In children, as in adults, airway inflammation is a characteristic feature of asthma (1). Inhaled glucocorticoids are the most effective medications available for preventing asthma symptoms, reducing the frequency of acute asthma exacerbations and preventing hospitalizations for asthma. When these medications were introduced more than two decades ago, they were recommended only for patients with severe persistent asthma, in whom they replaced oral glucocorticoids. Now, they are used for the treatment of mild or moderate persistent asthma, and in many countries, even in very young children, they have become the first-line treatment. In the present article, inhaled glucocorticoid use in children is briefly reviewed with regard to efficacy (when to start them, dose-response relationships, when to stop them), and safety, with special consideration of their effect on growth.

**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 1 in 1s is dose-related (4). In children with mild or moderate asthma, the beneficial effects occur with a total beclomethasone dipropionate dose of 400 μg/day or less, a budesonide dose of 400 μg/day or less, or a fluticasone propionate dose of 200 μg/day or less. The doses needed to normalize airway responsiveness to bronchoconstricting agents and to eliminate exercise-induced bronchospasm are generally higher than those needed to reduce symptoms at rest and to improve baseline pulmonary function (5).

An open study demonstrated that inhaled glucocorticoid treatment may be more effective if started early during the course of childhood asthma rather than after symptoms have been present for several years (6). Unfortunately, accurate diagnosis of asthma remains difficult during the first few years of life; many infants and toddlers with wheeze, cough and shortness of breath do not have asthma (16) and will be overtreated if inhaled glucocorticoids are recommended routinely for all ‘little wheezers’.

The onset of action of inhaled glucocorticoids in asthma is 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: 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

Inhaled glucocorticoids in asthma

result in delayed onset of puberty and preadolescent deceleration of height increase. Studies in which a delay in short term growth is assessed over weeks using knemometry to measure lower leg length must be interpreted with particular caution because their predictive value for long term growth is unknown (21).

There is evidence from prospective, randomized, double-blind studies, several of which are placebo-controlled (10,12) (Figure 2), that intermediate term growth, defined as growth monitored for at least six months, is delayed by equivalent doses of other inhaled glucocorticoids in children with mild to moderate asthma (9-12,21-24). The delay appears soon after starting treatment, is not progressive and is not necessarily associated with adrenal insufficiency (25). A five-year, placebo controlled, double-blind study of budesonide is in progress (26). Studies of fluticasone propionate 100 µg/day or 200 µg/day suggest that at these low doses it does not affect growth in most children (27,28).

There is no information from prospective randomized, double-blind studies about the effect of inhaled glucocorticoids on long term growth from infancy to adulthood, although a recent retrospective study suggests that despite glucocorticoid use, normal adult height is reached (29) (Figure 3).

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 cysteinyi 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

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