Review Article

Inhaled corticosteroids: effects on growth and adrenal suppression*

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ABSTRACT

This is a review of the medical literature regarding inhaled corticosteroids and their effects on growth and adrenal suppression in children and adolescents. A review of the literature, principally that published over the last five years, was conducted using Medline and searching indexes of articles published in national and international scientific journals. There is considerable controversy regarding the side effects of inhaled corticosteroids. In 21 studies evaluating the effect that inhaled corticosteroids have on growth, a statistically significant reduction (growth retarded by 1-1.5 cm) was observed within the first year of treatment with Beclomethasone or Budesonide inhalers. However, in studies of longer duration, no significant difference was found between final adult height and adult height of the parents. However, in ten studies of the use of inhaled corticosteroids and their effect on adrenal suppression, hypoglycemia and arrested development (no height or weight gains), as well as changes in morning serum levels and 24-h urinary levels of cortisol, were reported, especially when high doses of inhaled corticosteroids were used. Inhaled corticosteroids can reduce growth during the first year of use but do not affect adult height. However, further long-term studies are needed in order to determine the full impact of inhaled corticosteroids on final adult height. Height measures are a means of evaluating the safety and efficacy of the use of inhaled corticosteroids in children. Tests that evaluate the hypothalamic-pituitary-adrenal axis and adrenal insufficiency should be correlated with clinical symptoms and side effects.

Keywords: Adrenal cortex hormones/therapeutic use; Administration, inhalation; Adrenal cortex hormones/adverse effects; Body height/drug effects; Asthma/drug therapy; Asthma/prevention & control; Corticotropin/diagnostic use; Beclomethasone/therapeutic use; Budesonide/therapeutic use; Hydrocortisone/therapeutic use; Pituitary-adrenal function tests

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INTRODUCTION

Since the emergence, two decades ago, of the concept of asthma as a chronic inflammatory disease, inhaled corticosteroids have been used with increasing frequency, and with success, in the management and prevention of moderate and persistent asthma.

Corticosteroids act in the cell, inducing or suppressing various genes involved in the production of cytokines, adhesion molecules and receptors related to inflammation. Inhaled corticosteroids are used for fast relief in crises and for significant reduction of inflammation and improvement of pulmonary function over the course of days or weeks, modifying bronchial hyperreactivity over the course of a few months.

In a study[1] involving 1041 children, budesonide, nedocromil and placebo were used. The authors found that there was a lessening of bronchial hyperreactivity and better asthma control with inhaled budesonide, the use of which resulted in a 43% lower hospitalization rate ($p = 0.04$), 45% fewer visits to emergency rooms ($p = 0.02$), a 43% lower rate of prednisone use ($p < 0.001$), reduced use of albuterol for symptom relief ($p < 0.001$), fewer symptoms ($p = 0.005$) and more symptom-free episodes ($p = 0.01$).

Despite the benefits, it remains in doubt as to whether the prolonged use of inhaled corticosteroids may present the same side effects as their systemic use, especially if used at high doses for more seven days or at conventional doses for 30 days. Neither has it been established whether sudden discontinuity results in suppression of the hypothalamic-hypophyseal-adrenal axis, with cessation of the endogenous production of the corticosteroid hormone and involution of the adrenal gland, resulting in the presence of cushingoid features, growth changes, osteoporosis,[3] glaucoma, subcapsular cataract and hypoglycemia.

The focus of this review of the literature was the use of inhaled corticosteroids that affect growth and cause adrenal suppression.

GROWTH AND INHALED CORTICOSTEROIDS

There are studies which demonstrate that, in the first year of use, inhaled corticosteroids, mainly beclomethasone, may decrease growth by 1.1 cm,[1] although final heights are similar at the end of the monitoring period (four to six years). A follow-up study of children over a 9.2-year period showed that they reached an appropriate final height.[2] In children, stature is a health indicator that is easy to obtain, is noninvasive and can be used to evaluate the efficiency and safety of the use of inhaled corticosteroids.

Due to the myriad factors that may be involved in growth, the debate regarding evaluation methods and the safety of the prolonged use of inhaled corticosteroids is ongoing. Glucocorticosteroids are potent inhibitors of each component of the growth axis, including insulin factor 1 (the hormone controlling growth, secretion and action), bioactive growth, collagen synthesis and endogenous production.

When evaluating growth, we should be aware of its three phases, which are affected by various influences:[3] rapid growth until the age of three (depending on nutritional factors); growth from three years of age up to puberty (regulated by the growth hormone and later decelerating); pubertal growth (characterized by combined acceleration promoted by the growth hormone and by sexual hormones, declining when the pituitary gland halts production). Growth does not occur at a constant rate. There may be intervals of two or more years without growth.

Reductions in the rate of growth over the course of a year may not be accompanied by a decrease in the subsequent year. It has been observed that recording the rate of growth over a three-year period can predict 34% of the variation in the final stature, whereas recording the rate at which the leg grows (knemometry) over a one-month period predicts virtually nothing regarding annual variations in stature.[4]

There is a decrease in the rate of growth prior to puberty. This decrease must be taken into consideration so that this physiological phenomenon is not attributed to the inhaled corticosteroid.

It has also been reported that asthma can retard growth by 0.9 cm per year and may be related to a delay in the onset of puberty, as is the case in other chronic diseases. The frequency of the symptoms and the loss of good control over asthma affect the growth rate and may be confounding factors in studies of growth.

In order to evaluate growth, knemometry,[3] a sensitive technique of measuring the short-term

growth of the leg, is used in order to compare the effects of various corticosteroids on children.

Other studies have shown that the effect of growth retardation by exogenous steroids can be overstated.[4] Stature is reduced by 1 cm on the same day by the compression of articular cartilage when supporting body weight, and a one-hour rest may mimic a 2-mm increase in the rate of growth, which corresponds to the monthly average leg growth. This generates errors in the long-term evaluation growth.[3]

The final height observed, in relation to the final height expected, constitutes the only reliable result in the measurement of human growth, taking into account differences in gender and average height of the parents. Therefore, monitoring height with a stadiometer for more than one year would be the best method to determine the effect of inhaled corticosteroids on growth.[3]

ADRENAL SUPPRESSION

Measurements of baseline serum cortisol, 24-h urinary cortisol and cortisol metabolites are used to determine whether there are systemic effects caused by inhaled corticosteroids. It has been observed that even in the presence of altered levels of cortisol and its metabolites there may not be clinical repercussion.[5]

In order to detect whether there is involution of the adrenal gland resulting from suppression of the hypothalamic-hypophyseal-adrenal axis, other tests would have to be carried out using adrenocorticotropic hormone at microdoses of 0.5 mcg and analyzing the post-stimulus serum cortisol level response.

If morning plasmatic cortisol is less than 10 mcg/dl, an endocrinological evaluation must be performed since it might become necessary to use hydrocortisone in surgical procedures or severe diseases.[3]

FACTORS THAT INFLUENCE SYSTEMIC ABSORPTION

The systemic concentration of inhaled corticosteroids is the sum of what is topically absorbed by the mouth, lungs and digestive tract, taking into account the hepatic inactivation.

When the spray version is used, only 10% is topically distributed in the lung and 80% in the oropharynx. With the use of spacers, 20% goes to the airways, and 70% to 80% to the oropharynx. Using the Turbohaler® device, 40% goes to the oropharynx and a greater portion is topically absorbed in the lung, thereby increasing the efficacy of the corticosteroid and potentially decreasing systemic absorption.

Fluticasone has the lowest active percentage of drug available after hepatic inactivation (< 1%), whereas triamcinolone has 10%, budesonide 21% and beclomethasone 41%. Beclomethasone may therefore have a greater systemic effect and present more side effects. The pharmacological industry has been concerned with enhancing topical potency in order to decrease systemic absorption and thereby decrease side effects. The available agents, listed in descending order by potency, are fluticasone, budesonide, beclomethasone, triamcinolone and flunisolide.

Hydrofluoroalkane, rather than chlorofluorocarbon, should be used as a propellant in the sprays since the latter damages the ozone layer of the atmosphere.

It is believed that, in individuals with moderate asthma, the airways are more permeable, the deposition/absorption of the drug is greater, and the adverse effects are more pronounced than in those with severe asthma.

The lipophilic corticosteroids, such as fluticasone, are more easily distributed systemically, and smaller doses should therefore be used.

Chart 1 presents 21 studies of the relationship between inhaled corticosteroids and growth, together with 10 studies that focus on adrenal suppression.

A critical analysis of these articles was carried out according to the guidelines established by Oxford Centre for Evidence-based Medicine:[6] level of evidence (*); degree of recommendation (+); Excellent levels of evidence = A (1a, 1b or 1c). The conduct is widely recommended = B (2a, 2b or 2c). Level l = evidence that recommends the action. The conclusion is that it is beneficial, and that there is reasonable evidence for the action. Minimum evidence in the analysis of the outcome, benefits and damages do not justify the generalization of the conduct = C (4, 2 or 3). Inconclusive study or opinion of an expert = D.[5] The meta-analyses were classified according to the quality of reporting of meta-analyses (QUOROM) statement.[7] In 11 studies, no significant difference was observed regarding growth, whereas in 10 studies there were such differences (1 to 1.5 cm), mainly in the first year of follow-up. This difference was not observed when the patients were monitored for a number of years (until adulthood) or when the growth was calculated according to the height of the parents.

Chart 1 - Characteristics of the articles reviewed

Study and critical analysis (*)	Study profile	Number of children/ages	Treatment	Study results
Childhood Asthma Management Program Research Group (2000)[1]	Multicenter, randomized 3 groups: budesonide, nedocromil and placebo Follow-up of 4 to 6 years	1041 children 5 to 12 years	Budesonide 400 mcg on average	Inhaled budesonide group presented 1.1 cm less than the placebo group in the first year (p = 0.005). All groups presented similar growth by the study endpoint
Agetoft & Pedersen, 2000[2]	Prospective randomized controlled Follow-up of 9.2 years	211 children 3 to 13 years	Budesonide 412 mcg/day on average (110 to 877)	Adult height significantly (p < 0.001) dependent on pretreatment height. Although growth rates in the budesonide group were reduced in the initial years, the alterations were not significant when compared to adult height,
Benedictis et al. 2001[8]	Prospective multicenter randomized double-blind 52 weeks	343 children 4 to 11 years	Beclomethasone and fluticasone 200 mcg/day	Rate of growth in the fluticasone group was greater than in the beclomethasone group (5.01 x 4.10 cm/year) difference of 0.99 cm (p < 0.01), 95% confidence interval. Pulmonary function improved in the fluticasone group. In the beclomethasone group, baseline serum cortisol was unchanged although nocturnal cortisol was reduced.
Visser et al. 1998[9]	Nonrandomized, open knemometry	21 asthmatic children 6 to 10 years	Fluticasone 200 mcg/day	There was no significant suppression of the rate of leg growth in asthmatic children observed for six weeks.
Rao et al. 1999[10]	Prospective randomized double-blind placebo controlled	23 children 5 to 10 years	Beclomethasone 400 mcg/day and fluticasone 200 mcg/day for 20 months	Serum cortisol was reduced in the beclomethasone group but not in the fluticasone group. Growth was slower in the beclomethasone group.
Sharek et al. 2000[11] Quorum: Excellent level	Meta-analysis Simple or double-blind 1966 to 1998	Children 0 to 18 years	Beclomethasone fluticasone, vs. with no inhaled corticosteroid use for at least 3 months	Beclomethasone (3 studies, 450 children): reduced rate of growth 1.51 cm in 1 year. Fluticasone (1 study, 183 children): 0.43 cm/year reduction in the rate of growth Effects of the use of inhaled corticosteroids for more than 54 weeks or on final adult height are unknown.
Skoner et al. 2000[12]	3 open studies, 52 weeks, comparative, multicenter, 12 weeks double-blind controlled	670 children, 6 months to 8 years	Budesonide nebulized 0.5 mg, 1 or 2 times per day	In the budesonide group, growth decreased in comparison with patients not previously treated with corticosteroids and therapy without the use of inhaled corticosteroids (significant difference). In patients with severe asthma previously exposed to glucocorticosteroids, there was no difference between the budesonide group and the conventional treatment group in terms of height, rate of growth and bone age. Studies involving longer-term treatments (2 years or more) and evaluating the adult height attained are needed to clarify.
Allen et al. 1998[13]	Prospective, double-blind, paired, multicenter randomized placebo(boys) controlled	325 prepubescent children: boys (4 to 11 years) and girls (4 to 9 years)	Fluticasone mcg/day and placebo	Less than significant difference (p = 0.3) 100 mcg/day, fluticasone group 200 in measurements of height, rate of growth and bone age.

Study and critical analysis (*)	Study profile	Number of children/ages	Treatment	Study results
Shapiro et al. 1998[14]	Randomized double-blind placebo controlled multicenter	178 children 4 to 8 years	Inhaled 0.25, 0.5 and 1 mg budesonide, 2 times per day with a nebulizer and compressed air system	Nebulized budesonide was superior to the placebo in reducing asthma symptoms, as well as the use of relief medication, and increasing morning peak flow. Heights and weights observed in the 12 months of treatment were similar, with no difference between children treated for 12 months with adrenocorticotropin stimulation and those receiving a placebo in terms of baseline cortisol values and cortisol values at the study endpoint. Only 1 patient presented an abnormal cortisol response after 1 year of treatment with a high dose of budesonide.
Efthimiou & Barnes 1998[15]	Data review, retrospective and prospective	1240 patients 11 studies	Inhaled corticosteroids	In the majority of asthmatic children, doses of inhaled corticosteroids < 400 mcg/day have no significant effect on bones and growth.
Verberne et al. 1997[16]	Randomized, double-blind, controlled 54 weeks	67 children 6 to 16 years	Salmeterol and beclomethasone for 6 weeks	FEV_1 increase was significantly greater and growth rate was lower (1.4 cm) in the beclomethasone group than in the salmeterol group ($p = 0.001$).
Simons et al. 1997[17]	Randomized, double-blind, paired, 1 year	141 children (9.3 ± 2.4 years)	Compared beclomethasone (400 mcg/day) with salmeterol (100 mcg/day) and placebo	Beclomethasone was more effective in reducing bronchial hyperreactivity and asthma symptoms and was not correlated with a reduction in 1-year linear growth: 3.96 cm/year in the beclomethasone group vs. 5.40 cm/year in the salmeterol group ($p = 0.004$) and 5.04 cm/year in the placebo group ($p = 0.018$). However, no significant effect on final height was found ($p = 0.22$)
Silverstein et al. 1997[18]	Retrospective corticosteroid study in the city of Rochester comparing adult height with similar asthmatics, with and without corticosteroids and including similar nonasthmatics.	778 children 153 with asthma	Inhaled and oral glucocorticosteroids	The adult height of the patients with asthma adjusted for the height of the parents was not statistically different when compared to that of the nonasthmatics. The adult height of the asthmatics using corticosteroids did not differ significantly from that of those not using corticosteroids.
Visser et al. 2001[19]	Randomized, double-blind	6 to 10 years	Fluticasone 1000 mcg/day reduced to 100 mcg/day or use of a constant dose of 200 mcg/day for 1 year	Clinical effects were not superior. Height was not altered significantly in either study.
Doull et al. 1995[20]	Randomized, double-blind, controlled, with placebo for 7 months	94 children 7 to 9 years	400 mcg/day of beclomethasone	At the end of 7 months, children receiving-beclomethasone grew less than did those receiving the placebo (2.66 vs. 3.66, $p < 0.0001$). Production of urinary cortisol was unafected.
Allen et al. 1994[21] Quorum: Did not meet the criteria for best evidence	Meta-analysis, effect of inhaled and oral corticosteroids on growth	95 articles	Inhaled beclomethasone and oral prednisone	Oral prednisone use was correlated with reduced final height in 21 of the 95 articles. Inhaled beclomethasone was significantly correlated with normal stature. No evidence of a correlation between high doses of beclomethasone and stunted growth in long-term use or cases of severe asthma.

Study and critical analysis (*)	Study profile	Number of children/ages	Treatment	Study results
Price et al. 1997[22]	Multicenter randomized for 1 year	60 patients 4 to 10 years	Fluticasone 100 mcg/day and disodium cromoglycate	No significant difference in the rate of growth or in levels of 24-h free cortisol. Improved pulmonary function (morning peak flow) in the fluticasone group 20 mg 4 x day
Van Bever et al. 1999[23]	Retrospective case reports comparing asthmatics treated with corticosteroids to those not so treated	85 patients 18 to 29 years	Inhaled beclomethasone and budesonide	Adult height is the same in young adults treated with inhaled corticosteroids in infancy as in those not so treated. A significant difference was found between the 2 groups for adult height minus target height, suggesting a slight inhibition of growth in patients that had used corticosteroids, although this appears to be a function of the severity of the asthma.
Doull et al. 1998[24]	Double-blind, randomized placebo controlled for 7 months and a 4-month follow-up period	52 prepubescent children	Beclomethasone 200 mcg 2 x day	Significant suppression of growth in the first 6 weeks of treatment. By 19 weeks, growth had equaled that of the controls.
Fitzgerald et al. 1998[25]	Double-blind, crossover randomized, 12 weeks of treatment, comparing one corticosteroid with another	34 children 5 to 16 years with persistent asthma	Fluticasone 750 mcg/day and beclomethasone 1500 mcg/day	Fluticasone 750 is as affective as beclomethasone 1500. Rates of growth were similar. There were (similar) drops in adrenal function, although this may be related to prior corticosteroid use and to the degree of asthma severity.
Saha et al. 1997[26]	Retrospective, comparative, for 5 years	201 children 1 to 11 years	Beclomethasone or budesonide, mean of 500 mcg/m^2	Greatest difference in reductions of growth in the first year of treatment. Not dose dependent. Longer duration of treatment was correlated with less growth. The degree of growth inhibition increased in parallel with disease severity.
Thomas et al. 1994[27]	Report of 6 cases of stunted growth	6 patients 0.5 to 5.3 years	Beclomethasone 200 to 800 µg/day	4 patients received higher doses of beclomethasone (400 to 800 µg/day). In 1 patient (using 300 µg/day of beclomethasone), there was adrenal suppression.
Dunlop et al. 2002[28]	Report of a case of hypoglycemic crisis	21 months	Nebulization with budesonide: increased by 2 mg/day for 16 months then reduced by 0.5 mg and later increased by 1 mg/day	Adrenal insufficiency Growth fell from the 22nd to the 3rd percentile.
Carrel et al. 1996[29]	Report of a case of hypoglycemia	3.5 years	Nebulization with triamcinolone, alternated with oral corticosteroid	Low serum cortisol, presenting persistent adrenal suppression 5 months after the attack.
Patel et al. 2001[30]	Case series of adrenal insufficiency (8 cases) treated with inhaled corticosteroids	4.5 to 10 years	A higher than standard dose of an inhaled corticosteroid was used in 1 case.	Hypoglycemia, little height gain, and limited weight gain, together with altered serum cortisol, response to adrenocorticotropin stimulus and 24-h urinary cortisol metabolites
Grebe et al. 1997[5] 1996[29]	Controlled, observational paired	21 patients 16+ years	4 to 8 years of treatment with beclomethasone	24-h urinary cortisol ($p < 0.08$), serum cortisol and tetracosactrin test were significantly ($p < 0.05$) lower than that of controls. Hypothalamic-pituitary axis function was inversely correlated with beclomethasone dose level, The significance of axis suppression as a marker of corticosteroid effects

Study and critical analysis (*)	Study profile	Number of children/ages	Treatment	Study results
Yallouros et al. 1997[31]	Double-blind, randomized (6 weeks plus 6 weeks, crossover) of severe asthma	34 children: group A: mean mean 7.3 years; group B: mean 8.8 years	Group A used fluticasone; Group B used beclomethasone (equipotent doses)	In therapeutically equivalent doses, fluticasone caused less adrenal suppression than did beclomethasone.
Lipworth et al. 1997[32]	Randomized, placebo-controlled, double-blind	8 asthmatic schoolchildren (mean age, 12.1 years)	Fluticasone or budesonide (200 mcg/day or 400 mcg/day) for 4 days	Neither drug suppressed nocturnal urinary cortisol in comparison with the placebo, and no difference was found between the two drugs.
Kannisto et al. 2000[33]	Randomized	75 children (mean age, 9.5 years; range, 5.5 to 14.7)	30 children received fluticasone; 30 received budesonide; 15 received cromoglycate	Test with 0.5 mcg of adrenocorticotropin revealed slight adrenal suppression in 23% of the children using conventional doses of inhaled corticosteroids. Fluticasone caused less suppression and growth inhibition in 1 year than did budesonide. Growth reduction was significant in the budesonide group but not in the other groups.
Broide et al.1995[34]	Randomized, controlled, test of adrenal stimulation with a low dose of adrenocorticotropin	46 patients: 30 children (5 to 14 years), and 16 adults (18 to 30 years) 33 controls: 15 children and 18 adults	Beclomethasone (482 ± 42) and budesonide (507 ± 628) for more than 6 months	In the study of adrenal stimulation with a low dose (0.5 mcg) of adrenocorticotropin, one-fourth of the patients treated with inhaled corticosteroid in conventional doses presented a reduction in the adrenal response.
Zimmerman et al. 1998[35]	Case reports	2 patients: 8 years and 32 years	Fluticasone 250 mcg/day and 500 mcg/day	Levels of serum cortisol were low on the adrenocorticotropin test, and growth inhibition was reduced.

In the 9 studies of adrenal suppression, there were alterations in 24-h urinary cortisol levels, in serum levels of morning cortisol and in the results of the test with adrenocorticotropic hormone to stimulate the adrenal glands. The patients presented hypoglycemia, altered consciousness, arrested development (stunted growth and weight loss), especially when high doses of inhaled corticosteroids were used, although, in some studies,[28,31-32] there have been alterations even when conventional doses were used. The authors point out that more studies are necessary to check the significance of these exams with the clinical correlation. Some[3] call attention to the fact that, in patients with serum cortisol levels of 10 mcg/dl, there must be an endocrinological follow-up, including a test with adrenocorticotropic hormone, in order to detect adrenal insufficiency.

CONCLUSIONS

After a review of the literature, the authors have come to the conclusion that there is a significant difference in height in the first year of use, principally when inhaled beclomethasone or budesonide are used. In addition, there was no difference in the final adult height when the studies were conducted over the long-term or when a correlation was made between the growth and the height of the parents. Nevertheless, in 10 articles evaluating cases of adrenal suppression, hypoglycemia, arrested development (no height or weight gains) and changes in the morning cortisol serum test results were reported, mainly with the use of high doses of inhaled corticosteroids. Inhaled corticosteroids can limit growth in the first year but not the final adult height.

Regarding the use of inhaled corticosteroids for treating asthma safely and efficaciously, the safest corticosteroid should be selected, and a minimum efficacious dose should be used (a morning dose when prescribed once a day). If the control of asthma is unsatisfactory, a long-term bronchodilator or leukotriene antagonists should be added before doubling the dosage of the inhaled corticosteroid. As accompanying strategies, the family should be informed about the importance of reducing allergens and smoke, and vaccination should be recommended. It is necessary to investigate and treat rhinosinusitis or gastroesophageal reflux and monitor growth at all doses of the inhaled corticosteroids used, as well as vision and bone density when higher doses are used. Finally, in cases of persistent asthma, it should be determined whether other topical (nasal or dermatological) corticosteroids are being used, thereby avoiding dose accumulation.

This review of the literature was limited because only the Medline database, the Cochrane library and article references were used. However, 32 studies were found, most of which with a recommendation level of B. Only 12 studies were categorized as evidence level C by the Oxford Evidence Center.

After reviewing these articles, we concluded that, in order to safely maintain the efficacy of inhaled corticosteroids, children should be monitored, especially in terms of their height. Should high doses be used or growth rate slow, exams evaluating the function of the hypothalamic-hypophyseal-adrenal axis should be carried out in order to detect, and treat if necessary, adrenal insufficiency. Further long-term follow-up studies of children using inhaled corticosteroids are necessary so that their impact on final growth can be evaluated. Monitoring height is a means of evaluating efficacy and safety of the use of inhaled corticosteroids in children. The relevance of exams evaluating the hypothalamic-pituitary-adrenal axis and adrenal insufficiency, as well as the correlation with clinical symptoms or side effects should be further elucidated.

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