In children, as in adults, airway inflammation is a characteristic feature of asthma (1). Inhaled glucocorticoids decrease symptoms and exacerbations, decrease the need for rescue bronchodilator medications, improve airway patency and reduce airway hyperresponsiveness. When administered in the lowest doses that prevent symptoms and eliminate the need for supplemental courses of oral glucocorticoids, they are unlikely to cause clinically important systemic adverse events. Inhaled glucocorticoids have a favourable risk to benefit ratio in this population.

**Key Words:** Asthma, Beclomethasone dipropionate, Budesonide, Children, Fluticasone propionate, Growth, Inhaled glucocorticoids

**BENEFITS**

Inhaled glucocorticoids are remarkably effective in controlling inflammation in the airways. They reduce the number and activation of lymphocytes, macrophages, mast cells and eosinophils. They also inhibit microvascular leakage induced by inflammatory mediators, restore disrupted epithelium, normalize the ciliated cell to goblet cell ratio, decrease mucous secretion and restore responsiveness to beta-adrenergic bronchodilators. Most important, they down-regulate the production and release of proinflammatory cytokines and other proteins (2).

Children using inhaled glucocorticoids regularly for persistent asthma treatment have significantly reduced hospitalizations (3), symptoms (4-15), need for rescue beta2-agonist medication and airway hyperresponsiveness, as well as im-
proved pulmonary function. The improvement in symptoms, rescue medication use, peak expiratory flow, and forced expiratory volume in 1 s is dose-related (4). All study medications were administered using a dry powder inhaler (Diskhaler, GlaxoWellcome), followed by rinsing and expectorating. The primary outcome measure, airway hyperresponsiveness to methacholine, was evaluated before and after three, six, nine and 12 months of treatment. Peak expiratory flow, rescue medication use, symptoms and adverse effects were recorded twice daily on a diary card. All outcome measures were standardized among the centres. Beclomethasone dipropionate had a significantly better effect than salmeterol or placebo in reducing airway hyperreactivity, but this was lost two weeks after treatment was discontinued (shown). Salmeterol did not increase airway hyperreactivity or cause rebound airway hyperreactivity. Beclomethasone dipropionate and salmeterol both improved airway patency significantly, as seen by spirometry and twice-daily monitoring of peak expiratory flows, but beclomethasone dipropionate was significantly better than salmeterol at decreasing symptoms, decreasing rescue beta2-agonist use and improving quality of life (not shown). PC20 Provocation concentration of methacholine to cause a fall in FEV1 of 20% Adapted with permission from reference 10.

Figure 1) In a randomized, double-blind, placebo controlled, parallel group, one-year, multicentre study in 241 glucocorticoid-naive children, age 9.3±2.4 years, beclomethasone dipropionate (BDP) 200 µg bid was compared with salmeterol 50 µg bid. All study medications were administered using a dry powder inhaler (Diskhaler, GlaxoWellcome), followed by rinsing and expectorating. The primary outcome measure, airway hyperresponsiveness to methacholine, was evaluated before and after three, six, nine and 12 months of treatment. Peak expiratory flow, rescue medication use, symptoms and adverse effects were recorded twice daily on a diary card. All outcome measures were standardized among the centres. Beclomethasone dipropionate had a significantly better effect than salmeterol or placebo in reducing airway hyperreactivity, but this was lost two weeks after treatment was discontinued (shown). Salmeterol did not increase airway hyperreactivity or cause rebound airway hyperreactivity. Beclomethasone dipropionate and salmeterol both improved airway patency significantly, as seen by spirometry and twice-daily monitoring of peak expiratory flows, but beclomethasone dipropionate was significantly better than salmeterol at decreasing symptoms, decreasing rescue beta2-agonist use and improving quality of life (not shown). PC20 Provocation concentration of methacholine to cause a fall in FEV1 of 20% Adapted with permission from reference 10.

Figure 2) In the study described in Figure 1, during months 1 through 12, height increased by 5.40 cm in the salmeterol-treated children (P=0.004 versus beclomethasone), 5.04 cm in the placebo treated children (P=0.018 versus beclomethasone) and 3.96 cm in the beclomethasone-treated children.

not immediate. Significant improvement in symptoms may occur within weeks, but maximum improvement takes longer. Airway hyperresponsiveness continues to decrease even after many months of regular treatment (7-10) (Figure 1).

Tachyphylaxis to long term inhaled glucocorticoid treatment does not occur. Permanent remission is uncommon. The effectiveness of inhaled glucocorticoid treatment begins to disappear within weeks of discontinuing the medication (10,17).

The comparative efficacy of inhaled glucocorticoids has not been adequately studied in children. Delivery systems differ markedly in their efficiency (18). A glucocorticoid administered using the new hydrofluoroalkane propellants has enhanced deposition in the peripheral airways compared with the same glucocorticoid administered using chlorofluorocarbon propellants, and its benefit to risk ratio needs to be redefined (19).

Persistent asthma in children generally responds extremely well to inhaled glucocorticoid treatment. If it does not, the following issues should be considered: poor compliance, psychosocial problems, or missed diagnosis of vocal cord dysfunction, hyperventilation syndrome, gastroesophageal reflux or sinusitis. Rarely, a lack of response is due to persistent inflammation, abnormal glucocorticoid pharmacokinetics or glucocorticoid resistance (20).

**RISKS**

Local adverse effects of inhaled glucocorticoid treatment include oropharyngeal candidiasis, hoarseness, throat irritation and coughing. These problems are not usually troublesome and seldom necessitate discontinuation of treatment (20).

Inhaled glucocorticoids have the potential to reduce linear growth in children (9-12,21-25). Height measurements must be interpreted carefully because persistent asthma itself may
Inhaled glucocorticoids in asthma

Results of five stadiometer measurements of adult height, adjusted for sex and parental height, was analyzed. One hundred and fifty-three patients with asthma (mean age at onset 6.1 ± 4.8 years), and 153 age- and sex-matched nonasthmatic subjects were studied. The adult height of patients with asthma (mean age at measurement 25.7 ± 5.2 years) did not differ significantly from the adult height of nonasthmatic subjects. The adult height of asthmatic children treated with glucocorticoids did not differ significantly from the adult height of patients not treated with glucocorticoids. The figures show the difference between the measured adult height of patients with asthma and midparental height versus logarithm of cumulative potency-adjusted steroid exposure from onset of asthma to age of adult height (17 years of age for girls, and 19 years of age for boys) (Adapted with permission from reference 29).

Table 1

Inhaled glucocorticoids: Enhancing the margin of safety

- Recommend the lowest dose that prevents symptoms
- Monitor height velocity and pulmonary function regularly
- Reduce systemic absorption by teaching children to rinse and expectorate after inhalation*
- If a pressurized metered-dose inhaler is used, add a spacer device to reduce oral deposition*

*Especially important for beclomethasone dipropionate, which has little inactivation by first-pass metabolism

In addition to measuring linear growth, bone metabolism may be assessed using biochemical markers of osteoblast and osteoclast activity or by using imaging techniques such as dual-energy x-ray absorptiometry to measure cortical and trabecular bone mineral density (30).

Abnormalities in tests of hypothalamic-pituitary-adrenal (HPA) axis function vary with the inhaled glucocorticoid administered, dose, delivery system and duration of treatment. At a total daily beclomethasone dipropionate dose of 400 μg/day or greater, tests of HPA axis function, such as single morning serum cortisol measurement or HPA response to metyrapone stimulation, are normal. Other more sensitive tests, such as serial early morning cortisol measurements or the area under the curve of 24-h serum or 24-h urine free cortisol measurements, may show evidence of HPA axis suppression (20,31,32). The clinical significance of these biochemical abnormalities is not fully understood. Adrenal insufficiency during or after discontinuing, inhaled glucocorticoid treatment is extremely rare.

Compared with oral glucocorticoids, inhaled glucocorticoids are much less likely to cause any systemic adverse effects in children, not only linear growth suppression or HPA axis suppression as described above, but also posterior subcapsular cataracts, skin thinning or bruising, disseminated or opportunistic infection, or adverse central nervous system effects (20,33,34). The risks of inhaled glucocorticoid treatment, which are already low, can be minimized further (Table 1).

ALTERNATIVES

In children with persistent asthma, available pharmacological alternatives such as beta2-adrenergic agonists, methylxanthines, antiallergics and antihistamines (7-11,27,35-37) are less effective than inhaled glucocorticoids. Long term comparative studies of cysteinyl leukotriene antagonists (38) and of immune modulators (39,40) with inhaled glucocorticoids in children are awaited with interest.

SUMMARY

Although inhaled glucocorticoids do not cure asthma, they are the most efficacious medications available for reducing morbidity in this increasingly prevalent disorder. In-
haled glucocorticoid treatment has allowed most children, even those with severe persistent disease, to be symptom free. The benefits of inhaled glucocorticoids are worth the risks.

REFERENCES