Acute and short-term effect of an extra dose of formoterol in COPD patients

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Summary
Rationale: Formoterol action may decrease progressively after its inhalation. It is unknown if this decrease of bronchodilation following formoterol use could be associated with worsening hyperinflation.
Objectives: To investigate whether the use of an extra daily dose of formoterol could promote a greater reduction in lung hyperinflation and a greater improvement in inspiratory capacity (IC) compared to usual doses.
Methods: 56 hyperinflated COPD patients were divided into two groups: F2 and F3. Basal evaluation was carried out after 5 days of formoterol washout. In order to evaluate the acute effect, spirometry and body plethysmography were performed 8 h after the first formoterol dose in both groups and repeated 1 h after an additional formoterol dose (F3) or placebo (F2). The short-term effect was evaluated by measuring the resting lung function after a 14-day period of formoterol t.i.d. (F3) or formoterol b.i.d. + placebo (F2).
Measurements and main results: A second formoterol dose inhaled 8 h after the previous dose promoted additional improvements in lung function, as demonstrated by higher IC (118 ± 140 mL, p < 0.001) and lower functional residual capacity (FRC) (−383 ± 367 mL, p < 0.001). On day 15, the mean differences from baseline regarding all lung function variables were similar between the groups.

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Conclusion: An extra daily dose of formoterol inhaled 8 h after a previous dose could result in an acute additional peak of bronchodilation. However, short-term formoterol t.i.d. showed no advantages over formoterol b.i.d. concerning reduction of hyperinflation in resting lung function.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation and decreased elasticity of the lung parenchyma resulting in hyperinflation and gas trapping, particularly in moderate to severe patients. As a consequence, during exercise, as ventilatory demands increase in flow-limited patients, progressive air trapping and further dynamic lung hyperinflation above the already increased resting values is inevitable. Moreover, it is known that measurements of forced expiratory volume in 1st second (FEV1) is not always reliable as a surrogate marker of pulmonary function improvement following bronchodilator use, as reductions in lung hyperinflation in COPD patients can occur with almost no change in FEV1.

Long-acting β2-agonists (LABA), such as formoterol, are widely used bronchodilators in the management of COPD, usually prescribed twice a day. However, previous studies have shown that formoterol action may decrease progressively 8 h after its inhalation. It is unknown if this decrease in bronchodilation following formoterol use could be associated with worsening hyperinflation.

The purpose of this study was to investigate whether the administration of an extra dose of formoterol could result in a greater increase in inspiratory capacity (IC) and a greater reduction in static hyperinflation in two different situations: acutely, eight hours after a previous formoterol dose vs. placebo; and in the short-term, after a 14-day period of formoterol t.i.d. (three times daily) vs. formoterol b.i.d. (twice daily).

Methods

Study design

This study was a randomized, double blind, placebo-controlled, parallel-group trial. Randomization was conducted by envelopes in blocks of four patients, with patients being randomly divided into two groups: F2 and F3. The primary outcome was an increase from baseline in IC on days 1 and 15. Secondary outcomes on day 15 included the difference from baseline in other lung function parameters, namely forced vital capacity (FVC), FEV1, slow vital capacity (SVC), residual volume (RV), functional residual capacity (FRC) and total lung capacity (TLC). We also evaluated the improvement in basal dyspnea scores, incidence of side effects and the use of relief medication as secondary outcomes. The study was approved by the local ethics committees, and all patients signed an informed consent prior to participation.

Subjects

Patients referring to the pulmonary division of a tertiary hospital in Brazil from July 2007 to May 2009 who met the following inclusion criteria were invited to participate in the study: moderate to very severe COPD according to the Global Initiative for Obstructive Lung Disease (GOLD) guidelines with post-bronchodilator FEV1 ≤ 60% of predicted values, former smokers (≥10 pack-years), absence of FEV1 reversibility after albuterol in spirometry, age 40 years or older, clinical stability within four weeks prior to randomization (no occurrence of increased dyspnea, increased sputum and/or change in sputum purulence or change in medication use), hyperinflation as demonstrated by FRC ≥ 130% or RV ≥ 140% or TLC ≥ 120% of predicted values. Exclusion criteria were: presence of asthma or any other active pulmonary disease and the inability to perform pulmonary function tests or carry out reproducible maneuvers.

Measurements

Screening visit (Day-5): Patients were screened for eligibility and familiarized with the pulmonary lung function tests, and instructed to discontinue all bronchodilators (LABAs, tiotropium or methylxantines)(Fig. 1). They were,
however, permitted to use albuterol 200 μg, via a metered
dose inhaler (MDI) device, every 6 h or as needed for
symptom relief up until 12 h before baseline examinations.

**Baseline visit (Day 0):** patients were randomized and
lung function tests were performed (spirometry and body
plethysmography), following discontinuation of albuterol
12 h prior. They were then sent home with instructions to
inhale a single dose of formoterol 12 μg at midnight and
return to the laboratory the next day.

**Acute bronchodilator effect evaluation (Day 1):** patients
underwent a body plethysmography at 8.00 a.m. in order to
detect any improvements in lung function 8 h after for-
merol use. Following these tests, patients inhaled an
additional dose of formoterol (F3 group) or placebo
(F2 group), and lung function was reevaluated by body
plethysmography 1 h later (10.00 a.m.).

**Short-term effect bronchodilator evaluation (Day 15):**
between days 2–14, both groups inhaled three capsules per
day in a regimen chosen to suit as best as possible their
normal daily routine (6.00–7.00 a.m., 1.00–2.00 p.m.,
8.00–9.00 p.m.), with morning and evening capsules con-
taining formoterol 12 μg in both groups, and the afternoon
capsule containing an additional dose of formoterol 12 μg
(F3 group) or placebo (F2 group). During this visit, patients
underwent spirometry and body plethysmography, with
formoterol having been withdrawn 12 h before. All for-
merol or placebo doses were administered via a single-
dose, breath-activated device inhaler (Aerolizer), with all
capsules being provided by Mantecorp Pharmaceutical
Company®; São Paulo; Brazil.

**Lung function tests:** Spirometry included both forced
and slow vital capacity maneuvers, in accordance with the
American Thoracic Society (ATS) criteria. Functional residual capacity was measured by body plethysmography using a volume variable pressure body plethysmograph (Elite Series Breeze PF System, MGC, St. Paul, USA). IC was calculated as SVC – ERV (expiratory reserve volume).

Other measurements: Dyspnea was evaluated using the modified Medical Research Council (mMRC) scale and Baseline Dyspnea Index (BDI). The response to therapy in terms of dyspnea was evaluated by the Transition Dyspnea Index (TDI) with a 1-point difference considered as the minimal significant difference. Incidence of side effects and the use of relief medication were recorded on a diary card. Compliance was evaluated by counting unused capsules in both devices on day 15.

Statistical analysis

SPSS Version 16.0 statistical software was used for data analysis (IBM, Chicago, IL). Sample size was calculated in order to have an 80% power to detect a mean difference of 0.150 L in resting IC between F3 and F2 groups on day 15, assuming two-sided $\alpha = 5\%$ and a standard deviation (SD) of 0.190 L according to a pilot study. The minimal number of patients required in each group was set at 26. Descriptive and numerical data were reported as means ± SD or means ± CI 95%. Comparisons between groups were performed using Student’s $t$ test or Mann–Whitney $U$ test according to the type of distribution. For the comparison of variables within the same group, Paired $t$ or Wilcoxon tests were used as appropriate. The level of statistical significance was set at $p < 0.05$ for all tests.

Results

A total of 90 patients were evaluated. Fifty-six patients were considered eligible and subsequently entered the study. The main reason that 34 patients were not included was that they were unable to perform reproducible FRC maneuvers during the screening visit. The average age of patients was 64 years (range, 50–83), and 86% were males. Mean FEV$_1$ was 1.10 ± 0.35 L (39 ± 11% of predicted). Hyperinflation was demonstrated by abnormally high mean values of FRC (157 ± 27% of predicted) and RV (209 ± 45% of predicted). The mean TLC was 116 ± 15% of predicted, with 20 patients presenting TLC ≥ 120% of predicted values (9 patients in the F3 group). The sample included 11 patients (19.6%) in GOLD Stage 2, 36 in GOLD Stage 3 (64.3%) and 9 in GOLD Stage 4 (16.1%). The baseline characteristics of the two treatment groups were similar (Table 1).

Day 1 — acute effect of an additional formoterol dose vs. placebo 8 h after a previous formoterol dose

Eight hours (8.00 a.m.) after inhalation of the first formoterol dose, the measurement of lung function variables (SVC, IC, RV, FRC) still showed a statistical improvement from baseline in both groups. These results did not differ between the two groups. At 10.00 a.m., the group that inhaled an extra formoterol dose showed an additional improvement in lung function, achieving higher SVC (122 ± 215 mL, $p = 0.006$), higher IC (118 ± 140 mL, $p < 0.001$), lower FRC (−383 ± 367 mL, $p < 0.001$), lower RV (−371 ± 460 mL, $p < 0.001$) and lower TLC (−263 ± 376 mL, $p = 0.001$). On the other hand, the group that received placebo showed no statistical change in SVC, IC, FRC, RV and TLC, with all differences between the two groups being statistically significant (Fig. 2). The cumulative bronchodilator effect from baseline after two formoterol doses (F3 group) compared to that after a single formoterol dose plus placebo (F2 group) is shown in Fig. 3, with the former showing a greater decrease in RV (−768 ± 483 mL vs. −385 ± 621 mL, $p = 0.014$) and TLC (−386 ± 357 mL vs. 152 ± 343 mL, $p = 0.016$).

Day 15 — short-term effect of formoterol t.i.d. vs. formoterol b.i.d

Lung function: The mean differences from baseline regarding all lung function variables were similar between
the groups. However, only the F3 group showed a statistically significant reduction from baseline in RV ($p < 0.001$) and in TLC ($p = 0.01$) (Table 2).

Dyspnea: scores in TDI scale showed a clinically significant improvement in both F3 and F2 groups, 3.4 ± 0.7 units and 3.4 ± 1.4 units, respectively, with no difference between the two groups ($p = 0.95$).

Other measurements: High treatment compliance was observed. Only one patient in the F3 group and two patients in the F2 group forgot to inhale one afternoon capsule (formoterol or placebo) during the study.

Relief medication: Fourteen patients in the F3 group (51.7%) and 15 patients in the F2 group (53.5%) did not use any albuterol during the trial. The average number of doses of albuterol per day was similar, 0.69 ± 1.11 puffs and 0.70 ± 1.58 puffs in the F3 and F2 groups, respectively ($p = 0.78$).

Side effects: these were quite rare and similar in both groups, with no episodes of hospitalization, death, arrhythmias or palpitation being detected or self-reported by patients. The most common adverse event was COPD exacerbation, which occurred in two patients in the F3 group and one patient in the F2 group, requiring a course of antibiotics and prednisone. One patient in the F3 group reported an episode of tremors on day 2 after using a formoterol dose, with no recurrence during the trial. A headache was also reported by a patient in the F3 group; however this cannot necessarily be associated with formoterol use.

Discussion

There is a great deal of controversy regarding the timing and optimal dose of inhaled β2-agonists in the treatment of COPD. In a study by Cazzola et al. it was demonstrated that a single high dose of formoterol is as effective as the same dose administered in a cumulative manner, with the same tolerability. In spite of this interesting finding we preferred to test the cumulative approach, considering the relatively advanced age of our case series, to privilege as much as possible the aspect of safety.

The objective of this study was to evaluate the acute and short-term effects of an additional dose of formoterol on lung volumes in hyperinflated COPD patients. Our results clearly demonstrate that an extra dose of formoterol inhaled 8 h after a previous dose resulted in a greater increase of IC and a greater reduction of hyperinflation. However, after a 14-day treatment of formoterol t.i.d. vs.
formoterol b.i.d., no difference in prebronchodilator lung function was found between groups.

In order to evaluate the acute effect of an additional dose of formoterol on lung volumes, patients were asked to inhale a dose of formoterol at midnight (first dose), having pulmonary function tests performed an hour after the inhalation of an additional dose of formoterol (second dose) or placebo, both administered 8 h after the first dose of formoterol.

Significant improvements in lung function were still observed 8 h after the inhalation of the first dose of formoterol in both groups, as formoterol action is expected to last for 12 h. However, only the group that received the second dose of formoterol evolved with a significant increase in IC and a reduction of hyperinflation, confirming the existence of a formoterol dose-response curve (Fig. 2).

In line with these data Cazzola et al. also observed a greater bronchodilator effect (FEV₁ increase) following progressive doses of formoterol (12, 24 and 36 μg) in COPD patients and they observed, in a subsequent study, a dose-dependent increase in FEV₁ with formoterol, with a maximum mean increase from the 2-h value, showing that regular treatment with formoterol does not compromise the bronchodilator response to further cumulative inhalations of formoterol.

All these previous data support the rationale of our study, but to the best of our knowledge, no previous studies have evaluated this specific pharmacological strategy (two formoterol doses, administered at an 8-h interval), allowing a marked increase of IC of 280 mL and a decrease of FRC of approximately 700 mL compared to the baseline. These results are similar to findings of Celli et al. who found an increase of 350 mL in IC and a decrease of 600 mL in FRC at the peak bronchodilator effect of tiotropium. As this additional dose of formoterol was administered in the morning (at 9.00 a.m.), with important reductions in static hyperinflation, it is reasonable to also expect a lesser degree of dynamic hyperinflation and, probably, a better exercise capacity. This could be corroborated by the study of Partridge et al. who demonstrated that formoterol/budesonide combination, due to a more rapid onset of bronchodilation compared to salmeterol/fluticasone, was associated with greater improvements in the ability of COPD patients to perform morning activities.

On day 15, no differences in resting lung function, use of relief medication or dyspnea scores were observed between the two groups. One possible explanation for these results is that the use of a third daily dose of formoterol is not able to promote a greater reduction in resting airway smooth muscle tone compared to a twice-daily dose, with any additional benefits disappearing as soon as formoterol finishes its bronchodilator effect.

Tachyphylaxis is a possibility in this context; however as we used a short duration protocol, and as a reduction of formoterol-related bronchodilation effects in COPD patients, even after longer periods of treatment, has not been reported by other authors, this is unlikely. On the other hand, this does not necessarily mean that a patient from the F3 group would not benefit from this intervention. A clinical follow up could help to discern which patients would really benefit from the use of formoterol three times a day. Furthermore, in the same way that an acute reduction of the lung hyperinflation was noticed in the morning after the use of an additional dose of formoterol, it is also possible to infer that this same benefit could occur an hour after the use of an extra dose of formoterol in the afternoon.

One important concern of our trial was that the use of higher formoterol doses in elderly patients could result in possible side effects. Our data showed that the prescription of formoterol t.i.d. or b.i.d. appeared to be a safe intervention, with the incidence of side effects being similar in both groups. Rossi et al. did not also observe a higher incidence of side effects in COPD patients receiving formoterol 24 μg b.i.d. vs. formoterol 12 μg b.i.d. in other studies evaluating formoterol, no clinically significant changes in potassium levels, heart rate, or electrocardiography measurements were associated with the use of formoterol, regardless of dose or treatment duration.

Our study presents some limitations. Firstly, our findings should not be extrapolated to other subgroups of COPD, such as patients in GOLD stage I. It is well noted that even mild COPD patients have some degree of air trapping which is decreased by bronchodilator use. Similarly, COPD patients may develop acute exacerbations; further aggravating lung hyperinflation and dyspnea. Our results, nevertheless, may not be applied to these situations, as we analyzed only stable COPD patients. Another limitation of our study was that we did not perform a more detailed surveillance of possible known side effects related to formoterol use, which could have included, for example, measurement of corrected QT interval in the electrocardiogram.

In conclusion, an additional dose of formoterol was able to reduce acutely the static hyperinflation in patients with COPD. Hence, considering the low incidence of side effects, it is reasonable to consider prescribing formoterol t.i.d. for...
stable COPD patients who experience significant continued breathlessness despite inhaling formoterol twice a day. Naturally, this strategy needs to be targeted to the individual, and in cases displaying clinical improvement, the clinician could evaluate the possibility of maintaining it. Other trials with a larger sample of patients could provide better evidence in support of this strategy.

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Mantecorp Pharmaceutical Company® supplied all drugs (formoterol 12 μg or placebo) used in this trial.

Authorship

Conception and design: FSS, LEN, JRJ, OAN
Analysis and interpretation: FSS, MI, JRJ, LVFO, OAN
Drafting the manuscript for important intellectual content: FSS, MI, LEN, CFD, LVFO, JRJ, OAN

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Conflict of interest statement

The authors have all read and approved the enclosed version of the manuscript, and declare that there are no conflicts of interest related to the subject treated in this paper.

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