Formoterol Turbuhaler® as reliever medication in patients with acute asthma


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Running Header: Formoterol reliever in acute asthma
ABSTRACT
To compare the efficacy and safety of formoterol versus salbutamol as reliever medication in patients presenting to an emergency department with acute asthma. A randomised, double-blind, double-dummy, parallel group study in four Australian emergency treatment centres with 78 adult patients (mean baseline FEV_1 1.83 L; 59% predicted normal [PN]) with acute asthma. Based on the expected dose equivalence of formoterol Turbuhaler® 4.5 µg (delivered dose) and salbutamol pMDI 200 µg (metered dose), patients received formoterol Turbuhaler® 36 µg (delivered) or salbutamol pMDI with spacer 1,600 µg (metered) at 0 and 30 min. FEV_1, PEF and systemic β_2-agonist effects were monitored for 4 h. The primary variable was FEV_1 % PN at 45 min. At 45 min, mean increases in FEV_1 expressed in % PN were 6.6% and 9.3%, respectively, with a small adjusted mean difference in favour of salbutamol (3.0% [95% CI: –2.0, 8.0]; p=0.24). Transient increases in systemic β_2-agonist effects occurred predominantly with salbutamol, although no significant treatment differences were observed. Eight patients discontinued due to adverse events.
In this study of patients presenting to emergency departments with acute asthma, formoterol Turbuhaler® 36 µg was well tolerated and, as rescue therapy, had an efficacy not different from that of salbutamol pMDI with spacer 1600 µg in the number of patients studied.

Key words: Acute asthma; formoterol; reliever medication; salbutamol; Turbuhaler®.
INTRODUCTION

In hospital emergency departments, the first-line treatment for patients presenting with acute exacerbations of asthma is the administration of a rapid-acting β₂-agonist, either continuously or at regular intervals during the first hour [1, 2]. Although rapid-acting β₂-agonists are often administered by nebulization, equivalent, and more rapid bronchodilation, with fewer side effects, can be achieved with a pressurised metered-dose inhaler (pMDI) and spacer [2–4]. In the event of a severe exacerbation or no immediate response to β₂-agonist therapy, oxygen, systemic glucocorticosteroids, and further inhaled or intravenous β₂-agonist therapy may be needed.

Traditionally, rapid- and short-acting β₂-agonists (e.g. salbutamol, terbutaline) have been used for symptom relief. Formoterol is a selective β₂-agonist with similar onset of effect to salbutamol [5] but with a longer duration of action (≥12 h in patients with stable asthma) [6]. Politiek and colleagues [7] found that formoterol via Turbuhaler® was as effective as salbutamol via pMDI, relieving methacholine-induced bronchospasm within 3 min, a model for severe-acute bronchospasm. Importantly, in contrast to its topical bronchodilator activity, the systemic effects of inhaled and oral formoterol are short-lived and similar to short-acting β₂-agonists [8, 9]. Moreover, a comparative dose-response study in patients with asthma suggested that the therapeutic index (i.e. the dose ratio between lung function improvements and systemic activities, e.g. effects on serum potassium and QT interval corrected for heart rate [QTc]) was 2.5 times more favourable for formoterol Turbuhaler® compared with salbutamol pMDI, although the difference in this study was not statistically significant [10]. Several studies have established a role for regular formoterol treatment in combination with inhaled glucocorticosteroids in preventing severe asthma exacerbations [11, 12]. Furthermore, these effects have been confirmed when formoterol has been used as needed compared with terbutaline or salbutamol as needed [13, 14]. Formoterol is the only long-acting β₂-agonist that has been approved for use as both maintenance and reliever therapy, for chronic symptomatic asthma. As a result, some patients may be using formoterol as their only β₂-agonist bronchodilator. In the event of acute asthma worsening, such patients must be able to rely on their inhaler and may use several doses within a short period of time. It is therefore important to understand the efficacy and tolerability of higher than normal doses in an emergency situation.

Although formoterol as needed is well tolerated and effective in preventing severe exacerbations, few studies have addressed its efficacy compared with more traditional reliever therapy during severe, acute asthma exacerbations. Salbutamol by pMDI and spacer, at a dose of up to 1,000 µg at regular intervals within the first hour is recommended for the initial treatment of acute asthma [2]. The present study compares the efficacy and safety of two administrations of formoterol Turbuhaler® (4 x 4.5 µg inhalations [18 µg]) given 30 min apart with salbutamol via pMDI with spacer (four separate inhalations of two actuations of 100 µg [800 µg]) for up to 4-h in patients with acute asthma presenting to a hospital emergency department. The doses selected in the study were based on an expected dose equivalence of formoterol Turbuhaler® 4.5 µg, and salbutamol pMDI 200 µg established in previous studies in patients with stable asthma [9, 10].
METHODS

Study design and patients
This was a randomised, double-blind, double-dummy, parallel group study conducted at four centres in Australia. Patients (aged 18–70 yrs) presenting to the emergency department with acute asthma [15], were included in the study if their forced expiratory volume in 1 second (FEV₁) was >30% of the predicted normal value and, if aged ≥50 yrs, they had a pulse rate ≥100 beats/min on presentation. Patients were excluded from the study if they had a significant cardiovascular or respiratory disease (other than asthma); they required transfer to the intensive care unit, or required nebulised or intravenous β₂-agonists at the initial assessment; or their oxygen saturation (SaO₂) was < 93% on room air. Women who were pregnant, lactating or of childbearing potential, not using adequate contraception, were excluded.

The study was conducted according to the principles of the Declaration of Helsinki. An agreed protocol was followed, which was approved at each institution by independent ethics committees. Patients gave initial verbal informed consent before participation in the study and detailed written informed consent was obtained as soon as improvement in asthma symptoms permitted. Eligible subjects were assigned to receive either formoterol or salbutamol therapy, according to a computer-generated randomization code. Treatment was initiated within 30 min of arriving in the emergency department. Each treatment was given twice, at time 0, and 30 min, and consisted of either formoterol Turbuhaler® (Oxis®, AstraZeneca, Sweden) administered as 4 x 4.5 µg inhalations (18 µg), or salbutamol pMDI (Norton Healthcare, UK) via spacer (Volumatic™, GlaxoSmithKline, UK) as four separate inhalations of x2 actuations of 100 µg (800 µg). To achieve double-dummy conditions, patients also used either four inhalations of placebo Turbuhaler® or four inhalations of two actuations of pMDI as appropriate; inhalations were started with Turbuhaler® or pMDI in pre-arranged order according to randomisation number. Oral prednisolone (50 mg) was administered as a single dose 60 min after the first dose of study drug. If the investigator considered that an oral formulation would not be tolerated, a single dose of intravenous hydrocortisone (100–200 mg) was administered instead. Oxygen was administered throughout the study.

Assessments
FEV₁ and peak expiratory flow (PEF) were measured by spirometry at baseline (0), 15, 45, 75, 90, 120, 180, and 240 min after first administration of the study drug. Spirometry was performed three times at each assessment and the highest FEV₁ value recorded. All centres used the same type of spirometer (MicroLab™), which met the American Thoracic Society standard for accuracy (±3% of reading or ±0.05 L). The primary efficacy variable was the change from baseline in percentage predicted normal FEV₁, 45 min after the first dose of study drug, and 15 min before the administration of prednisolone. Secondary efficacy variables included the increase from baseline in percentage predicted normal FEV₁ between 45 and 240 min after administration of study drug. PEF was also assessed at each time point. Estimations of percentage predicted normal FEV₁ and PEF values were made for each patient taking into account age, height, and gender [16, 17].

Safety variables were measured at baseline, 15, 45, 75, 120, 180, and 240 min during the 4-h observation period. Blood samples were taken for serum potassium measurements. Radial pulse, blood pressure (systolic and diastolic), and electrocardiogram (ECG) were recorded using standard local procedures. The QTc was calculated using Bazett’s formula. Adverse
events (AEs) reported or observed during the treatment period were also recorded. Both direct and open-ended questioning at the end of the 4-h study period was used to collect AE reports. Patients who failed to respond to the second dose of study medication (\(\text{SaO}_2 < 93\%\), or \(\text{FEV}_1 \leq 30\%\) predicted normal, or there was a fall or no improvement in \(\text{FEV}_1\) within 15 min of the second dose of study drug) were withdrawn and received routine emergency department treatment.

**Statistical analysis**

The primary efficacy variable, change in percentage predicted normal \(\text{FEV}_1\) at 45 min, was compared between treatments using an additive analysis of variance (ANOVA) model with treatments and centre as fixed factors, using baseline \(\text{FEV}_1\) as covariate. Similar ANOVA models were used to compare the secondary efficacy variables based on \(\text{FEV}_1\) and PEF and the safety variables (average and minimum serum potassium and diastolic blood pressure, maximum and average systolic blood pressure, pulse rate, QTc). Treatment difference was expressed as the mean difference and 95% confidence intervals (CI). Sinus rhythm and overall ECG were presented by descriptive statistics. All efficacy analyses followed the intention-to-treat approach. Only patients who took at least one dose of study treatment were included in the safety analysis. The number of patients withdrawn from the study within 4 h of administration of first dose of study drug was compared between treatments using a chi-squared test. A p-value of less than 0.05 was considered statistically significant.

Due to limitations in recruitment rates at the participating sites, the total number of patients had to be maximised at 80. With 40 patients in each group, an 80% power existed to detect a difference of 7% in predicted \(\text{FEV}_1\) at 45 min, assuming a standard deviation of 11% and a two-sided t-test at the 5% significance level.
RESULTS

Of the 78 patients enrolled in the study, 38 were randomised to formoterol, and 40 to salbutamol treatment (table 1). The treatment groups were generally well matched for the level of airway obstruction at entry (the mean percentage predicted normal FEV₁ was 57% in the formoterol group, 60% in the salbutamol group). However, some differences in demographics between the groups were apparent with a higher male ratio in the formoterol group (formoterol group 42% versus salbutamol group 25%), and greater use of concomitant medications before study entry in the formoterol group versus the salbutamol group – the mean dose of inhaled corticosteroid was higher (1,313 µg/day versus 908 µg/day) and more patients had previously used long-acting β₂-agonists (42% versus 30%). At 60 min, all patients received oral prednisolone except for three patients who received intravenous hydrocortisone. During the study, 22 patients discontinued treatment (nine in the formoterol group, 13 in the salbutamol group; p=0.39); eight were due to AEs (three formoterol, five salbutamol), two (one in each group) failed to meet eligibility criteria, and 12 (five formoterol, seven salbutamol) were due to other reasons.
Table 1.–Patient demographics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Formoterol 36 µg (n=38)</th>
<th>Salbutamol 1,600 µg (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>16 (42)</td>
<td>10 (25)</td>
</tr>
<tr>
<td>Age, yrs; mean (range)</td>
<td>36 (18–69)</td>
<td>37 (19–67)</td>
</tr>
<tr>
<td>Patients using ICS at entry, n (%)</td>
<td>25 (66)</td>
<td>23 (58)</td>
</tr>
<tr>
<td>Patients using regular LABA or LABA/ICS combinations at entry, n (%)</td>
<td>16 (42)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>IGCS dose at entry, µg; mean (range)</td>
<td>1313 (200–3,200)</td>
<td>908 (50–2,000)</td>
</tr>
<tr>
<td>FEV1, L; mean (range)</td>
<td>1.90 (0.59–4.10)</td>
<td>1.77 (0.65–3.37)</td>
</tr>
<tr>
<td>FEV1 (% predicted normal); mean (range)</td>
<td>57 (31–101)</td>
<td>60 (30–107)</td>
</tr>
<tr>
<td>Pulse rate (beats/min); mean (range)</td>
<td>102 (67–136)</td>
<td>99 (72–138)</td>
</tr>
<tr>
<td>SaO2 (%); mean (range)</td>
<td>96 (93–100)</td>
<td>97 (93–100)</td>
</tr>
</tbody>
</table>

ICS: inhaled corticosteroid; LABA: long-acting β2-agonist; FEV1: forced expiratory volume in 1 second; SaO2: oxygen saturation.

Efficacy

The change from baseline in percentage predicted normal FEV1 at all time points was similar in the formoterol and salbutamol groups (fig. 1). The mean change in percentage predicted normal FEV1 at 45 min (primary variable) was 6.6% with formoterol and 9.3% with salbutamol, without a statistically significant difference between treatments (adjusted mean difference 3.0% [95% CI: −2.0, 8.0]; p=0.24) (table 2). No statistically significant difference in percentage predicted normal FEV1 was seen at any other time point between the treatment groups.

The PEF data essentially confirmed the result on FEV1. The mean increase in percentage predicted normal PEF at 45 min was 3.7% in the formoterol group compared with 6.0% in the salbutamol group (adjusted mean difference −3.6% [95% CI: −9.5, 2.3]; p=0.23). The maximum mean increase in percentage predicted normal PEF was 12.1% in the formoterol group, and 14.3% in the salbutamol group (adjusted mean difference −2.8% [95% CI: −9.3, 3.6]; p=0.38).

Table 2.–Change in percentage predicted normal FEV1 from baseline

<table>
<thead>
<tr>
<th>Change from baseline</th>
<th>Adjusted mean difference formoterol/salbutamol (95% CI) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol n=38</td>
<td>Salbutamol n=39</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean baseline % predicted normal (range)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------------------</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>n=38/39</td>
<td>(-20.1 to 28.8)</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>n=38/39</td>
<td>(-20.8 to 31.0)</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>n=37/37</td>
<td>(-22.0 to 30.1)</td>
</tr>
<tr>
<td></td>
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<tr>
<td>n=37/37</td>
<td>(-17.7 to 34.1)</td>
</tr>
</tbody>
</table>

*ANOVA: analysis of variance; n: formoterol group/salbutamol group; E_{15}: effect at 15 min after dose administration; E_{45}: effect at 45 min after dose administration; E_{av}: average effect between 45 and 240 min; E_{max}: maximal effect between 45 and 240 min; CI: confidence interval.

**Safety**

Mean safety parameter measurements are shown in table 3. There were no statistically significant differences between the two treatment groups. Both systolic and diastolic blood pressure decreased after the first dose of study drug in both treatment groups. Mean heart rate decreased on treatment in both groups over the 4-h period, however, an initial transient and minor increase in heart rate was observed in the salbutamol group and this was accompanied by similar changes in QTc at the 45-min time point (fig. 2). During the 4-h study period, the profiles of changes in mean serum potassium values were similar to the changes in QTc, i.e. minor in both treatment groups, with numerically greater decreases in the salbutamol group (fig. 3).

Both treatments were well tolerated. Twenty-three patients reported a total of 27 AEs (32% in the formoterol group, 28% in the salbutamol group). The most commonly reported AEs were ‘asthma aggravation’ (three formoterol, four salbutamol), hypokalemia (two formoterol, three salbutamol), pneumonia (one formoterol, two salbutamol), tachycardia (two formoterol, one salbutamol), and headache (two formoterol). There were 10 patients in whom serious adverse events (SAEs) were recorded: three (8%) in the formoterol group and seven (18%) in the salbutamol group. Of these patients, three in the formoterol group (one of whom also had pneumonia), and five in the salbutamol group were discontinued as a result of ‘asthma aggravation’ to allow for additional treatment. The two patients in the salbutamol group with pneumonia as a SAE continued in the study.
Table 3. Effect of test treatments on systemic parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Adjusted mean difference *, formoterol–salbutamol (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formoterol mean (range)</td>
<td>Salbutamol mean (range)</td>
<td>Formoterol mean (range)</td>
<td>Salbutamol mean (range)</td>
</tr>
<tr>
<td>SBP (mmHg) Eav</td>
<td>134.1 (100–186)</td>
<td>132.9 (110–169)</td>
<td>126.5 (98–169)</td>
<td>124.7 (101–151)</td>
</tr>
<tr>
<td></td>
<td>SBP (mmHg) Emax</td>
<td>134.1 (100–186)</td>
<td>132.9 (110–169)</td>
<td>135.5 (100–187)</td>
</tr>
<tr>
<td>DBP (mmHg) Eav</td>
<td>82.1 (60–102)</td>
<td>79.7 (60–102)</td>
<td>75.7 (53–93)</td>
<td>73.4 (49–92)</td>
</tr>
<tr>
<td>DBP (mmHg) Emin</td>
<td>82.1 (60–102)</td>
<td>79.7 (60–102)</td>
<td>68.9 (50–86)</td>
<td>67.7 (45–91)</td>
</tr>
<tr>
<td>ECG heart rate (beats/min) Eav</td>
<td>99.4 (62–137)</td>
<td>96.3 (67–144)</td>
<td>93.4 (60–122)</td>
<td>93.5 (69–128)</td>
</tr>
<tr>
<td>ECG heart rate (beats/min) Emax</td>
<td>99.4 (62–137)</td>
<td>96.3 (67–144)</td>
<td>102.1 (70–130)</td>
<td>101.7 (72–137)</td>
</tr>
<tr>
<td>ECG QTc (ms) Eav</td>
<td>412.6 (325–505)</td>
<td>423.3 (338–527)</td>
<td>409.8 (340–492)</td>
<td>422.2 (374–496)</td>
</tr>
<tr>
<td>ECG QTc (ms) Emax</td>
<td>412.6 (325–505)</td>
<td>423.3 (338–527)</td>
<td>435.4 (372–554)</td>
<td>453.2 (394–634)</td>
</tr>
<tr>
<td>S-potassium (mmol/L) Eav</td>
<td>3.85 (3.0–4.9)</td>
<td>3.88 (3.0–4.7)</td>
<td>3.83 (3.1–4.6)</td>
<td>3.82 (3.0–4.6)</td>
</tr>
<tr>
<td>S-potassium (mmol/L) Emin</td>
<td>3.85 (3.0–4.9)</td>
<td>3.88 (3.0–4.7)</td>
<td>3.63 (2.9–4.5)</td>
<td>3.60 (2.8–4.6)</td>
</tr>
</tbody>
</table>

*ANOVA: analysis of variance; CI: confidence interval; SBP: systolic blood pressure; Eav: average effect between 45 and 240 min; Emax: maximal value between 45 and 240 min; DBP: diastolic blood pressure; Emin: minimal value between 45 and 240 min; ECG: electrocardiogram; QTc: QT interval corrected for subject’s heart rate.
**DISCUSSION**

A severe asthma exacerbation can be life threatening, and needs emergency intervention to provide relief from bronchospasm. Previous studies have shown that formoterol has a rapid onset of effect in asthma patients [6], which is as fast as salbutamol [5, 7]. Furthermore, there is some evidence to suggest that formoterol Turbuhaler® has a more favourable therapeutic index than salbutamol delivered by pMDI [10]. In the current study in patients with acute asthma, formoterol 36 µg by Turbuhaler® produced a rapid and clinically relevant improvement in FEV₁, which was not statistically significantly different from that of salbutamol 1,600 µg by pMDI and spacer at all time points. Acute asthma is characterised by breathlessness, wheeze and change in airway function over a short period of time. In this study, mean baseline FEV₁ was 59% predicted normal. Despite the wide range of FEV₁ in both groups (varying from approximately 30% to more than 100% predicted normal), all patients presented with acute breathlessness, audible wheeze and clinical criteria consistent with acute asthma. The actual acute decrease in FEV₁ was unknown, a scenario often encountered in patients with acute asthma presenting to the emergency department.

There was a male predominance and a more extensive previous use of inhaled corticosteroids and long-acting β₂-agonists by patients in the formoterol treatment group. We cannot explain these baseline differences, but they are most likely chance findings in a randomised study. Patients were not stratified according to these criteria as all fulfilled the same symptomatic characteristics of acute worsening of asthma, precipitating a visit to the emergency department. The higher level of previous treatment in the formoterol group may indicate more severe disease in this group, with less potential for acute response than the salbutamol group.

For the emergency treatment of acute asthma with a salbutamol pMDI and spacer at home, Global INitiative for Asthma (GINA) guidelines [2] suggest up to 1,000 µg of salbutamol should be used at less than hourly intervals, with further subsequent doses depending on the level and sustainability of response over 3–4 h. The total salbutamol dose chosen for the present study, 1,600 µg, is consistent with these guidelines for initial treatment, and well within the Australian National Asthma Council guidelines [1]. Previous experience in patients with asthma and healthy volunteers suggested that a dose of formoterol 36 µg via Turbuhaler® (48 µg metered dose) would be the nearest equivalent dose to salbutamol 1,600 µg [9, 10].

Another similar emergency department study comparing formoterol 54 µg via Turbuhaler® and salbutamol 2,400 µg via pMDI plus spacer [18] reported that formoterol was at least as effective as salbutamol in patients with acute asthma. That study used the same dosing ratio for formoterol 4.5 µg versus salbutamol 200 µg, although the total doses were higher with an additional 18 µg formoterol or 800 µg salbutamol dose at 60 min. Some important differences between the two studies were evident, apart from the dosing regimen. Mean baseline FEV₁ percentage predicted normal was lower in the Boonsawat et al study [18] (44% predicted) than in our study (59%). They reported greater maximal improvements in FEV₁ (expressed as percentage increase from baseline: formoterol 51% versus salbutamol 36%), than in our study (formoterol 24% versus salbutamol 26%, data not shown). There are a number of possible explanations for the differences in maximal improvements in FEV₁ between the studies: (a) higher doses of β₂-agonists in the Boonsawat et al study [18] may have produced the greater responses; (b) there may be a difference in responsiveness to β₂-agonists between Thai and Australian patients; (c) treatment before presentation to the emergency department may have been different in the two groups. Nearly all our patients had taken (often considerable) doses of salbutamol or terbutaline and
presented due to treatment failure. We are not aware of how the data in the Boonsawat study compare in this regard.

As formoterol is known to be well tolerated at higher doses [19, 20] and to have a defined dose-response with no plateau in effect over the dose range investigated here [10, 21], it is possible that a subgroup of patients with partial responses to treatment might have gained from further doses of formoterol and salbutamol. Indeed, in one cumulative-dose study, comparing formoterol Turbuhaler® with terbutaline Turbuhaler® in acute asthma, 20 as-needed doses of formoterol up to a maximum of 90 µg were safely administered, with improved tolerability compared with 20 as-needed doses of terbutaline (total dose 10 mg) [20].

Safety was an important aspect of our study as stimulation of β2-adrenoceptors can result in extrapulmonary effects, especially at the high doses required to treat acute bronchoconstriction [22]. Therefore, blood pressure, heart rate, ECG, and serum potassium were monitored during the study. Importantly, no clinically meaningful increases in systemic/extrapulmonary effects were apparent with the dose of formoterol used, and there were no significant differences between the active treatments. Both treatments appeared to be well tolerated. Although several AEs were reported, most of them were pharmacologically predictable side effects or were related to the disease under study. Discontinuations due to AEs occurred due to ‘asthma aggravation’ in slightly fewer formoterol than salbutamol patients. There was a non-significant trend with salbutamol to produce greater effects on serum potassium, heart rate, and QTc after completion of dosing, but any differences with salbutamol were transient in nature and not considered clinically important.

One limitation of the current study was the relatively small sample size. As a consequence, a lack of a statistically significant difference alone cannot be judged to indicate an equal effect of the two drugs. Bronchodilating effects and systemic potencies of β2-agonists are dose dependent [9, 10]. In this study, cumulative doses of salbutamol 800 µg tended to give numerically higher effects than cumulative doses of formoterol 18 µg regarding both bronchodilation and systemic effects. This likely indicates a difference in potency at the dose-relation chosen, i.e. a somewhat higher formoterol dose than 18 µg should have been chosen to match salbutamol 800 µg. Salbutamol pMDI was in this study administered via spacer, and this was not accounted for when choosing the dose-relation.

Another possible limitation of this study was the lack of follow-up, which may have allowed detection of a difference in efficacy or side-effect profile between the treatment groups. We could speculate that if a follow-up period had been added, formoterol-treated patients may have been less inclined to repeat dose with reliever therapy due to its longer duration of bronchodilation [6, 23] with potential for less side effects. A further study is warranted to examine this potential benefit of formoterol. Nevertheless, this study confirms the findings of others [18, 20] that formoterol Turbuhaler® is similarly effective and well tolerated as salbutamol or terbutaline as reliever therapy in treating acute asthma.

Although the results of this study are unlikely to warrant a revision of current guidelines for treating asthma in an emergency setting [2, 24], they offer reassurance that formoterol may be used as needed for treatment of mild-to-moderate asthma worsening. The as-needed use of formoterol could simplify bronchodilator therapy and may be clinically important since, compared with traditional reliever therapy, as-needed formoterol has been shown to decrease the risk of experiencing a severe asthma exacerbation [13, 14]. In the 3-month study by Tattersfield et al [13], formoterol 4.5 µg as needed, decreased the risk of a first severe exacerbation compared with terbutaline 0.5 mg as needed, in a patient population with poorly controlled asthma, despite moderate-to-high doses of inhaled glucocorticosteroids. More recently, the large RELIEF study showed that as-needed formoterol 4.5 µg decreased the risk of a severe exacerbation compared with as-needed salbutamol 200 µg [14].
In conclusion, the results of this study support formoterol as an alternative to salbutamol as reliever therapy in the case of an acute exacerbation of asthma. Patients having formoterol Turbuhaler® as their only β₂-agonist bronchodilator can also rely upon its function and efficacy in an emergency situation. The exact comparative dose potencies between formoterol Turbuhaler® and salbutamol pMDI and spacer in the acute asthma situation need further investigations.
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Figure legends

Fig 1.–Effect of formoterol via Turbuhaler® (2 x 18 µg) and salbutamol (2 x 800 µg) via pressurised metered-dose inhaler (pMDI) plus spacer on forced expiratory volume in 1 second (FEV₁), expressed as mean change in percentage predicted normal values from baseline.

Fig 2.–Effect of formoterol via Turbuhaler® (2 x 18 µg) and salbutamol (2 x 800 µg) via pressurised metered-dose inhaler (pMDI) plus spacer on mean change in QTc.

Fig 3.–Effect of formoterol via Turbuhaler® (2 x 18 µg) and salbutamol (2 x 800 µg) via pressurised metered-dose inhaler (pMDI) plus spacer on mean change in serum potassium.