POST-MARKETING SURVEILLANCE STUDY TO SUBSTANTIATE THE EFFICACY AND SAFETY FOR THE COMBINATION OF PARACETAMOL, PHENYLEPHRINE AND CHLORPHENIRAMINE MALEATE IN INDIAN PATIENTS OF COMMON COLD

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Abstract:

Introduction: Common cold is frequently occurring medical condition in developing countries like India. Common cold is self-limiting in nature so symptomatic treatment is always suggested. This study was conducted to test the efficacy and safety for the fixed dose combination of Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Chlorpheniramine Maleate 2 mg per tablet for the treatment of common cold.

Methodology: Total 180 patients were enrolled out of which 159 completed the study. Efficacy assessment was done by decrease in total symptom score (TSS) of common cold at day 3 and 5 as compared to the baseline (day 1). Safety assessment was made by analyzing the reported adverse events through the study.

Results: Mean TSS at baseline was 6.62 which was decreased to 3.55 at day 3 and was further decreased to 0.68 at day 5. Majority of patients had complete relief from the symptoms of common cold and nearly all the patients had >50 % reduction in TSS. Also no unexpected or serious adverse event was found to be reported in the study duration of 5 days.

Conclusion: Fixed dose combination of Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Chlorpheniramine Maleate 2 mg per tablet was found to be efficacious and safe for the symptomatic treatment of common cold in Indian patients.

Keywords: Common cold, Paracetamol, Chlorpheniramine Maleate and Phenylephrine

Introduction:

Common cold or acute coryza is majorly known as acute upper respiratory disease which affects people of all ages including not only adults but also children. Common cold is most commonly encountered by the healthcare professionals during their clinical practices. In a year adults and children can have around two to four and six to eight episodes of common cold respectively. Most commonly it is considered to be caused by Rhinovirus and also other viruses can cause the same including but not limited to respiratory syncytial virus, adenovirus, coronavirus, parainfluenza and influenza viruses.⁽¹⁾ As

common cold is a 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 so ideally the treatment should focus on symptomatic relief rather than treatment for the same.⁽¹⁾ Single drug therapy is not effective for the symptomatic relief from the majority symptoms of common cold so combination drug therapy is always suggested for the symptomatic treatment of common cold. As per the Cochrane review, Picon PD et al, Eccles R et al and guidelines of DPHHS the combination

of analgesics, decongestants and antihistamines can provides significant benefits for multi symptom relief in common cold.^(2,3) So this study was conducted to test the efficacy and safety for the treatment of common cold in Indian patients for the fixed dose combination of Paracetamol 500 mg, Phenylephrine 10 mg and Chlorpheniramine Maleate 2 mg per tablet.

Paracetamol which is also commonly known as Acetaminophen is a Non-Steroidal Anti-Inflammatory Drug. It has good and prompt antipyretic action and also it does not depress respiration, alter acid base balance or cause gastric irritation. Paracetamol is useful for the symptomatic treatment of common cold including fever, headache and bodyache.⁽³⁾ 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.⁽⁴⁾ Phenylephrine is an efficacious as well as safe nasal decongestant when it is taken by either nasal or oral route. It is a selective alpha 1 -adrenergic receptor agonist. Phenylephrine at therapeutic doses causes vasoconstriction in the nasal mucosa which relieves the nasal blockage caused due to inflammation. Phenylephrine can be used for the symptomatic treatment common cold symptoms including blocked nose or nasal congestion.⁽³⁾ One of the most commonly prescribed and used 1st generation antihistaminic agents is Chlorpheniramine maleate (CPM). CPM's primary action is competitive binding to the vascular tunica medius H1 receptors in the nasal mucosa to avoid the vasoactive response to histamine. The anti-histaminic activity of CPM in the nasal mucosa translates to its anti-allergic and anti-inflammatory action. The additional anticholinergic activity of CPM is responsible for reducing the number of infectious nasal discharges.⁽⁵⁾

For the treatment of common cold, a combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate is often used. These combinations are available as OTCs in developed countries such as the US, Australia, New Zealand, etc.⁽²⁾ This post marketing surveillance study was

conducted to document the efficacy and safety for the combination of Paracetamol, Phenylephrine and Chlorpheniramine Maleate for the treatment of common cold in Indian patients.

Methodology:

This post marketing surveillance study was conducted at 12 ENT specialty clinical trial sites all across India. The study design was of non-randomized, non-comparative and user-initiated nature. Total 180 patients were recruited for the study out of which 159 completed the study.

Inclusion and Exclusion Criteria:

Patients for the clinical trial were recruited by the investigator as per the inclusion and exclusion criteria as mentioned below.

As per the inclusion criteria, patients of both sex including male and female, of age between 18 to 65 years old and patients with the confirmed diagnosis of common cold with at least 4 out of 9 symptoms including fever, headache, body ache, rhinorrhea, nasal congestion, sore throat, sneezing, malaise and dysphonia were recruited for the study. Also, for the clinical trial, only those patients were recruited who could strictly adhere to the study procedure.

As per the exclusion criteria, patients hypersensitive to any of the drug present in the investigational product including Paracetamol, Phenylephrine and Chlorpheniramine Maleate were excluded from the study. Also, patients with hepatic and renal failure were excluded as Paracetamol was present in the investigational product. Patients with hypertension were excluded from the study due to presence of Phenylephrine in the investigational product which may contribute to an increase in blood pressure which can be caused by vasoconstriction. Also, pregnant and lactating woman were excluded from the study.

Investigational product:

Investigational product used for the study was the fixed dose combination of Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Chlorpheniramine Maleate 2 mg per tablet. The

investigational product to all the investigators were provided by the sponsor at no cost and those investigational products were dispensed to all the patients at no cost by the investigator.

Study design:

Since this was a multicentric post marketing surveillance (PMS) study, it was conducted at 12 clinical trial sites on 180 patients and was completed on 159 patients. As the study design was of non-comparative, non-randomized and open label nature, all investigators, clinical research staff and patients or any other people either from the side of investigator, patient or the sponsor involved in the study were aware of the investigational product and its composition.

Study Procedure:

All eligible patients as per the inclusion and exclusion criteria were recruited for the study by the investigator. Before recruiting patients for the study, they were well informed about the study procedures and investigational product and all doubts of the patients were resolved. Detailed medication history was obtained from all enrolled patients, which was followed by thorough clinical examination. Investigational product i.e. fixed dose combination of Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Chlorpheniramine Maleate 2 mg per tablet was provided to all the recruited patients at no cost by the investigator. Patients were asked to take the investigational product in the dose of 1 tablet thrice a day in the interval of 8 hours for the study duration of 5 days. Patients were instructed to maintain the diary of daily symptoms to get the information about any adverse events if any. In case of serious adverse event the investigator was authorized to withdraw the patient by choice and treat according to the severity. After the baseline visit/ visit 1 (day 1), all the patients were asked to visit the clinical trial site on day 3 (visit 2) and 5 (visit 3) for efficacy and safety assessment. Efficacy and safety assessment was done by the total symptom score which was further extrapolated to the 4-point Likert type symptom severity scale and by the reported adverse events (if any) respectively.

Concomitant therapy:

During the study, no pharmacological intervention or medication including but not limited to antibiotics, topical decongestants including sprays or drops and aromatic oils, multivitamins or multiminerals were allowed to the patient to take. But, non-pharmacological measures such as steam inhalation and/ or drinking of warm water at regular intervals were permitted and encouraged.

Efficacy Assessment:

Total symptom score (TSS) was used as an efficacy assessment parameter. Total symptom score was measured by the use of TSS scale which was an eleven-point scale ranging from 0 to 10 where 0 was no symptom to 10 was the maximum tolerable symptoms. TSS was further extrapolated to 4-point Likert-type symptom severity scales where 0 TSS was no symptom, 1 to 3 TSS was mild, 4 to 6 TSS was moderate and 7 to 10 TSS was severe intensity symptoms. At all the visits, patients were asked to rate the TSS and was further extrapolated to 4-point Likert-type symptom severity scale.

Safety assessment:

At visit 2 and 3, patients were asked for any adverse event and the same, if found to be present, was recorded by the investigator. These adverse events were categorized into either expected or unexpected adverse drug reactions of either serious and non-serious nature. WHO UMC scale was used for the causality assessment.

Regulatory Matters:

The investigational product was approved in India for manufacturing and marketing. The investigational product was available under the category of schedule H drugs which means that the product should be sold to the patient only if the patient has prescription of the licensed medical practitioner.

The informed consent form was read and signed freely by all the patients recruited in this study and before signing the informed consent form. If the patient had any doubts about the

investigational product or the study procedure then it was resolved by the investigator in patients local and understandable language.

Results

At 12 clinical trial sites throughout India, a total of 159 patients completed the PMS study. Mean

TSS at baseline (day 1), before treating patient with the investigational product was 6.62. At visit 2, re-evaluation visit on day 3, the mean TSS was reduced to 3.55. The mean TSS at visit 3, conclusion visit on day 5, was further reduced to 0.68. Mean TSS at visit 1, 2 and 3 is graphically presented in figure 1 below.

Figure1: Mean TSS at visit 1, 2 and 3

The percentage reduction in the mean TSS at visit 2 and 3 as compared to the baseline was 46.24 % and 89.64 % respectively. Graphical presentation for the percentage reduction in the mean TSS at visit 2 and 3 was as presented in the fig. 2.

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

The data was extrapolated to the Likert type symptom severity Scale and the number of patients with the mild, moderate, severe and no symptoms of the common cold at visit 1, 2 and 3 were calculated and graphically presented in the fig. 3.

Figure 3: No. of Patients with no symptom, mild, moderate and severe intensity symptoms as per the Likert type symptom severity Scale at visit 1, 2 and 3

At visit 1, 83, 63 and 13 patients were of severe, moderate and mild intensity symptoms respectively. At visit 2 there was no patient of severe intensity symptoms and 91, 63 and 5 patients were of moderate intensity, mild intensity and no symptom respectively. At visit 3, 93, 60 and 6 patients were of no symptom, mild intensity symptom and moderate intensity symptoms

respectively. Through the study it was observed that, the patients has had less severity symptoms as compared to baseline in the post-baseline visits.

Safety Assessment:

Total 6 patients showed 10 episodes of adverse events which is presented in the tabular form below in the table 1.

Table 1: List of adverse drug reactions along with the no. of episodes reported and the no. of patients

Adverse Event	Number of patients	Number of episodes
Drowsiness	3	3
Hyperacidity	1	1
Dryness of mouth	2	6

All the reported adverse events were of mild intensity, expected and of non-serious nature.

Discussion:

Common cold is a self-limiting disease but it is also responsible for significant absenteeism in job and schools. For the treatment of common cold or allergic rhinitis there is no effective therapy but symptomatic treatment is advisable to reduce the absenteeism at job or school. Single drug therapy is not enough to give complete symptomatic relief to the patient of common cold so commonly the combination therapy of nasal decongestant, antipyretic and antihistaminic is given.⁽³⁾ This was a post marketing surveillance study conducted to analyze the safety and efficacy for the fixed-dose combination of the Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Chlorpheniramine Maleate 2 mg per tablet in the Indian patients of common cold. For this study total 180 patients were enrolled out of which 159 patients completed the study. At visit 1, the mean TSS was 6.62 which was reduced to 3.55 at visit 2 which was 46.24 % reduction as compared to the baseline. At visit 3 the mean TSS was 0.68 which was reduction of 89.64 % as compared to the baseline. At visit 1, 83 (52.20 %), 63 (39.62 %) and 13 (8.17 %) patients were of severe, moderate and mild intensity symptoms respectively. At visit 2 there was no patient of severe intensity symptoms and 91 (57.23 %), 63 (39.62 %) and 5 (3.14 %) patients were of moderate intensity, mild intensity and no symptom respectively. At visit 3, 93 (58.49 %), 60 (37.73 %) and 6 (3.77 %) patients were of no symptom, mild intensity symptom and moderate intensity symptoms. At visit 2 and 3 the major reduction in the no. of patients with the severe, moderate and mild intensity symptoms of common cold was observed. Below we have discussed some of the similar studies which were conducted before.

Kiran M et al. conducted a post marketing surveillance study with a study objective to evaluate the efficacy and safety for the fixed dose combination of Phenylephrine 5 mg, Paracetamol 125 mg, Chlorpheniramine Maleate 1 mg, Menthol 1 mg and Sodium Citrate 60 mg per 5 ml. The study was conducted on 220 Indian patients common cold of weight ranging between

8 to 40 kg and age above 2 years. Baseline efficacy assessment was done on day 1 and then after on day 3 and 5. Similar to the study we have conducted, TSS was used for efficacy evaluation. Mean TSS at day 1, 3 and 5 was found to be 5.66, 2.99 and 0.7 respectively. 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 Phenylephrine 5 mg, Paracetamol 125 mg, Chlorpheniramine Maleate 1 mg, Menthol 1 mg and Sodium Citrate 60 mg per 5 ml was efficacious as well as safe for the symptomatic treatment of common cold.⁽⁶⁾

Kiran M et al conducted a phase IV clinical trial to study the efficacy and safety for the combination of Levocetirizine, Phenylephrine and Paracetamol in the patients of common cold and allergic rhinitis. The study was completed on 201 patients in India. The study was conducted for the duration of 5 days for all the recruited patients. Efficacy and safety assessment was done in the clinical trial by the TSS which was extrapolated to the Likert type symptom severity scale and reported adverse events respectively. At baseline the mean TSS was 6.82 which was reduced to 3.62 at day 3 which was the reduction of 46.77 %. At day 5, the mean TSS was further reduced to 1.14 which was the reduction of 83.82 % as compared to baseline. Total 11.94 % patients reported adverse events of non-serious and expected nature. At the end of the study, it was concluded that the combination of Levocetirizine, Phenylephrine and Paracetamol was efficacious and safe for the symptomatic treatment of common cold and allergic rhinitis.⁽³⁾

The drawback of the research was that a common cold is a self-limiting disease and can be naturally cured in 10 days as per the literature.^(7,8) So to minimize the same, the clinical trial duration was kept 5 days so the maximum efficacy results presented in this paper were considered to be because of the investigational product.

Conclusion:

The fixed dose combination of Paracetamol 500 mg, Phenylephrine 10 mg and Chlorpheniramine Maleate 2 mg 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 was Sinarest New Tablet which is a fixed dose combination of Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg and Chlorpheniramine Maleate 2 mg per tablet which is manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd.

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