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POST-MARKETING SURVEILLANCE STUDY TO EVALUATE THE EFFICACY AND SAFETY FOR THE COMBINATION OF PARACETAMOL, PHENYLEPHRINE AND CHLORPHENIRAMINE MALEATE IN PAEDIATRIC PATIENTS OF COMMON COLD

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ABSTRACT

Introduction: Common cold is one of the most frequently occurring disease in clinical practices. Common cold is self-recovering in nature so symptomatic treatment is often accepted. A combination of an antipyretic (Paracetamol), nasal decongestant (Phenylephrine) and antihistaminic (Chlorpheniramine Maleate) with Sodium Citrate as expectorant and Menthol for cooling effects can be used for the symptomatic treatment of common cold. This post marketing surveillance (PMS) study was conducted to evaluate the efficacy and safety for the combination of Paracetamol, Phenylephrine, Chlorpheniramine maleate, Sodium Citrate and Menthol for the treatment of common cold. **Methodology:** Of 200 enrolled, 182 patients completed the study. Efficacy assessment was made by reduction in total symptom score (TSS) and then was further extrapolated to four-point Likert-type symptom severity scale. Safety assessment was done by analysing the adverse events during the study. **Results:** At baseline visit, the mean TSS was 5.703 which was reduced to 3.335 at day 3 and was further reduced to 0.802 at day 5. At day 3 and 5, reduction in the mean TSS as compared to the baseline was 41.522% and 85.934% respectively. During the study only 6 adverse drug reactions were reported and all of them were of non-serious nature. **Conclusion:** The fixed dose combination of Paracetamol 250mg, Phenylephrine 2mg, Chlorpheniramine Maleate 2mg, Sodium Citrate 60mg and Menthol 1mg per 5ml was found to be efficacious and safe for the symptomatic treatment of common cold In the Indian patients of age 2 to 12 years.

KEYWORDS: Paracetamol, Phenylephrine, Chlorpheniramine Maleate, Common cold.

INTRODUCTION

Common cold is a self-limiting viral respiratory disease. It can be caused by viral infection by the viruses like influenza, rhinovirus etc. Signs and symptoms of the common cold includes fever, rhinorrhoea, cough, nasal congestion, myalgias, sore throat, headache, cough with productive sputum. Productivity and alertness of the daily life is largely affected by common cold which was highlighted in survey conducted in United States attitudes of consumers towards health, Cough and Cold.[1] During previous studies it was found that within the duration of the year in adults normally 2 to 5 episodes of the common cold can occur whereas in children it can be up to 7 to 10 episodes. The common cold creates significant economical as well as social burden because of its high rate of occurrence.[2] Patients seek care for cold symptoms during all seasons of the year.[3] Symptomatic relief should be the main focus for the treatment of common cold as currently no antivirals including vaccines are available for the treatment of common cold.[1] Single drug therapy is not adequate to relieve all the symptoms of common cold so frequently multiple drug combinations are used for the symptomatic relief to the patient from the multiple symptoms of common cold.[4] As per Picon PD et al the combination of analgesics, decongestants and antihistamines can provide benefits for multi symptom relief in common cold.[5]

Paracetamol is generally recommended drug for the symptomatic treatment of the common cold. It acts as an antipyretic as well as analgesic which inhibits the synthesis of prostaglandins in cellular system and inhibits cyclooxygenase (COX-2) enzymes which is responsible for synthesis of arachidonic acid to prostaglandin. Paracetamol can be used as an analgesic and antipyretic for the symptomatic relief of common cold of mild, moderate and severe intensity.[6] Phenylephrine is a sympathomimetic and primarily used as a systemic nasal decongestant. Phenylephrine activates postjunctional alpha 1-adrenergic receptors found on precapillary and post capillary blood vessels of the nasal mucosa. Activation of these receptors by distinct binding of the sympathomimetic agent to the binding site of the receptor or by enhanced release of norepinephrine leads to vasoconstriction. Such vasoconstriction leads to shrinkage of the tissue by decreasing blood flow through the nasal mucosa.[7] Chlorpheniramine maleate (CPM) is the first generation antihistaminic drug acts by antagonizing H1 receptor which is indicated for the treatment of hay fever, common cold (symptomatic treatment), rhinitis, urticaria, allergic reactions and asthma.[8,9] Sodium citrate

is a mucolytic, it increases the bronchial secretion which facilitates the removal of cough. Dry mouth is common adverse drug reaction of CPM which can be reduced by Sodium Citrate. By touching nociceptors, menthol produces cooling as well as soothing effects in throat.

This Post marketing surveillance (PMS) study was done to test the efficacy and safety for the fixed dose combination of Paracetamol 250 mg, Phenylephrine Hydrochloride 2 mg, Chlorpheniramine Maleate 2 mg, Sodium citrate 60 mg and menthol 1 mg per 5 ml in Indian patients of age between 2 to 12 years suffering from common cold.

METHODOLOGY

For this post marketing surveillance 12 clinical trial sites all across the India were selected. All investigators selected for the study were of paediatric speciality. Duration of the study was of 5 days. Total 200 patients were recruited out of which 182 completed the study.

Inclusion and Exclusion criteria

As per the inclusion criteria, patients of both the genders including male and female of age between 2 to 12 years old of weight between 12 to 39.9 kg were recruited for the study. The only patients with confirmed diagnosis of common cold having 4 out of the 9 symptoms including headache, fever, body ache, nasal congestion, rhinorrhoea, sneezing, sore throat, dysphonia and malaise present for at least 48 hours were included in the study. Only the patients and their guardians who were ready to strictly adhere to the protocol were recruited for the study.

Patients with hypersensitivity to the individual drugs present in the investigational product, patients having hepatic and renal impairment as Paracetamol was present in the investigational product were excluded from the study. Patients on hypertensives were also excluded from the study due to the presence of Phenylephrine in the investigational product which can cause vasoconstriction which may result into the increase of BP.

Study intervention

Investigational product used for the study was the fixed dose combination of Paracetamol 250 mg, Phenylephrine Hydrochloride 2mg, Chlorpheniramine Maleate 2mg, Sodium citrate 60 mg and menthol 1 mg per 5 ml. The investigational product was provided by the sponsor to the investigator at no cost and those investigational products were dispensed to the guardians of the patient at no cost by the investigator.

Study design

This was a multicentric post marketing surveillance study, it was conducted at 12 clinical trial sites and 200 patients were recruited for the study and completed on 182 patients. As the study design was of open label nature, no control medication was applicable to this study and all investigators, clinical research staff and patient or guardians of the patients were aware of the investigational product, its composition and the study procedures.

Study procedure

Patients enrolled for the study as per inclusion/exclusion criteria by the investigator. All eligible patients and their guardians were well informed about the study procedure and the investigational product by the investigator and were asked for their consent. A detailed medical history was obtained from all enrolled patients, which was followed by thorough clinical examination. Each patient was given two 50 ml free physician samples of the investigational product. Patients and their guardians were advised to take in the dose as mentioned below for study duration of 5 days.

Table no. 1: Dose of the investigational product for the patient as per Age and Weight.

Weight in Kg	Age	Dose
12 – 16.5	2 – 4 years	2.5 ml three times daily
16.5 – 28.6	4 – 9 years	5 ml three times daily
28.6 – 39.9	9 – 12 years	5 ml three times daily

For the study duration of 5 days, guardians of the patient were instructed to keep a diary of daily symptoms experienced by the patient to detect the adverse event if any. In case of any safety-related issues including adverse events or serious adverse events, the investigator was authorized to withdraw the patient from the study and treat according to the severity of the symptoms. Patients recruited for this study were asked to visit the clinical trial site at day 3 (visit 2) and day 5 (visit 3) for the efficacy and safety assessment.

Concomitant therapy

In the study duration of 5 days all the patients were instructed not to take any pharmacological intervention in addition to the investigational product for the symptomatic treatment of common cold including but not limited to decongestants or multi-vitamins etc. At the same time non-pharmacological measures such as drinking of warm water, steam inhalation at the regular interval were permitted and encouraged.

Efficacy assessment

At all the visits, all the patients were asked to rate their symptoms on an eleven point scale named total symptom score (TSS) scale ranging from 0 to 10 where 0 was no symptom to 10 was the highest tolerated symptoms. TSS at all the visits were recorded for all the patients and was further extrapolated to Likert-type symptom severity scale as no symptom for 0 on TSS scale, mild intensity symptoms for 1-3 on TSS scale, moderate intensity symptoms for 4-6 on TSS scale and severe intensity symptoms for 7-10 on TSS scale.

Safety assessment

Patients and their guardians were asked for any adverse events and if present, were reported during each post-dose visit. Investigators were instructed to provide the complete the medical management to the patients experienced any of the adverse events till their resolution.

Regulatory matters

The investigational product was approved for manufacturing and marketing in India and is under the category of schedule H drug. The informed consent form was read and signed freely by all the guardian of the patients as the patients were of less than 18 years old.

RESULTS

At 12 clinical trial sites, 182 patients completed the study. At baseline (day 1) the mean TSS was 5.703 which was decreased to 3.335 at day 3 and was further decreased to 0.802 at day 5. Graphical presentation for the mean TSS at visit 1, 2 and 3 at day 1, 3 and 5 is graphically presented in figure 1.

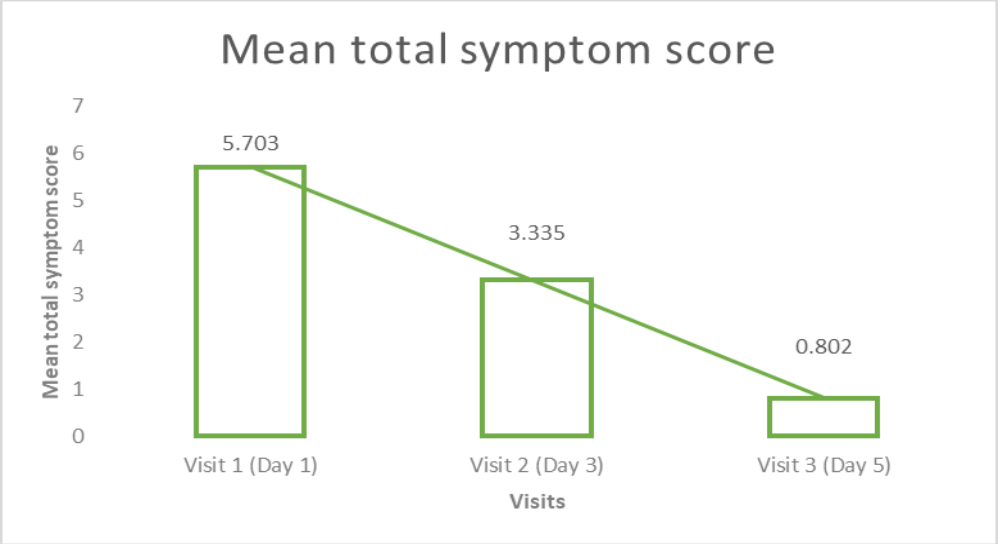

Fig. 1: Mean TSS at visit 1, 2 and 3.

At visit 2 and 3 the percentage reduction in mean TSS as compared to the baseline was 41.52% and 85.93 %. Graphical presentation for the percentage reduction in the mean TSS at visit 2 and 3 as compared to baseline is presented below in figure 2.

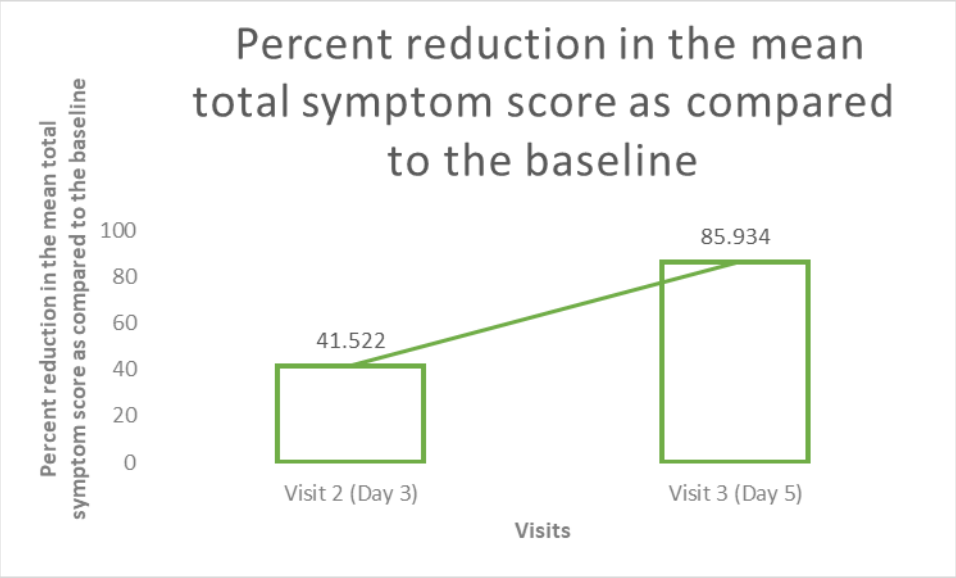

Fig. 2: Percentage reduction in the mean TSS at visit 2 and 3 as compared to the baseline.

The TSS data was extrapolated to Likert Scale as mentioned in the section "Efficacy Assessment". No. of patients with mild, moderate and severe intensity symptoms of common cold as per the Likert-type symptom severity scale at visit 1, 2 and 3 is graphically presented in the figure 3.

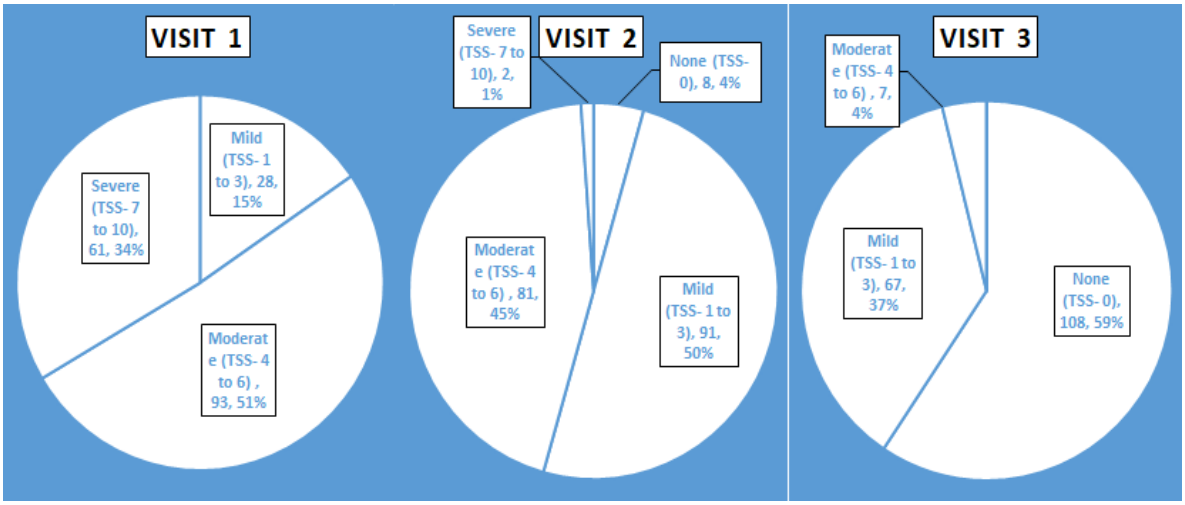

Fig. 3: No of patients of mild, moderate and severe intensity symptoms as per the Likert-type symptom severity scale at visit 1, 2 and 3.

At day 1, 61 (34 %), 93 (51 %) and 28 (15 %) patients had severe, moderate and mild intensity symptoms of common cold. At day 3, visit 2, 2 (1 %), 81 (45 %) and 91 (50 %) patients had severe, moderate and mild intensity symptoms and 8 (4 %) patients had no symptoms of common cold of 0 TSS. At visit 3, 108 (59 %) patients had no symptoms of common cold. Also at visit 3, 7 (4 %) and 67 (37 %) patients had moderate and mild symptoms of common cold respectively.

Safety analysis

Of the total population of patients, 6 adverse drug reactions were reported in the study duration of 5 days. All the adverse drug reactions reported were of expected and non-serious nature. Investigational product was found to be a beneficial to use for the symptomatic treatment of common cold after benefit risk assessment. Below mentioned adverse drug reactions were reported in the study duration of 5 days.

Table no. 2: adverse drug reactions reported by the patients.

Adverse drug reactions	No of episodes	No of patients
Nausea	1	1
Drowsiness	4	2
Dryness of mouth	1	1

DISCUSSION

Globally common cold is one of the most commonly recognized upper respiratory disease. Till date there is no treatment available for the common cold including vaccination as well as antivirals and as it is self-recovering in nature so the symptomatic treatment should be the main focus for the treatment. Single drug therapy is not adequate to relieve all the symptoms of common cold so frequently multiple drug combinations are used for the symptomatic relief to the patient from the multiple symptoms of common cold.[4] As per Picon PD et al the combination of analgesics, decongestants and antihistamines can provide multi symptom relief in common cold.[5] Fixed dose combination of Paracetamol 250 mg, Phenylephrine Hydrochloride 2 mg, Chlorpheniramine Maleate 2 mg, Sodium citrate 60 mg, Menthol 1 mg per 5 ml can be used for the symptomatic relief from the common cold. This post marketing surveillance study was conducted to test the efficacy and safety for the above-mentioned investigational product in the Indian population. For the study, 200 patients were recruited out of which 182 patients completed the study. Efficacy assessment was done by the total symptom score which is an 11-point scale and was further extrapolated to Likert-type symptom scale. During the study period of 5 days decrease in TSS was observed in all the

recruited patients. Mean TSS reduced from 5.70 at visit 1 to 3.33 at visit 2 and further reduced to 0.80 at visit 3. The percentage reduction in the mean TSS at visit 2 and 3 as compared to the baseline was 41.52 % and 85.93 % respectively. In the total 200 recruited patients, 6 episodes of adverse drug reactions were reported and all of them were of expected and non-serious nature including nausea and drowsiness and dryness of mouth. Also, after the benefit risk assessment the investigational product was found to be beneficial to use it for the symptomatic treatment of common cold. Below we have discussed few studies which were found to be supportive for the study we have conducted.

Kiran M et al. conducted a phase IV clinical trial to evaluate the efficacy and safety for the combination of Paracetamol, Phenylephrine and Levocetirizine on 201 Indian patients of allergic rhinitis and common cold. Efficacy assessment was made by TSS in the same way as it is done in the study we have conducted on day 3 and 5 considering the baseline visit as day 1. Safety assessment was made by the reported adverse events in the study duration. Mean TSS at day 1, 3 and 5 was found to be reduced from 6.82 to 3.63 to 1.14. At day 3 and 5, the reduction in the mean TSS was 46.77 % and 83.82 % respectively as compared to the baseline. Also no serious or unexpected adverse events were found to be reported. At the end of the study, it was concluded that the combination of Paracetamol, Phenylephrine and Levocetirizine was efficacious as well as safe for the treatment of common cold and allergic rhinitis in Indian patients.[10]

Kiran M et al, conducted a clinical trial with an objective to evaluate the efficacy and safety for the combination of Paracetamol, Phenylephrine and Chlorpheniramine Maleate for common cold and allergic rhinitis. It was a phase IV clinical trial and was conducted on 187 Indian patients for the duration of 5 days. Efficacy assessment was made by TSS which was further extrapolated to Likert type symptom severity scale and safety assessment was made by the reported adverse events. In first 3 days mean total symptom score was found to be reduced from 6.58 to 3.76, reduction of 42.85% and in the next 2 days TSS was reduced from 3.76 to 1.78, reduction of 52.65%. Only 16.57% patients experienced adverse events of mild intensity and non-serious nature, including sedation and drowsiness. It was concluded by the study that the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate was efficacious and safe for the symptomatic treatment of common cold and allergic rhinitis in Indian patients.[11]

Common cold is a self-resolving disease so in this study the cause of reduction in the TSS in

the recruited patients could not be purely because of investigational products used but the common cold resolves by itself in about 9 days according to most of the papers. So, the benefits of the investigational products studied in this study were majorly because of the investigational product.[10]

CONCLUSION

The fixed dose combination of Paracetamol 250 mg, Phenylephrine Hydrochloride 2 mg, Chlorpheniramine Maleate 2 mg, Sodium citrate 60 mg and menthol 1 mg per 5 ml was found to be safe and efficacious for the symptomatic treatment of common cold in the Indian patients of age 2 to 12 years.

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Disclosure

This study was conducted as a part of Pharmacovigilance activity for investigational product whose brand name was Sinarest Plus Suspension which was a fixed dose combination of Paracetamol 250 mg, Phenylephrine Hydrochloride 2 mg, Chlorpheniramine Maleate 2mg, Sodium citrate 60 mg and menthol 1 mg per 5 ml which is manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd.

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