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Efficacy and Safety of a Fixed Dose Combination of Paracetamol, Chlorpheniramine Maleate, Phenylephrine and Caffeine in Treatment of Common Cold: A Phase IV, Open-Labelled, Multi-Centric Study.

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ABSTRACT

Background: Common cold affects the upper airways, sometimes in association with low-grade fever and systemic symptoms, and usually presents with at least two of the following symptoms: cough, dysphonia, throat discomfort, sore throat, nasal congestion, rhinorrhoea, sneezing, headaches, myalgia and fever. It also leads to reduction in subjective alertness and impaired psychomotor functioning. A combination of Paracetamol as an analgesic, anti-inflammatory and antipyeretic, Chlorpheniramine maleate, an anti-histaminic, and Phenylephrine as a nasal decongestant is popular in the treatment of common cold. Addition of caffeine enhances alertness and psychomotor functioning. Hence the present study was planned to evaluate efficacy and safety of this combination in treatment of common cold. **Methods:** This was a phase IV, open-labelled, multicentric study in 262 patients. Efficacy assessment was done by analyzing the reduction in mean TSS at each follow-up visit and safety assessment was done by analyzing the adverse events during the study. **Results:** There was reduction in mean TSS from 7.67 (day 1) to 3.78 (day 3) and 0.66 (day 5). Most of the patients had >50% reduction in total symptom score at visit 3 and 59.16 % patients had complete relief from the symptoms at the end of study. Out of 262 patients, 46 i.e. 17.56% experienced adverse event. Sedation and drowsiness (12.21%) was the most common adverse event seen in patients. **Conclusion:** A fixed dose combination of Chlorpheniramine maleate, Paracetamol, Phenylephrine and Caffeine is safe and effective in the treatment of common cold.

Keywords: Paracetamol, Chlorpheniramine maleate, Phenylephrine, caffeine, common cold.

INTRODUCTION

Acute upper respiratory tract infections (URTI), often referred to as common cold and flu, are the most common diseases of humans with adults suffering from 2 - 5 common colds each year and school-children suffering from 7 - 10 colds each year.[1] It accounts for up to 40% of sick leaves among US employees.[2] In India, four out of every 10 individuals experienced symptoms of cold or cough at least once in six months.[3] The symptoms of URTI are so common that self-diagnosis of common cold or flu is common amongst the general public and are widespread, frequent and a major cause of absenteeism from education and work.

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In addition, recent research has demonstrated that these illnesses reduce well-being and can impair the efficiency of mental functioning.[4,5]

Common cold usually presents with at least two of the following symptoms: cough, dysphonia, throat discomfort, sore throat, nasal congestion, rhinorrhoea, sneezing, headaches, myalgia and fever.[6] Symptoms usually peak at 2 to 3 days and have a mean duration of 7 to 10 days. When the etiology is presumably bacterial, treatment is antibiotics and medication for symptomatic relief but for common cold and the flu-like syndrome, having a viral etiology. Symptomatic treatment remains, in most cases, the standard recommendation.[7] Each symptom can be treated with a separate active ingredient, but multi-symptom relief, using combination products with multiple active ingredients is chosen by many health care professionals.[4] According to the guidelines of DPHHS,[8] Cochrane review,[9] Picon PD et al,[7] and Eccles R et al,[4] a combination of analgesics,

decongestants and antihistamines provides better relief for multiple symptoms in common cold and allergic rhinitis. Upper respiratory tract illness also leads to reduction in subjective alertness and impaired psychomotor functioning.[5] Caffeine is a psychostimulant and has been found to quicken reaction time, enhance vigilance performance, increases self-rated alertness and also improves mood and therefore addition of caffeine to the combination of analgesics,[10] decongestants and antihistamines provides better relief of symptoms in common cold.

Paracetamol belongs to a class of Nonsteroidal Anti-inflammatory Drugs (NSAID) and exhibits good central analgesic and antipyretic action. Chlorpheniramine maleate (CPM) is a first generation antihistaminic agent and competitively binds to H1 receptors in the nasal mucosa to prevent the histamine induced vasoreactive responses, exhibiting anti-inflammatory as well as anti-allergic actions. Phenylephrine is a selective adrenergic receptor agonist, which is an effective nasal decongestant.[11] Caffeine in moderate amounts decreases fatigue, potentiates postsynaptic neurotransmission in the sympathetic nervous system, enhances physical, motor and cognitive performance and increases alertness and wakefulness.[12] Thus, the combination of paracetamol, CPM, phenylephrine and caffeine helps to take care of constellation of symptoms in common cold.

In clinical practice, the treatment for common cold is routinely symptomatic and not directed towards specific etiological agent. There are very few studies evaluating the safety and efficacy of this specific fixed-dose combination in the symptomatic treatment of the common cold in adults and therefore the present study was planned.

MATERIALS AND METHODS

This was a phase IV, multicentric, open labelled, non-comparative, user initiated study conducted in 17 centers across India, with centers in each region (North, South, East, West or Central) from January 2017- June 2017. A total of 280 patients were enrolled in the study with 18 patients lost to follow up. Hence data of 262 patients was analyzed.

Inclusion and Exclusion criteria

Patients with confirmed diagnosis of common cold (having 4 out of 9 symptoms of headache, fever, bodyache, nasal congestion, rhinorrhea, sneezing, sore throat, dysphonia and malaise) and willing to participate in the study were enrolled. Patients of both the gender between 18-75 years of age were recruited for this study.

Patients having hypersensitivity to any of the drugs in combination or to any of the ingredient present in the dosage form and patients suffering from hepatic or renal dysfunction were excluded from the study.

Study procedure

All eligible patients were informed about the nature of the study and written consent was taken to participate in the study. A detailed medical history was obtained from all enrolled patients, followed by thorough clinical examination. Patients were given free physician samples of Sinarest Tablet (FDC of Paracetamol 500 mg, Phenylephrine hydrochloride 10 mg, Caffeine 30 mg and Chlorpheniramine maleate 2 mg per tablet) and asked to take 1 tablet thrice a day for a total of 5 days. Follow up visits were scheduled at day 3 and day 5 for efficacy and safety assessment after initial assessment and sample distribution at day 1. TSS scale was used by the physician during each visit for symptoms evaluation. Patients were instructed to keep a diary to record daily symptoms and adverse events if any. In case of any safety-related issues and adverse events or serious adverse events, the investigator withdrew the patient from the trial and treated accordingly. No other medications 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 and Safety assessment

The efficacy assessment was done by analyzing the reduction in Total Symptom Score (TSS) which was a score of all the symptoms related to common cold 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. The average TSS of all the patients at each visit, percent reduction in average TSS at all the follow up visits and the number of patients having no symptoms i.e. TSS 0 on day 5 were analyzed.

At each follow up visit, patients were asked for any adverse events and their diaries were assessed. Adverse events were noted and classified into two categories as serious or non-serious. Causality assessment of adverse events was done using Naranjo's scale. Adverse events observed were followed up at each visit and treated if necessary by the investigators till their resolution.

Ethical and 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), and Central Drugs Standard Control Organization (CDSCO).

Statistical analysis

The data collected was entered into Microsoft excel 2016 and analyzed using mean and percentages.

RESULTS

Data of 262 patients was analyzed out of 280 patients enrolled as 18 patients were lost to follow up.

Efficacy analysis

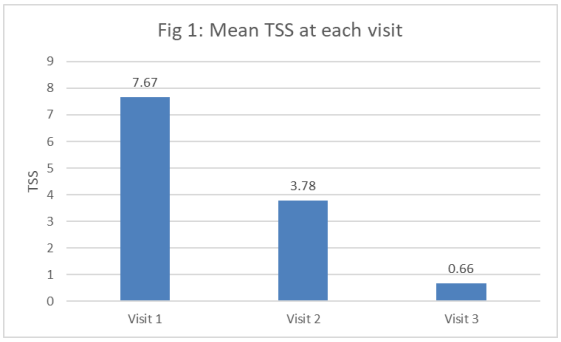
The mean age of patients in our study was 34 years. Out of all patients, 172 (65.65%) were male and 90 (34.35%) were female.

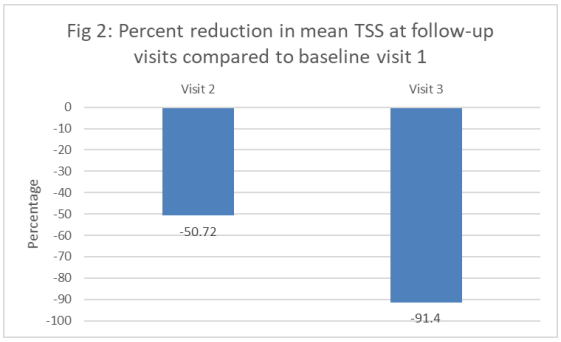
Mean of TSS was calculated at all the visits and at the same time percent reduction in TSS at visit 2 and 3 was recorded. Mean TSS at visit 1 was 7.67 which was reduced to 3.78 at visit 2 and further reduced to 0.66 at visit 3 as shown in figure no. 1. There was a reduction of 50.72 % in mean TSS at visit 2 compared to baseline visit 1. Reduction in TSS means improvement of symptoms. Similarly, there was reduction of 91.40 % in mean TSS at visit 3 as compared to baseline. This is shown in figure no. 2.

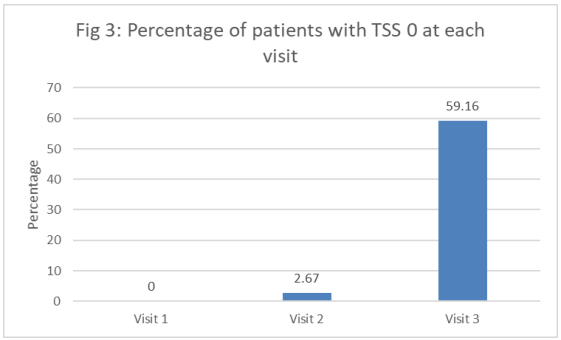
TSS 0 means patient has no symptoms of common cold or is completely cured. At visit 1, no patient had TSS of 0. At visit 2, 7 (2.67%) patients had TSS score of 0 whereas at visit 3, 155 i.e. 59.16% patients were having TSS score of 0. This is shown in figure 3. This shows that at each follow-up visit, number of patients getting completely cured of symptoms i.e TSS 0 went on increasing as compared to visit 1 where no patient had TSS 0.

Further the data was extrapolated to Likert-type symptom scale in which TSS 0 = no symptoms, TSS 1-3 = mild symptoms, TSS 4-6 = moderate symptoms and TSS 7-10 = severe symptoms.

[Figure 4] shows that at follow-up visit 2, percentage of patients with mild and moderate symptoms increased whereas there were only 6 patients with severe symptoms and 2.67% of patients are completely cured as compared to initial visit 1. At follow-up visit 3, total no. of patients getting completely cured increased drastically to 59.16%, with only 1 patient having severe symptoms and few patients with mild to moderate symptoms as compared to visit 1. Thus we can say that with the combination drug treatment, severity of symptoms decreased at each visit and patients getting cured increased.







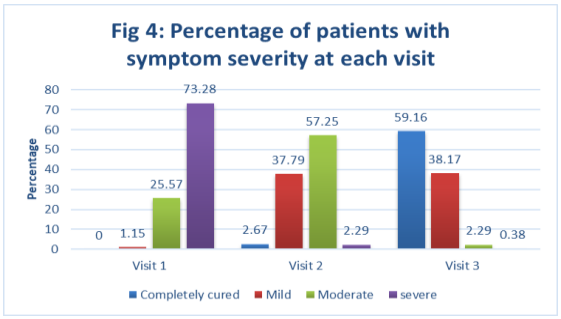


Table 1: Adverse event seen in patients

Adverse events	No. of episodes	No. of patients	Percentage of patients
Sedation & Drowsiness	84	32	12.21
Hyperacidity	12	7	2.67
Dryness of mouth	3	2	0.76
Nausea	7	4	1.53
Dizziness	4	1	0.38
Total	110	46	17.56

Safety analysis

Among all the patients, 46 (17.56%) experienced adverse event. Sedation and drowsiness was the

most common adverse event seen in 12.21% of patients followed by gastritis (2.67%), nausea (1.53%), dryness of mouth (0.76%) and dizziness (0.38%) [Table 1]

DISCUSSION

According to the guidelines of DPHHS,[8] Cochrane review,[9] Picon PD et al and Eccles R et al,[4,7] a combination of analgesics, decongestants and antihistamines provides better relief for multiple symptoms in common cold and allergic rhinitis. Caffeine is a psychostimulant and has been found to quicken reaction time and enhance vigilance performance which can take care of reduced subjective alertness and impaired psychomotor functioning in common cold.[5,10] Therefore addition of caffeine to the combination of analgesics, decongestants and antihistamines provides better relief of symptoms in common cold.

Mean TSS at visit 1 was 7.67 which was reduced to 3.78 at visit 2 and further reduced to 0.66 at visit 3. From visit 1 to visit 2 there was a reduction of 50.72 % in mean TSS and from visit 1 to visit 3 there was reduction of 91.4 % in mean TSS. At visit 1, no patient had TSS score of 0. At visit 2, 7 (2.67%) patients had TSS score of 0 whereas at visit 3, 155 i.e. 59.16% patients were having TSS score of 0. At follow-up visit 2, percentage of patients with mild and moderate symptoms increases whereas there were only 6 patients with severe symptoms and 2.67% of patients are completely cured as compared to initial visit 1. At follow-up visit 3, total no. of patients getting completely cured increases drastically with only 1 patient having severe symptoms and few patients with mild to moderate symptoms as compared to visit 1.

Out of 262 patients, 46 i.e. 17.56% experienced adverse event. Sedation and drowsiness (12.21%) was the most common adverse event seen in patients which may be due to Chlorpheniramine maleate present in the combination. Hyperacidity and nausea can be contributed to Paracetamol. Dryness of oral/nasal cavity and dizziness may be due to the anticholinergic property of 1st generation antihistaminic like Chlorpheniramine maleate. The vital signs (Blood Pressure, Respiratory rate and Pulse rate) showed no significant change from the baseline readings at follow up visits which are particularly important as Phenylephrine, a vasoconstrictor is a component of the study drug.

Lieberman H et al,[13] reported in a study that caffeine is thought to have stimulant-like behavioural effects on mood and performance and only few behavioural studies have examined caffeine's acute effects when administered in a range of doses that include the low doses typically found in foods and over-the-counter drugs. He therefore gave single doses of caffeine (32, 64, 128 and 256 mg) to 20 healthy male subjects and assessed various aspects of performance and self-reported mood states, as well as plasma caffeine concentration. The study reported that dose little as 32 mg (which elevated plasma caffeine concentration to less than 1 pg/ml), typical of the dose found in a single serving of a cola beverage, and less than that found in a single cup of coffee or a single dose of over-the-counter drugs, significantly improved auditory vigilance and visual reaction time. All other caffeine doses administered also significantly improved performance on these tests. No adverse behavioral effects, such as increased anxiety or impaired motor performance, were noted even at the highest dose administered.

Kim SW et al,[14] conducted a study to evaluate the effects of chlorpheniramine on psychomotor performance and the counteracting effects of caffeine on those sedative antihistamine actions in 16 healthy young men. Each subject was administered one of the following conditions in a random order with a one-week interval: 'placebo-placebo', '4 mg of chlorpheniramine-placebo', 'placebo-200 mg of caffeine' or '4 mg of chlorpheniramine-200 mg of caffeine'. Before and after the treatments, psychomotor functions were assessed using a battery of tests. Additionally, subjective responses were assessed using a visual analogue scale (VAS). In the 'chlorpheniramine-placebo' condition, reaction times of the compensatory tracking task were significantly impaired compared with the other three conditions. However, the response pattern of the 'chlorpheniramine-caffeine' condition was not significantly different from that of the 'placebo-placebo' condition. Changes of VAS for sleepiness were significantly greater in the 'chlorpheniramine-placebo' condition compared with the other three conditions. The study concluded that chlorpheniramine significantly increases subjective sleepiness and objectively impairs psychomotor performance. However, caffeine counteracts these sedative effects and psychomotor impairments.

Renner B et al,[15] conducted a study to determine the analgesic effect of acetaminophen compared to a combination of both caffeine and acetaminophen or caffeine alone using tonic and phasic pain stimulation in 24 subjects. They were treated orally with 1000 mg acetaminophen, 130 mg caffeine, and a combination of both in a 4-way crossover study. Pharmacokinetics and analgesic effects were assessed by means of an experimental pain model based on pain-related cortical potentials after phasic stimulation of the nasal mucosa with CO2 and based on pain ratings after tonic stimulation with dry air. Analgesic effects of acetaminophen and acetaminophen plus caffeine but not caffeine alone caused a significant reduction of pain-related cortical potentials beginning 30 minutes after medication. The study concluded that caffeine accelerated acetaminophen absorption, indicated by enhanced

early AUCs and enhanced and prolonged the analgesic activity of acetaminophen.

Smith A et al,[5] conducted a study to investigate the effects of naturally occurring colds on mood and objective measures of performance. This was done by first conducting a cross-sectional comparison of 37 healthy people and 158 volunteers with colds and then a longitudinal study in which 100 volunteers developed colds and 87 remained healthy. The results showed that having a cold was associated with reduced alertness and slowed reaction times. These effects were observed both for colds where the infecting virus was identified and those where it was not. The study concluded that there is need to identify mechanisms linking infection and illness with the behavioural changes, impact of these effects on real-life activities such as driving and methods to not only treat the local symptoms of the illnesses but remove the negative mood and the performance impairments.

Picon et al,[7] conducted a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of a fixed-dose combination of paracetamol, chlorpheniramine maleate and phenylephrine in 146 individuals aged 18 to 60 years who had moderate to severe flu-like syndrome or common cold. The reduction of total symptom score in the fixed drug 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. Comparison of overall symptom scores in the two groups revealed a significantly greater reduction in the treatment group than in the placebo group ($p = 0.015$). 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 was safe and more effective than placebo in the treatment of common cold as well as flulike syndrome in adults. Similar results were obtained in our study.

The cause for reduction in total symptoms score of common cold may be due to study drug combination or self-resolving nature of the disease itself. Several papers have suggested that common cold mostly resolves in average 7 days.[16] So to minimize this limitation in our study, duration was decided to be kept 5 days, so the benefit observed on day 5 would be mostly due to the study drug combination.

CONCLUSION

Common cold is a self-limiting disease, resolves by itself and only symptomatic treatment is required. Our study showed that fixed dose combination of Paracetamol 500 mg, Phenylephrine 10 mg, Chlorpheniramine maleate 2 mg and Caffeine 30 mg provides optimum relief in the symptoms of common cold as well as enhances alertness and psychomotor functioning and is safe for use.

Disclosure

This study is done for Sinarest Tablets manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd. Study samples were provided by Centaur Pharmaceuticals, Mumbai.

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