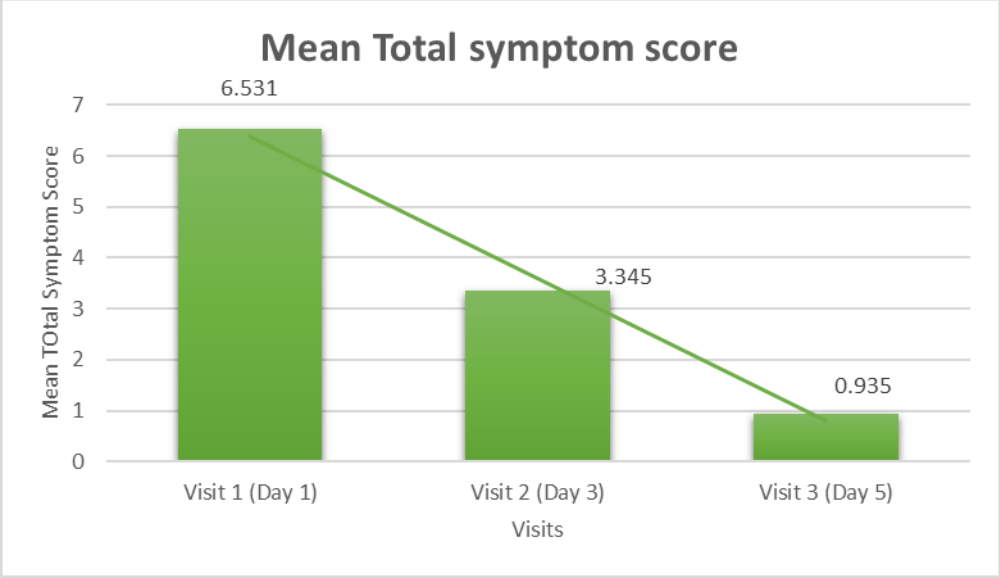

Fig.1 Mean TSS at visit 1 (day 1), 2 (day 3) and 3 (day 5)

Percentage reduction in the mean TSS at visit 2 and 3 was 48.778% and 85.672% respectively as compared to baseline. Graphical presentation for the percentage reduction in the mean TSS at visit 2 and 3 as compared to baseline is provided below in the fig. 2.

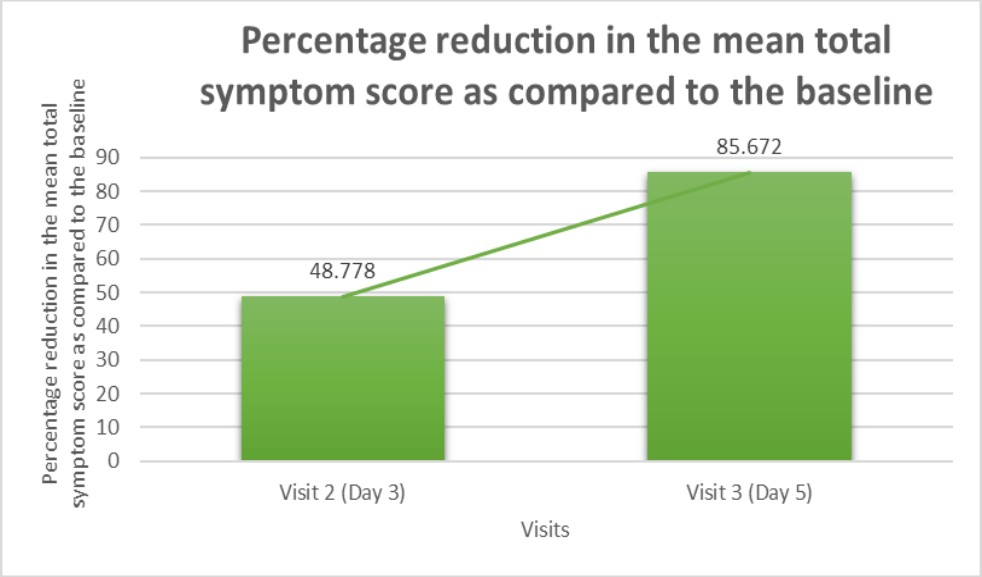

Fig. 2 Percentage reduction in the mean TSS at visit 2 and 3 as compared to the baseline.

The TSS data was further extrapolated to Likert type symptom severity Scale as no symptoms (0 on TSS), mild (1-3 on TSS), moderate (4-6 on TSS) and severe (7-10 on TSS). No. of trial subjects of mild, moderate, extreme and no intensity symptoms as per the Likert-type symptom severity scale at visit 1, 2 and 3 are graphically presented below in figure 3.

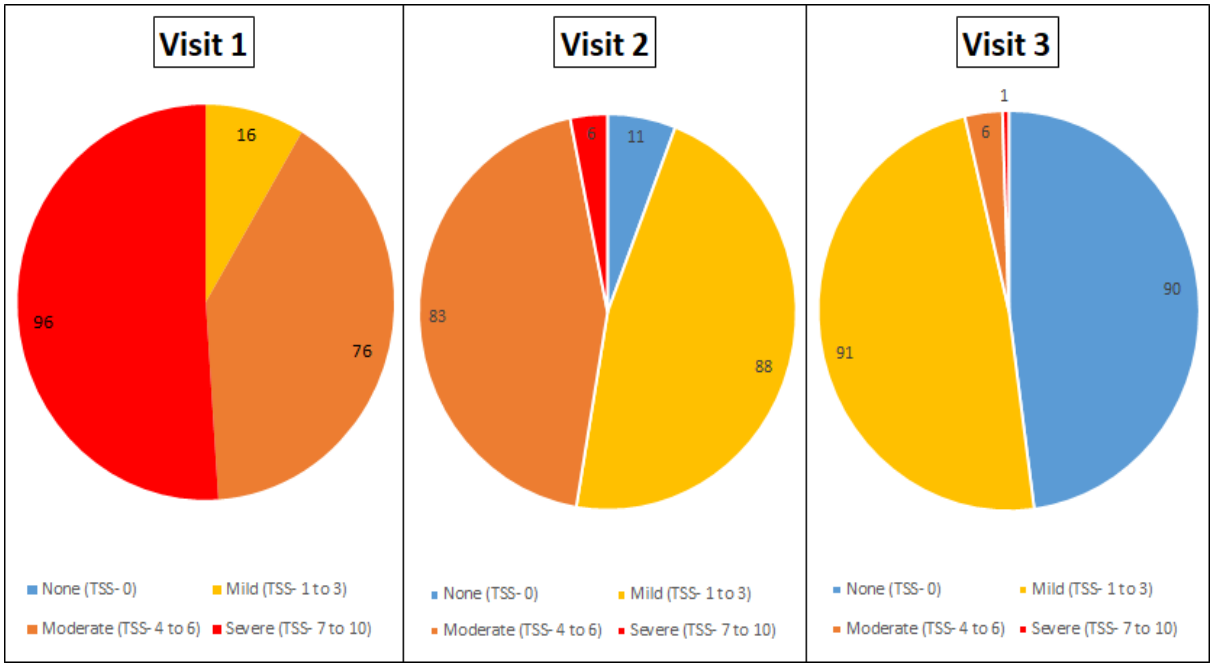

Fig.3: No. of trial subjects of no symptom, mild intensity, moderate intensity and severe intensity symptoms at visit 1, 2 and 3.

At baseline visit (day 1) out of 188 trial subjects, 96 (51.063%) had severe intensity symptoms of TSS ranging between 7 to 10, 76 (40.425%) had moderate intensity symptoms of TSS ranging between 4 to 6 and 16 (8.510%) had mild intensity symptoms of TSS ranging from 1 to 3.

At re-evaluation visit (day 3) 11 (5.851%) trial subjects had no symptom of TSS 0, 88 (46.808%) trial subjects had mild intensity symptoms of TSS ranging from 1 to 3, 88 (44.148%) trial subjects had moderate symptoms of TSS ranging from 4 to 6 and 6 (3.191%) trial subjects had severe intensity symptoms of TSS ranging from 7 to 10.

At conclusion visit (day 5), 90 (47.872%) trial subjects had no symptom of TSS 0, 91 (48.401%) trial subject had mild intensity symptoms of TSS 1 to 3, 6 (3.191%) trial subject had moderate symptoms of TSS 4 to 6 and

only 1 (0.531%) trial subject had severe intensity of TSS ranging from 7 to 10.

Safety assessment

In the population of 188 recruited trial subjects, 22 adverse drug reactions were reported by 17 trial subjects. All the adverse drug reactions reported by the trial subjects were of expected and non-serious nature. After the benefit risk assessment, the investigational product was found to be beneficial to use it for the symptomatic treatment of common cold and allergic rhinitis. Below mentioned adverse drug reactions were reported in the clinical trial duration of 5 days.

Table no. 1: List of reported adverse drug reactions.

List of adverse drug reactions	No of episodes	No of Trial subjects
Nausea	4	3
Sedation	11	5
Hyperacidity	7	4

All the reported adverse events were of mild intensity, expected and of non-serious nature.

DISCUSSION

Common cold is a self-limiting disease but it is also responsible for significant absenteeism in schools and job. For the treatment of common cold or allergic rhinitis there is no effective therapy but the symptomatic treatment can be given to the patient to reduce the absenteeism at job or school. Single drug therapy may not be enough to give complete symptomatic relief to the patient of allergic rhinitis and common cold so commonly the combination therapy of analgesic/ antipyretic, antihistaminic and nasal decongestant is given.[1] This Post marketing surveillance study was conducted to test the efficacy and safety for the fixed dose combinations of Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Levocetirizine hydrochloride 2.5 mg per tablet in the Indian patients of common cold or allergic rhinitis. Fourteen ENT specialty clinical trial sites were selected all across India to conduct this post marketing surveillance study. Considering the 20% lost to follow-up, total 200 trial subjects were recruited for the study out of which 188 trial subjects were completed the clinical trial. In the study duration of 5 days, 3 visits were scheduled including the baseline visit on day 1, re-evaluation visit on day 3 and conclusion visit on day 5. At baseline visit (day 1) the mean TSS was 6.531 which was decreased to 3.345 by 48.778% (as compared to the baseline) at visit 2 (day 3), re-evaluation visit and was further decreased to 0.935 by 85.672% (as compared to the baseline) at visit 3 (day 5). TSS data was further extrapolated to Likert-type symptom severity scale as no symptoms (0 on TSS scale), mild (1-3 on TSS scale), moderate (4-6 on TSS scale) and extreme (7-10 on TSS scale). At baseline visit (day 1) out of 188 trial subjects, 51.063% had severe intensity symptoms, 40.425% had moderate intensity symptoms and 8.510 % had mild intensity symptoms. At re-evaluation visit (day 3), 5.851 % trial subjects had no symptom i.e. they were completely cured and had no symptom at all, 46.808% trial subjects had mild intensity symptoms, 44.148% trial subjects had moderate symptoms and 3.191% trial subjects had severe intensity symptoms. At conclusion visit (day 5), 47.872% trial subjects had no symptom, 48.404% trial subject had mild intensity symptoms, 3.191% trial subject had moderate intensity symptoms and only 0.531% trial subject had severe intensity symptoms. So, at the conclusion visit there was 85.672% reduction in the TSS score as compared to the baseline and also as per the TSS data extrapolated to Likert-type symptom severity scale, there was major reduction in the severity of symptoms of trial subjects. Below we have discussed some of the studies which were conducted in the similar way the study we have conducted.

Kiran M. et.al. conducted a phase IV clinical trial which was of open label, non-comparative and multicentric nature and was conducted at 13 clinical trial sites of ENT speciality clinical trial sites for the fixed dose combination of Fexofenadine 60 mg, Paracetamol 500 mg and Phenylephrine 10 mg per tablet. Similar to the study we have conducted above, the efficacy assessment was done by the TSS scale and safety assessment was done by the assessment of reported adverse events. The study was conducted on 154 patients of common cold and allergic rhinitis. At day 1, the mean TSS was 6.90, which was found to be reduced to 3.42 on day 3 and was further reduced to 0.88 on day 5. Also, no serious or unexpected adverse event was found to be reported by any of the patient through the study. It was concluded by the clinical trial that the combination of Fexofenadine, Paracetamol and Phenylephrine was efficacious as well as safe for the treatment of common cold and allergic rhinitis.[7]

A phase IV clinical trial for the combination of Paracetamol, Levocetirizine and phenylephrine for the symptomatic treatment of common cold and allergic rhinitis in adult patients was conducted by Kiran M et al. in 234 patients, to get the efficacy and safety data. Efficacy evaluation was carried out by the TSS which was further extrapolated to Likert type symptom severity scale. At baseline, the mean TSS was found 6.82 which was decreased to 3.63 at day 3 and was further decreased to 1.14 at day 5. Also no serious or unexpected adverse event was found to be reported during the clinical trial. The study concluded that the combination of Paracetamol, Levocetirizine and Phenylephrine was safe

and effective for the treatment of common cold and allergic rhinitis.[8]

The only limitation of the study was, common cold or allergic rhinitis are self-limiting diseases because of which, Investigational product may not be fully responsible for reduction in TSS. By keeping the study duration of 5 days we have tried to minimize the limitation of the study as common cold or allergic rhinitis can be resolved in 10 days as per the literature search.[7] So the benefit offered in day 5 after treatment could be majorly due to the investigational product.

CONCLUSION

The fixed dose combination of Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Levocetirizine hydrochloride 2.5 mg was found to be efficient and safe for the treatment of common cold and allergic rhinitis.

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DISCLOSURE

This study was conducted as a part of Pharmacovigilance activity for investigational product whose brand name is Sinarest LP New Tablet which is a fixed dose combination of Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Levocetirizine hydrochloride 2.5 mg per tablet which is manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd.

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