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Asthma treatment and growth

It is generally acknowledged that asthma may have an effect on children's growth independent of any treatment they may be receiving. The many studies showing this have been reviewed recently by Russell in this journal.¹ In summary, children with moderate to severe asthma may have a characteristic pattern of slowing of prepubertal growth, delayed puberty, and a late pubertal growth spurt, with catch up to an adult height within the expected target range. It is because of this effect that difficulties can arise in trying to separate the effects of asthma from the effects of any treatment in studies of growth in children with asthma.

Oral corticosteroids

There is little doubt that oral corticosteroids such as prednisolone can have a detrimental effect on growth. Martin *et al.*,² in a prospective survey over 14 years, showed that children who had received oral steroids were significantly shorter than either asthmatic children who had not received steroids or non-asthmatic controls. However, this difference in height was only seen at age 14 years, and no difference was apparent by 21 years, indicating that the main effect of oral corticosteroids was to cause growth delay and affect the timing of puberty. The degree of growth retardation has been clearly linked to the frequency of oral corticosteroid use.³ However, there is also evidence that adult height can be permanently reduced in some children who have received long term oral corticosteroids for asthma.⁴

Inhaled corticosteroids

These were initially introduced in the 1970s and have revolutionised the management of asthma. Earlier work on the possible effects of inhaled corticosteroids on growth was contradictory and was often based on retrospective studies. Littlewood *et al.*,⁵ in a report on 346 children, 81 of whom were receiving inhaled beclomethasone in doses ranging from 200 to 800 µg daily, showed that those on inhaled corticosteroids had significantly lower height standard deviation scores than those not on steroids. However, there was also a difference in age between the two groups, so they may have been demonstrating the natural pattern of prepubertal growth deceleration seen in the older corticosteroid treated patients. Although Balfour-

Lynn showed a high prevalence of delayed puberty in his study,⁶ there were no apparent adverse growth effects with beclomethasone doses of up to 600 µg daily. Similarly Ninan and Russell,⁷ in a study of 58 prepubertal children receiving budesonide or beclomethasone in doses ranging from 200 to 1600 µg daily, did not detect a relation between height standard deviation score and corticosteroid use. There was, however, a clear relation with asthma severity.

Despite these reassuring studies it has become apparent to some paediatricians, particularly those running growth clinics, that certain children on inhaled corticosteroids can grow extremely slowly, with growth rates far below those expected for delayed puberty alone. Wales *et al* reported six children with marked suppression of height velocity while receiving 400 to 1000 µg/day of beclomethasone,⁸ four of whom showed catch up growth on dose reduction. A similar observation was reported by Thomas *et al.*⁹

Additional information has come from the studies of Pedersen's group in Denmark, studying children with mild asthma to eliminate the potential effect of asthma severity on growth. They have used the technique of knemometry, which accurately measures changes in lower leg length velocity as an index of short term growth. An initial placebo controlled double blind study¹⁰ of eight weeks' treatment with budesonide showed a significant reduction in lower leg length growth velocity in children receiving 800 µg daily, whereas no difference from placebo was seen with doses of 200 or 400 µg daily. A further study¹¹ showed marked reductions in lower leg length growth velocity with beclomethasone when given in doses of 400 or 800 µg daily. The degree of suppression of growth rate was similar to that seen when they studied children receiving oral prednisolone in a dose of 2.5 mg/day.¹²

Although these studies have been criticised on the basis that short term changes in lower leg length velocity are not predictive of long term growth, their findings have been supported by three intermediate term studies. Crowley *et al* studied 56 prepubertal children with asthma over a 12 month period.¹³ They were divided into four groups: those children receiving no steroids, those receiving budesonide in a mean dose of 762 µg/m², those receiving beclomethasone in a mean dose of 560 µg/m², and a group of children

receiving oral steroids. The mean growth velocity standard deviation score was normal in the no steroid group, but significant reductions were seen in the beclomethasone (-1.04) and prednisolone (-1.58) groups, whereas only a slight reduction in growth velocity was seen in those taking budesonide (-0.2). A wide range of individual variation in growth rates was also seen in this study. A similar effect on growth velocity was seen in the study of Doull *et al* who studied 104 prepubertal children with mild asthma who had not previously received steroids.¹⁴ They were randomised to receive either beclomethasone 400 μg daily or placebo. Over a seven month period growth velocity was significantly reduced in the steroid treated group, with a mean difference in height velocity of 1 cm over the treatment period. In the study by Tinkelman *et al* beclomethasone in a dose of 336 μg daily given by metered dose inhaler was compared with theophylline.¹⁵ The mean growth velocity in those receiving beclomethasone was 4.4 cm/year, while in the theophylline group it was 6.0 cm/year.

The additional feature that became apparent from these studies was that the mode of administration of the inhaled steroid has an influence on the risk of growth retardation. This was greater in those children receiving beclomethasone from a dry powder inhaler than in those receiving budesonide from a large volume spacer. This is related to differences in oral bioavailability, systemic absorption from the lungs, and first pass metabolism.¹⁶ There is also evidence that the percentage of the dose of budesonide delivered to the lungs by a Turbohaler is twice that from a large volume spacer.¹⁷ The delivery system is therefore an additional determinant of the potential systemic effect of inhaled corticosteroids and should be considered in decisions about treatment and dose. In addition intranasal corticosteroids, which are systemically absorbed, may contribute to potential adverse effects.

Fluticasone propionate was introduced in 1993 with the theoretical advantage of less systemic effects due to low oral bioavailability. This has been the subject of several studies in children. Wolthers and Pedersen were unable to show a significant reduction in lower leg length velocity when it was given in a dose of 200 μg daily.¹¹ Price *et al* compared fluticasone in a dose of 100 μg daily to sodium cromoglycate in a one year multicentre study of 122 prepubertal children.¹⁸ Both groups had normal growth velocities but lung function was better in those receiving fluticasone. Whitaker *et al*,¹⁹ in a study based in general practice, showed significant reductions in growth velocity of 66 prepubertal children receiving beclomethasone or budesonide in doses of 200 to 400 μg daily given as dry powder inhalers. Twenty of the children with the lowest growth velocities showed catch up growth when changed to fluticasone in equipotent doses. In one study adverse effects of fluticasone on growth were found.²⁰ In this study, six children with severe asthma were changed from beclomethasone or budesonide in doses of more than 800 μg daily to high dose fluticasone (more than 1000 $\mu\text{g}/\text{day}$). Each child showed a reduction in growth velocity despite improvements in asthma control. This study has been extensively criticised,^{21, 22} particularly on the grounds that five of the children received an increased dose of inhaled corticosteroid rather than an equipotent dose. It did, however, show that fluticasone may have adverse effects on growth when used in doses substantially above the recommended dosage of 200 μg daily.

Mechanism of effect

The potential mechanism of the effect of inhaled corticosteroids on growth has been studied in some detail. Crowley *et al* performed 24 hour growth hormone secretion pro-

files along with measurements of insulin-like growth factor 1 (IGF-1) and found no abnormalities.¹³ Wolthers *et al* also saw no abnormality in IGF-1 concentrations or the main growth hormone dependent binding protein IGFBP-3.²³ There is evidence of reduced excretion of adrenal androgens in children with asthma but this is seen in both corticosteroid dependent children and in children not on corticosteroids,²⁴ indicating that it is due to the underlying disease rather than its treatment.

A dose related reduction in biochemical markers of bone and collagen turnover has been shown in children receiving oral prednisolone in doses of 2.5 and 5 mg daily.²⁵ There is some evidence for such an effect with inhaled corticosteroids with one study showing a reduction in synthesis of type I and type III collagen with beclomethasone and budesonide in doses of 800 μg per day, given as dry powder inhalers.²⁶ However, Doull *et al* did not find such an effect in their study, which showed growth retardation in children receiving beclomethasone 400 μg daily.²⁷ There is therefore some evidence of a direct suppressive effect of inhaled corticosteroids on bone and collagen turnover which results in slowing of growth velocity.

Conclusions

There is good evidence that inhaled corticosteroids in high dose can slow growth velocity in some children with asthma. This can occur with doses of beclomethasone of 400 μg or more daily or budesonide 800 μg or more daily, especially when given as dry powders. Fluticasone appears to be without adverse effects on growth when used in conventional doses but may also have adverse effects in high dose. It is apparent that there is a wide range of individual responses, and some children may show adverse effects with relatively small doses. It is not clear at present whether this is a transient phenomenon causing a slowing of growth and maturational delay with no adverse effect on adult height, or whether the growth of the most severely affected children may be permanently compromised. A recent meta-analysis has indicated that inhaled beclomethasone treatment does not reduce final height,⁴ but this was with relatively low doses.

None of the most recent studies has followed children through to adult height and therefore, as commented by Wolthers in a recent review,²⁸ no firm conclusions can be drawn.

It is important for clinicians to be aware of the significant benefits of inhaled corticosteroids. A recent study has shown that early introduction of inhaled budesonide led to progressive increments in per cent predicted FEV₁ and a reduction in hospital admissions.²⁹ On the other hand those children not treated with budesonide showed an annual decrease in per cent predicted FEV₁ of 1–3%. This suggests that early introduction of inhaled corticosteroids may be important and can prevent irreversible airway obstruction.

We therefore do not advocate withholding inhaled corticosteroids in the management of childhood asthma and it is very important that patients receive the dose that controls their symptoms and improves lung function. It is also important to step down the dose as the asthma control and lung function improves, as advocated in the recent British guidelines on asthma management.³⁰ We would, however, make the following recommendations. If children require doses of beclomethasone or budesonide of more than 400 μg daily it is better to give this using a metered dose inhaler and large volume spacer than a dry powder inhaler. The use of budesonide may be more appropriate in doses of between 400 and 800 μg daily, remembering that for equivalent pulmonary effect only half the dose of budesonide is required by dry powder inhaler as by large

volume spacer. If doses of more than 800 µg per day are required we would consider changing to fluticasone. When control is not achieved on low dose inhaled corticosteroids alone, an alternative option to using high doses corticosteroids is to introduce a long acting inhaled bronchodilator such as salmeterol³¹ as advocated in step 3 of the British guidelines on asthma management.³⁰ It is also important that children requiring high dose inhaled corticosteroids are under the supervision of a paediatrician and all children on inhaled corticosteroids have regular growth measurements as part of their management.

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