study, global evaluations of the simplicity of asthma management and child health care status were obtained from caregivers and physicians.

Results. Improvements from baseline values in domain-specific (activities and emotional function) and total quality of life scores were greater at each time point (weeks 8, 28, and 52) for caregivers of patients treated with budesonide, compared with caregivers of patients treated with cromolyn sodium. Only the budesonide group met the criterion of a clinically important improvement (≥0.5-unit change) in all quality of life domains by week 8, which was maintained at weeks 28 and 52. Budesonide resulted in greater caregiver satisfaction, treatment convenience, ease of use, and compliance, compared with cromolyn sodium. Therefore, 90.7% of caregivers in the budesonide group were completely or very satisfied, compared with 53.4% in the cromolyn sodium group. More than one-half (54.6%) of caregivers in the budesonide group rated budesonide highly or very convenient, compared with 23% for cromolyn sodium; 77% rated budesonide extremely or very easy to use, compared with 47% for cromolyn. Adherence with daily medication regimens was reported for 76% of children in the budesonide group, compared with 57% in the cromolyn sodium group. Child health status showed improvements from baseline values for both groups at weeks 8, 28, and 52. There was a trend for these improvements to be superior in the budesonide group. In addition, budesonide was superior to cromolyn sodium in caregiver and physician global assessments.

Conclusions. Budesonide inhalation suspension improved the quality of life for caregivers of children with asthma. Caregivers of children treated with budesonide reported significantly fewer limitations in daily activities and emotional functioning, compared with caregivers of children treated with cromolyn sodium nebulizer solution. Children treated with budesonide inhalation suspension and cromolyn sodium experienced improvements in health status. Treatment with budesonide inhalation suspension resulted in significantly lower mean rates of asthma exacerbations, significantly longer times to first asthma exacerbation, significantly longer times to first additional use of chronic asthma therapy, and significant improvements in asthma symptom scores and breakthrough medication use, compared with cromolyn sodium therapy. Safety profiles were similar for the 2 treatment groups. Budesonide inhalation suspension was associated with significantly greater caregiver satisfaction, convenience, ease of use, and compliance, compared with cromolyn sodium nebulizer solution.

Reviewer’s Comments. This was a nice study but the results are certainly not surprising. How many of us would have predicted that cromolyn would prove superior to an inhaled corticosteroid for caregivers of patients treated with budesonide? A randomized, double-blind trial.


Purpose of the Study. To determine whether treatment with low-dose inhaled budesonide would prevent severe asthma-related events and accelerated lung function decline among patients with recent-onset, mild, persistent asthma.

Study Population. A group of 7241 patients, 5 to 66 years of age, with mild asthma symptoms for 3 months to 2 years, were recruited from 499 sites in 32 countries.

Methods. Patients were randomly allocated to receive 400 μg of budesonide (200 μg for patients <11 years of age) or placebo once daily. The primary outcome measure was time to the first severe asthma-related event (admission, emergency treatment, or death), analyzed with an intent-to-treat approach. Follow-up visits, with spirometry and adverse event monitoring, occurred at 6 and 12 weeks after randomization and then every 3 months for 3 years. Patients recorded asthma-related events between visits. Changes in medication regimens, including the addition of inhaled corticosteroids, were allowed if considered clinically necessary.

Results. Budesonide reduced the risk of severe asthma-related events by 44% (hazard ratio: 0.56; 95% confidence interval: 0.45–0.71; P < .0001) and prolonged the time to the first asthma-related event. Budesonide-treated patients experienced significantly fewer severe asthma-related events, life-threatening exacerbations, days with symptoms, and courses of inhaled or systemic corticosteroids. The improvements in postbronchodilator forced expiratory volume in 1 second (FEV1) after 3 years were more pronounced among adults than among children (P = .004), although the improvements in postbronchodilator FEV1 after 1 year and in prebronchodilator FEV1 were similar.

Surprisingly, budesonide did not improve postbronchodilator FEV1 among adolescent patients. Children in the budesonide group exhibited slowed growth (mean height difference: −0.43 cm/year; 95% confidence interval: −0.54 to −0.32 cm/year; P < .0001) to a lesser degree with each successive year.

Conclusions. Long-term, once-daily treatment with low-dose budesonide decreased the risk of severe exacerbations and improved asthma control among patients with mild persistent asthma of recent onset.

Reviewers’ Comments. Data on asthma-related events, symptoms, and medication use were not reported separately for the 2 pediatric age groups included in the study (5–10 years and 11–17 years). However, the morbidity associated with mild persistent asthma and the improvements in prebronchodilator FEV1 with budesonide treatment observed in this study suggest that children with mild persistent asthma may benefit from budesonide treatment early in the course of their disease. As always, the benefits of inhaled corticosteroids among children must be weighed against the potential side effect of mild growth delay.
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 (68%), 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 (12%), 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.

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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
FLUTICASONE PROPIONATE IN ASTHMA: A LONG-TERM, DOSE-COMPARISON STUDY
Frederick E. Leickly
Pediatrics 2004;114:545

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FLUTICASONE PROPIONATE IN ASTHMA: A LONG-TERM, DOSE-COMPARISON STUDY
Frederick E. Leickly
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