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 sBPTs 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 ASTHMATIC PATIENTS RECEIVING CONCOMITANT 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 affect 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
all parameters except wheezing were significantly improved in the salmeterol group vs the montelukast group. Subjects in the salmeterol group used significantly less rescue albuterol than the montelukast group. Regarding patient satisfaction with the drug, the salmeterol group had greater satisfaction other than in how long the medication worked, where there was no difference in scores. The number of asthma exacerbations and the number of adverse events was similar in both groups, with 13 in each group withdrawing from the study because of adverse events.

**Conclusion.** The addition of salmeterol in moderate to severe persistent adult asthmatics poorly controlled on ICS was superior to the addition of montelukast in improvement in PEF and overall symptom control.

**Reviewer’s Comments.** The addition of inhaled salmeterol in subjects who were not adequately controlled on ICS showed significantly greater improvement in lung function and control of symptoms (other than wheezing) compared with oral montelukast. Other groups have compared salmeterol as an additive agent versus doubling the ICS dose and versus another leukotriene modifier, but not all in that study were on baseline ICS. Future studies are needed to determine if these findings will hold true over longer study periods and whether either long-acting β-agonists or leukotriene modifiers have a bearing on the natural history of asthma. In addition, similar studies in children are needed to see if the same patterns of response occur in all age groups.

**MARY BETH BOLLINGER, DO**
Baltimore, MD

**STEROID THERAPY**

**COMPARISON OF THE COST-EFFECTIVENESS OF Budesonide AND SODIUM Cromoglycate IN THE MANAGEMENT OF CHILDHOOD ASTHMA IN EVERYDAY CLINICAL PRACTICE**


**Purpose of the Study.** Both inhaled glucocorticosteroids and sodium cromoglycate are recommended as first-line maintenance drugs for the control of persistent asthma. The objective of this study was to compare the cost-effectiveness of these 2 treatment strategies in everyday clinical practice.

**Study Population.** Children, 5 to 11 years old, with mild to moderate persistent asthma not previously treated with inhaled steroids or Cromones.

**Methods.** The children were recruited from 10 secondary care centers in Sweden. The study was performed as a randomized, parallel-group, open-label pharmacoeconomic clinical trial. After the asthma was first stabilized using 4 to 6 weeks of inhaled budesonide, the children received either budesonide 200 to 400 µg twice daily (N = 69) or sodium cromoglycate 20 mg 3 times a day (N = 69) as maintenance therapy for 12 months. To better simulate normal clinical practice, investigators were instructed to maintain asthma control with normal procedures, including the ability to switch patients from one study treatment to the other, use additional therapy when required, or alter dosages as needed. Direct health care consumption costs and indirect costs attributable to loss of productivity by the family were recorded along with lung function and asthma symptoms.

**Results.** Twenty-nine children (42%) in the cromoglycate arm were switched to budesonide, with 24 (35%) attributable to lack of effect. Despite this, budesonide treatment resulted in a 24% lower annual cost than in those treated with cromoglycate. This trend was not statistically significant. Most of the reduction reflected the direct cost of medication with cromoglycate more than double the daily cost of budesonide. No statistically significant differences were noted in peak flow rate, symptoms, albuterol use or exacerbation rates, although budesonide was superior in almost all categories. However, there was a significant 14% increase in the number of symptom-free days after the change to budesonide from cromoglycate.

**Conclusion.** The study demonstrates that budesonide resulted in lower costs and less drug switches than a maintenance treatment strategy using sodium cromoglycate.

**Reviewers’ Comments.** This important long-term study suggests that an inhaled corticosteroid in asthmatic children not only results in lower costs than cromoglycate, but is more effective over a 12-month period. This is supported by the striking findings of the large number (35%) of children who had to switch from cromoglycate to budesonide because of inadequate control. The lack of statistical significance of several of the clinical and economic parameters may be a reflection of the rather small numbers compared and the fact that those remaining in the cromoglycate group were less severe.

**Otto Liao, MD**
**Stanley Galant, MD**
Orange, CA

**EFFECTIVE ONCE-DAILY ADMINISTRATION OF Budesonide Inhalation Suspension BY NEBULIZER WITH FACEMASKS OR MOUTHPIECES FOR PERSISTENT ASTHMA IN INFANTS AND YOUNG CHILDREN**


**Purpose of the Study.** A retrospective analysis comparing the efficacy and safety of nebulized budesonide inhalation suspension (Pulmicort Respules, AstraZeneca, Lund, Sweden) administered once daily by facemask or mouthpiece for mild persistent asthma.

**Study Population.** A total of 359 children aged 6 months to 8 years with mild, persistent asthma.

**Methods.** Children were randomized to receive 0.25, 0.5, or 1.0 mg budesonide inhalation suspension once daily or placebo for 12 weeks via facemask or mouthpiece. Efficacy variables included nighttime and daytime asthma symptom scores, use of breakthrough bronchodilator medications, and pulmonary function tests (in children capable of consistently performing spirometry or peak flows).

**Results.** Changes in nighttime and daytime asthma symptom scores were not significantly different between children using facemasks and those using mouthpieces. Use of breakthrough medications and pulmonary function test results (in the subset of children able to perform them) also were not significantly different in facemask users and mouthpiece users.

**Conclusions.** These results suggest that budesonide inhalation suspension is equally effective whether administered by facemask or mouthpiece and that young children who require the use of a facemask may be successfully treated.

**Reviewers’ Comments.** The efficacy and safety of once-daily budesonide inhalation suspension in this age group was previously reported in a multicenter, randomized,
Salmeterol Powder Provides Significantly Better Benefit than Montelukast in Asthmatic Patients Receiving Concomitant Inhaled Corticosteroid Therapy
Mary Beth Bollinger
Pediatrics 2002;110;459

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/110/Supplement_2/459.1

References
This article cites 1 articles, 0 of which you can access for free at:
http://pediatrics.aappublications.org/content/110/Supplement_2/459.1.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Allergy/Immunology
http://classic.pediatrics.aappublications.org/cgi/collection/allergy:immunology_sub
Asthma
http://classic.pediatrics.aappublications.org/cgi/collection/asthma_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints
Salmeterol Powder Provides Significantly Better Benefit than Montelukast in Asthmatic Patients Receiving Concomitant Inhaled Corticosteroid Therapy
Mary Beth Bollinger
*Pediatrics* 2002;110;459

The online version of this article, along with updated information and services, is located on the World Wide Web at: http://pediatrics.aappublications.org/content/110/Supplement_2/459.1