Effect of fluticasone propionate–salmeterol therapy on seasonal changes in airway responsiveness and exhaled nitric oxide levels in patients with pollen-induced asthma

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Background: There has been concern that in allergic asthmatic patients there might be an interactive effect on inflammation between regular salmeterol use and exposure to allergens, resulting in increased airway responsiveness.

Objective: To determine the effects of salmeterol on allergen-induced changes in airway responsiveness and exhaled nitric oxide (ENO) levels in allergic asthmatic patients concomitantly taking inhaled corticosteroids.

Methods: Forty-two asthmatic patients sensitized to pollen allergens were randomly allocated to treatment with fluticasone propionate–salmeterol (n = 21) or fluticasone propionate alone (n = 21). Spirometry, the methacholine provocation concentration causing a 20% decline in forced expiratory volume in 1 second (PC_{20}), the adenosine 5′-monophosphate (AMP) PC_{20}, and ENO levels were measured before and at the height of the pollen season after 6 weeks of treatment.

Results: Changes in the methacholine PC_{20}, the AMP PC_{20}, and ENO levels were not significantly different between treatment groups. No significant changes in the AMP PC_{20} were observed among the fluticasone propionate–salmeterol and fluticasone propionate groups during natural pollen exposure. However, a significant increase in the methacholine PC_{20} was observed in the fluticasone propionate–salmeterol group ($P = .03$) and in the fluticasone propionate group ($P = .04$); ENO concentrations decreased significantly in both groups during natural allergen exposure ($P = .009$ and .005).

Conclusions: In patients with pollen-induced asthma, treatment with either fluticasone propionate or fluticasone propionate–salmeterol is associated with significant reductions in methacholine responsiveness and ENO concentrations, even during natural pollen exposure. Furthermore, at least in patients with mild asthma, natural allergen exposure and the regular use of fluticasone propionate–salmeterol are not associated with a greater increase in ENO levels and airway responsiveness than natural allergen exposure and fluticasone propionate use alone.

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INTRODUCTION

Asthma is a disease characterized by airway inflammation and smooth muscle dysfunction. To achieve optimum asthma control, therapy should be targeted against these 2 underlying components. The addition of a long-acting β_2-agonist to a low-to-moderate dose of inhaled corticosteroid (ICS) is a recommended treatment in the National Heart, Lung, and Blood Institute guidelines,[1] and, therefore, treatment with regular long-acting β_2-receptor agonists has increased in recent years in Europe and the United States.

Salmeterol is an effective β_2-agonist with long-lasting bronchodilator activity up to 12 hours. Preclinical work[2] has shown that fluticasone propionate and salmeterol have complementary mechanisms of action and, in addition, interact in a synergistic manner at the receptor, molecular, and cellular levels. In addition, the results of a recent study[3] demonstrate that combined fluticasone propionate–salmeterol achieves sustained control of asthma in more patients, more rapidly, and at a lower dose of ICS than fluticasone alone. Therefore, salmeterol is recommended in combination with ICSs (such as fluticasone propionate) in patients with chronic persistent asthma.[1] However, several studies have demonstrated that the regular use of inhaled salmeterol produces tolerance to its bronchoprotective effect against bronchospasm induced by exercise,[4] allergens,[5] and methacholine.[6] The loss of β-agonist protection against bronchoconstriction has been described to be more pronounced in relation to the effect of inhaled adenosine 5′-monophosphate (AMP),[7] which acts indirectly, causing primed mast cell degranulation and the release of histamine and other mediators, with subsequent smooth muscle contraction,[8] than to the effect of inhaled methacholine, which causes bronchoconstriction mainly by the direct stimulation of cholinergic receptors on airway smooth muscle. In patients with asthma, exhaled nitric oxide (ENO) levels are known to be related to eosinophilic inflammation in the lower airways,[9,10] to decrease with corticosteroid therapy,[11] and to increase as the dose of ICS is reduced.[12]

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Thus, ENO has been proposed as a noninvasive marker of airway inflammation in asthma.[13] In addition, measurements of ENO demonstrate changes associated with airway responses after inhaled allergen[14] and, therefore, determination of ENO is a safe, noninvasive method of indirectly obtaining information about the effect of allergen exposure on airway inflammation.

Clinical studies have suggested that regular treatment with salmeterol enhances allergen-induced early bronchoconstrictor responses[15] and that, compared with placebo, 1 week of regular therapy with salmeterol may lead to an increase in airway inflammation 24 hours after allergen challenge.[16] Furthermore, it has been postulated[17] that allergen-induced bronchoconstriction might be a primitive defense mechanism that prevents allergens from entering the lower airways. Inhibition of this defense system by the regular use of β_2-agonists could lead to an increased antigen load, with the subsequent potentiation of airway responsiveness and inflammation. On the basis of this, there has been some concern that, especially in patients with allergic asthma, there might be an interactive effect on inflammation between the regular use of salmeterol and exposure to allergens, resulting in increased airway responsiveness.[18] In a previous study[19] of patients with pollen-induced asthma that used a model of natural allergen exposure, we did not detect any potentiating effect of regular treatment with salmeterol on the allergen-induced increases in ENO levels and airway responsiveness to either direct or indirect bronchoconstrictor agents. However, in this previous study,[19] patients were not using ICSs, and one could question the clinical relevance of these data because patients would not normally be taking regular long-acting β_2-agonists in the absence of background ICS therapy. Furthermore, although there is convincing evidence that in patients with pollen-sensitive asthma therapy with ICSs protects against the seasonal increase in airway responsiveness,[20] a significant reduction in glucocorticosteroid receptor binding affinity has been observed in ragweed-allergic patients with asthma during the pollen season compared with preseasonal measurements.[21] In addition, long-acting β_2-agonists, including salmeterol, have been shown to prime corticosteroid receptors for increased corticosteroid binding and nuclear translocation,[22] and this provides a potential mechanism for complementary anti-inflammatory cellular effects of ICSs and salmeterol. Thus, it could be argued that the effects of salmeterol on the allergen-induced increases in airway responsiveness might be different in patients treated concomitantly with ICSs.

The aim of the present study was, therefore, to evaluate whether salmeterol would enhance allergen-induced airway responsiveness and inflammation in patients with allergic asthma treated concomitantly with ICSs. This was a 6-week, double-blind, parallel-group, randomized controlled trial in which the effects of treatment with either fluticasone propionate or combined fluticasone propionate–salmeterol on bronchial responsiveness to methacholine and AMP and on ENO concentrations during natural allergen exposure were evaluated.

PATIENTS AND METHODS

Patients

Forty-two patients with asthma aged 18 to 72 years from the outpatient allergy clinic at the Hospital Universitario Dr Peset were studied. All of these patients met the following inclusion criteria: a history of mild seasonal asthma[23] for at least 2 years; a forced expiratory volume in 1 second (FEV_1) of 80% or greater of the predicted value and an FEV_1/forced vital capacity (FVC) of 70% or greater; and a skin prick test result that was positive (wheal diameter $\geq$3 mm) for pollen allergens (eg, grass pollen, *Parietaria judaica*, and *Olea europea*). The diagnosis of asthma had been previously established (during a pollen season) by the presence of asthmatic symptoms only (n = 9), asthmatic symptoms plus methacholine airway hyperresponsiveness with a methacholine provocation concentration that caused a 20% decline in FEV_1 (PC_{20}) of less than 8 mg/mL (n = 18), or symptoms plus an improvement in the FEV_1 from predicted of 15% or more after the administration of 200 μg of inhaled albuterol (n = 15). Outside the pollen season, these patients had no asthma symptoms, and none required asthma therapy, including β_2-agonists, for at least 4 months before the first evaluation. All 42 patients were lifelong nonsmokers, and none had a history of chronic bronchitis, emphysema, or respiratory tract infections during the 4 weeks before the study began. Current and former smokers, pregnant women, and patients with significant renal, hepatic, or cardiovascular disease were excluded. The study was performed and data were collected according to the principles of good clinical practice. The blinded code was broken after a clean file had been declared and the data files had been locked in the computer. The study protocol was approved by the ethics committee of the Hospital Universitario Dr Peset and the health authorities. Written informed consent was obtained from each patient before participation.

Study Design

This was a double-blind, randomized, parallel-group study. Patients were first evaluated between mid-January and the end of February (preseasonal evaluation), before the pollen season had begun in Valencia, Spain (Fig 1).[24] During this period, patients had 3 laboratory visits. At the first visit, all patients were evaluated for suitability, and spirometry was performed. At each of the next 2 visits (7–9 days apart), spirometry and concentration-response studies with either methacholine or AMP were performed. The challenges were performed on separate days, with the order of challenge randomized. At the second visit, ENO levels were measured before spirometry and challenge testing. Patients were then randomized to receive fluticasone propionate (100 μg) twice a day or combined fluticasone propionate–salmeterol (100/50 μg) twice a day administered using a dry powder inhaler (Diskus/Accuhaler; GlaxoSmithKline R & D, Uxbridge, England), which they commenced taking in March. Albuterol metered-dose inhaler, oral antihistamines (ie, cetirizine and loratadine), and nasal topical antihistamines (levocabastine and azelastine) were used on an as-needed basis to control

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