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Research Article

EFFICACY AND SAFETY FOR THECOMBINATION OF BROMHEXINE, SALBUTAMOL AND ETOFYLLINE IN PATIENTS OF ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: POST-MARKETING SURVEILLANCE STUDY

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ABSTRACT

Introduction - Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) can be treated with a combination of bronchodilators with various mechanisms of action and durations of action, as well as mucolytic agents. So the combination of Salbutamol, Etofylline and Bromhexine can be used for the treatment of AECOPD and to test the efficacy and safety this post marketing surveillance study was conducted.

Methodology –This study was conducted at 12 clinical trial sites and total 180 patients were recruited for the study out of which 168 patients completed the study. The reduction in cough Severity Score (CSS) and increase in %FEV1 were the efficacy assessment parameters for this study. Safety assessment was done by analysing the reported adverse events.

Results -CSS at baseline was 5.97 which was reduced to 3.35at day 3 and further reduced to1.01at day 5.FEV1 at baseline was 40.01%increased to59.84%at day 3 and further increased to 81.13% at day 5. Nearly all the Patients showed reduction in CSS and increase in FEV1 at all visits and the majority of Patients had complete relief from the symptom. There were 14 episodes of adverse events, all of them were mild in severity and non-serious in nature.

Conclusion - A fixed dose combination of Salbutamol 1mg, Etofylline 50mg and Bromhexine 4mg per 5ml was efficacious and safe for the treatment of AECOPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease that causes substantial morbidity and mortality worldwide and necessitates a significant investment in healthcare resources.[(1)]Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are characterised as a rapid deterioration of the underlying respiratory function that causes a worsening of COPD symptoms.[(2)]AECOPD is characterised by increased shortness of breath, increased sputum production, a change in the colour of the sputum from clear to green or yellow or an increase in cough in someone with COPD.[(3)]The main objective for the treatment of AECOPD should be to get rid of the symptoms as quickly as possible while lowering the failure rate. The typical COPD patient has two episodes of AECOPD every year, with 10% of these episodes necessitating hospitalisation. An episode lasts on average of 7 days, but the patient not always return to baseline functional status for several months.[(8,9)] In COPD, neutrophilic inflammation is the most prominent innate immune response. The adaptive immune system is activated by cells of the innate immune system, of which CD8+-cells, CD4+ Thelper1 cells and B-cells plays a key role in COPD. This activation of the adaptive immune response sets off a chain reaction that results in widespread chronic inflammation, oxidative stress and remodelling, results in the destruction of alveolar space and the deposition of connective tissue in the airway wall's sub-epithelium and adventitium. Increased inflammation induces increased flow obstruction, results in an exacerbation. Controlling the exacerbated inflammation and optimising bronchodilation should be the goals of medical treatment. Short-acting bronchodilators such as Salbutamol is widely used to get full bronchodilation.[(10)]Combining bronchodilators with different pathways and periods of activity increases the degree of bronchodilation with a lower risk of adverse events as compared to increasing the dose of single bronchodilator. According to the global initiative for chronic obstructive pulmonary disease guidelines for healthcare professionals, COPD can also be treated with combination of bronchodilators and muco-regulatory medications which reduces the viscosity of the mucus by breaking the tenacious sputum according to the WHO.[(10)]So accordingly, the combination of Bromhexine, Salbutamol and Etofylline can be used for the treatment of AECOPD.

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Bromhexine is a mucolytic and mucokinetic drug. By altering the composition of mucous, it reduces viscosity. It breaks down the network of fibres in tenacious sputum by directly depolymerizing mucopolysaccharides and by liberating lysosomal enzymes.(11)

Salbutamol activates beta (2)-adrenergic receptors since it is a beta (2)-adrenergic agonist which causes bronchial smooth muscle relaxation. Salbutamol increases cAMP production by activating adenylate cyclase, and its activities are mediated by cAMP. Increased intracellular cyclic AMP boosts the activity of cAMP-dependent protein kinase A, which blocks myosin phosphorylation and lowers intracellular calcium levels. Smooth muscle relaxation and bronchodilation are caused by a decrease in intracellular calcium concentration. Salbutamol prevents the release of Broncho constricting agents from mast cells, inhibits microvascular leakage, and improves mucociliary clearance in addition to bronchodilation.(12) Etofylline inhibits the phosphodiesterase enzyme, which degrades cyclic nucleotides intracellularly, results in the accumulation of cyclic AMP in the cell. This drug causes increased cardiac muscle contraction by releasing calcium from the sarcoplasmic reticulum, particularly in cardiac muscles. Adenosine receptors are also blocked by this drug (adenosine acts as a local mediator in CNS & CVS and other organs- which contracts smooth muscles, especially in bronchi, blood vessels etc.) because of which bronchodilation occur as a result.(13)

The objective of this post marketing surveillance study was to evaluate the efficacy and safety for the investigational product which was the fixed dose combination of Bromhexine 4 mg, Salbutamol 1 mg and Etofylline 50 mg per 5 ml syrup for the treatment of AECOPD in Indian population.

METHODOLOGY

This post-marketing surveillance study was conducted at 12 clinical trial sites and for the study only investigators of ENT speciality were selected. Total 180 patients were recruited for the study. The study design was of prospective and non-comparative nature. For the study duration of 5 days, patients were requested to visit the clinical trial site on day 3 (visit 2) and day 5 (visit 3) considering the baseline visit as day 1 (visit 1).

Inclusion and Exclusion Criteria

For this post marketing surveillance study patients of AECOPD of both the sex including male and female of age between 2 to 12 years of weight ranging from 9 to 40 kg were recruited. Also, only those patients were recruited where patients and guardians of the patient were ready to strictly follow the study procedures.

Patients having hypersensitivity to Bromhexine or Etofylline or Salbutamol were excluded. Patient with severe Hepatic or Renal dysfunction and thyrotoxicosis were excluded from the study. Patients or guardians of the patients who could not adhere to study procedures like mentally ill or patients with psychological illness were excluded from the study.

Study Intervention

The Investigational product used for the post marketing surveillance study was the fixed dose combination of Bromhexine 4 mg, Salbutamol 1 mg and Etofylline50 mg per 5 ml. The Investigational product was provided by the sponsor to the investigator at no cost and those Investigational products were dispensed to the patients or guardians of the patient at no cost by the investigator.

Study design

The post-marketing surveillance study was conducted on total 180 patients at 12 clinical trial sites out of which 168 patients completed the study. Due to the non-randomized, non-comparative and open label nature of the study design, control drug was not used in this study and all patients, clinical research staff from the sponsor, investigator and any other people involved in the study well informed about the investigational product and its composition.

Study Procedure

Patients were enrolled by the investigator as per the inclusion and exclusion criteria. All eligible patients and their guardians were well informed about the study procedure and the investigational product by the investigator. A detailed medical history was obtained from all enrolled patients, which was followed thorough the study duration. Each guardian of the patient was dispensed with 100 ml of the investigational product on baseline visit. Guardians of the patient were advised to give the investigational product to the patient in the dose as mentioned in table no 1 for a study period of 5 days.

Table 1 Dose criteria for administration of Investigational Product

Age	Body weight	Dose
2 - 6 years	9 -18.8 kg	5 ml thrice in a day
6 – 12 years	14 - 40 kg	10 ml thrice in a day

For the patients recruited in this study, three visits were planned. Baseline visit was on day 1 (Visit 1) where physical examination and detailed medication history of patient was taken and investigational product was dispensed to patient also baseline efficacy assessment was done and for further efficacy and safety assessment, patients were asked to visit on day 3 (visit 2) and day 5 (visit 3).

Concomitant therapy

In the study duration, no pharmacological intervention other than the investigational product for the treatment of AECOPD was allowed to be taken by the patient.

Efficacy Assessment

In the post-marketing surveillance study duration of 5 days, the efficacy assessment was made by cough severity score (CSS) and %forced expiratory volume 1 (%FEV1) on day 1, 3 and 5. Cough severity score scale was an eleven-point scale ranging from 0 to 10 where 0 was no symptom to 10 was the highest tolerated symptoms where patients were asked to rate all AECOPD related symptoms based on their severity. The CSS was further extrapolated with 4 grades as no symptoms (0 on CSS), mild intensity symptom (1-3 on CSS), moderate intensity symptom (4-6 on CSS) and severe intensity symptom (7-10 on CSS) to the symptom severity scale.%FEV1 recorded by the investigator was the percentage of detected FEV1 value to the normal value.

Safety assessment

Patients and guardians of the patient were asked by the investigator for any adverse events, if experienced by the patient in the study duration of 5 days. Safety assessment for

the investigational product was done by analysing the adverse events.

Regulatory Matters

The Investigational product was approved for manufacturing and marketing in India. In India the Investigational product is categorized under schedule H drug i.e., to be sold only in the presence of licensed medical practitioners' prescription.

The informed consent form was read and signed freely by all the guardians of the patients as the patients were of less than 18 years old. Also, all the guardians of the patients were well informed about the investigational product and the study procedure prior to the recruitment of the patient to the study.

RESULTS

12 clinical trial sites across India were selected for post marketing surveillance study where total 180 patients were recruited, out of which 168 patients completed the study. At baseline, the mean CSS was 5.97 which was reduced to 3.35 at day 3 and was further reduced to 1.01 at day 5. Graphical presentation for the mean CSS at day 1, 3 and 5 is graphically presented below in the figure 1.

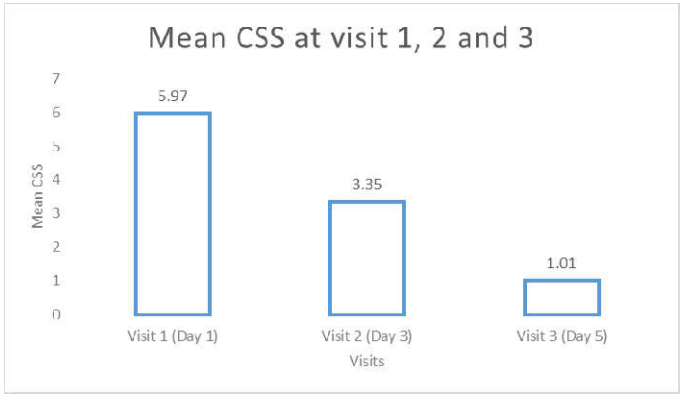

Fig 1 Mean CSS at visit 1, 2 and 3

The mean CSS at day 3 and 5 was decreased by 43.92% and 83.06%, respectively, as compared to the baseline, which is graphically presented below in figure 2.

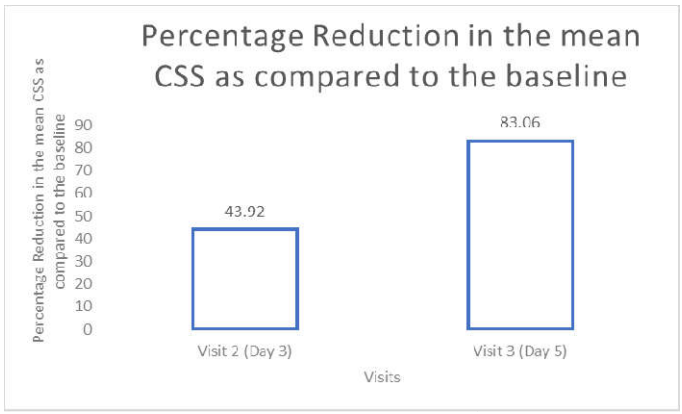

Fig 2 Percentage Reduction in mean CSS as compared to baseline

Mean CSS data was further extrapolated to symptom severity scale as no symptoms (0 on CSS), mild intensity symptoms (1-3 on CSS), moderate intensity symptoms (4-6 on CSS) and severe intensity symptoms (7-10 on CSS). At baseline, 41, 109 and 18 patients had severe, moderate and mild intensity symptoms respectively. On day 3;4, 86 and 73 patients had severe, moderate and mild intensity symptoms and 5 patients had no symptom. On day 5 no patient had severe intensity CSS, only 3 patients had moderate intensity symptoms and 102 patients had mild intensity symptoms and 63 patients had no symptom.

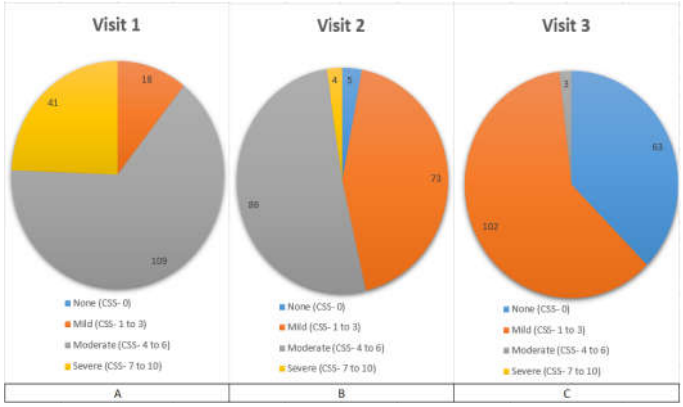

Fig 3 No. of Patients with severe, moderate or mild intensityCSSor no symptom A) Visit 1 B) Visit 2 C) Visit 3

At day 1, 3 and 5, mean %FEV1 was 40.01%, 59.84% and 81.13% respectively which is graphically presented below in figure 4.

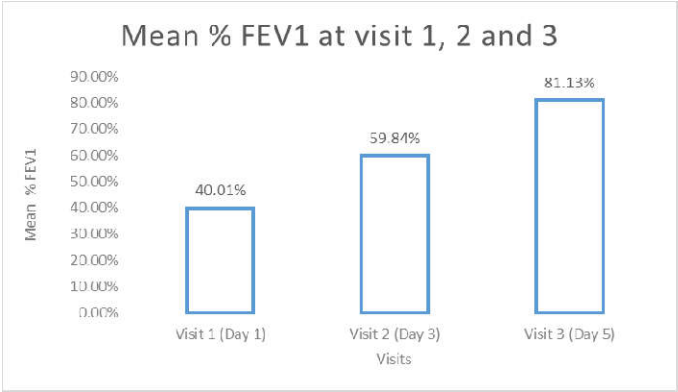

Fig 4 Mean %FEV1 at visit 1, 2 and 3

Safety Analysis

The total number of adverse drug reactions reported were 14 which were reported by 8 patients in the study duration of 5 days. Table 2 shows the list of adverse drug reactions along with the number of episodes and number of patients. All the reported adverse drug reactions were of non-serious nature and of mild intensity.

Table 2 Adverse drug reactions reported by the patients

Adverse Events	Number of episodes	Number of patients
Drowsiness	3	3
StomachUpset	6	2
Headache	5	3

DISCUSSION

COPD is a categorized as a progressive lung disease, when a patient with COPD has a prolonged (e.g., 24–48 h) rise in cough, sputum production, and/or dyspnea, it is diagnosed as an AECOPD. The objectives of treatment should be to control the exacerbated inflammation and improve bronchodilation. To achieve complete bronchodilation, short-acting bronchodilators such as Salbutamol is commonly used. Combining bronchodilators with various pathways and cycles of operation can increase the degree of bronchodilation with a lower risk of adverse events than raising bronchodilator dosage. AECOPD can be treated with the combination of bronchodilators and muco-regulatory drugs, according to the

WHO.[14]So the fixed dose combination of Bromhexine 4 mg, Salbutamol 1 mg and Etofylline 50 mg per 5 ml can be used for the treatment of AECOPD, where Salbutamol and Etofylline were two bronchodilators and Bromhexine was an oral mucolytic agent. This post marketing surveillance study was conducted to test the efficacy and safety for the investigational product in AECOPD patients. CSS and %FEV1 were the efficacy assessment parameters used in this study. Also, adverse events reported by the patient or observed by the investigator were used for safety evaluation. During the study, it was observed that there was markable reduction in the CSS in all the recruited Patients. Mean CSS was reduced from 5.97 to 3.35 from day 1 (baseline) to day 3 i.e., 43.92 % reduction and from 3.35 to 1.01 in the next 2 days which was a reduction of 83.06 % as compared to the baseline. The overall reduction in CSS in 5 days was 82.89 % in all the patients as compared to the baseline. The %FEV1 at baseline was 40.01% which was found to be increased to 59.84 at day 3 and was further increased to 81.13% at day 5. In overall efficacy assessment, the improvement in the CSS and %FEV1 was found in all the patients and the investigational product was found to be efficacious. In all the recruited patients only 14 episodes of adverse drug reactions were found to be reported and all of them were of non-serious nature and mild in intensity. So according to the benefit risk analysis, the investigational product was beneficial for the treatment of AECOPD. Below we have discussed a similar study which was used as a reference for the conduct of this study.

A similar study was conducted by Kiran et al to test the efficacy and safety for the combination of Bromhexine, Salbutamol and Etophylline on 302 patients out of which 267 completed the study. The efficacy evaluation parameter was CSS and %FEV1 like the current study. During the study it was found that there was significant improvement in the CSS and %FEV1 in all the patients recruited for the study. In the study mean CSS at day 1 was 6.03 reduced to 3.46 at day 3 and further reduced to 1.52 at day 5. Also, the % FEV1 was 57.61% at day 1 which was increased to 70.49% at day 3 and further increased to 81.17% at day 5. It was concluded that the combination of Bromhexine, Salbutamol and Etofylline was efficacious and safe for the treatment of COPD.[14]

CONCLUSION

The fixed dose combination of Bromhexine 4 mg, Salbutamol 1 mg and Etofylline 50 mg per 5 ml was found to be efficacious and safe for the treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

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Disclosure

This study was conducted as a part of Pharmacovigilance activity for an Investigational product whose brand name is Albutamol Plus Syrup which was the fixed dose combination of Bromhexine 4 mg, Salbutamol 1 mg and Etofylline 50 mg per 5 ml which is a product of Centaur Pharmaceuticals Pvt. Ltd.

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