



Post-Marketing Surveillance Study to Substantiate the Efficacy and Safety for the Combination of Paracetamol, Phenylephrine, Chlorpheniramine Maleate, Sodium Citrate and Menthol in Indian Patients of Common Cold

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Abstract

Introduction: Common cold is frequently encountered by people and it also largely affects productivity of the daily routine life. Combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate which acts as an antipyretic, nasal decongestant and anti-histaminic respectively, can be used for the symptomatic treatment of common cold. To the above-mentioned combination, Sodium Citrate was added as an expectorant and Menthol for cooling effect and this post marketing surveillance study was conducted to test the efficacy and safety for the symptomatic treatment of common cold. **Methodology:** Out of 200 enrolled, 174 patients completed the study. Safety assessment was made by analysing the adverse events reported by the patient or their guardian. Efficacy was evaluated by total symptom score [TSS] (eleven-point scale ranging from 0 to 10 where 0 is no symptom to 10 is the maximum symptoms) which was extrapolated to four-point Likert-type symptom severity scales. **Results:** TSS was reduced from 5.57 at baseline visit to 3.40 at day 3 to 1.69 at day 5. At day 3 and day 5 there was TSS reduction of 38.865 % and 69.690 % respectively as compared to baseline. 18 episodes of adverse drug reactions were reported and all of them were of expected and non-serious nature. **Conclusion:** Fixed-dose combination of Paracetamol 125mg, Phenylephrine 5mg, Chlorpheniramine Maleate 1mg, Sodium Citrate 60mg and mentholated flavoured syrupy base q.s. per 5ml was found to be safe and efficacious for the treatment of common cold in children of age between 2 to 12 years.

Keywords: Paracetamol, Phenylephrine, chlorpheniramine, Common Cold.

Introduction

Common cold is a group of mixed diseases generally caused by different respiratory viruses like Rhinovirus (30-50%), Coronavirus (10-15%), Influenza (5-15%), Respiratory Syncytial Virus (5%), Parainfluenza Virus (5%), Adenovirus (less than 5%) or Metapneumovirus (+2%) ^[1]. Common cold is characterized by the stiffness of nasal tract with simultaneous sneezing, cough or sore throat with discharge. Cause of the common cold largely depends on the factors like season, age and/ or also types of virus. It was found that common cold usually decreases the working capacity or it may lead to absence from the work ^[2]. During previous studies it was found that within the time duration of 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 high rate of occurrence ^[3].

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 rather than treatment for the same ^[4]. Single drug therapy would not be 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 ^[5]. As per the guidelines of DPHHS, Cochrane

review, Picon PD et al and Eccles R et al combination of analgesics, decongestants and antihistamines can provide benefits of multi symptom relief in common cold [4].

Paracetamol which is also called as Acetaminophen is a non steroidal anti-inflammatory drug (NSAID) which is the most well known and commonly utilized medication as antipyretic as well as analgesic. Paracetamol inhibits Prostaglandin synthesis in cellular systems under specific conditions and has an apparent selectivity for cyclo-oxygenase (COX) enzymes, namely COX-2. Dissimilar to other NSAIDs it is collectively considered to have no anti-inflammatory action and does not produce gastrointestinal trouble or unpleasant cardiorenal impacts. Hence Paracetamol can be used for the symptomatic treatment of common cold [6]. Phenylephrine hydrochloride is a non-specific sympathomimetic agent that stimulates alpha-adrenergic receptors and produces pronounced vasoconstriction. Due to its mechanism of action it is used as an nasal decongestants and when it is taken orally it relieves nasal congestion caused by allergies, colds, sinus or ear infections [7]. Chlorpheniramine Maleate (CPM) is a histamine H1 antagonist and indicated for the treatment of hay fever, common cold (symptomatic treatment), rhinitis, urticaria, allergic reactions and asthma [8]. Sodium citrate is an expectorant (mucolytic), it increases the bronchial secretion which facilitates the removal of cough. Dry mouth is common adverse drug reaction of Chlorpheniramine Maleate which can be reduced by Sodium Citrate. Menthol produces soothing and cooling effect to the throat by touching nociceptors [9]. Combination of analgesic, nasal decongestant and antihistaminic drugs can be used for the treatment of common cold by using combination of Paracetamol, Phenylephrine Hydrochloride and Chlorpheniramine Maleate respectively [10]. Such combinations are available in New Zealand, US, Australia etc. which was reviewed by Cochrane Drug Review in 2012. However, there is lack of clinical data available on Indian patients for this combination hence this Post-Marketing Surveillance (PMS) study was conducted to document the efficacy and safety of 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.

Methodology

This PMS study was conducted at 12 paediatric specialty clinical trial sites all across India. The study design was of non-randomized, non-comparative and user-initiated nature. The study was conducted for the duration of 5 days. Total 200 patients were recruited for the study out of which 174 patients were adhered to the PMS study procedure till end and completed the study. For the PMS study duration of 5 days, patients were asked to visit the clinical trial site at day 3 and day 5 considering the baseline visit as day 1. Visit on day 3 was considered as re-evaluation visit and day 5 was considered as conclusion visit.

Inclusion and Exclusion Criteria:

This PMS study involved patients of both the genders including male and female having age between 2 to 12 years and having body weight in between 6 to 39.9 kg. The only patients with confirmed diagnosis of common cold having 4 out of the 9 symptoms of headache, fever, body ache, nasal congestion, rhinorrhoea, sneezing, sore throat, dysphonia and malaise present for at least 48 hours were included in the PMS study. Only the patients who were ready to strictly adhere to the protocol were recruited for the PMS study.

Patients with hypersensitivity to the individual study drugs (including Paracetamol, Phenylephrine, Chlorpheniramine Maleate, Sodium Citrate and Menthol) and patients having hepatic and renal impairment were excluded as Paracetamol is present in the investigational product. Patients on hypertensives were also excluded from the PMS study as Phenylephrine which is present in the investigational product can result in vasoconstriction can cause increase in blood pressure.

Study Intervention:

Investigational product used for the PMS study was the fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 5 mg, Chlorpheniramine Maleate 1 mg, Sodium Citrate 60 mg and Menthol 1 mg per 5 ml.

Study design:

Since this was a multicentric PMS study, the study was conducted at 12 clinical trial sites and was completed on 174 patients. As the study design was of non-randomized, non-comparative and open label nature, no control medication was applicable to this.

Study Procedure:

Patients were enrolled for the study by the investigators as per inclusion/exclusion criteria to determine the eligibility. 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 and if guardian of the patient were found to be ready to give his/ her consent for the study then the consent for the study was taken by the investigator on the informed consent form and then the patients were recruited for the study. 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 were advised to take in the dose as mentioned in table no 1 for a study period of 5 days and information was given to the guardians of the patients as patients were of age below 18 years.

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

Guardians of the patients were instructed to keep a diary of daily symptoms to detect the adverse event if any. In case of any safety-related issues i.e. adverse events or serious adverse events, the investigator was authorized to withdraw patient from the study and treat according to the severity of the symptoms.

For the patients recruited in this PMS study, three visits were planned: V1 (baseline visit) on day 1, V2 (re-evaluation visit) on day 3 and V3 (conclusion visit) on day 5. During each visit, the total symptom score and adverse events occurred along with medical history and physical examination, was noted in the case record form. Investigators were asked to discontinue the investigational product in the event of any significant adverse event and discrepancy.

Concomitant therapy:

In the PMS study duration, no pharmacological intervention and medication, including antibiotics, topical decongestants (sprays/drops and aromatic oils), multi-vitamins and multi-minerals, other than study drugs, were permitted. Non-pharmacological measures such as steam inhalation and drinking of

warm water at regular intervals were permitted and encouraged during PMS study duration of 5 days.

Efficacy Assessment:

In the PMS study duration of 5 days, the efficacy assessment was done by calculating the decrease in the Total Symptom Score (TSS). Total Symptom Score scale was used to record the TSS which was 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), mild (1-3 on TSS), moderate (4-6 on TSS) and extreme (7-10 on TSS) to the Likert-type symptom severity scale.

Safety assessment:

At each post dose visit, patients were asked for any adverse events. These adverse events were categorized into serious and non-serious adverse events and also causality assessment for the adverse events was done by the WHO UMC scale.

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.

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

A total 200 patients were recruited at 12 clinical trial sites all across the India out of which 174 patients completed the study. Patients had mean TSS 5.57 at V1 i.e., baseline visit or day 1 where patients were untreated with the investigational product. Mean TSS was reduced to 3.40 at V2 on day 3 which further decreased to 1.68 at V3. Figure 1 showed graphical presentation of mean TSS at every visit.

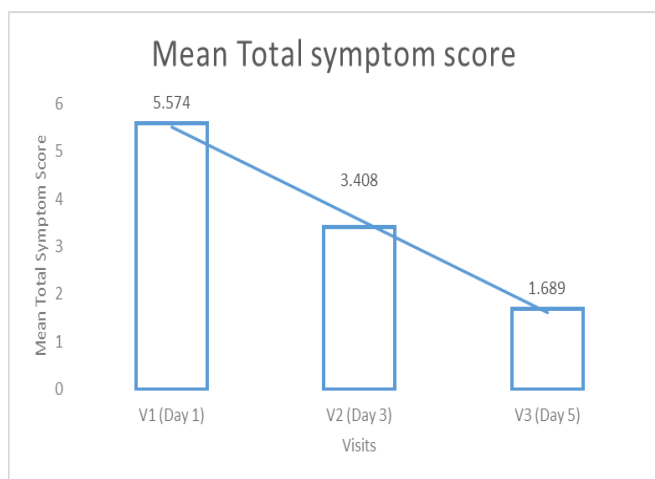


Fig.1 Mean Total Symptom Score at visit 1, 2 and 3

The percentage decrease in TSS at V2 and V3 as compared to visit 1 was calculated, at V2 (day 3) and V3 (day 5) there was 38.865 % and 69.690 % decrease in the TSS, respectively as compared to the baseline which was graphically presented below in fig 2.

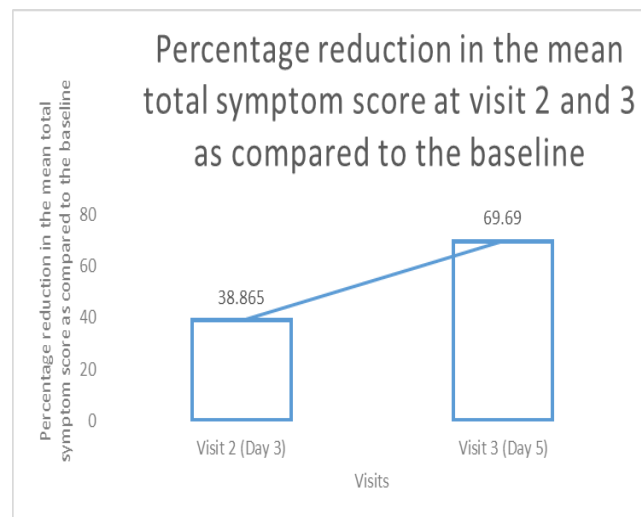


Figure: 2 Percentage reduction in the mean TSS at visit 2 and 3 as compared to the baseline.

The TSS data was extrapolated to Likert-type symptom severity scale as mentioned in the section “Efficacy Assessment” which has been put under the section “Methodology” as- no symptoms (0 on TSS), mild (1-3 on TSS), moderate (4-6 on TSS) and severe (7-10 on TSS) to the Likert-type symptom severity scale.

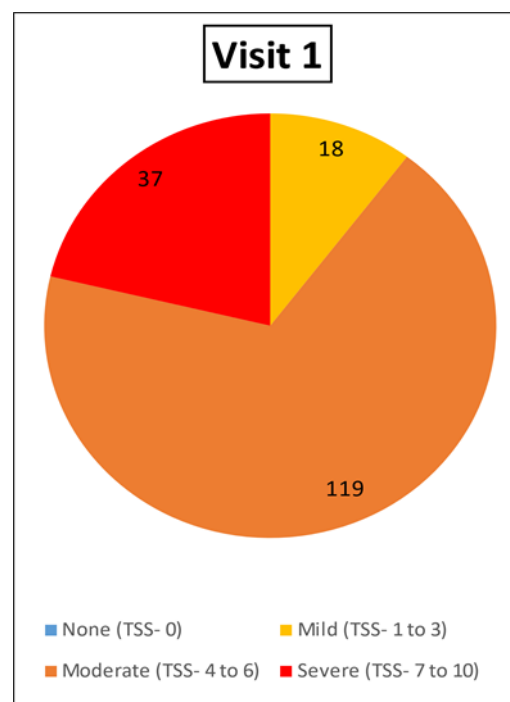


Figure 3: No of patients of mild, moderate and severe intensity symptoms of common cold as per the Likert-type symptom severity scale at visit 1.

At day 1, baseline visit, 18 patients had mild intensity symptoms with TSS 1-3, 119 had moderate intensity symptoms with TSS score 4-6 and remaining 37 patients had TSS 7-10 which showed severe intensity symptoms. As per Likert-type symptom severity scale 10.34% patients had mild intensity symptoms, 68.39 % patients had moderate intensity symptoms and 21.26% patients had severe intensity symptoms.

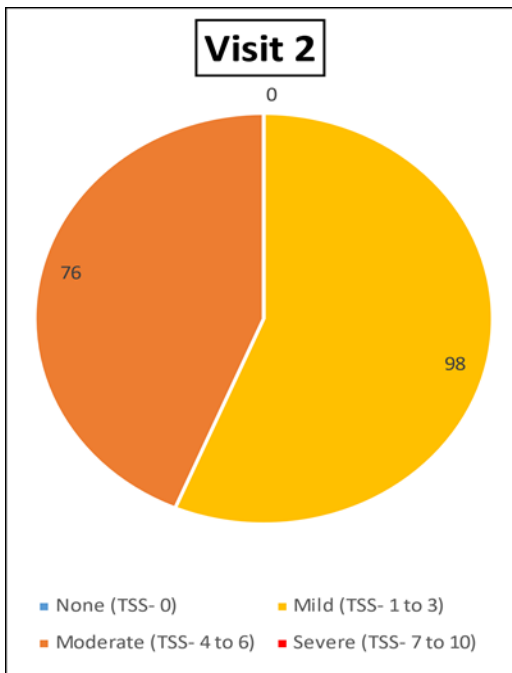


Figure 4: No of patients of mild and moderate intensity symptoms of common cold as per the Likert-type symptom severity scale at visit 2.

The patients were reevaluated at V2 i.e., day 3 where 98 patients had TSS 1-3 i.e. mild intensity symptoms and 76 patients had mean TSS 4-6 i.e. moderate intensity symptoms, which indicated 56.32 % patients had mild intensity symptoms and 43.67 % patients had moderate intensity symptoms. This visit revealed that there was mark reduction in the patients having TSS 7-10 which showed that there was no patient with severe intensity symptoms at visit 2.

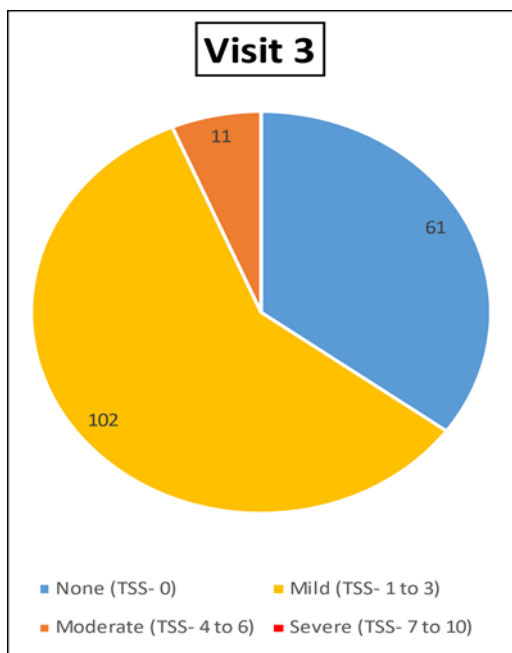


Figure 5: No of patients of none, mild, moderate and severe intensity symptoms of common cold as per the Likert-type symptom severity scale at visit 3.

At visit 3, 61 patients had TSS 0 which showed that 35.05% treated patients had no symptom at day 5. 102 patients had mild symptoms with TSS score 1-3 at day 5 and only 11 patients had TSS score 4-6.

Safety Analysis:

During this PMS study, 18 adverse drug reactions were reported by 14 patients. All the adverse drug reactions reported were of expected and non-serious nature. 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 mentioned adverse drug reactions were reported in the PMS study duration of 5 days.

Table 2: List of adverse drug reactions with number of episodes and patients

List of adverse drug reactions	No of episodes	No of Patients
Nausea	2	2
Sedation and drowsiness	10	7
Hyperacidity	4	4
Dryness of mouth	2	1

Discussion

Common cold is a symptomatically treatable, self-limiting disease but it is also responsible for significant absenteeism in job, schools as well as daily life. Minimizing number of days lost by common cold can be offered by treating the symptoms of common cold. 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 can be used for the symptomatic relief from the common cold as mentioned in the introduction part. This PMS 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 174 patients completed the study. Efficacy assessment was done by the TSS scale which is an 11-point scale and was further extrapolated to Likert-type symptom severity scale. TSS scale has 11 grades for symptom assessment as compared to 4 graded Likert-type symptom score scale, which makes TSS more sensitive. The data of TSS was extrapolated to Likert-type symptom scale which is internationally accepted scale for common cold symptom assessment. During PMS study it was observed that there was markable reduction in the TSS in all the patients during the post marketing surveillance study. Mean TSS reduced from 5.574 to 3.408 from visit 1 (baseline) to visit 2 which was on day 3 i.e., 38.86 % reduction and from 3.408 to 1.689 in the next 2 days which was a reduction of 69.69 % as compared to the baseline. The overall reduction in TSS in 5 days was average 69.690 % in all the patients. According to the study data 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 was effective for the reduction of TSS in all the patients for the symptomatic treatment of common cold and also during the study no serious adverse event was found. In the total patients, 18 adverse drug reactions were reported by 14 patients and all of them were of expected and non-serious nature including nausea, sedation and drowsiness, hyperacidity 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.

Kiran M et al. conducted a post marketing surveillance study to evaluate the efficacy and safety for the fixed dose combination of Paracetamol 125 mg, Phenylephrine 5 mg, Chlorpheniramine Maleate 1 mg, Sodium Citrate 60 mg and Menthol 1 mg per 5 ml for the study indication of common cold on 220 patients of age above 2 years and of weight 8 to 40 kg. The

efficacy evaluation was done by total symptom score which was done at day 1, 3 and 5. The mean total symptom score was found to be reduced from 5.66 at baseline visit to 2.99 at day 3 and 0.7 at day 5. Also, during the study no serious or unexpected adverse event was found to be reported. So it was concluded by the author that, the fixed dose combination of Paracetamol 125 mg, Phenylephrine 5 mg, Chlorpheniramine Maleate 1 mg, Sodium Citrate 60 mg and Menthol 1 mg per 5 ml was efficacious and safe for the symptomatic treatment of common cold [11].

Kiran M et al. studied the safety and efficacy for the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate on 187 Indian patients of common cold or allergic rhinitis in a phase IV clinical trial. In first 3 days mean TSS 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 %. The overall reduction in TSS in 5 days was 72.95 %. A Total of 16.57 % patients experienced adverse events majority being sedation and drowsiness which could be due to Chlorpheniramine maleate. The study concluded that the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate was efficacious and safe for the treatment of common cold and allergic rhinitis [12].

Common cold is a self-resolving or self-limiting disease so the cause of TSS reduction may not be purely attributed to the investigational product of the study. Several papers say common cold resolves in around 7 days [13] and as the study was conducted for the duration of 5 days so it can be considered that the symptomatic relief benefits provided to the patient could be due to the investigational product which 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.

Conclusion

Safe and optimum symptomatic relief from the symptoms of common cold was found to be provided by 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 in Indian patients 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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