AN OPEN-LABELED, MULTICENTRIC, POST-MARKETING SURVEILLANCE (PMS) TO SUBSTANTIATE THE SAFETY AND EFFICACY OF SINAREST SYRUP IN PATIENTS OF COMMON COLD.

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ABSTRACT

Background: The common cold and other viral airway infections are highly prevalent in the population, and their treatment often requires the use of medications for symptomatic relief. Paracetamol is as an analgesic and antipyretic; chlorphenamine is an antihistamine; and phenylephrine, a vasoconstrictor and decongestant. This randomized, double-blind, placebo-controlled trial sought to evaluate the safety and efficacy of a fixed-dose combination of paracetamol, chlorphenamine and phenylephrine in the symptomatic treatment of the common cold and flu-like syndrome in adults. Methods: 220 patients aged above 2 years with weight between weight of 8 to 40 kg who had moderate to severe flu-like syndrome or common cold. After clinical examination, patients were randomly assigned to receive the fixed-dose combination for 5 days. The efficacy endpoint was the sum of the scores symptoms on a scale. To evaluate safety, the occurrence of adverse events was measured. Results: Mean age was 10.82 (± 6.48) years in the treatment group. There were 115 females and 95 males in the treatment group. The overall symptom scores revealed a significantly greater reduction from baseline till the end of the study. (p = 0.015). the adverse events were mild to moderate and none required discontinuation of the study medication. Conclusion: A fixed-dose combination syrup formulation of paracetamol, chlorphenamine and phenylephrine was safe and more effective than placebo in the symptomatic treatment of the common cold or flu-like syndrome in adults.

KEYWORDS: Paracetamol, chlorphenamine, phenylephrine common cold.
INTRODUCTION AND BACKGROUND

Common colds are infections of the nose and throat, which are very common in young children and are caused by many viruses. Occasionally, the common cold can be complicated by a bacterial infection such as ear infection, sinus infections, or pneumonia. These complications can be treated with appropriate antibiotics. Common cold is a very common condition present almost during entire time of the year making a patient visit the doctor repeatedly. It mainly involves viruses like Rhinovirus, Corona virus, Respiratory syncytial virus and Para-influenza virus. Rhinovirus is most active in early fall, spring, and summer. They cause 10%-40% of colds.

This syndrome affects the upper airways, sometimes in association with low-grade fever and systemic symptoms, and usually presents with at least two of the following symptoms: cough, dysphonia, throat discomfort, sore throat, nasal congestion, rhinorrhea, sneezing, headaches, myalgia and fever. Symptoms usually peak at 2 to 3 days and have a mean duration of 7 to 10 days. This definition has been prospectively validated in other studies and is that most frequently used in clinical studies of patients with the common cold. Although most cases are caused by the rhinovirus, other agents may be involved, such as the respiratory syncytial virus, adenovirus, coronavirus, and influenza and parainfluenza viruses.

Flu-like syndrome is characterized by sudden onset of fever, headache, cough, sore throat, myalgia, nasal congestion, weakness and loss of appetite. Complications, such as pneumonia, otitis and sinusitis, may occur.

The main symptoms of cold include, sore throat, blocked or runny nose, sneezing and cough. Upper respiratory symptoms usually commence with a single symptom such as a scratchy dry irritating sensation in the throat which develops into other symptoms such as runny nose, sneezing, sore throat, dysphonia, headache, bodyache, blocked nose or nasal congestion, cough, sinus pain, watery eyes, loss of appetite, muscle aches and pains, chilliness, low-grade fever, sleep problems and malaise. More severe symptoms include high temperature (fever), headache and aching muscles.

So the main target is to treat the cold and cough associated with fever and pain. Our FDC comprises of all the constituents to reduce these symptoms. Since anti-virals are generally not used to treat common cold and there are no vaccines available which were prevent common cold, our major objective is to offer symptomatic
relief, to reduce the loss of study days and school absenteeism of children suffering from common cold and reduce its impact on society.

Our fixed dose combination of Paracetamol, Chlorpheniramine Maleate, Phenylephrine, Sodium citrate and Menthol provides anti-pyretic, analgesic, anti-histaminic, expectorant, and soothing action. It may be used to treat cold/flu symptoms which include sinus and nasal congestion, rhinorrhea, cough, sore throat, headache, fever, minor aches and pains.

Paracetamol is a non-steroidal anti-inflammatory drug with anti-pyretic and analgesic activity. It is a weak inhibitor of COX and is free of gastric toxicity. It reduces pain by increasing the pain threshold and reduces fever which is associated with common cold and Rhinoviral Infection by acting on temperature regulating centre of brain. It relieves headache, heaviness in head and fever which is mainly associated with respiratory infections.

Chlorpheniramine maleate is mildly sedative first generation, anti-histamine, which competitively blocks H1 receptors with additional anti-cholinergic action. It relieves runny nose, sneezing, itchy nose and throat and itchy, watery eyes. It also has anticholinergic, sedative, local anesthetic, and anti-5-HT effects, which may favorably affect the symptoms of common cold.

Phenylephrine is a directly acting α1 sympathomimetic which produces vasoconstriction and thus relieves congestion in nasal and bronchial mucosa. It relieves nasal stuffiness thereby relieving nasal congestion associated with sinusitis.

Sodium citrate is a directly acting Expectorant (Mucokinetic) which increases bronchial secretion by salt action. It is believed to increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing. It also counteracts the side effects of Chlorpheniramine which involves dryness of mouth.

Menthol benefits by touching the ‘nociceptors’ which are sensory receptors in throat giving cooling and soothing effect.

This fixed dose combination is used to treat symptoms associated with common cold with cough and allergic rhinitis. This is a study which was conducted to evaluate efficacy and safety of Paracetamol, Phenylephrine, Chlorpheniramine maleate, sodium citrate and menthol in treatment of common cold in children and young adults.
MATERIAL AND METHODS

Study Population
This clinical trial was conducted in sixteen investigation centers. A total of 256 patients were screened for the study and 220 patients completed the study.

Inclusion criteria
This study included patients of both genders, aged above 2 years, weight ranging from 8 to 40 kg. with a duration of symptoms no longer than 72 hours. The common cold was defined by the presence of at least two of the following 10 symptoms: sneezing, rhinorrhoea, nasal congestion, headache, myalgia, throat discomfort, sore throat, dysphonia, cough and fever. Symptoms should be moderate to severe on a Visual analogue symptom severity scale. This study included Patients adhering to the Protocol.

Patients known, or thought to be hypersensitivity to study drugs, having severe Hepatic or Renal dysfunction were excluded from the study.

Study Design
Since, this trial was conducted in sixteen centers on 220 patients, it is a multi-centric clinical trial. Being a phase IV study, there is no control medication applicable here; hence no randomization is needed for this study. Similarly, all the study staff and the patient knew the identity of the medication; hence the design was an “open-label”. The Flow chart of the study was as given in figure no 1.

Table no 1: Flow chart of the study.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Visit-1 Screening Day (Baseline)</th>
<th>Visit-2 Day 3</th>
<th>Visit-3 Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent form signed</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Drug dispensing</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Efficacy evaluation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Safety monitoring</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Study methods and procedures
All eligible patients or their legally accepted representatives were informed about the nature of the study and consent was be taken. A detailed medical history was obtained from all enrolled patients, which were be followed by thorough clinical examination as shown in table
no 2. Patients were enrolled as per inclusion/exclusion criteria to determine the eligibility of the patient.

Table no 2: clinical examination.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Examination</td>
<td>Temperature, pulse, respiration rate, blood pressure, body weight</td>
</tr>
<tr>
<td>Clinical assessment of rhinosinusitis</td>
<td>Local nasal examination, nasal symptom score.</td>
</tr>
</tbody>
</table>

Intervention
Patients were given the FDC of Chlorpheniramine maleate (1mg), Phenylephrine (5mg), Paracetamol (125mg), Sodium citrate (60mg), Menthol (1mg) per 5ml in the dose of 5 ml thrice a day for the period of 5 days. Patients were instructed to keep a diary of daily symptoms. In case of any safety-related issues and adverse events or serious adverse events, the investigator by choice could withdraw the patient from the trial and treat according to the severity of the symptoms. In case of death due to underlying disease, all the details were recorded in the case recording form.

Study Assessments
The study lasted 5 days and included three clinical visits (V1, V2 and V3). On positive inclusion criteria they received the study drug, a diary to keep note of symptoms and adverse events.

At the end of treatment, which lasted 5 days, the patients returned for re-evaluation. The second visit included medical history, clinical and physical examination, as well as an analysis of the following aspects: symptoms, using pre-defined scales; adverse events; duration of symptoms; time to return to usual activities. The third and last follow-up visit took place after 5 days, when the following parameters were evaluated: persistent symptoms, according to predefined scales; duration of symptoms; time to return to usual activities; adverse events; and use of other medications after stopping use of the study drug.

Safety analysis
Drug safety was evaluated by the occurrence of adverse events detected in clinical history, physical examination findings, during treatment or up to 7 days after the last dose of the medication. All serious and non-serious adverse events were fully documented using clinical charts, original documents, and specific forms. In addition, all adverse events occurring
within 7 days of the treatment were investigated, recorded and compared between groups. Adverse events were followed until their resolution or until follow-up was classified (in writing) as complete by the investigators.

RESULTS
Demography
256 patients were recruited. 220 patients completed the study receiving the study medication. There 36 dropouts reason being lost to follow up. The Baseline characteristics of the study population is as shown in table no 3.

Table no 3: Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10.82 (±11.48)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>115</td>
</tr>
<tr>
<td>Male</td>
<td>95</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.67 (±0.11)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.95 (±6.03)</td>
</tr>
<tr>
<td>Mean symptom score</td>
<td>5.66 (± 3.78)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>26.27 (±18.53)</td>
</tr>
</tbody>
</table>

Efficacy analysis
Mean symptom scores were calculated in the groups at V1 and V2 and V3 (before and after treatment), without any data loss, as 100% of the patients attended the visits. At V1, the mean (±SD) overall symptom score was 5.66 in the treatment group. At V2, the overall symptom score was markedly reduced in the treated group, from 5.66 to 2.99 and in visit 3 it
reduced to 0.7. Comparison of mean overall scores of symptoms as evaluated by physicians at V2 and V3 showed that scores were lower in the treatment group, with a trend toward statistical significance (p = 0.063).

![Figure no : 3](image)

**Safety analysis**

The overall incidence of patient-reported adverse events was 61 in the treatment group. Furthermore, analysis of the incidence of specific symptoms in each group did not reveal any statistically significant differences, and the distribution of the number of adverse events was homogeneous in the two groups. The main adverse event reported was drowsiness (n = 43), followed by nausea (n = 18).

Mean (±SD) heart rate (HR) was 76.60 (±11.04) bpm in the treatment group. At V3, mean HR was 76.72 (±10.53) bpm in the treatment. Comparisons of HR variation before and after treatment did not reveal any significant differences (p = 0.834).

Mean (±SD) systolic blood pressure (SBP) at V1 was 119.22 (±13.09) mmHg in the treatment group which at V3, mean SBP was 120.82 (±15.93) mmHg in the treatment group. Comparison of BP variation before and after treatment did not reveal any significant differences (p = 0.092).

No serious adverse events were recorded during the study, and no patients withdrew from the study due to adverse events. The reasons for exclusion from the sample are shown in Figure 1.

There were no patient-reported adverse events in the treatment group, at both the visits. Furthermore, analysis of the incidence of specific symptoms in each group did not reveal any
statistically significant differences. No serious adverse events were recorded during the study, and no patients withdrew from the study due to adverse events.

DISCUSSION
This was a phase clinical trial to demonstrate the efficacy of a fixed-dose combination of Sinarest syrup, an FDC of Paracetamol 125mg + Phenylephrine Hydrochloride 5mg + Chlorpheniramine Maleate 1mg + Sodium citrate 60mg + menthol 1mg per 5 ml based on objective evaluation of symptoms by the investigators and subjective reports provided by patients. There are very few studies talking about the rationale for Treatment of Common Cold and Flu with Multi-Ingredient Combination.

The comparison of baseline and final scores revealed that both groups experienced a major reduction in the total symptom score, both as assessed by the investigators and as reported by the patients themselves. Analysis of the HR variation attributable to treatment revealed that the active formulation did not increase HR. Furthermore, treatment did not increase systolic BP. A small between-group difference in this variable was already detectable at baseline.

As per a study conducted by Eccles, et.al, rationale for Treatment of Common Cold and Flu with Multi-Ingredient Combination Products for Multi-Symptom Relief in Adults was studied. The study was published in Open Journal of Respiratory Diseases, which concluded that multi-symptom relief of combination products containing several active ingredients provided a safe, effective, cost-effective and convenient way of treating the multiple symptoms of common cold and flu, when used as directed.\[9\]

According to a study published by Sutter AI, et.al, in Pubmed, antihistamines were given for common cold as monotherapy was results were studied. It was concluded that antihistamines as monotherapy in children as well as in adults did not alleviate to a clinical extend nasal congestion, rhinorrhea and sneezing, or lead to subjective improvement of the common cold.\[10\]

According to De Sutter, et.al, an article was published in Cochrane database of systematic reviews, in which oral antihistamine-decongestant-analgesic combinations for the common cold was reviewed. The objective of the study was to assess the effectiveness of antihistamine-decongestant-analgesic combinations in reducing the duration and alleviating the symptoms of the common cold in adults and children. In the study a total of 27 trials (5117 participants) of common cold treatment were included. Fourteen trials studied
antihistamine-decongestant combinations; two antihistamine-analgesic; six analgesic-decongestant; and five antihistamine-analgesic-decongestant combinations. In 21 trials the control intervention was placebo and in six trials an active substance.

Some of the medications studied for the treatment of the common cold are antihistamines, anticholinergics, alpha-adrenergic agonists, membrane stabilizers, nonsteroidal anti-inflammatory drugs, vitamin C, glucocorticoids, zinc, herbal medications and alpha-interferon. Clinical trials of high-dose vitamin C have not found any benefits in the treatment of the common cold.[8]

The symptomatic treatment of the common cold has been evaluated in Cochrane meta-analyses. The first included 32 studies with a total of 8930 patients and investigated the administration of antihistamines in the common cold. Results showed that monotherapy did not improve symptoms in either children or adults.[12] The combined use of antihistamines and decongestants may alleviate symptoms in adults, but results are heterogeneous.[11,13]

Safety analysis did not reveal any clinically relevant change in any clinical or laboratory variables at the two time points of evaluation, whether within-group.

The major limitations of study included carrying it out in school going children. and prescribing the anti-cold combination in children without fever. Managing Follow ups and Compliance in children was a drawback in this study.

CONCLUSION
Administration of the study drug at the dose suggested in its package insert was efficacious and safe in the symptomatic treatment of the common cold or flu-like illness. These findings suggest that a fixed-dose combination of paracetamol, chlorphenamine and phenylephrine may be an effective and safe alternative for treatment of these clinical entities.

DISCLOSURE
Dr. Mayuresh Kiran, principal investigator of this study is an employee of Centaur Pharmaceuticals Pvt. Ltd. This study was conducted as a part of Pharmacovigilance activity for Sinarest syrup manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).
REFERENCES


