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Bronchodilator response to formoterol Turbuhaler in patients with COPD under regular treatment with formoterol Turbuhaler

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Abstract

Formoterol Turbuhaler has been suggested for as-needed use in asthmatic patients. We investigated whether regular treatment with formoterol would modify the dose-response curves to formoterol in patients with partially reversible COPD. In this randomised, double-blind, cross-over study taking place over four non-consecutive days 16 outpatients with moderate to severe COPD, who were under regular treatment with formoterol Turbuhaler (18 μg in two daily doses) from at least 4 months, inhaled a conventional dose of formoterol Turbuhaler 9 μg or placebo. Two hours later, a FEV_1 value was established, following which a dose-response curve to formoterol (4.5 μg/inhalation) or placebo was constructed using four inhalations (1 + 1 + 2)—total cumulative delivered dose of 18 μg formoterol—with the following sequences: (1) formoterol pre-treatment + formoterol 18 μg, (2) formoterol pre-treatment + placebo, (3) placebo pre-treatment + formoterol 18 μg, (4) placebo pre-treatment + placebo. Formoterol 9 μg induced significant ($P < 0.0001$) bronchodilation at 2 h after inhalation (best mean increase in FEV_1: 0.170 L). Afterwards, dose-dependent increases in FEV_1 occurred with formoterol (maximum mean increase from 2-h value with formoterol: 0.072 after formoterol pre-treatment, and 0.201 L after placebo pre-treatment). Both maximum values of bronchodilation after the last inhalation of formoterol were statistically different ($P < 0.001$) from 2-h levels. These results show that dose-dependent bronchodilatation of formoterol is maintained despite regular treatment.

Keywords: COPD; Formoterol; Turbuhaler

1. Introduction

The underlying bronchospasm associated with chronic obstructive pulmonary disease (COPD) may be worsened during acute exacerbations. As the airway obstruction becomes more severe, the first therapeutic option is to add an inhaled short-acting β_2-agonist to give rapid relief of bronchospasm [1]. However, since there is evidence for down-regulation of β_2-adrenoceptor protein and mRNA in human lung tissue after selective β_2-adrenoceptor agonist treatment [2], large doses of short-acting β_2-agonist may be necessary to relieve symptoms [3,4]. The introduction of long-acting β_2-agonist bronchodilators has given physicians additional therapeutic options for COPD [5], but the suitability of these drugs for the treatment of acute exacerbations in COPD is currently not known. Inhaled formoterol and salmeterol are not normally used for repeated inhalations in acute relief therapy [6] but recent studies have demonstrated that formoterol can be used as reliever medication to control asthma symptoms [7]. In fact, formoterol has been shown to produce dose-proportional bronchodilation in patients with partially reversible obstructive airway disease [8]. The onset of action of formoterol is as rapid as both salbutamol and terbutaline [9–11], and a significant effect occurs with formoterol within minutes of inhalation of a therapeutic dose [12].

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Nonetheless, some clinicians avoid the use of formoterol as relief medication in patients already taking it as regular treatment. Although not seen clinically [13], it has been suggested that there could be a greater tendency for bronchodilator subsensitivity to develop with longer-acting than with shorter-acting β_2-agonists because of the longer duration of β_2-adrenoceptor occupancy and consequent down-regulation. However, the development of bronchodilator subsensitivity is only partial [14]. Equally, pre-treatment with formoterol or salmeterol could reduce the airway responses to repeated doses of another inhaled β_2-agonist. In particular salmeterol, being a partial β_2-receptor agonist, may act as a β_2-antagonist in the presence of a second β_2-agonist [15].

The aim of the present study was to evaluate if there is a potential in vivo interaction between formoterol used as maintenance therapy and formoterol used as relief medication in patients with partially reversible COPD.

2. Methods

We assessed 16 outpatients with moderate to severe COPD, who were in a stable phase of the disease and were under regular treatment with formoterol Turbuhaler (18 μg in two daily doses) from at least 4 months. All patients reported a good compliance with formoterol before the study. All received budesonide Turbuhaler 200 μg twice daily in a regular manner and did not receive other bronchodilators. Table 1 outlines the baseline characteristics of the population studied. All patients had partially reversible airway obstruction, confirmed at an initial screening visit when they were required to demonstrate an increase of FEV_1 of at least 15% from baseline following inhalation of 200 μg salbutamol. All patients fulfilled the criteria proposed by the American Thoracic Society [1]: i.e. they were >40 years of age, current or former smokers (>10 pack-years) without a history of asthmatic attacks, reporting chronic cough with or without sputum production and/or dyspnea when walking quietly on level ground. Patients had experienced no change in symptom severity or treatment in the preceding 4 months, had shown no signs of a respiratory tract infection in the month preceding or during the trial, and had not taken oral or inhaled corticosteroids for at least 3 months. In addition, all patients had $FEV_1 \leq 65\%$ and $FVC \leq 70\%$ of predicted normal after bronchodilators had been withheld for 24 h, and a best post-bronchodilator FEV_1/FVC of less than 0.8.

Patients with allergic rhinitis, atopy, positive skin test or with a total blood eosinophil count $>400\ mm^{-3}$ were excluded. Patients were also excluded if they had any coexisting cardiovascular or lung disorder. Use of inhaled budesonide was not discontinued, whereas inhaled short-acting bronchodilator drugs and inhaled long-acting bronchodilator agents, included regular formoterol Turbuhaler, were not permitted for at least 6 and 12 h, respectively, prior to each test. Patients were asked to refrain from consumption of cola drinks, coffee, tea, and from smoking, in the 12 h before and also during the investigation.

The study was conducted according to the rules of the declaration of Helsinki and each patient gave informed consent to all procedures.

A flow diagram of the study is shown in Fig. 1. A randomised, double-blind crossover design was used, and each patient received one of the following sequences on each of four non-consecutive days with a wash-out time of at least 48 h between each sequence: (1) formoterol 9 μg as initial treatment + formoterol 18 μg, (2) formoterol 9 μg as initial treatment + placebo, (3) placebo as initial treatment + formoterol 18 μg, or (4) placebo as initial treatment + placebo.

Table 1
Demographic data and pulmonary function of patients

Patient	Sex	Age (years)	FEV_1 (% predicted)	FVC (% predicted)	Reversibility 30 min after 400 μg salbutamol (%)	Absolute increase in FEV_1 30 min after 400 μg salbutamol (L)
1	M	59	49	50	17	0.250
2	M	68	40	66	22	0.210
3	M	67	47	63	15	0.190
4	M	70	56	59	20	0.290
5	M	65	57	62	16	0.250
6	M	75	53	64	15	0.200
7	M	71	64	66	16	0.240
8	F	54	55	70	18	0.300
9	M	58	56	56	17	0.270
10	M	73	65	60	15	0.200
11	M	73	40	54	19	0.150
12	M	61	51	55	15	0.200
13	M	68	26	42	23	0.160
14	M	69	39	59	29	0.300
15	M	65	62	71	16	0.270
16	M	68	53	64	25	0.340

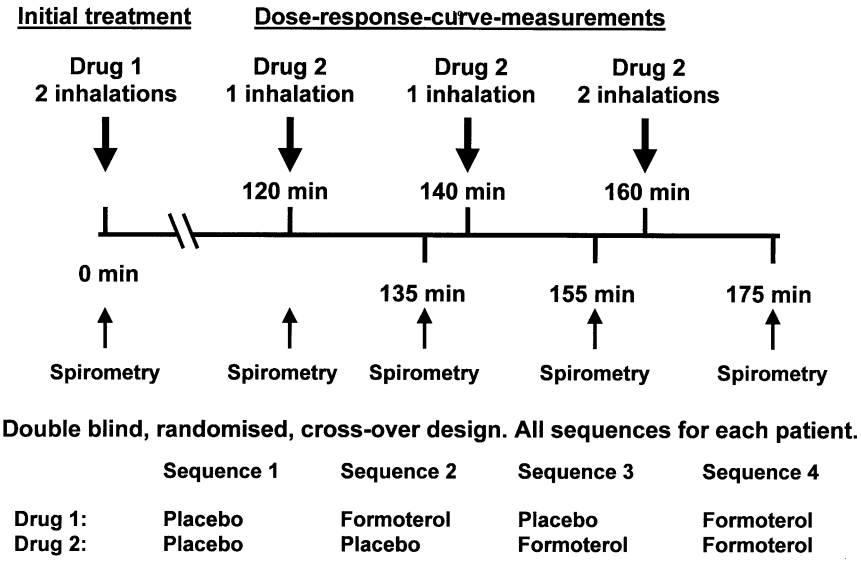

Fig. 1. Flow diagram of the study. Formoterol Turbuhaler 4.5 μg/inhalation.

Baseline spirometric testing was performed according to the procedures described in the American Thoracic Society's 1994 Update [16]. Patients then received pre-treatment of two inhalations of formoterol 4.5 μg/inhalation (Oxis®, AstraZeneca, Milan, Italy) or placebo from matched Turbuhaler® devices. Three acceptable forced expiratory manoeuvres were performed in order to obtain two reproducible results for FVC and FEV_1. The higher of the two FEV_1 results was kept for analysis. Spirometric measurements were repeated 2 h after the pre-treatment inhalations.

Following the 2-h (120 min) spirometry reading, a dose-response curve to inhaled formoterol (4.5 μg/inhalation) or placebo was constructed using four inhalations—i.e. a total cumulative dose of 18 μg formoterol. The four inhalations were given in three dose increments at 20-min intervals (single inhalations at 120 and 140 min, and two inhalations at 160 min). FEV_1/FVC measurements were made 15 min after each dose.

Increases in functional indices from baseline and after 2 h were assessed for all sequences. The maximum FEV_1 value during the dose-response curve to formoterol or placebo was chosen as the primary outcome variable. The study had a power of 80% to detect a difference in FEV_1 of at least 0.11 L between treatments.

Analysis of spirometric data for each treatment was performed using Student's *t*-test for paired variables. Mean responses were also compared by multifactorial analysis of variance (ANOVA) to establish any significant overall effect between all four treatments. In the presence of a significant overall ANOVA, Duncan's multiple range testing with 95% confidence limits was used to identify where differences were significant. A probability level of $P < 0.05$ was considered significant for all tests.

3. Results

All patients completed the 4-day study. There were no significant differences between the baseline spirometric values of the four treatment groups (FEV_1 $P = 0.964$; Table 2).

Spirometry values are shown in Tables 2 and 3. Initial administration of formoterol Turbuhaler 9 μg induced a significant ($P < 0.0001$) bronchodilation 2 h after inhalation (best mean increase in FEV_1 0.170 L), whereas placebo did not modify the baseline values (Fig. 2). Furthermore, formoterol, but not placebo, elicited a dose-dependent increase in FEV_1. This response occurred after both formoterol and placebo initial treatment. A further mean

Table 2
Baseline values and changes in FEV_1 2 h after placebo (P), or formoterol 9 μg Turbuhaler (F), and changes from 2 h values after four cumulative inhalations of formoterol Turbuhaler 4.5 μg (F) or placebo (P). Values are mean (95% CI)

	Baseline	Mean change from baseline after 2 h	Mean change from 2 h value after four inhalations of F 4.5 μg or P
F + F	1.239 (1.061–1.417)	+0.125 (0.069–0.182)	+0.072 (0.038–0.106)
F + P	1.244 (1.044–1.444)	+0.170 (0.125–0.215)	−0.058 (−0.106– − 0.010)
P + F	1.218 (1.029–1.406)	−0.019 (−0.055–0.017)	+0.201 (0.155–0.246)
P + P	1.281 (1.106–1.457)	−0.011 (−0.047–0.025)	−0.035 (−0.069– − 0.001)

Table 3
Baseline values and changes in FVC 2 h after placebo (P), or formoterol 9 μg Turbuhaler (F), and changes from 2 h values after four cumulative inhalations of formoterol Turbuhaler 4.5 μg (F) or placebo (P). Values are mean (95% CI)

	Baseline	Mean change from baseline after 2 h	Mean change from 2 h value after four inhalations of F 4.5 μg or P
F + F	2.013 (1.856–2.169)	0.125 (0.057–0.193)	0.109 (−0.0031–0.248)
F + P	2.047 (1.834–2.260)	0.175 (0.063–0.287)	−0.029 (−0.079–0.21)
P + F	2.028 (1.816–2.239)	−0.112 (−0.221– − 0.003)	0.222 (0.151–0.294)
P + P	2.101 (1.930–2.273)	−0.026 (−0.110–0.057)	−0.036 (−0.124–0.062)

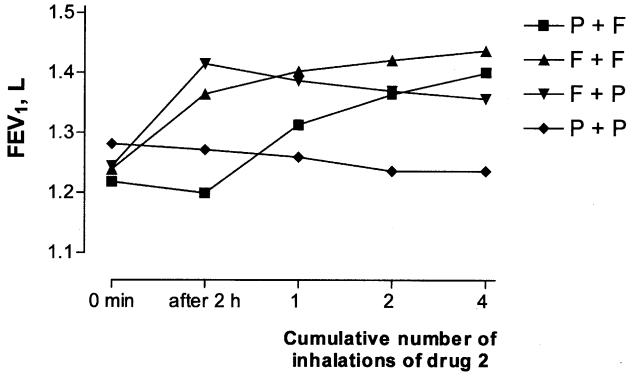

Fig. 2. Mean dose-response curves to inhaled formoterol Turbuhaler (F) (4.5 μg inhalation) or placebo (P) after initial treatment with formoterol 9 μg Turbuhaler (F) or placebo (P).

maximum increase over the 2-h value of 0.072 L occurred in the formoterol initial treatment group (Table 2). The maximum value of bronchodilation induced by initial treatment with formoterol, as measured by FEV_1, was statistically significantly different from its corresponding baseline ($P < 0.0001$) and post-inhalation values ($P = 0.0004$). The mean difference between the highest change in FEV_1 induced by formoterol after initial treatment with formoterol and that after placebo initial treatment was not statistically significant ($P = 0.242$), although the first tended to be greater (0.037 L; 95% CI: −0.027–0.101 L) (Fig. 2).

No patient reported adverse symptoms (palpitations or a significant increase in heart rate) during the study.

4. Discussion

This study shows that regular treatment with formoterol does not compromise the bronchodilator response to further cumulative inhalations of formoterol. Patients suffering from partially reversible COPD, who are taking formoterol as regular maintenance therapy, can use an additional dose of formoterol during the dose interval for the control of their symptoms.

This conclusion conflicts with several in vitro studies that have demonstrated interactions in contracted human bronchi between long-acting and other β_2-agonists [15,17]. However, it has been demonstrated that pre-treatment with formoterol 24 μg (metered dose) did not alter bronchodilator response to repeated doses of salbutamol in patients suffering from partially reversible COPD [18]. The present study seems to confirm the lack of subsensitivity after inhalation of formoterol in patients with COPD. Apparently, after regular dosing of formoterol, further significant bronchodilation still occurs.

In this study, high 2-h values for FEV_1 were achieved following formoterol pre-treatment and further improvements were observed with cumulative formoterol doses. Nevertheless, the dose-response curve was relatively flat and, consequently, there was no statistically significant difference between the highest formoterol FEV_1 after formoterol initial inhalation and that after placebo initial inhalation. This can probably be attributed to the high 2-h FEV_1 values obtained following initial formoterol taking, which left relatively little room for bronchodilator improvement in response to cumulative doses of formoterol. This was not a surprise because each patient with COPD has his/her own optimal function, that is regarded to be the best lung function that patients can achieve either spontaneously or as a result of treatment. It is conceivable that the subjects studied in this specific clinical situation were near the top of their bronchodilation response after inhalation of the first dose of formoterol. In any case, we must highlight even though the changes in FEV_1 induced by formoterol after initial formoterol inhalation were statistically significant, their clinical significance may be doubtful. However, many patients with COPD show a benefit from bronchodilator treatment despite their relatively weak bronchodilator response as assessed through FEV_1 [19]. In fact, the change in FEV_1 following bronchodilator therapy is poorly predictive of improved symptoms and exercise endurance in advanced COPD [20]. We cannot exclude, therefore, that even a small improvement in FEV_1 may be beneficial in patients suffering from COPD.

The present study has shown that a maximum effect was already achieved after a cumulative inhalation of formoterol 18 μg delivered dose in most patients. This finding contrasts with a previous research, which demonstrated that formoterol (12–36 μg metered doses) caused a dose-dependent increase in FEV_1 when

administered via pMDI [8]. Both the differences in the used inhalation devises, which influence lung deposition and bronchodilating effect of the drug, and the individual response to formoterol, might justify this discrepancy. In fact, some studies suggest that when a β_2 agonist is given via Turbuhaler, only half the dose be required compared with drug administered by pMDI [21,22]. If this is the case also in this study, it means that formoterol Turbuhaler 18 μg delivered dose was a higher dose that formoterol pMDI 36 μg metered dose. In any case, we believe that the dose of the bronchodilator is not the true problem. As stressed before, each patient with COPD has his/her own best function that cannot be overcome once that it has been reached. If formoterol Turbuhaler 18 μg has induced the maximum possible bronchodilation in our patients, a higher dose was clearly ineffective. However, since six out 16 patients examined in this investigation benefited by the highest used dose of formoterol, it is advisable to administer a cumulative 27 μg delivered dose of formoterol to patients with COPD who are under regular treatment with formoterol when they need additional help because of severe dyspnea.

Further studies with a larger population are now required to evaluate the real value and safety of adding formoterol to patients who are under regular treatment with this long-acting β_2-agonist. Resting spirometric measurements do not obviate the need for direct pre- and postbronchodilator assessments of symptom alleviation, whereas uses of scales for measurement of dyspnea such as the visual analog scale, the baseline dyspnea index and transition dyspnea index, are tools to relate the severity of symptoms with observed levels of pulmonary response. They will probably help us to establish the factual impact of adding cumulative doses of formoterol to COPD patients.

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