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Salmeterol *versus* formoterol in patients with moderately severe asthma: onset and duration of action

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Salmeterol versus *formoterol in patients with moderately severe asthma: onset and duration of action. J.A. van Noord, J.J. Smeets, J.A.M. Raaijmakers, A.M. Bommer, F.P.V. Maesen. ©ERS Journals Ltd 1996.*

ABSTRACT: We evaluated the profile of the bronchodilatory effect of three inhaled β_2-agonists, 24 µg formoterol, 50 µg salmeterol and 200 µg salbutamol, in patients with stable, moderately severe asthma.

Thirty asthmatics (mean±SD age 54±8 yrs; forced expiratory volume in one second (FEV_1) 58±12% predicted; reversibility of FEV_1 21±8% from baseline) participated in a single-centre, double-blind, randomized, single-dose, cross-over study. FEV_1 was obtained in baseline condition and 10, 20, 30, 60 min, and every hour up to 12 h after inhalation of the trial drug. Specific airway conductance (sG_{aw}) was measured at baseline condition and 1, 3, 5, 7, 10, 20, 30, 60 min, and every hour up to 12 h after inhalation.

Formoterol produced a mean increase in sG_{aw} (as % of baseline) of 44% after 1 min, maximal (135%) after 2 h, and 56% after 12 h. The mean increase in FEV_1 was maximal (27%) after 2h, and 10% after 12 h. After salmeterol, mean increase in sG_{aw} amounted to 16% after 3 min, maximal (111%) after 2–4 h, and 58% after 12 h. The mean increase in FEV_1 was maximally 25% after 3h, being 11% after 12 h. After salbutamol, mean increase in sG_{aw} was 44% after 1 min and maximal (100%) after 30 min. The peak increase in FEV_1 was 25%.

We conclude that formoterol (24 µg) and salmeterol (50 µg) had an equal bronchodilatory capacity, which was similar to that of 200 µg salbutamol and lasted for at least 12 h in patients with asthma. However, formoterol had a more rapid onset of action than salmeterol, equal to that of salbutamol.

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Formoterol and salmeterol are the first two drugs of a new generation of β_2-agonists with prolonged effect. Both compounds, when administered as an aerosol by a metered-dose inhaler (MDI) or when inhaled as a powder, have the property of retaining a bronchodilatory effect for up to 12 h, which accounts for their use in patients with nocturnal asthma. Moreover, the long duration of action allows for a twice daily treatment frequency, for example, on arising in the morning and on going to bed at night, which could be helpful in promoting patient compliance [1–6].

In vitro work and noncomparative studies on formoterol and salmeterol have shown evidence that there are small differences between the two inhaled drugs with regard to the speed of onset of a bronchodilatory effect, duration of action and dose-dependency of the duration of effect [6–13]. At the present time, a few comparative studies in patients with chronic obstructive pulmonary disease (COPD) have been published [14, 15], however, a direct comparison of the profile of the bronchodilatory effect in asthma is still lacking.

The purpose of the present study was to compare the onset and duration of action of 24 µg formoterol, 50 µg salmeterol and 200 µg salbutamol in patients with moderately severe asthma.

Patients and methods

Thirty adults with asthma, 8 females and 22 males, who met the American Thoracic Society (ATS) diagnostic criteria for asthma [16], volunteered to participate in the study. To be included in the study they had to fulfil the following criteria: age 18–70 yrs; in a stable phase of asthma, baseline forced expiratory volume in one second (FEV_1) 40–80% of predicted value and not varying more than 15% over the three study days; reversibility in FEV_1 more than 15% of the baseline value after 200 µg of inhaled salbutamol *via* a MDI. They did not suffer from other disorders, for example, liver, kidney or metabolic diseases, and had no history of pulmonary infection or acute exacerbation of their asthma during the previous 6 weeks. None of them used β-blockers or had taken any experimental drug in the 4 weeks prior to the test. The patients abstained from long-acting β_2-agonists for at least 72 h prior to the test days, for 36 h from slow release theophylline, and for 24 h from oral β_2-agonists, including those with extended effect, and for 8 h from anticholinergic drugs. The following drugs were permitted if taken in a stable dose: nedocromil sodium, cromolyn sodium, inhaled or oral steroids and antihistamines. Smoking and drinks containing caffeine were forbidden.

The study was approved by the Medical Ethics Committee of the study hospital, and informed consent was obtained from all the subjects.

The study had a single-centre, double-blind, randomized, single-dose, cross-over design. Each patient received three treatments on different study days with a washout period of 3–7 days between. The patients were allocated to the following three treatments in random order: 200 µg salbutamol, 24 µg formoterol or 50 µg salmeterol, all from a MDI attached to an aerosol chamber (Volumatic®). FEV_1 and forced vital capacity (FVC) were obtained in baseline condition and 10, 20, 30, 60 min, and every hour up to 12 h after inhalation of the trial drug. As a deep inspiration, necessary for the FEV_1 manoeuvre, may influence bronchial tone over several minutes, response during the first 10 min after inhalation was only assessed by the measurement of specific airway conductance ($_sG_{aw}$). Airway resistance (R_{aw}) and $_sG_{aw}$ were obtained at baseline condition and 1, 3, 5, 7, 10, 20, 30, 60 min, and every hour up to 12 h after inhalation of the trial drug. Measurements were always started around 08:30 h and completed around 21:00 h.

In case FEV_1 dropped during the day below the baseline value of the relevant day, 200 µg salbutamol was given by MDI as rescue medication. FVC and FEV_1 were recorded at the mouth using a pneumotachograph with electronic integration. The highest value of three manoevres was retained. R_{aw} and $_sG_{aw}$ were measured in a pressure-compensated integrated flow plethysmograph (Sensormedics 2800 Autobox) as the chord slopes between inspiratory and expiratory flow of 0.5 $L \cdot s^{-1}$ at a respiratory rate of 0.5 Hz. Means of nine measurements are reported. Measurements of heart rate and blood pressure were performed in baseline condition, and every hour up to 12 hr after inhalation of the study drug. In addition, before randomization, venous blood and urine samples were collected in the mornings for a safety screen. Any adverse events were carefully noted.

Statistical assessment

The objective of the trial was to provide evidence about the equivalence of 24 µg formoterol and 50 µg salmeterol, and about the treatment difference of salbutamol with respect to either formoterol or salmeterol. The two primary outcome variables were FEV_1 and $_sG_{aw}$. The sample size was calculated on 30 patients in order to detect treatment differences with an alpha of 0.025 (two-sided) and a power of at least 90%, assuming a standard deviation of 0.62 L for FEV_1 [1, 3, 17] and 0.16 $kPa \cdot L^{-1} \cdot s$ for R_{aw} [18, 19], a detectable difference of 0.18 L and 0.10 $kPa \cdot L^{-1} \cdot s$ for FEV_1 and R_{aw}, respectively, and a correlation coefficient of replicate measurements of 0.9 L for FEV_1 and 0.7 $kPa \cdot L^{-1} \cdot s$ for R_{aw} [19].

Changes in FEV_1 and $_sG_{aw}$ from baseline within treatment days were analysed with Student's t-tests per time-point. Analyses for both efficacy and safety parameters were performed using Student's t-test for testing differences in change from starting level between the treatment periods at each corresponding time-point within the treatment period. An overall test between the treatments was performed by using the area under the curve (AUC), integrating changes from starting level over all time-points in each treatment period, as dependent variable in a repeated measurement analysis of variance (RMAOV). In the latter analysis, two independent factors are involved: treatment period and first order carry-over effect, each with three levels.

Results

The 30 patients who participated in the study all met the inclusion criteria. Their demographic data and baseline lung function are shown in table 1. The treatment given before the start of the study was as follows: 29 patients took inhaled steroids (average daily dosage 733 µg), 2 had oral steroids, 22 short-acting β_2-agonists, and 17 long-acting β_2-agonists, 2 patients took theophylline, 1 terfenadine and 2 acetylcysteine. On the salmeterol and formoterol treatment days, there was no need for rescue medication in any patient. Three patients receiving salbutamol needed rescue medication after 6, 7 and 10 h.

The onset of action of salmeterol, formoterol and salbutamol measured as improvement in $_sG_{aw}$ and FEV_1 is shown in figure 1 and 2. The time course of the bronchodilation following the three drugs over a period of 12 h after inhalation is shown in figures 3 and 4. There were no significant differences in baseline FEV_1 and $_sG_{aw}$ between the three treatment days. Salbutamol produced a significant increase in $_sG_{aw}$ of 44% ($p<0.0001$) after 1 min, and a maximum increase of 100% after 30 min, followed by a slow decline. After 5 h, $_sG_{aw}$ fell below 20% of the maximum bronchodilatory capacity (fig. 3). The peak increase in FEV_1 after salbutamol was 25% and occurred after 30 min, whereas the FEV_1 fell below 20% of the peak bronchodilating capacity after 5 h.

After the inhalation of formoterol, there was a significant 44% increase in $_sG_{aw}$ after 1 min ($p<0.0001$). Maximum increase in $_sG_{aw}$, achieved after 2 h, amounted to 135% and afterwards there was a slowly declining plateau, the increase in $_sG_{aw}$ after 12 h still being 56%. The peak increase in FEV_1 2 h after formoterol was 27%, and after 12 h the improvement was still 10% ($p<0.0001$).

The inhalation of salmeterol led to significant improvement in $_sG_{aw}$ after 3 min (16%; $p<0.0001$), whilst the maximum increase (111%) was present between 2 and 4 h, and after 12 h improvement was 58%. The maximum increase in FEV_1 was 25%, and after 12 h the value of FEV_1 was 11% above baseline ($p<0.0001$).

Table 1. – Characteristics of the 30 patients in the study

Sex F/M	8/22
Age yrs	54±8
Height cm	171±8
Weight kg	77±13
FEV_1 at baseline L	1.88±0.60
FEV_1 at baseline % pred	58±12
FVC at baseline L	3.15±0.91
FVC at baseline % pred	90±12
R_{aw} at baseline $kPa \cdot L^{-1} \cdot s$	0.53±0.16
$_sG_{aw}$ at baseline $kPa \cdot L^{-1} \cdot s$	0.46±0.20

Values are presented as mean±SD. F: female; M: male; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted value; FVC: forced vital capacity; R_{aw}: airway resistance; $_sG_{aw}$: specific airway conductance.

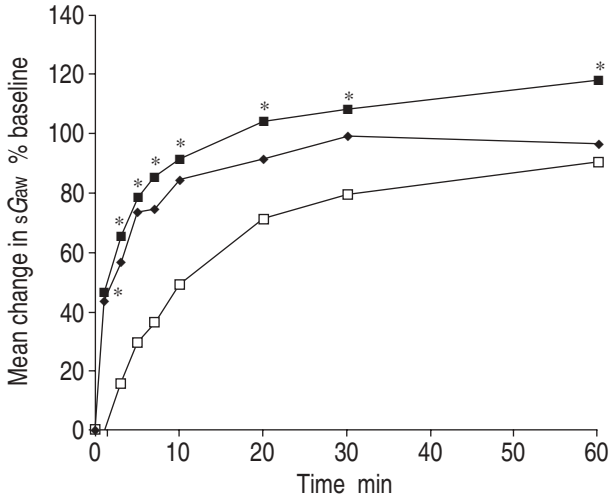

Fig. 1. – Mean change in specific airway conductance (s*G*aw) (% baseline) during the first 60 min after salmeterol, formoterol and salbutamol. Mean baseline s*G*aw: salmeterol 0.42 $kPa^{-1} \cdot s^{-1}$; formoterol 0.43 $kPa^{-1} \cdot s^{-1}$; salbutamol 0.45 $kPa^{-1} \cdot s^{-1}$. *: significant difference ($p<0.05$) between salmeterol and formoterol. —■—: formoterol 24 µg; —□—: salmeterol 50 µg; —◆—: salbutamol 200 µg.

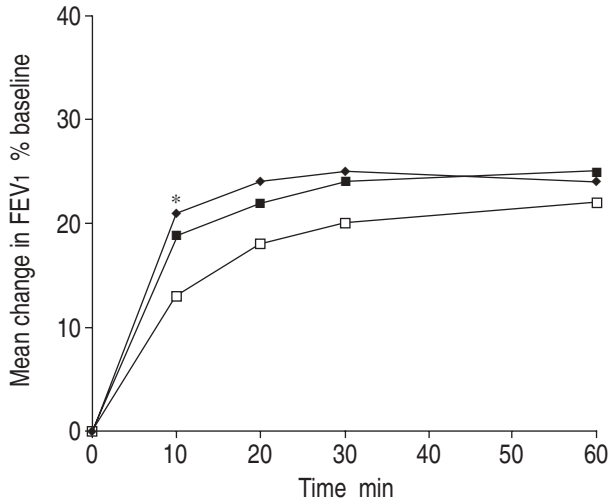

Fig. 2. – Mean change in forced expiratory volume in one second (FEV1) (% baseline) during the first 60 min after salmeterol, formoterol and salbutamol. Mean baseline FEV1: salmeterol 1.85 L; formoterol 1.89 L; salbutamol 1.85 L. *: significant difference ($p<0.05$) between formoterol and salmeterol. —■—: formoterol 24 µg; —□—: salmeterol 50 µg; —◆—: salbutamol 200 µg.

Concerning the onset of action, during the first 2 h after inhalation the increase in s*G*aw was greater after formoterol than after salmeterol, and for the increase in FEV1 this was true during the first 10 min. Comparing the onset of action of salbutamol and formoterol, there was no significant difference in the measurements of FEV1 and s*G*aw during the first hour and 30 min, respectively, but afterwards formoterol caused a greater improvement in both indices.

If we compare the AUC values of the parameters investigated (FEV1, FVC, *R*aw and s*G*aw), with the baseline values as minimum after administration of the three drugs (table 2), then it is apparent from the RMAOV that there is no difference between the AUC for formoterol and salmeterol for all parameters. The AUC

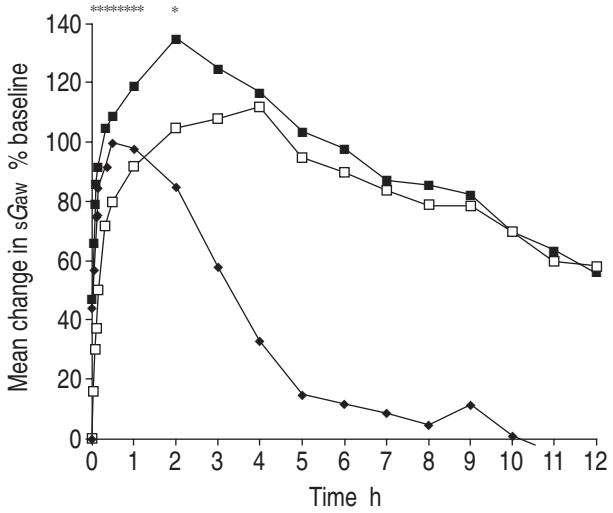

Fig. 3. – Mean change in specific airway conductance (s*G*aw) (% baseline) during 12 h after salmeterol, formoterol and salbutamol. *: significant difference ($p<0.05$) between salmeterol and formoterol (see fig. 1 for more details). —■—: formoterol 24 µg; —□—: salmeterol 50 µg; —◆—: salbutamol 200 µg.

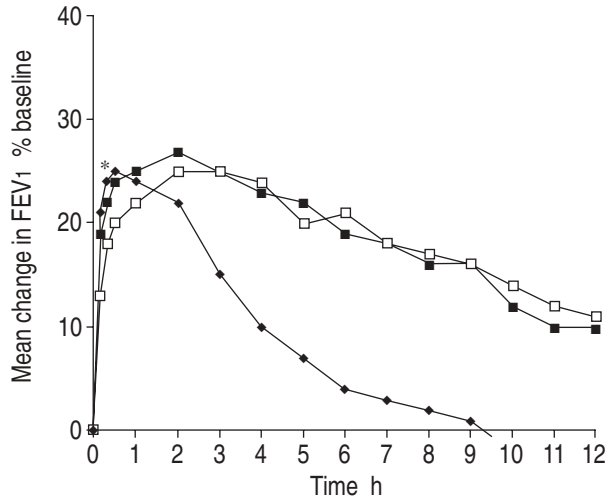

Fig. 4. – Mean change in forced expiratory volume in one second (FEV1) (% baseline) during 12 h after salmeterol, formoterol and salbutamol. *: significant difference ($p<0.05$) between salmeterol and formoterol at 10 min (see fig. 2). —■—: formoterol 24 µg; —□—: salmeterol 50 µg; —◆—: salbutamol 200 µg.

for both formoterol and salmeterol when compared with that of salbutamol are significantly ($p<0.02$) in favour of the former compounds. It should be noted that carry-over effects were found with regard to the comparison of salmeterol *versus* salbutamol ($p<0.05$) for s*G*aw and *R*aw. In the RMAOV, treatment effects are adjusted for first order carry-over effects.

There were no significant changes in systolic and diastolic blood pressure except for a drop in the diastolic blood pressure on the formoterol day at the 4 h time-point. This phenomenon was witnessed previously, directly after the consumption of a warm meal. Heart rate did not change significantly during the three test days.

There were no adverse events reported and the safety screen showed no abnormal data.

Table 2. – Area under the curve (AUC) of the change in FEV_1, FVC, sG_{aw} and R_{aw} *versus* time after 50 µg salbutamol, 24 µg formoterol and 200 µg salmeterol

	FEV_1	FVC	sG_{aw}	R_{aw}
AUC (treatment)#				
FRM	4.23±3.15	4.68±3.77	4.33±2.57	-2.30±1.42
SLM	3.88±3.07	4.71±4.16	3.73±2.34	-2.19±1.51
SLB	1.78±1.75	2.21±2.55	1.51±1.27	-0.51±0.95
RMAOV on AUC with baseline as minimum‡				
FRM/SLM	0.250	0.752	0.04	0.352
FRM/SLB	0.000	0.004	0.000	0.000
SLM/SLB	0.000	0.005	0.000	0.000
Carry over effect‡				
FRM/SLM	0.302	0.401	0.461	0.310
FRM/SLB	0.444	0.732	0.057	0.128
SLM/SLB	0.831	0.075	0.010	0.010

#: mean±SD; ‡: p-value. FRM: formoterol; SLM: salmeterol; SLB: salbutamol; RMAOV: repeated measurement analysis of variance. For further definitions see legend to table 1.

Discussion

This is the first study in which the profile of the bronchodilatory effect of salmeterol and formoterol has been directly compared in patients with stable, moderately severe bronchial asthma. The results demonstrate that, in these patients, 50 µg salmeterol and 24 µg formoterol inhaled through a MDI have an equal bronchodilatory capacity, which is similar to that of 200 µg salbutamol and lasts for at least 12 h. However, formoterol has a more rapid onset of action and bronchodilation is greater than after salmeterol during the first 2 h postinhalation.

In general, a dose of 12 or 24 µg formoterol and 50 or 100 µg salmeterol, both twice daily, is recommended for clinical practice. In the present study, we chose to compare 24 µg formoterol, the highest clinically recommended dose, with 50 µg salmeterol, the lowest recommended dose, hypothesizing after studying data from the literature that these doses might have a comparable duration of action.

In vitro work has shown that formoterol is a more potent β_2-adrenoceptor agonist and has a faster onset of action than salmeterol [8, 9], but that the duration of action is longer for salmeterol [8, 9]. In addition, *in vitro*, the duration of action of formoterol, but not of salmeterol, was found to be concentration-dependent [9]. Differences in the speed of onset and duration of action between salbutamol, formoterol and salmeterol can be explained by the difference in interaction of these β_2-agonists with β_2-adrenoceptors. Salbutamol is hydrophilic in nature, and interacts directly with the active site of the receptor. Its onset of action will, therefore, be rapid, but because it quickly re-equilibrates with the extracellular aqueous phase, its duration of action will be short [20]. Formoterol is moderately lipophilic. It has the capacity to stimulate the receptor directly, but a significant fraction (500:1) enters the cell membrane in the form of a depot, from where it leaches out gradually to interact with the receptor [21]. The onset of action of formoterol may, therefore, be expected to be either equivalent or slightly slower than salbutamol, but its duration of action will be longer and will depend on the size of the membrane depot. Salmeterol, on the other hand, is highly lipophilic. It is avidly (20,000:1) taken up into the cell membrane, but does not leach out and instead approaches the receptor by slow lateral diffusion through the membrane. Its onset of action will, therefore, be slower than that of salbutamol or formoterol. Once at the receptor, the long side-chain of salmeterol binds to an anchoring site, termed the exosite, which allows the saliformin head of the molecule to repeatedly engage and disengage the active site, resulting in a long duration of action [22].

In asthma, there have been a number of noncomparative studies investigating the effects of formoterol and salmeterol on airway tone. From the studies on formoterol, it seems clear that the 12 and 24 µg doses achieve similar peak values of FEV_1 [6], and that the onset of action is not dose-dependent [23]. Concerning the duration of action of formoterol, there are conflicting data. In most studies [1, 6], the mean bronchodilating effect both of 12 and 24 µg formoterol was longer than 12 h. However, in one study [6], there was a considerable variation among the patients, and in another study [10] the bronchodilating effect was less than 12 h and dose-dependent, *i.e.* 24 µg formoterol showed a longer duration of effect than 12 µg. From the dose-finding studies on salmeterol it is likely that the registered doses, 50 and 100 µg have an equal bronchodilating effect and a similar duration of action of more than 12 h in patients with moderate asthma [11].

At present, data on direct comparisons between different doses of the two compounds in asthma are not readily available. RABE *et al*. [24] found that 12 µg formoterol and 50 µg of salmeterol were equally effective in mild asthmatics in protecting against methacholine-induced bronchoconstriction for up to 24 h. In a study by ZELLWEGER *et al*. [25], 50 µg salmeterol and 24 µg formoterol produced comparable protection against methacholine-induced bronchoconstriction during at least 16 h. CAZZOLA *et al*. [14] compared the effects of 50 µg salmeterol and 24 µg formoterol in 16 patients with COPD and concluded that both compounds were equivalent in terms of maximum bronchodilation and duration of action. However, in a second study in patients with COPD, the same authors [15] concluded that 50 µg salmeterol had a longer duration of action than 12 or 24 µg formoterol.

In our study, 24 µg formoterol and 50 µg salmeterol both showed a duration of action of at least 12 h. However, it remains to be determined whether we would have obtained different results if we had compared 12 µg formoterol with 50 µg salmeterol. Moreover, our results, as in nearly all cross-over studies, were obtained in patients with stable asthma and are not necessarily valid for patients with more serious disease.

What are the clinical and practical implications of the differences between the two long-acting β_2-agonists? The position of these drugs in asthma therapy has not yet been clearly defined. In the guidelines issued by the National Heart, Lung and Blood Institute/World Health Organization (NHLBI/WHO) [26], long-acting inhaled β_2-agonists are recommended as maintenance therapy when standard doses of inhaled corticosteroids fail to achieve control of asthma, especially nocturnal symptoms. As chronic airway inflammation is not modified by these β_2-agonists, other authors prefer to raise the

dose of inhaled corticosteroids before the prescription of the long-acting β_2-agonists. Under those circumstances, a rapid onset of action, experienced by some asthmatics after inhalation of formoterol as a so-called "kick", is probably not a major advantage, but on the other hand, especially with salmeterol, patients should be instructed to have at hand a short-acting β_2-agonist with a quick response for relief of acute bronchoconstriction.

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