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Potential masking effect on dyspnoea perception by short- and long-acting β_2-agonists in asthma

C.P. van Schayck*,#, I.D. Bijl-Hofland*, S.G.M. Cloosterman*, H.T.M. Folgering¶, F.J.J. van der Elshout+, C. Van Weel*

Potential masking effect on dyspnoea perception by short- and long-acting β_2-agonists in asthma. C.P. van Schayck, I.D. Bijl-Hofland, S.G.M. Cloosterman, H.T.M. Folgering, F.J.J. van der Elshout, C. Van Weel. ©ERS Journals Ltd 2002.

ABSTRACT: Asthma patients evaluate the effect of medication treatment through the degree of their asthma symptoms, which might be affected by their ability to perceive these symptoms. It has been suggested that β_2-agonists may mask the effects of an increase in airway inflammation. This study compared the perception of histamine-induced bronchoconstriction during monotherapy with short- or long-acting β_2-agonists.

Asthmatic patients (68 male and 60 female, mean age 35±11 yrs, forced expiratory volume in one second (FEV_1) 86±15% of the reference value, provocative concentration causing a 20% fall in FEV_1 (PC_{20}) geometric mean 0.97 mg·mL^{-1} (95% confidence interval (CI): 0.73–1.30)) were selected and randomly allocated to use either a short-acting (salbutamol, n=41) or long-acting β_2-agonist (formoterol, n=46) or placebo (n=41) for 12 weeks. Perception of dyspnoea provoked by histamine-induced bronchoconstriction was measured at the start and every 4 weeks thereafter. Subjects quantified their sensation of breathlessness during the challenge tests on a modified Borg scale at the start of the study and every 4 weeks thereafter. The sensitivity to changes in FEV_1 was analysed by the linear regression slope (α) Borg *versus* % fall in FEV_1. The absolute perceptual magnitude (PS_{20}) was determined by the perception score at the 20% fall in FEV_1.

Although the geometric mean PC_{20} decreased significantly within the group using short-acting β_2-agonists (in the group with initial $PC_{20} \geqslant 2$ mg·mL^{-1} there was a drop from 5.26–1.94 mg·mL^{-1}; p=0.013), repeated measurement analysis showed no difference in the course of time of perception (both slope α and PS_{20}) between the three medication groups.

This study showed that chronic use of short- or long-acting β_2-agonists in asthmatics for a period of 12 weeks, did not significantly change the perception of histamine-induced bronchoconstriction compared with placebo. Further investigation is required to establish whether this suggests that these drugs do not mask a deterioration of asthma.
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*Dept of General Practice, University of Nijmegen, #Dept of General Practice, University of Maastricht, ¶Dept of Pulmonary Diseases, Dekkerswald, University of Nijmegen and +Dept of Pulmonary Diseases, Rijnstate Hospital, Arnhem, the Netherlands.

Correspondence: C.P. van Schayck
Dept of General Practice
University of Maastricht
P.O. Box 616
6200 MD Maastricht
The Netherlands
Fax: 31 433884225
E-mail: onno.vanschayck@hag.unimaas.nl

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It has been suggested that β_2-agonists may mask the effects of an increase in airway inflammation [1]. This may be particularly true for patients who use little or no anti-inflammatory treatment. There are several reasons why perception of asthma symptoms might be influenced by chronic bronchodilator use. First, chronic bronchodilator use leads to a decrease in bronchoconstriction, which might influence perception of the severity of the disease. The reduced perception of asthma symptoms could influence the patient's healthcare behaviour. For example, a patient might be more exposed to allergens because they have no inclination to stay away from them, as there is no warning against repeated exposure. Patients could also become noncompliant with anti-inflammatory treatment and, in the meantime, develop progressive inflammation with increasing bronchial hyperresponsiveness (BHR). Secondly, several studies have observed that chronic use of short-acting β_2-agonists may have detrimental effects, resulting in increased BHR [1–5]. Chronic use of β_2-agonists has led to tolerance of their protective effects against bronchoconstrictor stimuli, whereas their bronchodilator properties have remained unchanged [4, 6, 7]. Furthermore, it has been found that BHR may have a negative influence on the perception of asthma symptoms [8, 9]. Previously, ROISMAN *et al.* [10] showed that both the degree of eosinophil inflammation and epithelial damage presented in the airways are negatively related to the patient's ability to perceive bronchoconstriction. Finally, the patient's increased bronchial responsiveness may chronically adapt them to their increased bronchoconstriction [8].

It is therefore important to study the effects of bronchodilator use on the perception of airway obstruction. In this study, it was hypothesized that increased BHR after chronic use of β_2-agonists would lead to a decrease in the perception of airway obstruction. The perception of histamine-induced bronchoconstriction has been assessed by two indices

representing different aspect of the perception: the sensitivity index and the absolute perceptual magnitude (PS20) [9–13].

Recently, the authors showed that in a small group of 64 asthmatic patients, additional use of inhaled corticosteroids resulted in an improved perception of bronchoconstriction in patients using long-acting β_2-agonists [14]. In the study, patients used either a short- or long-acting β_2-agonists or placebo over a period of 12 weeks, followed by another period of 12 weeks in which beclomethasone diproprionate was added. However, as the study group was a subgroup of the present population, it was too small to compare the effects of long- and short-acting β_2-agonists. The number of subjects in the present study population was sufficient to study differences between long- and short-acting β_2-agonists.

The perception of bronchoconstriction during chronic use of β_2-agonists was examined both for short-acting and long-acting β_2-agonists. This was performed through measurement of the perception of dyspnoea during histamine-induced bronchoconstriction in asthmatic patients who randomly received salbutamol (2 inhalations 100 μg *b.i.d.*), formoterol (12 μg *b.i.d.*) or placebo for 12 weeks.

Methods

Patient selection

Selection of the patients was performed through a two-step procedure. Initially, patients (aged 16–60 yrs) were selected by their general practitioner (GP) if they had a history of bronchial symptoms or a clinical diagnosis of asthma [13, 14]. Eligible patients then visited the lung function laboratory for an inclusion assessment. Patients had to have lower airway complaints, a forced expiratory volume in one second (FEV1) of $\geqslant$50% of predicted and either airway hyperresponsiveness (provocative concentration causing a 20% fall in FEV1 (PC20) on histamine $\leqslant$8 mg·mL^{-1})) or reversibility of obstruction (of $\geqslant$15% compared to baseline FEV1 after inhalation of 800 mg salbutamol) to be eligible for inclusion in the study. Bronchodilator response was assessed after histamine provocation when the FEV1 had returned to the baseline value. A total of 258 patients met these criteria, of whom 204 agreed to participate in the study. Informed consent was obtained from each patient and the ethical committee of the Academic Hospital of Nijmegen University, the Netherlands, approved the study.

Study design

At the start of the 8-week washout period, patients ceased all their pulmonary medication (inhaled corticosteroids, cromoglycates, bronchodilators), if used, and were instructed to use only rescue medication on demand (Berodual® dry powder inhalation with ipratropium bromide 40 μg and fenoterol hydrobromide 100 μg). After the washout period, each subject randomly received either a short-acting (salbutamol metered-dose inhaler with two inhalations 100 μg *b.i.d.*) or a long-acting (formoterol metered-dose inhaler with 12 μg *b.i.d.*) β_2-agonist or a placebo for 12 weeks. Patients came to the laboratory at the start of the treatment period and every 4 weeks thereafter. Patients received the study medication on the entry day and were carefully instructed on how to use the medication (inhaler technique and time schedule). Their use of the medication was then checked during every visit to the laboratory: used canisters were collected and weighed before and after use in order to check compliance.

A subgroup of 64 of these patients was followed up for a second period in which they received additional inhaled corticosteroids. That study has been recently reported elsewhere [14].

Bronchial provocation

During each visit to the laboratory, patients underwent a histamine challenge test according to European Respiratory Society (ERS) standards [15]. No study medication was used for $\geqslant$12 h before the test. Doubling doses of histamine, starting with 0.03 and going up to 16 mg·mL^{-1}, were administered until FEV1 had dropped by $\geqslant$20% compared to baseline value, or a maximum of 16 mg·mL^{-1} histamine was given. The bronchial response to each dose of histamine was expressed as the reduction in FEV1 as a percentage of baseline value, according to ERS standards [15]. The dose of inhaled histamine, causing a 20% fall in FEV1 below baseline, was obtained from the log dose-response curve by linear interpolation of the last two points. PC20 was recorded in noncumulative units.

Assessment of breathlessness

Breathlessness was measured during the histamine challenge, before each measurement of FEV1 with a modified Borg scale [16]. The Borg scale is a 12-point ordinal scale ranging from 0 (no respiratory complaints) and 0.5 (very, very slight respiratory complaints) to 10 (maximal respiratory complaints). Subjects were instructed that the term "respiratory complaints" meant "complaints of respiratory sensation such as shortness of breath, chest tightness and breathlessness". Subjects were asked to score the overall magnitude of all three symptoms together in one assessment. Other histamine-related symptoms, such as pharyngitis or conjunctivitis, headaches or cough, were not scored. In order to determine the patient's "perceptiveness" during the study, they had to have a baseline FEV1 $\geqslant$50% pred at the start of the bronchial provocation test, and, during this test, the PC20 value had to be established with at least two doubling doses of histamine.

Analysis

Perception of bronchoconstriction during the histamine challenge test was analysed by calculating the

linear regression coefficient (slope α) between Borg scores and the reduction in FEV1 as a percentage of the baseline value in the linear regression analysis of Borg=y+α%ΔFEV1, indicating the patient's sensitivity towards changes in FEV1 [8, 10, 12, 13]. Furthermore, Borg scores corresponding to a reduction in FEV1 of 20% were determined by interpolation, reflecting the PS20 [9, 11, 13, 17]. All PC20 values were log-transformed before analysis. The effect of chronic bronchodilator use on BHR was determined with a paired t-test between baseline and the last follow-up measurement of PC20.

Repeated measurement analysis was used to analyse the changes in PC20 and Borg scores, based on the mixed model (PROC MIXED in SAS) and with special parametric structure on the covariance (correlation) matrices. Both within- and between-group factors can be analysed in this model. All analyses were corrected for baseline perception score, baseline bronchial responsiveness (PC20) and baseline FEV1 % pred by means of covariance analysis. All analyses were performed on the group of patients with either an initially high or low bronchial responsiveness (PC20 <2 mg·mL^{-1} *versus* PC20 $\geqslant 2$ mg·mL^{-1}), in order to investigate the affect on PC20 in asthmatic patients in which there was "enough room for deterioration" (patients with a relatively high baseline PC20). A cut-off point of 2 mg·mL^{-1} was chosen as this was the median of the PC20 baseline. Finally, the perceptual sensitivity (slope α) and PS20 of patients with either an initially high or low bronchial responsiveness were compared by an unpaired t-test. This was performed at baseline and every 4 weeks thereafter (four measurements).

Power calculation

A clinically relevant difference in perception was assumed to be at least 1.0 step on the Borg scale. Assuming an SD of 1.5 steps (which was found in these allergic asthmatic patients), an α of 0.05 and a β of 0.2, $\geqslant 36$ evaluable patients were needed per group. With a drop-out rate of 15%, the number of patients starting per group was $\geqslant 41$.

Results

Patients

Of the 204 patients who started the washout period, 42 subjects dropped out before the medication treatment period began, mainly because they could not stop using inhaled corticosteroids. During the medication period, five subjects dropped out because they needed inhaled corticosteroid treatment, five subjects refused to take the study medication, and six patients stopped due to motivational factors. Baseline perception measurement and/or the follow-up perception measurements could not be assessed in 18 subjects, because their FEV1 was <50% pred at the time of assessment. Therefore, the total number of patients left for analysis was 128. The clinical characteristics of these asthmatic patients are presented in table 1. During the study, there was no difference in the number of patients using rescue medication (78% in the short-acting, 83% in the long-acting and 83% in the placebo group; p=0.82).

Bronchial hyperresponsiveness

The course of BHR during 12 weeks of chronic bronchodilator use in the group with an initially high and low BHR (PC20 <2 mg·mL^{-1} *versus* PC20 $\geqslant 2$ mg·mL^{-1}) is shown in figures 1 and 2. In the group with an initially low bronchial responsiveness using chronic short-acting β_2-agonists, the PC20 decreased significantly from 5.26 mg·mL^{-1} (95% confidence interval (CI): 3.71–7.45) to 1.94 mg·mL^{-1} (95% CI: 0.84–4.48; p=0. 013).

Perceptive sensitivity for changes in forced expiratory volume in one second

There were no significant differences in the perceptive sensitivity of changes in FEV1 (slope α) between

Table 1. – Baseline characteristics of the study population

	Short-acting	Long-acting	Placebo	p-value
Patients n	41	46	41	
Age yrs	34.8±10.6	33.7±11.5	35.8 ± 12.3	0.687
Sex F/M	17/24	23/23	20/21	0.697
PC20 mg·mL^{-1}#	1.03 (0.60–1.78)	0.89 (0.54–1.47)	1.00 (0.64–1.58)	0.911
FEV1 ml	3362±719	3195±611	3056±787	0.150
FFV1 % pred	88±13	86±14	83±17	0.315
Patients on inhaled steroids before the start of the trial %	44	54	56	0.486
Perception indices				
Slope >Borg/% reduction in FEV1	0.12±0.06	0.11±0.08	0.11±0.06	0.834
PS20 >Borg at 20% reduction in FEV1	4.4±2.9	3.6±1.8	4.2±2.0	0.222

Data are presented as mean±SD unless otherwise stated. FEV1: forced expiratory volume in one second; PC20: provocative concentration causing a 20% fall in FEV1; PS20: absolute perceptual magnitude; F: female; M: male. #: geometric mean (95% confidence interval).

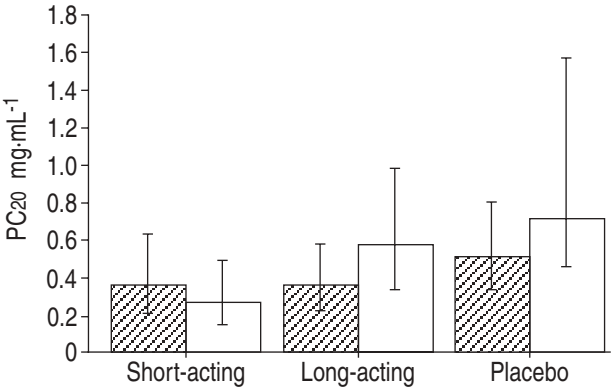

Fig. 1. – Effects of 12 weeks of chronic β_2-agonist use on the provocative concentration causing a 20% fall in forced expiratory volume in one second (PC_{20}) in patients with an initially high bronchial hyperresponsiveness (PC_{20} <2 mg·mL^{-1}). ▨: baseline; □: 12 weeks.

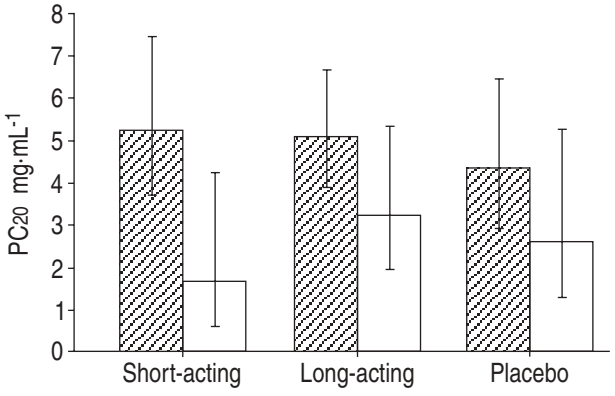

Fig. 2. – Effects of 12 weeks of chronic β_2-agonist use on the provocative concentration causing a 20% fall in forced expiratory volume in one second (PC_{20}) in patients with an initially low bronchial hyperresponsiveness (PC_{20} ⩾2 mg·mL^{-1}). ▨: baseline; □: 12 weeks.

the three medication groups at the start of the study (table 1). Repeated measurement analysis showed no difference in the course of time of slope α between the three medication groups both for the total group and the group of patients with either an initially high or low bronchial responsiveness (p=0.98 and p=0.42, respectively, fig. 3).

Absolute perceptual magnitude

There were no significant differences in the perception score at 20% reduction in FEV_1 (PS_{20}) between the three medication groups at the start of the study (table 1). Repeated measurement analysis also showed no difference in the course of time of PS_{20} between the three medication groups both for the total group and for the group of patients with either an initially high or low bronchial responsiveness (p=0.72 and p=0.18, respectively, fig. 4).

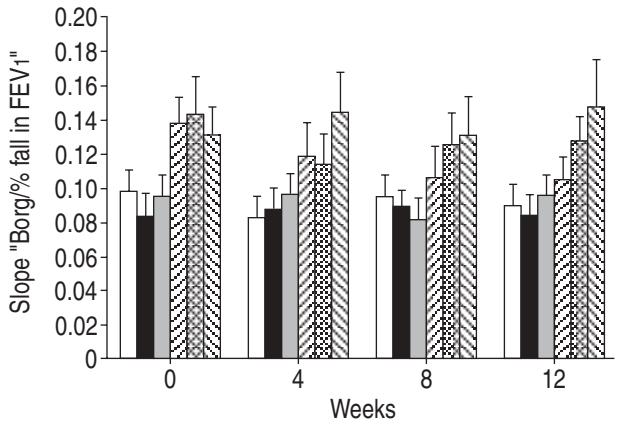

Fig. 3. – Perceptual sensitivity of histamine-induced bronchoconstriction (slope α) during regular use of β_2-agonists in subjects with an initially high provocative concentration causing a 20% fall in forced expiratory volume in one second (FEV_1) (PC_{20} <2 mg·mL^{-1}; □: short-acting; ■: long-acting; ■: placebo) and low bronchial hyperresponsiveness (PC_{20} ⩾2 mg·mL^{-1}; ▨: short-acting; ■: long-acting; ▧: placebo).

Discussion

This study shows that chronic use of β_2-agonists does not significantly change perception of histamine-induced bronchoconstriction compared with placebo, either for short- or long-acting β_2-agonists during a period of 12 weeks of daily use. In addition, it confirms the results of BOULET *et al.* [9], who also studied the perception of induced bronchoconstriction in asthmatic patients and showed that use of long-acting β_2-agonists (salmeterol 1×50 μg *b.i.d.* during 4 weeks) does not impair the perception of bronchospasm [11].

Chronic use of β_2-agonists might increase the risk of BHR, cause greater airway inflammation and eventually lead to a reduction in the perception of bronchoconstriction. The authors previously reported

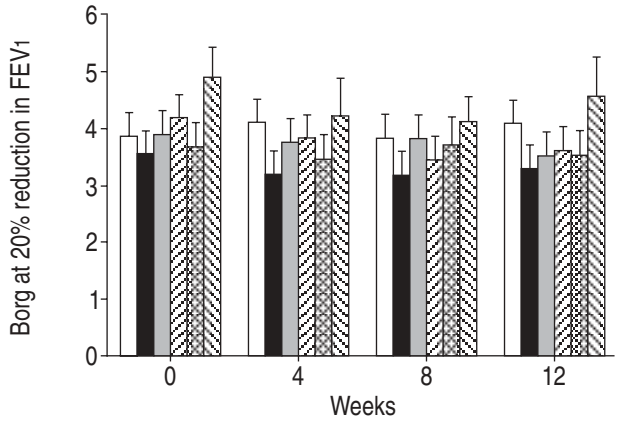

Fig. 4. – Absolute perceptual magnitude (PS_{20}) of histamine-induced bronchoconstriction during regular use of β_2-agonists in subjects with an initially high provocative concentration causing a 20% fall in forced expiratory volume in one second (FEV_1) (PC_{20} <2 mg·mL^{-1}; □: short-acting; ■: long-acting; ■: placebo) and low bronchial hyperresponsiveness (PC_{20} ⩾2 mg·mL^{-1}; ▨: short-acting; ■: long-acting; ▧: placebo).

that chronic use of short-acting β_2-agonists in subgroups of patients resulted in increased BHR and a greater decline in lung function [18]. In the present study, BHR increased in the group with an initially low bronchial responsiveness using chronic short-acting β_2-agonists. However, the increase in bronchial responsiveness did not lead to a decrease in the perception of bronchoconstriction.

It could be suggested that a study period of 12 weeks is too short to demonstrate the influence of increased hyperresponsiveness on the perception of bronchoconstriction. This is because the perception of bronchoconstriction may only be influenced after a prolonged reduction in BHR.

It was not possible to measure eosinophilic airway inflammation and epithelial damage in this study. Therefore, the study did not assess whether chronic β_2-agonist use led to increased inflammation in the airways of asthmatic subjects. It is important to emphasize that the perception of bronchoconstriction was measured, whereas the perception of a deteriorating asthma was not. This is important as β_2-agonists may prevent bronchoconstriction despite an increase in airway inflammation, underlying a deterioration of asthma.

An increase in BHR was only observed in the group using short-acting β_2-agonists but not when compared with the placebo group, as the difference in changes between these two groups was not significant. Recently, in a subgroup of the present study population [14], the authors showed that the additional use of inhaled corticosteroids resulted in an improvement in the perception of bronchoconstriction in patients using long-acting β_2-agonists but not in patients using short-acting β_2-agonists. This difference might be related to the increase in BHR in the group using short-acting β_2-agonists, resulting in greater airflow inflammation and perhaps a reduction in perception. Another possibility may be the suggested enhancement of the anti-inflammatory effects of corticosteroids by long-acting β_2-agonists [19].

The relevance of studying the effects of β_2-agonist monotherapy in asthma may be questioned, as it is advised that long-acting β_2-agonists are used in combination with inhaled steroids, whilst short-acting β_2-agonists should only be used without inhaled steroids in very mild intermittent asthma. However, there is still some concern that β_2-agonists might mask the effects of asthma, particularly because long-acting β_2-agonists suppress bronchoconstriction and may therefore eventually reduce compliance toward inhaled steroids. The present authors therefore believe that it is still clinically relevant to study the potential masking effects of these monotherapy drugs.

In summary, this study has shown that although chronic use of short-acting β_2-agonists led to increased bronchial hyperresponsiveness, it did not significantly change perception of histamine-induced bronchoconstriction compared with placebo, either for short- or long-acting β_2-agonists after a period of 12 weeks of daily use.

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