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Efficacy and Safety for the combination of Paracetamol, Phenylephrine, Chlorpheniramine Maleate, Sodium Citrate and Menthol in the patients of common cold (Indian population): Post marketing surveillance study

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Abstract

Introduction: Common cold frequently occurs in developing countries like India. Common cold is a self-limiting disease and only symptomatic treatment is advisable. This study was conducted to evaluate the efficacy and safety for the combination of antipyretic (Paracetamol), nasal decongestant (Phenylephrine), antihistaminic (Chlorpheniramine Maleate), expectorant (Sodium Citrate) and cool aid (Menthol) for the symptomatic treatment of common cold.

Methodology: Total 400trial subjects were enrolled out of which 336 completed the study. Efficacy assessment was made by decrease in total symptom score (TSS) of common cold. Safety assessment was made by analysing the reported adverse events through the study.

Results: Mean TSS was 6.41at baseline which was reduced to 2.65at day 3 and was further reduced to 0.47at day 5. Majority of trial subjects had complete relief from the symptoms of common cold. Nearly all the trial subjects had >50% reduction in their TSS at all visits. At day3 and 5, the percentage reduction in mean TSS was 58.56 % and 92.66 % as compared to baseline. Only 12 episodes of adverse events were reported by the trial subjects and all of them were of non-serious in nature and mild in intensity.

Conclusion: The fixed dose combination of Paracetamol 125 mg, Phenylephrine 5 mg, Chlorpheniramine Maleate 1 mg, Sodium Citrate 60 mg and mentholated flavoured syrupy base q.s. per 5 ml was found to be efficacious as well as safe for the treatment common cold in the trial subjects of age between 2 to 12 years.'

Keywords: Common Cold, Paracetamol, Chlorpheniramine Maleate, Phenylephrine, Sodium Citrate, Menthol

Introduction

The common cold is a frequently occurring illness and is caused by viruses of several families. Metapneumovirus (+2%), Adenovirus (less than 5%), Parainfluenza virus (5%), Respiratory Syncytial virus (5%), Influenza (5-15%), Coronavirus (10-15%), Rhinovirus (30-50%) are the species of viruses which are commonly responsible for Common cold.[1] Rhinorrhoea, sore throat, nasal congestion, coughing, headaches, low-grade fever are collectively recognized as symptom of common colds.[2] Symptoms, which usually relate to the common cold are typically on top at 1–3 days and lasts long till 7–10 days, although they may persist for three weeks.[3] The severity and type of symptoms may vary among individuals and with different infective agents. The occurrence of common cold declines according to age like fever is common in children but not in adults.[4] Children can suffer from 7-10 episodes and adults can suffer 2-5 episodes of common cold per year.[5,6] There is no doubt that only appropriate symptomatic treatment can help trial subject to get the symptomatic relief from the common cold as there is no effective antiviral for the treatment of common cold.[7]

As per the guidelines of DPHHS, Cochrane review, Picon PD et al and Eccles R et al the combination of analgesics, decongestants and antihistamine can provide benefits for multi symptom relief in common cold.[8,9] As a combination of analgesic, decongestant and antihistamine i.e. the combination of Paracetamol, Phenylephrine and Chlorpheniramine Maleate respectively can be used for the symptomatic treatment of common cold and in addition to this combination, Sodium Citrate and Menthol can be used for mucolytic as well as cooling and soothing action respectively.

Paracetamol (acetaminophen)is a non steroidal anti-inflammatory drug (NSAIDs) which is the most popular and commonly used medication. It acts as an antipyretic as well as analgesic by inhibiting the synthesis of prostaglandins in cellular system and inhibits cyclooxygenase (COX-2) enzymes which is responsible for synthesis of arachidonic acid to prostaglandin.[10] Phenylephrine hydrochloride is a nasal decongestant, it is considered to be reduces the symptoms of nasal congestion caused by allergic rhinitis and common cold.[11]It is a non-specific sympathomimetic agent that stimulates alpha-adrenergic receptors and produces marked vasoconstriction.[12] Chlorpheniramine Maleate (CPM) is a histamine H1 antagonist which is indicated for the treatment of allergic reactions, hay fever, urticaria, common cold, rhinitis and asthma.[13] Sodium citrate can be used as a direct acting muco-kinetic expectorant. Sodium citrate increases the bronchial secretion which claims the removal of cough through bronchi. Dry mouth is the common adverse drug event caused because of Chlorpheniramine Maleate which can be decreased by Sodium Citrate due to its mucolytic action. Menthol can be used to produce the cooling and soothing effect.[14]

This post-marketing surveillance study was conducted to document the efficacy and safety for the fixed-dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 5 mg, Chlorpheniramine Maleate 1 mg, Sodium citrate 60 mg and mentholated flavoured syrupy base qs per 5 ml in Indian patients of common cold of age 2 to 12 years.

Methodology

This post marketing surveillance study was conducted at 14 clinical trial sites of paediatric speciality at pan India. The study was conducted for the duration of 5 days. Total 400trial subjects were recruited for the study out of which 336 completed the study. For the study duration of 5 days, trial subjects were asked to visit the clinical trial site on day 3 (visit 2) and day 5 (visit 3) considering the baseline visit as day 1 (visit 1). Visit on day 3 was considered as re-evaluation visit and day 5 was considered as conclusion visit.

Inclusion and Exclusion Criteria:

Patients of both genders including male and female were recruited for the post marketing surveillance study having age between 2-12 years of weight 6 to 39.9kg. Only patients with the confirmed diagnosis of common cold were

recruited. Patients having symptoms of common cold for less than 48 hours were selected for the study. All the guardians of the patients were well informed about the post marketing surveillance study procedures and the investigational product and only patients were recruited for the post marketing surveillance study, whose guardians were ready to strictly adhere to the study protocol through the study duration.

Patients having hypersensitivity to any of the drug present in the investigational product were excluded from the study. Patients with hepatic and renal impairment were also excluded from the study due to the presence of Paracetamol in the investigational product. Hypertensive patients were excluded from the study due to the presence of Phenylephrine in the investigational product which may contribute to increase in blood pressure caused by vasoconstriction. Also, the patients who cannot adhere to the study procedures including but not limited patients with psychological issues were excluded from the post marketing surveillance study.

Investigational product:

Investigational product used for the study was the fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 5 mg, Chlorpheniramine Maleate 1 mg, Sodium Citrate 60 mg and mentholated flavoured syrupy base q.s. 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 trial subject at no cost by the investigator.

Study design:

Since this was a multicentric post marketing surveillance study, it was conducted at 14 clinical trial sites with paediatrician as investigator. Study was conducted on 400 trial subjects and completed on 336 trial subjects. The investigational product and its composition was known to all investigators and clinical research staff from the sponsor and trial subjects.

Study Procedure:

Before recruiting patient for the study as trial subject, the patient (wherever possible) and guardian of the patient were well informed about the investigational product, objective of the study and study procedure. All the information given to the patient and guardian of the patient was in the local and understandable language. Medical history of all the trial subjects was recorded at baseline visit. All the trial subjects were provided with 2 x 50 ml free samples of investigational product from the investigator and were asked to take it in the dose as mentioned below.

Table 1 Dose of investigational product as per weight and age criteria

Weight in kg	Age	Dose
6-22.9	2-7 years	5 ml twice daily
22.9-39.9	7-12 years	5 ml thrice daily

As all the trial subjects were of less than 18 years old, guardians were advised to keep a register of everyday symptoms to record the adverse events if any. In case of any safety related issues or adverse events or serious adverse event, all the investigators were authorized to remove the trial subject from the study by choice and could be treated according to the severity of the symptoms.

Trial subjects recruited in this study were asked to visit the clinical trial site at visit 1 (baseline visit) on day 1, visit 2 (re-evaluation visit) on day 3, and visit 3 (conclusion visit) on day 5 for efficacy and safety assessment. Efficacy and safety assessment was done as mentioned in the section below named as “efficacy assessment” and “safety assessment” respectively.

Concomitant therapy:

During the study, no pharmacological intervention other than investigational product was permitted to the trial subject to take for the treatment of common cold but at the same time, non-pharmacological intervention were permitted to the trial subject.

Efficacy Assessment:

Efficacy assessment was done by analysing the decrease in the Total Symptom Score (TSS) which was measured on TSS scale which was an eleven-point scale ranging from 0 to 10 where no symptom was scored as 0 to the highest tolerated symptoms were scored as 10.Trial subjects were asked to rate the TSS on TSS scale and was recorded on day 1, day 3 and day 5. The TSS was further extrapolated to Likert-type symptom severity scale with 4 grades as no symptoms (0 on TSS), mild intensity symptom (1-3 on TSS), moderate intensity symptom (4-6 on TSS) and severe intensity symptom (7-10 on TSS).

Safety assessment:

At each post baseline visit, i.e. at visit 2 and 3, all the trial subjects and their guardians were asked to report any adverse events if experienced by the trial subject. These adverse events were categorized into serious and non-serious adverse events and also causality assessment for the adverse event was done.

Regulatory Matters:

The investigational product was approved in India for production and marketing. The investigational product is available in India as a schedule H drug, i.e., to be sold only in the presence of licensed medical practitioners' prescription. The informed consent form was read and signed freely by all the guardians of the trial subjects involved in this study as trial subjects were of age less than 18 years.

Results

At 14 clinical trial sites all across India, out of 400 total recruited trial subjects, 336 completed the study. At visit 1 i.e., baseline or day 1, where trial subjects were not treated with the investigational product, mean TSS was 6.41. At revaluation visit (V2) on day 3, the mean TSS was reduced to 2.65, which was further decreased to 0.47 on day 5(V3), which was conclusion visit. Figure 1 shows a graphical presentation of the mean TSS score at all the visits.

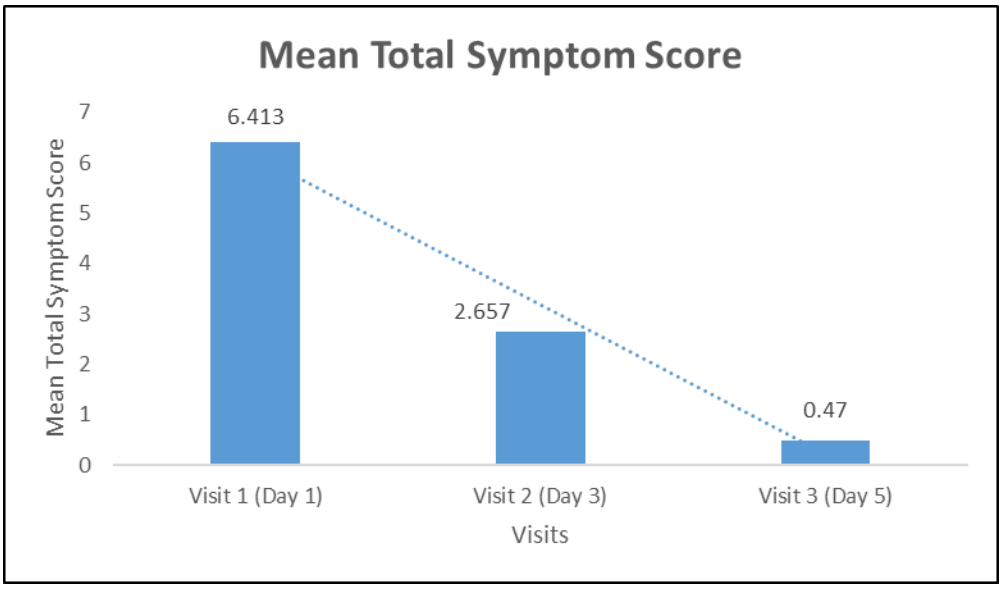

Fig.1 Mean TSS at visit 1, 2 and 3

At visit 2 and 3 the percentage reduction in the mean TSS as compared to the baseline was 58.561 % and 92.668 % respectively. Graphical presentation of the percentage reduction in the mean TSS at visit 2 and 3 as compared to the baseline is graphically presented in figure 2.

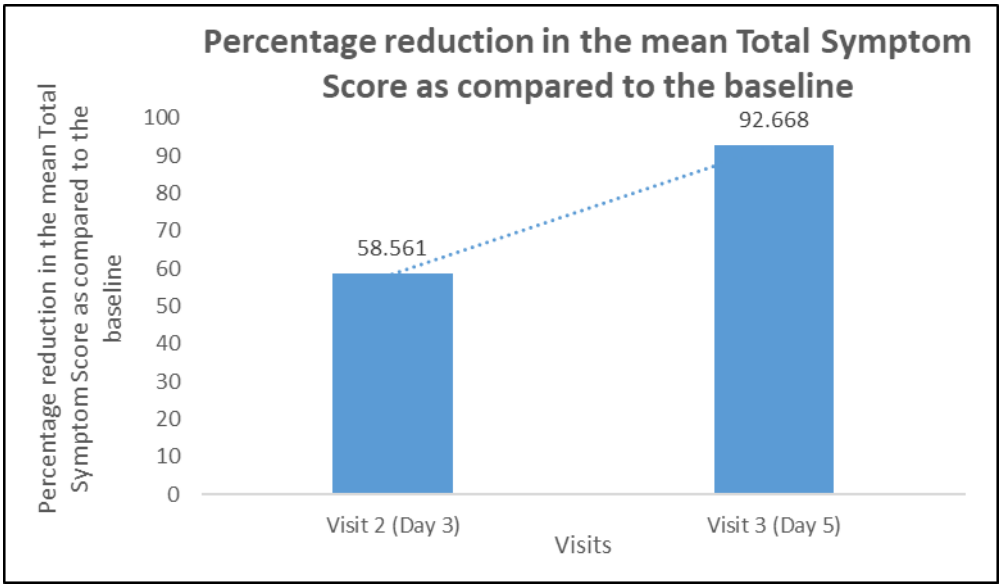

Fig.2 Percent reduction in the mean total symptom score at visit 2 and 3 as compared to the baseline

The TSS data was further extrapolated to Likert-type symptom severity scale as trial subjects with 0, 1 to 3, 4 to 6 and 7 to 10 were considered as trial subjects of no symptoms, mild intensity symptoms, moderate intensity symptoms and severe intensity symptoms respectively. All the trial subjects who completed the study of different TSS score at visit 1, 2 and 3 as per the Likert-type symptom severity scale of different severity is graphically presented in fig. 3.

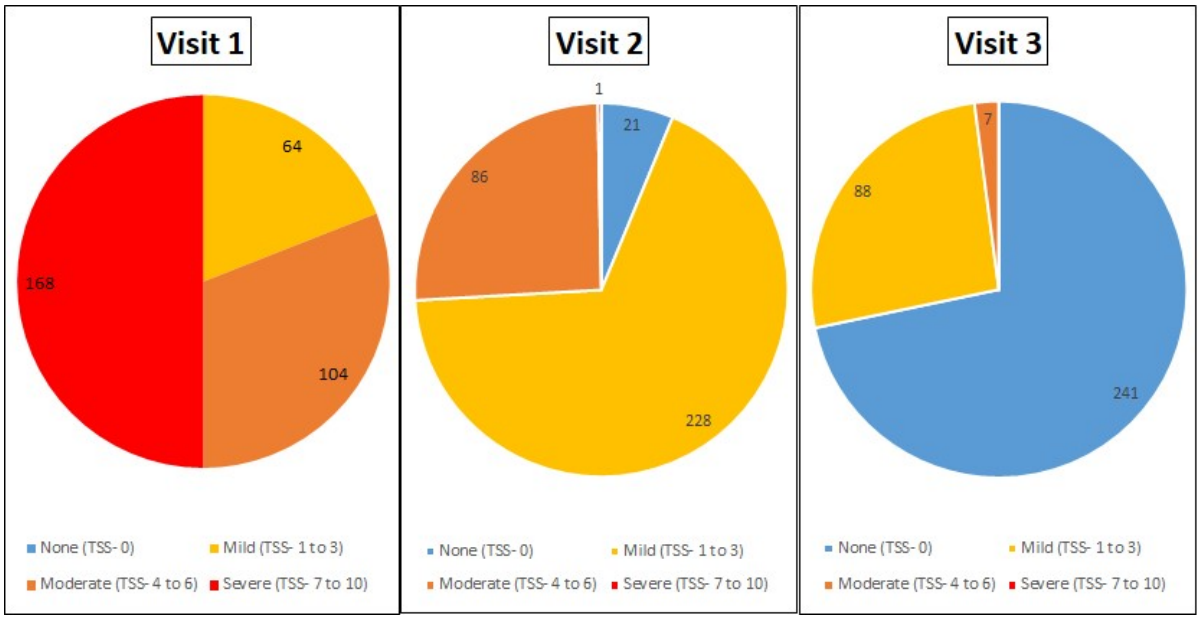

Fig. 3 No of trial subjects of no symptom, mild, moderate and severe intensity symptoms of common cold as per the Likert-type symptom severity scale at visit 1, 2 and 3.

At baseline visit (day 1) out of 336 trial subjects, 168 (50 %) had severe intensity symptoms of TSS ranging between 7 to 10, 104 (30.952 %) had moderate intensity symptoms of TSS ranging between 4 to 6 and 64 (19.047 %) had mild intensity symptoms of TSS ranging from 1 to 3.

At re-evaluation visit (day 3) 21 (6.25 %) trial subjects had no symptom of TSS 0, 228 (67.857%) trial subjects had mild intensity symptoms of TSS ranging from 1 to 3, 86 (25.595%) trial subjects had moderate intensity symptoms of TSS ranging from 4 to 6 and only1 (0.297 %) trial subject had severe intensity symptoms of TSS ranging from 7 to 10.

At conclusion visit (day 5), 241 (71.726 %) trial subjects had no symptom of TSS 0, 88 (26.190 %) trial subject had mild intensity symptoms of TSS 1 to 3, 7 (2.083 %) trial subject had moderate symptoms of TSS 4 to 6 and there was notrial subject had severe intensity of TSS ranging from 7 to 10.

Safety Analysis:

During this study, only 12 adverse drug reactions were reported by 10 trial subjects. All the adverse drug reactions reported were of expected and non-serious nature. Below mentioned adverse drug reactions were reported in the clinical trial duration of 5 days.

Table no. 2- List of adverse drug reactions reported during the PMS study

List of adverse drug reactions	No of episodes	No. of Trial subjects
Nausea	2	1
Sedation and drowsiness	8	6
Dryness of mouth	2	3

Discussion

Common cold is a self-limiting illness which can only be treated symptomatically as till date there is no effective treatment for the common cold of viral origin. Common cold is responsible for severe absenteeism in work, schools and everyday life. By the symptomatic treatment of common cold trial subjects, no. of missing days can be minimised. The study was conducted for the fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 5 mg, Chlorpheniramine Maleate 1 mg, Sodium citrate 60 mg and mentholated flavoured syrupy base qs per 5 ml to test the efficacy and safety in the patients of common cold. For the study total 400 trial subjects were recruited out of which only 336 completed the study. All the trial subjects were asked to visit the clinical trial site on day 3 and 5 considering the baseline visit as day 1. Efficacy and safety assessment was done by TSS score which was further extrapolated to Likert type symptom severity scale and the reported adverse events respectively. During the study, it was found that there was decrease in TSS in all trial subjects. At baseline the mean TSS was 6.413 which was decreased by 58.561 % at visit 2 (day 3), re-evaluation visit and which was further decreased to 0.470 by 92.668 % as compared to the baseline at visit 3 (day 5). At baseline visit, 168 (50 %), 104 (30.95 %) and 64 (19.04 %) trial subjects had severe, moderate and mild intensity symptoms of common cold as per the Likert-type symptom severity scale respectively. At re-evaluation visit (day 3), 1 (0.29 %), 86 (25.59 %) and 228 (67.85 %) trial subjects had severe, moderate and mild intensity symptoms of common cold and 21 (6.25 %) trial subjects were found to be completely cured as they had TSS 0. At conclusion visit (day 5),241 (71.72 %) trial subjects had TSS 0 i.e. they were completely cured, 88 (26.19 %) trial subjects had mild intensity symptoms and only 7 (2.08 %) trial subjects had moderate intensity symptoms. So severity of symptoms were found to be decreased at all the visits in majority of the trial subjects. Below we have mentioned some of the clinical trials which supports the study we have conducted.

Picon et al. conducted a phase III clinical trial to evaluate the efficacy and safety for the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate for the symptomatic treatment of common cold. The clinical trial was conducted on total 146 patients. The reduction of symptom score was found from baseline score of 14.09 to score at day 10 of 3.54 for the study combination and from baseline score of 14.23 to score at day 10 of 4.64 for placebo. Both the group of patients whether treated with placebo or study combination were found to had similar adverse events. It was concluded by the study that the combination of Chlorpheniramine maleate, Phenylephrine and Paracetamol was better than placebo for the symptomatic treatment of common cold and flulike syndrome in adults.[15]

Kiran M. et.al. conducted a phase IV multicentric clinical trial to evaluate the safety and efficacy for the combination of Fexofenadine, Paracetamol and Phenylephrine in 154 trial subjects with common cold and allergic rhinitis. Symptoms associated with common cold and allergic rhinitis were measured using the TSS at day 1, 3 and 5 using 11 point TSS scale ranging from 0 to 10 where 0 was no symptom to 10 was the maximum tolerated symptoms. The baseline TSS was 6.90, which was reduced to 3.42 i.e. decrease of 50.43 % on day 3 and to 0.88 i.e. decrease of 74.26 % as compared to the baseline on day 5. In the conclusion of the clinical trial, the fixed dose combination of Fexofenadine 60mg, Paracetamol 500mg and Phenylephrine 10mg was found to be efficacious as well as safe for the treatment of common cold and allergic rhinitis.[16]

The downside of the study was that the common cold could spontaneously resolve as it is a self-limiting illness, the cause of symptom relief could not be solely related to the investigational product. Several papers state that common cold resolves in around 9 days, so the benefit of the investigational product was mainly due to the benefit offered in 5 days.[16]

Conclusion

Investigational product, fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 5 mg, Chlorpheniramine Maleate 1 mg, Sodium citrate 60 mg and mentholated flavoured syrupy base q.s., was found to be efficacious as well as safe for the symptomatic treatment of common cold.

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Disclosure

This study was conducted as a part of pharmacovigilance activity for investigational product whose brand name is Sinarest Syrup which is a fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 5 mg, Chlorpheniramine Maleate 1 mg, Sodium citrate 60 mg and mentholated flavoured syrupy base q.s. per 5 ml which is manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd.

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