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EFFICACY AND SAFETY OF A COMBINATION OF PHENYLEPHRINE, CHLORPHENIRAMINE AND DEXTROMETHORPHAN IN COLD AND DRY COUGH IN CHILDREN

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Abstract
Common cold with cough is one of the most frequently encountered condition in clinical practice. Due to the post nasal drip caused by common cold, irritation of the posterior pharyngeal wall results in dry cough thus distressing the quality of life. A combination of Phenylephrine, a nasal decongestant, chlorpheniramine maleate, an antihistaminic and Dextromethorphan, an antitussive are popularly used in the treatment of common cold with dry cough. This Phase IV study evaluated the efficacy and safety of the combination of Phenylephrine, Chlorpheniramine maleate and Dextromethorphan in the treatment of common cold with dry cough. Total 201 patients were recruited for the study of which 160 patients completed the study and 41 patients were lost to follow up. Assessment of the efficacy was made by the reduction in TSS and four point Likert-type scales. Safety assessment was done by analyzing the adverse events during the trial. The reduction in TSS from 6.58 (baseline) to 4.27(day 3) and 1.53(day 5) was observed. 49 episodes of adverse events occurred and were of mild intensity. A combination of Phenylephrine, Chlorpheniramine maleate and Dextromethorphan is safe and effective in the treatment of common cold with dry cough.

Keywords: Phenylephrine, Chlorpheniramine maleate, Dextromethorphan, Common cold, Dry Cough.

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INTRODUCTION

Common Cold, also referred to as acute viral nasopharyngitis [1] is one of the most frequently encountered minor illnesses in the world and usually the most common cause of the outpatient visits [2,3]. Itis an acute, mild, self-limiting infectious disease that can be caused by more than 100 different viruses. Of these, human rhinoviruses (HRVs) and coronaviruses are responsible for approximately 50-70 percent of all colds [1]. Other viruses such as adenovirus, influenza, parainfluenza virus, syncytial virus may also be involved. This virus usually spreads by hand contact with secretions from an infected person either directly or indirectly or through aerosol of the secretions and virus [4]. Common coldis often a debilitating condition with dominant bothersome symptoms of rhinorrhea, nasal congestion, nasal itching, an acute cough, excessive sneezing, sore throat [5,6] which typically peaks at 1–3 days and lasts 7–10 days and is generally related to the infected mucosa.[4]Colds clear up without causing any further problems however, if untreated the infection can sometimes spread to the chest causing (bronchitis or pneumonia), ears (Otitis media) or sinuses (sinusitis), tonsillitis and pharyngitis [7].

The incidence of the common cold declines with age, with 4-6 episodes in adults, 6-8 episodes in children and 2-3 episodes in older people.[4]The prevalence in United States in course of a year is 1 billion individuals suffering from colds.[4]Being a leading cause ofmorbidity and mortality, Influenza infection accounts for 20-25 million doctor visits and 36,000 deaths per year in the United States [1].

As per the American Academy of Family Physicians, since there are no effective antivirals available to cure common cold, treatment focuses on reducing the symptom duration and intensity thereby minimizing the risk of complication [8]. As a single drug maybe inadequate to relieve all the symptoms of common cold frequently multiple drug combinations are used to treat the variety of symptoms [9]. At times, Common cold is often associated with Post Nasal Drip (PND), due to which secretions from the nose or the paranasal sinuses are drained into the pharynx causing irritation of the posterior pharyngeal wall resulting in dry cough. It produces little or no mucus (phlegm)but an increase in the sensitivity of the cough reflex is observed [10].

Dry cough may further progress to a serious illness or respiratory morbidity such as bronchiectasis if untreated [11]. Symptomatic relief for dry cough can be effectively done with antitussive preparations or cough suppressants. Thus, for the effective management of common cold with cough the combination of an antihistamine-decongestant therapy along with an

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antitussive can be used [12]. Phenylephrine is a selective sympathomimetic agent and a nasal decongestant that has been demonstrated to have potent vasoconstrictor properties. Since it is an alpha-1-adrenergic receptor agonist after the intranasal administration, Phenylephrine stimulates the alpha-1-adrenergic receptors on the nasal mucosa causing vasoconstriction of the local vessels [13]. This decreases the mucosal edema, thereby leading to a decongestant action Chlorpheniramine maleate (CPM) is a synthetic alkylamine derivative and an antihistaminic agent or H1 receptor histaminergic antagonists [10] used to relieve symptoms of allergy, hay fever, runny nose, and sneezing, itchy eyes. CPM works by blocking histamine that the body makes during an allergic reaction. By blocking acetylcholine another natural substance, it helps dry up some body fluids to relieve symptoms such as watery eyes and runny nose.

Dextromethorphan (3-methoxy-N-methylmorphinan) is a synthetically produced drug that is available as one of the most commonly used antitussive agent for the treatment of dry cough [11,12]. Dextromethorphan is devoid of analgesic or addictive property and it readily crosses the blood-brain-barrier activating the sigma opioid receptors in the cough center of the central nervous system, thereby suppressing the cough reflex [14]. A combination of Phenylephrine, Chlorpheniramine maleate and Dextromethorphan formulated as a syrup dosage form is readily available and studied for the treatment of common cold with dry cough. However, due to the inadequacy of the clinical data available for this combination a phase 4 clinical study trial was conducted so as to corroborate the safety and the efficacy profile of the combination of Phenylephrine, Chlorpheniramine Maleate and Dextromethorphan for the treatment of common cold with dry cough.

METHODOLOGY

A Phase IV, open label, multi-centric, clinical trial was conducted at 12 Centers across India for a period of 5 days in February to March 2017.Total of 201 patients were recruited for the study which included 104 male patients and 56 female patients. Out of which 160 patients completed the study and 41 patients were lost to follow up.

Inclusion criteria

The study subsumed children of both the gender having the age between 1 to 12 years of age with body weight of 9 to 41.5 kg. Patients included in this study were confirmed with diagnosis of common cold and non-productive dry cough, having symptoms of rhinorrhea, nasal congestion, nasal itching, an acute dry cough, excessive sneezing, sore throat were enrolled in this study.

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Exclusion criteria

This clinical study trial excluded patients known, or thought to be hypersensitive to the study drugs either individual or in combination present in the dosage form. Also patients with psychiatric illness and those who cannot give informed consent were excluded from the study. Pregnant and lactating women were also excluded from the study.

Study intervention

A combination of Phenylephrine Hydrochloride (5mg) + Chlorpheniramine Maleate (2mg) + Dextromethorphan (10mg),in 5ml formulated in syrup dosage form was provided by the sponsor free of cost to the patients enrolled in the study. Patients included in this study were given50 ml Sinarest CC New Syrup (a combination of Phenylephrine, Chlorpheniramine Maleate and Dextromethorphan) free Sample. Patients were advised to take the dose of 5ml twice a day for a study period of 5 days.

Study procedure

The clinical trial conducted was for a period of 5 days and all the eligible patients of common cold and cough satiating the inclusion and exclusion criteria were recruited for the study.A detailed medical history was taken by thorough clinical examination and physical examination that included the vital signs, systemic and general examination was conducted by the investigators. Patients would be informed about the nature of the study and an informed consent would be taken. Patients are given one 50 ml Sinarest CC New syrup free samples and advised to be taken in the dose of 5ml twice a day for study period of 5 days. A diary of the daily symptoms has to be maintained. In case of any safety-related issues and adverse events or serious adverse events, the investigator by choice can withdraw the patient from the trial and treat according to the severity of the symptoms. Three visits were outlined for the patients recruited in this study-V0 (Baseline visit), V1 (reevaluation visit) and V2 (conclusion visit).Medical history of the patient and physical examination along with the Total Symptom Score and adverse event occurring were esteemed during each visit. Investigators were asked to discontinue the study drug in case of serious adverse events and with discretion, clinical experience in case of mild to moderate adverse events.

Concomitant Therapy

No Pharmacological intervention and medication including topical decongestants (sprays, drops and aromatic oils), antibiotics, multi-vitamins and multiminerals were allowed during the study duration other than the study drug.

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Non-pharmacological interventions like drinking warm/hot water at regular intervals and steam inhalation were allowed and encouraged during the study.

Efficacy Assessment

The primary assessment was done by analyzing the reduction in TSS (Total symptom score) which was a score of all the symptoms related to common cold on a eleven-point scale (0 to 10) where 0 is no symptom and 10 means maximum tolerated symptoms. The TSS scale was further extrapolated to the Likert-type symptom severity scale with 4 grades- no symptoms (0 on TSS), mild (1-4 on TSS), Moderate (5-8) and Severe (9-10 on TSS).

Safety Assessment

Patients were questioned regarding the occurrence of the adverse event. All the serious and non-serious adverse events were fully documented using clinical charts, original documents and case report form. The adverse events were categorized into non-serious adverse events and serious adverse events. Naranjo's scale of probability was used to classify the adverse event as non –drug related or drug related. Adverse events were followed up by the investigators till the symptoms subside.

Regulatory and Ethical Matters

The said combination is available in India and is classified as the schedule H drug which means it should be sold only in presence of prescription of a registered medical practitioner. All the patients participating in the study have read and signed the ICF.

RESULTS

A Total of 201 patients were recruited at 12 centers across India. Out of which 160 patients completed the study and were analyzed. Other demographic characteristics are mentioned in the table below-

Table 1: Demographic Characteristics of the patients recruited for the study

Mean age of the Patients (years)	8.5 years
No of Males	104
No of Females	56

Efficacy Analysis

Mean of the total symptom score (TSS) was recorded at all the visits (V0, V1 and V2) and thus the reduction onTSS was calculated. The mean TSS at V0 or the baseline visit was 6.6 which was reduced to 4.27 at V1 or day 3 and further reduced to 1.593 on V2 or day 5. The reduction in TSS corresponded with the improvement in general and physical examination of the patients.

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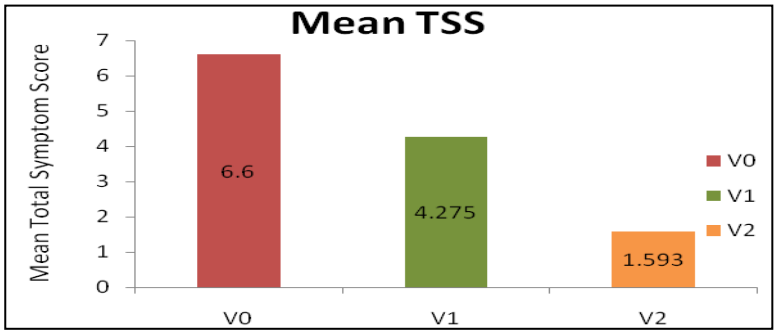

Fig. 1: Reduction in TSS at each visit

Extrapolating the data to Likert-type symptom scale, at V0 or baseline the mean TSS corresponds to Moderate symptoms which was reduced to Mild in V2 or Day5.

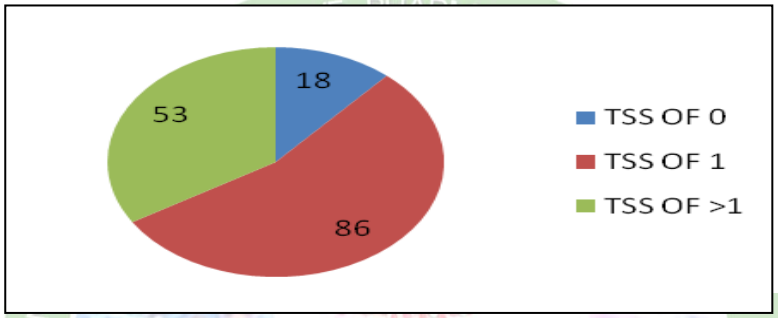

Fig. 2: No of patients with TSS Score of 0,1 and >1 at V2 on day 5

Out of the 201 patients, 18 patients had a TSS of 0 i.e no of symptoms on likert type symptom scale and another 86 had the TSS of 1 (Figure 2) at the end of 5 days.

Safety Analysis

The overall incidence of reported study drug related adverse effects was seen in was 49 seen in 22 patients. The list of adverse events with the number of episodes is mentioned in Table 2.

Table 2: Adverse event episodes occurred in the study.

Adverse Events	No. of events	No. of patients	% of patients
Dizziness	6	4	1.9%
Drowsiness	24	18	8.9%
Dry mouth	9	6	2.98%
Total	49	22	10.94%

Majority of adverse effects were study drug related with Dizziness, Drowsiness and Dry mouth.

DISCUSSION

Common cold with cough has a greater impact on daily life and is responsible for majority of the cases of the outpatient visits and results in the significant costs to the economy in terms of lost workdays and school attendance. Since, it is treated symptomatically; the treatment is fixated

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towards symptom control. As per the author's knowledge this was the first clinical trial conducted to assess the efficacy and safety of a fixed-dose combination of Phenylephrine, Chlorpheniramine maleate and Dextromethorphan for symptomatic relief of common cold with cough. Our study includes an antihistamine-decongestant therapy i.e. combination of Phenylephrine and Chlorpheniramine Maleate, for treating the symptoms of cold such as excessive sneezing, rhinorrhea, nasal congestion and nasal itching for the effective treatment of common cold [15]. For the treatment of dry or non–productive cough associated with common cold antitussive preparations or cough suppressants are used in combination with anti-histamine–decongestant therapy [16]. Strong arm of this clinical study is that the Total Symptom Score is used as a criterion for efficacy assessment and that this data of TSS is extrapolated to Likert-type symptom scale which is the internationally acknowledged scale for assessment of the symptoms. One of the most impressionable thing of the TSS scale lies in the fact that it has 11 grades for the symptom assessment compared to the Likert-type symptom scale which has 4 grades thus increasing the sensitivity of the study. A reduction in Total Symptom score (TSS) in all the patients was observed in the phase IV post marketing surveillance study. The TSS reduced from 6.6 to 4.27 in first 3 days which is reduction of 63.63% and from 4.27 to 1.59 in the next 2 days which is reduction of 22.72%.The Total mean symptom score (TSS) was found to reduce at the conclusion visit i.e. at Visit 3. In all the patients there was a reduction in the TSS scale. Majority of patients had no (TSS score of 0) to very less (TSS score of 1) at the end of 5 study days. Nearly all the patient's had 50% reduction in symptoms at every visit.

A total of 49 adverse events were related to the study drug, of which drowsiness was the most documented adverse event affecting 8.9% the study population. Picon PDet al. [17] conducted a double-blind, placebo-controlled trial of combination of Phenylephrine and Chlorpheniramine maleate to evaluate its efficacy and safety. Efficacy and safety was evaluated in 146 individuals aged 18 to 60 years who had moderate to severe flu-like syndrome or common cold. Of which 73 individuals were randomly assigned to receive the fixed-dose combination and 73 to receive the placebo for 48 to 72 hours. The primary efficacy endpoint was the sum of the scores of 10 symptoms on a four-point Likert-type scale. Comparison of overall symptom scores in the two groups revealed a significantly greater reduction in the treatment group as compared to the placebo group ($p = 0.015$). Analysis at the first 13 dose intervals (± 66 h of treatment) showed a greater reduction of symptom scores in the treatment group than in the placebo group ($p < 0.05$). However, the number and distribution of adverse events were similar in both the groups. The

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study concluded that a fixed-dose combination of chlorpheniramine maleate and phenylephrine was safe and more effective than placebo in the symptomatic treatment of the common cold or flu-like syndrome in adults. Lee PCL et al. [18] conducted a double-blind, stratified, randomized and parallel group design. Both objective and subjective measurements of cough were recorded over 10-min recording periods in a quiet room before (baseline) and at 90, 135 and 180 min after treatment. Forty-three patients (30 females and 13 males), mean age 22.9 years (range 18-46 years), with acute dry or slightly productive cough and otherwise healthy were included in the study.

Patients were randomized to placebo treatment (n = 22) and dextromethorphan treatment (n=21). The results showed similar trends in both treatment groups with statistically significant reductions ($P < 0.05$) in cough sound pressure level (CSPL), cough frequency (CF) and subjective scores for cough severity within treatment groups but little difference between the treatment groups during the study period. The only statistically significant difference between treatment groups was for the mean CSPL changes from baseline to 90 min (P=0.019). There was a significant positive correlation between CSPL and CF ($r = 0.752$, P= 0.000) for changes in cough measurements from baseline to 90 min after treatment and this indicates that CSPL may be a useful measure of cough severity. Similar study trials were conducted stating self- medication for cough and common cold-information needs of the consumers which identified gaps in consumers' perceived knowledge and concerns, to better target consumer medicines information and improve quality use of medicines [19].

The limitation of our study was that common cold itself is self-limiting and usually resolves on its own within a short span of 7-9 days. Due to this the cause of reduction in the symptoms may not be solely attributed to the study drug. Since, this study is carried out in pediatrics and children, managing follow ups and compliance is a drawback.

CONCLUSION

The findings in this study suggest that a fixed dose combination of Phenylephrine, Chlorpheniramine maleate and Dextromethorphan provides optimum and symptomatic relief and is safe for the treatment of common cold with dry cough.

DISCLOSURE

This study was conducted as a part of Pharmacovigilance activity for Sinarest CC New Syrup in accordance with Pharmacovigilance Program of India (PvPI).

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