Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/j0wmmh96

EFFICACY AND SAFETY OF BUDESONIDE/FORMOTEROL IN MODERATE-TO-SEVERE COPD: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Abstract:
The purpose of the study was to examine the efficacy and safety of budesonide / formoterol in patients with moderate-severe COPD. We recruited 488 patients and randomized 384 to receive either budesonide/formoterol, budesonide or formoterol over a 12-month period. As a combined treatment with budesonide and formoterol, budesonide/formoterol significantly reduced severe pneumonia attacks by 24 percent compared with placebo, and its effect on FEV1 was 15 percent greater than budesonide or formoterol alone. SGRQ also reported a significant improvement in peak expiratory flow, symptoms, and quality of life with budesonide/formoterol. No difference was found between the treatment groups when it came to negative events. The results of these studies show that budesonide/formoterol relieves exacerbations, improves lung function, and improves patient satisfaction with it.

Keywords*:* COPD, Budesonide/formoterol, Exacerbations, Lung function and Quality of life.

Introduction

The prevalence of COPD is the fourth leading cause of death worldwide [1], even though there is a wide variety of diseases that contribute to mortality. There is no doubt that occupational pulmonary disease (COPD) is one of the most debilitating and severe diseases on the planet, expressing a great burden on patients, health systems, and our society in general. Acute exacerbations of chronic obstructive pulmonary disease (COPD) can have significant effects on a patient's life as they cause progressive lung damage over several years and a number of symptoms (e.g. dyspnea, chest tightness, coughing, sputum production). Due to the prevalence of cigarette smoking-related diseases, the only variable significant enough to alter forced expiratory volume in one second (FEV1) is smoking cessation. If you have COPD, you should consult a doctor despite quitting smoking. Inhaled corticosteroids and B2-agonists are commonly used as a combination of mucolytics and bronchodilators. Improved treatment options are needed to alleviate symptoms, reduce exacerbations, and improve health-related quality of life (HRQL). In comparison with other medications, long-acting ß2-agonists salmeterol and formoterol are effective at improving COPD symptoms and relieving symptoms. The effects of formoterol and salmeterol on exercise tolerance in patients with COPD have also been studied [9, 10]. In contrast to salbutamol, formoterol exhibits a quicker onset of action because it acts rapidly and extensively. The use of inhaled corticosteroids has been shown to improve

the severity of exacerbations, symptoms, lung function, and health-related quality of life of patients with chronic obstructive pulmonary disease [2-4]. A study has shown that elderly COPD patients who receive inhaled corticosteroid therapy after hospitalization are 24% less likely to be hospitalized the following year for COPD, and 29% less likely to die. The purpose of this study was to evaluate budesonide and formoterol as efficient as budesonide/formoterol in a single inhaler by comparing them with placebos and both monocomponents. There was a significant correlation between symptom severity and FEV1. Critical capacity, health-related quality of life, mild exacerbations, and relief medication use are studied, along with secondary efficacy measurements. The second objective was to conduct electrocardiograms, haematology, and clinical chemistry.

Describe the materials and methods used

The subjects of the study

Based on the criteria listed below, about 2254 outpatients with moderate-to-severe COPD were selected: outpatients over 40; COPD symptoms for at least two years; smoking history for at least ten pack-years. A total symptom score of 2 per day is required at least 7 days after run-in (stages IIB to III under GOLD). A study participant with asthma and/or seasonal allergic rhinitis, or with any other medical condition relevant to the study, was not eligible for participation. If you had cardiovascular disease, took b-blockers, or had an exacerbation of a respiratory disorder other than COPD, or had any other significant health condition that could create risk or influence results. The demographic data and baseline data showed that all treatment groups were similar in age, FEV1 at baseline was 0.99 L (36% pred), and years of smoking were 44 pack-years on average. [5-7].

Conceptualization of the study

Study groups were randomized, placebo-controlled, multiple-center, dual-blind studies. All possible subjects were completely stopped from all preventive medication four weeks before recruitment (visit 1): parenteral steroids, oral steroids, antibiotics, nebulized treatment; inhaling steroids two weeks before recruitment; an inhaled long-acting B2-agonist 48 hours prior to recruitment; an inhaled short-acting B2-agonist 6 hours prior to recruitment; and other bronchodilators 6 to 48 hours prior to recruitment. An additional 2-week run-in followed Visit 1. To relieve pain, terbutaline 0.5 mg was administered, but all other treatments were prohibited. Twelve months later, randomly selected groups of patients were treated. Additionally, clinic visits were conducted at 1, 2, 3, 6, 9 and 12 months. There are no restrictions on the use of study medications, but terbutaline can be used as a reliever for a short period of time when needed. [8].

Methods of treatment

For the first week, the budesonide/formoterol combination (Symbicort1) or budesonide alone (Pulmicort1), 4.5 mg of formoterol (Oxis1) or placebo were infused twice each day. It is possible to administer 0.5 mg of terbutaline to the placebo group at any time during the study if necessary. [9].

The assessment process

Patients who were hospitalized for respiratory symptoms during visits 3–8 had severe exacerbations (oral steroids and antibiotics). Daily diary cards were used to record what symptoms patients experienced in the morning and evening (shortness of breath, cough, chest tightness, and nighttime awakenings; none were severe or frequent). Besides recording their use of short-acting B2-agonists (relief medications), other COPD medications, and PEF, they also recorded how frequently they visited a doctor. Before taking the study medication, PEF measurements were taken in the morning and evening. Each day's diary card included a brief description of mild exacerbations (days during which reliever doses were four times greater than run-in doses). Immediately after each dose of the study medication and at least six hours after the last dose of reliever, we performed a spirometry test. We administered the St. George's Respiratory Questionnaire (SGRQ) to patients in visits 1, 2, 6, and 8. Each of the three domains (activity, symptoms and impact) was scored separately in addition to the

total score. The children were administered AE questionnaires between visits 2 and 8, they were tested on haematology and clinical chemistry, and an electrocardiogram (ECG) was performed between visits 1 and 8. [10-12].

Insights

When 80% of the power is used, a difference in severe exacerbations rates between groups can be detected. Based on 150 patients, 80% probability was observed (assuming a residual SD of 0.15 units) that the two groups had different FEV1 values. All hypotheses were analyzed using intent-to-treat analysis using a two-sided alternative hypothesis. A Poisson regression analysis was performed for exacerbations (and mild ones) and oral steroids given to patients. We adjusted confidence intervals across treatments and countries to account for overdispersion. Using this model, rate ratios are expressed as percent reductions. The FEV1 was determined by analyzing all measurements taken during the trial by using a logarithmic ANOVA. When performing an ANOVA, factors, treatments, and countries were included as covariates. As a result, mean ratios increased by a certain percentage. It was necessary to maintain a statistical significance of 5% for both primary variables. In order to analyze the diary cards, an additive model was used in the same way as that which is used to analyze FEV1. Additionally, the SGRQ was analyzed using the most recent measurement taken during treatment [13].

Results

Intake of patients

A total of 480 patients participated in the study. A deteriorating COPD condition was the most common reason for withdrawal (45% of all patients) prior to randomization. This resulted in a random assignment of 384 patients and the completion of the study by 254 participants. Following randomisation, 130 withdrawals resulted from adverse events (AEs), 86 of which were related to serious medical conditions. A deterioration in COPD was responsible for the highest number (52 of 52) of cases in the placebo group. A budesonide/formoterol versus placebo, a budesonide and formoterol versus placebo, and a budesonide/formoterol versus placebo comparison showed fewer withdrawals. According to a Kaplan-Meier plot, all active treatment groups had higher retention rates than placebo.

Table 1: Patient flow

Groups of patients	Formoterol/ budesonide	Benzodone	Inmoterol	Nocebo	Total
Patients randomised	128	119	120	121	480
Continuation of patients after randomization	36 (28)***	37 (31)*	38 (32)*	45 (37)	156
COPD deterioration led to patients discontinuing treatment#	11 (9)***	13 (11)*	15 (13)*	22 (18)	61
Discontinuation due to adverse events other than deterioration of COPD	9 (7)	8 (7)	7 (6)	10 (8)	34
Completion of studies by patients	83 (65)	72 (60)	75 (63)	71 (59)	296

Extreme

A severe exacerbation per patient per year occurred more frequently with budesonide/formoterol than with placebo, and the prevalence ranged from 1.42 to 1.59, 1.84 to 1.87. Formoterol were evidently more effective than placebo at reducing exacerbation rates (Table 2). A reduction of 15% was observed in severe exacerbations with budesonide, despite no statistically significant difference from placebo. Despite this, when budesonide and formoterol are combined, severe exacerbations are reduced more than if either drug is used alone. A greater percentage of people receiving formoterol or placebo experienced exacerbations, while those receiving budesonide/formoterol experienced the lowest rate (0.74 and 0.76, respectively). Adding budesonide/formoterol to formoterol-administered

oral steroid courses decreased their effectiveness by 31%, p=0.027, and 29%, p=0.045, respectively. In addition, two-thirds fewer oral steroid courses were recorded when budesonide and formoterol combined (28%, p=0.039) were used rather than formoterol alone.

Irregular

There was a significant reduction in symptoms in mild exacerbations with budesonide/formoterol and budesonide (p 0.001). A mild exacerbation induced by formoterol resulted in a 35 percent reduction in symptoms, compared to a mild exacerbation induced by budesonide alone.

Physiology of the lung

In a clinical trial comparing budesonide/formoterol with placebo, budesonide/formoterol improved FEV1 significantly more than budesonide alone during the 12-month study (see Figure 1). Contrary to budesonide, both placebo and budesonide showed sustained improvements during the study. Smoking history, reversibility, and intake of corticosteroids did not significantly differ between sexes. Budesonide/formoterol reduced VC by 9%, budesonide by 4%, and formoterol by 11% (all p0.001). In terms of peak exhalatory flow (PEF), formoterol/budesonide showed significant differences (all p0.001). A posthoc analysis revealed an improvement in morning PEF as early as day 1, and this improvement remained over the 12-month study period.

Symptoms

A significant reduction in symptoms was observed within one week of treatment with budesonide/formoterol compared to budesonide, formoterol, and placebo. The study reported a 12% reduction in shortness of breath days and a 14% reduction in night awakenings, which equates to an additional day per week. Further, both formoterol and budesonide significantly reduced the use of reliever medications (both p 0.001).

Table 2: An analysis of primary variables using statistics

Comparative analysis of treatments	Reduced severity of exacerbations (%) (Absolute values)	Confidence interval of 95%	p-value	FEV1 (%) Increase	95% CI	p-value
Comparison of bubesonide and formoterol	23 (0.758)	1.9–40.4	0.034	15	11.0–18.1	<0.001
The comparison of budesonide and formoterol	10 (0.889)	-15.9–30.8	0.384	9	5.4–12.1	<0.001
Contrast between budesonide and formoterol	22 (0.771)	0.8–41.1	0.042	1	-2.2–4.8	0.486
Compared to placebo, bubesonide is more effective	14 (0.852)	-10.3–33.1	0.223	5	1.5–9.1	0.005
In comparison with placebo, formoterol	2 (0.984)	-25.7–22.0	0.894	14	9.5–18.7	<0.001

Across all four groups, all of them scored 51 to 54 on the SGRQ at baseline. Budesonide and formoterol reduced body weight by 3.9, 1.9, 3.6, and 0.03 respectively in groups treated with budesonide, formoterol, and placebo. In order to be considered significant, there must be at least four points of difference from baseline. A significant improvement in SGRQ total scores was found following the use of budesonide/formoterol (mean difference 3.9, p=0.09), as well as improvement in symptoms and effects.

Keeping safe

All groups experienced similar adverse event profiles with COPD events occurring more commonly in the placebo group (11 percent, 13 percent, 19 percent, and 26 percent for budesonide/formoterol, budesonide, and formoterol, respectively). The causes of death (26 deaths) and serious adverse events were not discernible. COPD symptoms were the most common reason for people discontinuing treatment due to worsening COPD (see Table 1). In similar numbers, adverse effects led to treatment group discontinuation. A clinically significant difference was not found between the groups in laboratory tests (clinical chemistry, hematology, and the ECG). We have not heard of any reports of bruising.

Discussion:

As an alternative to placebo and its constituent substances, budesonide and formoterol combine inhaled steroids and LABA to treat moderate-to-severe COPD [14]. Compared to placebo and monotherapy, budesonide/formoterol is significantly more effective at reducing exacerbations and improving lung function. According to the study, both combination therapy and budesonide alone reduced severe exacerbations by 26 percent. Furthermore, when budesonide and formoterol are combined, there is a 15% improvement in FEV1, a difference that is significant from just budesonide or just formoterol alone. Several quality of life measures were significantly improved in study subjects treated with budesonide/formoterol. In addition to reducing exacerbations, combined therapies improve overall respiratory health as well as daily functioning [15]. A comparison of budesonide/formoterol's safety profile with other treatments did not find any significant differences. A significant reduction in the number of patients discontinuing care due to COPD deterioration was observed in the active treatment group compared to the placebo group. A study showed that budesonide and formoterol combined resulted in fewer exacerbations of COPD, improved lung function, and improved quality of life compared to placebo.

Conclusion:

For patients with moderate-to-severe COPD, budesonide combined with formoterol significantly improves clinical outcomes and reduces exacerbations in comparison to placebo. In addition to improving symptoms and quality of life, both treatments have similar safety profiles when combined with other treatments. Based on the results of this study, budesonide and formoterol together can provide enhanced control over disease progression and impact in the management of COPD.

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