ISSN: 2395-6429

INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

IJCMPR

Available Online at http://www.journalcmpr.com

DOI: http://dx.doi.org/10.24327/23956429.ijcmpr20170094

RESEARCH ARTICLE

EFFICACY AND SAFETY FOR A COMBINATION OF PARACETAMOL, CHLORPHENIRAMINE MALEATE, PHENYLEPHRINE, SODIUM CITRATE AND MENTHOL IN THE SYMPTOMATIC TREATMENT OF COMMON COLD AND ALLERGIC RHINITIS: PHASE IV CLINICAL STUDY

Mayuresh Kiran[1]., Lalit Pawaskar[2] and Shruthi George[3]

[1,3]Medical Services, Centaur Pharmaceuticals Pvt. Ltd
[2]Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd

ARTICLE INFO

Article History:

Received 20th February, 2017
Received in revised form 15th March, 2017
Accepted 12th April, 2017
Published online 28th May, 2017

Key words:

Paracetamol, Chlorpheniramine maleate, Phenylephrine, common cold, Allergic rhinitis

ABSTRACT

Introduction and Background: Common cold and allergic rhinitis are most frequently encountered diseases in clinical practices. It is self-limiting but it accounts for major loss of school or work days so symptomatic treatment is often employed. A combination of Paracetamol as an anti-inflammatory and antipyeretic, Chlorpheniramine maleate, an anti-histaminic and Phenylephrine as a nasal decongestant is popular in the treatment of common cold. The study medication also contains Sodium citrate which liquefies mucus and helps expectoration and menthol has cooling and soothing effect. This Phase IV study was conducted for evaluating the efficacy and safety of a combination of Paracetamol, Phenylephrine, Chlorpheniramine maleate, Sodium Citrate and Menthol in the treatment of common cold.

Methodology: Out of total 216 patients, 162 completed the study. Efficacy assessment was made by analysing the reduction in TSS and four point Likert-type scales. Safety assessment was made by analysing the adverse events during trial.

Results: Reduction in TSS from 6.10 (baseline) to 2.87 (day 3) and 0.48 (day 5). One point reduction in Likert-type symptom scale from Moderate to Mild took in just 3 days. Most of the patients had >50% reduction in total symptom score at all visits and 67 % patients had complete relief from the symptoms at the end of clinical trial. 50 episodes of adverse events occurred and were of mild intensity.

Conclusion: A combination of Chlorpheniramine maleate, Paracetamol, Phenylephrine, Sodium Citrate and Menthol is safe and effective in the treatment of common cold and allergic rhinitis.

INTRODUCTION

Acute Coryza is also known as common cold which is a major and recurrent cause of morbidity which affects both, children and adults.[1] Common cold is mostly caused due to viral infection of upper respiratory tract. Most of the times it is caused due to viruses belonging to different families among which rhinoviruses are most common. Sore throat, sneezing, acute cough, nasal congestion, nasal stuffiness and discharge are most common symptoms of common cold.[2] Common cold of viral infection origin is a self-limited disease which usually lasts up to 10 days; therefore, management of it is directed by symptomatic treatment.[3]

Allergic rhinitis is nasal hypersensitivity symptom induced by an immunologically mediated inflammation (most often IgE-dependent) after the exposure of the nasal mucous membranes to an offending allergen. Nasal blockage or obstruction, nasal itching, postnasal drip, paranasal/ nasal pain and sneezing are the most common symptoms of allergic rhinitis.[4]

As per the guidelines of DPHHS [5], Cochrane review[6], Picon PD *et al*[7] and Eccles R[8] *et al* combination of analgesics, decongestants and antihistamines provides benefits for multi symptom relief in common cold and allergic rhinitis. Paracetamol belongs to Nonsteroidal Anti-inflammatory Drug (NSAID) category and it exhibits good central analgesic and antipyretic action. It does not cause gastric irritation, alter acid-base balance or depress respiration. So, Paracetamol is useful in the symptomatic treatment of common cold like - bodyache, headache or fever.[1] Chlorpheniramine maleate (CPM) is a type of 1st generation antihistaminic agents. CPM competitively binds to the H1 receptors of the vascular tunica medius located in the nasal mucosa to prevent the histamine vasoreactive response. This mechanism is responsible for its anti-inflammatory as well as anti-allergic action in the nasal mucosa. The anti-cholinergic action of CPM is also responsible for decrease in the nasal discharge. Thus CPM is useful for controlling the symptoms related common cold like-

sneezing and Running Nose. Phenylephrine is a selective adrenergic receptor agonist, which is an effective nasal decongestant that can be administered by intranasal or oral route 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 which leads to nasal decongestion.[9]

Common cold is often treated by the combination of Chlorpheniramine maleate, Paracetamol and Phenylephrine. Such combinations are also available as OTC in developed as well as highly regulated countries like Australia, New Zealand, US, etc. This Phase IV (Post-Marketing Surveillance) study was conducted to document the efficacy and safety of the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate in the treatment of common cold.

MATERIALS AND METHODS

This was a Phase IV Clinical study conducted with 11 Paediatric speciality investigators all across the India form November 2016 to February 2017. Total 216 patients were recruited for the study out of which 162 patients completed and 54 patients were lost to follow-up.

Inclusion and Exclusion criteria

Patients with confirmed diagnosis of common cold or allergic rhinitis (having 4 out of 9 symptoms of headache, fever, bodyache, nasal congestion, rhinorrhea, sneezing, sore throat, dysphonia and malaise) were enrolled in the study. Patients of both the genders (male as well as female) having age of 2 to 12 years and having weight of 12 to 41.5 Kg 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 having hypersensitivity to any individual study drug of the combination or to any of the ingredient present in the dosage form and patients suffering from hepatic or renal dysfunction were excluded as the study drug combination contains Paracetamol.

Sample size

A Phase III clinical study was conducted in Brazil for the same combination in 146 patients [7]; 73 patients were treated by the combination and remaining by placebo. This being a non-comparative Phase IV study, hence a sample size was decided to keep more than 146 and kept 216. To account the loss to follow-up of 20%, finally 216 patients were recruited in this study but 54 patients were left and actual study was conducted on 162 patients.

Study Intervention

Study drug-Suspension containing combination of Paracetamol 250 mg, Phenylephrine Hydrochloride 5 mg, Chlorpheniramine Maleate 2 mg, Sodium Citrate 60 mg and Menthol 1 mg per 5 ml was provided by the sponsor. Two 50 ml bottles of study medication provided to patient at a free of cost. All the samples were dispensed by the investigator to the patient. Study dosage and administration-Patients were advised to take study drug medication as mentioned in the table no. 1.

Table no. 1

Weight in Kg	Age	Dose
12 - 18	2-5 years	2.5 ml td
20-41.5	6-12 years	5 ml td

Study procedure

The study duration was kept 5 days. Patients of common cold or allergic rhinitis who met with the decided exclusion and inclusion criteria were recruited for the clinical study. A detailed medical history was obtained from each patient and physical examination was conducted by the investigators. The only investigators holding post-graduate degree in ENT were involved as an investigator for conducting this study. Patients were dispensed with two 50 ml bottles of study drug medication by investigators and asked to consume in the dose of 2.5 ml thrice a day for 2 to 5 years of childrens whose weight is in the range of 12 to 18 kg and 5 ml thrice a day for 6 to 12 years of childrens whose weight is in the range of 20 to 41.5 kg. 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-the first visit was baseline visit (V1) on day 1 before treating patient with the study drug combination, the second visit was revaluation visit (V2) on day 3 and third visit was 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 any medication including nasal decongestants (sprays or drops or any aromatic oils), multi-vitamins, multiminerals or antibiotics other than study drug combination were allowed during study duration of 5 days. Non-Pharmacological interventions like steam inhalation or drinking of hot water at regular intervals were allowed and encouraged during the study period.

Efficacy assessment

The primary 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 secondary assessment, average TSS of all the patients at each visit, percent reduction in average TSS at all the visits and the number of patients having no symptoms i.e. 0 on TSS on day 5 and having more than 50% reduction in average TSS were analysed.

Safety assessment

Throughout the clinical study patients were asked by the investigators for any adverse events and if present noted in the case record 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. 2512/17.

RESULTS

A total 216 patients were recruited at 11 centers across India, 162 patients completed the study and were analysed.

Efficacy analysis

Mean of TSS was calculated at all the visits and at the same time percent reduction in TSS was recorded. Mean TSS at visit 1 was 6.10 which was reduced to 2.87 at visit 2 and further reduced to 0.48 at visit 3 as shown in figure no. 1. From visit 1 to visit 2 there was a reduction of 52.88 % in mean TSS and form visit 2 to visit 3 there was reduction of 92.01 % in mean TSS as shown in figure no. 2.

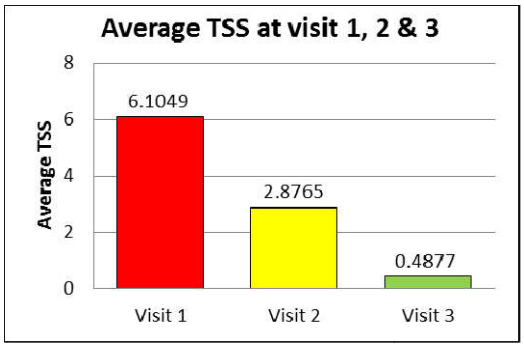

Fig 1 Average TSS at visit 1, 2 and 3 for all the patients

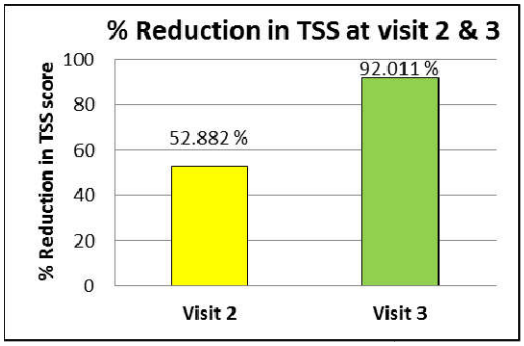

Fig 2 percentage of reduction in average TSS at visit 2 and visit 3

Further the data was extrapolated to Likert-type symptom scale in which at baseline the intensity of symptoms was moderate which was reduced to mild at visit 2 and further reduced to negligibly mild at visit 3.

At visit 2, 9 patients had TSS score of 0 i.e. they were completely cured, 27 patients were having TSS score of 1 and 126 patients were having TSS score of more than 1. At visit 3, 108 i.e. 67 % patients were having TSS score of 0, 36 i.e. 22 % patients were having TSS score of 1 and 18 i.e. only 11 % patients were having TSS score of more than 1 as shown in figure 3.

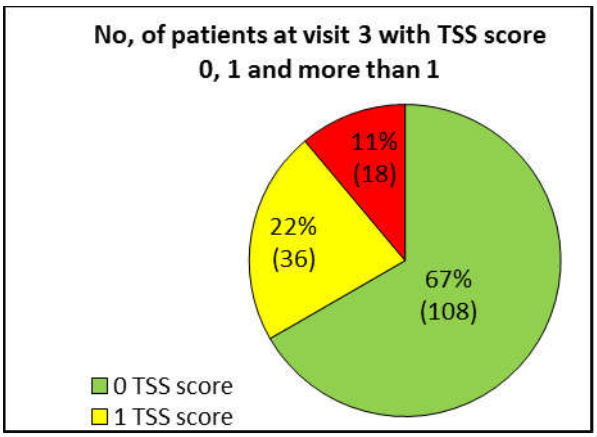

Fig 3 No. of patients at visit 3 with TSS score 0, 1 and more than 1

Safety analysis

The overall incidences of reported study drug related adverse effects were 29 seen in 24 patients. The list of adverse events with the number of episodes is mentioned in Table 2.

Table no. 2 Adverse events, no. of episodes, no. of patients and percentage of patients experienced from total population

Adverse events	No. of episodes	No. of patients	Percentage of patients
Sedation and Drowsiness	26	31	19.13 %
Hyperacidity	4	2	1.23 %
Dryness of Mouth	8	3	1.85 %
Nausea	2	2	1.23 %
Dizziness	7	5	3.08 %
Palpitation	3	2	1.23 %
Total	50	35	21.60 %

DISCUSSION

Common cold is a self-limiting disease, it resolves by itself and only symptomatic treatment is required. Though it is self-limiting, it is responsible for significant absenteeism in school and job. Hence symptomatic treatment is necessary.[10]

Average TSS at visit 1/ baseline/ before treatment was 6.10 which was reduced to 2.87 at visit 2 and at visit 3 i.e. at the end of the treatment it was further reduced to 0.48. So at visit 2 and 3 there was reduction of 52.88 % and 92.01 % respectively. Further the data was extrapolated to Likert-type symptom scale in which at baseline the intensity of symptoms was moderate which was reduced to mild at visit 2 and further reduced to negligibly mild at visit 3.

At visit 2, 9 patients had TSS score of 0 i.e. they were completely cured, 27 patients were having TSS score of 1 and 126 patients were having TSS score of more than 1. At visit 3, 108 i.e. 67 % patients were having TSS score of 0 which means they were completely cured, 36 i.e. 22 % patients were having TSS score of 1 and 18 i.e. only 11 % patients were having TSS score of more than 1.

Out of total patients population, 35 i.e. (21.60 %) patients experienced adverse effects related to study drug. Sedation and drowsiness was a major adverse effect which was observed in 31 (19.13 % of patients) which can be contributed to the antihistaminic, Chlorpheniramine maleate present in the combination. Hyperacidity and nausea can be contributed to Paracetamol. Dryness of oral/nasal cavity may be due to the anticholinergic property of 1st generation antihistaminic

Chlorpheniramine maleate. The vital signs (Blood Pressure, Respiratory rate and Pulse rate) showed no significant change from the baseline readings which are particularly important as Phenylephrine, a vasoconstrictoris a component of the study drug.

Picon *et al*., [7] conducted a Phase III clinical study in Brazilian population for the combination of Chlorpheniramine maleate, Paracetamol and Phenylephrine (different strength capsules) for the treatment of common cold. The combination was clinically tested on 146 patients and compared with the placebo to study its safety and efficacy. The reduction of total symptom score in the test combination was from score of 14.09 at baseline to 3.54 at the end of 10 days of study period where as the reduction in case of placebo it was form 14.23 at baseline to 4.64 at the end of 10 days. The number, distribution and type of adverse events observed were similar in both the groups. The study concluded that the combination of Chlorpheniramine maleate, Paracetamol and Phenylephrine is better than placebo in the treatment of common cold as well as flulike syndrome in adults. [7]

A Cochrane review 7 analysed 32 studies or meta-analysis of 8930 patients for the treatment of common cold, inferring that decongestant, antihistamine andanalgesiccombinations 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. [6]

Eccles *et al* [8] recommended the combination of products for symptomatic treatment of common cold and flu. Multi-ingredient combination products for multi-symptom relief are formulated to safely, simply, and simultaneously treat multiple symptoms when used as directed. The rationale for the formulation combination products for common cold and flu is therefore practical, logical and reasonable. No evidence has been found that multi-symptom relief medicines are inherently less safe than single-active ingredient medicines. Multi-symptom relief combination products containing several active ingredients provide a safe, effective, cost-effective, and convenient way of treating the multiple symptoms of common cold and flu, when used as directed. This therapy requires some special information for the patient to be provided by the physician and the pharmacist.[8]

Eccles *et al*.,[8] stated that, for the treatment of common cold there is no evidence stating multi-symptom relief medicines are inherently less safe than single-active ingredient medicines. Multi-symptom relief combination products containing several active ingredients provide a safe, effective, cost-effective, and convenient way of treating the multiple symptoms of common cold and flu, when used as directed. This therapy requires some special information for the patient to be provided by the physician and the pharmacist.[8]

Kiran M *et al*.[11] conducted a phase IV multicentric clinical study for evaluating the safety as well as efficacy for the combination of Levocetirizine, Paracetamol and Phenylephrine on 201 patients of common cold and allergic rhinitis in Indian population. Symptoms related to common cold and allergic rhinitis measured by using Total Symptom Score (TSS) scale on baseline, day 3 and day 5. At baseline TSS score was 6.82 which reduced to 3.63 at day 3 and 1.14 at day 5 where reduction was 46.77 % and 83.28 %respectively. Total of 11.94 % patients of total study population had adverse events in which majority were sedation and drowsiness which could be because of Levocetirizine.[11]

Kiran M *et al*.[12] conducted a phase IV multicentric clinical study for evaluating the safety as well as efficacy for the combination of Fexofenadine, Paracetamol and Phenylephrine on 154 adult patients of common cold and allergic rhinitis in Indian population. Symptoms related to common cold and allergic rhinitis were measured by using Total Symptom Score (TSS) scale on baseline, day 3 and day 5. At baseline TSS score was 6.90 which was reduced to 3.42 at day 3 and 0.88 at day 5 where reduction was 50.43 % and 74.26 % respectively. Out of total 154 patients 3 i.e. 2.60 % of patientshad adverse events in which majority were hyperacidity and nausea/ vomiting which could be because of Fexofenadine.[12]

Kiran M *et al*.[13] conducted a phase IV multicentric clinical study for evaluating the safety as well as efficacy for the combination of Chlorpheniramine maleate, Paracetamol and Phenylephrine on 187 adult patients of common cold and allergic rhinitis in Indian population. Symptoms related to common cold and allergic rhinitis are measured by using Total Symptom Score (TSS) scale on baseline, day 3 and day 5. At baseline TSS score was 6.58 which was reduced to 3.76 at day 3 and 1.78 at day 5 where reduction was 42.85 % and 52.65 % respectively. Total of 16.57 % patients of total study population had adverse events in which majority were sedation and drowsiness which could be because of Chlorpheniramine maleate.[13]

Common cold is a self-limiting disease which may resolve spontaneously sothe cause for reduction in symptoms of common cold and allergic rhinitis may not be solely because of study drug combination. So to minimize this limitation study duration for this study was decided to be kept 5 days where as for earlier study it was 10 days. Several papers have suggested that common cold mostly resolves in average 7 days[10], so the benefit offered on day 5 would be majorly due to the study drug.

CONCLUSION

Combination of Paracetamol 250 mg, Phenylephrine 5 mg, Chlorpheniramine maleate 2 mg, Sodium citrate 60 mg and menthol 1 mg per 5 mlprovides optimum symptomatic relief and is safe for use in the symptomatic management of common cold and allergic rhinitis.

Acknowledgement

We would like to acknowledge Dr. Mahendra Patel (Mumbai), Dr. Annie Romell (Mumbai), Dr. Bhupendra Asudani (Nagpur), Dr. Swapnil Kadam (Mumbai), Dr. Manoj Kumar Agrawal (Odisha), Dr. V Chandrashekar (Hyderabad), Dr. Girish N. Hadli (Bangalore), Dr. MalathiSreedhara (Bangalore), Dr. Gaikwad Pandit A (Bangaluru), Dr. Rahan Chopra (Ratlam), Dr. Aniruddha Jawalgikar (Mumbai) who were the co-investigators in this study.

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 Plus Suspension manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

References

1. Kiran M, Pawaskar L, Yadav P. Efficacy and Safety of a combination of Paracetamol, Chlorpheniramine maleate and Phenylephrine in the symptomatic treatment of Common Cold: Phase IV Clinical study. The Indian Practitioner 2017; 70(2):1-6.
2. Mahmoud S. Al-Haddad, Qasem M. Abdallah, Abdulrahman H. Alhamyani, Abdullah J. Althomali, Sami M. Alshakhshir. General public knowledge and practices about the common cold. *Journal of Taibah University Medical Sciences* 2016;11(2):104-109
3. Julia Fashner, Kevin Ericson, Sarah Werner. Treatment of the Common Cold in Children and Adults. *American Family Physician.* 2012;86(2)
4. http://www.whiar.org/docs/ARIAReport_2010.pdf last reviewed on 1-05-2017
5. https://dphhs.mt.gov/Portals/85/dsd/documents/DDP/MedicalDirector/CommonCold101713.pdf last reviewed on 1-05-2017
6. De Sutter *et al*., Oral antihistamine-decongestant-analgesic combinations for the common cold (Review), The Cochrane Library 2012, Issue 2.
7. Picon *et al*., 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; 13:1-8.
8. Eccles, R., Fietze, I. and Rose, U.-B. (2014) Rationale for Treatment of Common Cold and Flu with Multi-Ingredient Combination Products for Multi-Symptom Relief in Adults. *Open Journal of Respiratory Diseases* 2014; 4:73-82.
9. https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-03-CHPA.pdf last reviewed on 1-05-2017
10. Dr Mayuresh Kiran, LalitPawaskar, Dr Pramila Yadav. Efficacy and safety of a combination of paracetamol, levocetrizine and phenylephrine in the symptomatic treatment of common cold and allergic rhinitis. *International Journal of Current Research in Medical Sciences*, 2017; 3(1): 53-59.
11. Dr Mayuresh Kiran, LalitPawaskar. 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; 6(4): 1624-1634
12. Kiran M, Pawaskar L, Yadav P. Efficacy and Safety of a combination of Paracetamol, Chlorpheniramine maleate and Phenylephrine in the symptomatic treatment of Common Cold: Phase IV Clinical study. *The Indian Practitioner*, 2017;70(2)

****