

Do intranasal corticosteroids affect childhood growth?

Topical intranasal corticosteroids (INS) are the most effective treatment for allergic rhinitis and are being increasingly prescribed to children. Due to the potent inhibition of childhood growth seen with oral corticosteroids, it is important to examine whether INS could have similar effects. The evidence available suggests that some INS, such as beclomethasone dipropionate (BDP), may slow growth when used regularly for prolonged periods. However, newer INS such as fluticasone propionate (FP) and mometasone furoate, which have substantially reduced bioavailability via gastrointestinal absorption, are unlikely to do so. Well-designed prospective studies are needed to distinguish those INS with reduced or absent effects on growth. In practice, choosing an INS which optimises the ratio of therapeutic effect to systemic bioavailability will probably reduce the risk of growth suppression to a negligible level.

D. B. Allen

University of Wisconsin Children's Hospital, H4/448
CSC, 600 Highland Avenue, Madison, WI 53792-4108,
USA

Introduction

Topical intranasal corticosteroids (INS) are the most effective treatment for allergic rhinitis, and are being prescribed to increasing numbers of children at younger ages for longer periods. Since corticosteroids, when administered orally, are potent inhibitors of childhood growth, it is important to examine whether continued and long-term use of INS could have similar effects.

Oral corticosteroids: effects on growth

Oral corticosteroids may have adverse effects on growth (Fig. 1). These include suppression of pulsatile growth hormone (GH) secretion from the pituitary; reduction of the bioactivity of insulin-like growth factor-I (IGF-I), the major second messenger of the GH system; down-regulation of the GH receptor; and profound suppression of the synthesis of the new connective tissue required for growth. It is also likely that corticosteroids suppress adrenal androgen production, one of the most important stimuli for early pubertal growth acceleration (1).

Inhaled and intranasal corticosteroids: factors influencing systemic effects

In contrast, the systemic effects of inhaled and intranasal corticosteroids are influenced by a number of factors which reduce their potential for harm.

Pharmacokinetics

The systemic burden of inhaled corticosteroids (ICS) comprises that absorbed through the gastrointestinal tract plus that absorbed through the airway.

Although virtually all the drug that is deposited in an appropriate part of the airway is available for absorption into the systemic bloodstream, it is important to recognise that various ICS show important differences in their hepatic absorption and metabolism. For instance, budesonide (BUD) undergoes significantly greater first-pass hepatic inactivation (~90%) than either beclomethasone dipropionate (BDP) or triamcinolone (~80%). The first-pass inactivation of more modern agents such as fluticasone propionate (FP) and mometasone (both ~99%) is even more marked than that of BUD (2).

Age

During childhood, there are various transition points where the mechanism controlling the growth-axis changes. Particularly important are the 2–3 years immediately before the pubertal growth spurt, during which time growth-hormone secretion can wane prior to later stimulation by sex steroids, and childhood growth velocity is at its lowest. At this age, children appear to be especially vulnerable to growth suppression by medication or illness (3). Studies on ICS (specifically BDP) in children with asthma, which have focused on this pre-adolescent age group, have revealed detectable growth suppression with long-term continuous treatment, with doses above 400 µg/day (4). On the other hand, reassuring observations of normal growth have been reported in prepubertal children treated for 1 year with clinically comparable doses of inhaled FP (100–200 µg/day) (5).

Disease severity

It is well known that chronic illnesses such as asthma can retard the tempo of growth. While this can be an

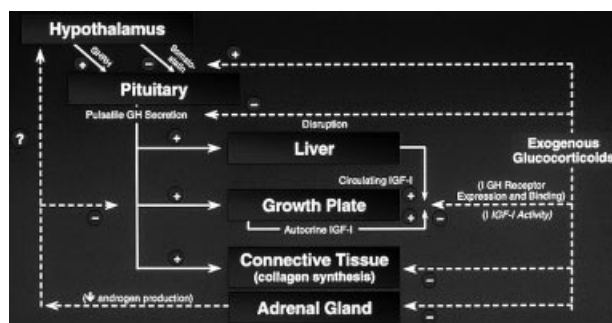


Figure 1. Glucocorticoids: effect on growth.

important influence, it appears that only children with severe asthma show a detectable decrement in their height during the adolescent years (6). There are no data, however, to suggest that allergic rhinitis *per se* slows growth. Thus, this is unlikely to be a confounding factor in growth studies with INS.

Timing of administration

In children prior to puberty, most pulsatile GH secretion occurs during the night while the child is asleep. Interestingly, the initiation of nocturnal GH secretion pulses coincides with the normal nadir in cortisol levels. The administration of corticosteroid immediately before bedtime might therefore provide a physiologically inappropriate increase in late evening plasma cortisol levels. Compared with the same dose administered earlier in the day, this might have a greater dampening effect on the growth axis. Although studies demonstrating a disproportionate influence of bedtime ICS administration on growth are lacking, data from a short-term knemometry study suggest that this effect may occur during INS treatment (7).

Route of administration: INS vs ICS

In general, systemic effects of corticosteroids are reduced when administered via the intranasal rather than the inhaled route. For example, in a placebo-controlled study of INS in patients treated with a once-daily, evening, 200 µg dose of mometasone, triamcinolone, or BUD, sequential plasma cortisol evaluations showed no significant differences compared to placebo (8). The systemic bioavailability of INS FP (~0.5%) is considerably lower than when administered by MDI (~26%) (9). This conclusion is supported by the finding of extremely low (≤ 53 pg/ml) or undetectable levels of FP in the blood in subjects following four 800 µg doses of the nasal spray (9). This contrasts with higher plasma levels measured in children with asthma receiving 50–100 µg FP by MDI (9). Differences in INS absorption and metabolism, however, may still result in significant differences in their systemic effects.

Effects of intranasal steroids on growth

Conducting well-designed studies of childhood growth with adequate duration is difficult. Consequently, the value of studies in predicting clinically significant effects varies when different techniques are used to assess short- and long-term growth. A number of studies have relied on short-term techniques such as knemometry or markers of bone metabolism. While these can be sensitive indicators of the *presence* of an ICS in the bloodstream, their predictive value for long-term effects on growth is poor. Knemometry measurements at 1 month, for example, do not correlate with the annual growth rate (10). Although sequential knemometry over 6 months improves the correlation, careful stadiometry studies, which can be conducted over similar periods, are to be preferred. Reliable information about the growth effects of INS is obtained only in longer-term studies, of at least 12 months' and preferably 3 years' duration.

One of the first studies of the growth effects of INS used knemometry to compare BUD and the antihistamine terfenadine, with an injection of methylprednisolone administered at the beginning of the pollen season. Interestingly, intranasal BUD (200 µg bd.) inhibited growth to the same extent as the methylprednisolone injection (11). A subsequent, placebo-controlled study of intranasal BUD 400 µg given *once daily* found children in the placebo group who showed marked short-term changes in growth (Fig. 2) (7) – a potentially confounding factor in any knemometry study – with no consistent effect of intranasal BUD on growth. From these data, the investigators concluded that once-daily intranasal BUD, in contrast to twice-daily administration at the same dose, had no effect on mean growth rate. However, such observational studies have not been adequately controlled for confounding factors, such as the onset of puberty, and provide no information about compliance. These issues were addressed in a more recent placebo-controlled, blinded study conducted over 1 year, which used careful stadiometry measurements to examine the effects of intranasal BDP (336 µg/day) (13). Children treated with INS experienced reduced growth velocity compared to placebo – a difference which, by 6 months, had reached statistical significance (Fig. 3). Results from this study were complicated by some confounding factors. Mean age, height, and bone age were each significantly greater at baseline in the INS-treated group; therefore, these children would have been expected to have a slightly lower growth rate regardless of treatment. Nevertheless, a re-analysis of sex and age-matched pairs from that study revealed a persistent statistically significant effect of intranasal BDP on growth.

What factors were likely to contribute to these different growth results from observational *vs* prospective controlled studies of intranasal BDP treatment for

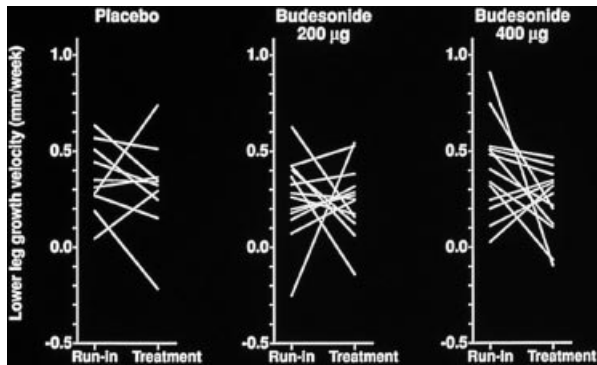


Figure 2. Lower leg growth during IN-BUD treatment (Wolthers & Pedersen [11]).

childhood rhinitis? Perhaps the most important is the duration and consistency of administration. In observational studies, it is unlikely that children were prescribed INS consistently throughout the year. A further difference is that compliance is more adequately ensured in prospective controlled studies, increasing the exposure of the child to daily therapeutic corticosteroid effects.

Drug-specific vs class-specific effects

An important question is whether other INS share the growth-inhibiting effect of BDP, particularly in light of differing effects of various ICS preparations on growth in the treatment of asthma. In a 1-year comparative study of ICS, BDP (200 µg bd.) and salmeterol, for example, BDP treatment significantly impaired growth rate by ~1.5 cm/year (14). In contrast, in a 1-year study of ICS, FP administered at doses approximately clinically equivalent to those of 400 µg/day BDP, no statistically significant effect on growth was observed (Fig. 4) (15). This difference between the effects of different INS on growth was probably due mainly to differences in gastrointestinal absorption and hepatic inactivation, with FP demonstrating both reduced absorption and more efficient first-pass hepatic inactivation when compared to BDP.

In another recent study, children with asthma were randomised to receive ICS therapy with FP or BDP for

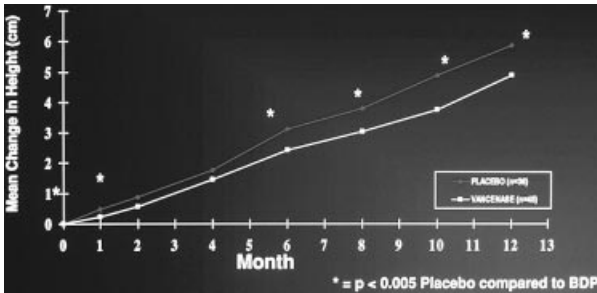


Figure 3. INS BP-AQ growth study: mean change in height from baseline (Rachelefsky et al. [13]).

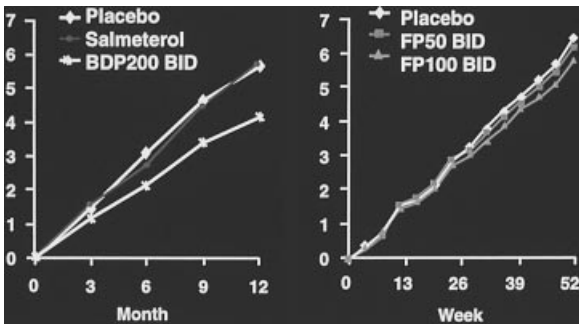


Figure 4. Mean change in height from baseline: all patients (BDP and FP) (Simons [14]; Allen et al. [15]).

1 year. Annual growth rates were significantly higher in the former. Moreover, the addition of INS FP did not further affect the growth of the children in either group, whereas the addition of INS BDP caused additional growth suppression in both groups (Table 1) (16).

Conclusions

From the evidence available from short-term studies of intranasal BUD and longer-term studies of intranasal BDP, it appears that slowing of linear growth can occur in children treated with INS. The clinical relevance of these observations, however, remains uncertain. Most importantly, continuous and long-term, rather than intermittent, therapy is needed to cause a significant effect of INS on growth; this is an uncommon requirement for the treatment of allergic rhinitis. For this reason alone, INS in general are likely to have less effect than ICS on growth. Furthermore, recent and emerging data suggest that the newer INS, such as fluticasone propionate and mometasone furoate, which demonstrate low absorption across the nasal mucosa combined with very efficient first-pass metabolism and very low intestinal absorption, are highly unlikely to affect growth. However, further well-designed placebo-controlled prospective studies using stadiometry to assess growth over at least 1 year are needed to

Table 1. Effects of ICS and INS on 1-year growth: comparison of FP with BDP (Fiocchi et al. [16])

	Inhaled FP	Inhaled BDP
No INS		
No. of patients	127	135
Mean growth (cm/year)	5.04	4.05
Concomitant INS (all)		
No. of patients	32	26
Mean growth (cm/year)	5.02	4.24
Intranasal FP		
No. of patients	16	12
Mean growth (cm/year)	5.16	4.66
Intranasal BDP		
No. of patients	9	7
Mean growth (cm/year)	4.42	3.65

distinguish those INS with reduced or absent effects on growth. Such studies with FP are currently in progress.

In practice, selection of the INS which optimises the ratio of therapeutic effect to systemic bioavailability, and titration to the lowest effective dose is likely to reduce risk of growth suppression to a negligible level. To insure early detection of a rare growth

effect, and to provide reassurance to families administering INS and/or ICS, any child receiving corticosteroids should undergo regular monitoring of growth, at ~4-month intervals during the first year of treatment, and at 6-month intervals thereafter.

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