for at least 4 weeks before enrollment. Participants in the study were also required to have experienced at least 1 exacerbation of asthma that required oral/parenteral corticosteroid treatment or hospitalization in the previous 12 months. The children were not receiving any long-acting β-receptor agonists.

Methods. This was a multicenter, double-blind, parallel-group study that involved 39 sites, all in Europe. After a 2-week run-in period, patients were randomized to receive either 100 μg or 200 μg of FP twice daily, delivered with a Diskus inhaler (GlaxoSmithKline, Research Triangle Park, NC). Clinic visits occurred at regular intervals, and daily symptom scores were maintained. Peak flow measures were recorded twice daily. The frequency of rescue medication use was noted. The primary outcome measure was the time to the first asthma exacerbation. Exacerbations were defined as a 20% decline in peak flow for 2 consecutive days, increased use of quick reliever medications (more than twice daily for 2 consecutive days), or the use of systemic corticosteroids.

Results. Demographic characteristics were well matched between the 2 treatment groups. The median dose of ICS at baseline for both groups was 800 μg/day (range: 200–1600 μg/day). A subgroup of children experienced severe asthma (defined as ICS usage of >800 μg/day) in each arm of the study and were studied separately. The risk ratio for an asthma exacerbation with 200 μg FP versus 100 μg FP was 0.85. The risk of experiencing an exacerbation at any time was reduced by 15% for patients receiving the higher dose (200 μg) of FP. This was not statistically significant. In the subgroup analysis, there was a much larger, significant, 33% reduction in the risk of experiencing an exacerbation at any time during the study. Secondary outcomes included improved peak flow measures in the 200 μg FP group. In both groups, symptoms were controlled and few side effects were experienced.

Conclusion. The use of FP at 200 μg twice daily may offer benefits, compared with a lower dose, especially among children with more severe asthma.

Reviewer’s Comments. ICSs, alone and in combination with other agents, are the preferred treatment for all forms of persistent asthma. Increasing the dose of the ICS is frequently performed to help provide control. However, dose-response studies of ICS use among adults have yielded conflicting results, and there have been very few such studies among children. The lack of a clear dose-response relationship may lead to reluctance in optimizing the dose to increase control. This study provides insight into a dose-response relationship for the ICS FP. A difficulty with this study and many like it involves the initial mixtures of ICSs and the reporting of the doses used at baseline. It is also important to note that the modality of drug delivery was the Diskus inhaler, which is not used as frequently as metered dose inhalers. ICS usage, especially among children, has been hampered by a paucity of data providing dose-response information. One dose for all forms of persistent asthma is clearly not the way to treat children. Children with moderate asthma do not benefit from higher doses, but those with more significant disease require higher doses to achieve control.

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SURVEY OF ADRENAL CRISIS ASSOCIATED WITH INHALED CORTICOSTEROIDS IN THE UNITED KINGDOM


Purpose of the Study. Rare reports of acute adrenal crisis associated with inhaled corticosteroid (ICS) use have been published. How commonly does this occur? To which patients? At what dose? With which drugs?

Study Population. Patients of pediatricians and endocrinologists in the United Kingdom were studied.

Methods. Questionnaires were sent to the physicians, asking whether they had encountered asthmatic patients with acute adrenal crises associated with ICS use. Physicians who responded positively completed a more detailed questionnaire. Patients receiving orally administered corticosteroids were excluded, and the case definition required both symptoms of an adrenal crisis and abnormal hypothalamic-pituitary-adrenal axis function test results.

Results. Thirty-three patients met the case definition criteria for acute adrenal crises developing in relation to ICS therapy, including 28 children (mean age: 6.4 years; range: 3.3–10 years) and 5 adults. Twenty-three children presented with acute hypoglycemia (13 with decreased levels of consciousness or coma, 9 with coma and convulsions, and 1 with coma, convulsions, and death). The remainder of the children and the majority of the adults presented with a more insidious onset of symptoms, such as lassitude, weakness, nausea, and dizziness. There were 37 total episodes of adrenal crisis among the 33 patients. There was no obvious precipitating cause in 24 cases (65%), there was evidence of infection (mostly respiratory) in 8 cases (21%), the ICS had been stopped, reduced, or changed to a lower-potency ICS in 4 cases (11%), and 1 episode (3%) occurred postoperatively. The vast majority of child and adult patients (30 of 33 patients) were treated with fluticasone; 1 child was treated with both fluticasone and budesonide, and 1 adult and 1 child were treated with beclomethasone. The mean dose of fluticasone among children was 980 μg/day (range: 500–2000 μg/day), and the mean dose among adults was 1380 μg/day (range: 1000–2000 μg/day). The mean durations of ICS treatment were 1.7 years for children and 3.3 years for adults.

Conclusions. The frequency of acute adrenal crises was greater than expected. Despite being the least prescribed and most recently introduced ICS, fluticasone was associated with 94% of the cases.

Reviewer’s Comments. Clearly ICSs can cause adrenal suppression and consequent adrenal crises. This appears to be especially true with fluticasone. The author of an editorial that accompanied this article explained that, although fluticasone has high first-pass hepatic metabolism, which decreases the systemic bioavailability of the swallowed portion of the dose, it also has high lipophilicity, allowing the pulmonary portion of the dose to be easily absorbed, which, “combined with its high receptor affinity and prolonged duration of activity, ensure systemic potency and accumulation.” Once again, we are reminded to use the lowest effective dose of ICS. Furthermore, when higher doses are required, perhaps an ICS other than fluticasone would be a better choice.

John M. Kelso, MD
San Diego, CA

VASCULAR COMPONENT OF AIRWAY REMODELING IN ASTHMA IS REDUCED BY HIGH DOSE OF FLUTICASONE


Purpose of the Study. To assess the effect of short-term treatment with high-dose (500 μg, twice daily) and low-dose (100 μg, twice daily) inhaled fluticasone propionate
(FP) on the vascular component of airway remodeling among asthmatic patients.

Study Population. Thirty nonsmoking patients with mild/moderate asthma and baseline forced expiratory volume in 1 second values of ≥70% of predicted values. All patients had experienced no asthma attacks in the previous 2 months and controlled their symptoms with inhaled salbutamol only. Patients did not receive corticosteroids in the 6 months before the study and had not experienced any respiratory infections for 4 weeks before the investigation.

Methods. This was a double-blind, randomized, parallel-group study, with patients receiving FP at either 500 or 100 µg twice daily, with a spacer device. Treatments were administered for 6 weeks, and patients were assessed in the clinic on 5 separate days. Symptom diaries were maintained, spirometry and methacholine challenges were performed, and fiber-optic bronchoscopies were undertaken at specific time points during the investigation. Healthy volunteers underwent bronchoscopies for comparison.

Results. Eighteen of 30 patients completed the study protocol, and adequate paired biopsy material for immunostaining was obtained for 16 patients, 8 in the group that received 500 µg of FP twice daily and 8 in the group that received 100 µg of FP twice daily. At baseline, patients with asthma differed significantly from the healthy volunteers with respect to the number of vessels and the vascular area. Among the asthmatic patients, the number of vessels was correlated with vascular area ($P < .01$) and the number of mast cells ($P < .01$). Bronchial responsiveness to methacholine, asthma symptom scores, and numbers of inflammatory cells decreased significantly after both low- and high-dose FP ($P < .05$); however, basement membrane thickness decreased only after high-dose FP ($P < .05$).

Conclusions. The results from this investigation demonstrated that, among patients with mild/moderate asthma, a high dose of inhaled FP, administered for 6 weeks, could significantly affect airway remodeling by reducing both submucosal vascularity and basement membrane thickness.

Reviewer’s Comments. The authors claim that this is the first published evidence that short-term treatment with high-dose FP significantly reduced the vascular component of airway remodeling among patients with mild/moderate asthma. The small number of subjects who completed the investigation and the short time of medication administration seem to limit the overall conclusions regarding the effects of high-dose FP on airway remodeling. These data could have significant clinical implications for the use of higher doses of inhaled corticosteroids in the ongoing treatment of patients with mild/moderate asthma, who might be receiving lower doses of these medications to control their disease.

JOHN M. JAMES, MD
Fort Collins, CO

LEUKOTRIENE ANTAGONIST THERAPY
A RANDOMIZED, CONTROLLED TRIAL OF INTRAVENOUS MONTELUKAST IN ACUTE ASTHMA

Camargo CA, Smithline HA, Malice MP, Green SA, Reiss TF. Am J Respir Crit Care Med. 2003;167:528–533

Purpose of the Study. To determine whether the addition of intravenously administered montelukast to standard therapy for patients with acute asthma would cause rapid improvement in airflow obstruction, as well as improvement in clinically relevant outcomes such as hospitalization or prolonged or additional antiasthma therapy.

Study Population. Patients, 15 to 54 years of age, who were presenting with acute asthma were screened for enrollment. Requirements included a history of asthma for ≥1 year, a history of tobacco use of <10 pack-years, and no concomitant therapy with systemic corticosteroids, leukotriene modifiers, anticholinergic agents, or long-acting β-agonist bronchodilators.

Methods. This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study with a screening period and an active study period. Two doses of intravenously administered montelukast (7 and 14 mg) or matching placebo were evaluated. Serial spirometric assessments were performed at 10, 20, 40, 60, and 120 minutes and 3 and 6 hours after intravenous study drug infusion.

Results. A total of 201 patients were randomized, and complete data were available for analysis for 194. During the screening period, there was no difference in forced expiratory volume in 1 second responses between the 7-mg and 14-mg montelukast groups. Montelukast improved forced expiratory volume in 1 second values in the first 20 minutes after intravenous administration (mean percentage change from prerandomization baseline value: 14.8% and 30.6% for the pooled montelukast and placebo treatment groups, respectively; $P = .007$). This benefit was observed at 10 minutes and for 2 hours after intravenous therapy. Patients treated with montelukast tended to receive less β-agonist and to experience fewer treatment failures, compared with patients receiving placebo. The study drug and placebo were similarly tolerated, and no unexpected adverse effects were observed.

Conclusions. Intravenously administered montelukast, in addition to standard therapy, provided rapid benefits and was well tolerated among patients with acute asthma.

Reviewer’s Comments. A substantial proportion of asthma exacerbations continue to require prolonged management in an emergency department setting or hospitalization. In addition to standard asthma therapies, interventions involving inhaled ipratropium, intravenously administered magnesium, and inhaled helium/oxygen mixtures have been investigated. Intravenously administered montelukast, as an adjunctive therapy for these patients, may provide added benefits with current treatment options. These results must be confirmed and, in future studies, montelukast use among pediatric patients <15 years of age should be investigated.

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EFFECTS OF MONTELUKAST AND BECLOMETHASONE ON AIRWAY FUNCTION AND ASTHMA CONTROL


Purpose of the Study. The primary objective of asthma therapy is the maintenance of asthma control, and the most common measures of such control in clinical studies reflect pulmonary function; forced expiratory volume in 1 second (FEV1) is often used. The authors sought to use a different parameter, ie, days of asthma control, as the primary measure, because observations regarding the need for both rescue medications and unscheduled asthma-related health care are central to perceived wellness.

Study Population. This multicenter study involved 782 individuals, ≥15 years of age, with a ≥1-year history of moderate persistent asthma (baseline FEV1; 50–85% of predicted values) but no controller therapy at the time of...
VASCULAR COMPONENT OF AIRWAY REMODELING IN ASTHMA IS REDUCED BY HIGH DOSE OF FLUTICASONE

John M. James

Pediatrics 2004;114;546

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John M. James

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