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CLINICAL EFFICACY AND SAFETY OF COMBINATION OF TERBUTALINE, AMBROXOL AND GUAIPHENESIN IN PRODUCTIVE COUGH

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ABSTRACT

Introduction: Productive cough leads to expectoration of sputum for more than 8 weeks and is a common symptom that affects a large portion of the general population. A phase IV clinical study was conducted to determine the efficacy and safety of an FDC containing Terbutaline, Ambroxol and Guaiphenesin for the treatment of productive cough on Indian patients.
Methodology: Out of 450 patients, 437 patients completed the study. Efficacy assessment was evaluated by reduction of Cough severity score (CSS) in relation to cough intensity, frequency and ease of cough and extrapolating to four point Likert-type scale. Safety assessment was made by scrutinising the adverse events during the clinical trial.
Results: Reduction in mean CSS was from 6.81 (baseline) to 3.56 (day 3) to 0.90 (day 5). One point reduction in Likert-type symptom scale from Severe to Moderate took just 3 days. Majority of patients had more than 80% reduction in their mean CSS score at conclusion visit (day 5) in all the parameters. Overall 2.97% of patient's observed mild intensity adverse events which include palpitation, stomach upset/acidity and nausea/vomiting.
Conclusion: The combination of Terbutaline, Ambroxol and Guaiphenesinis efficacious and safe for the treatment of productive cough.

INTRODUCTION

Productive cough or wet cough associated with bronchospasm is common and frustrating symptom for many children and adults and a frequent reason for primary and secondary care visit to respiratory clinics. Most guidelines and reviews suggested the cause of productive cough are same as those of non-productive cough, therefore for both same diagnostic pathway should be followed. [1,2]Associated symptoms and negative outcomes with productive coughing leads to loss of sleep, exhaustion, irritability, cough syncope, and inability to perform daily activities. Many patients experience productive coughing as secondary to other medical condition, such as bronchial asthma, COPD, bronchiectasis, or unknown etiology. [2]

Productive cough is considered to be a cough regularly leading to expectoration of sputum for more than 8 weeks. Acute bronchitis is a lower respiratory tract infection (LRTI) causes reversible bronchial inflammation. In up to 95% causes, the main cause is viral.[1] Acute bronchitis is characterized by bronchial tree infection with resultant mucus formation and bronchial edema. Because of these changes, the patients develop a productive cough and the signs of bronchial obstruction, such as dyspnea or wheezing on exertion. Bronchial wall inflammation can occur in asthmatic patients or can be a secondary symptom to mucosal injury in an acute event, such as chemical fume or smoke inhalation. [3]Productive cough is a disease of developing countries which have an incidence of about 20 to 30% in developing countries as compared to 3 to 4 % in developed countries. [4]

Terbutaline sulphate is an ethanolamine derivative with bronchodilating and tocolytic properties. It selectively binds and activatesbeta-2 adrenergic receptors which leads to intracellular adenyl cyclase activation via trimeric G protein and which increases cAMP production. Increased cAMP production results in relaxation of vascular and bronchial smooth muscle mediated through the activation of protein kinase A (PKA) which leads to phosphorylation of proteins in control of muscle tone. cAMP also inhibits calcium ion which releases from intracellular stores. It reduces calcium entry into cells and induces the seizure of intracellular calcium which supports the relaxation of airway muscles. It increases mucociliary clearance and also reduces release of inflammatory cell mediators. [5]

Ambroxol hydrochloride is a mucolytic agent, which increases bronchial secretion or reduces the viscosity of tenacious sputum, it also facilitates its removal by coughing. It also improves mucocilary clearance of secretion. Guaiphenesin is

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an expectorant which leads to increase in the output of sputum and bronchial secretions. It reduces the adhesiveness and surface tension of sputum. The increased flow of bronchial secretions promotes ciliary action which changes a dry, unproductive cough to more productive and less frequent. By reducing the viscosity and adhesiveness of sputum, it also increases the efficacy of the mucociliary mechanism in removing accumulated bronchial secretions from the upper and lower airway. [6,7]Menthol has a cooling effect on the throat. It has been suggested that the benefits of menthol may be due to an effect on calcium channels of sensory nerves.

A combination of Terbutaline sulphate, Ambroxol hydrochloride, Guaiphenesin is quite popular in the treatment of productive cough. Though it has some side effects, such as palpitation, acidity and nausea/vomiting but it is considered to be safe and effective for treating patients of productive cough. Due to shortfall of clinical data the current clinical study was conducted to document the safety and efficacy of this combination of Terbutaline sulphate, Ambroxol hydrochloride, Guaiphenesin in treatment of productive cough in children and adults.

MATERIALS AND METHODS

The phase IV, multi-centre clinical trial was conducted in 15 ENT and 15 paediatrician speciality centres in various states of India. The study was conducted from the month of February 2017 to September 2017. A total number of 450 patients were signed up, out of which 437 patients completed the study and 13 patients were mislaid to follow-up.

Inclusion and Exclusion Criteria

Patients with both the gender having age group above 2 years were included in the study. After confirmed diagnosis, patients with productive cough were only included. Patients with known or thought to be hypersensitive to individual study drug or having renal and hepatic impairment were excluded from the study. Patients who would strictly adhere to the protocol were only signed up for the study. Pregnant women, lactating mothers and psychiatric patients were excluded from the study.

Study intervention

Study drug - Syrup for children aged 2-12 years containing FDC of Terbutaline Sulphate 1.25 mg, Ambroxol hydrochloride 15 mg, Guaiphenesin 50 mg and mentholated flavoured syrupy base quantity sufficient per 5 ml and patients were advised to take study drug in the dose of 5 ml tid. Syrup for adults aged 18 or above containing FDC of Terbutaline Sulphate 2.5 mg, Ambroxol Hydrochloride 30 mg, Guaiphenesin 100 mg and mentholated flavored syrupy base quantity sufficient per 10 ml and patients were advised to take study drug in the dose of 10 ml bid. Two 60 ml bottles both syrup, study medication provided to patients at free of cost for children and adults respectively. All the free samples were dispensed by the investigator all the recruited patient.

Study procedure

The study was decided to be of 5 days. Patients with productive coughing satiating the inclusion and exclusion criteria were recruited for the study. Physical examination (including the vital signs, systemic and general examination) was conducted with medical history by the investigators. Patients were given free samples by the investigator. Patients were asked to maintain a diary note of symptoms if any adverse events occurring during the study duration. Three visits were delineated for the patients mustered in this study – V1 (baseline visit) on day 1, V2 (re-evaluation visit) on day 3 and V3 (conclusion visit) on day 5. Cough Severity Score (CSS) in relation to cough intensity, frequency and ease of cough with any adverse events arising were esteemed during each visit along with physical examination and medical history. Investigators were asked to abstain the study drug in case of severe adverse event and with discretion, clinical experience dependent upon mild to moderate adverse events.

Concomitant Therapy

No Pharmacological medication and intervention were including, topical decongestants i.e. sprays/ dropsand aromatic oils; antibiotics, multi-vitamins and multi-minerals were allowed during the study interval, other than study drug. Non-Pharmacological interventions like drinking of hot/warm water at regular intervals and steam inhalation were encouraged and allowed during the study.

Statistical Analysis

Efficacy Assessment

The primary assessment for the this study was reduction in Cough Severity Score (CSS) which was a score of cough intensity, frequency and ease of cough symptoms on an eleven-point scale (0 to 10) where 0 is no symptoms and 10 is maximum tolerated symptoms. The CSS was further extrapolated to the Likert-type symptom severity scale with 4 grades – 0 on CSS (no symptoms), 1-4 on CSS (mild), 5-8 on CSS (Moderate) and 9 – 10 on CSS (Severe). The secondary assessment was the number of patients having 0 on CSS i.e. no symptoms on day 5 and number of patients having more than 50% reduction in mean CSS.

Safety Assessment

Patients were interrogated for any adverse event and if any adverse effect is observed during each post-dose visit was noted in the case record form. If any adverse events observed in patients were recorded in the case report form after thorough examination by the investigator. These adverse events are categorized into serious adverse events and non-serious adverse events. Naranjo's ADR (Adverse drug reaction) probability scale was used to classify the adverse event as non-drug related or drug related. Adverse events were monitored by the investigators till all the symptoms subside.

Regulatory and Ethical Matters

The study formulation has been approved for manufacturing and marketing in 2008 by CDSCO. The study formulation is available under various brands but is classified as schedule 'H' drug in India, i.e. to be sold in presence of prescription of a registered medical practitioners only. Patients mandatorily read and signed the informed consent form (ICF).

RESULTS

A total of 450 patients were mustered at 15 ENT and 15 paediatrician speciality centres all across India. 426 patients completed the clinical trial.

Efficacy Analysis

CSS in relation to cough intensity, frequency and ease of coughing was recorded at all the visits i.e. on V1, V2 & V3 and thus the reduction on CSS was calculated. The mean CSS

at V1 (baseline visit) was found to be 6.81, which was reduced to 3.56 at V2 (day 3) and 0.90 on V3 (day 5) as shown in figure 1.

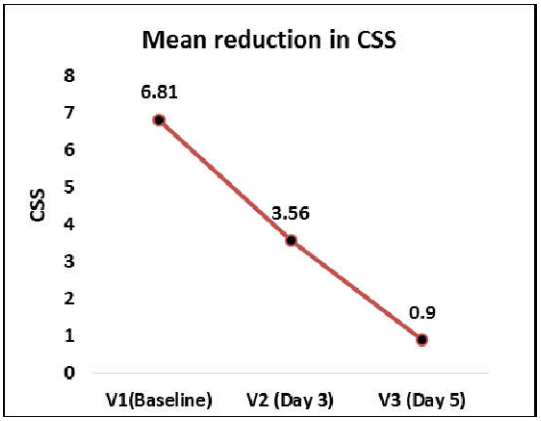

Figure 1 Reduction in mean CSS at each visit

At V1 (baseline visit) the mean CSS corresponds to severe intensity symptoms which was reduced to moderate at V2 (day 3) and further reduced to mild at V3 (day 5). On conclusion visit i.e. on day 5, out of 437 patients, 32.95% patients had a CSS of 0 i.e.no symptoms, 52.25% patients had a CSS of 1 i.e. mild symptoms which are about to cure and 15.78% patients had a CSS of >1 i.e. mild to moderate symptoms as shown in figure 2.

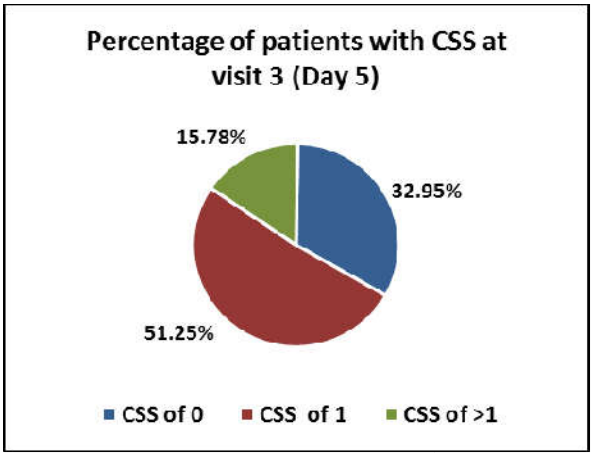

Figure 2 Percentage of patients with CSS of 0, 1 and >1 at V3 (day 5)

The percentage reduction in CSS was found out to be 47.72% on V2 (day 3) and overall percentage reduction of CSS was found out to be 86.78% on V3 (day 5). The percentage reduction in CSS is shown below in figure 3.

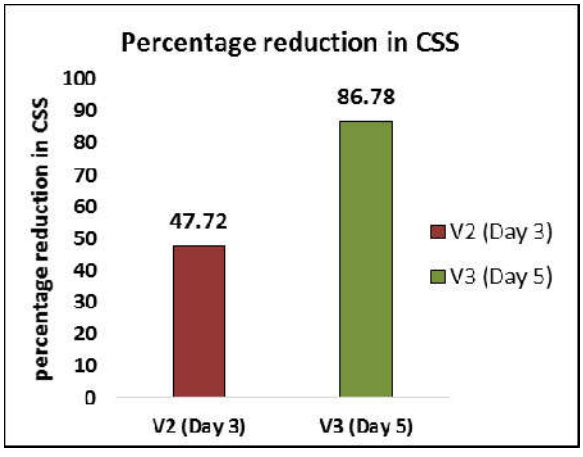

Figure 3 Percentage of reduction in CSS

Safety Analysis

The overall reported incidence of study drug formulation related adverse events was 41 seen in 13 patients. The list of adverse events related to study drug formulation with the number of episodes is mentioned in Table 1.

Table 1 Adverse events, no. of episodes, no. of patients and percentage of patients experience from total population

Adverse event	No. of episodes	No. of patient	Percentage of patients
Palpitation	18	10	2.28
Stomach upset/ Acidity	16	7	1.60
Nausea/Vomiting	7	4	0.91
Total	41	13	2.97

DISCUSSION

Productive cough is significant medical problem worldwide and caused discomfort in breathing which makes a greater number of people to seek medical attention. In author's knowledge, this was the first clinical study for the combination of Terbutaline sulphate, Ambroxol hydrochloride and Guaiphenesin in Indian patients suffering from productive coughing. A 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.

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 6.81, which was reduced to 3.56 at V2 (day 3) and 0.90 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). On conclusion visit, from the total population of 437 patients 32.95% patients had a CSS of 0 i.e.no symptoms, 52.25% patients had a CSS of 1 i.e. mild symptoms which are about to cure and 15.78% patients had a CSS of >1 i.e. mild to moderate symptoms. The percentage reduction in CSS in relation to cough intensity, frequency and ease of cough was found out to be 47.72% on V2 (day 3) and overall percentage reduction of CSS was found out to be 86.78% on V3 (day 5). Overall 41 adverse events related to study drug formulation was reported. Palpitation, stomach upset/acidity and nausea/vomiting was the most documented adverse event in this study affecting 2.97% of the study population.

Yakoot, M., *et al*. has conducted a comparative, randomised and single-blinded study for the efficacy assessment of marketed Farcosolvin syrup (Ambroxol 7.5mg + Guaiphenesin 15mg + Theophylline 25mg per 2.5ml) to evaluate the declining score of cough/sputum severity and breathlessness symptoms. Patients with ≥ 45 years of age were randomised into two groups of 50 patients. One group was treated with combination syrup i.e. 5ml tid and another with guaiphenesin syrup i.e. 0.1 g per 5 ml tid for 7 days. In addition with both the therapies, all patients received the standard treatment of ciprofloxacin 0.5 g bid for 7 days, ipratropium 0.5 mg and salbutamol bronchodilators (2 puffs) and as needed for 4 days. On a 7-point Likert scale and by using the Modified Questionnaire for Ease of Cough and Sputum Clearance, breathlessness and severity of cough and sputum clearance was measured respectively. At the end of 7 days treatment, all patients were questioned to grade their impression of improvement or change in their illness using the Change Scale or Clinical Global Impression of Improvement (CGIC), 11

which is a 7-point rated scale where 0 = not assessed; 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worsened; 6 = much worsened; and 7 = very much worsened. The two experimental groups were almost matched at baseline in breathlessness and severity of cough. The breathlessness score for combination syrup group at baseline was 4 which reduced to 2 at day 3 and 1 at day 7 whereas for Guaiphenesin syrup group at baseline was 4 which reduced to 3 at day 3 and 2 at day 7. The severity of cough score for combination syrup group at baseline was 16 which reduced to 10 at day 3 and 8 at day 7 whereas for Guaiphenesin syrup group at baseline was 16 which reduced to 13 at day 3 and 12 at day 7. Around 96% and 82% patients were showed improvement in combination and Guaiphenesin group respectively. All subjects were interrogated about any possible adverse events occurred during the study duration. Seven patients were reported with adverse events mostly nausea and heart burn in each of the groups. The difference was statistically significant ($P < 0.05$) and therefore from the study it was concluded that the combination syrup of Ambroxol, Theophylline and Guaiphenesin was more efficacious than Guaiphenesin syrup.[7]

Ellul-Micallef, R., *et al*. has conducted a clinical trial to determine the efficacy of Terbutaline. The study was conducted on 30 patients having chronic cough for at least 3 months. For efficacy assessment, every patients were given 3 baseline weeks, 3 respective weeks for treatment with placebo and Terbutaline and the day and night cough score was recorded. Therefore the analysis showed that placebo tablets did not result in any significant improvement ($p<0.1$) for both day and night. Terbutaline sulphate group showed significant improvement ($p<0.001$) in both day and night by first week of treatment and sustained for other two weeks. However out of 30, 21 patients were completely cure with Terbutaline sulphate. In all the patients FEV1 was recorded before and after two puffs of metered dose inhaler of Terbutaline and it was observed that there was increase from 2-22% (mean=12.6) in all the patients.

CONCLUSION

The combination of Terbutaline, Ambroxol and Guaiphenesinis efficacious and safe for the treatment of productive cough.

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Disclosure

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References

1. Martin, Matthew J, Tim W, Harrison. Causes of chronic productive cough: an approach to management. *Respiratory medicine.2015;*109(9): 1105-1113.
2. Sylvester, Deborah C, *et al*. Chronic cough, reflux, postnasal drip syndrome and the otolaryngologist. *International Journal of Otolaryngology*. 2012.
3. Huestan, William J, *et al*. Acute Bronchitis. *American Family Physician.1998;*57(6): 1270-1276.
4. Vijay, Sunil, Gaurav Dalela. Prevalence of LRTI in patients presenting with productive cough and their antibiotic resistance pattern. *Journal of clinical and diagnostic research: JCDR.2016;* 10(1): DC09.
5. Brunton, Laurence L, Bruce Chabner, Björn C, Knollmann, eds.Goodman & Gilman's the pharmacological basis of therapeutics. 2011; 720.
6. Tripathi, K. D, Textbook of Essentials of Medical Pharmacology. published by *Jaypee Brothers. Medical Publishers Pvt. Ltd*. 2013; 7: 218.
7. Yakoot, Mostafa, Amel Salem, and Abdel-Mohsen Omar. Clinical efficacy of farcosolvin syrup (ambroxol–theophylline–guaiphenesin mixture) in the treatment of acute exacerbation of chronic bronchitis. *International journal of chronic obstructive pulmonary disease.2010 (*5): 251.
8. Ellul-Micallef, R.Effect of terbutaline sulphate in chronic allergic cough. *Br Med J (Clin Res Ed). 1983:* 287(6397): 940-943.

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