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Efficacy And Safety For A Combination Of Paracetamol, Chlorpheniramine Maleate And Phenylephrine In The Symptomatic Treatment Of Common Cold And Allergic Rhinitis In Infants: Phase Iv Clinical Study

Dr. Mayuresh Kiran*, Lalit Pawaskar#

*Vice President, Medical Services, Centaur Pharmaceuticals Pvt. Ltd *

#Executive, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd #

Corresponding Author: Dr. Mayuresh Kiran**,** Vice President, Medical Services, Centaur Pharmaceuticals Pvt. Ltd, Santacruz – East,Mumbai

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Abstract

Common cold and allergic rhinitis are most common diseases in Indian clinical practises. Both are self-limiting but it accounts for loss of school and work days. Symptomatic therapy is often used to treat the symptoms. Combination of anti-histaminic, anti-inflammatory/ analgesic/ antipyretic and nasal decongestant is popular in the treatment of common cold and allergic rhinitis. This Phase IV study was conducted to evaluate the efficacy and safety for the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate for the treatment of common cold and allergic rhinitis Of total 200 enrolled patients, 169 patients completed the study. Efficacy assessment was done by reduction in Total Symptom Score (TSS) extrapolated to four point Likert-type scales. Safety assessment was done by analysing the adverse events through the study. At visit 1 (baseline) mean TSS was 6.165 which was reduced to 2.822 at visit 2 (day 3) and further reduced to 0.834 at visit 3 (day 5). At visit 2 and visit 3 there was reduction of 54.22% and 86.46% respectively in TSS as compared to baseline. Adverse events were observed in only 2.366% of total population through the clinical study. Combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate is safe and effective for the treatment of common cold and allergic rhinitis.

Key words:

Paracetamol, Phenylephrine, Chlorpheniramine maleate, Common cold, allergic rhinitis, Efficacy, safety.

Introduction

Common cold is a worldwide most frequently encountered viral respiratory disease which is self-limiting in nature. [1] Most of the patients suffer from common cold is due to viral infection of upper respiratory tract. Common cold is caused by so many different types of viruses, which causes similar symptoms. The same virus can cause another episode of common cold after re-exposure. However, the second illness experienced by the patient is of usually milder intensity and lasts for a shorter duration as compared to first one. Some of the viruses can also have seasonal patterns. [2] Common cold of viral origin is a self-limited disease which usually takes up to 10 days to cure by itself; therefore it is treated symptomatically. [3]

Allergic rhinitis is clinically defined by nasal hypersensitivity symptoms persuaded 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. [4] Allergic rhinitis is nasal hypersensitivity symptoms persuaded by an immunologically mediated (predominantly IgE-dependent) inflammation as mucous membrane gets exposed to allergens. Symptoms of allergic rhinitis include postnasal drip, nasal itching, rhinorrhoea, nasal blockage or obstruction, paranasal/nasal pain and sneezing that are naturally reversible or under treatment. [4] As per the United States Attitudes of Consumers toward Health, Cough, and Cold (ACHOO) survey, common cold adversely impacts on productivity and daily life of individual and causes absenteeism. [5]

The signs and symptoms of common cold overlap with those of other conditions like allergic rhinitis presenting similarly. [6] Common cold is generally caused by the viruses and as per the DPHHS guidelines it is self-limited and it will go away with time and only symptomatic treatment is needed. Common cold and allergic rhinitis. [2] As per the Cochrane review,[7] DPHHS guidelines,[2] Picon PD et al[6] and Eccles R et al [8] combination of analgesic, antihistamine and decongestant provides benefits in adults for multi symptom relief in common cold and allergic rhinitis.

Paracetamol is one of the most popular and most commonly used antipyretic, analgesic and anti-inflammatory drug used all around the world and also available as an OTC, both in single dose or in fixed dose combination preparations. [9] It does not alter acid base balance, cause gastric irritation or depress respiration. So Paracetamol is commonly used for symptomatic treatment of common cold to treat most of the symptoms like headache, bodyache and fever. And it can also be used for the symptomatic treatment of allergic rhinitis including nasal and paranasal pain. [10]

As per CHPA docket no. 2007P-0047 Phenylephrine is a selective adrenergic receptor agonist which is an effective nasal decongestant that can be orally administered. Its core and direct effect is vasoconstriction of capacitance blood vessels present in the nasal mucosa that decreased blood vessel diameter gives nasal decongestion action. [11]

Common cold can be treated by the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate. Such combinations are also available as over the counter (OTC) in developed as well as highly regulated countries like New Zealand, Australia, US, etc. [3] This Phase IV (Post-Marketing Surveillance) study was conducted to document the efficacy and safety for the combination of Paracetamol 125 mg, Phenylephrine 2.5 mg and Chlorpheniramine maleate 1 mg per ml of study drops for the treatment of common cold of infants.

Materials and methods:

This phase IV clinical trial was conducted with paediatric speciality investigators all across India. This clinical trial was started in the month of November 2016 and completed in February 2017. Total 200 patients were recruited for the study out of which 169 patients completed and 31 patients were lost to follow-up.

Inclusion and Exclusion criteria

Patients with confirmed diagnosis of common cold and / or allergic rhinitis (having minimum 4 out of 9 symptoms of sore throat, sneezing, headache, fever, body-ache, rhinorrhoea, nasal congestion, dysphonia and malaise), male as well as female patients of age under 1 year, whose body weight was up to 11.8 kg were shortlisted for the clinical trial. And in the final shortlisted patients the patients who were ready to sign the informed consent

form and strictly adhere to the protocol were recruited for the clinical trial

Patients having hypersensitivity to any individual study drug or to any excipient present in the dosage form or patients suffering from hepatic or renal dysfunction were excluded as the study drug combination contains Paracetamol. Also the patients who were not ready to adhere to the protocol were excluded from the study.

Sample size

A Phase III clinical trial for the same drug combination was conducted on 146 Brazilian patients; 73 patients were treated by the combination and remaining by placebo.[6] As it was a non comparative Phase IV clinical trial, sample size was decided to keep more than 146 and kept 200. To account the lost to follow-up of 15 %, finally study was completed with 169 patient.

Study Intervention

Trial drug combination of Paracetamol 125 mg, Phenylephrine Hydrochloride 2.5 mg and Chlorpheniramine Maleate 1 mg per ml was provided by the sponsor. All the patients were dispensed with 10 ml physician sample pack of trial drug combination drops. All the samples were dispensed by the investigator to guardian of the patient at no cost. Guardians of the patients were advised to give study drug combination drops to the infants as mentioned in the table no. 1.

Table 1: dose of the trial drug combination to be administered to the patient by the guardian

Weight	Age	Dose
2.5 – 9.7 kg	1-6 months	0.2 ml tid / qid
6.7 – 11.8 kg	7-12 months	0.2 – 0.4 ml tid / qid

Study procedure

Clinical trial duration was kept 5 days. Only the patients who met with the decided inclusion and exclusion criteria were recruited for the clinical trial. Detailed medical history was obtained from all the patients and also physical examination was conducted by the investigators. Investigators having post graduate degree in Paediatrics were selected as investigators. Before recruiting any patient into the clinical trial all the investigators physically examined each patient and also the detailed history was obtained. Patients were dispensed with 10 ml physician sample bottle of trial drug combination drops. Every patient was asked to maintain the diary to record if any adverse event experienced during the study duration after started taking the trial drug combination drops. 3 visits were planned for each patient in which the first visit (V1) was baseline visit which was day at which the patient is recruited in the clinical trial as per the inclusion and exclusion criteria before taking the trial drug combination drops. Second visit (V2) was revaluation visit conducted on day 3 and visit 3 (V3) was done on day 5 which was conclusion visit. Adverse events occurring and total symptom score (TSS) were recorded on case report form (CRF) along with the detailed medical history obtained by the patient and physical examination done by the investigator. Guardians were instructed to discontinue the trial drug combination in case of any adverse event of severe intensity.

Concomitant therapy

No Pharmacological intervention or any medication including nasal decongestants (any aromatic oils or drops or sprays), antibiotics, multi-vitamins, multiminerals or any medication other than study drug combination were allowed during study duration of 5 days. Non-Pharmacological interventions like drinking of hot water at regular intervals or steam inhalation were allowed and encouraged during the clinical trial duration of 5 days.

Efficacy assessment

The primary efficacy assessment was done by analysing the reduction in TSS which was a score of all the symptoms related to common cold or allergic rhinitis on

an 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 where 0 on TSS scale means no symptoms, 1 to 3 on TSS scale means mild symptoms, 4-6 on TSS scale means moderate symptoms and 7-10 on TSS means severe symptoms. In primary efficacy assessment, average TSS of all the patients at each visit and percent reduction in average TSS at visit 2 and visit 3 as compared to baseline was analysed. And in secondary efficacy assessment the number of mild, moderate and severe patients at visit 1, 2 and 3 were calculated.

Safety assessment

Throughout the clinical study patients were asked by the investigators for any adverse events and if present noted in the case report form (CRF) during each post-dose visit. Noted adverse events were classified into 2 categories as serious or non-serious adverse events. Adverse event were classified as drug related or nondrug related adverse events by using Naranjo's scale of probability. Adverse events observed were followed up and treated if necessary by the investigators till their resolution.

Regulatory matters

The said combination is available in India and classified as schedule H drug which means it should be sold only in the presence of prescription of a registered medical practitioner. All the patients participated in the study have read and signed the ICF. The protocol, ICF, CRF, investigators undertaking form, investigators CV, ethics committee registration certificates and investigators medical registration certificates (including post-graduation certificates and certificate of registration of additional qualification) were submitted to DCGI office (Drug Controller General of India), Central Drugs Standard Control Organization (CDSCO) and are registered under ref. no. **2506/17**.

Results

A total of 200 patients were enrolled at 11 centers across India, 169 patients completed the study and were analysed and 31 lost to follow-up. Other demographic characteristics are in Table 2.

Table 2: Demographic Characteristics of the patients recruited for the study.

Mean age of patients	7.5 months
Males	87
Females	82

Efficacy analysis

Mean TSS at all the visits was calculated and at the same time percent reduction in TSS at visit 2 and visit 3 as compared to baseline was calculated. Mena TSS at baseline (visit 1) was 6.165 which was reduced to 2.822 at visit 2 and there was reduction of 54.22 % in TSS as compared to baseline. At visit 3 TSS was 0.834 so there was reduction of 86.46 % in TSS as compared to baseline. Mean TSS score at all the visits and percentage reduction in TSS score at visit 2 and visit 3 as compared to visit 1 is presented graphically in figure 1 and figure 2 respectively. By extrapolating the TSS to Likert scale at visit 1 the mean TSS was of moderate intensity which was reduced to mild at visit 3.

At visit 1 out of total 169 patients 102 patients were of severe intensity, 47 of moderate and 20 of mild intensity symptoms of common cold and allergic rhinitis. At visit 2 the number of patients of severe intensity were reduced to 41, of moderate intensity were reduced to 14 and of mild intensity patients were 103 and 11 patients were having no symptoms. At visit 3, there was only 1 patient of severe intensity, 7 patients of moderate intensity, 65 of mild and 96 patients were having no symptoms. Patients of different intensity of common cold and / or allergic rhinitis along with the percentage is presented graphically in figure no. 3.

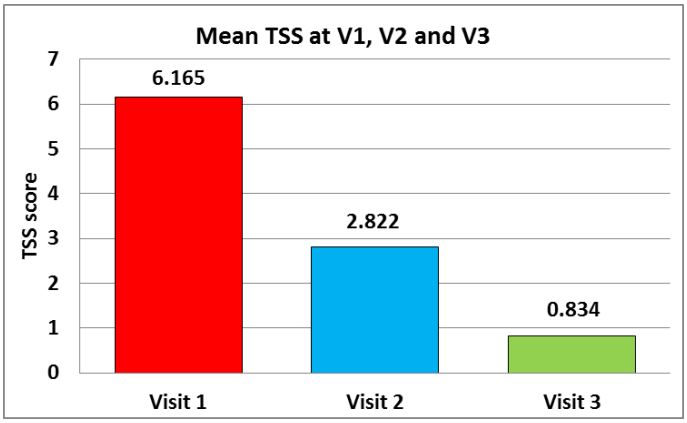

Fig. 1: Mean TSS score at visit 1, visit 2 and visit 3

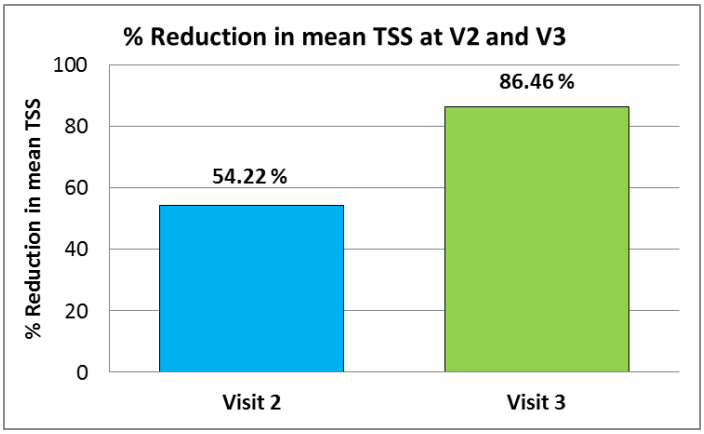

Fig. 2: Percentage reduction in mean TSS score at visit 2 and visit 3 as compared to visit 1

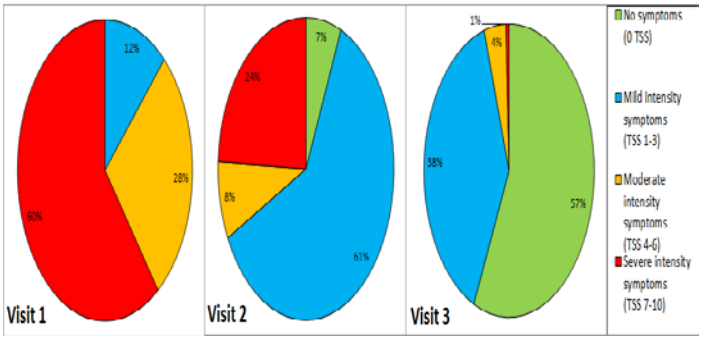

Fig. 3: Percentage of patients having no, mild, moderate and severe intensity symptoms of common cold or allergic rhinitis.

Safety analysis

The overall drug related adverse event incidences were 21 seen in 4 patients i.e. 2.336 % of total population. The list of adverse events with the number of patients is mentioned in Table 3 as below and presented graphically in figure 4.

Table 3: List of adverse events, no of episodes and no. of patients experienced adverse events

Adverse events	No. of patients	No. of patients	% of patients
Sedation and Drowsiness	12	3	1.775 %
Nausea	5	2	1.183 %
Dryness of mouth	4	3	1.775 %
Total	**21**	**4**	**2.336 %**

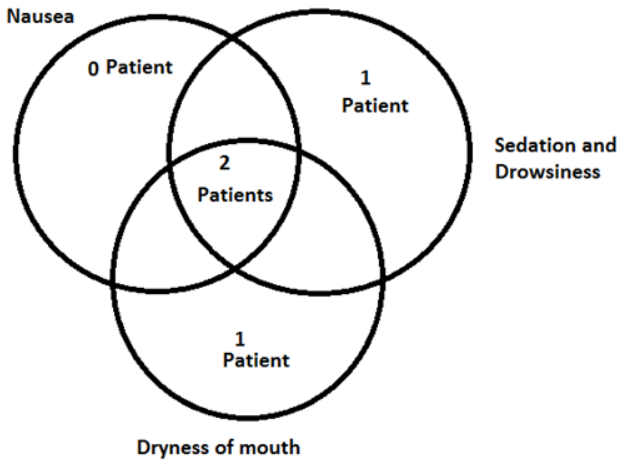

Fig. 4: Adverse events experienced by the number of patient

Discussion

Common cold is generally a self-limiting disease but it is responsible for significant absenteeism in job as well as schools. Symptomatic control treatment helps to reduce the number of days missed because of common cold or allergic rhinitis hence treatment is focused towards symptom control.

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 and allergic rhinitis for symptom assessment. [3]

At baseline mean TSS was 6.165 which was reduced to 2.822 at day 3 and further it was reduced to 0.834 at day 5. So at day 3 there was reduction of 54.22 % and at day 5 there was reduction of 86.46 % as compared to the baseline. So by extrapolating the TSS to Likert scale it can say that at baseline as per the mean TSS patients were having symptoms of moderate intensity which was reduced to mild at the conclusion visit i.e. at day 5.

As per the Likert scale, at visit 1 there were 102 patients of severe intensity (TSS 7 to 10), 47 patients of moderate intensity (TSS 4 to 6) and 20 of mild intensity (1 to 3) symptoms. At visit 2 the no. of patients of severe intensity were decreased to 41, no. of patients of moderate intensity were decreased to 14 and of mild intensity were increased to 103 and 11 patients had no symptom which can be counted as completely cured patients. At visit 3 there was only 1 and 7 patients of severe and moderate intensity respectively, 65 of mild intensity and 96 patients were completely cured.

Picon et al., [6] conducted a double-blind, randomized, placebo-controlled phase III clinical trial on Brazilian patients of age 18 to 60 years for the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate for the treatment of common cold. The clinical trial was conducted on 146 patients and compared efficacy as well as safety of the combination with the placebo. Mean total symptom at the baseline was 14.09 which was reduced to 3.54 at day 10 at the end of the study. And in case of placebo the reduction in total symptom score was from 14.23 to 4.64 at the end of the study at day 10. Same adverse events were observed in both the groups. So finally it was concluded that the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate is better than placebo in the treatment of flulike syndrome and common cold. [6]

A Cochrane review 7 analysed 32 studies or meta-analysis of 8930 patients for the treatment of common cold, inferring that decongestant, antihistamine and analgesic combinations have some general benefit in older childrens as well as adults for the treatment of common cold. Chlorpheniramine maleate, Paracetamol and Phenylephrine are mentioned in the list provided for antihistamine-analgesic-decongestant. [7]

Kiran M et al.[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. [10]

Kiran M et al.[12] 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. [12]

The limitation of the study was, common cold and allergic rhinitis are self-limiting diseases and can be resolved by itself. Trial drug combination may not be fully responsible for TSS reduction. So as to minimize this limitation the study duration was kept 5 days unlike earlier study where

it was 10 days. So the benefits offered by trial drug combination were major as compared to auto limitation of the disease.

Conclusion

Combination of Paracetamol 125 mg, Phenylephrine 2.5 mg and Chlorpheniramine Maleate 1 mg per ml provides optimum symptomatic relief and is safe for use in the symptomatic management of common cold and allergic rhinitis in infants.

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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 Oral Drops marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

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