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# Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency

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*Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. M. Palmqvist, G. Persson, L. Lazer, J. Rosenborg, P. Larsson, J. Lötvall. ©ERS Journals Ltd 1997.*

**ABSTRACT: Salmeterol and formoterol are two long-acting $\beta_2$-agonists for inhalation, currently being used in clinical practice. The aim of the present study was to investigate the onset of action, duration of effect and potency of these two $\beta_2$-agonists in asthmatic patients.**

**Patients (n=28) were included on the basis of salbutamol stepwise reversibility (100, 100 and 200 μg, given cumulatively; total reversibility ≥15%). In a double-blind placebo-controlled crossover study, the bronchodilating properties of formoterol 6, 12 and 24 μg were compared with the effects of salmeterol 50 μg. Formoterol was given *via* Turbuhaler® and salmeterol *via* Diskhaler®, and forced expiratory volume in one second ($FEV_1$) was monitored during 12 h.**

**Formoterol at all doses had a more rapid onset than salmeterol as judged from bronchodilation at 3 min after the dose. Formoterol at all doses had a similar duration of effect to salmeterol 50 μg, as judged from bronchodilation at 12 h after dose administration. When the relative potency of the two drugs was compared, salmeterol 50 μg was estimated to correspond to formoterol 9 μg (95% confidence interval: 3–19 μg).**

**We confirm that formoterol and salmeterol are both long-acting $\beta_2$-agonists, but with some differences in effect profile. We confirm the more rapid onset of action of formoterol compared with salmeterol, and furthermore, no difference in duration of effect is evident.**

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$\beta_2$-agonists, used by inhalation, have a central role in the treatment of patients with asthma, both as acute and chronic medication. In general, bronchodilation occurs rapidly to inhaled $\beta_2$-therapy, but with generally used short-acting $\beta_2$-agonists, such as salbutamol and terbutaline, the duration of action is only 4–6 h. For many asthmatic patients, this is not sufficient, particularly when night-time symptoms such as dyspnoea and early morning wheeze cannot be prevented with an evening dose of a short-acting $\beta_2$-agonist. Therefore, long-acting $\beta_2$-agonists for inhalation, such as formoterol and salmeterol, have been developed. Both these drugs have been shown to cause bronchodilation for at least 12 h after single dose administration [1–4]. Twice daily treatment with inhaled formoterol or salmeterol has been shown to reduce diurnal airway calibre fluctuations and asthma symptoms [5–7], and inhaled long-acting $\beta_2$-agonists are therefore important components in the therapy of patients with chronic asthma, who are not fully controlled with inhaled anti-inflammatory therapy [8].

Both salmeterol and formoterol have been compared with salbutamol or terbutaline. In one study, salbutamol was shown to have a more rapid onset of action than salmeterol [9]. Comparisons between terbutaline and formoterol suggest a rapid onset of action of formoterol [10]. Thus, these previous studies together suggest that formoterol may have a more rapid onset of action than salmeterol.

Only few direct comparisons between salmeterol and formoterol have been presented [4, 11], but these studies are limited to the comparison between one or two doses of formoterol and/or salmeterol. In brief, formoterol 12 μg has a greater bronchodilating effect than salmeterol 50 μg 1–4 min after inhalation [11], whereas a similar result on forced expiratory volume in one second ($FEV_1$) and bronchial reactivity to methacholine is observed after 30 min [4].

Because of the limited number of doses in the direct comparisons between formoterol and salmeterol in earlier studies, the present study was performed to clarify the dose relationship and differences between those two drugs. Thus, the aim of the present study was to investigate the onset of action, duration of effect and potency of the bronchodilating effect of formoterol Turbuhaler® (Astra Draco, Lund, Sweden), 6, 12 and 24 μg, respectively, in comparison with a standard dose of inhaled salmeterol (50 μg - Serevent Diskhaler®, Glaxo Wellcome Ltd, Ware, UK) in asthmatic patients.

## Methods

### *Patients*

The study was approved by the local Ethics Committees at the centres named below. Twenty eight asthmatic patients (17 females) were recruited at three centres: Sahlgrenska University Hospital (centre 1), Malmö General Hospital (centre 2), and University Hospital Lund (centre 3). Twenty six patients were included and four patients discontinued the study. Two of these attended only one study day, and were not evaluated statistically. Patient data are presented in table 1. All patients were treated with short-acting $\beta_2$-agonists as required, and all patients, except two, were treated with inhaled glucocorticoids. The inhaled glucocorticoids used were beclamethasone dipropionate and budesonide (total daily doses ranging 200–1,600 μg). Slow-release theophylline and/or slow-release $\beta_2$-agonist were used by six patients.

### *Inclusion criteria*

Only nonsmoking stable asthmatic patients (18–70 yrs of age) with FEV1 >40% predicted were included. A reversibility of at least 10% of FEV1 should be seen 30 min after 100 μg salbutamol delivered by pressurized metered-dose inhaler (pMDI). An additional increase of FEV1 after a total dose of 200 or 400 μg salbutamol pMDI (100+100+200 μg) should be at least 50% of the effect observed with 100 μg, *i.e.* patients were only to be included if they had a reversibility of at least 15% of FEV1 compared with baseline. The reason for this stepwise reversibility was to ensure a dose-response relationship for a bronchodilating drug in the included patients. This stepwise procedure was performed at the separate inclusion visit.

### *Protocol*

A randomized double-blind, placebo-controlled, crossover, double-dummy design was used, to evaluate the effects of placebo, three different doses of inhaled formoterol (6, 12, 24 μg; given *via* Turbuhaler®) and a single dose of salmeterol (50 μg; given *via* the Diskhaler® device). Every second patient started the inhalations with Turbuhaler®, and the others with Diskhaler®. Peak inspiratory flow through the relevant devices was monitored with Vitalograph MDI (Vitalograph Ltd, Buckingham, UK), and was aimed to exceed 50 $L \cdot min^{-1}$ with Turbuhaler® and 80 $L \cdot min^{-1}$ with Diskhaler®. FEV1 was measured before inhalation of the study drug, and 3, 15, 30 and

Table 1. – Patient characteristics, lung function data and reversibility inclusion data

| Patient No. | Sex | Age yrs | Asthma medication | FEV1 | FEV1 % pred | FEV1 % reversibility salbutamol | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | *vs* baseline | *vs* 0.1 mg | *vs* 0.1 mg |
| **Centre 1** | | | | | | | | |
| 1 | F | 48 | ISB, IC | 2.24 | 83 | 13 | 100 | |
| 2 | F | 60 | ISB, IC, ILB | 1.55 | 62 | 17 | 54 | |
| 3 | F | 26 | ISB, IC, ILB | 2.98 | 86 | 11 | 45 | 61 |
| 4 | M | 51 | ISB, IC | 3.35 | 88 | 14 | 59 | |
| 5 | F | 61 | ISB, IC, ILB | 2.15 | 112 | 16 | 34 | 83 |
| 6 | M | 69 | ISB | 2.52 | 86 | 10 | 52 | 60 |
| 7 | F | 24 | ISB, IC | 2.56 | 78 | 10 | 31 | 54 |
| 8 | M | 61 | ISB, IC | 1.75 | 59 | 14 | 72 | |
| 9 | M | 25 | ISB, IC | 3.58 | 80 | 13 | 53 | |
| **Centre 2** | | | | | | | | |
| 10 | M | 63 | ISB, IC | 1.75 | 58 | 20 | 40 | 57 |
| 11 | M | 66 | ISB | 2.75 | 89 | 17 | 35 | 63 |
| 12 | F | 36 | ISB, IC | 1.60 | 62 | 14 | 65 | |
| 13 | F | 61 | ISB, IC, ILB, T | 1.98 | 76 | 11 | 64 | |
| 14 | F | 55 | ISB, IC, ILB, T | 2.19 | 71 | 12 | 70 | |
| 15 | F | 25 | ISB, IC, ILB, OB, T | 2.72 | 64 | 26 | 18 | 49 |
| 16 | M | 36 | ISB, IC, T | 2.38 | 66 | 24 | 39 | 77 |
| 17 | M | 57 | ISB, IC | 2.54 | 61 | 20 | 116 | |
| **Centre 3** | | | | | | | | |
| 18 | M | 41 | ISB, IC | 4.06 | 87 | 21 | 20 | 55 |
| 19 | M | 20 | ISB, IC | 2.48 | 71 | 18 | 20 | |
| 20 | F | 29 | ISB, IC | 2.48 | 72 | 10 | 96 | |
| 21 | F | 32 | ISB, IC | 2.50 | 93 | 16 | 13 | 51 |
| 22 | F | 38 | ISB, IC, ILB | 2.34 | 83 | 13 | 45 | 68 |
| 23 | F | 40 | ISB, IC | 2.58 | 71 | 11 | 50 | |
| 24 | F | 40 | ISB, IC, OB | 2.37 | 83 | 12 | 3 | 62 |
| 25 | F | 46 | ISB, IC, T | 1.86 | 69 | 10 | 68 | |
| 26 | F | 46 | ISB, IC | 1.53 | 65 | 18 | 33 | 78 |
| 27 | F | 66 | ISB, IC | 1.51 | 44 | 19 | 79 | |
| 28 | M | 55 | ISB, IC, ILB | 1.75 | 55 | 17 | 3 | 62 |
| Mean | | | | 2.36 | 74 | 15 | 50 | |

M: male; F: female; FEV1: forced expiratory volume in one second; % pred: % of predicted value; ISB: inhaled short-acting $\beta_2$-agonist; IC: inhaled corticosteroid; ILB: inhaled long-acting $\beta_2$-agonist; OB: oral $\beta_2$-agonist; T: oral theophylline.

60 min after inhalation, and subsequently every hour up to 12 h. At least 48 h were required between each visit, and baseline $FEV_1$ on study days was not allowed to vary more than 12% from the baseline on the screening day. Furthermore, to avoid a carryover effect, baseline $FEV_1$ on a study day should not be more than 15% higher than the baseline $FEV_1$ of the preceeding study day. If this criterion was not met, the patients were allowed to return once for another attempt. Radialis cardiac frequency and systemic blood pressure sphygmomanometer were monitored before inhalation of the study drug, and 1, 2, 4, 6, 8, 10 and 12 h after inhalation. A follow-up visit was made within 2 weeks after the last study day.

### *Data analysis*

The primary objective of this study was to assess the potency of formoterol Turbuhaler® (6, 12, 24 μg), compared with that of salmeterol Diskhaler® 50 μg. The primary variable for this comparison was the 12 h average $FEV_1$ (area under the $FEV_1$ *versus* time curve divided by 12 h). Secondary objectives of the study were to compare the onset of action and duration of the effect of formoterol Turbuhaler® and salmeterol Diskhaler®.

The primary objective was addressed by using a multiplicative analysis of variance model, including the factors: patient, treatment and period. Baseline $FEV_1$ was used as covariate. The dose of formoterol Turbuhaler® equipotent to salmeterol 50 μg Diskhaler® was estimated by fitting a straight line to the adjusted 12 h average $FEV_1$ for the three doses of formoterol. The 95% confidence interval (CI) for the equipotent dose was calculated by using Fieller's method. Onset of action was evaluated using Wilcoxon's signed rank test on the onset time, defined as the interpolated time for the first increase in $FEV_1$ of at least 15% over baseline within 1 h after inhalation. In this evaluation, an onset time of 60 min was used for patients not showing a 15% increase within 1 h. Onset was also addressed by comparing the $FEV_1$ measured 3 and 15 min after inhalation of the study drug. Duration of action was evaluated using Wilcoxon's signed rank test on the duration time, defined as the time from onset (defined as above) until the interpolated time for the first $FEV_1$ under the 15% increase over baseline. The duration was also evaluated by comparing the residual $FEV_1$ at 12 h. Data are presented as means and variations as SEM.

For the description of time of duration, arithmetic mean data from only responders, reaching improvement of $FEV_1$ of at least 15% within 1 h of treatment, are described. However, for the statistical analysis, nonresponders are also included (nonresponders given an onset of 1 h, and duration of 0).

## Results

Mean baseline values of $FEV_1$ were: on the placebo day 2.27 L; on the formoterol days (dose administered: 6, 12 and 24 μg) 2.32, 2.32, 2.26 L, respectively; and on the salmeterol 50 μg day 2.31 L. Patient No. 15 did not fully reach the stepwise reversibility test for inclusion (second improvement 49% instead of defined 50%), but was still included because the discrepancy was not considered to be of importance. The mean inhalation flow for the active devices was 68.1, 79.0 and 80.0 $L \cdot min^{-1}$ for formoterol Turbuhaler® (6, 12 and 24 μg, respectively), and 93.8 for salmeterol Diskhaler® (50 μg).

### *Responders and onset*

The percentage of patients having an increase in $FEV_1$ of at least 15% over baseline at different time-points within 1 h after inhalation of the study drug, is shown in figure 1a. The number of patients responding with an $FEV_1$ of at least 15% over baseline within 60 min after dosing ("responders") was for formoterol 6, 12 and 24 μg 12, 19 and 18 patients, respectively, for salmeterol 17 patients, and for placebo one patient. The median onset time (including all patients) was 12.4 min for formoterol 12 μg, 3.6 min for formoterol 24 μg, and

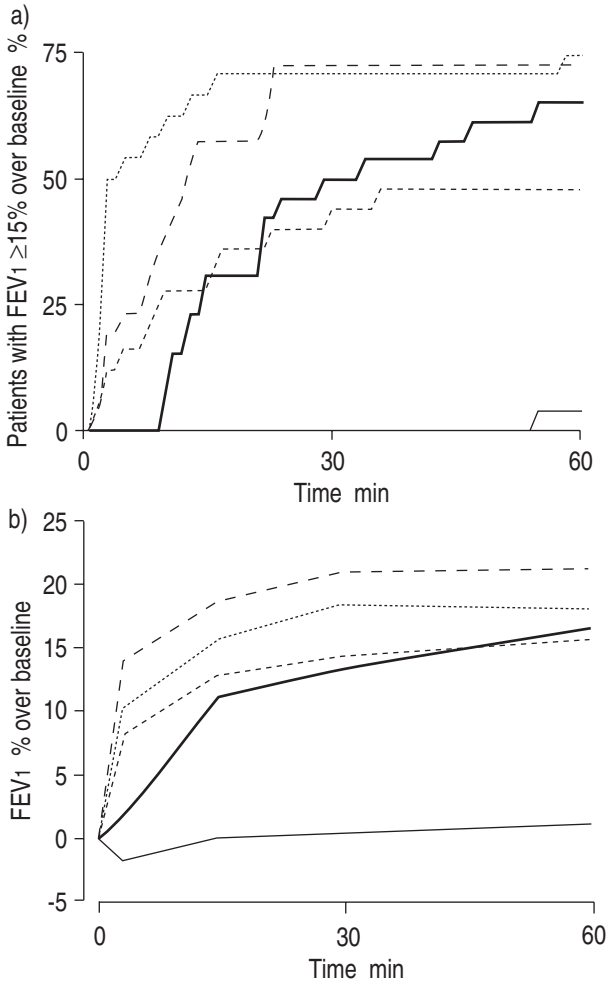


Fig. 1. – a) The probability (% of patients) of having a clinically significant effect forced expiratory volume in one second ($FEV_1$) ≥15% over baseline) of formoterol (6, 12 and 24 μg) and salmeterol (50 μg) up to 1 h after inhalation, compared with placebo. b) Mean $FEV_1$ (% over baseline) after formoterol (6, 12 and 24 μg) and salmeterol (50 μg) up to 1 h after inhalation, compared with placebo. ——: salmeterol 50 μg; - - - -: formoterol 6 μg; ·····: formoterol 12 μg; - – -: formoterol 24 μg; ——: placebo.

31.0 min for salmeterol 50 μg. For formoterol 6 μg, less than half of the patients responded within 1 h. When evaluating the onset time, Wilcoxon's signed rank test showed that formoterol 12 and 24 μg had a more rapid onset of action compared with salmeterol 50 μg ($p<0.05$). With this test, the onset of action of the lowest dose of formoterol (6 μg) could not be discriminated from the effect of salmeterol 50 μg, because of the low number of responders with formoterol 6 μg compared with salmeterol. However, when analysing mean $FEV_1$ data over the first hour (fig. 1b), a clearer difference between formoterol 6 μg and salmeterol 50 μg can be found, for example, at 3 min after dosing, all doses of formoterol caused a statistically significant better effect compared with salmeterol (fig. 1b; $p<0.05$). However, at 15 min, formoterol 12 and 24 μg caused a statistically significant greater improvement of $FEV_1$ than salmeterol 50 μg, whereas no significant difference was found between salmeterol and formoterol 6 μg (fig. 1b).

*Duration of effect*

The time course of mean percentage change in $FEV_1$ over the 12 h observation, including all patients, is shown in figure 2. All doses of formoterol and salmeterol caused improvement in $FEV_1$, reaching peak values at approximately 1–3 h after dosing, and subsequently a slow drop in $FEV_1$ was observed. The arithmetic mean duration of at least 15% increase in $FEV_1$ compared with baseline (including only responders) was 244, 337, and 459 min after formoterol 6, 12 and 24 μg, respectively, and 345 min after salmeterol 50 μg. Comparing the treatments, using zero as duration for nonresponders, formoterol 6 and 12 μg had similar duration of effect compared with salmeterol 50 μg, whereas formoterol 24 μg had a numerically but not statistically significantly longer duration of effect than salmeterol ($p=0.051$). When analysing the mean residual $FEV_1$ values for all patients at 12 h after dosing, all doses of formoterol and salmeterol 50 μg produced significantly higher $FEV_1$ compared with placebo. The $FEV_1$ at 12 h was for formoterol 24 μg significantly higher than the two lower doses of formoterol ($p<0.05$), but not compared with salmeterol 50 μg (fig. 2).

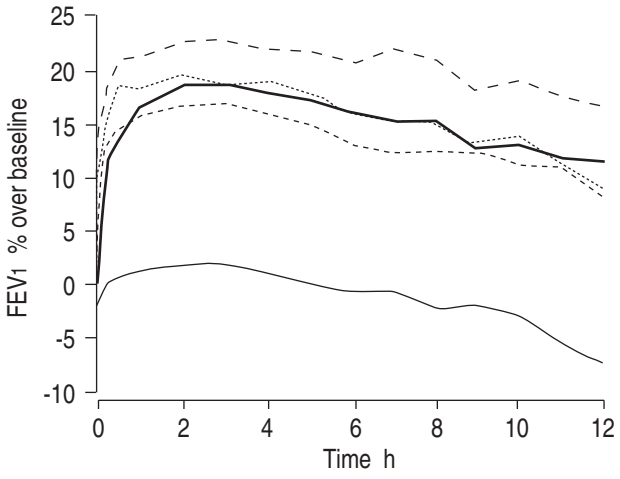


Fig. 2. – Mean forced expiratory volume in one second ($FEV_1$) (% over baseline) after formoterol (6, 12 and 24 μg) or salmeterol (50 μg) up to 12 h after inhalation, compared with placebo. ——: salmeterol 50 μg; - - - -: formoterol 6 μg; ·····: formoterol 12 μg; – – -: formoterol 24 μg; ——: placebo.

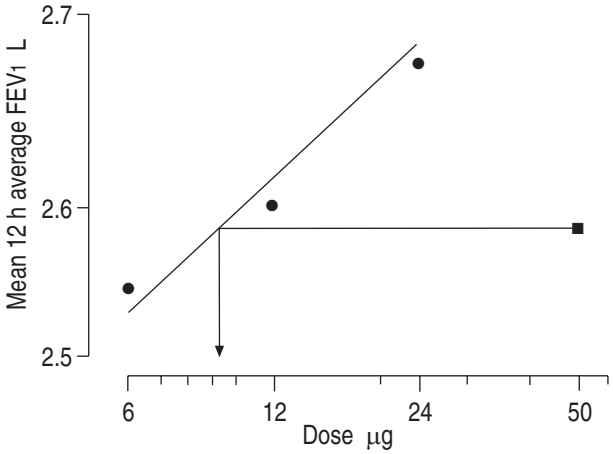


Fig. 3. – Average forced expiratory volume in one second ($FEV_1$) (geometric mean) over 12 h after formoterol (6, 12 and 24 μg) and salmeterol (50 μg), and comparison of potency by fitting a straight line to the average $FEV_1$. salmeterol 50 μg is estimated to be equipotent to 9 μg formoterol (3–19 mg). ■: salmeterol; ●: formoterol.

*Dose comparisons*

The mean 12 h average $FEV_1$ (primary variable) was for placebo 2.23±0.62, for formoterol 2.62±0.68, 2.68±0.68, 2.71±0.70 (6, 12 and 24 μg, respectively), and for salmeterol 50 μg 2.65±0.62 L. When relative potency of salmeterol was estimated by fitting a straight line to the 12 h average $FEV_1$ after the three formoterol doses, salmeterol 50 μg was estimated to be equipotent with 9 μg formoterol. This value was not significantly different from 6 or 12 μg of formoterol when evaluating the 95% CIs (3–19 mg; fig. 3). However, formoterol 24 μg was significantly more potent than salmeterol 50 μg ($p<0.05$).

*Adverse reactions*

The mean values of cardiac frequency did not increase over the study day compared with placebo (data not shown). The most common adverse event reported was headache, which was observed in six to seven patients after all treatments, including placebo. Typical $\beta_2$-receptor-mediated subjective symptoms (reported as adverse reactions) (tachycardia/palpitation and tremor) were not reported in any patients after placebo or salmeterol, but occurred with mild or moderate degree in one, one and five patients after formoterol 6, 12 and 24 μg, respectively.

## Discussion

This study shows that formoterol dry powder given *via* Turbuhaler®, causes a dose-dependent and rapid bronchodilation with a duration of action of at least 12 h. Formoterol has a more rapid onset of action compared with salmeterol. Furthermore, the data suggest

that formoterol 12 μg given *via* Turbuhaler® is approximately equipotent with salmeterol 50 μg given *via* Diskhaler®.

Only limited data of direct comparisons between salmeterol and formoterol in clinical studies have been available. The slow onset of action of salmeterol in the present study confirms previous *in vitro* and clinical studies [9, 11–14]. Furthermore, in the present study, the rapid onset of action of formoterol is confirmed [15–17]. In fact, in the present study, all doses of formoterol produced a statistically significant improvement in lung function 3 min after inhalation, compared with salmeterol. With comparison to placebo, salmeterol also produced an improvement in lung function 3 min after inhalation. Fifteen min after inhalation, the effect of salmeterol 50 μg approached the effects of the lowest dose of formoterol. It could be argued that formoterol, but perhaps not salmeterol, can be used as occasional rescue medication in asthma. However, the safety of such a treatment has not been studied.

It has been speculated that the duration of effect of salmeterol may last longer than that of formoterol, which seems to be the case *in vitro* [18, 19]. However, in the present study, almost equipotent doses of formoterol and salmeterol (12 and 50 μg, respectively) caused very similar bronchodilation at 12 h, arguing that formoterol and salmeterol have a similar duration of effect. It should be emphasized that both drugs most likely have a substantially longer duration of action than 12 h, but because of the large differences between the treatments and the placebo at this time-point, further studies are required to evaluate this. At the highest dose of formoterol (24 μg), it seems that the improved maximal effect also results in a prolonged duration of action, compared to the lower doses of the same drug, although the decline of the effect compared to placebo does not seem to be different between the treatments (fig. 2). This finding is in parallel with a recently published study [17], showing a very similar off-set of action of salmeterol and formoterol.

When comparing potency between different drugs, it is very important to use several doses of at least one of the compounds which are compared often. Direct comparisons between formoterol and salmeterol have utilized single doses of each drug [17], which is not sufficient for potency comparisons. In the present study it was estimated that salmeterol 50 mg was equipotent with formoterol 9 μg (95% CI: 3–19 μg). The inhaled dose of formoterol 12 μg and salmeterol 50 μg showed similar values for average $FEV_1$ over 12 h, as well as peak $FEV_1$. Thus, the clinical dose relationship between formoterol and salmeterol was found to be similar to that proposed by indirect comparisons [2, 9]. It is often difficult to show dose-related bronchodilation in clinical studies. In many patients, only a low dose of a $\beta_2$-agonist is required to reach maximal bronchodilating effect. It should be emphasized that we have included only patients with a stepwise bronchodilator response to a short-acting $\beta_2$-agonist, which may be important for our findings of dose-related bronchodilation with formoterol.

$\beta_2$-receptor-mediated adverse events such as tremor and tachycardia were mild and occurred in very few patients, except after the highest dose of formoterol. This argues that such doses, after single inhalation, are well tolerated.

In the present study, salmeterol was delivered by the dry-powder Diskhaler® device, whereas formoterol was delivered by the Turbuhaler®. Turbuhaler® has previously been suggested to deliver higher amounts of salbutamol to the airways than other inhalation devices such as pMDI or Diskhaler® [20, 21]. Thus, it should be emphasized that this study does not give us a direct comparison of the two chemical entities in the asthmatic airways *in vivo*, as delivery and distribution of drug in the airway tree may differ, due to the use of two different inhalation devices.

Formoterol and salmeterol are both potent, efficacious and long-acting bronchodilators, with few and mild side-effects at recommended doses. Perhaps the most important difference of these drugs, shown in the present study, is that formoterol has a more rapid onset.

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