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CLINICAL EFFICACY AND SAFETY OF KOFAREST DROPS IN PRODUCTIVE COUGH

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ABSTRACT

Introduction- Cough accounts for the most frequent reason for the visit to the pulmonologist and the primary care physicians along with being one of the commonest symptoms that the physicians face with the pediatric population at majority. **Methods-** A Non-randomized, non-comparative, user-initiated trial was conducted across the 12 investigational centers for a duration of 5 days. A total of 231 patients were enrolled and screened for the study out of which 217 patients completed the study trial and 14 patients were lost to followup. **Results-** A reduction in CSS was observed and the mean of the cough symptom score (CSS) was recorded at all the visits (V0, V1 and V2). The mean CSS at V0 or the baseline visit at day 1 or V1 was 6.09 which was reduced to 3.31 at V2 at day 3 and further reduced to 0.61 on V3 or day 5. The reduction in CSS corresponded with the improvement in general and physical examination of the patients. The overall incidence of reported study drug related adverse events were **49 seen in 28 patients.** Overall 41 adverse events related to study drug formulation was reported. Adverse event such as vomiting was the most documented adverse event in this study affecting 3.68 % of the study population. **Conclusion-** Thus, Kofarest drops (ambroxol drops) is considered to be safe and effective and provides symptomatic relief for the treatment of productive cough.

KEYWORDS: CSS, Adverse Events, Cough, Ambroxol.

INTRODUCTION

Cough is one of the most frequent reason for visits to the primary care physicians and pulmonologists. It is one of the most commonest symptom that the doctors and physicians

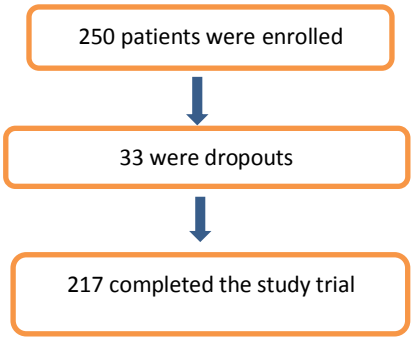
face in working with the pediatric population at majority.[1] A cough is usually a sudden, involuntary, expulsion of air from the lungs with a characteristic and easily recognizable sound. Although it is known as the most common symptom of the respiratory disorders, it serves the functions of defending the respiratory tract (defence mechanism) against noxious substances and foreign bodies thus maintaining the airway patency by removing excessive secretions from the air passages with the help of mucous and cilia.[2] The cough reflex is characterized by complexicity and plasticity that is triggered by physical and chemical stimuli. The irritant receptors and the C-fibre receptors are activated in the airways, pleura, pericardium and oesophagus. The impulse is then transmitted to the brainstem cough generator circuit via the vagus nerves to the medulla oblongata, considered as the cough centre leading to the generation of the cough.[3] Cough is usually classified based on the quality, duration, severity and etiology. Based on the quality, cough is either **productive** (wet) cough or chesty coughs and **unproductive** (dry) cough or tickly cough based on the amount of the daily expectoration. Based on the severity and duration cough can be acute (<8 weeks) and chronic (>8 weeks) or recurrent or persistent. Dry cough usually arises due to the an infection due to cold and flu viruses or can be triggered by the atmospheric pollutants. **In Wet cough or productive cough** the amount of the daily expectoration is >30 mL. The phlegm produced can be mucous, serous, purulent or bloody type.[4] Productive cough suggests lower respiratory diseases, such as asthma (bronchial asthma–mucoid mucus which is purulent–a sign of bacterial superinfection and severe allergic reactions) or pneumonia, as well as chronic pulmonary disease like cystic fibrosis, bronchiectasis (purulent or very purulent) etc. Some of them include viral or bacterial lung infections like that of common cold. If there is a productive cough, it is usually caused by the presence of secretion in the respiratory system and in the pediatric population pneumonia is the most common cause of productive cough.[5] Since, the productive cough produces phlegm or mucus (sputum), it may drain down the back of the throat from the nose or sinuses or may come up from the lungs.

Ambroxol is a secretolytic agent used in the treatment of respiratory diseases associated with viscid or excessive mucus.[6] This agent is thought to stimulate surfactant and mucous secretion, yet promoting normalization of mucous viscosity in viscid secretions. Thus, acts as mucolytic in function leading to the breaking of the mucous as well as mucokinetic in nature that promotes the movement of the mucous.[7] Ambroxol is also reported to be used in COPD and asthma to increase the mucociliary clearance and regulate surfactant levels, perhaps through anti-oxidant and anti-inflammatory activities.[8] Another effect of ambroxol lies in

the anti-oxidant activity. Ambroxol has been shown to have anti-oxidant properties and reduce the oxidant production from the inflammatory cells.[8] Oxidative stress causes damage in the airways and exaggerates airway diseases including asthma or in cases of airway allergic inflammation. Thus, ambroxol is generalized for a range of parameters such as secretolytic activity (promoting mucous clearance), anti-inflammatory and anti-oxidant activity and exerts the local anesthetic effect.[8] The main property of Ambroxol for treating sore throat by its local anaesthetic effect. The main goal of treatment is thus to reduce pain for symptomatic treatment.

METHODS AND MATERIALS

A Non-randomized, non-comparative, user-initiated trial was conducted at 12 investigational centres namely the (North, South, East, west or central) zones conducted for a duration of 5 days. A total of 231 patients were enrolled and screened for the study out of which 217 patients completed the study trial and 14 patients were lost to followup.



Inclusion criteria: The inclusion criteria included infants of weight upto 9.2 kg. Both the males and females were enrolled for the study. And the patients with confirmed diagnosis of common cold were taken into consideration. Only the patients who adhered to the protocol were taken into consideration.

Exclusion criteria: This clinical study trial excluded patients that were thought to be hypersensitive to the study drugs. Patients with hepatic and renal dysfunction were barred from the study. Also patients diagnosed with mental and psychiatric illness and those who cannot give informed consent and adhere to the protocol were excluded from the present study trial.

Study intervention

Patient's guardian will be given 10 ml free physician sample of Kofarest Drops and advised to give it to the infant patient in the dose of 0.5 ml tid for a period of 5 days.

Activity	Visit -1	Visit-2	Visit-3
Physical Examination	Done	Done	Done
Drug Dispensing	Done	Not done	Not done
Safety Evaluation	Not done	Done	Done
Efficacy Evaluation	Not done	Done	Done

Study procedure: All eligible patients and their guardians would be informed about the nature of the study and consent would be taken. A detailed medical history will be obtained from all enrolled patients, which will be followed by thorough clinical examination. Patients will be enrolled as per inclusion/exclusion criteria to determine the eligibility of the patient. Patient's guardian were given 10 ml free physician sample of Kofarest Drops and advised to give it to the infant patient in the dose of 0.5 ml tid for the period of 5 days. The patient's guardian will be instructed to keep a diary of daily symptoms. In case of any safety-related issues and adverse events or serious adverse events, the investigator by choice can withdraw the patient from the trial and treat according to the severity of the symptoms. Three visits were outlined for the patients recruited in this study- namely V0 (Baseline visit) day 1, V1 (reevaluation visit) day 3 and V2 (conclusion visit) day 5. Complete Medical history of the patient was recorded and physical examination along with the Total Symptom Score and adverse event occurring were estimated during each visit. Investigators were asked to discontinue the study drug in case of serious adverse events and with discretion or clinical experience in case of mild to moderate adverse events.

Concomitant Therapy: No Pharmacological intervention and medication including topical decongestants (sprays, drops and aromatic oils), antibiotics, multi-vitamins and multiminerals were allowed during the study duration other than the study drug. Non-pharmacological interventions like drinking warm/hot water at regular intervals and steam inhalation were allowed and encouraged during the study.

Efficacy Assessment: The primary assessment was done by analyzing the reduction in CSS (Cough symptom score) which was a score of all the symptoms on a 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- no symptoms (0 on CSS), mild (1-4 on CSS), Moderate (5-8) and Severe (9-10 on CSS).

Safety Assessment: Patients were questioned for any adverse event. All the serious and non-serious adverse events were fully documented using clinical charts, original documents and case report form. The adverse events were categorized into non-serious adverse events and serious adverse events. Naranjo's scale of probability was used to classify the adverse event as non –drug related or drug related. Adverse events were followed up by the investigators till the symptoms subside.

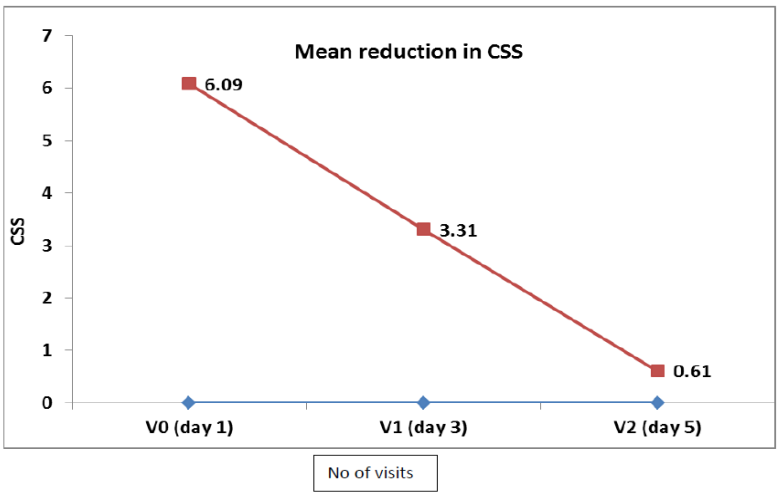
Regulatory and Ethical Matters

The study drug is currently available in India and classified under schedule H drugs i.e. it can be sold only in the presence of a prescription of a registered medical practitioner. All the patients recruited in the study have read informed consent form and signed the same. Clinical trial protocol, ICF, CRF, undertaking by the investigators form, ethical committee certificates were collected before initiating the clinical study.

RESULTS

A Total of 250 patients were recruited at 12 centres across India. Out of which 217 patients completed the study and were analyzed.

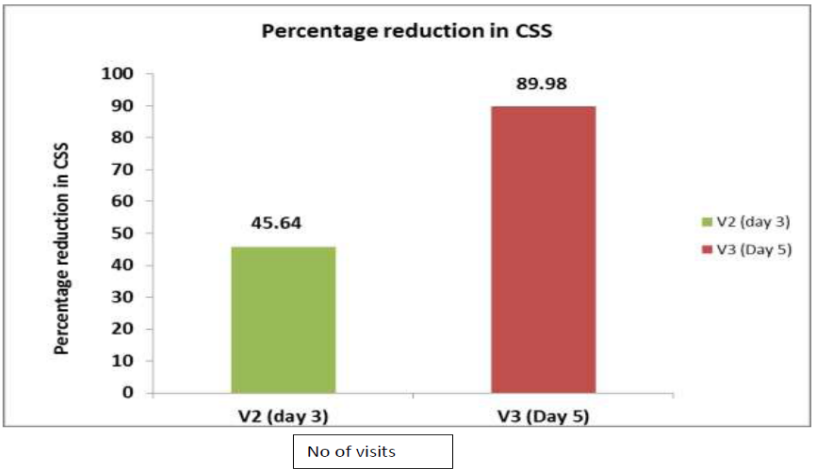
Efficacy Analysis: Mean of the total symptom score (CSS) was recorded at all the visits (V0, V1 and V2) and thus the reduction on CSS was calculated. The mean CSS at V0 or the baseline visit at day 1 OR V1 was 6.09 which was reduced to 3.31 at V2 at day 3 and further reduced to 0.61 on V3 or day 5. The reduction in TSS corresponded with the improvement in general and physical examination of the patients.



X axis- No of visits, Y axis- Total symptom Score

Figure. 1: Reduction in TSS at each visit.

The percent reduction in TSS is represented as follows



X axis- No of visits, Y axis- Percentage reduction in CSS

Figure. 1: Reduction in TSS at each visit.

Safety analysis

The overall incidence of reported study drug related adverse events were **49 seen in 28 patients.** The list of adverse events with the number of episodes is mentioned in **Table 2.**

Adverse Events	No. of episodes	No. of patients	% of population
Vomiting	18	8	3.68 %
Diarrhoea	5	3	1.38 %
Total	23	11	5.06 %

DISCUSSION

Productive cough is a cough which produces mucus or phlegm. Thus this causes significant medical problem worldwide along with difficulties in breathing wherein a large number of people seek medical attention from physicians and the pulmonologists. In children, productive cough is the second symptom of respiratory disease after runny nose, with 46-56% representation depending on the age of the child. In author's knowledge, this was the first clinical study for ambroxol drops in paediatric patients suffering from productive or wet coughing. Strength of this study is reduction in Cough Severity Score (CSS) in relation to cough intensity, cough frequency and ease of cough were studied over a period of study duration. One of the strongest arm of this clinical study is that the total Symptom Score is used as a criterion for efficacy assessment. One of the most impressionable thing of the CSS scale lies in the fact that it has 11 grades for the symptom assessment that increases the sensitivity of the study. A reduction in Total Symptom score (CSS) in all the patients was observed in the phase IV post marketing surveillance study.

At baseline visit (V1) on day 1, the mean CSS in relation to cough intensity, frequency and ease of cough was found out to be 6.09 (day 1) which was reduced to 3.31 at V2 (day 3) and 0.61 on V3 (day 5). The mean CSS corresponds to severe symptoms at baseline visit (V1) on day 1 which was reduced to moderate at V2 (day 3) and further reduced to mild at V3 (day 5). The percentage reduction in CSS in relation to cough intensity, frequency and ease of cough was found out to be 45.64% on V2 (day 3) and overall percentage reduction of CSS was found out to be 89.98% on V3 (day 5). The percentage reduction in CSS in relation to cough intensity, frequency and ease of cough was found out to be 45.64% on V2 (day 3) and overall percentage reduction of CSS was found out to be 89.98% on V3 (day 5). Overall 41 adverse events related to study drug formulation was reported. Adverse event such as vomiting was the most documented adverse event in this study affecting 3.68% of the study population.

CONCLUSION

Thus, Kofarest drops (ambroxol drops) is considered to be safe and effective and provides symptomatic relief for the treatment of productive cough.

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