

EFFICACY AND SAFETY FOR THE COMBINATION OF DEXTROMETHORPHAN HYDROBROMIDE AND CHLORPHENIRAMINE MALEATE FOR THE TREATMENT OF UNPRODUCTIVE COUGH: A PHASE IV CLINICAL TRIAL

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ABSTRACT

Introduction: Cough is one of the most common global complaint for which most of the patients requires the medical attention as it adversely affects the quality of life and lifestyle. Allergic rhinitis is one of the most common cause of unproductive cough. Unproductive cough due to allergic rhinitis can be treated by the combination of Dextromethorphan Hydrobromide (DMH) and Chlorpheniramine Maleate (CPM). So the study drug combination of DMH 10 mg and CPM 2 mg per 5 ml syrup was used to conduct an open-labelled, multicentric, post-marketing surveillance to substantiate the Safety and Efficacy in patients of unproductive cough caused due to allergic rhinitis. **Methods:** Of total 200 enrolled patients, 146 patients completed the study. Efficacy assessment was made by reduction in cough severity score (CSS) extrapolated to four point Likert-type scales. Safety assessment was done by analysing the adverse events throughout the study. **Results:** Reduction in mean CSS was done from 6.157 (baseline) to 3.335 (day 3) to 1.034 (day 5). One point reduction occurred in Likert-type symptom scale from moderate to mild occurred in 3 days. At visit 2 and 3 there was decrease in CSS by 45.828 % and 83.203 % respectively as compared to baseline. Adverse events occurred in the duration of clinical trial were of mild intensity. **Conclusion:** A combination of Dextromethorphan Hydrobromide and Chlorpheniramine Maleate is safe as well as efficacious for the treatment of unproductive cough caused due to allergic rhinitis.

KEYWORDS: Dextromethorphan Hydrobromide, Chlorpheniramine Maleate, Allergic Rhinitis, Unproductive cough.

INTRODUCTION

Cough is one of the most common global complaint for which most of the patients requires the medical attention. Presence of cough adversely affects the quality of life, lifestyle and sense of well-beingness.^[1,2] Cough is a forceful expiration against closed glottis. This maneuver prevents the foreign harmful substances from entering into the lungs, movements of secretions and other constituents of airway upward from mouth. Coughing is not only a physiological barrier that prevents the irritant substances from being reached to the respiratory tract but is also a symptom of diseases of both respiratory and non-respiratory origin.^[2] Cough can be productive or unproductive. Productive cough is the cough with respiratory tract secretions and unproductive cough is the cough with no respiratory tract secretions.^[3,4]

Allergic rhinitis is one of the most common cause of cough.^[1] Allergic rhinitis can be characterised by a loud barking sound with force and intensity comparable to sneezing in hay fever. The cough causing because of

allergic rhinitis is normally paroxysmal and unproductive in nature and it can may last in few minutes or hours or days.^[2]

Chlorpheniramine Maleate (CPM) belongs to 1st generation antihistaminic agents and can be used for the treatment of allergic rhinitis.^[5] Dextromethorphan Hydrobromide (DMH) is a cough suppressant and it can be used for the treatment of unproductive cough.^[6] So the combination of Chlorpheniramine Maleate and Dextromethorphan Hydrobromide can be used for the treatment of unproductive cough caused due to allergic rhinitis.^[5,6]

CPM is an antihistaminic agent of 1st generation. It competitively binds to the H1 receptors of the vascular tunica medius located in the nasal mucosa to prevent the histamine vasoreactive response. Due to this mechanism anti-allergic as well as anti-inflammatory action occurs in the nasal mucosa. Also decrease in nasal mucosa happens due to anti-cholinergic action of CPM. Thus

CPM is useful for controlling the symptoms related to unproductive cough.^[5]

Dextromethorphan Hydrobromide (DMH) is a centrally acting antitussive drug. It elevates the threshold for coughing, without inhibiting ciliary activity. The antitussive activity of dextromethorphan lasts for approximately 5-6 hours and has a plasma half-life of 2-4 hours.^[7] Dextromethorphan and codeine has equivalent efficacy but Dextromethorphan does not depress mucociliary function of the airways mucosa and does not causes constipation and addiction to the patient.^[8]

This phase IV post marketing clinical trial was conducted to test the safety and efficacy for the combination of CPM and DMH on the patients suffering from unproductive cough due to allergic rhinitis.

MATERIALS AND METHODS

It was a Phase IV Post marketing Clinical study conducted with 11 Paediatric speciality investigators all across the India from July to November 2017. Total 200 patients were recruited for the study out of which 146 patients completed and 54 patients were lost to follow-up.

Inclusion and Exclusion criteria

Children of both the genders of age 2 years and above having weight more than 12.5 Kg were shortlisted for the study. Then the patient with the confirmed diagnosis of unproductive cough and allergic rhinitis who are willing to sign the informed consent form and can adhere to the protocol were recruited for the study.

The patients hypersensitive to the study drug or any of the excipient of the study drug formulation and the patients who cannot adhere to the protocol were strictly excluded from the study.

Sample size

The minimum sample size was decided to be kept 125 patients and by considering the loss of approximately 75 patients total 200 patients were recruited for the study out of which 54 patients were lost to follow-up and the total study was conducted on 146 patients.

Study Intervention

For conducting the phase IV clinical trial, combination of DMH 10 mg and CPM 2 mg per 5 ml was the study drug combination. The study drug combination was given in the different dose for the different age and weight groups as mentioned in the table below.

Table 1: Dosage of the study drug combination given to the patient as per weight and age.

Weight	Age	Dose
12.5 – 20.6 kg	2- 6 years	5 ml bd
20.6 – 40 kg	2- 6 years	5 ml bd
40 kg and above	12 years and above	10 ml td

Study procedure

Clinical trial was conducted for the duration of 5 days. Patients of un-productive cough and allergic rhinitis who were meeting with all the inclusion and exclusion criteria were recruited for the study. A detailed medical history and physical examination (including vital signs, general and systemic examination) of the patient was done at baseline before initiating the study. The only investigators of ENT speciality were selected for the clinical trial as a clinical trial investigator. Patients were dispensed with 2 bottles of study drug combination of each containing 50 ml study drug combination. Patients were instructed to record adverse events occurring and experienced after taking the study drug combination. Three visits were planned for all the recruited patients. First visit (V1) was baseline visit at day 1 before treating patient with the study combination, second visit was the reevaluation visit (V2) on day 3 and third or final visit was the conclusion visit which was on day 5. Cough severity score and adverse events occurring were noted during each visit along with the medical history and physical examination. Clinical trial investigators were instructed to discontinue the study drug combination in case of severe adverse events and in case of mild and severe adverse events the patient will be treated till the adverse event resolves completely.

Concomitant therapy

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

Efficacy assessment

The primary assessment was done to analyse the reduction in the cough severity score (CSS) which was a score of all the symptoms related to cough on an eleven-point scale. On the scale, 0 means no symptom and 10 means maximum tolerated symptoms. CSS scale was further extrapolated to Likert-type symptom severity scale with 4 grades including – no symptoms for 0 on CSS, mild for 1 to 4 on CSS, moderate for 5 to 7 on CSS and severe for 8 to 10 on CSS. The secondary assessment was done by measuring the mean CSS; percentage reduction in mean CSS at visit 2 and visit 3 as compared to baseline and the number of patients having mild, moderate and severe intensity of cough by Likert-type symptom severity scale at visit 1, 2 and 3 was calculated. All the efficacy assessment was done to check the improvement in CSS score of the patient after initiating the treatment with the study drug combination.

Safety assessment

During the clinical trial Patients were asked for any adverse event after initiating the treatment with the study drug combination and if the same is present was noted in

the case record form (CRF) during visit 2 and 3. These adverse events were classified into serious and non-serious adverse events. Naranjo's scale of probability was used to classify the adverse event as drug related or non-drug related. Adverse events were followed up by the investigators till their resolution.

Regulatory matters

The said combination is already available in India under different brand names and is classified as schedule H drug in India, i.e. it should be sold in presence of prescription of registered medical practitioners only. All the patients participated in the study have read and

voluntarily signed the informed consent form (ICF) The informed consent form.

RESULTS

Mean baseline cough severity score at baseline (V1) was 6.157 reduced to 3.335 at V2 and further reduced to 1.034 at V3. Mean CSS score at each visit is graphically presented in fig. 1. Mean CSS at V3 was reduced for more than 80 % as compared to V1. At V2 and V3 there was reduction of 45.828 % and 83.203 % in mean CSS compared to baseline CSS. Percentage reduction in mean CSS at V2 and V3 compared to V1 is graphically presented in figure 2.

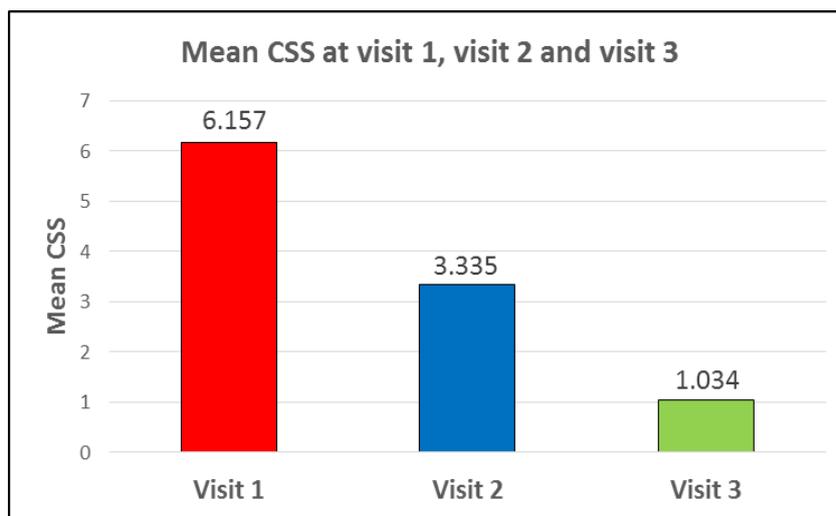


Figure 1: Mean CSS at Visit 1, 2 and 3.

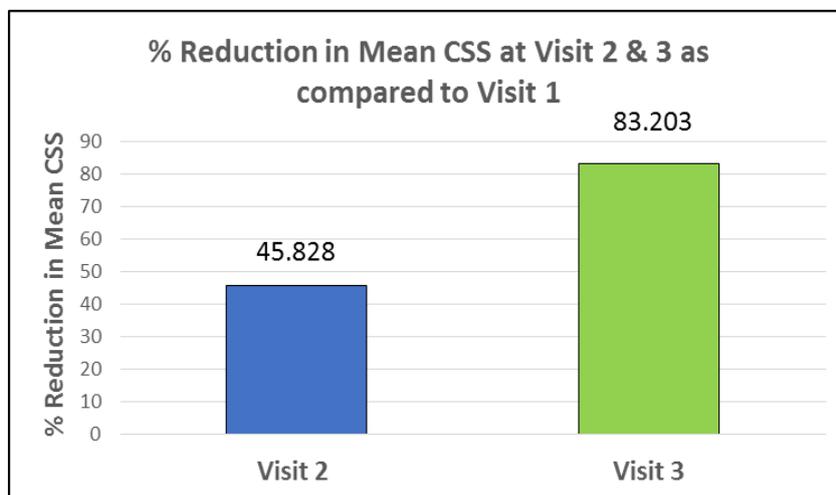


Figure 2: Percept reduction in mean CSS at visit 2 and 3 as compared to visit 1.

After extrapolating the CSS to Likert-type symptom severity scale it was found that at visit 1 there was 7, 86 and 53 cases of mild, moderate and severe intensity CSS. At visit 2 the number of patients of severe intensity was reduced to 3 and there were 90 and 51 patients of mild and moderate intensity respectively and 2 patients were not having any symptom of cough. At V3; 4 and 70

patients had CSS of moderate and mild intensity respectively and 72 patients were not having any symptom of cough. At V3 there was no patient found to be having the severe symptom of CSS. The percentage of patients having mild, moderate, severe or no symptoms of cough are presented graphically in figure no. 3.

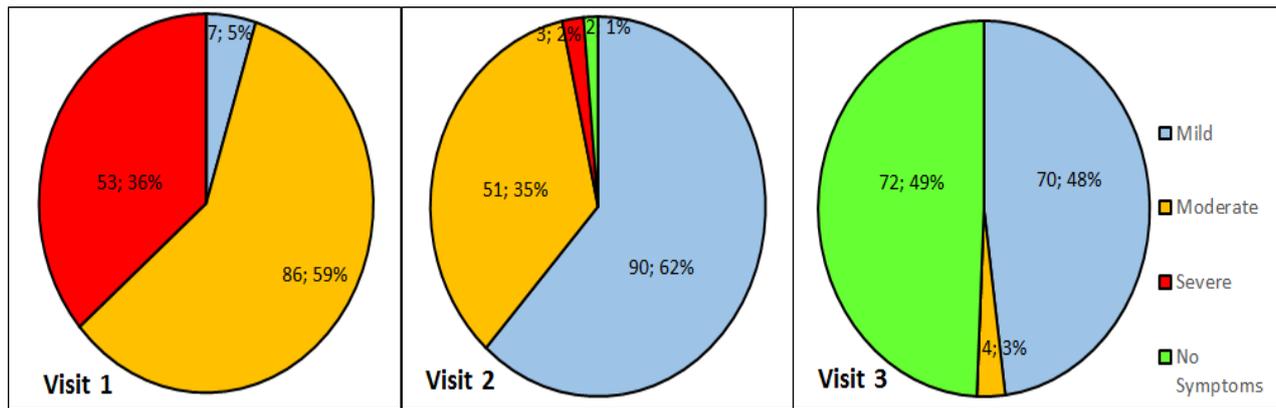


Figure 3: Number and percentage of patients having none, mild, moderate and severe CSS at visit 1, 2 and 3.

Safety analysis

The overall drug related adverse event incidences were 52 seen in 25 patients i.e. 1.94 % of total population. The list of adverse events with the number of patients is mentioned in Table 2 as below.

Table 2: Adverse Events and their Incidence.

Adverse Events	No. of episodes	No. of Patients	Percentage of total population
Dizziness	11	6	4.054 %
Headache	7	5	3.378 %
Dry mouth	8	3	2.027 %
Drowsiness	18	12	8.108 %
Nausea	8	3	2.027 %
Total	52	25	16.891 %

DISCUSSION

Allergic rhinitis is one of the main causing factor of cough. Allergic rhinitis can be characterised by a loud barking sound with force and intensity comparable to sneezing in hay fever. The cough developed because of allergic rhinitis is normally paroxysmal, unproductive and acute in nature.^[1,2] CPM and DMH can be used for the treatment of allergic rhinitis and un-productive cough respectively. So the combination of Chlorpheniramine Maleate and Dextromethorphan Hydrobromide can be used for the treatment of allergic rhinitis and unproductive cough.^[5,6] This PMS study was conducted to test the safety and efficacy for the combination of CPM and DMH for the treatment of unproductive cough caused by allergic rhinitis.

At baseline, before initiating the clinical trial CSS was measured and recorded in CRF. At visit 1 mean CSS was found to be 6.157 which was reduced to 3.335 at V2 after initiating the clinical trial day 3. And at day 5 or V2 the CSS was further reduced to 1.034. Mean CSS at V3 was reduced by more than 50 % as compared to V2. CSS at V2 was decreased by 45.828 % and at V3 it was decreased by 82.203 % as compared to baseline. CSS was extrapolated to Likert-type symptom severity scale at baseline and found that 53, 86 and 7 patients were having severe, moderate and mild intensity. The number of patients having severe intensity were reduced from

53 to 3 at visit 2 from baseline. The number of patients having moderate and mild intensity symptom were 51 and 90 and 2 patients were not having any symptom of dry cough. At V3 the number of patients having moderate and mild intensity symptom were 4 and 70. 72 patients at V3 were not having any symptom of cough.

P. C. L. LEE *et al.* conducted a stratified, double-blind, parallel and randomized clinical trial. Objective as well as subjective measurements of cough were recorded over 10-min recording periods in a quiet room before (baseline) and at 90, 135 and 180 min after treatment. Patients having only with acute dry or slightly productive cough and otherwise healthy were included in the study. Total number of patients recruited were 43 including 30 female and 13 male of mean age 22.9 years (range 18 to 46 years). 22 patients were treated with placebo and 21 by dextromethorphan. And at the end of the study it was found that there was significant reduction in the in the cough sound pressure level compared to baseline at 90 minute ($P = 0.019$). So there was positive correlation between CSPL and CF ($r = 0.752$, $P = 0.000$) for changes in cough measurements from baseline to 90 min after treatment and this indicates that CSPL may be a useful measure of cough severity.^[9]

Dr. M. Kiran *et al.* had conducted an open labelled, multicentric, post marketing surveillance study to substantiate the safety and efficacy for the combination of Dextromethorphan Hydrobromide 10 mg, Phenylephrine Hydrochloride 5 mg and Chlorpheniramine maleate 2 mg per 5 ml in the patients of common cold and unproductive cough of age 1 to 12 years. Study was conducted on total 160 Indian patients. The study drug combination was taken by the patient in the dose of 5 ml twice a day for the study period of 5 days with no concomitant therapy. Efficacy assessment was done by recording the total symptom score (TSS) at baseline before treating patient with the study medication, then at day 3 as a reevaluation visit and at day 5 as a conclusion visit. At baseline i.e. at day 1 TSS was 6.600 which was reduced to 4.275 at day 3 and was further reduced to 1.593 at day 5. In clinical trial duration of 5 days only 10.94 % patients were experienced adverse events of non-serious intensity. So it

was concluded that the study drug combination of Dextromethorphan Hydrobromide 10 mg, Phenylephrine Hydrochloride 5 mg and Chlorpheniramine maleate 2 mg per 5 ml was efficacious and safe for the treatment of common cold with an un-productive cough.^[5]

CONCLUSION

Combination of Dextromethorphan Hydrobromide 10 mg and Chlorpheniramine Maleate 2 mg per 5 ml provides optimum relief and is safe for use in the symptomatic management of un-productive cough caused due to allergic rhinitis.

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DISCLOSURE

This study was conducted as a part of Pharmacovigilance activity for Kofarest Dx marketed by Centaur Pharmaceuticals Pvt Ltd.

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