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Safety of formoterol Turbuhaler® at cumulative dose of 90 μg in patients with acute bronchial obstruction

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Safety of formoterol Turbuhaler® at cumulative dose of 90 μg in patients with acute bronchial obstruction. J. Malolepszy, G. Böszörményi Nagy, O. Selroos, P. Larsson, R. Brander. ©ERS Journals Ltd 2001.

ABSTRACT: This study compared the safety of formoterol (Oxis® Turbuhaler®; 90 μg delivered dose; 120 μg metered dose) with terbutaline (Bricanyl® Turbuhaler®; 10 mg), in patients with acute bronchoconstriction.

Forty-eight patients (31 females) with a mean age of 45 yrs, were randomized into two parallel groups (double-blind design). Mean baseline forced expiratory volume in one second (FEV_1) was 0.98 L (33% of predicted normal). Study drugs were administered on six occasions during 3 h (formoterol 4.5 μg or terbutaline 0.5 mg·inhalation^{-1}, 20 inhalations). Patients received intravenous prednisolone after 1.5 h and oxygen during the first 3 h. Pulse rate, serum potassium, 12-lead electrocardiogram (ECG), Holter ECG, arterial blood gases and FEV_1 were assessed during 12 h after the first dose.

Four patients (one formoterol, three terbutaline) discontinued. The 12-h mean values of serum potassium decreased from 4.02 to 3.89 mmol·L^{-1} for formoterol and from 4.22 to 3.76 mmol·L^{-1} for terbutaline. Mean 12-h pulse rate was significantly ($p<0.01$) higher in the terbutaline group (101.7 beats per minute (bpm)) than in the formoterol group (93.5 bpm). No individual patient value was considered clinically important or alarming. FEV_1 improved in both groups but with no statistically significant difference between treatments.

Oxis® Turbuhaler® (90 μg) was at least as safe and well tolerated as terbutaline (110 mg) in patients with acute bronchoconstriction.

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In patients with moderate to severe asthma, the use of long-acting β_2-agonists is recommended as one option in maintenance treatment, in combination with glucocorticoids and as-needed short-acting β_2-agonists [1, 2]. This treatment has proved to be highly efficient, as demonstrated in the Formoterol and Corticosteroids Establishing Therapy (FACET) [3] and other clinical studies [4, 5].

β_2-agonist drugs relax bronchial smooth muscle and provide highly effective bronchodilation. However, β_2-adrenoceptors occur in a variety of tissues, including the heart [6], and potential adverse effects associated with high doses of inhaled β_2-agonists need to be investigated. Inhaled short-acting β_2-agonists, even at high doses, appear less likely to produce these adverse effects to the same extent as with oral administration [7]. Indeed, the long-acting β_2-agonist formoterol has well documented long-term efficacy and safety at therapeutic maintenance doses [8, 9].

Formoterol has a duration of action up to 12 h [10] but has also been shown to have a fast onset of action, similar to that of the short-acting β_2-agonist salbutamol [11]. In addition, the duration of systemic effects with formoterol is as short as that after administration of salbutamol [12]. A tolerability study with formoterol in patients with stable asthma showed that treatment with 90 μg·day^{-1} over 3 days resulted in less systemic effects than treatment with terbutaline 10 mg·day^{-1} [13]. The fast onset of action of formoterol, combined with prolonged bronchodilation, good tolerability and safety at high doses in patients with stable asthma, suggest that this drug may also be of use as relief medication for acute bronchoconstriction. However, in episodic exacerbation of asthma this may result in administration of high doses within a short period of time. Therefore, the safety of high doses of inhaled formoterol needs to be investigated in acute bronchoconstriction.

Currently, formoterol Turbuhaler® is approved for regular treatment in patients using glucocorticoids; if required for relief of asthma symptoms, additional doses may be given up to a total daily dose of 54 μg. The aim of this study was to evaluate the safety of high doses of formoterol inhaled *via* Turbuhaler® in patients admitted to an emergency room with acute bronchoconstriction. Patients were treated with a total cumulative dose of either 90 μg formoterol (delivered dose, corresponding to 120 μg metered dose) or 10 mg terbutaline, both treatments administered *via* Turbuhaler®.

Material and methods

Study subjects

Forty-eight outpatients, all Caucasians, were randomized for treatment. Their mean age was 45 yrs (range: 20–64). Thirty-three patients had a diagnosis of asthma, eight had chronic obstructive asthma and seven had chronic obstructive pulmonary disease (COPD). Baseline characteristics are shown in table 1.

Most patients used β_2-agonists prior to the study enrolment but discontinued at entry. At study entry 26 patients used corticosteroids, oral or inhaled, in doses of up to 1,600 $\mu g \cdot day^{-1}$ (inhaled dose). Thirty-seven patients used theophylline. Patients included in this study (male or female) were aged 18–65 yrs with acute bronchoconstriction due to asthma or COPD, and with a forced expiratory volume in one second (FEV_1) 20–50% of predicted normal value and pulse rate $\geqslant$100 beats per minute (bpm).

Exclusion criteria were: need for therapy other than the study or reference drug; requirement for assisted ventilation in COPD patients with an elevated carbon dioxide tension in arterial blood (P_{a,CO_2}) value; patients given initial treatment by medical personnel prior to admission to the hospital; known or suspected allergy to study drugs; β-blocker therapy; clinically relevant current cardiovascular diseases that could influence participation in the study; other concomitant relevant diseases (haematological, hepatic, renal *etc.* as judged by the investigator); pregnancy, planned pregnancy or breast feeding.

Informed consent was obtained from each patient and the study was approved by health authorities and local ethics committees.

Study design

The study was blinded, randomized and had a parallel-group design. The primary analysis was clinical evaluation of serum potassium, electrocardiogram (ECG), pulse rate and blood pressure. Terbutaline *via* Turbuhaler® was chosen as reference treatment because it is a worldwide recommended drug for the treatment of acute bronchoconstriction and its efficacy has been well documented in patients attending the emergency room with acute asthma [14].

To test the safety and feasibility of the practical procedures, the first four patients enrolled were treated single-blind. For these patients, the study drug was known to the physician and safety was continuously evaluated by a Safety Evaluation Committee. Thereafter the study was double-blind. Data from the next eight double-blind patients were also evaluated continuously, case by case. The study was performed at four clinics in Hungary and four in Poland.

Methods

At the first visit to the hospital/clinic, patients enrolled in the study underwent a brief review of their medical/surgical history and a physical examination. They were then randomly assigned to receive one of the two study drugs, either formoterol Turbuhaler® 90 μg (delivered dose; formoterol fumarate dihydrate, Oxis® Turbuhaler® 4.5 μg, AstraZeneca, Lund, Sweden) or terbutaline Turbuhaler® 10 mg (total dose; terbutaline sulphate, Bricanyl® Turbuhaler® 0.5 mg, AstraZeneca, Lund, Sweden). Study drug was administered on six occasions during a 3-h period, starting within 1 h after admission to hospital (at time points 0, 30, 60, 120, 150, and 180 min). At times 0 and 120 min four inhalations were administered and at all other time points, three inhalations were administered. Twenty inhalations were administered in total for each drug.

All patients received continuous oxygen therapy, and each was administered 40 mg of methylprednisolone intravenously 90 min after the first inhalation of study drugs. Before the first dose and at regular intervals over the 12 h following the first inhalation of study drug, pulse, blood pressure, respiratory rate, 12-lead ECG and 1-lead ECG surveillance (using standard hospital equipment) as well as Holter ECG (Dyna Cord, Model 423, Del Mar Avionces, CA, USA) were recorded. Blood samples for measurement of serum potassium and arterial blood gases were obtained *via* an indwelling cannula. Lung function was assessed by FEV_1. All patients were

Table 1. – Baseline characteristics of patients randomized to treatment with formoterol or terbutaline (range)

Variable	Formoterol	Terbutaline
Patients n	24	24
Mean age (yrs)	46 (20–64)	44 (20–62)
Primary diagnoses		
Asthma (intrinsic and extrinsic)	13	13
Unspecified asthma	3	4
Chronic obstructive asthma	3	5
Obstructive chronic bronchitis	5	2
Mean FEV_1 L	0.95 (0.48–1.74)[#]	1.01 (0.48–1.81)
Mean FEV_1 % pred	32 (21–50)[#]	35 (21–63)
Mean respiratory rate ($breaths \cdot min^{-1}$)	22 (17–36)[#]	22 (16–38)
Mean pulse rate bpm	109 (100–135)[#]	106 (88–122)
Mean serum potassium ($mmol \cdot L^{-1}$)	4.02 (3.23–4.80)	4.22 (3.20–5.81)

FEV_1: forced expiratory volume in one second; bpm: beats per minute. [#]: n=23.

Table 2. – Serum potassium and pulse rate parameters at baseline and following treatment with formoterol (n=23) and terbutaline (n=24)

	Parameter	Formoterol	Terbutaline	Formoterol–terbutaline#	
				Δ mean	95% CI
Serum potassium mmol·L^{-1}	C_0	4.02	4.22		
	C_{min}	3.43	3.16	0.32	0.14–0.50
	C_{ave}	3.89	3.76	0.19	0.02–0.35
Pulse bpm	E_0	109.2	105.1		
	E_{max}	106.7	115.8	-11.0	-17.1–-4.9
	E_{ave}	93.5	101.7	-9.7	-15.3–-4.0

Data are presented as mean unless otherwise stated. #: results from analysis of variance. C_0: serum concentration at time zero; C_{min}: minimum serum concentration; C_{ave}: 12-h average serum concentration; E_0: value recorded at time zero; E_{max}: maximum value; E_{ave}: 12-h average value; bpm: beats per minute; CI: confidence interval.

observed for a total of 24 h; adverse events were evaluated at 1, 12 and 24 h by asking: "Have you had any health problems since the last drug administration/last questioning?"

No other therapy, except antibiotics, was allowed during the first 3 h; thereafter, during the following 9 h, no other asthma therapy was allowed except for ipratropium bromide if needed.

A follow-up visit was scheduled for 2–3 weeks later when the patient's condition had stabilized. No study therapy was given between the two visits. At visit 2, the adverse event question was asked again and the patients were given a physical examination.

Analysis

Forty patients were judged an adequate number for a clinical evaluation of the safety variables. No primary safety variable was identified for the study and therefore no sample size calculation was made.

The 12-h average and the maximum effects (lowest concentration of serum potassium, maximum pulse rate) were analysed using an analysis of variance (ANOVA) model with treatment as fixed factor and the baseline value as a covariate. Additive models were used, except for FEV_1 where a multiplicative model was used. Treatment differences (or the ratio for FEV_1) were described with mean and 95% confidence limits for the mean. Q-T interval was corrected using Q-T interval corrected for heart rate (QT_c) ($QT_c=QT/\sqrt{60/HR}$) [15]. p-Values of <0.05 (two-sided alternatives) were considered as showing statistically significant differences.

The non-numerical ECG data and Holter report data were only evaluated descriptively.

Results

Safety population

Of 48 patients randomized to treatment, four withdrew from the study (formoterol n=1; terbutaline n=3). However, only one of these (formoterol group) was excluded from analysis; this patient received only four out of 20 inhalations and had only one post-drug measurement. The other three withdrawn patients all took at least half the dose of study drugs. Thus, safety was evaluated in 47 patients (formoterol n=23; terbutaline n=24).

Serum potassium

Both the 12-h average (C_{ave}) and the average of minimum serum potassium concentrations in all patients (C_{min}) were statistically significantly lower for the terbutaline group, compared with the formoterol group (table 2). In the terbutaline group C_{ave} was 3.76 mmol·L^{-1} (baseline 4.22 mmol·L^{-1}), compared with 3.89 mmol·L^{-1} (baseline 4.02 mmol·L^{-1}) in the formoterol group. Changes in serum potassium over time are shown in figure 1 as mean curves.

At baseline, the mean serum potassium value (all patients) was 4.11 mmol·L^{-1} (range: 3.20–5.81). Eight patients had a serum potassium value outside the reference range; two above the upper limit (terbutaline group) and six below (four in the formoterol group and two in the terbutaline group). During treatment, 17 patients in the formoterol group and 19

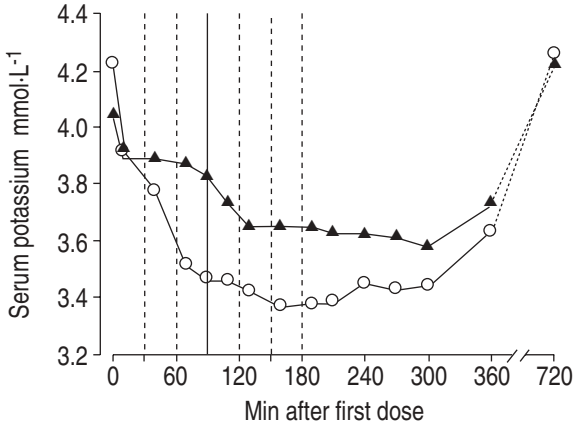

Fig. 1. – Mean serum potassium values after administration of study drug. Patients were administered formoterol (90 μg; ▲) or terbutaline (10 mg; ○) on six occasions during a 3-h period at time points of 0, 30, 60, 120, 150 and 180 min. The vertical lines indicate administration of formoterol/terbutaline (---), methylprednisolone (—) was administered at 90 min.

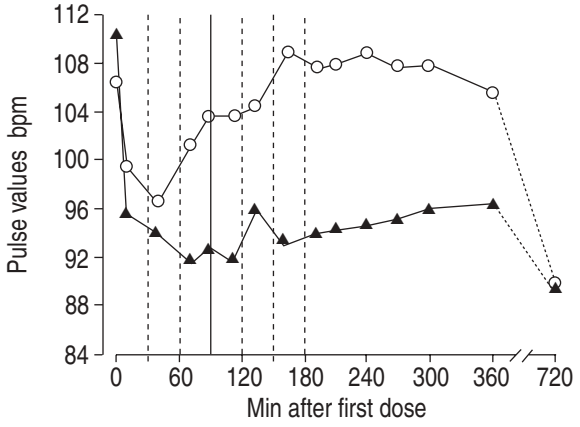

Fig. 2. – Mean pulse values after administration of study drug. Patients were administered formoterol (90 μg; ▲) or terbutaline (10 mg; ○) on six associations during a 3-h period at time points of 0, 30, 60, 120, 150 and 180 min. The vertical lines indicate administration of formoterol/terbutaline (- - -), methylprednisolone (—) was administered at 90 min. bpm: beats per minute.

in the terbutaline group had values below the lower reference. One patient in the formoterol group and seven in the terbutaline group had a value <3.0 mmol·L^{-1}. The lowest observed individual value, 2.6 mmol·L^{-1}, was in the terbutaline group (baseline value 3.80 mmol·L^{-1}).

Pulse and electrocardiogram

Both the 12-h average (E_{ave}) and the average maximum pulse rates in all patients (E_{max}) were significantly higher in the terbutaline group than in the formoterol group (table 2).

Mean pulse rate decreased initially in both treatment groups. However, there was a pronounced increase in pulse rate after 40 min in the terbutaline group. The mean pulse rate in the terbutaline group remained above 100 bpm for up to 9 h after the first dose, whereas in the formoterol group it never rose >100 bpm after the initial decrease (fig. 2). Although there was a decrease in the mean systolic and diastolic blood pressures, no statistically significant difference was observed between the treatment groups (table 3).

With regard to the other ECG variables, no statistically significant differences could be seen between the treatments for the pharmacodynamic parameters for QRS duration, PR interval or QT_c (table 4).

All patients had sinus rhythm at baseline and following the treatment. Two patients in the formoterol group and one in the terbutaline group had extrasystoles after the treatment.

Holter recordings

Analysis showed arrhythmias in four patients of the formoterol group and five patients in the terbutaline

Table 3. – Systolic and diastolic blood pressure at baseline and following treatment with formoterol (n=23) and terbutaline (n=24)

	Parameter	Formoterol	Terbutaline	Formoterol–terbutaline#	
				Δ mean	95% CI
Systolic blood pressure mmHg	E_0	139.0	135.9		
	E_{max}	143.4	146.4	-5.3	-11.5–0.9
	E_{ave}	128.7	131.8	-4.9	-10.3–0.5
Diastolic blood pressure mmHg	E_0	88.1	88.4		
	E_{min}	69.7	70.6	-0.7	-5.5–4.1
	E_{ave}	78.7	78.7	0.1	-4.2–4.4

Data are presented as mean unless otherwise stated. #: results from analysis of variance. E_0: value recorded at time zero; E_{max}: maximum value; E_{min}: minimum value; E_{ave}: 12-h average value; CI: confidence interval.

Table 4. – QRS duration, PR interval and QT_c interval at baseline and following treatment with formoterol (n=23) and terbutaline (n=24)

	Parameter	Formoterol	Terbutaline	Formoterol–terbutaline#	
				Δ mean	95% CI
QRS duration ms	E_0	86.1	85.4		
	E_{max}	96.0	94.4	1.0	-4.1–6.1
	E_{ave}	89.0	88.2	0.1	-3.3–3.6
PR interval ms	E_0	128.7	124.1		
	E_{max}	139.8	137.4	0.0	-11.7–11.8
	E_{ave}	126.7	122.4	1.0	-6.4–8.5
QT_c interval ms	E_0	419.2	417.8		
	E_{max}	464.9	474.3	-9.4	-34.0–15.1
	E_{ave}	437.4	437.3	0.0	-11.9–12.0

Data are presented as mean unless otherwise stated. #: results from analysis of variance. E_0: value recorded at time zero; E_{max}: maximum value; E_{ave}: 12-h average value; CI: confidence interval.

Table 5. – Blood gases

	Formoterol[#]		Terbutaline[¶]	
	0 min	90 min	0 min	90 min
P_{a,O_2} kPa	10.1 (7.3–16.8)	10.8 (7.3–21.7)	9.8 (5.7–13.5)	11.6 (7.8–36.4)
P_{a,CO_2} kPa	4.8 (3.7–5.6)	4.9 (4.1–5.8)	4.9 (3.6–6.2)	4.9 (3.9–6.3)

Data are presented as mean (range), according to treatment. [#]: n=23; [¶]: n=24. P_{a,O_2}: oxygen tension in arterial blood; P_{a,CO_2}: carbon dioxide tension in arterial blood.

group. The arrhythmias consisted of: supraventricular tachycardia (1), supraventricular runs (2), ventricular extrasystoles (2) and sinus tachycardias (3). On analysis of the Holter recordings, three patients in the formoterol group and four in the terbutaline group had findings considered to be clinically important *i.e.* deviated from normal.

Blood gases

Assessments of arterial blood gases at study entry (breathing room air) and 90 min after first dose of study drug (breathing oxygen) did not show any differences between the treatment groups. The mean values for oxygen tension in arterial blood (P_{a,O_2}) and P_{a,CO_2} are shown in table 5.

Lung function

The mean FEV1 value at baseline in the formoterol group (0.95 L) was lower than in the terbutaline group (1.01 L). This difference was still present at 90 min, just before the intravenous corticosteroid was administered. The FEV1 improved in both treatment groups, to 1.21 L (range: 0.65–2.05 L) in the formoterol group and to 1.33 L (range: 0.56–3.13 L) in the terbutaline group. No difference was found between the treatments at 12 h (both 1.33 L) (fig. 3).

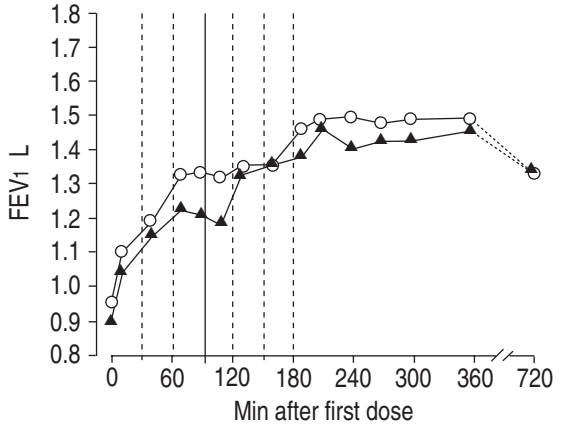

Fig. 3. – Geometric mean forced expiratory volume in one second (FEV1) values after administration of study drug. Patients were administered formoterol (90 μg; ▲) or terbutaline (10 mg; ○) on six occasions during a 3-h period at time points of 0, 30, 60, 120, 150 and 180 min. The vertical lines indicate administration of formoterol/terbutaline (- - -), methylprednisolone (—) was administered at 90 min.

Adverse events

Three serious adverse events were reported during the study. Two patients in the formoterol group had status asthmaticus reported 5 days after treatment with the study drug. One patient in the terbutaline group had bronchoconstriction 8 h after the first dose of the study drug. However, these adverse events were not considered to be related to the study treatments.

Four patients discontinued due to adverse events. One patient in the formoterol treatment group was withdrawn because of hypoxia and dyspnoea <1 h after the first dose of the study drug. This patient was not included in the safety analysis. Three patients in the terbutaline group discontinued, two due to hypokalaemia and one due to bronchospasm. However, since these three patients all took at least half of the dose of study drugs, their data were included in the safety analyses.

Clinical findings, *i.e.* changes compared with study entry considered clinically relevant, were reported for seven patients (formoterol n=4; terbutaline n=3). One formoterol-treated patient had prolonged QRS recorded as a clinical finding, another had prolonged QT with sinus tachycardia. Other clinical findings were tachycardia (formoterol n=1; terbutaline n=3) and bradycardia (formoterol n=1).

Up to the end of the follow-up period, nine patients in total reported 18 adverse events in the formoterol group, and 16 patients reported 28 adverse events in the terbutaline group. The most frequently reported adverse events during the 24-h observation period were categorized as respiratory system disorders (formoterol n=5; terbutaline n=9) or heart rate and rhythm disorders (formoterol n=4; terbutaline n=3).

Discussion

This study evaluated the clinical safety of high doses of formoterol inhaled *via* Turbuhaler in patients with acute bronchoconstriction, admitted to an emergency room. Formoterol is a β_2-adrenoreceptor agonist with rapid onset of action. Additionally, its bronchodilating effect is sustained for up to 12 h after inhalation [10, 16]. Maesen *et al.* [17] have shown that formoterol at doses of up to 228 μg, inhaled *via* a pressurized Metered Dose Inhaler (pMDI) , is safe in terms of known β_2-agonist side effects *i.e.* pulse rate, ECG and serum potassium concentrations, in patients with asthma.

In the present study, predictable side-effects were observed *e.g.* a decrease in serum potassium, with

increase in heart rate and ECG changes. Serum potassium fell below the lower reference limit in 17 patients in the formoterol group and in 19 patients in the terbutaline group. The lowest individual value (2.6 $mmol \cdot L^{-1}$) was observed in the terbutaline group.

These results are in agreement with a recent study on patients with stable asthma, where daily doses of 6 mg and 10 mg terbutaline *via* Turbuhaler® had greater effect on serum potassium and heart rate than 54 μg and 90 μg formoterol *via* Turbuhaler®, respectively [13]. The systemic effects of formoterol Turbuhaler® and salbutamol pMDI have also been compared and indications found that the therapeutic index is more favourable for formoterol Turbuhaler regarding bronchodilating effect *versus* influence on serum potassium levels [18].

The systemic effects on pulse rate were shown to be less pronounced in the formoterol group than in the terbutaline group. For the ECG variables (QRS duration, PR and QT_c interval), no differences were found. Neither were any serious arrhythmias observed in the treatment groups in the analysis of Holter recordings. These results are in agreement with data from other studies [13, 18] and indicate that the pattern of systemic side effects of formoterol is similar to or less pronounced than that of traditional short-acting β_2-agonists.

In this study, the pattern of adverse events was not different from that in the previously mentioned high-dose studies [13, 17], and represents expected β_2-agonist effects. When comparing the treatments regarding adverse events, the differences were generally small and in favour of formoterol.

In a safety study such as this, it is important to analyse individual patients who experience adverse reactions. Three serious adverse events were reported, two patients with status asthmaticus that occurred 5 days after the treatment with study drugs and one patient with a severe bronchoconstriction. It would be interesting to know whether the patients were discharged from hospital too early, or whether they were undertreated with glucocorticoids at home. However, this study was not designed to investigate this issue. Only one of the events (bronchospasm in the terbutaline group) occurred during the 24-h observation period. The event was not considered to be causally related to the treatment.

Of the four patients who discontinued during treatment, two had hypokalaemia (both in the terbutaline group). One patient in the formoterol group discontinued the study because of hypoxaemia and dyspnoea, which occurred after the first dose of formoterol, and one patient in the terbutaline group was withdrawn because of severe bronchospasm, which occurred 180 min after the first dose of terbutaline. A similar pattern of adverse reactions was reported by MAESEN *et al.* [17].

Collectively, the results of this study and previous results [12, 16, 17, 19, 20] provide new evidence regarding the way in which formoterol inhaled *via* Turbuhale® may be used. According to current guidelines for asthma treatment, long-acting β_2-agonists may be used on a regular basis in patients using inhaled corticosteroids, and short-acting β_2-agonists should be given as needed. The results show that formoterol *via* Turbuhaler®, in a high dose, is safe in patients with severe bronchoconstriction. Other studies have shown that formoterol is as effective as short-acting β_2-agonists [11, 16]. Therefore, the next important step would be to investigate the efficacy of formoterol not only as a long-acting β_2-agonist but also on an "as needed" basis because of its rapid onset of bronchodilation. This issue has recently been investigated in a 3-month study in patients with moderate asthma by TATTERSFIELD *et al.* [21], which showed that formoterol *via* Turbuhaler®, used as needed, was as effective and safe as terbutaline *via* Turbuhaler® used under the same conditions. More studies need to be carried out to further elucidate the effectiveness of using formoterol *via* Turbuhaler® in the treatment of acute bronchoconstriction.

To conclude, this study showed that formoterol Turbuhaler, 90 μg (metered dose 120 μg) was as safe and well tolerated in patients with acute bronchoconstriction as terbutaline 10 mg.

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