Formoterol fumarate inhalation powder vs albuterol nebulizer for the treatment of asthma in the acute care setting

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Background: Although albuterol remains the standard treatment for asthma in the emergency department, formoterol fumarate may be more advantageous, with its rapid and long-lasting bronchodilation.

Objective: To compare formoterol fumarate with albuterol in controlling acute asthma exacerbation.

Methods: Patients aged 18 to 65 years who presented to the emergency department with mild to moderate asthma exacerbation (peak expiratory flow rate [PEFR], 40%–60% of predicted) were randomized to receive either formoterol fumarate aerosolizer (12 μg) or albuterol nebulizer (2.5 mg) every 30 minutes up to 2 treatments. Symptom scores and PEFRs were measured at each treatment.

Results: Thirty-four patients (19 in the albuterol arm and 15 in the formoterol fumarate arm) were enrolled. At 30 and 60 minutes, the mean PEFR of the albuterol group increased from 43.7% of predicted to 51.9% of predicted and 54.6% of predicted, respectively, and the formoterol fumarate group had changes in the mean PEFR from 49.3% of predicted to 55.5% of predicted and 57.3% of predicted, respectively, and the mean change in the 2 groups was not significantly different at 30 and 60 minutes (P = .64 and .57, respectively, by t test). The albuterol group improved in symptom scores by 3.7 and 5.5 from 0 minutes to 30 and 60 minutes, respectively, and in the formoterol fumarate group these values were 3.1 and 4.9 at 30 and 60 minutes, respectively, and the mean change in the 2 groups was not significantly different at 30 and 60 minutes (P = .61 and .76, respectively, by t test).

Conclusion: Formoterol fumarate is as effective as albuterol inhalation for the treatment of adults with mild to moderate asthma exacerbations in the acute care setting.


INTRODUCTION

In patients with moderate to severe asthma, the use of long-acting β2-agonists is recommended as an option in maintenance treatment, along with the use of glucocorticoids and as-needed short-acting β2-agonists.1,2 The long-acting β2-agonist formoterol has well-documented long-term efficacy and safety at therapeutic maintenance doses.3,4 This treatment has been proved to be highly effective, as was demonstrated in the Formoterol and Corticosteroids Establishing Therapy study3 and other clinical studies.5,6 The therapeutic effects of formoterol fumarate last up to 12 hours,7,8 and this drug also has the unique property of rapid onset of action (1–3 minutes), similar to the short-acting β2-agonist albuterol.9 The rapid onset of action of formoterol, together with its prolonged bronchodilation, good tolerability, and safety at high doses in patients with stable asthma, suggests that this drug may also be of use as relief medication for acute bronchospasm. However, to our knowledge, formoterol fumarate aerosolizer has not been studied for the relief of acute symptoms of asthma.10

The goal of this study is to determine whether formoterol fumarate aerosolizer can potentially replace albuterol nebulizer as the standard of care for the treatment of asthma exacerbation in the emergency department (ED). Albuterol nebulizer was chosen as the reference treatment because it is the drug used as the standard of care for the treatment of acute bronchoconstriction. In addition, its efficacy has been well-documented in patients presenting to the ED with acute asthma.11 Albuterol aerosolized via nebulizer, currently the standard in many EDs, provides bronchodilation at 5 minutes, has its peak effect at approximately 1 to 2 hours, and continues for approximately 3 to 4 hours.12 It may be beneficial and conducive for patients to use a drug such as formoterol fumarate aerosolizer, which does not require the nebulizer method of delivery, has a longer duration of action, and may be safe and effective treatment for acute bronchoconstriction. Formoterol fumarate may replace albuterol as standard ED therapy and may also lead to its acceptance as an effective rescue medication.

METHODS

Patients and Study Design

Thirty-four patients aged 18 to 65 years were enrolled between January 1, 2003, and March 31, 2004. We consulted multiple statisticians and confirmed that with the proposed sample sizes of 19 and 15 for the 2 groups, the study would
Subsequently assigned to receive either formoterol aerolizer parallel-group study (Fig 1). The patient was asked to draw 1 breath before each treatment to ensure that the patient could complete the questionnaires. Patients gave written informed consent. The study was performed with the approval of the Beth Israel Medical Center Institutional Review Board. All the study requirements were met.

All the patients were recruited after triage by the ED triage nurse. Before administering the first treatment, all the investigators performed pertinent histories, including history of the present illness, home medications, medications taken before coming to the ED, medical history, social history, asthma history (age at onset, daily albuterol use, previous intubations, and last corticosteroid use), and drug allergies. The study was performed with the approval of the Beth Israel Medical Center Institutional Review Board. All the study patients gave written informed consent.

The study was performed as a prospective, randomized, parallel-group study (Fig 1). The patient was asked to draw 1 breath before each treatment to ensure that the patient could complete the questionnaires. Patients gave written informed consent. The study was performed with the approval of the Beth Israel Medical Center Institutional Review Board. All the study patients gave written informed consent.

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RESULTS

Baseline Characteristics and Patients

Thirty-four patients (19 in the albuterol arm and 15 in formoterol fumarate arm) were enrolled in this study, and all the participants completed the protocol without any adverse reactions. Both groups were similar in baseline demographics and disease intensity characteristics, except for baseline symptom score (Table 1).

Peak Expiratory Flow Rate

The mean PEFR in the albuterol group increased from 43.7% of predicted at 0 minutes to 51.9% of predicted at 30 minutes and 54.6% of predicted at 60 minutes (Figure 3). In the formoterol fumarate group, the mean PEFR increased from 49.3% of predicted at 0 minutes to 55.5% of predicted at 30 minutes and 57.3% of predicted at 60 minutes. The mean change in the 2 groups was not significantly different at 30 and 60 minutes ($P = .64$ and .57, respectively, by $t$ test).

Symptom Scores

The albuterol group improved in symptom scores by 3.7 and 5.5 from 0 minutes to 30 and 60 minutes, respectively, and for the formoterol fumarate group these values were 3.1 and 4.9, respectively (Fig 4). The mean change in the 2 groups
Asthmatic patient arrives at the triage area for acute bronchospasm relief. Determination of inclusion and exclusion criteria (through a history and physical examination) first by the triage nurse and then by the researchers.

Obtain informed consent from participants.

History taking,

**Time = 0 min**

Initial symptom score sheet and determination of blood pressure, heart rate, respiratory rate, peak expiratory flow rate, and lung examination; nasal cannula oxygen, 2-4 L, will be started, along with 60 mg oral prednisone

12 μg of formoterol fumarate via aerolizer 2.5 mg of albuterol via nebulizer

**Time = 30 min**

(Determination of heart rate, peak expiratory flow rate, respiratory rate, blood pressure, pulse oximetry, and symptom score and lung examination).

Delivery of second dose

**Time = 60 min**

(Determination of heart rate, peak expiratory flow rate, respiratory rate, blood pressure, pulse oximetry, and symptom score and lung examination).

End of the study

Figure 1. Study protocol. See the “Patients and Study Design” subsection for inclusion and exclusion criteria.
was not significantly different at 30 and 60 minutes \( (P = .61 \) and \( .76 \), respectively, by \( t \) test).

Other Variables

None of the baseline vital signs were significantly different in the 2 groups except for blood pressure (mean, 141/81 mm Hg in the albuterol group and 125/77 mm Hg in the formoterol group; \( P = .03 \), by \( t \) test) (Table 2). The vitals signs did not differ significantly with treatment except for blood pressure after both treatments and heart rate after the second treatment. The mean heart rate in the formoterol group (79.6/min) was lower than that in the albuterol group (89.7/min) \( (P = .05 \), by \( t \) test). Five of 19 patients in the albuterol group were hospitalized: 4 for further monitoring and 1 for recurrent exacerbation. Two of the 15 patients in the formoterol group were hospitalized for further monitoring.

DISCUSSION

Currently, formoterol fumarate inhalation powder is indicated (in the United States) for long-term twice-daily administration and administration of a 24-\( \mu \)g daily dose for the maintenance treatment of asthma and for the prevention of bronchospasm in adults and children 5 years and older with reversible obstructive airways disease. This includes patients with symptoms of nocturnal asthma who require regular treatment with inhaled, short-acting \( \beta_2 \)-agonists. Formoterol aerolizer is also indicated 15 minutes before exercise for the short-term prevention of exercise-induced bronchospasm in adults and children 12 years and older, when administered on an as-needed basis.

This is the first study, to our knowledge, to explore clinical efficacy in comparing formoterol fumarate with albuterol for rescue asthma treatment in an adult population. A similar study has been conducted with the pediatric population with...
A mild acute asthma crisis. It was consistent with our findings, demonstrating that formoterol, 12 μg, has a similar onset of action and potency as albuterol, 200 μg, when administered via a turbuhaler. In the present study, neither PEFRs nor symptom scores were significantly different in the 2 groups. The results show that the patients in the formoterol fumarate arm responded both to formoterol as well as the albuterol, suggesting that formoterol fumarate could function as alternative rescue therapy during acute asthma exacerbation. Tattersfield et al16 compared formoterol and terbutaline, another short-acting β-agonist, given via Turbuhaler, for rescue therapy accompanied with inhaled corticosteroids in mild-moderate asthma. This double-blind, randomized, parallel-group study demonstrated that for as-needed treatment of asthma, formoterol provides better control than terbutaline. Formoterol fumarate may prove to be an excellent alternative medication to albuterol.

In this study, all the participants completed the study without major or minor adverse effects. Blood pressure and heart rate were stable in all the patients, and none complained of any symptoms leading to the cessation of either study medication. We did not check the QTc interval or the serum potassium or glucose levels because electrocardiography and such blood tests are not routinely performed for mild to moderate asthma exacerbation.

The adverse effects of formoterol are similar to those of other selective β2-agonists, such as albuterol, and include angina, hypertension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis, and insomnia. The short-term adverse effect profile of formoterol may be similar or more favorable to that of short-acting β2-agonists (such as albuterol) and is dose related.17,18 In a tolerability study19 with

### Table 1. Characteristics of the 34 Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Albuterol group (n = 19)</th>
<th>Formoterol group (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F/M, No.</td>
<td>15/4</td>
<td>12/3</td>
<td>&gt;.99a</td>
</tr>
<tr>
<td>Present age, mean, y</td>
<td>47.1</td>
<td>40.67</td>
<td>.12b</td>
</tr>
<tr>
<td>Smoking status, No.</td>
<td></td>
<td></td>
<td>.72a</td>
</tr>
<tr>
<td>Never</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Peak expiratory flow rate, mean, % of predicted</td>
<td>43.7</td>
<td>49.3</td>
<td>.38c</td>
</tr>
<tr>
<td>Baseline symptom score</td>
<td>12.8</td>
<td>10.2</td>
<td>.002c,d</td>
</tr>
<tr>
<td>Daily albuterol use, % of patients</td>
<td>66.7</td>
<td>73.3</td>
<td>.72a</td>
</tr>
<tr>
<td>Maintenance medication use, % of patients</td>
<td>57.9</td>
<td>57.1</td>
<td>.99c</td>
</tr>
</tbody>
</table>

*By Fisher exact test.*

**Median score.**

*b Significant at P < .05.*

### Table 2. Vital Signs by Study Group

<table>
<thead>
<tr>
<th>Time and vital sign</th>
<th>Albuterol group</th>
<th>Formoterol group</th>
<th>P value (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature, °F</td>
<td>98.8</td>
<td>98.6</td>
<td>.39</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td>141/81</td>
<td>125/77</td>
<td>.03a</td>
</tr>
<tr>
<td>HR, /min</td>
<td>90.8</td>
<td>91.1</td>
<td>.96</td>
</tr>
<tr>
<td>RR, /min</td>
<td>22.7</td>
<td>21</td>
<td>.34</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>96</td>
<td>96.4</td>
<td>.81</td>
</tr>
<tr>
<td>30 min (after first treatment)</td>
<td>got</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td>133/75</td>
<td>116/69</td>
<td>.03a</td>
</tr>
<tr>
<td>HR, /min</td>
<td>85.3</td>
<td>83.2</td>
<td>.67</td>
</tr>
<tr>
<td>RR, /min</td>
<td>20.7</td>
<td>18.6</td>
<td>.15</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>97.7</td>
<td>97.4</td>
<td>.62</td>
</tr>
<tr>
<td>60 min (after second treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td>130/73</td>
<td>117/70</td>
<td>.05a</td>
</tr>
<tr>
<td>HR, /min</td>
<td>89.7</td>
<td>79.6</td>
<td>.05a</td>
</tr>
<tr>
<td>RR, /min</td>
<td>19.4</td>
<td>18.6</td>
<td>.48</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>98.1</td>
<td>97.6</td>
<td>.33</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; HR, heart rate; RR, respiratory rate.

* Data are given as means.

**Significant at P ≤ .05.**

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[Graphs and figures are not transcribed here due to the image format constraints.]
formoterol and terbutaline, another short-acting β-agonist, the authors compared serum potassium level, pulse rate, blood pressure, heart rate, and QTc interval in patients with stable asthma. Formoterol, maximum dose of 120 µg/d for more than 3 days, had significantly fewer effects than terbutaline, 10 mg, and they were both well tolerated. Rosenberg et al. showed that the duration of systemic effects (heart rate, QTc interval, blood pressure, serum potassium level, glucose level, and lactate level) with formoterol, 54 µg, is brief, similar to albuterol, 1,200 µg, and well tolerated in asthmatic and healthy subjects.

In episodic exacerbations of asthma, this standard of care may result in the administration of high doses in a short period. A study compared the safety of formoterol Turbuhaler at a cumulative dose of 90 µg and terbutaline at a 10-mg cumulative dose in patients with acute bronchial obstruction presenting to the ED with moderate to severe asthma, and formoterol and terbutaline were well tolerated. Mann et al. suggested that high-dose formoterol therapy (24 µg twice a day) may be associated with slightly more frequent severe asthma exacerbations. Possible hypotheses include the development of desensitization of the β-receptors, but, as mentioned at the beginning of this article, other studies indicate that formoterol decreases asthma exacerbation.

There are some limiting factors in these studies. First, sex and race are heavily skewed to Hispanic females. We know that there are ethnic differences in the prevalence and severity of asthma, partially because of the socioeconomic reasons—the genetic predisposition is ethnicity related and ethnic independence. Second, we did not set up a run-in period in the protocol. Although none of the participants used formoterol fumarate before this study, we included those who received albuterol nebulizer treatments either at home or in an ambulance on the way to the ED and those who took albuterol inhaler treatments before coming to the ED in the same day. To set up a run-in period in a study like this is difficult because we cannot predict when asthma exacerbations will occur, and it is difficult to ensure the safety of the participants unless they are hospitalized if we try to wash out rescue medications. In the real-life clinical setting, this finding should be justified by considering the data suggesting that both groups were largely equivalent in asthma severity and asthma medication histories. The third limiting factor is the size of this study. Only 34 patients were enrolled, and the finding is in need of verification with a larger cohort, preferably in a double-blind, double-dummy study. Careful monitoring of time to discharge from the ED, admission rate, need for additional therapy, and return to the ED after discharge would be important to follow in the future study. We would also need to recruit larger populations with more diverse racial and ethnic demographics.

ACKNOWLEDGMENTS
We thank the Beth Israel Medical Center Emergency Medicine Department for their cooperation and support and Drs Patricia Friedman and Sharon A. Petronella for their statistical support and suggestions.

REFERENCES


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