



Effects of long-acting bronchodilators and placebo on histamine-induced asthma symptoms and mild bronchusobstruction

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Summary

Study objective: Accurate perception of airway caliber remains an important issue in asthma management. The way bronchodilation is perceived is partly related to the perception of the efficacy of bronchodilators in relieving complaints. In the present study, we compared the effects of salmeterol, formoterol and placebo on relief of histamine-induced asthma symptoms and mild bronchusobstruction.

Methods: In this randomized controlled, double blind study, 30 asthmatics were challenged with histamine until forced expiratory volume in 1 s (FEV₁) fell with $\geq 20\%$. Subjects received salmeterol, formoterol or placebo after the histamine provocation. Pulmonary function (FEV₁) and asthma symptoms (Asthma Symptom Checklist, Borg Dyspnea Scale) were assessed 5 and 20 min later.

Results: FEV₁ improved significantly more in the salmeterol and formoterol group than in the placebo group ($P < 0.001$, $P < 0.001$ and $P < 0.05$, respectively). Salmeterol and formoterol were not different with regard to the pulmonary function recovery. No significant differences were found between the effects of salmeterol, formoterol and placebo on any of the symptom responses at the different time points.

Conclusions: We conclude that after a histamine-induced mild bronchusobstruction, a similar asthma symptom recovery occurred when inhaling salmeterol, formoterol or placebo, despite better recovery of pulmonary function in the active drug conditions.

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Introduction

In asthmatics, a poor correlation has often been observed between perceived symptoms and pulmonary function measures, indicating over- or underperception in many cases.¹ Psychological factors, such as previous asthma experiences and personality, have been studied to explain the inconsistent relationship between asthmatic symptoms and pulmonary function.²⁻⁴ Most often, blunted perception of bronchusobstruction has been studied. Misperceiving bronchodilation is, however, another important aspect, considering its potential impact on therapeutic compliance when underperceived and on life-threatening consequences when overperceived. Few studies have focused mainly on perception of bronchodilation.⁵⁻⁷

The way bronchodilation is perceived is partly related to the perception of the efficacy of bronchodilators in relieving complaints. Short- and long-acting inhaled β_2 -agonists play an important role in treating bronchusobstruction in asthmatics. The long-acting β_2 -agonists, salmeterol and formoterol, have been shown to be very efficient as maintenance treatment in asthmatics who, despite treatment with inhaled glucocorticosteroids, have persistent nocturnal asthma and require short-acting β_2 -agonists frequently.⁸ Formoterol has a rapid onset of action, compared to salmeterol with a slow onset of action. Previous study findings have shown that metacholine-induced severe bronchusobstruction and dyspnea were more rapidly relieved by formoterol and salbutamol than by salmeterol.^{9,10}

In the present study, we compared the effects of salmeterol, formoterol and placebo on relief of histamine-induced asthma symptoms and mild bronchusobstruction.

Methods

Participants

The patients included in this study were between 18 and 60 years old. Patients were referred to the pulmonary function laboratory to perform a histamine provocation test, in order to confirm their diagnosis of asthma, in agreement with the GINA guidelines.^{11,12} Exclusion criteria were occupational asthma, non-Dutch speaking, a fall of forced expiratory volume in 1 s (FEV_1) <20% at the end of the histamine provocation and previous experience with histamine provocation as this can influence

participants' responses. On the day of the study, patients had not taken any short-acting β_2 -agonists and anticholinergics for 8 h, long-acting β_2 -agonists and theophyllines for 24 h and antihistamines and long-acting anticholinergics for 48 h.

Measures

Asthma symptom measurements

- Asthma Symptom Checklist (ASC): The ASC is a 36-item questionnaire developed to assess subjective symptomatology in asthmatics.^{13,14} We used a Dutch translation, consisting of 6 symptom scales: symptoms of airway obstruction (5 items), dyspnea (3 items), fatigue (6 items), anxiety (8 items), irritation (6 items), and symptoms suggestive for hyperventilation (6 items) (7). The Cronbach's α is 0.93, 0.88, 0.86, 0.87, 0.92 and 0.76, respectively. The subjects were instructed to indicate on an 11-point scale, the intensity with which they experienced a symptom (0 = no symptom, 10 = symptom as bad as possible).
- Modified 0–10 Borg Dyspnea Scale: A modified Borg Scale has been proven a valid tool to measure the degree of dyspnea in patients with respiratory diseases.¹⁵ Patients rated their 'difficulty of breathing' on a modified 0–10 Borg Scale, going from no difficulty at all (score = 0) to highly difficult (score = 10).

Pulmonary function measurements

FEV_1 was measured by performing forced expiratory maneuvers on a Mass-flow Sensor (Sensormedics, Vmax 20C, 2000). Measurements were in accordance with ERS guidelines.¹⁶ FEV_1 values are expressed in liter or % of the predicted value. Two pulmonary function measurements were performed at every measure moment; the best of the two measurements was used for analyses.

Procedure

In this randomized controlled, double blind study, participants were allocated to one of the three conditions, depending on the study drug that was administered at the end of the histamine provocation: 1/salmeterol, 2/formoterol or 3/placebo. Pulmonary function and symptoms were assessed at baseline (measure moment 1), after the histamine provocation (measure moment 2), 5 min (measure moment 3) and 20 min (measure moment 4) after the study drug was administered. Every patient received 400 μ g of salbutamol at the end of the study. To ensure full recovery of the patients,

pulmonary function and symptom measures were assessed a last time 15 min after salbutamol was inhaled (measure moment 5).

The study was performed in the pulmonary function laboratory of the University Hospital Gasthuisberg, Leuven (Belgium). Patients came to the laboratory on a regular weekday to perform a histamine provocation test. Before the test started, the researcher (VL) gave standard instructions on the study and asked oral informed consent. When the patient was willing to participate, baseline symptom measurements were assessed, as well as smoking status and medication intake. Subsequently, the technician started the histamine provocation test according to the Cockcroft method.¹⁷ At the end of the provocation, the technician administered two devices to every subject while giving standard instructions of bronchodilation: 'The substances you will be asked to inhale are bronchodilators. You might well or not know them. After inhaling them, you may feel that your symptoms subside. You may feel your airways opening up. Your chest will loosen up. It will feel easier to get your breath'. Every patient had to take first one inhalation of a white turbohaler and immediately afterwards one inhalation of a green diskus. None or one of the two devices contained an active drug, according to the condition the patient was allocated to. In the placebo condition, none of the two devices contained an active drug. In the formoterol condition, the turbohaler contained an active drug (AstraZeneca, Oxis[®] 9 µg), while the diskus did not. In the salmeterol condition the diskus contained an active drug (GlaxoSmithKline, Serevent[®] 50 µg), while the turbohaler did not. Active and placebo devices were visually identical. Neither patients nor technicians knew the condition the patient was allocated to, as the researcher took care of the randomization (alternate between conditions). Symptoms (ASC and Borg-Score) and pulmonary function (FEV₁) were evaluated 5 and 20 min after the technician administered an active drug or placebo. Every patient received salbutamol at the end of the study (GlaxoSmithKline, Ventolin[®] 400 µg), to guarantee a maximal reversion of the bronchusobstruction. Fifteen minutes after salbutamol was administered, the fifth and last measure moment took place. The local Ethical Committee approved the study.

Data analysis

The three conditions were compared on their baseline clinical measures and on their socio-

demographic measures, using chi-square (χ^2), one-way ANOVA and Kruskal–Wallis as appropriate.

The main goal of our analyses consisted of comparing the effects of salmeterol, formoterol and placebo on symptoms experienced by the patients and pulmonary function measures. These analyses were based on the observed time period going from measure moment 2–4. We performed repeated measures analyses, using within-subject difference scores: [measure moment 3—measure moment 2] and [measure moment 4—measure moment 2]. These values were used in 2 (difference scores) \times 3 (conditions) repeated measures ANCOVA's with measure moment 1 and 2 as covariates. Measure moment 5 was kept out of the analyses, as this measure was only used to guarantee patient's maximal reversion of the bronchusobstruction.

To compare formoterol and salmeterol, means of the difference scores [measure moment 3—measure moment 2] and [measure moment 4—measure moment 2] were used for analyses. Unpaired *t*-tests were performed to compare groups on the symptom measures and the pulmonary function measures.

Computational analyses were performed with the statistical program SPSS version 10.0.

Results

Demographic and clinical characteristics at baseline

Thirty subjects participated in the study (14 females, 16 males) with a mean age of 36 years (range 19–58 years). The subjects' characteristics are described per condition in Table 1. The three conditions significantly differed at baseline for Borg Score ($\chi^2 = 7.069$, $P < 0.05$). Only 23% of the patients had earlier experience with long-acting β_2 -agonists (20%, 20% and 30% in placebo-, formoterol- and salmeterol-condition, respectively).

Pulmonary function and symptom reporting in the three conditions

The evolution of FEV₁ and ASC from baseline to measure moment 5 is represented in Figs. 1 and 2. For convenience sake, values are expressed in % of the baseline score.

Repeated measures analyses of covariance showed a significant interaction effect between measure moment and condition for FEV₁ ($F(2.25) = 5.571$, $P = 0.010$), indicating greater FEV₁-changes in formoterol and salmeterol condition compared to placebo condition at measure moment 4. No interaction or main effects were found for the

Table 1 Demographic and clinical characteristics at baseline.

	Condition			P-value
	Placebo <i>n</i> = 10	Formoterol <i>n</i> = 10	Salmeterol <i>n</i> = 10	
Gender/sex (% males)	60	40	60	
Age (years)	42 (10.9)	32.5 (9.6)	34 (9.6)	
PC ₂₀ histamine (mg/ml)	3.6	3.4	3.5	
FEV ₁ (% predicted)	101 (12.9)	94 (13.2)	105 (13.1)	
ASC	31 (32.6)	37 (27.7)	27 (32.4)	
Borg Score	1 (1.3)	4 (2.4)	2 (2.5)	Kruskal–Wallis <i>P</i> < 0.05*
Medication prescribed (%)				
Anti-histaminic	30	30	40	
Inhaled steroids	30	20	40	
Short-acting β ₂ -agonists	10	20	0	
Long-acting β ₂ -agonists	20	20	30	

Data are presented as mean (sd), unless otherwise stated.

PC₂₀: provocative concentration of histamine used for a ≥20% fall in FEV₁; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; ASC: Asthma Symptom Checklist Score.

*Significant difference between groups at a *P* < 0.05-level.

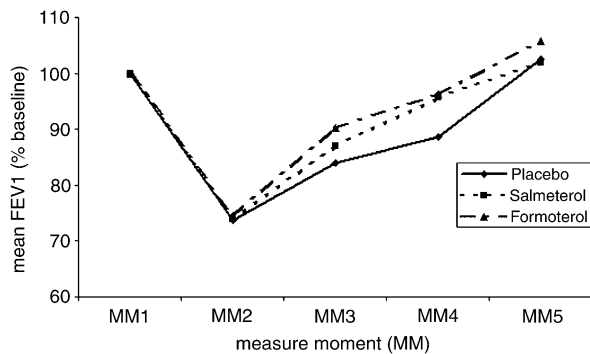


Figure 1 Mean FEV₁ (% baseline) per condition from measure moment 1–5. MM: measure moment. MM1: baseline; MM2: after histamine provocation; MM3: 5 min after study drug and instructions; MM4: 20 min after study drug and instructions; MM5: 15 min after salbutamol.

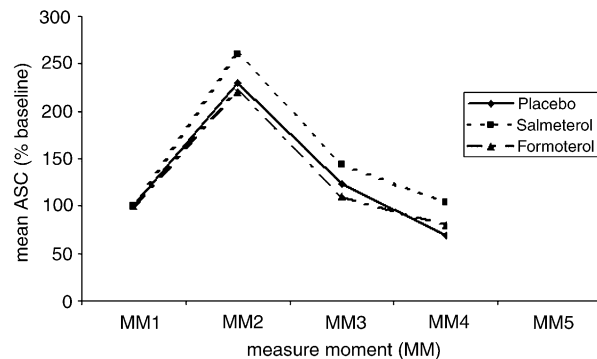


Figure 2 Mean ASC-score (% baseline) per condition from measure moment 1–5. MM: measure moment. MM1: baseline; MM2: after histamine provocation; MM3: 5 min after study drug and instructions; MM4: 20 min after study drug and instructions; MM5: 15 min after salbutamol.

different symptom measures, indicating similar recovery of the asthma symptoms in the placebo and active drug conditions.

Unpaired *t*-tests performed to compare the effects of formoterol and salmeterol on the symptom measures and pulmonary function did not reveal any significant differences between conditions, neither for the [measure moment 4–measure moment 2] nor for the [measure moment 3–measure moment 2] difference scores.

The absolute mean changes in pulmonary function and symptom measures following bronchodilator or placebo are shown in Table 2.

Discussion

In the present study, we compared the effects of salmeterol, formoterol and placebo on relief of histamine-induced asthma symptoms and mild bronchusobstruction.

Our data showed greater improvements of the pulmonary function measures in the conditions in which an active bronchodilator was administered compared to a placebo condition. FEV₁ showed better improvement in the formoterol and salmeterol condition than in the placebo condition 20 min after intake of the drug (*P* < 0.05). We were

Table 2 Absolute mean symptom and pulmonary function changes 5 and 20 min following bronchodilator or placebo.

	Placebo <i>n</i> = 10		Formoterol <i>n</i> = 10		Salmeterol <i>n</i> = 10	
	5 min	20 min	5 min	20 min	5 min	20 min
FEV ₁ (% predicted)	10	15	16	21	12	21
ASC total	33	50	40	51	29	40
Obstruction Scale	8	12	6	9	6	9
Dyspnea Scale	7	12	10	13	6	11
Fatigue Scale	8	10	8	10	5	6
Hyperventilation Scale	1	3	3	3	1	2
Anxiety Scale	2	2	4	5	2	3
Irritability Scale	2	4	4	6	3	3
Borg Score	2	4	3	4	2	4

FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; ASC: Asthma Symptom Checklist Score.

surprised to find a spontaneous improvement of FEV₁ in the placebo condition after 5 min. Different reasons may account for this improvement. First, it could be that the deep inspiration patients performed when inhaling the drugs or placebo elicited a bronchodilatory reaction in the patients' airways. Second, the instructions of bronchodilation might have influenced the changes in FEV₁. In a previous study, Leigh et al.¹⁸ observed a significant fall in FEV₁ in suggestible asthmatics when saline was suggested to be a bronchoconstrictor, although it is not clear through which mechanisms this might occur. Third, as we know that significant spontaneous improvements in FEV₁ can occur within 10 min after airway challenge, we think the improvement could be due to natural recovery of the bronchusobstruction. Even if the pulmonary function technician was a trained technician and the patients were quickly skilled in filling in the questionnaires, we do realize that the time needed for performing the measurements might have had a slight impact on the exact time the measurements took place. Therefore, measure moment 3 might have varied around 5 min after administration of the study drugs or placebo, giving FEV₁ more time to improve spontaneously after the challenge. This is, however, unavoidable in a study evaluating symptom and pulmonary function relief after bronchoconstriction.

No significant differences in mean improvement were found in the observed time window (after 5 and 20 min) among the formoterol and salmeterol conditions, neither for the pulmonary function measure nor for the symptom measures. In line with the findings of Politiek et al.⁹ we expected faster recovery of the pulmonary function in the formoterol group than in the salmeterol group, which should be noticeable 5 min after the drug was

administered. Although Fig. 1 shows a slight tendency towards faster recovery for formoterol after 5 min, this was not significant. We have some possible explanations for this finding. First, we think that a more substantial difference may be found with higher levels of bronchusobstruction: it was mild (fall in FEV₁ ≥ 20%) in our study and severe (fall in FEV₁ ≥ 30%) in the Politiek study. Second, it might be related to the lower dose of formoterol administered in our study. However, 9 μg of formoterol was estimated to correspond to 50 μg of salmeterol in a previous study and is known to be the dose used in clinical practice.¹⁹ The fact that the first measure of bronchodilator effect was only performed 5 min after the inhalation of the drugs, could be another explanation for the lack of difference between salmeterol and formoterol in recovery of pulmonary function. The setup of our study, however, did not allow performing earlier measurements.

Unlike for the pulmonary function measures, no differences among conditions were found for any of the symptom measures. The patients' symptoms in the placebo condition recovered to the same extent as those in the other two conditions, despite less recovery in pulmonary function. The full clinical relevancy of these remains uncertain, as more studies are needed on this topic. In the present study it is likely that the effects of the instructions, suggesting bronchodilation prior to taking drugs or placebo, did overrule the effects of the drugs themselves. Indeed, previous studies have shown important effects of suggestion of bronchodilation and bronchusobstruction on symptom reporting in asthmatics.^{20–23} Symptom perception in asthmatics has often been studied by administering study drugs and by assessing pulmonary function and symptoms in a parallel way. In

many of those studies we could not find any indication of the instructions that were given to the patients when administering the study drugs. It is, however, important to pay attention to those instructions, as they can be partly responsible for the reported symptoms.

Although the study was performed with a limited number of subjects therefore influencing the study power, we believe that the mild bronchusobstruction provoked with histamine reproduces a real life situation of a mild asthmatic attack well. The applied dosages of the drugs were similar to those used in clinical practice. In that perspective it is relevant to conclude that after a histamine-induced mild bronchusobstruction, a similar asthma symptom recovery occurred when inhaling salmeterol, formoterol or placebo, despite better recovery of pulmonary function in the active drug conditions.

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References

- Rietveld S, Everaerd W. Symptom perception in asthma. In: Kaptein A, Creer T, editors. *Respiratory disorders and behavioral medicine*. London: Martin Dunitz; 2000. p. 117–38.
- Put C, Demedts M, Van den Bergh O, Demyttenaere K, Verleden G. Asthma symptoms: influence of personality versus clinical status. *Eur Respir J* 1999;13:751–6.
- Put C, Van den Bergh O, Demedts M, Verleden G. A study of the relationship between self-reported non-compliance and symptomatology and psychological variables in patients with asthma. *J Asthma* 2000;37:503–10.
- Rietveld S, Everaerd W, Van Beest I. Excessive breathlessness through emotional imagery in asthma. *Behav Res Ther* 2000;38(10):1005–14.
- Teeter JG, Bleeker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. *Chest* 1998;113:272–7.
- Nosedá A, Schmerber J, Prigogine T, Yernault JC. How do patients with either asthma or COPD perceive acute bronchodilation? *Eur Respir J* 1993;6(5):636–44.
- Massasso DH, Salome CM, King GG, Seale JP, Woolcock AJ. Perception of bronchodilation in subjects with asthma and smokers with airflow limitation. *Respirology* 1999;4(2): 117–24.
- Kips JC, Postma RA. Long-acting inhaled β_2 -agonist therapy in asthma. *Am J Respir Crit Care Med* 2001;164:923–32.
- Politiek MJ, Boorsma M, Aalbers R. Comparison of formoterol, salbutamol and salmeterol in methacholine-induced severe bronchoconstriction. *Eur Respir J* 1999;13:988–92.
- Van der Woude HJ, Postma DS, Politiek MJ, Winter TH, Aalbers R. Relief of dyspnea by beta2-agonists after methacholine-induced bronchoconstriction. *Respir Med* 2004;98(9):816–20.
- Global strategy for Asthma Management and Prevention. April report 2002, no 02-3659, National Institutes of Health, National Heart, Lung and Blood Institute.
- Cockcroft DW, Hargreave FE. Airway hyperresponsiveness. Relevance of random population data to clinical usefulness. *Am Rev Respir Dis* 1990;142:497–500.
- Kinsman RA, Luparello T, O'Banion K, Spector S. Multi-dimensional analysis of the subjective symptomatology of asthma. *Psychosom Med* 1973;35(3):250–67.
- Ritz T, Bobb C, Edwards M, Steptoe A. The structure of symptom report in asthma. A reevaluation. *J Psychosom Res* 2001;51:639–45.
- Kendrick KR, Baxi SC, Smith RM. Usefulness of the modified 0–10 Borg Scale in assessing the degree in dyspnea in patients with COPD and asthma. *J Emerg Nurs* 2000;26(3): 216–22.
- Quanjer PH, Tammeling GJ, Cotes JE, Pederson OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 16(S):250–67.
- Cockcroft DW, Killian DN, Mellan JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allerg* 1977;7:235–43.
- Leigh R, MacQueen G, Tougas G, Hargreave FE, Bienenstock J. Change in forced expiratory volume 1 second after sham bronchoconstrictor in suggestible but not suggestion-resistant asthmatic subjects: a pilot study. *Psychosom Med* 2003;65:791–5.
- Palmqvist M, Persson G, Lazer L, Rosenborg L, Larsson P, Lotvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. *Eur Respir J* 1997;10:2484–9.
- Pastorello EA, Codecassa LR, Pravettoni V, et al. The role of suggestion in asthma. I. Effects of inactive solution on bronchial reactivity under bronchoconstrictor or bronchodilator suggestion. *Ann Allerg* 1987;59:336.
- Pastorello EA, Codecassa LR, Gerosa A, Buonocore E, Sillano V, Zanussi C. The role of suggestion in asthma. II. Effects of a bronchoconstrictor drug on bronchial reactivity under bronchoconstrictor or bronchodilator suggestion. *Ann Allerg* 1987;59:339–40.
- Isenberg SA, Lehrer PM, Hochron S. The effects of suggestion and emotional arousal on pulmonary function in asthma: a review and a hypothesis regarding vagal mediation. *Psychosom Med* 1992;54:192–216.
- Put C, Van den Bergh O, Van Ongeval E, Demedts M, Verleden G. Negative affectivity and the influence of suggestion on asthma symptoms. *J Psychosom Res* 2004;57: 249–55.