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IP Indian Journal of Immunology and Respiratory Medicine

Journal homepage: https://www.ijirm.org/

Original Research Article

Post marketing surveillance study (PMS) to assess the safety of fixed-dose combination therapy of paracetamol, phenylephrine, and chlorpheniramine maleate for the symptomatic treatment of common cold in Indian adults

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ARTICLE INFO

Article history:
Received 19-11-2024
Accepted 18-12-2024
Available online 31-12-2024

Keywords:
Common cold
Paracetamol
Phenylephrine
Chlorpheniramine maleate
FDC (fixed dose combination)

ABSTRACT

Introduction: The common cold is a frequent acute infection of the upper respiratory tract, with adults typically experiencing 4 to 6 episodes annually. For symptomatic treatment of common cold fixed dose combination (FDC) of paracetamol, phenylephrine and chlorpheniramine maleate are commonly used in clinical practice since long, However, there is limited research on the safety assessment of such fixed-dose combination therapies. This study evaluates the safety and effectiveness of a FDC containing 500 mg paracetamol, 10 mg phenylephrine and 2 mg chlorpheniramine maleate tablets for the symptomatic treatment of common cold in Indian adults.

Materials and Methods: A total of 200 patients aged 18 to 65 years were recruited for this study. The primary focus was on evaluating the safety of a FDC containing 500 mg of paracetamol, 10 mg of phenylephrine and 2 mg of chlorpheniramine maleate in a tablet formulation (Febrex Plus). The study spanned 5 days, with patients visiting the clinical trial site on the first day for a baseline assessment, followed by re-evaluation visits on the 2^{nd}, 3^{rd}, 4^{th} and 5^{th} day. Safety assessments were based on adverse events reported by the patients. Effectiveness was evaluated only on the basis of symptomatic relief.

Results: During the study, a total of 24 adverse events were reported, all of which were mild in intensity and completely resolved. Eleven patients (5.5%) reported mild allergic reactions, six patients (3%) reported nausea, one patient (0.5%) reported vomiting, and six patients (3%) reported sleepiness. No unexpected or serious adverse events were reported in any of the patients. Nearly all patients experienced symptomatic relief by the third day of treatment.

Conclusion: The FDC containing 500 mg of paracetamol, 10 mg of phenylephrine and 2 mg of chlorpheniramine maleate tablets was found to be safe and effective for the symptomatic treatment of common cold in adults. CTRI/2020/06/026030.

1. Introduction

The common cold is an acute, self-resolving condition that primarily affects the upper respiratory tract (URT) and is commonly associated with symptoms such as fever, nasal congestion, a runny nose, sore throat, cough, sneezing, and headache.[1] On average, adults experience 4 to 6 episodes of the common cold annually. The duration of each episode can vary based on an individual's health status, with typical cases in healthy individuals resolving within 1 to 2 weeks.[2]

In 2019, the Global Burden of Diseases, Injuries, and Risk Factors Study reported that the global incidence of the common cold reached 17.2 billion cases. The common cold represented nearly 50% of all cases contributing to

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https://doi.org/10.18231/j.ijirm.2024.029

the global burden of disease.[3] In 2018, the National Health Portal of India reported that more than 4 million individuals were impacted by the common cold.[4]

Due to the significant impact of the common cold on daily activities and overall health, various strategies are employed to prevent infection and treat the illness once contracted. The ideal treatment would aim to reduce both the severity and duration of the illness. Since the common cold is primarily caused by a viral infection, antibiotics are not effective unless a secondary bacterial infection occurs. As a result, prompt symptomatic treatment is crucial to avoid complications associated with upper respiratory tract infections (URTI).[5]

An episode of common cold can significantly affect quality of life, mood, and daily activities. As a result, there is an increasing demand for healthcare services and treatments aimed at alleviating cold symptoms. Current therapies mainly focus on primarily reducing symptom severity and shortening the duration of a cold. These treatments typically include analgesics, antihistamines, and nasal decongestants. In addition, a range of supplements, including vitamins, minerals, and herbs, are promoted as treatments for the common cold. Although these products may provide relief from certain symptoms, they typically do not reduce the duration of the illness.[2] This underscores the potential benefits of a holistic approach to effectively managing cold symptoms.

Paracetamol is a commonly used medication, valued for its better safety profile, which causes significantly less gastrointestinal toxicity compared to NSAIDs. Oral phenylephrine has been used since the 1970s. Phenylephrine and other oral decongestants work by stimulating adrenergic receptors, which causes the vasoconstriction of small blood vessels in the nasal mucosa, thereby reducing swelling and alleviating congestion.[6] Decongestants can be used for short periods alongside antitussives or antihistamines to offer symptomatic relief from coughs associated with rhinitis or the common cold.[7] Chlorpheniramine, a first-generation antihistamine, treats the common cold by binding to H1 receptors and exerting an antimuscarinic effect, helping to relieve symptoms like rhinorrhea and nasal irritation.[8]

De Sutter et al.'s review highlights the practical advantages of combination therapy in managing common cold symptoms. Their analysis indicates that the combined use of antihistamines, decongestants, and analgesics offers more effective relief than relying on a single medication.[9] The fixed-dose combination (FDC) of paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg is approved by DCGI for relieving common cold symptoms among adult patients.

The primary aim of this study was to evaluate the safety of the FDC containing 500 mg paracetamol, 10 mg phenylephrine, and 2 mg chlorpheniramine maleate tablets (Febrex Plus Tablet) in Indian patients with the common cold.

2. Materials and Methods

This was a prospective, multi-centre, open label, post marketing surveillance study (PMS) conducted in India on adult patients suffering from common cold. This study was carried out at 4 different locations in India covering 200 patients across different geography (Orissa, Andra Pradesh, Maharashtra & Kanpur).

All the pertinent documents such as the protocol, CRF and investigator's brochure etc. were submitted to the Institutional Ethics Committee for ethical approval. Approval for these documents was obtained before commencement of the trial. The conduct of the trial followed ethical principles enshrined in the Declaration of Helsinki by the World Medical Association (WMA).

The study included 200 Indian adult patients, both male and female, between the ages of 18 and 65, who had been diagnosed with the common cold. Diagnosis was based on the presence of symptoms including fever, nasal congestion, rhinorrhea, sore throat, coughing, sneezing, and headache. Patients with hypersensitivity to paracetamol, phenylephrine, and chlorpheniramine maleate, patients with hepatic or renal or cardiac dysfunction and pregnant and lactating females were excluded.

Patients were screened and were identified and explained about the trial procedures. This was followed by the history taking & medical examination. If the patients were found to fulfil all the inclusion criteria listed in the protocol and had no criteria for exclusion, then they were considered eligible for the trial. Before enrolment, patients were informed of the procedure and their consent was obtained. Medical histories were obtained, and clinical evaluations were conducted on the first visit.

The investigational product was FDC containing paracetamol (500 mg), phenylephrine (10 mg), and chlorpheniramine maleate (2 mg) in a tablet formulation (Febrex Plus). It was provided to the enrolled patient as per recommended dosage and duration.

During the 5-days treatment schedule, patients visited the clinical trial site almost every day for the evaluation of safety and effectiveness (symptom relief) of the drug treatment. Adverse event reporting was done and the patients were questioned about any adverse experience during the treatment period (Both anticipated and unexpected side effects).

All the statistical procedures were performed using the Statistical Package for the Social Sciences statistical software (SPSS) version 16.

3. Results

The total 200 patients which were enrolled in study were in the age group of 18 to 65 years with 57% being male

patients.

3.1. Safety assessment

During the study, a total of 24 adverse event were reported which were of mild in intensity which resolved completely without any intervention. Eleven patients (5.5%) reported mild allergic reaction, six patients (3%) reported nausea, one patient (0.5%) reported vomiting & six patient (3%) reported sleepiness.

No unexpected or serious adverse events were reported in any of the patients. Notably, all these adverse events were deemed non-serious, requiring no medical intervention during the study. No additional complications were observed among the participants.

3.2. Effectiveness assessment

Effectiveness was assessed by considering symptomatic relief after taking medication evaluated on 2^{nd}, 3^{rd}, 4^{th} & 5^{th} visit. All the patients got substantial symptomatic relief after 3 days of treatment.

4. Discussion

The common cold is one of the most commonly encountered illnesses in the medical practice. Its symptoms typically peak within 2 to 3 days and last for an average of 7 to 10 days. The condition is generally self-limiting, with only symptomatic treatment needed. [10]

In this study, we investigated the safety of the FDC therapy comprising paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg (Febrex Plus tablet) for managing common cold symptoms in adult patients.

Our study analyzed data from 200 adults suffering from common cold. The results indicated that almost all the patients got symptomatic relief on 3^{rd} day of treatment and indicated most common duration of therapy was for 2 to 3 days. During the study, no serious adverse events were reported. The only adverse events reported were mild allergic reactions, sleepiness nausea and vomiting, which resolved on their own and did not require any medical intervention.

In their Phase IV clinical trial in Indian patients, Kiran et al. evaluated the safety and efficacy of a FDC containing paracetamol (500 mg), phenylephrine (10 mg), chlorpheniramine maleate (2 mg), and caffeine (30 mg) for the treatment of the common cold. The trial had participants in the age range of 18 to 75 years. They reported mild sedation and gastritis as the key adverse drug events. The study concluded that the FDC of an antihistamine, decongestant, and analgesic was both effective and safe for alleviating the symptoms of the common cold. [11]

The study conducted by Kiran, Waghambare & Pawaskar, et al evaluated the efficacy and safety of a fixed-dose combination (FDC) containing paracetamol (500 mg), phenylephrine (10 mg), and chlorpheniramine maleate (2 mg) in treating common cold symptoms in Indian adults. Among the 420 patients aged 18–65 years who were enrolled, 318 completed the 5-day study. Efficacy was assessed using the total symptom score (TSS), which showed a significant reduction from a mean of 9.016 on the first day to 5.011 on the third day and 0.495 by the fifth day, with 84.28% of patients reporting no symptoms by the end of the study. [12] Statistical analysis confirmed a significant improvement in symptoms over the treatment period ($p < 0.0001$). Safety assessments revealed no serious adverse drug reactions, with only thirteen non-serious adverse events, such as hyperacidity and drowsiness, reported. These findings demonstrate that this FDC containing paracetamol (500 mg), phenylephrine (10 mg), and chlorpheniramine maleate (2 mg) is proven to be both effective and safe in the management of common cold symptoms in adults. [13]

Based on the guidelines from the Department of Public Health and Human Services (DPHHS), the Cochrane review, as well as studies by Picon PD et al. and Eccles R et al., a triple combination of analgesics, decongestants, and antihistamines offers enhanced relief for multiple symptoms associated with the common cold and allergic rhinitis. [10,14,15]

Our study offers robust evidence confirming the efficacy and safety of the FDC of 500 mg paracetamol, 10 mg phenylephrine, and 2 mg chlorpheniramine maleate tablet in treating common cold symptoms in Indian adults. However, further randomized clinical trials are needed to evaluate the efficacy and potential side effects of this treatment in a larger cohort of Indian adults with the common cold. These findings align with previous research.

5. Conclusion

Typically, the common cold resolves on its own within about a week, with treatment mainly focused on relieving associated symptoms. This study revealed that the FDC of paracetamol (500 mg), phenylephrine (10 mg), and chlorpheniramine maleate (2 mg) exhibited a favorable safety profile, with only a few mild adverse events were resolved without any intervention.

These findings highlight the importance of the FDC of paracetamol (500 mg), phenylephrine (10 mg), and chlorpheniramine maleate (2 mg) as an effective treatment option for managing the common cold among the Indian patients.

6. Disclosure

The investigational FDC product utilized in this study is a tablet containing 500 mg of paracetamol, 10 mg of phenylephrine, and 2 mg of chlorpheniramine maleate, available in the Indian market under the brand name Febrex

Plus Tablets.

7. Limitation of Study

While the study provides robust evidence supporting the use of FDC therapy, several limitations should be acknowledged. The study's open-label design may introduce bias, and the duration of the study may not be sufficient to capture long-term safety and efficacy outcomes. Additionally, the study population, while representative of Indian patients, may not be generalizable to other ethnic groups within India or globally. Further studies are warranted to evaluate the long-term benefits and risks of FDC therapy in broader and more diverse patient populations.

8. Future Action Plan

Larger sample size and broader population can be considered: Include participants from diverse demographics and geographic regions to enhance the generalizability of the findings. In-depth Safety Analysis: Include a more comprehensive assessment of adverse events, especially with repeated dosing, to ensure safety for patients prone to recurrent common cold infections.

9. Conflict of Interest

Dr. Abhijit Trailokya, Dr. Amar Shirsat, Dr. Shaijesh Wankhede, Mr. Avinash Talware are associated with Indoco Remedies Ltd. And involve in research work.

10. Source of Funding

This study was funded by Indoco Remedies Ltd.

Acknowledgment

We would like to acknowledge Mr. Rahul Hiware Sr. Manager-Regulatory Affairs, Ms. Adity Sen Pal, Head of Regulatory Affairs & Dr. Kavita Inamdar, Chief Technical Officer, Indoco Remedies Ltd.

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Cite this article: Trailokya A, Shirsat A, Wankhede S, Talware A. Post marketing surveillance study (PMS) to assess the safety of fixed-dose combination therapy of paracetamol, phenylephrine, and chlorpheniramine maleate for the symptomatic treatment of common cold in Indian adults. *IP Indian J Immunol Respir Med* 2024;9(4):141-144.