Inhaled glucocorticoids in children: A favourable therapeutic index

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In children with persistent asthma, 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*

Les glucocorticoïdes en inhalation chez les enfants

RÉSUMÉ : Chez les enfants atteints d'asthme persistant, les glucocorticoïdes en inhalation diminuent les symptômes et les exacerbations, réduisent le besoin de médicaments bronchodilatateurs de secours, améliorent la perméabilité des voies respiratoires et diminuent l'hyperréactivité bronchique. Quand ils sont administrés aux doses les plus faibles qui préviennent les symptômes et qui éliminent le besoin d'administrer en plus des glucocorticoïdes par voie orale, il est peu probable qu'ils causent des événements systémiques indésirables et d'une importance clinique. Les glucocorticoïdes en inhalation ont un rapport risque:bénéfice favorable dans cette population.

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.

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 beta$_2$-agonist medication and airway hyperresponsiveness, as well as im-

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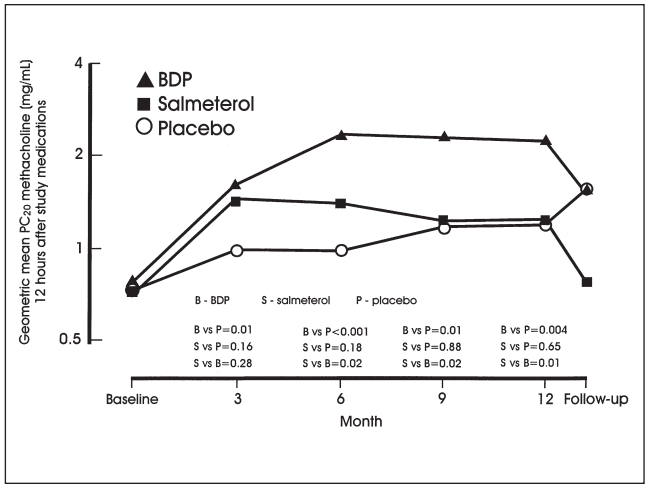

Figure 1) *In a randomized, double-blind, placebo controlled, parallel group, one-year, multicentre study in 241 glucocorticoid-naive children, age 9.3±2.4 years, beclomethasone dipropionate (BDP) 200 µg bid was compared with salmeterol 50 µg bid. All study medications were administered using a dry powder 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 beta$_2$-agonist use and improving quality of life (not shown). PC_{20} Provocation concentration of methacholine to cause a fall in FEV_1 of 20% Adapted with permission from reference 10*

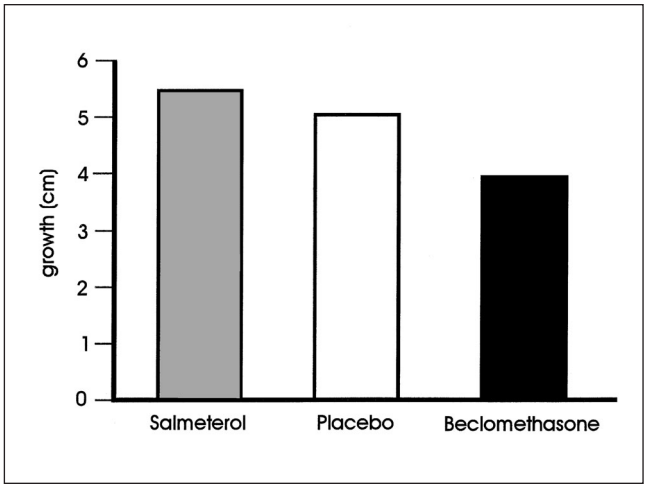

Figure 2) *In the study described in Figure 1, during months 1 through 12, height increased by 5.40 cm in the salmeterol-treated children (P=0.004 versus beclomethasone), 5.04 cm in the placebo treated children (P=0.018 versus beclomethasone) and 3.96 cm in the beclomethasone-treated children*

proved pulmonary function. The improvement in symptoms, rescue medication use, peak expiratory flow, and forced expiratory volume in 1 s 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

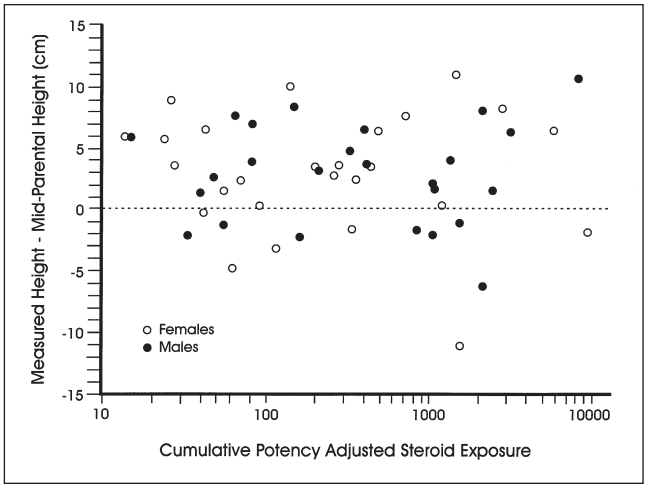

Figure 3) *This study was designed to compare the attained adult height of children with asthma with the attained adult height of non asthmatic children, and to compare the attained adult height of asthmatic children treated with glucocorticoids with that of asthmatic children who did not receive glucocorticoids. Glucocorticoid exposure was assessed from medical records retrospectively. The mean 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 figure shows the difference between the measured adult height of patients with asthma and midparental height versus logarithm of cumulative potency-adjusted glucocorticoids 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)*

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 beclomethasone dipropionate 400 µg/day or greater and possibly 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).

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 beta$_2$-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

1. Cutz E, Levison H, Cooper DM. Ultrastructure of airways in children with asthma. Histopathology 1978;2:407-21.
2. Barnes PJ. Glucocorticoids. In: Kay AB, ed. Allergy and Allergic Diseases. London: Blackwell Science Ltd, 1997:619-41.
3. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. JAMA 1997;277:887-91.
4. Shapiro G, Bronsky EA, LaForce CF, et al. Dose-related efficacy of budesonide administered via a dry powder inhaler in the treatment of children with moderate to severe persistent asthma. J Pediatr 1998;132:976-82.
5. Pedersen S, Hansen OR. Budesonide treatment of moderate and severe asthma in children: a dose-response study. J Allergy Clin Immunol 1995;95:29-33.
6. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Resp Med 1994;88:373-81.
7. Kerrebijn KF, van Essen-Zandvliet EEM, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. J Allergy Clin Immunol 1987;79:653-9.
8. Van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, et al. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. Am Rev Respir Dis 1992;146:547-54.
9. Verberne AAPH, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF, and the Dutch Paediatric Asthma Study Group. One year treatment with salmeterol compared with beclomethasone in children with asthma. Am J Respir Crit Care Med 1997;156:688-95.
10. Simons FER and the Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. N Engl J Med 1997;337:1659-65.
11. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. Pediatrics 1993;92:64-77.
12. Doull IJM, Freezer NJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. Am J Respir Crit Care Med 1995;151:1715-9.
13. Gustafsson P, Tsanakas J, Gold M, Primhak R, Radford M, Gillies E. Comparison of the efficacy and safety of inhaled fluticasone propionate 200 mcg/day with inhaled beclomethasone dipropionate 400 mcg/day in mild and moderate asthma. Arch Dis Child 1993;69:206-11.
14. Katz Y, Lebas FX, Medley HV, Robson R. Fluticasone propionate 50 micrograms BID versus 100 micrograms BID in the treatment of children with persistent asthma. Fluticasone Propionate Study Group. Clin Ther 1998;20:424-37.
15. Wennergren G, Nordvall SL, Hedlin G, Möller C, Wille S, Nilsson EA. Nebulized budesonide for the treatment of moderate to severe asthma in infants and toddlers. Acta Paediatr Scand 1996;85:183-9.
16. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133-8.
17. Waalkens HJ, Van Essen-Zandvliet EE, Hughes MD, et al. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. Am Rev Respir Dis 1993;148:1252-7.
18. Pedersen S. Drug delivery. Am J Respir Crit Care Med 1995;151:S27-42.
19. Gross G, Thompson PJ, Chervinsky P, Vanden Burgt J. Hydrofluoroalkane-134a beclomethasone dipropionate, 400 microg, is as effective as chlorofluorocarbon beclomethasone dipropionate, 800 microg, for the treatment of moderate asthma. Chest 1999;115:343-51.
20. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. Am Rev Respir Dis 1993;148:S1-S26.
21. Wolthers OD. Long-, intermediate- and short-term growth studies in asthmatic children treated with inhaled glucocorticosteroids. Eur Respir J 1996;9:821-7.
22. Hunt GJJ, Edmunds ATE, Kelnar CJH. Height velocity standard deviation scores in 162 prepubertal children receiving beclomethasone dipropionate, budesonide, or sodium cromoglycate. Thorax 1994;49:399P. (Abst)
23. Crowley S, Hindmarsh PC, Matthews DR, Brook CGD. Growth and the growth hormone axis in prepubertal children with asthma. J Pediatr 1995;126:297-303.
24. Doull IJM, Campbell MJ, Holgate ST. Duration of growth suppressive effects of regular inhaled corticosteroids. Arch Dis Child 1998;78:172-3.
25. Merkus PJFM, van Essen-Zandvliet EEM, Duiverman EJ, van Houwelingen HC, Kerrebijn KF, Quanjer PH. Long-term effect of inhaled corticosteroids on growth rate in adolescents with asthma. Pediatrics 1993;91:1121-6.
26. Childhood Asthma Management Program Research Group NHLBI/Division of Lung Diseases. The childhood asthma management program (CAMP): design, rationale, and methods. Control Clin Trials 1999;20:91-120.
27. Price JF, Russell G, Hindmarsh PC, Weller P, Heaf DP, Williams J. Growth during one year of treatment with fluticasone propionate or sodium cromoglycate in children with asthma. Pediatr Pulmonol 1997;24:178-86.
28. Allen DB, Bronsky EA, LaForce CF, et al. Growth in asthmatic children treated with fluticasone propionate. J Pediatr 1998;132:472-7.
29. Silverstein MD, Yunginger JW, Reed CE, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. J Allergy Clin Immunol 1997;99:466-74.
30. Gregson RK, Rao R, Murrills AJ, Taylor PA, Warner JO. Effect of inhaled corticosteroids on bone mineral density in childhood asthma: comparison of fluticasone propionate with beclomethasone dipropionate. Osteoporos Int 1998;8:418-22.
31. Tabachnik E, Zadik Z. Diurnal cortisol secretion during therapy with inhaled beclomethasone dipropionate in children with asthma. J Pediatr 1991;118:294-7.
32. Nicolaizik WH, Marchant JL, Preece MA, Warner JO. Endocrine and lung function in asthmatic children on inhaled corticosteroids. Am J Respir Crit Care Med 1994;150:624-8.
33. Simons FER, Persaud MP, Gillespie CA, Cheang M, Shuckett EP. Absence of posterior subcapsular cataracts in young patients treated with inhaled glucocorticoids. Lancet 1993;342:776-8.
34. Choong K, Zwaigenbaum L, Onyett H. Severe varicella after low dose inhaled corticosteroids. Ped Infect Dis J 1995;14:809-11.
35. Simons FER, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. Pediatrics 1997;99:655-9.
36. Tasche MJA, van der Wouden JC, Uijen JHJM, et al. Randomised placebo-controlled trial of inhaled sodium cromoglycate in 1-4-year-old children with moderate asthma. Lancet 1997;350:1060-4.
37. Simons FER. H1-receptor antagonists in children. In: Simons FER, ed. Histamine and H1-Receptor Antagonists in Allergic Disease. New York: Marcel Dekker Inc, 1996:329-56.
38. Knorr B, Matz J, Bernstein JA, et al. Montelukast for chronic asthma in 6- to 14-year-old children. A randomized, double-blind trial. JAMA 1998;279:1181-6.
39. Adkinson NF, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med 1997;336:324-31.
40. Jakobsson T, Croner S, Kjellman N-IM, Pettersson A, Vassella C, Björksten B. Slight steroid-sparing effect of intravenous immunoglobulin in children and adolescents with severe bronchial asthma. Allergy 1994;49:413-20.