dose of 400 μg twice daily. Blinded, add-on therapy was then done with either placebo (n = 21) or salmeterol 42 μg twice daily (n = 154) for 2 weeks at stable doses. Next was an ICS reduction phase over the next 8 weeks as all 21 patients on triamcinolone plus placebo were assigned to receive half the dose of triamcinolone 200 μg twice daily plus continued placebo (placebo–minus group). Patients on full dose ICS plus salmeterol were randomized to either continue on that same dose (salmeterol–plus group) or to continue on salmeterol with half the dose of ICS 200 μg daily (salmeterol–minus group). Last was an 8-week ICS elimination phase. The placebo–minus group (previously on ICS 200 μg bid plus placebo salmeterol) were assigned to receive placebo ICS and placebo salmeterol. The salmeterol–minus group (receiving a half dose of ICS plus salmeterol) were changed to placebo ICS plus salmeterol. The salmeterol–plus group (receiving a full dose of ICS plus a full dose of salmeterol) continued on that same dose (active control group). The main outcome measure was timed to asthma treatment failure (specifically defined by parameters of pulmonary function and/or clinical deterioration) in patients receiving salmeterol.

**Results.** Treatment failure occurred in 8.3% of the salmeterol–minus group 8 weeks after ICS treatment was reduced compared with 2.8% of the salmeterol–plus group (active control group, full dose) when the dose of ICS was not changed. Subsequent treatment failure occurred in 46.3% of the salmeterol–minus group 8 weeks after ICS therapy was eliminated compared with 13.7% of the salmeterol–plus group (active control group, full dose). The relative risk of treatment failure at the end of the ICS elimination phase in the salmeterol–minus group (plus placebo ICS) was 4.3% compared with the salmeterol–plus group (active control group, full dose). Secondary outcome measures included a lower mean presmalarol forced expiratory volume in 1 second (FEV₁) in the salmeterol–minus group versus the salmeterol–plus group and decreased salmeterol-protected methacholine response was less in the salmeterol minus versus the salmeterol plus group.

**Conclusions.** In patients with persistent asthma suboptimally controlled by triamcinolone therapy alone, but whose asthma symptoms improve after addition of salmeterol, a 50% reduction in ICS dose can occur without a significant loss of asthma control. However, total elimination of ICS therapy results in a significant deterioration of asthma control as well as decline in pulmonary function and loss of bronchoprotection.

**Reviewer’s Comments.** This study is entirely consistent with the current consensus that although salmeterol may improve asthma control when given along with an inhaled steroid and provide significant steroid-sparing effects. In addition, it supports the notion that salmeterol should not be used as monotherapy for persistent asthma.

**Alan B. Goldsobel, MD**
San Jose, CA

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**EFFECT OF SALMETEROL ON ALLERGEN-INDUCED AIRWAY INFLAMMATION IN MILD ALLERGIC ASTHMA**


**Purpose of the Study.** To evaluate the effect of salmeterol on allergen-induced airway inflammation.

**Study Population.** Sixteen atopic patients with mild asthma (10 male, 6 female) >18 years (mean 25.2) old with diagnosis of asthma for at least 6 months. The subjects had stable asthma for at least 1 month and baseline forced expiratory volume in 1 second (FEV₁) >70% (mean: 95%). Subjects had to have a late asthmatic response (LAR) to an allergen inhalation challenge, defined as a 15% decrease in FEV₁ between 2 and 8 hours after challenge. Patients had to be off of oral or inhaled steroids and any other anti-inflammatory medications for at least 1 month before the study.

**Methods.** The study was a randomized, double-blind, cross-over trial. The subjects underwent baseline allergen skin testing with titration to determine the specific allergen and dose to use for the inhalation challenge. Baseline FEV₁ was performed and inhalation challenge was performed to document early asthmatic response (EAR) and LAR. After a 2-week run-in without medication other than rescue albuterol, the subjects underwent a saline challenge a day before randomization. Subjects were randomized to receive either salmeterol 50 μg daily or 1 week of inhaled placebo. They were also allowed to use rescue salbutamol and record the use on diary cards. A 2-week washout period separated the 2 cross-over treatment periods. Subjects recorded asthma symptoms and medication usage on diary cards and had spirometry and methacholine (Mch) challenges before and at the end of each treatment period 24 hours after holding the study medication. They also underwent bronchoalveolar lavage (BAL) and bronchial biopsies 24 hours after an allergen challenge. The allergen challenges were performed before the run-in period and each allergen challenge was preceded the day before by an Mch challenge. Salmeterol or placebo was given on the day of the challenge and bronchoscopy. Allergen challenges were performed with increasing allergen doses until the FEV₁ dropped >15% or until the maximum dose was reached, and subjects had repeated spirometry up to 8 hours postchallenge.

**Results.** All 16 subjects completed the study. The mean baseline Mch PC20 (Mch dose causing a 20% decrease in FEV₁) was 1.53 ± 1.28. The mean percentage drop in FEV₁ after allergen challenge for EAR was 28.7 ± 1.7% and for LAR was 24.6 ± 1.8%. Mean PC20 for placebo was 1.15 ± 1.34 and after salmeterol was 2.20 ± 1.31 (P = .009). Salmeterol significantly increased the decline in FEV₁ during EAR compared with placebo, but LAR was similar between the 2 groups. There was no significant difference in BAL macrophage, lymphocyte, neutrophil, and eosinophil counts 24 hours after allergen challenge in the 2 treatment groups. However, the salmeterol treated group showed an increase in a number of inflammatory cells on bronchial biopsies after allergen challenge compared with placebo.

**Conclusion.** This study found an increase in lung mast cells and total leukocyte counts from bronchial biopsies obtained 24 hours after allergen exposure from allergen sensitized asthmatics taking salmeterol regularly for 1 week versus those taking placebo.

**Reviewer’s Comments.** This study showed an increase in inflammatory cells from bronchial biopsy 24 hours after antigen challenge in asthmatic subjects taking salmeterol for 1 week as monotherapy, versus those taking placebo control. Although salmeterol can improve baseline spirometry and reduce airway responsiveness to allergen, this study suggests that when used alone, salmeterol may be associated with mild increased allergen-induced airway cellular responses. Others studies have found some conflicting effects of salmeterol on various inflammatory markers, both in the serum, BAL fluid, and bronchial biopsies. Compared with inhaled corticosteroids, when used as monotherapy, long-acting β-agonists have been associated with increased frequency of asthma exacerbations.
These results support the concomitant use of inhaled corticosteroids with long-acting β-agonists.

Mary Beth Bollinger, DO
Baltimore, MD

TOLERANCE TO THE PROTECTIVE EFFECT OF SALMETEROL ON ALLERGEN CHALLENGE CAN BE PARTIALLY RESTORED BY WITHDRAWAL OF SALMETEROL REGULAR TREATMENT


Purpose of the Study. To determine if withdrawal of salmeterol for 3 days can restore its bronchoprotective ability on specific bronchial provocative testing with allergen that was completely lost after 1 week of regular treatment with salmeterol.

Study Population. Ten nonsmoking subjects (8 men/2 women), mean age 24 ± 8 years with stable mild intermittent asthma (mean baseline forced expiratory volume in 1 second [FEV₁] = 90%) without previous regular β-agonist treatment. All subjects had had previous early airway response (EAR) to screening allergen challenge to dust mite by bronchoprovocation.

Methods. All subjects had FEV₁, skin testing to dust mite and specific bronchial provocation testing (sBPT) at baseline (T₀). They then underwent sBPT with the same allergen after a single dose of inhaled salmeterol, 50 µg (T₁), followed by sBPT with allergen after 1 week of regular treatment of salmeterol 50 µg bid (T₂). They then continued on salmeterol 50 µg bid for 4 days and then changed to inhaled placebo 2 puffs bid for 3 days, after which they underwent sBPT (T₃). The treatments were single-blinded and the technicians performing the pulmonary function tests were not aware of the treatment periods. All sBPTs were performed 1 hour after the last drug inhalation with the same dose of allergen as T₀ determined by the dose required to cause a decrease in FEV₁ of >20%.

Results. The 4 mean baseline FEV₁ before the allergen challenges (T₀–T₃) were not significantly different. At T₀, the mean drop in FEV₁ was 39% (range: 29–45) and this decrease was almost completely abolished by a single dose of salmeterol 50 µg (T₁), (mean drop = 3%, range: 0%–13%). However, after 1 week of regular salmeterol treatment, the sBPT drop in FEV₁ (T₂) was not prevented (mean drop = 29.5%, range: 18%–49%). If salmeterol was then dropped 3 days before sBPT (T₃), the drop in FEV₁ was again not prevented (mean drop = 23%, range: 4%–41%), but the drop was lower than when subjects remained on regular salmeterol before sBPT (T₂).

Conclusions. The bronchoprotective effect of salmeterol on sBPT was lost after 1 week of regular treatment in a group of mild intermittent asthmatics. The withdrawal of inhaled salmeterol for 3 days before challenge only slightly improved its bronchoprotective ability on sBPT with allergen. Additional studies are needed to evaluate whether a longer period of withdrawal in such patients would completely restore the bronchoprotective effect of salmeterol on sBPT to allergen.

Reviewer’s Comments. Regular use of short-acting β-agonists may cause increased bronchial reactivity and loss of asthma control. Others have shown that regular use of salmeterol or formoterol may reduce the ability to block bronchoconstriction to methacholine. Inhaled steroids are known to reduce tolerance and their concurrent use with salmeterol could minimize the occurrence of tolerance. The results of this study also bring into question the washout periods used for β-agonists for many study protocols. For example, many study protocols will hold meds for 1 to 6 months, but allow β-agonist use without any washout period. Regular use of either short- or long-acting β-agonists before sBPT may affect the degree of bronchoconstriction. It is not clear what is a sufficient washout period for β-agonists, because in this study 3 days of withdrawal of salmeterol was not sufficient.

Mary Beth Bollinger, DO
Baltimore, MD

SALMETEROL POWDER PROVIDES SIGNIFICANTLY BETTER BENEFIT THAN MONTELUKAST IN ASTHOMATIC PATIENTS RECEIVING CONCOMMITANT INHALED CORTICOSTEROID THERAPY


Purpose of the Study. To compare inhaled salmeterol powder to oral montelukast in patients with persistent asthma who are not well-controlled on inhaled corticosteroids (ICS).

Study Population. Male and nonlactating, nonpregnant females ≥15 years of age with the diagnosis of asthma for at least 6 months were recruited from 71 private and university clinics in the United States and Puerto Rico. The group included 948 subjects (61% female, 85% Caucasian). All subjects were symptomatic with their asthma for at least 6 weeks before screening and at a constant dose of ICS for 30 days before screening. Baseline forced expiratory volume in 1 second (FEV₁) was 50% to 80% and all subjects had at least 12% improvement in FEV₁ postbronchodilator.

Methods. Two multicenter, randomized, double-blind, parallel-group clinical trials were conducted comparing 50 µg bid of salmeterol by dry powder inhaler (n = 476) versus 10 mg po daily of montelukast (n = 472). All subjects underwent baseline history and physical, and pulmonary function tests including FEV₁ reversibility. After a 7- to 14-day run-in period to assess symptoms, diary card completion, and patient proficiency with inhaler use, patients whose FEV₁ remained within 50% to 80% of normal were eligible for enrollment. Subjects also had to meet at least 1 of the following criteria during the 7 days before randomization: use of an average of ≥4 puffs per day of albuterol, a symptom score of ≥2 on ≥3 days, and/or ≥3 nights of nocturnal asthma symptoms. The subjects remained on their current ICS dose throughout the study and rescue albuterol, but no other asthma medications were allowed other than study drug. Subjects were asked to record am and pm peak flows (PEF), nocturnal awakenings, albuterol use, asthma symptoms, and daily study drug use. Symptoms were rated using a 5-point scale and were targeted to affects on activity level. Subjects returned for assessments at 1, 4, 8, and 12 weeks of treatment. The subjects completed a satisfaction survey at the end of the 12-week study.

Results. A total of 476 subjects received inhaled salmeterol and 472 received montelukast. The treatment groups had similar demographics and disease characteristics at baseline, with 61% women, >80% Caucasian, >70% with asthma ≥10 years, mean baseline FEV₁ 68% of predicted, and mean baseline PEF of 370 l/m. Morning PEF in the salmeterol treated group increased more significantly (mean = 35 l/m) than the montelukast treated group (mean = 21.7 l/m). The bronchodilator properties of salmeterol were superior than montelukast over all treatment weeks. Patients in the salmeterol group had a significantly greater increase in symptom-free days than the montelukast group (24% vs 16%; P < .001). Symptom scores for
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Mary Beth Bollinger

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Mary Beth Bollinger
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