

The rapid effects of budesonide plus formoterol in patients with obstructive airway diseases

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Introduction: The use of a combination inhaler containing budesonide and formoterol (BUD/FOR) to both maintenance and quick relief therapy has been recommended as an improved method of using inhaled corticosteroid/long-acting β agonist therapy. The aim of this study was to investigate the acute effects of BUD/FOR and testing the availability of BUD/FOR for early reversibility test in patients with airway obstruction.

Patients and methods: The study was conducted on patients who were admitted to the Department of Pulmonary Medicine, Samsun Medical Park Hospital, Samsun, Turkey.

Results: A total of 44 patients were included in the study. The mean age of patients was 48.5 ± 17.3 (range 10–75) years and the male-to-female ratio was 36:8. The pre-bronchodilator pulmonary function test results are as follows: the mean forced vital capacity, $3,025 \pm 1,162$ mL ($76.3\% \pm 23.2\%$); mean forced expiratory volume in 1 second (FEV_1), $1,898 \pm 725$ mL ($59.2\% \pm 19.1\%$); mean FEV_1 /forced vital capacity, $62.8 \pm 6.3\%$ (range 42%–70%); mean peak expiratory flow, $3,859 \pm 1,779$ mL ($48.0\% \pm 19.7\%$); and forced expiratory flow 25%–75%, $1,295 \pm 486$ mL ($35.8\% \pm 12.3\%$). The reversibility was positive in 26 (59.1%) patients. The absolute change and percentage of change in FEV_1 were 318 ± 228 mL and $17.7\% \pm 11.9\%$, respectively. The patients were divided into two groups according to reversibility (reversible and irreversible) and both groups were compared with changes according to spirometric results. FEV_1 values were statistically different between the two groups.

Conclusion: The fixed combination of BUD/FOR has rapid bronchodilator effect, and they can be used for early reversibility test.

Keywords: formoterol/budesonide, reversibility test, asthma, chronic obstructive pulmonary disease

Introduction

Obstructive lung diseases are one of the most common chronic diseases worldwide, and they are effectively controlled in most patients with a combination inhaler containing a corticosteroid and a long-acting β_2 agonist (LABA). In patients with airway obstruction, evaluation of acute response to bronchodilators (the test of reversibility of airway obstruction) is a commonly used procedure in clinical and research studies. We know that the use of a combination inhaler containing budesonide and formoterol (BUD/FOR) to both maintenance and quick relief therapy has been recommended as an improved method of using inhaled corticosteroid/LABA.¹ There is no clear consensus on what constitutes reversibility or a significant acute response to a bronchodilator. The aim of this study was to examine the acute effects of using BUD/FOR and testing the availability of BUD/FOR for early reversibility test in patients with airway obstruction.

Patients and methods

The study was conducted on patients who were admitted to the Department of Pulmonary Medicine, Samsun Medical Park Hospital, Samsun, Turkey. The following inclusion criteria were evaluated:

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Symptomatic patients (cough, dyspnea, and/or wheezing);

Obstructive breath sounds on chest auscultation;

Presence of airway obstruction in spirometry (forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] \leq 70% of expected);

Patients who had never used bronchodilators before, or;

Patients who had not received short- or long-acting inhaled bronchodilator therapy within the recent 12 hours.

The study was performed in accordance with the ethical principles in the Good Clinical Practice guidelines, in addition to applicable local regulatory requirements, and the protocol was approved by local Bahcesehir University Clinical Research Ethics Committee. The patients were informed of the study procedure, and written informed consents were obtained.

Pulmonary function test and reversibility assessment

The values of basal FVC, FEV₁, FEV₁/FVC, peak expiratory flow (PEF), and forced expiratory flow 25%–75% (FEF 25%–75%) were measured using the MIR (MIR Medical International Research Srl, Rome, Italy) MiniSpir PC-Based USB Spirometer by the same physician (Sevket Ozkaya) following a 30-minute resting period in an outpatient clinic setting. The test was performed in the seated position, when the nose was clamped and nasal respiration was hindered. The patients performed the forced expiratory maneuver at least three times, and the maximum FEV₁ value was recorded as the basal value.

Reversibility test

Following baseline spirometry, patients inhaled a fixed combination of BUD/FOR (Rolastym Combi®, Deva®, Turkey; 12/400 μ g [Halkalı Merkez Mah. Basın Ekspres Cad-desi, Istanbul, Turkey]) and dry powder inhaler capsule, and then spirometry was repeated after 15 minutes. Reversibility levels were evaluated as the absolute change in FEV₁ and the percentage of change from the initial FEV₁, calculated as $FEV_{1\%}\Delta_{init} = \frac{\text{post-FEV}_1 - \text{pre-FEV}_1}{\text{pre-FEV}_1} \times 100$ (according to American Thoracic Society guidelines), and bronchial reversibility is defined as a drug-induced increase in FEV₁ of \geq 200 mL and \geq 12% baseline.

Statistical assessment

Results were presented as means \pm standard errors of means. The probability $P < 0.05$ was considered significant. Descriptive group data were compared using the unpaired Student's *t*-test and Pearson chi-square test.

Results

A total of 44 patients were included in the study. The patients' demographic data and baseline pulmonary function test results are shown in Table 1. The mean age of patients was 48.5 ± 17.3 (range 10–75) years and the male-to-female ratio was 36:8. The basal (pre-bronchodilator) pulmonary function test results are as follows: mean FVC, $3,025 \pm 1,162$ mL ($76.3\% \pm 23.2\%$); mean FEV₁, $1,898 \pm 725$ mL ($59.2\% \pm 19.1\%$); mean FEV₁/FVC, 62.8 ± 6.3 mL (range 42%–70%); mean PEF, $3,859 \pm 1,779$ mL ($48.0\% \pm 19.7\%$); and FEF (25%–75%), $1,295 \pm 486$ mL ($35.8\% \pm 12.3\%$). The post-bronchodilator test results and changes in values are shown in Table 2. The reversibility was positive in 26 (59.1%) patients. The absolute change and percentage of change in FEV₁ were 318 ± 228 mL and $17.7\% \pm 11.9\%$, respectively. The patients were divided into two groups according to reversibility (reversible and irreversible), and results were shown in Table 3. Both groups were compared with changes according to spirometric results, and only in FEV₁, values were statistically different between two groups (Table 4) ($P \leq 0.05$).

Discussion

There is no consensus on which bronchodilator drug should be used for the reversibility test. The reversibility test might

Table 1 Baseline characteristics of patients

Characteristics	Values
Number of patients	44
Age (years)	
Mean \pm SD (range)	48.5 ± 17.3 (10–75)
Male/female	36/8
Smoking status	
Non-smoker, n (%)	13 (29.5%)
Current smoker, n (%)	21 (47.7%)
Ex-smoker, n (%)	10 (22.7%)
Baseline spirometry (mean)	
FVC	
mL \pm SD (range)	$3,025 \pm 1,162$ (990–5,890)
%pred \pm SD (range)	76.3 ± 23.2 (29–123)
FEV ₁	
mL \pm SD (range)	$1,898 \pm 725$ (620–3,360)
%pred \pm SD (range)	59.2 ± 19.1 (22–96)
FEV ₁ /FVC	
%pred \pm SD (range)	62.8 ± 6.3 (42–70)
PEF	
mL \pm SD (range)	$3,859 \pm 1,779$ (1,110–7,740)
%pred \pm SD (range)	48.0 ± 19.7 (14–90)
FEF (25%–75%)	
mL \pm SD (range)	$1,295 \pm 486$ (480–4,810)
%pred \pm SD (range)	35.8 ± 12.3 (12–62)

Abbreviations: FEF, forced expiratory flow; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; SD, standard deviation; %pred, % predicted.

Table 2 The post-bronchodilator pulmonary function test results

Spirometry	Post-bronchodilator results	Change
FVC (mean)		
mL ± SD (range)	3,279±1,099 (1,170–5,850)	276±284 (0–1,270)
%pred ± SD (range)	82.9±21.1 (39–125)	12±14.4 (0–69)
FEV ₁ (mean)		
mL ± SD (range)	2,219±836 (860–4,120)	318±228 (40–1,020)
%pred ± SD (range)	69.1±21.1 (25–109)	17.7±11.9 (3–58)
PEF (mean)		
mL ± SD (range)	4,752±1,998 (1,610–8,700)	899±719 (0–2,830)
%pred ± SD (range)	59.0±21.7 (19–108)	26.2±19.4 (0–78)
FEF (25%–75%) (mean)		
mL ± SD (range)	1,690±721 (540–3,610)	402±3,080 (0–1,230)
%pred ± SD (range)	44.4±16.9 (14–86)	29.7±20.4 (0–82)

Abbreviations: FEF, forced expiratory flow; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; SD, standard deviation; %pred, % predicted.

be performed using metered-dose inhaled bronchodilators, dry powder inhaler, and metered-dose inhaled bronchodilators through an air chamber or nebulizer.² Although the short-acting beta-2 agonists, salbutamol (SLB) and terbutaline, are the most commonly used bronchodilators for early reversibility test, the fixed combination of long-acting beta-2 agonist (LABA) plus inhaled steroid drugs are used in the treatment of patients with airway obstruction. LABA plus inhaled steroid drugs have also been reported to act in short term. In our previous study, the positive reversibility test with SLB was found in 61.9% of patients.³ Another study that compared the fixed combination of BUD/FOR (320/9 µg) with SLB reported that the positive reversibility test was higher in BUD/FOR group (50%) than in SLB group (20%).⁴ In the present study, the reversibility was positive in 26 (59.1%) patients. Recent study suggested a new approach for acute exacerbation – SMART (single inhaler maintenance and reliever therapy). This uses the combination inhaler, rather than the short-acting β₂ agonist, as the reliever.^{5–7}

We examined the relationship between reversibility and change in values of FVC, FEV₁, PEF, and FEF (25%–75%). Only the absolute change and percentage of change in mean FEV₁ were statistically significant ($P \leq 0.05$). These findings

show that FEV₁ is a true parameter for the evaluation of reversibility.

We used the short-acting beta-2 agonists (usually SLB) and a combination inhaler containing a corticosteroid plus a LABA for early and late reversibility tests in patients with airway obstruction, respectively. Also, we prescribed a combination inhaler containing a corticosteroid plus a LABA (usually BUD/FOR) for patients with airway obstruction, and trained the patients in the correct usage of inhaler devices. These results authenticate the idea of using a combination inhaler containing a corticosteroid and a LABA for early reversibility test. This study proves that a fixed combination of BUD/FOR can be used in early reversibility testing. Further studies are required to support this result.

Conclusion

The following results are observed regarding the usage of fixed combination of BUD/FOR in early reversibility test. They are fast acting. They can be used for early reversibility test (not only for treatment). The procedure contributes to the patients in the training of using inhaler devices during spirometry. Patients can immediately see the effects of the

Table 3 The results of reversibility test

Reversibility	n (%)	Pre-bronchodilator results	Post-bronchodilator results	Change
Yes	26 (59.1)			
FEV ₁ (mean)				
mL ± SD		1,943±707	2,389±832	442±218
%pred ± SD		57.5±17.5	70.6±20.1	24.3±11.1
No	18 (40.9)			
FEV ₁ (mean)				
mL ± SD		1,833±765	1,973±802	139±66
%pred ± SD		61.8±21.6	66.9±22.6	8.1±3.6

Abbreviations: FEV₁, forced expiratory volume in 1 second; SD, standard deviation; %pred, % predicted.

Table 4 The relationship between reversibility and spirometry results

Change	Reversible group (n=26)	Irreversible group (n=18)	P-value
FVC (mean)			
mL ± SD	360±315	154±177	0.072
%pred ± SD	15.2±16.3	7.4±9.8	0.096
FEV ₁ (mean)			
mL ± SD	442±218	139±66	0.000
%pred ± SD	24.3±11.1	8.1±3.6	0.001
PEF (mean)			
mL ± SD	1,167±721	512±522	0.210
%pred ± SD	34.7±19.0	14.0±12.3	0.150
FEF (25%–75%) (mean)			
mL ± SD	509±314	247±228	0.105
%pred ± SD	36.5±20.1	20.0±16.9	0.191

Abbreviations: FEF, forced expiratory flow; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; SD, standard deviation; %pred, % predicted.

drugs used in the treatment. It improves the treatment compliance of patients.

Author contributions

HB, SO, and AD designed the study and performed the statistical analysis. FE conceived the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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