Effects of Formoterol Inhaled Dry Powder on Exercise Performance in Chronic Obstructive Pulmonary Disease: A Single-Center, Randomized, Double-Blind, Placebo-Controlled, Crossover Study

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ABSTRACT

Background: Inhaled bronchodilators commonly are used to reduce the work of breathing in patients with chronic obstructive pulmonary disease (COPD). The effects of bronchodilators are assessed in terms of symptom relief and/or improvements in spirometric indices. However, disability in COPD patients also is related to determinants such as exercise tolerance, which cannot be predicted on the basis of respiratory function. The effect of bronchodilators, such as inhaled beta₂-agonists, on exercise performance of COPD patients needs to be tested.

Objective: This study investigated the effects of formoterol inhaled dry powder on exercise performance assessed using the shuttle walking test (SWT) in patients with mild to moderate COPD.

Methods: Patients having COPD with mild to moderate airway obstruction performed a pulmonary function test and an SWT before and after inhalation, on 2 consecutive days, of formoterol 12 µg or placebo, given by dry powder inhaler, according to a double-blind, placebo-controlled, crossover study design. Breathlessness was measured using the Borg scale (BS) and a visual analog scale at baseline and after an SWT.

Results: Twenty patients (15 men, 5 women; mean [SD] age, 65.95 [8.32] years) were included in the study. Forced expiratory volume in 1 second (FEV₁) ($P = 0.009$), forced mid-expiratory flow (FEF₂₅₋₇₅) ($P = 0.011$), and SWT ($P = 0.005$) improved significantly more with formoterol than placebo. Breathlessness decreased with formoterol, but the difference compared with placebo was statistically significant only when measured using the BS ($P = 0.023$). In the pooled placebo and formoterol tests, changes in the SWT were unrelated to changes in FEV₁ ($r = 0.18$) and in FEF₂₅₋₇₅ ($r = 0.31$).

Conclusions: The results of this study showed that formoterol inhaled dry powder significantly improved exercise performance in patients with COPD and that this effect was at least partially independent of achieved bronchodilation. A larger cohort of patients should be studied and a more comprehensive protocol performed to verify whether the increase in exercise tolerance after administration of formoterol is related to a decrease in expiratory flow limitation during exercise and/or to systemic effects of the drug. Another issue to be clarified is whether the improvement in exercise capacity can significantly decrease disability in patients with severe COPD. (*Curr Ther Res Clin Exp.* 2003;64:317–326) Copyright © 2003 Excerpta Medica, Inc.

Key words: chronic obstructive pulmonary disease, walking test, bronchodilator therapy, health status.

INTRODUCTION

Inhaled bronchodilators commonly are used to produce bronchodilation and to reduce the work of breathing in chronic obstructive pulmonary disease (COPD).¹ Short-acting beta₂-agonists are included in the American Thoracic Society (ATS) guidelines² for the treatment of all stages of COPD because they provide a rapid response that is useful for symptom relief. Long-acting beta₂-agonists also have a role in the treatment of COPD, as stated in more recent guidelines.³ Indeed, their lower dose frequency improves patient compliance with regular therapy.^{1,3} In a double-blind, placebo-controlled, crossover study⁴ of long-acting beta₂-agonists in COPD, salmeterol treatment over a 4-week period produced improvement in both clinical and respiratory function. In another trial,⁵ formoterol treatment caused long-lasting lung function improvements in patients with poorly reversible, moderate to severe COPD. Compared with salbutamol, formoterol inhaled dry powder showed greater clinical efficacy and comparable tolerability in the long-term treatment of patients with reversible obstructive airway disease.⁶ Formoterol also showed greater functional efficacy than ipratropium in patients with stable COPD.⁷

In all of these published studies, the effects of bronchodilators are assessed in terms of symptom relief and/or improvements in spirometric indices. However, disability in COPD patients also is related to determinants such as exercise tolerance, which cannot be predicted on the basis of respiratory function. In fact, a weak correlation exists between airway obstruction and exercise performance.⁸ For this reason, the effect of bronchodilators, such as inhaled beta₂-agonists, on exercise performance of COPD patients needs to be tested. Data on long-acting beta₂-agonists are limited. In 1 study,⁹ salmeterol did not significantly increase the distance walked, whereas the effect of formoterol has been expressed only by a significant effect on time to exhaustion.

The aim of the present study was to investigate the effects of formoterol inhaled dry powder on exercise performance assessed using the shuttle walking test (SWT) in patients affected by mild to moderate COPD.

PATIENTS AND METHODS

Patients

Patients having COPD with mild to moderate airway obstruction according to the ATS¹⁰ criteria who were in stable clinical condition were eligible for this double-blind, placebo-controlled, crossover study. The diagnosis of stable COPD conformed to criteria reported elsewhere.¹¹ Exclusion criteria were the inability to use the inhaler device and the presence of comorbid disease that could limit a patient's performance on an exercise test.

All patients regularly attended the outpatient service of the Respiratory Physiology Department of the Catholic University (Rome, Italy), which provided us with detailed knowledge of their characteristics. Informed written consent was obtained from each patient, and the study protocol was approved by the local ethics committee.

The study patients were receiving long-term treatment with inhaled corticosteroids and short-acting beta₂-agonists; therefore, they entered an 8-hour wash-out period before starting the study medication.

Measurements

A pulmonary function test with measurement of pulmonary flows and volumes was performed using the computerized Baires® system (Biomedin® s.r.l., Padua, Italy); forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and forced mid-expiratory flow (FEF₂₅₋₇₅) were recorded.

Health status and mood state were assessed at baseline by means of the St. George's Respiratory Questionnaire¹² (SGRQ) and the Hospital Anxiety and Depression (HAD) Scale,¹³ respectively. The SGRQ is a well-validated measure of impaired health in COPD and consists of 3 component scores (symptoms, activity, and impacts) and a summary score calculated from the 3 components. Each score ranges from 0 to 100, with 100 indicating maximum disability. The HAD score consists of 14 items that produce separate scores for anxiety and depression. The scores range from 0 to 21, with a score ≥ 10 indicating clinically significant anxiety or depression.

Exercise performance was assessed using the SWT. This test is an externally paced, incremental exercise test that uses a 10-m course, with the walking speed controlled by signals from an audiocassette and gradually increased. The test ended when the patient became too breathless to maintain a required speed. The results were expressed as distance (m) covered.¹⁴ During the SWT, oxygen-hemoglobin saturation was monitored using a pulse oximeter (Nonin® Model 8500M, Nonin Medical, Inc., Plymouth, Minnesota).

Breathlessness was measured using the Borg scale¹⁵ (BS) and a visual analog scale (VAS).¹⁵

Study Protocols

Each patient performed a forced expiratory maneuver and an SWT before and 30 minutes after the inhalation of formoterol dry powder* 12 µg or placebo, given by dry powder inhaler (Aerolizer®), administered on 2 consecutive days according to a randomized list. The BS and VAS also were computed at baseline and after SWT. Investigators were blinded to the treatment (formoterol or placebo) inhaled by the patients.

The plasma concentration of formoterol inhaled dry powder peaks 5 minutes after the completion of inhalation, whereas the maximal bronchodilating effect occurs ~2 hours later, although bronchodilation begins within a few minutes.^{16,17} It follows that bronchial and muscle effects might have different time courses. We chose to repeat the tests 30 minutes after inhalation (ie, before maximal bronchodilation) to assess the possibility of an earlier direct metabolic effect.

Statistical Analysis

Changes in spirometric parameters after treatment with formoterol or placebo were expressed as percentage of pretreatment values to assess the degree of reversibility of bronchial obstruction, according to recommended procedures.¹⁸ Differences between treatments were assessed by the paired *t* test, and simple regression analysis was used to calculate the correlation coefficients between different variables. Statistical significance was set at $P \leq 0.05$.

RESULTS

Twenty patients (15 men, 5 women; mean [SD] age, 65.95 [8.32] years) were included in the study. Baseline patient characteristics are shown in Table I. Comorbid diseases and the inherent therapy were as follows: hypertension, treated with calcium channel blockers and/or angiotensin-converting enzyme inhibitors, 7 patients (35%); diabetes mellitus, treated with oral hypoglycemic agents, 4 patients (20%); and peptic ulcer disease and/or gastritis, treated with omeprazole, 3 patients (15%). All patients had a moderately impaired health status at baseline (mean [SD] SGRQ summary score, 50.08 [22.27]). No clinically evident depression or anxiety was recorded. The mean (SD) distances covered (SWT) and the degree of breathlessness were similar at baseline before treatments.

Spirometric findings at baseline and after treatment with formoterol are shown in Table II; the comparisons of changes after treatment are shown in Table III. FVC changes were not significantly different between formoterol and

*Trademark: Foradil® (Novartis Pharmaceuticals Corp., Basel, Switzerland).

Table I. Baseline characteristics of the study patients. (Values are expressed as mean [SD] unless otherwise noted.)

Characteristic	Value
Age, y	65.95 (8.32)
Sex, no. of patients (%)	
Men	15 (75)
Women	5 (25)
Race, no. (%) of patients	
White	20 (100)
Comorbid diseases (treatment), no. (%) of patients	
Hypertension (CCBs or ACEIs)	7 (35)
DM (oral hypoglycemic agents)	4 (20)
PUD/gastritis (omeprazole)	3 (15)
SGRQ*: Summary score (normal value, 44.7; range, 28–63)	50.08 (22.27)
HAD score [†]	
Anxiety	8.90 (5.15)
Depression	7.20 (4.37)
SWT, m [‡]	
Before formoterol	196.50 (87.37)
Before placebo	193.50 (108.13)
BS score ^{‡§}	
Before formoterol	2.25 (2.09)
Before placebo	2.02 (2.31)
VAS score ^{‡§}	
Before formoterol	3.64 (3.47)
Before placebo	3.69 (3.60)

CCBs = calcium channel blockers; ACEIs = angiotensin-converting enzyme inhibitors; DM = diabetes mellitus; PUD = peptic ulcer disease; SGRQ = St. George's Respiratory Questionnaire; HAD = Hospital Anxiety and Depression Scale¹³; SWT = shuttle walking test; BS = Borg scale¹⁵; VAS = visual analog scale¹⁵.

*This scale calculated from 3 component scores (symptoms, activity, and impacts). Each score ranges from 0 to 100, with 100 indicating maximum disability.

[†]This scale consists of 14 items that produce separate scores for anxiety and depression. The scores range from 0 to 21, with a score ≥ 10 indicating clinically significant anxiety or depression.

[‡]No significant differences were found between the baseline values before treatments.

[§]Scale: 0 (no dyspnea) to 10 (maximal dyspnea).

Table II. Respiratory function parameters at baseline and after treatment with formoterol. (Values are expressed as mean [SD].)

Parameter	Before Treatment	% Predicted	After Treatment
FVC, L	2.82 (0.89)	88.05 (21.81)	3.04 (0.91)
FEV ₁ , L	1.53 (0.64)	59.75 (17.99)	1.76 (0.72)
FEV ₁ /FVC, %	52.17 (9.87)	N/A	56.03 (11.08)
FEF ₂₅₋₇₅ , L	0.66 (0.39)	21.25 (10.43)	0.93 (0.57)

FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second; N/A = not available; FEF₂₅₋₇₅ = forced mid-expiratory flow.

placebo. Improvements were significantly greater with formoterol than placebo for both FEV₁ (15.38% [14.35%] vs 5.07% [9.40%]; $P = 0.009$) and FEF₂₅₋₇₅ (46.26% [47.27%] vs 12.07% [27.68%]; $P = 0.011$). Ten patients had a partially reversible obstruction (ie, FEV₁ increased 12% and >200 mL¹⁷ but did not normalize after the administration of formoterol). The distance covered during the SWT increased significantly with formoterol but not placebo (35.50 [40.58] m vs -12.50 [46.78] m; $P = 0.005$). Breathlessness decreased with formoterol, but the difference compared with placebo was statistically significant only when measured using the BS (-0.35 [0.98] vs 0.22 [0.55]; $P = 0.023$).

No significant correlation was found between changes in the SWT and changes in indices of airway obstruction after pooling tests with formoterol and placebo: the correlation coefficients were 0.18 for FEV₁ versus SWT and 0.31 for FEF₂₅₋₇₅ versus SWT.

DISCUSSION

The primary findings of this study were that formoterol significantly improved exercise performance in patients with mild to moderate COPD and that this effect

Table III. Comparison between changes in shuttle walking test (SWT) and dyspnea indices (absolute values) and in respiratory function (mean [SD] %) after treatment.

Parameter	After Placebo	After Formoterol	Paired <i>t</i> Test	<i>P</i>
SWT, m	-12.50 (46.78)	35.50 (40.58)	3.18	0.005
BS score*	0.22 (0.55)	-0.35 (0.98)	-2.47	0.023
VAS score*	0.06 (0.54)	-0.92 (1.92)	-2.04	NS
FVC change, %	3.41 (6.75)	8.64 (9.65)	1.92	NS
FEV ₁ change, %	5.07 (9.40)	15.38 (14.35)	2.90	0.009
FEF ₂₅₋₇₅ change, %	12.07 (27.68)	46.26 (47.27)	2.84	0.011

BS = Borg scale; VAS = visual analog scale; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second; FEF₂₅₋₇₅ = forced mid-expiratory flow.

*Scale: 0 (no dyspnea) to 10 (maximal dyspnea).

was independent of the effect on airflow tone. This finding may have implications for the management of COPD patients because exercise performance is highly relevant to explaining perceived health-related quality of life (HRQL). Previous studies^{19–21} have demonstrated a weak relationship between pulmonary function and HRQL in COPD patients. In contrast, exercise performance, as determined by the 12-minute walking test, correlates negatively with the activity and impacts components of HRQL.²² Thus, the COPD patients who performed better on the walking test had less restricted activities of daily living (ADLs) and were less exposed to the negative impact of the disease on their ADLs. Moreover, limitations in exercise performance, as assessed by the SWT, were the primary determinant of disability in severely dyspneic COPD patients.²³ The well-known possibility of improving SWT performance after 2 months of pulmonary rehabilitation and maintaining the improvement for 10 months indicates that HRQL may improve with rehabilitation programs.^{24,25}

Our findings add to existing literature by showing that no statistically significant correlation exists between the effects of treatment with formoterol on airway patency and exercise performance. Thus, the observed significant improvement in expiratory flows after formoterol treatment did not support the seemingly obvious explanation of formoterol-induced lengthening of maximal walked distance. Furthermore, a trend toward decreasing dyspnea was evident after inhalation of formoterol. This effect was shown by changes in the BS but not in the VAS, probably because of greater intra- and interindividual variability of the VAS. These findings point to the possibility that formoterol improved exercise tolerance via an unidentified systemic effect independent of the induced changes in bronchial tone. Indeed, a small fraction of inhaled formoterol is absorbed through the bronchial tree and could improve contraction of peripheral and myocardial muscle.¹⁵ Formoterol increases the release and plasma concentration of noradrenaline,²⁶ and clenbuterol improves the contractile function of skeletal muscle fibers in mice.²⁷ Moreover, at least in myocardial cells, beta₂-adrenergic stimulation enhances calcium influx through the L-type channels.²⁸ Based on pharmacokinetic characteristics, decoupling of the bronchial and muscular effects of formoterol could account for the observed lack of correlation between improvements in bronchial flows and exercise tolerance.^{16,17} Furthermore, these effects seem to be dose dependent; formoterol improves lung function parameters with a positive dose-response relationship and exercise capacity with a negative relationship, probably because increased unevenness in ventilation-perfusion ratio at higher doses limits exercise capacity.²⁹

This study had several limitations. First, the relatively small sample size and the short period between dosing and measurements likely increased the threshold for some changes (eg, VAS results) achieving significance after the administration of formoterol. Second, we did not measure flow limitation using the negative pressure method³⁰; therefore, we could not test the hypothesis that the improvement in exercise performance in our patients was attributable to a decrease in expiratory flow limitation after treatment with formoterol.³¹

The lack of correlation in our patients between formoterol-induced increases in walked distance and FEF_{25-75} , an indirect estimate of flow limitation,³² seems to exclude this hypothesis. However, formoterol might have prevented exercise-induced increase in airway tone, which could not be predicted by the postinhalation but preexercise changes in airflows.

CONCLUSIONS

In our study of patients affected by mild to moderate COPD, formoterol inhaled dry powder significantly improved exercise performance, and this effect is at least partially independent of the achieved bronchodilation. A larger cohort of patients should be studied and a more comprehensive protocol performed to verify whether the increase in exercise tolerance after administration of formoterol is related to a decrease in expiratory flow limitation during exercise and/or to systemic effects of the drug. Another issue to be clarified is whether the improvement in exercise capacity can significantly decrease disability in patients with severe COPD.

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