Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma

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Received 22 July 2004; revised 21 April 2005; accepted 27 April 2005

Abstract

This study compared the efficacy and safety of budesonide/formoterol (Symbicort® Turbuhaler®) with salbutamol pressurized metered-dose inhaler (pMDI) with spacer for relief of acute bronchoconstriction in patients with asthma. In this randomized, double-blind, parallel-group study, patients (n = 104 allocated to treatment; n = 103 received treatment; mean age 45 years) seeking medical attention for acute asthma (mean FEV1 43% of predicted) received two doses repeated at t = 5 and 0 min of either budesonide/formoterol (320/9 mg, two inhalations) or salbutamol (100 mg × eight inhalations); total doses 1280/36 mg and 1600 mg, respectively. All patients received prednisolone 60 mg at 90 min and FEV1 was assessed over 3 h. FEV1 90 min after dosing (primary variable) increased compared with pre-dose FEV1 by an average of 30% and 32% for budesonide/formoterol and salbutamol, respectively (P = 0.66), with similar increases at all timepoints from 3 to 180 min for both groups. Mean pulse rate over 3 h was significantly higher in the salbutamol group versus the budesonide/formoterol group (92 vs. 88 bpm; P < 0.01). No treatment differences were seen for other vital signs, including ECG. High-dose budesonide/formoterol was effective and well tolerated for the treatment of acute asthma, with rapid onset of efficacy and a safety profile over 3 h similar to high-dose salbutamol.

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Keywords: Asthma; Budesonide/formoterol; Symbicort®; Reliever medication

1. Introduction

Short-acting β2-agonists are currently the gold standard for relief of acute asthma symptoms in all severities of asthma [1,2]. Inhaled corticosteroids (ICS) are the recommended maintenance therapy for the majority of patients with persistent asthma [1] because of their anti-inflammatory effects. In patients with persistent asthma, where low doses of ICS alone do not provide optimal control, the combination of ICS and long-acting β2-agonists is more effective than increasing the dose of ICS [1,3,4].

Combination inhalers containing an ICS and a long-acting β2-agonist are a relatively new addition to the pharmacological management of asthma. Currently, there are two single-inhaler combination products on the market: budesonide/formoterol (Symbicort® Turbuhaler®) and salmeterol/fluticasone (Seretide® Diskus®). Budesonide/formoterol has been shown to be effective and well tolerated as maintenance therapy in adults and children with persistent asthma [5–10]. Formoterol, the long-acting β2-agonist component, causes rapid bronchodilation within 1–3 min of inhalation [11–13]—comparable with that of salbutamol [13]—and is as well tolerated as short-acting β2-agonists in patients with stable asthma [13–16]. Moreover, high-dose formoterol is as effective and well tolerated as high doses of terbutaline and salbutamol in treating patients with acute asthma [17,18]. In addition to rapid bronchodilation, the use of formoterol as reliever...
medication has now been shown to be well tolerated in long-term studies of over 18,000 patients [19,20]. Budesonide/formoterol has a rapid onset of effect [21]. Indeed, it has been demonstrated that patients can feel relief from asthma symptoms (bronchodilation) within 1 min of inhalation with budesonide/formoterol [22]. Palmqvist and colleagues reported that, in addition to its more rapid onset of effect, two inhalations of budesonide/formoterol (160/4.5 μg) resulted in a more pronounced improvement in lung function than salmeterol/fluticasone (50/250 μg) at 3 h post-dosing [21]. In addition, previous studies have shown improvements in lung function within hours of a single dose of budesonide [23–25]. There is, therefore, favourable evidence to support the efficacy of both formoterol and budesonide in patients with acute bronchoconstriction.

Budesonide/formoterol has previously been found to be highly effective in a model of acute asthma whereby severe bronchoconstriction was induced in patients using methacholine provocation [22]. A recent study by Ankerst and co-workers [26] also demonstrated that budesonide/formoterol has a favourable tolerability profile following administration of high doses over 1 h (1600/45 μg in addition to a maintenance dose of 160/4.5 μg, two inhalations twice daily) corresponding to doses that might occasionally be used by patients for the relief of severe acute asthma. Budesonide/formoterol was as well tolerated as formoterol, and neither formoterol nor budesonide/formoterol was considered to produce clinically important differences in safety variables compared with placebo [26]. The efficacy and tolerability of budesonide/formoterol in real-life acute asthma have not been investigated. Consequently, the current study examined the efficacy and safety of reliever therapy with budesonide/formoterol compared with salbutamol—administered via pressurized metered-dose inhaler (pMDI) with spacer—in patients seeking medical attention for acute asthma.

2. Methods

2.1. Patients

Male and female patients aged ≥12 years seeking medical attention for acute asthma were enrolled into the study. Eligible patients had asthma as defined by the American Thoracic Society criteria [27], a forced expiratory volume in 1 s (FEV₁) 30–60% of the predicted normal and were able to use a Turbuhaler® and pMDI with spacer correctly. Patients with acute severe asthma—defined as patients either unable to generate an FEV₁ value, with an FEV₁ <30% of predicted normal or those who required transfer to the intensive care unit after initial assessment—were excluded. Other exclusion criteria included intake of oral or other systemic corticosteroids within 7 days before admission; history of ≥10 pack-years of smoking; β-blocker therapy, including eye drops; or concomitant diseases that might interfere with the study.

The study (0702) was conducted in accordance with the Declaration of Helsinki and good clinical practice. The local ethics committee approved the study protocol and all patients provided informed consent before starting the study. If the patient was unable to provide written consent immediately, oral consent was witnessed in writing and the patient’s written informed consent was obtained as soon as possible before the end of the study.

2.2. Study design

This was a multicentre, double-blind, double-dummy, parallel-group, randomized, 3-h study. Eligible patients received two doses, 5 min apart, of either budesonide/formoterol (Symbicort® Turbuhaler®, AstraZeneca Liquid Production, Södertälje, Sweden) 320/9 μg two inhalations (total dose 1280/36 μg) or salbutamol 100 μg via pMDI eight actuations (Norton Healthcare, London, UK; total dose 1600 μg) with a Volumatic® spacer (Glaxo-SmithKline, Uxbridge, UK). Both treatments were started as soon as possible after the patient’s arrival at hospital. After the second dose, the time was set at zero. After 90 min, patients received oral prednisolone 60 mg (Fig. 1). Study treatments were administered using a double-dummy technique to ensure blinding and either study drug or placebo could be administered first.

2.3. Measurements

FEV₁ was measured at baseline (value before inhalation of study treatment) and then at 3, 15, 30, 60, 90, 120 and 180 min after the last intake of study treatment. All spirometry was performed according to the European respiratory society recommendations [28]. Respiratory rate was determined over 1 min at baseline and at 15, 30, 60, 90, 120 and 180 min after the last intake of study treatment. Treatment success—defined as fitness for immediate discharge from hospital—was judged by the investigator at 90 and 180 min. Even if treatment was considered a success at 90 min, the patient continued in the study. Treatment failure was defined as the need for additional asthma treatment or hospitalization because of asthma within the study period (or both).

Safety was assessed by recording adverse events, serum potassium, oxygen saturation (SaO₂), electrocardiogram (ECG) and vital signs. Blood samples for analysis of serum potassium were drawn at baseline and at 30, 90 and 180 min after the last dose of study treatment. SaO₂ was assessed on arrival at hospital, before administration of oxygen and at 15, 30, 60, 90, 120 and 180 min after the last dose of study treatment. Local hospital equipment and procedures were used for assessing serum potassium, SaO₂, ECG and vital signs. Pulse rate over 30 s was measured by hand at baseline and at all timepoints during the 3-h study. A 6-lead ECG
was recorded at baseline and at 15, 60, 90 and 180 min. In addition to the overall ECG evaluation, heart rate, sinus rhythm and QTc interval were assessed. Abnormal laboratory results (i.e. for serum potassium), vital signs and ECG were not recorded as adverse events unless they resulted in discontinuation, were serious adverse events or the investigator considered the event to be of such clinical importance as to merit recording it as an adverse event.

2.4. Data analysis

The efficacy and safety analyses were performed on data from all patients who received active treatment. The primary endpoint was mean FEV₁ from the first intake of study treatment up until the 90-min assessment point. Average FEV₁ was calculated as the area under the curve (AUC) divided by the observation time, with AUC determined using the trapezoidal rule. Actual measurement times were used, except for baseline FEV₁ (which was assumed to have been performed immediately before the first intake of study treatment). Geometric mean values were calculated for FEV₁. Secondary efficacy variables included the increase in FEV₁ from baseline to 3, 15, 90 and 180 min after the last study treatment administration. A total of 50 patients were required per group to have an 80% chance of detecting a difference of 12% in average FEV₁ (from the first intake of study treatment up until the 90-min assessment point) between treatment groups (at the two-sided 5% level, with an assumed standard deviation of 0.21 log units).

The primary efficacy endpoint was compared between treatments using a multiplicative analysis of variance (ANOVA) model with fixed factors for treatment and country, and using baseline FEV₁ as a covariate. The treatment difference was expressed as a ratio (in percent). Similar ANOVA models were used to compare the secondary efficacy variables based on FEV₁.

The minimum and mean post-study treatment values for SaO₂, serum potassium and diastolic blood pressure were compared between treatments. Maximum and mean post-study drug treatment values for systolic blood pressure, pulse rate, heart rate and QTc interval were also compared. Additive ANOVA models, with treatment and country as fixed factors and using baseline values as covariates, were used to analyse treatment differences for all safety variables.

3. Results

In total, 112 patients were enrolled at 10 centres in five countries (China, Indonesia, The Philippines, Taiwan and Vietnam) and 104 patients were randomized to study treatment: 55 in the budesonide/formoterol group and 49 in the salbutamol group. One patient in the salbutamol group did not receive any study drug. Therefore, the analysis was based on data from 103 patients: 55 and 48 patients in the budesonide/formoterol and salbutamol groups, respectively. In total, 102 patients completed the study: 55 in the budesonide/formoterol group and 47 in the salbutamol group. One patient who did not fulfil the eligibility criteria was discontinued after randomization. All patients were Oriental, and the two treatment groups were well matched with regard to demography and baseline FEV₁ values.
The majority of patients enrolled \((n=86)\) had never smoked; of the remaining patients, only six were current smokers.

No difference could be detected between the budesonide/formoterol and salbutamol groups in average FEV\(_1\) from the first intake of study treatment to the 90-min assessment point (primary variable) (mean ratio: 98.4% [95% confidence interval (CI): 91.6, 105.7; \(P=0.66\)]) (Table 2). The maximum increase from pre-dose FEV\(_1\) during this period was 40% for patients in the budesonide/formoterol group and 42% for patients in the salbutamol group. Post-treatment FEV\(_1\) values at 3, 15, 90 and 180 min were similar for both groups (Fig. 2). Improvements in FEV\(_1\) were numerically greater in the budesonide/formoterol group than in the salbutamol group at timepoints after 90 min, but these differences were not statistically significant (Fig. 2).

Only one patient (in the budesonide/formoterol group) failed to meet the criteria for treatment success at 90 and 180 min; therefore, no formal analysis was performed for treatment failure. Respiratory rate decreased over time in both groups. Mean baseline values were 23.7 breaths min\(^{-1}\) (range 11–36) and 23.1 breaths min\(^{-1}\) (range 15–36) for the budesonide/formoterol and salbutamol groups, respectively. At the end of treatment (180 min), mean treatment values were 20.8 breaths min\(^{-1}\) (range 14–28) for the budesonide/formoterol group and 20.0 breaths min\(^{-1}\) (range 14–39) for the salbutamol group. No difference in mean change could be detected at 180 min between the treatments (budesonide/formoterol \(-2.7\) breaths min\(^{-1}\), salbutamol \(-3.3\) breaths min\(^{-1}\)).

The time profile curves for serum potassium, pulse rate, and QTc interval for budesonide/formoterol and salbutamol are shown in Fig. 3 (a)–(c). Mean serum potassium decreased to a similar extent in both groups (Table 3), with minimum concentrations decreasing to 3.52 mmol\(\cdot\)L\(^{-1}\) in the budesonide/formoterol group and 3.42 mmol\(\cdot\)L\(^{-1}\) in the salbutamol group over the treatment period.

Mean pulse rate over 180 min was significantly higher in the salbutamol group (92.1 beats min\(^{-1}\) [bpm]) compared with the budesonide/formoterol group (87.9 bpm; mean difference \(-4.6\) bpm [95% CI: \(-7.3,–1.8\)]; \(P<0.01\)). Maximum pulse rate recorded over 180 min was also significantly higher for the salbutamol group (102.4 bpm)

### Table 1

Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Budesonide/formoterol 1280/36 µg ((n=55))</th>
<th>Salbutamol 1600 µg ((n=48))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>23/32</td>
<td>19/29</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>47 (21–80)</td>
<td>42 (13–76)</td>
</tr>
<tr>
<td>12–18 years</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>FEV(_1), l (range)</td>
<td>1.13 (0.50–2.30)</td>
<td>1.23 (0.54–2.51)</td>
</tr>
<tr>
<td>FEV(_1), % of predicted normal (range)</td>
<td>42 (28–60)</td>
<td>45 (30–60)</td>
</tr>
<tr>
<td>Oxygen saturation, % (range)</td>
<td>96 (88–99)</td>
<td>96 (85–100)</td>
</tr>
<tr>
<td>Pulse, beats per minute (range)</td>
<td>93 (64–123)</td>
<td>93 (62–131)</td>
</tr>
<tr>
<td>Time since, diagnosis of asthma, years (range)</td>
<td>13 (0–42)</td>
<td>10 (0–48)</td>
</tr>
<tr>
<td>Asthma medication at study entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS, n (%)</td>
<td>21 (38)</td>
<td>14 (29)</td>
</tr>
<tr>
<td>ICS, µg/day (range)(^a)</td>
<td>667 (200–1200)</td>
<td>782 (400–1200)</td>
</tr>
<tr>
<td>Inhaled short-acting (\beta)-agonists, n (%)</td>
<td>25 (45)</td>
<td>23 (48)</td>
</tr>
<tr>
<td>Inhaled long-acting (\beta)-agonists, n (%)</td>
<td>6 (11)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Oral (\beta)-agonists, n (%)</td>
<td>6 (11)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Xanthines, n (%)</td>
<td>16 (29)</td>
<td>14 (29)</td>
</tr>
</tbody>
</table>

Values are presented as absolute numbers or as mean (range), except time since diagnosis (median). FEV\(_1\), forced expiratory volume in 1 s; ICS, inhaled corticosteroids.

\(^a\) For patients using ICS prior to study entry.

### Table 2

FEV\(_1\) over the 90-min assessment period

<table>
<thead>
<tr>
<th></th>
<th>Budesonide/formoterol 1280/36 µg ((n=55))</th>
<th>Salbutamol 1600 µg ((n=48))</th>
<th>Treatment comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean, l (range)</td>
<td>Adjusted ratio (% baseline)</td>
<td>Mean, l (range)</td>
</tr>
<tr>
<td>Baseline FEV(_1)</td>
<td>1.067 (0.50–2.30)</td>
<td>–</td>
<td>1.162 (0.54–2.51)</td>
</tr>
<tr>
<td>FEV(_1) over 90 min(^a)</td>
<td>1.381 (0.46–3.34)</td>
<td>130.19</td>
<td>1.516 (0.78–3.56)</td>
</tr>
<tr>
<td>Maximum value(^b)</td>
<td>1.484 (0.50–3.60)</td>
<td>139.73</td>
<td>1.625 (0.84–3.84)</td>
</tr>
</tbody>
</table>

FEV\(_1\), forced expiratory volume in 1 s; NS, non-significant.

\(^a\) Mean value up to the 90-min assessment.

\(^b\) Maximum value up to the 90-min assessment.
compared with the budesonide/formoterol group (97.9 bpm; mean difference -4.8 bpm [95% CI: -7.4, -2.1]; P < 0.001). Other vital signs, including the ECG QTc interval, were similar for both treatment groups and changes over time were minimal (Table 3).

In total, eight adverse events occurred during treatment (five in the budesonide/formoterol group and three in the salbutamol group)—all of which were of mild intensity. Four patients had hypokalaemia (one in the budesonide/formoterol group and three in the salbutamol group); extrasystoles, tachycardia, hypertension and bradycardia were reported for one patient each in the budesonide/formoterol group. One serious adverse event, not causally related to study treatment, was reported for one patient in the budesonide/formoterol group post-study. Approximately 4 h after completion of the study, the patient was hospitalized for pyrexia; the patient recovered without sequelae and was discharged the following day.

4. Discussion

The efficacy and tolerability of budesonide/formoterol for the management of stable asthma have been extensively documented [5–10]. This is the first study to compare the use of budesonide/formoterol for the relief of acute asthma bronchoconstriction with that of salbutamol, which is widely used both as a day-to-day reliever medication and in the hospital/emergency room management of exacerbations. Our study in patients seeking medical attention for acute asthma shows that budesonide/formoterol is well tolerated and provides similarly rapid and effective bronchodilation as salbutamol in adults and adolescents in this setting.

Both budesonide/formoterol and salbutamol improved FEV₁ and no difference could be detected between treatment groups for change from pre-dose FEV₁ to 3 min post-dose or to any subsequent timepoint. The rapid onset of
Fig. 3. (a) Mean serum potassium. No significant between-group difference was observed for average or minimum serum potassium values. (b) Pulse rate. Mean difference in pulse rate for budesonide/formoterol vs. salbutamol: −4.6 bpm. (c) QTc. No significant between-group difference was observed for average QTc interval. All data are shown over the 3-h treatment period. Study drug (budesonide/formoterol [320/9 μg, two inhalations] or salbutamol [100 μg, eight actuations]) was administered at −5 and 0 min.
effect of budesonide/formoterol confirms earlier reports that patients can feel relief from bronchoconstriction with budesonide/formoterol within 1 min of inhalation when methacholine provocation was used as a model of severe bronchoconstriction [22]. The rapid onset of effect of budesonide/formoterol is attributable to the formoterol component, which provides a bronchodilating effect as rapidly as salbutamol in patients with either stable [13] or acute asthma [18]. The efficacy of formoterol for reliever medication has been proven in two large studies comparing the number of severe exacerbations (defined as the need for oral steroids because of asthma or a ≥ 30% decrease from baseline in morning peak expiratory flow on 2 consecutive days [19], or defined as any increase in maintenance medication, the need for oral steroids for ≥ 5 days, hospitalization or emergency room treatment with nebulized β2-agonist or corticosteroid injection [20]) in patients receiving either formoterol or short-acting β2-agonists for as-needed relief. Patients receiving as-needed formoterol had fewer severe asthma exacerbations and improved asthma control compared with those receiving short-acting β2-agonists [19,20]. Our study demonstrates for the first time that patients seeking medical attention for acute asthma can respond as quickly and as favourably following repeated doses of budesonide/formoterol administered via Turbuhaler as they do after repeated doses of salbutamol via pMDI and spacer.

Improvements in FEV1 with budesonide/formoterol compared with salbutamol were more apparent with time in this 3-h study. In the salbutamol group, maximum FEV1 was observed at 60 min, whereas in the budesonide/formoterol group, FEV1 continued to improve up to the end of the study. This may be a result of formoterol’s longer duration of action compared with salbutamol [14,29]. A recent study performed in patients with acute severe asthma has confirmed that, when using even higher doses of formoterol and salbutamol (54 μg formoterol versus 2400 μg salbutamol) than examined here, formoterol provides as rapid an improvement in FEV1 as salbutamol—but with significantly greater maximal efficacy during the third and fourth hour after dosing [18]. Sustained effects of formoterol on lung function for up to 24 h have been demonstrated in several studies—in particular, when formoterol is co-administered with budesonide [8,30,31]. In order to examine fully the potential increases in FEV1 and additional beneficial effects that could have occurred after the initial 3-h acute phase in the present study, studies of longer duration are required. Such studies would also enable the acute effects of budesonide—reported to occur within hours [23,25]—to be investigated. High-dose inhaled budesonide has been shown to be as effective as prednisolone in the acute treatment of asthma exacerbations in children [32]. Similarly, nebulized budesonide has been demonstrated to be as effective as prednisolone in adults with acute asthma [33]. In addition, cost-effectiveness studies with appropriate follow-up are warranted to assess the drug costs associated with budesonide/formoterol treatment compared with salbutamol.

In this study, we decided to compare budesonide/formoterol with the most widely accepted reliever therapy available. Although salbutamol is often traditionally administered by nebulizer in the emergency department, the use of a pMDI and spacer is considered to be as effective as the nebulizer [1,2,34,35]. The two-dose regimen of salbutamol (800μg + 800 μg) used during the present study was selected based on guideline recommendations for the treatment of asthma exacerbations, which state that an inhaled short-acting β2-agonist should be administered at such doses at repeated intervals within the first hour for relief of an exacerbation [1]. The comparator dose of budesonide/formoterol was based on the observation that a 4.5 μg dose of formoterol via Turbuhaler provides equivalent acute bronchodilation to salbutamol 200 μg via pMDI in patients with stable asthma [13,36].

In the present study, budesonide/formoterol was well tolerated and the incidence of adverse events was low and comparable for both treatment groups—most were expected β2-agonist class effects. Mean serum potassium decreased from baseline but remained within the normal range throughout the study in both groups, and no between-group differences were observed. Changes in blood pressure, ECG, heart rate and QTc intervals were also comparable. Interestingly, budesonide/formoterol resulted in a significantly lower average pulse rate over the study versus salbutamol. These findings suggest that patients using budesonide/formoterol for acute relief of bronchoconstriction are unlikely to experience greater systemic effects than those treated with salbutamol. This is in line with the findings of Rosenborg and co-workers, who reported a short duration of systemic effects with inhaled formoterol (measured as changes in serum potassium)—similar to that of salbutamol at equi-effective doses [16]. In an acute tolerability study conducted by Ankerst and colleagues, temporary high doses of budesonide/formoterol in addition to maintenance treatment (1600/45 μg plus a maintenance dose of 160/4.5 μg, two inhalations twice daily) was not considered to result in clinically important changes versus placebo in serum potassium, pulse rate, blood pressure, QTc or blood glucose [26]. The present study provides further evidence of the favourable tolerability of high doses of budesonide/formoterol when used to relieve acute bronchoconstriction in patients with asthma.

The combination of a rapid- and long-acting β2-agonist and an ICS is effective and well tolerated in patients with persistent asthma [5–10]. To date, combination inhalers have only been recommended for maintenance treatment, with the addition of short-acting β2-agonists for the acute relief of symptoms as needed. However, the rapid onset of bronchodilation demonstrated in our study suggests that budesonide/formoterol has the potential to be used for symptom relief. The study also offers clear reassurance that budesonide/formoterol represents a well-tolerated and
effective alternative to salbutamol as reliever therapy at high doses during acute bronchoconstriction. These findings suggest that an asthma management approach using an ICS plus a fast-onset long-acting β2-agonist in one inhaler for both maintenance and as-needed relief is now theoretically possible. Further studies are required to establish the potential of budesonide/formoterol to provide improved asthma control when used for both maintenance and as-needed relief in addition to its proven role as maintenance therapy.

In conclusion, high-dose budesonide/formoterol administered via Turbuhaler is well tolerated and provides similarly rapid and effective bronchodilation as high-dose salbutamol via pMDI and spacer in the treatment of acute asthma.

References

[16] V.M. Balanag et al. / Pulmonary Pharmacology & Therapeutics 19 (2006) 139–147


