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

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Abstract:

Introduction: Common cold is Self-recovering respiratory diseases which can be caused by viral infection. As till date there is no treatment for the common cold and it is self-limiting in nature, symptomatic treatment is the only option. Symptomatic treatment of common cold with a single drug is not efficacious as compared to the multiple drug combination. Combination of antipyretic (Paracetamol), nasal decongestant (Phenylephrine) and anti-histaminic agent (Chlorpheniramine Maleate) can be used for the symptomatic treatment of common cold. This post marketing surveillance study was conducted to test the efficacy and safety for the fixed dose combination of Paracetamol 125mg, Phenylephrine Hydrochloride 2.5mg and Chlorpheniramine Maleate 1mg per ml in Indian patients of age 1 to 12 months.

Methodology: Out of 200 enrolled, 164 patients completed the study. Efficacy was evaluated by total symptom score (TSS) ranging from 0 to 10 where 0 was no symptom to 10 was the maximum tolerated symptoms. TSS was further extrapolated to four-point-Likert-type-symptom-severity-scale. Safety assessment was done by evaluation of adverse events reported by the patient.

Results: TSS was reduced from 5.91 on day 1 to 3.57 on day 3 and 1.47 on day 5. At day 3 and day 5 the percentage reduction in the TSS as compared to the baseline was 39.48 and 75.05 respectively. During the study only 8 episodes of ADRs were reported including sedation and drowsiness.

Conclusion: Combination of Paracetamol, Phenylephrine and Chlorpheniramine Maleate was found to be efficacious and safe for the treatment of common cold and allergic rhinitis.

Keywords: Paracetamol, Phenylephrine, Chlorpheniramine Maleate, Common Cold, Allergic Rhinitis.

Introduction:

Common cold is also known as Acute Coryza which majorly affects adults as well as children with recurrent morbidity. Although typically, it accounts for substantial job absence and first care visit. Common cold is also one of the most frequently encountered disease in clinical practices.⁽¹⁾ Adults have two to four episodes per year on an average, while young children may have as many as six to eight episodes per year. Flu, headache, body ache, running nose, blocked

nose and sneezing are common symptoms of a common cold.⁽²⁾ Allergic Rhinitis is a symptomatic nasal condition triggered by IgE-mediated hypersensitivity reactions to allergens. It is characterised by four cardinal symptoms including watery rhinorrhoea, nasal congestion, nasal itching, and sneezing. While allergic rhinitis is not as frequent as common cold, it still has a prevalence of 10-30% in adults and nearly 40% in children in the United States.⁽³⁾

Common cold is a self-limiting disease so the treatment should focus on symptomatic relief as there is no effective antivirals for the treatment of common cold.⁽⁴⁾ Optimum symptomatic relief from the single drug therapy is not possible which is why the combination therapy is always preferred by the healthcare professionals for the symptomatic treatment. As per the Cochrane review, guidelines of DPHHS, Picon PD et al and Eccles R et al the combination of antihistamines, decongestants and analgesics can provide significant symptomatic relief in common cold.⁽⁵⁾ So accordingly, the combination of Paracetamol (analgesic), Chlorpheniramine Maleate (antihistamine) and Phenylephrine (decongestants) can be used for the symptomatic treatment of common cold.

Paracetamol or Acetaminophen is one of the most commonly known Non-Steroidal Anti-Inflammatory Drug (NSAID) which has a good antipyretic action. Paracetamol is useful for the symptomatic treatment of common cold including fever, body ache and headache. It does not causes gastric irritation, depress respiration or alter acid base balance.⁽⁶⁾ 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.⁽⁷⁾ Phenylephrine is a nasal decongestant. It is selective agonist of the alpha 1-adrenergic receptor. Activation of these receptors by distinct binding of the sympathomimetic agent to the binding site of the receptor or by enhanced release of norepinephrine leads to vasoconstriction that alleviates the cause of nasal blockage due to inflammation. Such vasoconstriction leads to shrinkage of the tissue by decreasing blood flow through the nasal mucosa. Phenylephrine is effective in the treatment of common cold symptoms including blocked nose or nasal congestion.⁽⁸⁾ Chlorpheniramine maleate (CPM) is a first-generation antihistaminic agent which is generally prescribed for the treatment of Common Cold. It competitively binds to the vascular tunica medius H1 receptor in nasal mucosa which avoids

vasoactive response to histamine. The anti-histaminic activity of CPM in the nasal mucosa translates to its anti-allergic and anti-inflammatory action. Anticholinergic activity of CPM is also responsible for reducing the number of infectious nasal discharges.⁽⁹⁾

This study was conducted to test the efficacy and safety for the fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml in the Indian patients of common cold and allergic rhinitis of age 1 to 12 months old.

Methodology:

Eleven paediatric specialty clinical trial sites were selected for the conduct of post marketing surveillance study. At all the clinical trial sites post graduate paediatric speciality clinical trial investigators were selected as the study was conducted on paediatric population.

Inclusion and Exclusion Criteria:

As per the study protocol designed by the sponsor, the only patients who meet the inclusion and exclusion criteria were recruited for the study by the investigator. As per the inclusion criteria, patients of both gender of age below 1 year and having body weight between 2.5 to 11.8 kg, having confirmed diagnosis of common cold or allergic rhinitis whose guardians were ready to strictly adhere to the study procedure were recruited for the study.

Patients hypersensitive to the investigational product, patients having hypertension (as the investigational product contains Phenylephrine which may contribute to an increase in BP due to vasoconstriction), Also the guardian of the patient who could not adhered to the protocol including mentally ill or with psychological problems were excluded from the study.

Investigational product:

The investigational product used for the study was the fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml. The

investigational product was provided to all the patients at no cost by the investigator and the investigational product was provided to the investigator by the sponsor.

Study design:

This post marketing surveillance study was of user initiated, open label and multicentric nature which was conducted to test the efficacy and safety for the fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml as a part of pharmacovigilance activity. As it was multicentric, the study was conducted at 11 clinical trial sites all across the India. All clinical trial sites selected were of paediatric speciality as the study was performed on paediatric population.

Study Procedure:

Patients were recruited for the study by the investigator as per the inclusion and exclusion criteria. Before recruiting the patients to the multicentric post marketing surveillance study, guardians of the patients were well informed about the study procedures and the investigational product and they were given time to take a decision to whether to get recruited in the study or not, even if they had any doubt about the study procedure or the investigational product then the same were resolved by the investigator. All the communication was done to the guardians of the patient by the investigator was in understandable language by the guardian of the patient. After recruitment of the patient to this study, all the necessary information was recorded by the investigator. Investigational product was provided to the guardian of the patient and was asked to give it to the patient in the dose as mentioned in the table below.

Table 1: Dose of the investigational product in which the guardian of the patient was asked to give it to the patient

Weight	Age	Dose
2.5 – 9.7 kg	1-6 months	0.2 ml thrice in day / quarterly in day
6.7 – 11.8 kg	7-12 months	0.2 – 0.4 ml thrice in day / quarterly in day

Guardian of the patient were advised to keep a register of everyday symptoms. In case of any safety-related complications, adverse events the patient could be removed from the study by the investigator by his choice and could be treated according to the severity of the symptoms. All the patients recruited in the study were asked to visit the clinical trial site on 3 visits out of which visit 1 was the baseline visit, visit 2 was the re-evaluation visit on day 3 and last was the conclusion visit on day 5.

Concomitant therapy:

During the study period, no pharmacological intervention other than investigational product was permitted but, non-pharmacological measures were permitted.

Efficacy Assessment:

Efficacy assessment was done by total symptom score (TSS) which was recorded on total symptom score scale (TSS scale). At all the visits, symptoms of common cold or allergic rhinitis experienced by the patient were recorded on TSS scale ranging from 0 to 10 where 0 was no symptom to 10 was the highest tolerated symptoms. TSS at all the visits were recorded for all the patients and was further extrapolated to Likert-type symptom severity scale as no symptoms (0 on TSS scale), mild intensity symptom (1-3 on TSS scale), moderate intensity symptom (4-6 on TSS scale) and severe intensity symptom (7-10 on TSS scale).

Safety assessment:

Guardians of all the recruited patients for the study were asked to report the adverse events if any. All the adverse events were reported by the

investigator to the sponsor within stipulated time and accordingly the causality assessment was done.

Regulatory Matters:

fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml has been approved for manufacturing and marketing in India and it is categorised under schedule H. Also as all the patients recruited in this study was of age below 1 year, the consent for the study was taken by the guardian of the patient and all the

guardians of the patients were well informed about the study procedures and the investigational product.

Results:

At 11 clinical trial sites, 164 patients completed the study. At day 1 (baseline visit) the mean TSS was 5.914 which was decreased to 3.579 at re-evaluation visit which was day 3 and was further decreased to 1.475 at conclusion visit which was day 5. Graphical presentation for the mean TSS at visit 1, 2 and 3 is provided in figure 1.

Figure 1: Mean Total Symptom Score

Also, the percentage decrease in mean TSS at re-evaluation and conclusion visit as compared to baseline visit was calculated, at visit 2 (day 3) and visit 3 (day 5) there was 39.484 % and 75.051 % reduction in the mean TSS as compared to the baseline which was graphically presented as mentioned below in fig 2.

Figure 2: Percent Reduction in mean total symptom score as compared to baseline

The TSS data was further extrapolated to Likert-type symptom severity scale as patients with 0, 1 to 3, 4 to 6 and 7 to 10 were considered as patients of no symptoms, mild intensity symptoms, moderate intensity symptoms and severe intensity symptoms of common cold respectively. All the patients who completed the study of different TSS score at visit 1, 2 and 3 as per the Likert-type symptom severity scale of different severity is graphically presented in fig. 3.

Figure 3: No. of Patients with mild, moderate and severe intensity symptoms of common cold

At baseline visit, on day 1 out of 164 patients, 50 patients had severe intensity symptoms of TSS between 7 to 10, 100 patients had moderate intensity symptoms of TSS between 4 to 6 and 14 patients had mild intensity symptoms of TSS from 1 to 3. At re-evaluation visit, on day 3, 21 (6.25 %) clinical patients had no symptom of TSS 0, 77 patients had mild intensity symptoms of TSS ranging from 1 to 3, 87 patients had moderate symptoms of TSS from 4 to 6 and no patient had severe intensity symptoms of TSS from 7 to 10. At conclusion visit, on day 5, 95 patients had no symptom of TSS 0, 69 patients had mild intensity symptoms of TSS 1 to 3 and no patient had moderate or severe intensity symptoms.

Safety Assessment:

In the total population of patients recruited for the post marketing surveillance study, 8 adverse drug reactions were reported by 6 patients and all 8 episodes reported were of sedation and drowsiness as adverse events which was non-serious and expected due to the presence of Chlorpheniramine Maleate in the investigational product.

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 to the patient by treating the symptoms of common cold. Fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml can be used for the symptomatic relief from the common cold as mentioned in the introduction part. This post marketing surveillance 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 164 patients completed the study and remaining were lost to follow-up. Efficacy assessment was done by the TSS scale which was an 11-point scale and was further extrapolated to Likert-type symptom severity scale. During the study it was observed that, there was decrease in TSS in all the patients during post marketing surveillance study. Mean TSS reduced from 5.91 to 3.57 from visit 1 (baseline) to visit 2

and from 3.57 to 1.47 in the next 2 days. The percent reduction observed on day 3 was 39.48% from baseline evaluation. The overall reduction in TSS in 5 days was average 75.05 % in all the patients. Study data showed that the fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml was found to be efficacious for the symptomatic treatment of common cold. In the total 200 recruited patients, 8 episodes of adverse drug reaction were reported by 6 patients and all of them were sedation and drowsiness which was of expected and non-serious nature. Below we have also discussed some of the studies which reference was used for the conduct of this study.

Picon et al. conducted a phase III clinical trial for the combination of Chlorpheniramine maleate, Paracetamol and Phenylephrine to study its efficacy and safety for the treatment of common cold in 146 patients for the study duration of 10 days. 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 clinical trial duration of 10 days. Also, the adverse events reported in both the group of patients were equivalent to each other. Study concluded that the combination of Phenylephrine, Paracetamol and Chlorpheniramine maleate was better as compared to placebo for the treatment of common cold and flulike syndrome in adults.⁽¹⁰⁾

A post marketing surveillance study was conducted to test the efficacy and safety for the combination of Levocetirizine and Phenylephrine for the treatment of allergic rhinitis. TSS was used for the efficacy assessment and reported adverse events for the safety assessment. Total 172 patients were enrolled and out of which 152 patients completed the study. The reduction in TSS was found from 7.65 at day 1 to 3.65 at day 3 to 1.28 at day 5. Also in the study it was found that majority of the patients had >50% reduction in TSS. All the adverse events reported were of mild intensity and expected in nature and no serious adverse event was found to be reported. It was concluded by the author, that the

combination of Levocetirizine and Phenylephrine was efficacious and safe for the treatment of allergic rhinitis.⁽¹¹⁾

The downside of the research was that the common cold can spontaneously resolve by itself which makes it as a self-limiting illness. Several papers state that common cold resolves in around 7 days,⁽¹¹⁾ so the benefit of the investigational product was mainly due to the benefits offered on day 5. We have attempted to minimize this weakness by keeping the study duration of 5 days.

Conclusion:

The fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml was found to be efficacious and safe for the symptomatic treatment of common cold and allergic rhinitis in paediatric patients of age below 1 year.

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Disclosure:

This study was conducted as a part of pharmacovigilance activity for the fixed dose combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml which is available in India under the brand name Sinarest Oral Drops which is manufactured and marketed by Centaur Pharmaceuticals Pvt Ltd.

Reference:

1. Vitetta L, Du S. The common cold. Journal of Complementary Medicine: CM, The. 2008 Sep;7(5):56.

2. Arroll B. Non-antibiotic treatments for upper-respiratory tract infections (common cold). *Respiratory medicine*. 2005 Dec 1;99(12):1477-84.
3. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *Journal of allergy and clinical immunology*. 2001 Nov 1;108(5):S147-334.
4. Kiran MD, Vakharia MP, Pawaskar LJ, Sheikh SN. Efficacy and safety of a fixed dose combination of paracetamol, chlorpheniramine maleate and phenylephrine in treatment of common cold: a phase IV, open-labelled, multi-centric study. *International Journal of basic and clinical pharmacology*. 2019 January;8(1):34-38
5. Kiran M, Pawaskar L, George S, Yadav P. An open-labeled, multicentric, post-marketing surveillance (pms) to substantiate the safety and efficacy of sinarest syrup in patients of common cold. 2017;6(7):1559–69.
6. Kiran M, Pawaskar L, Yadav P. Efficacy and Safety of a combination of Paracetamol, Levocetirizine and Phenylephrine in the symptomatic treatment of Common Cold and Allergic Rhinitis: Phase IV Clinical Study. *International Journal of Current Research in Medical Sciences*3. 2017;1:53-9.
7. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*. 2013 Jun;21(3):201-32.
8. Kiran MD, Pawaskar LJ. Safety and Efficacy of a combination of Paracetamol, Phenylephrine and Fexofenadine in adult patients of Common Cold and Allergic Rhinitis: Phase IV Study. *World Journal of Pharmaceutical Research*. 2017 Feb 16;6(4):1624-34..
9. Peterlin MF, Keyser RE, Andres FF, Sherman G. Nonprescription chlorpheniramine maleate and submaximal exercise responses. *Archives of physical medicine and rehabilitation*. 1998 Jul 1;79(7):827-31.
10. Picon PD, Costa MB, da Veiga Picon R, Fendt LC, Suksteris ML, Saccilotto IC, Dornelles AD, Schmidt LF. Symptomatic treatment of the common cold with a fixed-dose combination of paracetamol, chlorphenamine and phenylephrine: a randomized, placebo-controlled trial. *BMC infectious diseases*. 2013 Dec;13(1):1-8.
11. Kiran M, Yadav P, Pawaskar L, George S. An open-labeled, multicentric, post-marketing surveillance (pms) to substantiate the safety and efficacy of Sinarest Levo Syrup in patients of common cold and allergic rhinitis. *European journal of pharmaceutical and medical research*. 2017 4(8);535-538.