SAFETY AND EFFICACY OF A COMBINATION OF PARACETAMOL, PHENYLEPHRINE AND FEXOFENADINE IN ADULT PATIENTS OF COMMON COLD AND ALLERGIC RHINITIS: PHASE IV STUDY

Dr. Mayuresh Dilip Kiran1* and Lalit Jeevan Pawaskar2

1General Manager, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.
2Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.

ABSTRACT

Introduction: Common cold and allergic rhinitis both are most commonly encountered diseases in clinical practises in India. Though self-limiting, it accounts for major loss of school and work days. Symptomatic therapy is often used to treat the symptoms. Combination of analgesic/anti-inflammatory/antipyretic, anti-histaminic and nasal decongestant is popular in the treatment of common cold and allergic rhinitis. This Phase IV study evaluated the efficacy and safety of one such combination of Paracetamol, Phenylephrine and Fexofenadine in treatment of common cold and allergic rhinitis. Materials and Methods: Of total 189 enrolled patients, 154 patients completed the study. Efficacy assessment was made by reduction in Total Symptom Score and four point Likert-type scales. Safety assessment was made by analysing the adverse events through the study. Results: Reduction in mean TSS was done from 6.90 (baseline) to 3.42 (day 3) to 0.88 (day 5). Two points were reduced in Likert-type symptom scale from Severe to Mild in 3 days. Nearly all the patients had >50% reduction in their total symptom score at all visit and majority of patients had complete relief from the symptoms at visit 3. Four episodes of adverse events occurred and all of them were of mild intensity. Conclusion: A combination of Paracetamol, Phenylephrine and Fexofenadine is safe and effective in the treatment of common cold and allergic rhinitis.

KEYWORDS: Paracetamol, Phenylephrine, Fexofenadine, Common Cold, Allergic Rhinitis.
INTRODUCTION

Common cold is the most common illness known and usually it presents with a range of symptoms such as nasal stuffiness/discharge, sore throat, cough and sneezing.\cite{1} As per the Department of Public Health & Human Services (DPHHS) stated that, the term “common cold” refers to a mild upper-respiratory tract viral illness. It is self-limited therefore only symptomatic treatment is needed. It is distinctly different illness than throat infection, influenza, bronchitis, pertussis and sinusitis in which treatment with antibiotics is warranted. On an average adult person suffers from common cold two or three times a year\cite{2} and young children’s have six to eight episodes of colds per year. Commonly the cold is caused by viruses (more than 200 viruses have been implicated), with an exception of RSV and influenza, there are no anti-viral or vaccinations available for prevention of viruses that cause the common cold, thus making it non-preventable disease.\cite{3, 4} Common cold has a huge impact on time or period lost from work or school and causes substantial discomfort.\cite{1}

Allergic rhinitis is clinically defined by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of allergic rhinitis include rhinorrhoea, nasal itching, nasal obstruction or blockage, nasal/paranasal pain, postnasal drip and sneezing that are reversible spontaneously or under treatment.\cite{5}

As per the DPHHS guidelines\cite{2}, Cochrane review\cite{1}, Eccles R\cite{6} et al and Picon PD et al\cite{7} combination of antihistamine, decongestant and analgesic provides benefits in adults for multi symptom relief in common cold and allergic rhinitis.

Fexofenadine belongs to second-generation, H1-receptor antagonist (having antihistaminic action). Histamine, a biological chemical causes many signs and symptoms that are a part of allergic and inflammatory reactions. Histamine releases from mast cells and attaches to other cells which have receptors for histamine. After histamine gets attached to the receptors it causes the cell to be activated, producing effects which are associate with allergy, inflammation and negative symptoms. Fexofenadine blocks a type of receptor for histamine, H1 receptors and thus prevents the activation of cells due to histamine blocking.\cite{8} Fexofenadine exhibits no anticholinergic, beta-adrenergic-receptor blocking or alpha1-adrenergic effects. Unlike other antihistamines, Fexofenadine doesn’t cross blood brain
barrier, therefore it does not causes sedation or drowsiness. Fexofenadine lacks cardio-toxic potential because it does not block the potassium channel involved in repolarization of cardiac cells. As per US FDA, Fexofenadine can be used in the strength of 60 mg twice daily for the treatment of rhinitis.\[^8\]

Paracetamol is one of the most commonly used and most popular analgesic, anti-inflammatory and antipyretic drug used all around the world, available as an OTC, both in mono- and multi-component preparations.\[^9\] It does not alter acid base balance, depress respiration or cause gastric irritation. So Paracetamol can be used in the treatment of most of the symptoms of common cold like fever, bodyache and headache. It can also be used treat nasal and paranasal pain associated with allergic rhinitis.\[^10\]

Phenylephrine, a selective adrenergic receptor agonist, is an effective nasal decongestant that can be administered intranasally or orally as per CHPA [Docket No. 2007P-0047]. Its dominant and direct effect is vasoconstriction of capacitance blood vessels of the nasal mucosa that decreases blood vessel diameter, leading to nasal decongestion.\[^11\]

A combination of Paracetamol and Phenylephrine with Chlorpheniramine maleate or Levocetirizine is popularly available in the treatment of common cold/allergic rhinitis. Instead of Chlorpheniramine maleate or Levocetirizine which are sedative antihistamines, a non-sedative Fexofenadine was developed in a combination with Paracetamol and Phenylephrine. This phase IV study was conducted to document safety and efficacy of the combination of Paracetamol, Fexofenadine and Phenylephrine in patients of common cold and allergic rhinitis.

**MATERIALS AND METHODS**

13 ENT centres were selected all over the India for conducting this Phase IV clinical study. Total 189 patients were recruited for the study out of which 154 patients completed the study. 35 patients were lost to follow-up. This study was conducted from October 2016 to January 2017.

**Inclusion and exclusion study**

Patients with confirmed diagnosis of common cold or allergic rhinitis (having 4 out of 9 symptoms of headache, fever, bodyache, nasal congestion, rhinorrhoea, sneezing, sore throat, dysphonia and malaise) were enrolled in the study. Patients of both the genders (male and
female) having age of 18 to 75 years were recruited for this study. Finally the patients who were ready to strictly adhere to the protocol and sign informed consent form were recruited for the study.

Patients with hypersensitivity to the individual study drug or to any of its ingredients, patients with Hepatic or Renal dysfunction were excluded as the study drug contains Paracetamol. Patients of hypertension (study drug contains Phenylephrine which can result in vasoconstriction causing rise of BP), pregnant or lactating women and mentally ill were excluded from the study.

**Study Intervention**

Study drug – An uncoated tablet containing combination of Paracetamol 500 mg + Phenylephrine 10 mg + Fexofenadine 60 mg per tablet was provided by the sponsor at free of cost to the patients involved in the study and dispensed by the investigator to the patient.

Study dosage and administration – One tablet was advised to be taken twice a day at 12 hours interval after meals (Breakfast and Dinner) with a glass of water by the patient.

**Study procedure**

The study duration was decided and kept 5 days. Patients of common cold who met with the decided inclusion and exclusion criteria were recruited in the study. A detailed medical history was obtained from the patient and physical examination (including vital signs, general and systemic examination) was conducted by the investigators. Investigators with postgraduate degree in ENT were involved in conducting this study. Patients were dispensed 10 tablets in a blister pack of the study drug medication by investigators and asked to consume in the dose of 1 tablet twice a day for a study period of 5 days. Patients were asked to maintain a diary to record any adverse events occurring during the study duration.

Three visits were planned for all the patients recruited in this study – baseline visit (V₁) on day 1 before treating patient with the medication, revaluation visit (V₂) on day 3 and conclusion visit (V₃) on day 5. Adverse events occurring and total symptom score were noted during each visit along with medical history and physical examination. Investigators were asked to discontinue the study drug in case of severe adverse event and with discretion, clinical experience in case of mild or moderate adverse events.
Concomitant therapy
No Pharmacological intervention and medication including topical decongestants (drops or sprays or aromatic oils), antibiotics, multi-vitamins or multi-minerals were allowed during study duration of 5 days, other than study drug. Non-Pharmacological interventions like drinking of hot water or steam inhalation at regular intervals were allowed and encouraged during the study duration.

Efficacy assessment
The primary assessment was done to analyse the reduction in the Total Symptom Score (TSS) which was a score of all the symptoms related to common cold and allergic rhinitis on an eleven-point scale (0 to 10) where 0 is no symptoms i.e. patients with no symptoms are who are completely cured and 10 is 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 – 3 on TSS), Moderate (4 – 6 on TSS) and Severe (7 – 10 on TSS). The secondary assessment was number of patients having no symptoms (0 on TSS) on day 5 and number of patients having more than 50% reduction in TSS.

Safety assessment
Patients were asked for any adverse event and if present were noted in the case record form (CRF) during each post-dose visit. These adverse events were classified into serious and non-serious adverse events. Naranjo’s scale of probability was used to classify the adverse event as drug related or nondrug related. Adverse events were followed up and also treated if necessary by the investigators till their resolution.

Regulatory and Ethical matters
The said combination is available in India and is classified as schedule H drug in India, i.e. it should be sold in presence of prescription of registered medical practitioners only. All the patients participated in the study have read and voluntarily signed the informed consent form (ICF). This study was conducted in accordance with schedule Y. The ICF, protocol, CRF, investigators CV, investigators undertaking, ethics committee registration certificates and investigators medical registration certificates (including post-graduation certificates) were submitted to the office of DCGI (Drug Controller General of India), Central Drugs Standard Control Organization (CDSCO) and are registered under ref. no. 2508/17.
RESULTS
Mean of TSS recorded at all the visits was 6.90 at baseline (V1) before treating patient with the study medication, was reduced to 3.42 at visit 2 (V2) on day 3 and further reduced to 0.88 at visit 3 (V3) at day 5. Mean TSS score at each visit 2 and visit 3 was found to be reduced more than 50% as compared to their previous visit. Graphical presentation of mean TSS score at each visit is graphically presented in the in the image below in Figure 1.

![Graph showing reduction in mean TSS at each visit.](image)

**Fig. 1: Reduction in mean TSS at each visit.**

Extrapolating the data to the Likert-type symptom scale, at V1 or baseline the mean TSS was corresponding to severe symptoms, which was reduced to mild in visit 2 (V2) at day 3 and which was further reduced to negligibly mild to no symptoms in visit 3 (V3) on Day 5. At visit 2, 10 subjects were having TSS score of 0 which states that after treating the subject with the study medication on day 3, 10 out of 154 patients i.e. 6.496% patients were completely cured on V2. As per Likert-type symptom scale 61 i.e. (39.61%) patients were having mild symptoms and out of which 8 i.e. (5.195%) patients were having TSS score of 1 i.e. symptoms were negligibly mild.

![Pie chart showing number and percentage of patients at V2 with TSS score.](image)

**Fig. 2: Number and percentage of patients at V2 with TSS score**
At visit 3, 90 subjects were having TSS score of 0 which states that after treating the subject with the study medication on day 5, 90 out of 154 patients i.e. 58.448% patients were completely cured on V3. As per Likert-type symptom scale 35 i.e. (22.727%) patients were having mild symptoms and 27 i.e. (17.533%) patients were having TSS score of 1 i.e. symptoms were negligibly mild.

Fig. 3: Number and percentage of patients at V3 with TSS score

Safety analysis
The overall drug related adverse effects incidences were 4 seen in 3 patients i.e. 2.60% of total population. The list of adverse events with the number of patients is mentioned in Table 1 as below.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>No. of Patients</th>
<th>% of total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacidity</td>
<td>3</td>
<td>1.94 %</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>1</td>
<td>0.649 %</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4</strong></td>
<td><strong>2.60 %</strong></td>
</tr>
</tbody>
</table>

DISCUSSION
Common cold is generally a self-limiting disease but it is responsible for significant absenteeism in job as well as schools. Providing symptom control would help to reduce the number of days missed by reason of common cold, hence the treatment is focused towards symptom control only in most of the cases.\(^{[10]}\)

In best of author’s knowledge, this is the first clinical study for the combination of Paracetamol, Phenylephrine and Fexofenadine in the treatment of common cold and allergic
rhinitis. Total Symptom Score (TSS) scale is used for analysis of efficacy and extrapolated to Likert-type symptom 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 is extrapolated to Likert-type symptom scale which is internationally accepted scale for common cold symptom assessment.

There was reduction in TSS in all the patients during the Phase IV clinical Study. Mean TSS reduced from 6.90 to 3.42 from visit 1 (baseline) to visit 2 which was on day 3 i.e. 49.85 % reduction and from 3.42 to 0.88 in the next 2 days which was a reduction of 74.27 %. The overall reduction in TSS in 5 days was 87.09 %. Two point reductions in Likert-type symptom scale from Severe to Mild took in just 3 days with the study drug combination. At visit 2, 10 subjects were having TSS score of 0 i.e. 6 % subjects were completely cured on third day. At visit 3, 90 subjects were having TSS score of 0 i.e. 58.441 % subjects were completely cured. Another 61 i.e. 39.61 % of subjects were having mild symptoms as per Likert type scale i.e. TSS score of 1 to 3. Thus study medication needs to be taken for full 5 days to achieve complete cure.

Adverse effects occurring in the study were 4 episodes of hyperacidity and nausea/vomiting which may have been caused by Paracetamol in the study drug. Interestingly, adverse effect of sedation and drowsiness was not seen in the study.

In a 2-week, multicentric, randomized, double blind, placebo controlled clinical trial was conducted in 1634 subjects of age 12 to 68 years of age who were suffered with seasonal allergic rhinitis, fexofenadine hydrochloride 60 mg twice a day reduced total symptom scores (the sum of the individual scores for rhinorrhea, sneezing, itchy/watery/red eyes, itchy nose/palate/throat) as compared to placebo. Statistically significant reductions in total symptom score was observed following the first 60 mg dose, and the effects were maintained throughout the 12-hour interval as the mean elimination half-life of fexofenadine is 14.4 hours. In these studies, there was no additional reduction in total symptom scores with higher doses of fexofenadine hydrochloride up to 240 mg twice daily.[8]

Picon et al.[7], conducted a phase III clinical trial for a combination of Phenylephrine, Paracetamol and Chlorpheniramine maleate studying its safety and efficacy in treatment of common cold in 146 patients. The reduction of symptom score was from baseline score of 14.09 to 3.54 for the combination and from baseline score of 14.23 to 4.64 for placebo, at end
of 10 days. The number, type and distribution of adverse events were similar in both the groups. Study concludes that the combination of Phenylephrine, Paracetamol and Chlorpheniramine maleate is better than placebo in the treatment of common cold and flulike syndrome in adults.

Kiran M et al.\textsuperscript{[10]} conducted a phase IV clinical trial for studying the safety and efficacy of a combination of Paracetamol, Phenylephrine and Levocetirizine on 201 Indian patients of common cold and allergic rhinitis. In first 3 days mean TSS reduced from 6.82 to 3.63 with a reduction of 46.77\%. In the next 2 days TSS was reduced from 3.63 to 1.14 with a reduction of 68.59\%. The overall reduction in TSS in 5 days was 83.28 \%. Total of 11.94 \% patients had adverse events, majority were sedation and drowsiness which may be because of Levocetirizine.

Kiran M et al.\textsuperscript{[13]} studied the safety and efficacy for a combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate on 187 Indian patients of common cold and allergic rhinitis in a phase IV clinical trial. In first 3 days mean TSS 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 may be due to Chlorpheniramine maleate.

The limitation of the study was, common cold is a self-limiting disease and it can be resolve spontaneously. Study drug may not be fully responsible for reduction in TSS. We have tried to minimize this limitation by keeping the study duration for 5 days as opposed to earlier study where it was 10 days. Several papers stated that common cold resolves in about 10 days\textsuperscript{[14]}, so the benefit offered on day 5 after treatment would be majorly due to the study drug.

**CONCLUSION**

Combination of Paracetamol 500 mg, Phenylephrine 10 mg and Fexofenadine 60 mg provides optimum symptomatic relief and is safe for use in the symptomatic management of common cold and allergic rhinitis.
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DISCLOSURE
Dr. Mayuresh Kiran, Study Director and Mr. Lalit Pawaskar, Research Associate for this study are employees of Centaur Pharmaceuticals Pvt. Ltd. This study was conducted as a part of Pharmacovigilance activity for Sinarest FxP Tablets manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

REFERENCES


