For the second part of the study, samples of MDIs (Flovent, Serevent, albuterol, and Qvar) were obtained from the manufacturers and studied in the laboratory. They evaluated the MDIs to determine how many actuations could be emitted and obtained weights during the process. They evaluated the usefulness of floating the MDIs in water to determine if they were full or empty, as has been suggested in the past for tracking the content of MDIs.

Results. The survey revealed that 72% of subjects determined that their MDI was empty when they could no longer hear a sound when actuated. Another 20% said they replaced it when it was “old” without giving specific details, although most said “within a month or so” or “after a while.” Four patients stated that they were told to float their MDI in water to determine if it was full (sinks to the bottom) or empty (floats), although none had actually done it. The majority (78%) said that they knew they were supposed to shake the MDI before using it, but only half shook the MDI when their technique was evaluated later. In the laboratory, MDIs had similar flotation patterns, with mean flotation angles of 27.6 to 31.7° when empty. Water obstructed the valve or collected near the valve during this procedure 27% of the time. The chlorofluorocarbon inhalers (Flovent, Serevent, and albuterol) had a mean of 86% more audible puffs and Qvar 54% more than the stated manufacturer actuations. Shaking the MDI before actuation increased the doses available for the chlorofluorocarbon inhalers significantly.

Conclusions. Most patients studied did not know how to tell if their MDI was empty, and many did not shake the MDI before actuation, which can limit the amount of drug delivered. These results may in part explain the poor adherence with refills for MDIs, because patients may not realize that they are not receiving a full dose of active drug (because all of the MDIs studied had significantly more actuations than noted on the canister), which the authors termed “pseudo-adherence.” The only way to truly track the number of remaining doses in MDIs is to count each dose. Most MDIs will emit more drug doses if the device is shaken before actuation. Floating MDIs in water is not accurate for assessing remaining doses and often will clog the valve.

Reviewer’s Comments. This article demonstrates one of the limitations of MDIs in the inability of patients to accurately assess when they are empty without counting each dose. It illustrates the need for better devices to track doses remaining (an advantage of dry-powder inhalers).

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MEDICAL THERAPIES

DOUBLING THE DOSE OF INHALED CORTICOSTEROID TO PREVENT ASTHMA EXACERBATIONS: RANDOMISED CONTROLLED TRIAL


Purpose of the Study. The investigators proposed to determine if doubling the dose of inhaled corticosteroids (ICSs) to treat deteriorating asthma control reduced the need for starting oral corticosteroids.

Study Population. The study population included 390 nonsmoking individuals aged ≥16 years, with stable asthma requiring regular ICS use and a course of oral corticosteroids or doubled dose of ICS in the past 12 months.

Methods. Participants recorded their daily morning peak flow and daytime symptom score on a 4-point scale. After a 2- to 4-week run-in period, an independent pharmacist randomly allocated participants to receive active or placebo study inhalers, matched to their usual ICS, inhaler type, and dose. Patients were stratified into low-to-moderate-dose (equivalent of beclomethasone dipropionate, ≤1000 µg/day) and high-dose groups based on their dose of ICS at study entry. They continued their usual ICS and added the study inhaler for 14 days if their morning peak flow fell by 15% or their daytime symptom score increased by 1 point compared with the run-in period means. Participants took 10 days of oral prednisolone (30 mg/day) if their peak flow fell 40% from the mean run-in value or if their asthma control deteriorated to where they would usually start oral corticosteroids.

Results. Of the 192 participants in the active-inhaler group, 110 started their study inhaler (88 in the low-to-moderate–dose group), and of the 198 participants in the placebo-inhaler group, 97 started their study inhaler (74 in the low-to-moderate-dose group). Twenty-two participants (11%) in the active-inhaler group and 24 (12%) in the placebo group started prednisolone, for a risk ratio of 0.95 (95% confidence interval [CI]: 0.55, 1.64). Prednisolone was started because of a 40% peak-flow drop in 6 participants in the active group and 4 controls. In the low-to-moderate-dose group, 13 of 158 in the active group and 17 of 162 in the placebo group started prednisolone, for a risk ratio of 0.8 (95% CI: 0.4, 1.6). Doubling the dose of ICS led to a small reduction in the mean maximum fall of peak flow but did not change the time taken for peak flow or symptom scores to return to the baseline.

Conclusions. These findings do not support the effectiveness of doubling the dose of ICS to prevent the need for oral corticosteroids during asthma exacerbations.

Reviewers’ Comments. This randomized, control trial questions a recommendation that is part of many asthma-exacerbation–management plans. Although the results of at least 1 other study support these findings, a longer study following individuals beyond their first need for oral corticosteroids, involving larger increases as well as doubling of ICS doses, evaluating objective measures such as peak flow and symptom scores in all patients at the time of starting oral corticosteroids, and including younger patients and those with milder disease may reveal a benefit to increasing the ICS dose in some situations and subgroups of asthmatics. However, if this study’s findings can be consistently replicated in children, we may need to modify our recommendations for early management of asthma exacerbations.

Elizor Simons, MD
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COST-EFFECTIVENESS ANALYSIS OF EARLY INTERVENTION WITH BUDESONIDE IN MILD PERSISTENT ASTHMA


Purpose of the Study. These investigators analyzed cost-effectiveness of a commonly prescribed inhaled corticosteroid from the perspectives of both direct and indirect costs.

Study Population. Patients aged 5 to 66 years from 32 countries were enrolled in the Inhaled Steroid as Regular Therapy in Early Asthma (START) study. Patients were eligible if they were diagnosed with asthma within 2 years of randomization and lacked significant comorbidity.
Methods. START was a randomized, 3-year controlled trial of budesonide versus usual asthma therapy in early-onset asthma among 7165 subjects. Three age groups (5–10, 11–17, and ≥18 years) were studied separately and collectively. All patients were allowed to receive other asthma treatments including inhaled and oral corticosteroids, according to local practice. The cost-effectiveness evaluation of the START study was conducted primarily from the health care payer perspective (direct costs) and secondarily from the societal perspective (indirect costs). The primary outcome measure for effectiveness was the number of symptom-free days. This parameter was defined as a complete 24-hour period with no asthma symptoms and has been recognized as a clinical outcome with relevance to patients, providers, and other decision-makers. Unit costs of the health care–resource items such as hospital days, emergency department visits, physician and nurse visits, and telephone contacts. These costs were derived from a large medical- and pharmacy-claims database. The costs for school and work losses were estimated by using standard methods.

Results. Compared with usual therapy, patients receiving budesonide had 14.1 more symptom-free days per year, fewer hospital days and emergency department visits, and less school and work absence. Budesonide added $0.41 per day to direct costs. After considering indirect cost offsets related to lower school and work absence, the net expense dropped to $0.14 per day. Early intervention was most effective and cost saving in the youngest age group.

Conclusion. Long-term treatment with budesonide seems to be cost-effective in patients with mild persistent asthma of recent onset.

Reviewers’ Comments. The health care system in the United States is only now beginning to experiment with methods that will raise awareness of direct health costs for patients/consumers. Although $0.14 per day for better asthma control sounds like a great value, any comments that we currently make to patients or parents regarding cost-effectiveness of a given therapy usually fall on deaf ears. At the present time, we can better appeal to them by touting the improved quality of life associated with fewer days with symptoms, fewer asthma attacks, and lowered hospitalization risk and also by making it clear that the risks of disease far outweigh the risks of usual doses of ICS. This latter fact, so obvious to us, needs continued restating to parents of children with asthma.

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EFFECTS OF SHORT-TERM TREATMENT WITH INHALED CORTICOSTEROID ON AIRWAY WALL THICKENING IN ASTHMA


Purpose of the Study. To examine the effect of inhaled corticosteroids (ICSs) on thickening of the asthmatic airway wall as measured by computed tomography (CT), pulmonary function, and serum levels of eosinophilic cationic protein (ECP).

Study Population. Fifty-one patients (mean age: 54.4 ± 13.8 years) with persistent asthma and 28 healthy controls (mean age: 48.1 ± 15.9 years).

Methods. Patients fulfilled American Thoracic Society criteria for asthma, and none had ever received systemic or inhaled steroids, cromones, or antileukotriene agents. Exclusion criteria included asthma exacerbations or respiratory tract infections within 8 weeks before enrollment or a history of smoking. Cross-sectional, thin-section CT images of the right upper lobe apical bronchus were obtained before and after treatment. Using an enlarged image on a workstation, luminal and total airway areas (in millimeters squared) were calculated after manually tracing the internal and external perimeters of the airway. The airway wall area and airway wall area as a percentage of total wall area were used as indices of airway wall thickness. In asthmatic patients, CT, blood sampling for ECP, and pulmonary function tests were performed before and after treatment with beclomethasone dipropionate (400 µg) administered twice daily for 12 weeks.

Results. Before treatment, airway wall thickness was greater in asthma patients than controls (P < .0001). After treatment, airway wall thickness decreased by 11% (P < .0001) but remained high (P < .0001 vs control). Serum ECP levels decreased significantly after treatment (P < .001). Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC improved significantly after treatment, but the values remained lower than in controls. The decrease in wall thickness was associated with a decrease in the level of ECP (r = 0.39; P = .009) and an increase in the FEV1 (r = 0.45; P = .003) and was inversely related to disease duration at entry (r = −0.38; P = .009). Posttreatment wall thickness was related to disease duration (r = 0.45; P = .003) and remaining airflow obstruction.

Conclusions. In patients with persistent asthma, treatment with inhaled beclomethasone for 12 weeks significantly reduced airway wall thickness as assessed by CT. Airway wall thickness remained significantly greater than in controls. ICSs had less of an effect on airway wall thickening in patients with long-standing asthma.

Reviewer’s Comments. This study raises questions. Is the reduction in airway wall thickness indicative of reductions in airway inflammation? Additional studies (eg, with airway biopsy specimens) are needed to confirm this. Would earlier intervention with ICSs result in normalization of airway wall thickness? This is a particularly important question for those who treat children with asthma.

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EFFECTS OF INHALED FLUTICASONE PROПIONATE IN CHILDREN LESS THAN 2 YEARS OLD WITH RECURRENT WHEEZING


Purpose of the Study. To evaluate the efficacy and safety of inhaled fluticasone propionate in children <2 years old with a history of recurrent wheezing and risk factors for asthma persisting into late childhood.

Study Population. Subjects were 30 children, aged 7 to 24 months, with ≥3 episodes of wheeze responsive to bronchodilators and a family history of asthma, allergic rhinitis, or eczema.

Methods. In this double-blind study, subjects were randomized to receive either inhaled 50 µg of fluticasone twice daily, 125 µg of fluticasone twice daily, or placebo for 6 months. Medication was administered with a metered-dose inhaler using an Aerohamcer and mask. Efficacy end points included number of wheezing episodes and number of days on which albuterol was required. Parents were trained to record these clinical symptoms and medication use on a chart. Subjects were seen monthly to assess proper use of the medication device and evaluate daily symptom...
**Cost-Effectiveness Analysis of Early Intervention With Budesonide in Mild Persistent Asthma**

James R. Banks and Timothy Andrews

*Pediatrics* 2005;116;564

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