Study Population. Five hundred eighteen patients, 5 to 12 years old with persistent asthma. Patients were receiving sodium cromoglicate, nedocromil sodium, and/or inhaled corticosteroids at stable doses for at least 1 month before entry in the study.

Methods. After the run-in period, all patients were randomized in a double-blind manner to receive 12 or 24 \( \mu g \) formoterol dry powder capsule or placebo capsule twice daily for 12 months. This was given in addition to their baseline antiinflammatory treatment, which was not changed. The primary study variable was the area under the curve for forced expiratory volume in 1 second (FEV\(_1\)) measured over 12 hours after the morning dose of study medication.

Results. The area under the curve for FEV\(_1\) after the first treatment dose and after 3 and 12 months of treatment was significantly greater in patients receiving formoterol 12 \( \mu g \) and 24 \( \mu g \) than in patients receiving placebo (all \( P \leq .0062 \)). Although numerically greater for formoterol 24 \( \mu g \), there was no statistically significant difference in FEV\(_1\) between the 2 active treatment doses. Compared with placebo, both doses of formoterol significantly improved am and pm peak expiratory flow rates. In the group treated with formoterol 24 \( \mu g \) twice daily, median symptom score and median dose of rescue medication at night were lower than during the run-in period, whereas with the 12-\( \mu g \) dose and the placebo group this did not change. Hospitalization for asthma was higher in the 2 formoterol groups than in the placebo group. The number of patients reporting asthma exacerbations during the study was the same for all 3 treatment groups.

Conclusions. In asthmatic children who are still symptomatic despite antiinflammatory therapy, the addition of formoterol 12 or 24 \( \mu g \) improves air flow obstruction, nocturnal symptoms and the use of rescue medication. The regular use of long-acting \( \beta \)-agonists was safe and well-tolerated in this patient population.

Reviewer’s Comments. Although the overall results are encouraging, the increase in hospitalization in the formoterol-treated patients is concerning. It is possible that this could result from a masking of airway inflammation with potent 12-hour bronchodilatation.

Alan B. Goldsobel, MD
San Jose, CA

BRONCHODILATOR THERAPY AND HYPERACTIVITY IN PRESCHOOL CHILDREN


Purpose of the Study. Parents often report that nebulized albuterol makes their children “hyper.”

Study Population. Nineteen children with asthma 25 to 64 months of age whose parents thought that albuterol made their children overactive.

Methods. This was a double-blind, crossover study with children randomized to receive nebulization with albuterol (5 mg) or saline, then the reverse [Note: the usual dose is 0.5 mL of the 0.5% solution = 2.5 mg]. Behavior was rated by parents using Conners’ Rating Scale at baseline and after nebulization. Professional observers rated the level of activity using Preschool Behavior Observation Scale (PS-BOS).

Results. Parental ratings of activity revealed no significant difference between baseline and postalbuterol scores. Professional observers ratings of activity revealed no evidence of an increase in the child’s activity after administration of albuterol.

Conclusions. Neither parental report nor observer ratings suggested any significant increase in the child’s level of activity after albuterol.

Reviewer’s Comments. Although often reported, when studied in a blinded fashion, an albuterol nebulization, even 5 mg, does not cause preschoolers to be “hyper.” Perhaps it is the setting (asthma attack) in which a nebulization is normally given that changes children’s behavior or their parents perception thereof.

John M. Kelso, MD
San Diego, CA

STEROID THERAPY

SIGNIFICANT VARIABILITY IN RESPONSE TO INHALED CORTICOSTEROIDS FOR PERSISTENT ASThma


Purpose of the Study. Clinical studies have suggested that considerable variability exists among individuals with asthma in both their responsiveness to inhaled corticosteroids (ICS) and side effects from such drugs. A clinical model is needed to compare various ICS with respect to efficacy and safety, as no standardized model has yet been developed.

Study Population. Study subjects were corticosteroid-naive individuals with mostly moderate persistent asthma who were 18 to 55 years of age. The study was designed as a feasibility study rather than a comparative trial.

Methods. Thirty subjects were randomized to receive either beclomethasone dipropionate (BDP) 168, 672, and 1344 \( \mu g \)/day (n = 15) or fluticasone propionate (FP) 88, 352, and 704 \( \mu g \) (n = 15) via metered-dose inhaler (MDI) with chlorofluorocarbon propellant and OptiChamber (Respironics, Cedar Grove, NJ) spacer in 3 consecutive 6-week intervals. Compliance was monitored with a Doser CT (Meditrack Products, Hudson, MA) device. All subjects then received 3 weeks of FP dry powder inhaler (DPI) 2000 \( \mu g \)/day. The primary outcome variable for assessing comparative efficacy was forced expiratory volume in 1 second (FEV\(_1\)). Secondary outcomes were methacholine PC-20, exercise-induced change in FEV\(_1\), exhaled nitric oxide (eNO), and induced sputum eosinophilia. Overnight cortisol suppression was measured by collecting hourly blood samples from 7 pm to 7 AM.

Results. Maximum FEV\(_1\) response occurred with the lowest dose of FP and the medium dose of BDP and was not further increased by high-dose FP-DPI. Near-maximum improvement in methacholine PC-20 occurred with low-dose FP and medium-dose BDP. Responsiveness to ICS varied markedly among subjects. Good (>15%) FEV\(_1\) response was associated with high eNO, high pretreatment bronchodilator reversibility, and low pretreatment forced expiratory volume in 1 second/forced vital capacity (FEV\(_1\)/FVC) when compared with poor (<5%) FEV\(_1\) response. Both BDP and FP caused dose-dependent cortisol suppression.

Conclusions. Near-maximum improvements in FEV\(_1\) and methacholine PC-20 occurred with low doses of FP and medium doses of BDP in these subjects with moderate persistent asthma. Higher doses did not improve efficacy but directly increased systemic side effects, as measured by overnight cortisol secretion. When comparing different ICS in future studies, larger numbers of subjects will be necessary to better define dose-response relationships for both efficacy and side effects.
asthma, IC reduce the risk of subsequent ED visits. The repeat ED visits to any greater extent than did low-dose IC. ever, medium- and high-dose IC did not reduce the rate of asthma were compared between the IC users and nonusers using the Cox proportional hazard regression. and between the low-, medium-, and high-dose groups CI 0.39 – 0.68; high-dose: RR: 0.67; 95% CI: 0.47 – 0.94). However, medium- and high-dose IC did not reduce the rate of repeat ED visits to any greater extent than did low-dose IC. Results. Six hundred fifty-eight (50.9%) of the cohort were not prescribed IC. Of those who were prescribed IC, 241 (18.6%) received low-dose, 96 (7.4%) received medium-dose, and 122 (9.4%) received high-dose IC. Corticosteroid users were older and were more likely to have used other asthma medications during the first 100 days of follow-up than nonusers. Inhaled corticosteroid use was associated with a decreased risk (relative risk [RR]: 0.64; 95% confidence interval [CI]: 0.52 – 0.79) of a subsequent ED visit. After adjusting for age, sex, use of other asthma medications, comorbidity and hospitalization, IC users still had a significantly reduced risk of a repeat ED visit (RR: 0.55; 95% CI: 0.44 – 0.69). Patients in all 3 dose categories had significantly reduced risks of repeat ED visit (low-dose: RR: 0.52; 95% CI: 0.39 – 0.68; medium-dose: RR: 0.51; 95% CI 0.39 – 0.68; high-dose: RR: 0.67; 95% CI: 0.47 – 0.94). However, medium- and high-dose IC did not reduce the rate of repeat ED visits to any greater extent than did low-dose IC. Conclusions. In this cohort with recent ED visits for asthma, IC reduce the risk of subsequent ED visits. The results suggest that this risk reduction is similar across all 3 dose groups and thus high-dose IC may not afford any greater protection than low-dose IC.

Patients treated with fluticasone (n = 224) experienced greater mean increases in FEV1 (0.24 L vs 0.08 L; P < .001), morning PEF (30 L/min vs 6 L/min; P < .001), and evening PEF (23 L/min vs 5 L/min; P < .001) during the study than did those treated with zafirlukast (n = 216). Fluticasone-treated patients had significantly greater increases in the mean percentages of symptom-free days (22% vs 8%; P < .001), rescue-free days (23% vs 10%; P = .002), nights with uninterrupted sleep (<1% vs ~5%; P = .006), and fewer asthma exacerbations (1% vs 6%; P = .005). Fewer fluticasone-treated patients were withdrawn because of a lack of efficacy (2% vs 13%; P < .001).

Conclusions. Inhaled fluticasone was more effective than zafirlukast in maintaining or improving asthma control in patients with relatively stable asthma who were switched from low-dose inhaled corticosteroids.

Reviewer’s Comments. So the debate rages on. What’s different here is that the dose of fluticasone used was very low; only slightly greater than waving the inhaler over the patient’s head. On the other hand, we all see patients whose symptoms are extremely well-controlled with leukotriene receptor antagonists.

Elizabeth C. Matsui, MD
Robert A. Wood, MD
Baltimore, MD

LOW-DOSE INHALED CORTICOSTEROID THERAPY AND RISK OF EMERGENCY DEPARTMENT VISITS FOR ASTHMA

Sin DD, Man SFP. Arch Intern Med. 2002;162:1591–1595

Purpose of the Study. To determine if inhaled corticosteroid (IC) therapy prescribed after discharge from the emergency department (ED) prevents relapse of asthma exacerbations.

Study Population. Twelve hundred ninety-three residents of Alberta, Canada, who were enrolled in a government drug plan and visited an ED for asthma exacerbations between April 1, 1997, and March 31, 1999.

Methods. The study cohort was identified using the Ambulatory Care Classification System database. Patients 5 to 60 years of age who had at least 1 ED visit for asthma were included in the cohort if they were enrolled in the government-sponsored drug plan. The cohort was followed from the time of the first identified ED visit to the date of a subsequent ED visit. Information regarding prescribed asthma medications was obtained through the Alberta Blue Cross database. The study population was stratified into nonusers and users of IC as well as into low(<500 μg/day beclomethasone dipropionate or equivalent per day), medium- (501–1000 μg/day), and high-dose (>1000 μg/day) users. Rates of subsequent ED visits for asthma were compared between the IC users and nonusers and between the low-, medium-, and high-dose groups using the Cox proportional hazard regression.

Results. Patients treated with fluticasone (88 μg) had significantly greater in FEV1 (0.24 L vs 0.08 L; P < .001), peak expiratory flow (PEF), albuterol use, asthma symptoms, withdrawals attributable to lack of efficacy, and asthma exacerbations. Patients treated with fluticasone (n = 224) experienced greater mean increases in FEV1 (0.24 L vs 0.08 L; P < .001), morning PEF (30 L/min vs 6 L/min; P < .001), and evening PEF (23 L/min vs 5 L/min; P < .001) during the study than did those treated with zafirlukast (n = 216). Fluticasone-treated patients had significantly greater increases in the mean percentages of symptom-free days (22% vs 8%; P < .001), rescue-free days (23% vs 10%; P = .002), nights with uninterrupted sleep (<1% vs ~5%; P = .006), and fewer asthma exacerbations (1% vs 6%; P = .005). Fewer fluticasone-treated patients were withdrawn because of a lack of efficacy (2% vs 13%; P < .001).

Conclusions. Inhaled fluticasone was more effective than zafirlukast in maintaining or improving asthma control in patients with relatively stable asthma who were switched from low-dose inhaled corticosteroids.

Reviewer’s Comments. Although ICs have been shown to improve lung function and reduce symptoms, the effect on ED visits and hospitalizations has been more difficult to ascertain because of the relative rarity of these outcomes as compared with symptom-based outcomes. The authors circumvented this issue by selecting a cohort of patients who had visited an ED for asthma thereby enriching the study population for those with more severe disease. This study underscores the significant role ICs play in preventing ED visits for asthma and suggests that the next step is to define the optimal dose range so that the risk:benefit ratio can be minimized.

Elizabeth C. Matsui, MD
Robert A. Wood, MD
Baltimore, MD

EFFICACY AND SAFETY OF LOW-DOSE FLUTICASONE PROPIONATE COMPARED WITH ZAFIRLUKAST IN PATIENTS WITH PERSISTENT ASTHMA


Purpose of the Study. The study was designed to compare the efficacy and safety of fluticasone propionate and zafirlukast in patients with relatively stable persistent asthma who were previously treated with inhaled corticosteroids and short-acting β2-agonists.

Patient Population and Methods. A total of 440 patients (≥12 years of age) previously treated with inhaled corticosteroids (beclomethasone dipropionate or triamcinolone acetonide) and short-acting β2-agonists were included in this randomized, double-blind study. After an 8-day run-in period, patients were treated with fluticasone (88 μg) or zafirlukast (20 mg) twice daily for 6 weeks. Outcome measures included pulmonary function (forced expiratory volume in 1 second [FEV1], peak expiratory flow [PEF], albuterol use, asthma symptoms, withdrawals attributable to lack of efficacy, and asthma exacerbations.

Results. Patients treated with fluticasone (n = 224) experienced greater mean increases in FEV1 (0.24 L vs 0.08 L; P < .001), morning PEF (30 L/min vs 6 L/min; P < .001), and evening PEF (23 L/min vs 5 L/min; P < .001) during the study than did those treated with zafirlukast (n = 216). Fluticasone-treated patients had significantly greater increases in the mean percentages of symptom-free days (22% vs 8%; P < .001), rescue-free days (23% vs 10%; P = .002), nights with uninterrupted sleep (<1% vs ~5%; P = .006), and fewer asthma exacerbations (1% vs 6%; P = .005). Fewer fluticasone-treated patients were withdrawn because of a lack of efficacy (2% vs 13%; P < .001).

Conclusions. Inhaled fluticasone was more effective than zafirlukast in maintaining or improving asthma control in patients with relatively stable asthma who were switched from low-dose inhaled corticosteroids.

Reviewer’s Comments. So the debate rages on. What’s different here is that the dose of fluticasone used was very low; only slightly greater than waving the inhaler over the patient’s head. On the other hand, we all see patients whose symptoms are extremely well-controlled with leukotriene receptor antagonists.
## SIGNIFICANT VARIABILITY IN RESPONSE TO INHALED CORTICOSTEROIDS FOR PERSISTENT ASTHMA

James R. Banks  
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James R. Banks

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