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An Open-Labeled, Multicentric, Clinical Trial to Substantiate the Safety and Efficacy for the Combination of Salbutamol, Etofylline and Bromhexine in the Treatment of COPD

Mayuresh Kiran[*1], Lalit Pawaskar[2]

[1]Vice President, Medical Services, Centaur Pharmaceuticals Pvt. Ltd
[2]Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd

Abstract

Background: *As per WHO, COPD is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. COPD can be treated by the combination of bronchodilators of different mechanisms and duration of action and mucolytic agents. So for the treatment of COPD we have selected the combination of Bromhexine, Salbutamol, and Etophylline. Different dose combination of these drugs were used for children of age 2 to 12 years and adults of age 18 to 65 years. For children the combination of Bromhexine 4mg, Salbutamol 1mg and Etophylline 50mg per 5ml syrup was used and for adults the combination of Salbutamol 2mg, Etofylline 200mg and Bromhexine 8mg per tablet was used.* ***Methodology:*** *Out of total 302 patients, 267 completed the study. Efficacy assessment was made by analysing the reduction in Cough Severity Score (CSS) extrapolated to four point Likert-type scale and FEV1. Safety assessment was made by analysing the adverse events experienced by the patients.* ***Results:*** *At baseline, mean CSS was found to be 6.03 which reduced to 3.46 (day 3) and further reduced to 1.52 (day 5). One point reduction in Likert-type symptom scale from Moderate to Mild took in just 5 days. At day 1, %FEV1 was 57.61% increased to 70.49% at day 3 and 81.17% at day 5. Overall 45 episodes of adverse events occurred and were of mild intensity.* ***Conclusion:*** *A combination of Bromhexine, Salbutamol and Etophylline is safe and effective for the treatment of COPD.*

Keywords: ***COPD, Bronchial Asthma, Bromhexine, Salbutamol, Etophylline, and Cough Severity Score***

Introduction

As per WHO, chronic obstructive pulmonary disease (COPD) is not one single disease but an umbrella term used to describe chronic lung diseases that causes limitations in lung airflow. WHO functionally defined COPD as preventable and treatable disease state characterized by airflow limitation that is not fully reversible. Usually the airflow limitation is progressive and mostly associated with an inflammatory response of the lungs in response to noxious agents including cigarette smoke, biomass fuels and occupational agents. The chronic limitation of airflow is an important characteristic of COPD which can be caused by a mixture of obstructive bronchiolitis (small airway disease) and emphysema (parenchymal destruction). COPD is a multicomponent disease with extra-pulmonary effects.[1][2] The British Medical Research Council (BMRC) defined chronic bronchitis as "daily productive cough for at least three consecutive months for more than two successive years.[3]

According to WHO, 65 million people have moderate to severe COPD. More than 3 million people died because of COPD in 2005, which was about 5% of all global deaths. It is known that almost 90% of COPD deaths occur in low- and middle-income countries.[4]

V. K. Vijayan et al[3] conducted an epidemiological study on Indian patients for Chronic Bronchitis, respiratory symptoms and asthma. This study was conducted on 85105 men, 84470 women from 12 urban As well as 11 rural sites. And it was seen that the overall prevalence of chronic bronchitis in adults over 35 years was 3.49 % (ranging from 1.1% in Mumbai to 10% in Thiruvananthapuram). In this study it was found that there was a wide variation at different regions of India for the prevalence COPD. As per the study, the national burden of chronic bronchitis was estimated as 14.84 million.[3]

As per the global initiative for chronic obstructive lung disease guidelines for healthcare professionals, report 2017, combination of bronchodilators with different mechanisms

and duration of action may increase the degree of bronchodilation with a lower risk of adverse effects as compare to increasing dose of bronchodilators.[5] And as per WHO, COPD can be treated by bronchodilator and mucoregulatory drugs.[6] So for the treatment of COPD we have selected the combination of Salbutamol (bronchodilator), Etophylline (bronchodilator) and Bromhexine (oral mucolytic agent).

Salbutamol stimulates β2 adrenergic receptors which are predominant or main receptors in bronchial smooth muscles of the lung. Activation of beta2-adrenergic receptors present on airway smooth muscle; results into the activation of adenylcyclase and leads to an an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP results into the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting into the relaxation. Salbutamol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Salbutamol acts as a functional antagonist and relaxes the airway irrespective of the spasmogen involved and protects against all bronchoconstriction challenges.[7]

Etophylline inhibits phosphodiesterase enzyme which intracellularly degrades cyclic nucleotides and results into the intracellular accumulation of cyclic AMP and causes bronchodialatation. This drug also blocks adenosine receptors adenosine acts as a local mediator in CNS & CVS and other organs which contracts smooth muscles, especially in bronchi which results in bronchodialatation.[8]

Bromhexine is an oral mucolytic agent. Bromhexine acts on the mucus formative stages in the glands, within the mucus-secreting cells. Bromhexine disrupts the structure of acid mucopolysaccharide fibres in mucoid sputum and produces less viscous mucus, which is easier to expectorate.[8]

This phase IV clinical trial was conducted to test the efficacy and safety for the trial drug combination on Indian patients. The study duration was kept of 5 days. Forced expiratory volume in 1 second (FEV1) and cough symptom score (CSS) were the efficacy parameters used for efficacy assessment. And for safety assessment, adverse effects experienced by the patient or observed by the investigator were recorded.

Methodology

Phase IV clinical trial conducted on 267 Indian patients with 20 investigators who were specialized in either paediatrics or ENT or chest. For the patients of age 2 to 12 years the post graduate paediatricians were selected as investigators. For the patients of age 18 to 65 years the investigators selected were having post graduate degree in ENT (MS ENT) or chest (MD Chest Physician). The study was conducted all across India from July to December 2017. Total 302 patients were recruited for the study out of which 267 patients completed and 35 patients were lost to follow-up.

INCLUSION AND EXCLUSION CRITERIA

Patients with confirmed diagnosis of COPD or bronchial asthma having FEV1/ FVC score less than 0.7 were enrolled in the clinical trial. Patients of both the genders (male as well as female) having age of 2 to 65 years were recruited for this clinical trial. Finally the patients who were ready to strictly adhere to the protocol and sign informed consent form were recruited for the clinical trial.

Patients having hypersensitivity to any individual study drug of the combination or to any of the excipient present in the dosage form, patients who is not ready to stick to the protocol and pregnant or lactating woman were excluded from the study.

SAMPLE SIZE

The minimum sample size was decided to be kept 250 patients and by considering the loss of approximately 52 patients total 302 patients were recruited for the study out of which 35 patients were lost to follow-up and the total study was conducted on 267 patients.

STUDY INTERVENTION

A study drug combination of Salbutamol, Etofylline and Bromhexine was used for the phase IV clinical trial. Different doses of these drugs were used for children and adults in different dosage forms. For children of age 2 to 12 years, the combination of Bromhexine 4 mg, Salbutamol 1 mg and Etophylline 50 mg per 5 ml syrup was used and for the adults of age 18 to 65 years the combination of Salbutamol 2 mg, Etofylline 200 mg, Bromhexine hydrochloride 8 mg per tablet was used.

Guardians of the children patients recruited in the study will be given 100 ml free physician sample of study drug combination Syrup and guardians will be advised to give it to the children patients in the dose as per the following table for the period of 5 days.

Table 1: Dose of study drug combination syrup to be given to the patients of different age group

Age	Body weight	dose
2 - 6 years	12 – 20 kg	5 ml tid
7 – 12 years	20- 40 kg	10 ml tid

Patients of age 18 to 65 years were given 15 tablets of free physician sample of study drug combination tablets and patient is advised to take in the dose of 1 tablet thrice a day for the study period of 5 days.

Study procedure

The study duration was kept 5 days. Patients of COPD and bronchial asthma who met with the decided exclusion and inclusion criteria were recruited for the clinical trial. A detailed medical history was obtained from each patient and physical examination was conducted by the investigators. The study was conducted in 2 groups of patients, in 1st group, patients of age 1 to 12 years and in 2nd group the patients recruited were of age 18 to 65 years. For the 1st group of patients the investigators selected were of paediatric speciality and for the 2nd group the investigators selected were of chest or ENT or internal medicine speciality. In the first group of patients of age 2 to 6 years and 7 to 12 years of body weight 12 to 20 kg and 20 to 40 kg were advised to take the study drug combination syrup in the dose of 5 ml and 10 ml three times a day respectively. In 2nd group the patients of age 18 to 65 years were advised to take the study drug combination tablet in the dose of 1 tablet thrice a day for the study period of 5 days. Patients were asked to maintain a diary to record any adverse events occurring during the study duration.

Three visits were planned for all the patients recruited in this study-the first visit was baseline visit (V1) on day 1 before treating patient with the study drug combination, the second visit was revaluation visit (V2) on day 3 and third visit was conclusion visit (V3) on day 5. Adverse events occurring, CSS and FEV1 were noted during each visit along with medical history and physical examination. Investigators were asked to discontinue the study drug in case of severe adverse event and with discretion, clinical experience in case of mild or moderate adverse events.

All the efficacy parameters and adverse events experienced by the patient or observed by the investigator were recorded in the case record form by the investigator, collected at the end of the trial and analysed.

Concomitant therapy

No Pharmacological intervention and any drug or drug combination other than study drug combination was allowed to take during clinical trial 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 assessment

The primary assessment was done by analysing the reduction in %FEV1 which is percentage of detected FEV1 value to the normal value and CSS which was a score of all the symptoms related to cough on an eleven-point scale [0 to 10] where 0 is no symptom and 10 means maximum tolerated symptoms. CSS scale was further extrapolated to Likert-type symptom severity scale where 0 on CSS scale means no symptoms, 1 to 3 means mild symptoms, 4-6 means moderate symptoms and 7-10 means severe symptoms. In primary efficacy assessment decrease in mean CSS, increase in %FEV1 at all the visits, percent decrease in CSS at visit 2 and visit 3 and increase in the %FEV1 at visit 2 and 3 as compared to baseline was calculated. In secondary efficacy assessment percentage of patients having mild, moderate and severe CSS and percentage of patients with different %FEV1 at V1, V2 and V3 was calculated and graphically presented.

Safety assessment

Throughout the clinical study patients were asked by the investigators for any adverse events and if present noted in the case record form (CRF) during each post-dose visit. Noted adverse events were classified into 2 categories as serious or non-serious adverse events. Adverse event were classified as drug related or nondrug related adverse events by using Naranjo's scale of probability. Adverse events observed were followed up and treated if necessary by the investigators till their resolution.

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 recruited in the study have read and signed the informed consent form. 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 collected before initiating the clinical study.

Results

Total 302 patients were recruited at 20 centres across India, 267 patients completed the study. Demographic characteristics are mentioned in the table 2.

Table 2: Demographic characteristics of the patients recruited in the clinical trial

Mean age of patients (years)	30.47 years
No. of males patients	107
No. of females patients	160

Efficacy analysis

For efficacy analysis CSS and %FEV1 at all the visits was recorded for all the patients. Mean CSS for all the patients at all the visits was calculated. At visit 1, visit 2 and visit 3 mean CSS was 6.03, 3.46 and 1.52 respectively. Mean CSS at all the visits is presented graphically in the figure 1.

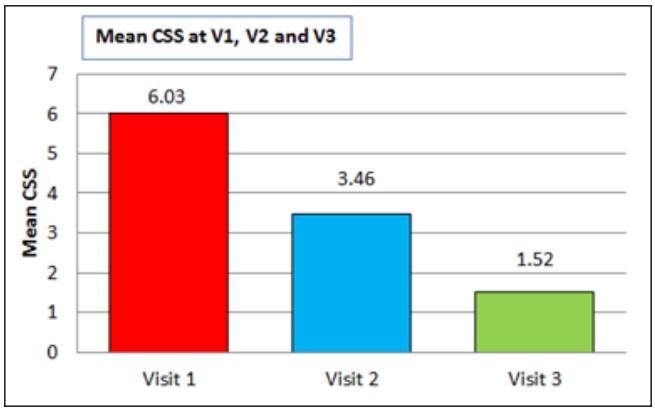

Figure 1: Mean CSS score of all the patients at V1, V2 and V3

Percentage reduction in mean CSS at visit 2 and 3 as compared to baseline was calculated. At visit 2 and visit 3, compared to baseline there was reduction of 42.62 % and 74.79 % in CSS respectively. Percent Reduction in CSS at visit 2 and visit 3 is presented graphically in figure 2.

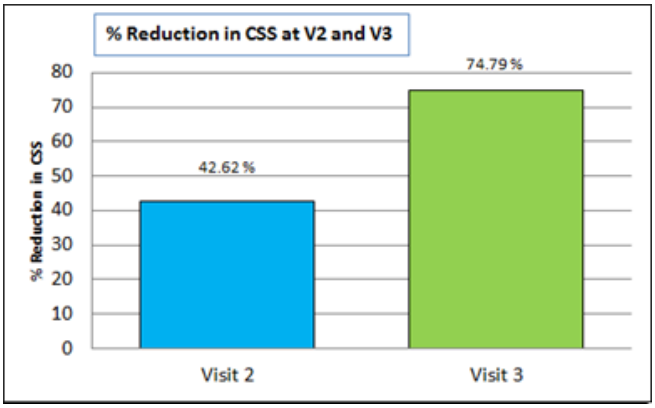

Figure 2: Percent Reduction in CSS at visit 2 and visit 3 as compared to baseline

% FEV1 at all the visits was recorded and from that mean % FEV1 was calculated at visit 1, visit 2 and visit 3. Mean % FEV1 at visit 1 was 57.61 % which was increased to 70.49 % at visit 2 and at visit 3 increased to 81.17 %. Mean % FEV1 at all visits is graphically presented in figure 3. And in figure 4 increase in % FEV1 at visit 2 and visit 3 as compared to baseline is presented graphically.

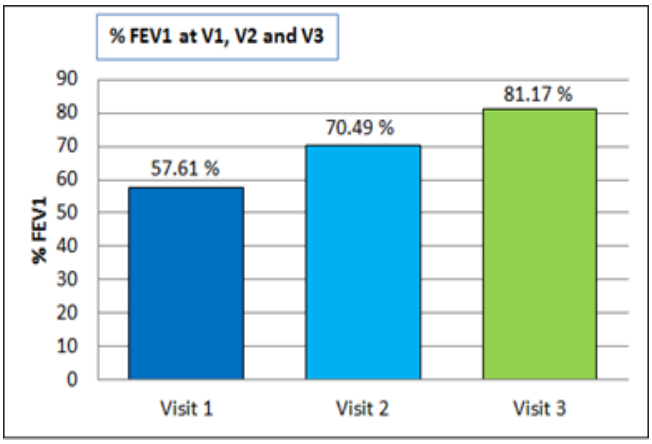

Figure 3: Percent FEV1 at visit 1, 2 and 3

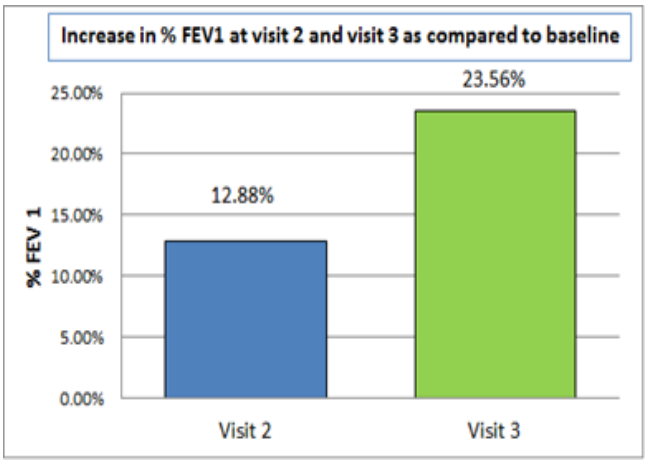

Figure 4: Increase in % FEV1 at visit 2 and visit 3 as compared to visit 1

CSS scale was further extrapolated to Likert-type symptom severity scale. As per that at visit 1; 106, 131 and 30 patients were of severe, moderate and mild intensity of CSS respectively. At visit 2; 8, 116 and 143 patients were of severe, moderate and mild intensity of CSS respectively. At visit 3; 6, 30 and 231 patients were of severe, moderate and mild intensity of CSS respectively. And at visit 2 and visit 3; 2 and 84 patients respectively had 0 CSS. All the patients having different cough symptom score at visit 1, 2 and 3 is presented graphically in figure 5.

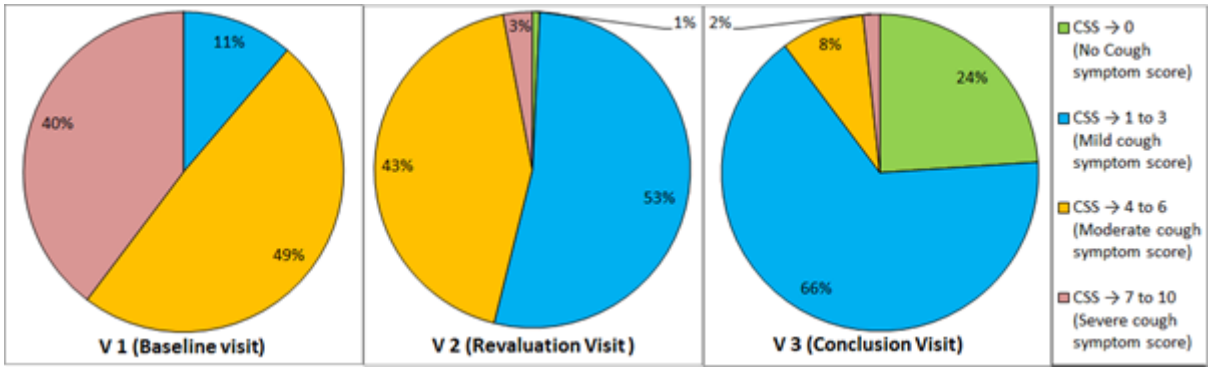

Figure 5: Patients having none, mild, moderate and severe CSS at visit 1, 2 and 3.

% FEV1 of all the patients was recorded and from that data, patients were grouped having FEV1 ≥ 80 %, in the range of 50 % to 80 %, 30 % to 50 % and ≤ 30 % and groups were named as patients of mild, moderate, severe and very severe intensity of airflow obstruction in COPD. The percentage of patients at each group is graphically presented in figure 6.

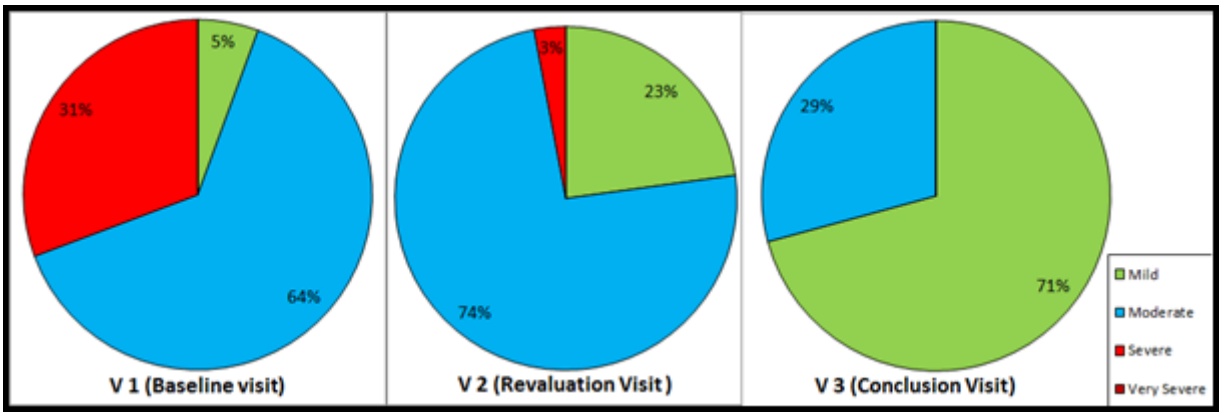

Figure 6: Patients having mild, moderate, severe and very severe intensity of airflow obstruction in COPD.

Safety analysis

The overall incidences of reported study drug related adverse effects were 45 seen in 16 patients. The list of adverse events with the number of episodes is mentioned in Table 3.

Table 3: Adverse events, no. of episodes, no. of patients and percentage of patients experienced from total population

Adverse Events	No. of episodes	No. of patients	% of patients
Dry mouth	12	6	2.24 %
Headache	10	8	2.99 %
Dizziness	3	2	0.74 %
Drowsiness	20	10	3.74 %
Total	45	16	5.99 %

Discussion

As per the global initiative for chronic obstructive lung disease guidelines for healthcare professionals, report 2017, combination of bronchodilators of different duration and different mechanisms of action increases the efficacy and safety as compared to the increasing dose of single bronchodilator.[5] As per WHO, COPD can be treated by bronchodilator and mucoregulatory drugs.[6] So for the treatment of COPD we have selected the combination of Salbutamol (bronchodilator), Etophylline (bronchodilator) and Bromhexine (oral mucolytic agent). To test efficacy of the product CSS and FEV1 was recorded at visit 1, 2 and 3. And to test the safety, adverse effects experienced by the patient and observed by the investigator were recorded during the study period.

At visit 1 mean CSS was 6.03, which was reduced to 3.46 at visit 2 and at visit 3; it was further reduced to 1.52. As we have extrapolated the CSS scale to Likert-type symptom severity scale, at visit 1 the average CSS was of moderate intensity which was reduced to mild intensity at visit 3 which was conclusion visit. At visit 2, percent reduction in mean CSS as compared to baseline was 42.62 % which was increased to 74.79 % at visit 3. At visit 1, 106 patients were of severe intensity, 131 patients were of moderate intensity and 30 patients were of mild intensity cough symptom score. In visit 2, patients of severe and moderate intensity were decreased to 8 and 116 respectively and 143 patients were of mild intensity. In visit 3, only 6 patients were of severe intensity, 30 patients were of moderate intensity and 231 were of mild intensity. Therefore, overall it was observed that there was decrease in intensity of CSS from severe to mild in most of the patients. At visit 2 and visit 3; 2 and 84 patients respectively were having 0 CSS.

Mean %FEV1 at visit 1, 2 and 3 was 57.61%, 70.49% and 80.17% respectively. However %FEV1 increase at V2 and V3 as compared to baseline was found out to be 12.88 % and 23.56 % respectively. At visit 1; 82 patients were of severe intensity, 170 patients were of moderate intensity and 15 patients were of mild intensity airflow obstruction in COPD. At visit 2, the number of patients of severe intensity was decreased to 8, 198 of moderate intensity and 61 of mild intensity airflow obstruction in COPD. At visit 3 there was no patient of severe intensity, 78 of moderate intensity and 189 of mild intensity airway obstruction in COPD. At visit 3 it was seen that there was no patient of severe intensity, 78 of moderate intensity and 189 of mild intensity airway obstruction in COPD. So at visit 2 and visit 3 it was seen that, the number of patients of higher intensity airway obstruction was decreased and number of patients of lower intensity airway obstruction was increased and there was no patient of severe intensity airway obstruction COPD at the end of the trial.

K Torén et al conducted a clinical trial to analyse different measures of bronchodilator response of FEV1, forced vital capacity (FVC) and slow vital capacity (SVC). Total 1050 participants of age 50 to 64 were recruited form the general population. Recruited patients were investigated using some

questions, FVC, FEV1 and SVC and recorded before and 15 minutes after inhalation of 400 µg of salbutamol. Change in baseline values are defines as bronchodilation response which is expressed in unit of percent predicted normal. Multiple regression models were used for the assessment of predictors of bronchodilator response. FEV1/FVC ratio below normal lower limits was defined as airway obstructions and COPD was defined as FEV1/FVC below lower limits of normal after bronchodilation. Among all the recruited patients, the greatest bronchodilator. Among all subjects, the mean ΔFEV1 was 118 mL and median was 100 mL, ranging from −470 mL to 1.7 L. The mean ΔFVC was 23 mL (and median was 0 mL) ranging from −980 to 910 mL. The mean ΔSVC was 6 mL (and median 0 mL) ranging from −3.1 to 2.9 L. The upper 95th percentile of bronchodilator responses in asymptomatic never-smokers was 8.7% for FEV1, 4.2% for FVC and 5.0% for SVC. The bronchodilator responses were similar between men and women. In a multiple linear regression model comprising all asymptomatic never-smokers, the bronchodilator response of FEV1 was significantly associated with airway obstruction and height.[9]

Jean H. M. Langlands et al conducted a double-blind clinical trial to test the efficacy of Bromhexine as a mucolytic drug in the patients of chronic bronchitis. This study was conducted to compare the efficacy of Bromhexine and identical placebo tablets. Total 27 patients were recruited for the study, out of which 13 patients were treated with Bromhexine 8 mg tid and 14 patients with placebo for 14 days. Bromhexine reduces the viscosity of mucoid sputum so the patients can expectorate more easily and clear his airways. The viscosity of the sputum was measured by two methods including Haake viscotester and Elmes-White method. And at end of this trial the viscosity of sputum for the patients who were taking Bromhexine was reduced as compared to the patients taking placebo.[10]

Kurli Sankar et al conducted a clinical trial on 204 Indian patients suffering from COPD to compare the efficacy and safety for the combination of Theophylline and Etophylline with Doxofylline. Patients were divided into 2 groups. Group 1 was treated with Theophylline 69 mg + Etofylline 231 mg once a day and group II was treated with Doxofylline 400 mg twice a day. Efficacy measurement was done by using the parameters like FEV1, FVC and % FEV. Efficacy parameters were recorded at each visit (baseline, day 7, day 14 and day 21). And the mean improvement done in FEV1, % FEV1 and FVC was 0.0356, 2.43 and 0.019 in the patients who were treated with the combination of Theophylline and Etophylline respectively. And the patients who were treated with Doxofylline the improvement done in FEV1, %FEV1 and FVC was 0.0345, 2.06 and 0.023 respectively. So the efficacy for the combination of Theophylline and Etophylline was equivalent to Doxofylline.[11]

Conclusion

Combination of Bromhexine 4 mg, Salbutamol 1 mg and Etophylline 50 mg per 5 ml syrup and salbutamol 2 mg, Etofylline 200 mg, Bromhexine hydrochloride 8 mg per tablet provides optimum relief and is safe for use in the management of airway obstructions in COPD.

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DISCLOSURE

This study was conducted as a part of Pharmacovigilance activity for Albutamol Plus Tablet and Albutamol Plus Syrup manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd.

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