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EDITORIAL

Inhaled steroids in children: adrenal suppression and growth impairment

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Inhaled steroids have been used for many years. The first report of their beneficial use in asthmatic children was published almost 30 yrs ago [1]. With increasing knowledge of the side-effects of systemically administered steroids, there has been a steady increase in the use of inhaled steroids, and they are presently considered to be the most important treatment for asthma. Inhaled steroids are the cornerstone of all guidelines on asthma treatment [2–4]. They reduce symptoms in children with asthma [5], improve quality of life in asthmatic children and their families [6], decrease patients′ and their parents′ absence from school/work [7], reduce airway inflammation [8], and improve lung function [9], bronchial responsiveness [10] and exercise-induced asthma [11, 12]. The sale and use of inhaled steroids has markedly increased in Nordic countries since the late 1980s, which has probably had an impact upon the admission rate of childhood asthma in these countries. In older children, the admission [13] and particularly readmission [14] rates for acute asthma have decreased in these countries. The use of inhaled steroids has thus had a major impact upon daily life and the "mastering" of asthma in asthmatic children.

Despite the beneficial effects of inhaled steroids in childhood asthma, general agreement as to how early to start treatment has not been reached. This is mostly due to the general fear of the side-effects of inhaled steroids, but also because of an awareness of the possible effects upon lung growth in young children, as has been reported by the use of systemic steroids in animal experiments [15].

The local side-effects of inhaled steroids on skin, the mucous membranes of the respiratory tract, and the oropharyngeal area are also well known, but have received much less attention than the systemic side-effects. The local side-effects consist of perioral dermatitis, oral candidiasis, hoarseness, dysphonia, cough during inhalation and a feeling of thirst [16].

However, systemic side-effects, including suppression of the hypothalamic-hypophyseal-adrenal axis [17–19], a possible reduction in growth velocity caused by inhaled steroids [20], effects upon bone structure and bone mass [21], markers of bone turnover [22] and carbohydrate and lipid metabolism [23], weight gain and Cushing′s Syndrome [24], cause the most concern. Posterior subcapsular cataracts have been described as developing after systemic steroids have been used and, in three patients, on inhaled beclomethasone dipropionate with occasional short courses of systemic steroids over several years [25]. However, systematic studies have not indicated an increased risk of cataracts with the use of inhaled steroids [26, 27].

Although practical experience throughout the past 30 yrs has proved that inhaled steroids are safe drugs for most patients, it has also been shown that in higher doses, a systemic effect is detectable by demonstrating an early morning dip in serum cortisol when measuring 24-h integrated and fractionated (overnight, 08.00 h, daytime) serum cortisol levels and urinary cortisol/creatinine excretion [28, 29]. Stimulation tests have also been used to detect the effect of inhaled steroids on the hypothalamic-pituitary-adrenal axis [29]. After a meta-analysis including 27 studies performed during 1966–1998, it was concluded that using >1.5 mg inhaled steroid·day^{-1} resulted in a marked adrenal suppression [30]. The studies included both healthy volunteers and asthmatic adults and children. In contrast, RUSSELL [31] noted that the risk of adrenal suppression and growth retardation was present when doses exceeded 400 μg of inhaled beclomethasone dipropionate or budesonide per day in children. It has been observed that a marked individual variation in the degree of adrenal suppression caused by use of inhaled steroids occurs. PRIFTIS *et al.* [24] reported an asthmatic child who developed a marked Cushingoid appearance and evidence of adrenal suppression and growth reduction while on a low dose of inhaled steroid. There was an improvement in the appearance, regression of adrenal suppression and improved growth when inhaled steroids were replaced by disodium cromoglycate.

Some studies have indicated varying degrees of adrenal suppression with different inhaled steroids. The results of the studies, however, have not been consistent. In a meta-analysis including seven trials comparing inhaled fluticasone propionate with inhaled budesonide and seven trials comparing inhaled fluticasone propionate with inhaled beclomethasone propionate, no difference in serum cortisol was found between fluticasone and budesonide in lower doses, but less suppression by fluticasone than

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budesonide was found in higher doses. No differences were found when comparing fluticasone and beclomethasone dipropionate [32]. However, in the meta-analysis including 27 studies previously referred to, LIPWORTH [30] reported that adrenal suppression occurred with a lower dose of fluticasone propionate than with other inhaled steroids. TODD *et al.* [33] reported growth and adrenal suppression in six children with fluticasone propionate at a daily dose of $\geqslant$1,000 $\mu g \cdot day^{-1}$ [33]. With regards to asthmatic children, it should be noted that PRIFTIS *et al.* [34] recommended that endocrine assessment should be performed when prescribing inhaled steroids in daily doses comparable to beclomethasone dipropionate ($\geqslant$400 μg).

In this issue of the *European Respiratory Journal*, TODD *et al.* [35] report on the most severe form of adrenal suppression, acute adrenal crisis, in four asthma patients aged 7–33 yrs taking fluticasone propionate in high doses (>1,000 $\mu g \cdot day^{-1}$). All patients were acutely ill due to severe adrenergic hypofunction. Three of the patients, all children aged 7–9 yrs, presented with acute hypoglycaemic convulsions. This study particularly underlines two important issues. 1) It is important to look for adrenal suppression in children treated with inhaled steroids and to assess adrenal function. 2) There is a marked individual variation in the systemic response to inhaled steroids, and even in moderately high doses, severe adrenal suppression may occur.

The other most widely recognized and feared systemic side-effect of inhaled steroids in children is growth retardation. Severe asthma may affect growth in children. BALFOUR-LYNN [36] performed a long-term follow-up study of 66 children with severe asthma. A delay in the onset of puberty in asthmatic children was found, giving the impression of growth retardation, but with a later "catch-up" growth, thus allowing the asthmatic children to reach normal adult height. Growth impairment caused by inhaled steroids has been reported in a number of studies. However, in a meta-analysis, ALLEN *et al.* [37] evaluated 95 articles and included 21 studies involving 810 patients. Both oral and inhaled steroids were assessed and it was concluded that a significant, though weak impairment was found for oral steroids, whereas inhaled beclomethasone dipropionate was not associated with growth impairment, but with attaining normal final stature. Several ways to assess growth have been developed. Short-term growth has been assessed by measurement of knemometry in the lower leg, and has shown significant short-term impairment of growth in a number of studies including oral and other inhaled steroids [38–40]. The long-term significance of measuring short-term growth has been questioned, and thus careful studies have been performed, including studies with lower doses of inhaled steroids. In children with mild asthma, a significant though small reduction in growth was seen with the use of beclomethasone dipropionate compared double-blind with a placebo [20] or theophylline [41]. In a study by DOULL *et al.* [42], a second analysis showed that a reduction in growth was found, for the most part, during the first 6 weeks of treatment [42]. Even in mildly asthmatic children on low-dose inhaled steroids (budesonide), a small but significant reduction in growth was found after 12 months compared to placebo in prepubertal (7–11 yrs) but not older children [43]. However, the clinical significance of a growth retardation of 1 cm may be questioned. In a long-term follow-up study of asthmatic children treated with inhaled budesonide over several years, AGERTOFT and PEDERSEN [9] concluded that, even after many years of treatment with inhaled steroids, children on inhaled steroids reached normal adult height. However, measurement of growth is important in the assessment of the possible systemic effects of inhaled steroids.

The studies reporting on possible growth impairment by inhaled steroids are very different, varying in type and dosage of the drug, ways of measuring growth, duration of follow-up, type of patients included with regard to the relationship between type and severity of asthma, age and use of other concomitant treatment for asthma, thus making it difficult to reach final conclusions. In this issue of the *European Respiratory Journal*, PRICE *et al.* [44] address this matter in a most comprehensive manner. In their first article they take the diverse factors into consideration, classifying the different types of studies and making recommendations as to how studies assessing growth and final height in asthmatic children using inhaled steroids should be set-up and conducted. Groups planning to set-up studies on this topic should read the article carefully and take their recommendations into consideration.

In their second article, PRICE *et al.* [45] present a systematic review of the effect of asthma therapy on growth in children based upon their own classification of studies as given in their first article [44].

Thus, in this issue of the *European Respiratory Journal*, the effect of inhaled steroids upon adrenal function with the possibility of severe systemic reactions [35], the effect of inhaled steroids upon growth and final height [44, 45] and two different and important aspects of the systemic side-effects of inhaled steroids when used in asthmatics are discussed. All three articles highlight the necessity of assessing and monitoring the asthmatic child treated with inhaled steroids, taking individual variations into consideration, and PRICE and co-workers [44, 45] outline the necessity for careful design and conduct of clinical research studies on the systemic effects of inhaled steroids.

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