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Formoterol Turbuhaler as reliever medication in patients with acute asthma

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ABSTRACT: The aim of this study was to compare the efficacy and safety of formoterol *versus* salbutamol as reliever medication in patients presenting at an emergency dept with acute asthma.

A randomised, double-blind, double-dummy, parallel group study was performed in four Australian emergency treatment centres. The study included a total of 78 adult patients (mean baseline forced expiratory volume in one second (FEV_1) 1.83 L; 59% predicted) with acute asthma. Based on the expected dose equivalence of formoterol Turbuhaler® 4.5 μg (delivered dose) and salbutamol pressurised metered-dose inhaler 200 μg (metered dose), patients received a total of formoterol Turbuhaler® 36 μg (delivered) or salbutamol pressurised metered-dose inhaler with spacer 1,600 μg (metered), divided into two equal doses at 0 and 30 min. FEV_1, peak expiratory flow and systemic β_2-agonist effects were monitored for 4 h. The primary variable was FEV_1 % pred at 45 min.

At 45 min, mean increases in FEV_1 expressed in % pred were 6.6% and 9.3%, respectively, with a small adjusted mean difference in favour of salbutamol (3.0%, 95% confidence interval -2.0–8.0). 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 at emergency depts with acute asthma, formoterol Turbuhaler® 36 μg was well tolerated and, as rescue therapy, had an efficacy that was not different from that of salbutamol pressurised metered-dose inhaler with spacer 1,600 μg in the number of patients studied.

KEYWORDS: Acute asthma, formoterol, reliever medication, salbutamol, Turbuhaler®

In hospital emergency depts, the firstline treatment for patients presenting with acute exacerbations of asthma is the administration of a rapid-acting β_2-agonist, either continuously or at regular intervals during the first hour [1, 2]. Although rapid-acting β_2-agonists are often administered *via* nebulisation, 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 β_2-agonist therapy, oxygen, systemic glucocorticosteroids, and further inhaled or intravenous β_2-agonist therapy may be needed.

Traditionally, rapid- and short-acting β_2-agonists (*e.g.* salbutamol, terbutaline) have been used for symptom relief. Formoterol is a selective β_2-agonist with a similar onset of effect to salbutamol [5] but with a longer duration of action ($\geqslant$12 h in patients with stable asthma) [6]. POLITIEK *et al.* [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 β_2-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; for example, effects on serum potassium and QT interval corrected for heart rate (QTc)) was 2.5 times more favourable for formoterol Turbuhaler® than 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]. These effects have been confirmed when formoterol has been used

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as-needed compared with as-needed terbutaline or salbutamol [13, 14].

Formoterol is the only long-acting β_2-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 β_2-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 as-needed formoterol 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 *via* pMDI and spacer, at a dose of $\leqslant$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® (Oxis®; AstraZeneca, Lund, Sweden; 4×4.5 μg inhalations (18 μg)) given 30 min apart with salbutamol *via* pMDI (Norton Healthcare, Harlow, UK) with spacer (Volumatic™; GlaxoSmithKline, Uxbridge, UK; four separate inhalations of two actuations of 100 μg (800 μg)) for up to 4 h in patients with acute asthma presenting at a hospital emergency dept. 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 at the emergency dept with acute asthma [15] were included in the study if their forced expiratory volume in one second (FEV1) was >30% of predicted and, if aged $\geqslant$50 yrs, they had a pulse rate $\geqslant$100 beats·min^{-1} 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 nebulised or intravenous β_2-agonists at the initial assessment; or their arterial oxygen saturation (S_{a,O_2}) was <93% on room air. Females who were pregnant, lactating or of childbearing potential, meaning they were 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 randomisation code. Treatment was initiated within 30 min of arriving in the emergency dept. Each treatment was given twice, at time 0 and 30 min, and consisted of either formoterol Turbuhaler®, administered as 4×4.5 μg inhalations (18 μg), or salbutamol pMDI *via* spacer, as four separate inhalations of two 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 was recorded. All centres used the same type of spirometer (MicroLab™ Rochester, UK), which met the American Thoracic Society standard for accuracy ($\pm$3% of reading or $\pm$0.05 L). The primary efficacy variable was the change from baseline in FEV1 % pred, 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 FEV1 (%), from baseline to 15 min, and the average and maximum change in FEV1 between 45 and 240 min after administration of study drug. PEF was also assessed at each time point. Estimations of FEV1 % pred and PEF values were made for each patient, taking into account age, height and sex [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 (S_{a,O_2} <93% or FEV1 $\leqslant$30% pred, or there was a fall or no improvement in FEV1 within 15 min of the second dose of study drug) were withdrawn and received routine emergency dept treatment.

Statistical analysis

The primary efficacy variable, change in FEV1 % pred at 45 min, was compared between treatments using an additive ANOVA model with treatments and centre as fixed factors, using baseline FEV1 as covariate. Similar ANOVA models were used to compare the secondary efficacy variables based on FEV1 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

TABLE 1 Patient demographics at baseline

	Formoterol 36 μg	Salbutamol 1600 μg
Subjects	38	40
Males	16 (42)	10 (25)
Age yrs	36 (18–69)	37 (19–67)
Patients using ICS at entry	25 (66)	23 (58)
Patients using regular LABA or LABA/ICS combinations at entry	16 (42)	12 (30)
ICS dose at entry μg	1313 (200–3200)	908 (50–2000)
FEV_1 L	1.90 (0.59–4.10)	1.77 (0.65–3.37)
FEV_1 % pred	57 (31–101)	60 (30–107)
Pulse rate beats·min^{-1}	102 (67–136)	99 (72–138)
S_{a,O_2} %	96 (93–100)	97 (93–100)

Data are presented as n, n (%) and mean (range). ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; FEV_1: forced expiratory volume in one second; % pred: % predicted; S_{a,O_2}: arterial oxygen saturation.

withdrawn from the study within 4 h of administration of the first dose of study drug was compared between treatments using a Chi-squared test. A p-value of <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 FEV_1 7% pred at 45 min, assuming an SD 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 FEV_1 % pred was 57% in the formoterol group and 60% in the salbutamol group). However, some differences in demographics between the groups were apparent, with a higher male ratio in the formoterol group (42 *versus* 25% in the salbutamol group) and greater use of concomitant medications before study entry in the formoterol group *versus* the salbutamol group. The mean dose of inhaled corticosteroid was also higher in the formoterol group (1,313 *versus* 908 μg·day^{-1}) and more patients had previously used long-acting β_2-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 of these 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.

Efficacy

The change from baseline in FEV_1 % pred at all time points was similar in the formoterol and salbutamol groups (fig. 1). The mean change in FEV_1 % pred at 45 min (primary variable)

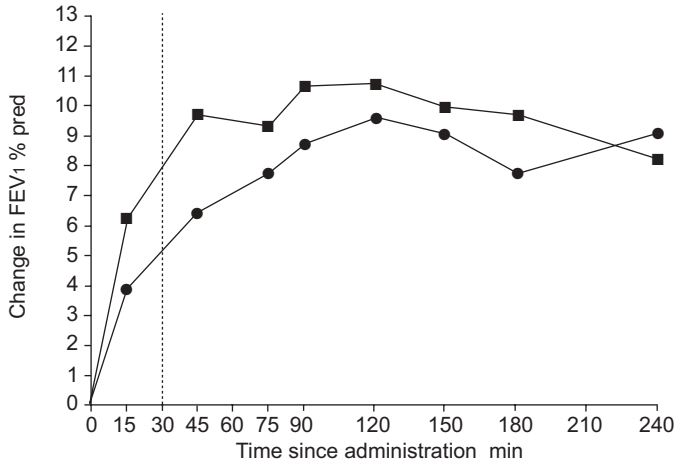

FIGURE 1. Effect of formoterol *via* Turbuhaler® (2×18 μg; ●) and salbutamol (2×800 μg; ■) *via* pressurised metered-dose inhaler plus spacer on forced expiratory volume in one second (FEV_1), expressed as mean change in % predicted from baseline. First dose administered at baseline; administration of second dose indicated by dotted line.

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 FEV_1 % pred was seen at any other time point between the treatment groups.

PEF data essentially confirmed the result on FEV_1. The mean increase in PEF % pred 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 PEF % pred was 12.1% in the formoterol group and 14.3% in the salbutamol group (-2.8%, 95% CI -9.3–3.6; p=0.38).

Safety

Mean safety parameter measurements are shown in table 3. There were no statistically significant differences between the two treatment groups. 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 the 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), hypokalaemia (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%)

TABLE 2 Change in forced expiratory volume in one second % predicted from baseline

	Change from baseline		Adjusted mean difference formoterol–salbutamol (95% CI)[¶]	p-value
	Formoterol*	Salbutamol[#]		
Baseline	57.4 (30.7–101.1)	59.4 (30.3–107.3)		
E_{15}[+]	4.1 (-20.1–28.8)	5.9 (-12.8–35.9)	-1.9 (-6.3–2.5)	0.39
E_{45}[+]	6.6 (-20.8–31.0)	9.3 (-11.4–45.9)	-3.0 (-8.0–2.0)	0.24
E_{av}[§]	8.4 (-22.0–30.1)	9.7 (-11.4–47.6)	-1.5 (-7.2–4.2)	0.6
E_{max}[§]	12.4 (-17.7–34.1)	14.6 (-11.4–55.1)	-2.3 (-8.2–3.6)	0.43

Data are presented as mean % predicted (range), unless otherwise stated. CI: confidence interval; 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. *: n=38; [#]: n=39; [¶]: performed using ANOVA; [+]: n=38 in formoterol group/39 in salbutamol group; [§]: n=37 formoterol/37 salbutamol.

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 an SAE continued in the study.

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% pred. Despite the wide range of FEV1 in both groups (varying from ~30% to >100% pred), 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 dept.

There was a male predominance and a more extensive previous use of inhaled corticosteroids and long-acting β_2-agonists by patients in the formoterol treatment group. These baseline differences cannot be explained; they are probably 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 dept. 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.

TABLE 3 Effect of test treatments on systemic parameters

Variable	Baseline		Treatment		Adjusted mean difference formoterol–salbutamol (95% CI)*	p-value
	Formoterol	Salbutamol	Formoterol	Salbutamol		
E_{av} on SBP mmHg	134.1 (100–186)	132.9 (110–169)	126.5 (98–169)	124.7 (101–151)	1.5 (-2.6–5.6)	0.48
E_{max} on SBP mmHg	134.1 (100–186)	132.9 (110–169)	135.5 (100–187)	133.1 (105–169)	2.1 (-2.9–7.0)	0.41
E_{av} on DBP mmHg	82.1 (60–102)	79.7 (60–102)	75.7 (53–93)	73.4 (49–92)	1.9 (-1.1–4.9)	0.21
E_{min} DBP mmHg	82.1 (60–102)	79.7 (60–102)	68.9 (50–86)	67.7 (45–91)	1.0 (-2.5–4.5)	0.56
E_{av} on ECG heart rate beats·min^{-1}	99.4 (62–137)	96.3 (67–144)	93.4 (60–122)	93.5 (69–128)	-2.0 (-6.5–2.6)	0.39
E_{max} on ECG heart rate beats·min^{-1}	99.4 (62–137)	96.3 (67–144)	102.1 (70–130)	101.7 (72–137)	-1.6 (-6.5–3.4)	0.53
E_{av} on ECG QTc ms	412.6 (325–505)	423.3 (338–527)	409.8 (340–492)	422.2 (374–496)	-7.9 (-19.4–3.6)	0.18
E_{max} ECG QTc ms	412.6 (325–505)	423.3 (338–527)	435.4 (372–554)	453.2 (394–634)	-13.2 (-29.4–2.9)	0.11
E_{av} on S-potassium mmol·L^{-1}	3.85 (3.0–4.9)	3.88 (3.0–4.7)	3.83 (3.1–4.6)	3.82 (3.0–4.6)	0.04 (-0.07–0.16)	0.44
E_{min} on S-potassium mmol·L^{-1}	3.85 (3.0–4.9)	3.88 (3.0–4.7)	3.63 (2.9–4.5)	3.60 (2.8–4.6)	0.06 (-0.07–0.18)	0.35

Data are presented as mean (range), unless otherwise stated. *: performed using ANOVA. CI: confidence interval; E_{av}: average effect between 45 and 240 min; SBP: systolic blood pressure; E_{max}: maximal effect between 45 and 240 min; DBP: diastolic blood pressure; E_{min}: minimal effect between 45 and 240 min; ECG: electrocardiogram. 1 mmHg=0.133 kPa.

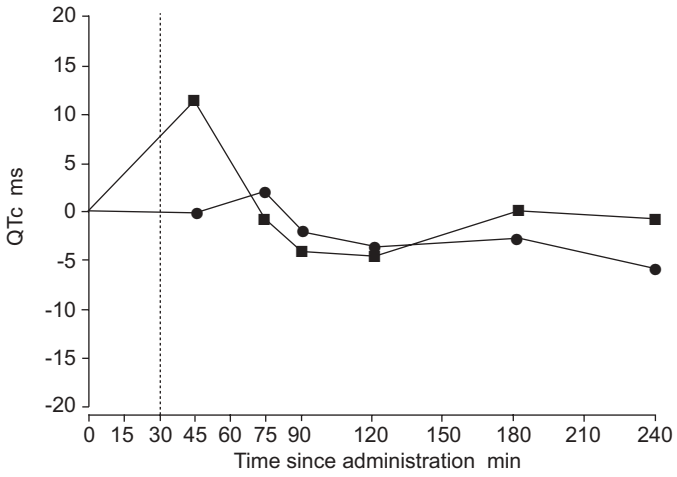

FIGURE 2. Effect of formoterol *via* Turbuhaler® (2×18 μg) and salbutamol (2×800 μg) *via* pressurised metered-dose inhaler plus spacer on mean change in QTc. First dose administered at baseline; administration of second dose indicated by dotted line.

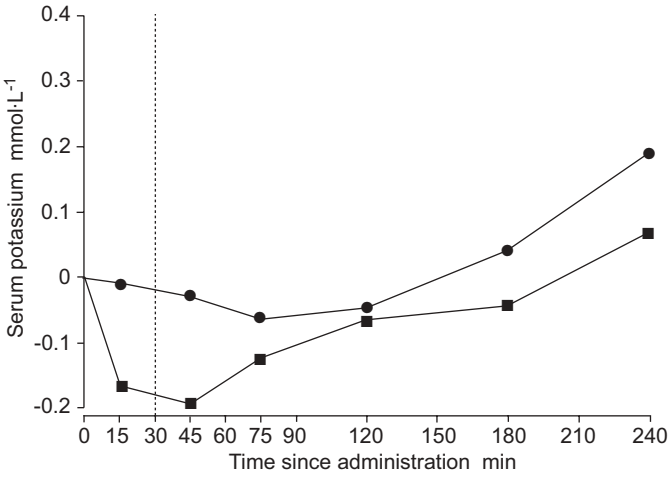

FIGURE 3. Effect of formoterol *via* Turbuhaler® (2×18 μg) and salbutamol (2×800 μg) *via* pressurised metered-dose inhaler plus spacer on mean change in serum potassium. First dose administered at baseline; administration of second dose indicated by dotted line.

For the emergency treatment of acute asthma with a salbutamol pMDI plus spacer at home, the Global Initiative for Asthma 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 dept 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.

As well as the dosing regimen, some other important differences between the two studies. Mean baseline FEV1 % pred was lower in the BOONSAWAT *et al.* [18] study (44% pred) than in the present study (59%). They reported greater maximal improvements in FEV1 (expressed as percentage increase from baseline: formoterol 51% *versus* salbutamol 36%) than in the present 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: 1) higher doses of β_2-agonists in the BOONSAWAT *et al.* [18] study may have produced the greater responses; 2) there may be a difference in responsiveness to β_2-agonists between Thai and Australian patients; and 3) treatment before presentation to the emergency dept may have been different in the two groups. Nearly all of the present study's patients had taken (often considerable) doses of salbutamol or terbutaline and presented due to treatment failure. The authors are unaware of how the data in BOONSAWAT *et al.* [18] 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 the present study, as stimulation of β_2-adrenoceptors can result in extrapulmonary effects, especially at the high doses required to treat acute bronchoconstriction [22]. Therefore, blood pressure, heart rate, ECG and S-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 nonsignificant trend with salbutamol to produce greater effects on S-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 its 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 β_2-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 probably 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. In this study salbutamol pMDI was 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. It could be speculated that if a follow-up period had been added, formoterol-treated patients may have been less inclined to repeat the dose with reliever therapy due to its longer duration of bronchodilation [6, 23] with potential for fewer 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 compared with 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 worsenings. 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 REal LIfe EFfectiveness of Oxis® Turbuhaler® as needed in asthmatic patients (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 the argument that formoterol can be used as an alternative to salbutamol as reliever therapy in acute exacerbations of asthma. Patients having formoterol Turbuhaler® as their only β_2-agonist bronchodilator can also rely upon its function and efficacy in an emergency situation. The exact comparative dose potencies between formoterol Turbuhaler® and salbutamol *via* pressurised metered-dose inhaler plus spacer in acute asthma needs further investigation.

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