Inhaled corticosteroids in children with persistent asthma: Effects on growth

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In the current issue of the *Journal*, we feature the Cochrane Reviews on the growth effects of inhaled corticosteroids for children with persistent asthma (1,2). We asked Dr Brian Kuzik to comment on and put these two reviews in context.

INHALED CORTICOSTEROIDS IN CHILDREN WITH PERSISTENT ASTHMA: EFFECTS ON GROWTH

Background

Treatment guidelines for asthma recommend inhaled corticosteroids (ICS) as first-line therapy for children with persistent asthma. Although ICS treatment is generally considered to be safe in children, the potential systemic adverse effects related to regular use of these drugs have been and continue to be a matter of concern, especially their effects on linear growth.

Methods

Selection criteria: Parallel-group randomized controlled trials comparing daily use of ICS, delivered using any type of inhalation device for ≥3 months, versus placebo or nonsteroidal drugs in children <18 years of age with persistent asthma.

Results

Twenty-five trials were included involving 8471 (5128 ICS-treated and 3343 control) children with mild to moderate persistent asthma. Six molecules (beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate and mometasone furoate) given at low or medium daily doses were used for a period of three months to four to six years. Most trials were blinded and more than one-half had drop-out rates >20%.

Compared with placebo or nonsteroidal drugs, ICS produced a statistically significant reduction in linear growth velocity (14 trials with 5717 participants; mean difference [MD] −0.48 cm/year [95% CI −0.65 to −0.30 cm/year], moderate-quality evidence) and in the change from baseline in height (15 trials with 3275 participants; MD −0.61 cm/year [95% CI −0.83 to −0.38 cm/year], moderate-quality evidence) during a one-year treatment period.

Subgroup analysis showed a statistically significant group difference between six molecules in the mean reduction of linear growth velocity during a one-year treatment period (χ^2=26.1, degrees of freedom (df) = 5; P<0.0001). The group difference persisted even when analysis was restricted to the trials using doses equivalent to 200 µg/day hydrofluoroalkane (HFA)-beclomethasone. Subgroup analyses did not show a statistically significant impact of daily dose (low versus medium), inhalation device or participant age on the magnitude of ICS-induced suppression of linear growth velocity during a one-year treatment period. However, head-to-head comparisons are needed to assess the effects of different drug molecules, dose, inhalation device or patient age. No statistically significant difference in linear growth velocity was found between participants treated with ICS and controls during the second year of treatment (five trials with 3174 participants; MD −0.19 cm/year [95% CI −0.48 to 0.11 cm/year]; P=0.22). Of two trials that reported linear growth velocity in the third year of treatment, one trial involving 667 participants showed similar growth velocity between the budesonide and placebo groups (5.34 cm/year versus 5.34 cm/year), and another trial involving 1974 participants showed lower growth velocity in the budesonide group compared with the placebo group (MD −0.33 cm/year [95% CI −0.52 to −0.14 cm/year]; P=0.0005). Among four trials reporting data on linear growth after treatment cessation, three did not describe statistically significant catch-up growth in the ICS group two to four months after treatment cessation. One trial showed accelerated linear growth velocity in the fluticasone group at 12 months after treatment cessation, but there remained a statistically significant difference of 0.7 cm in height between the fluticasone and placebo groups at the end of the three-year trial.

One trial including follow-up into adulthood showed that participants of prepubertal age treated with budesonide 400 µg/day for a mean duration of 4.3 years exhibited a mean reduction of 1.20 cm (95% CI −1.90 cm to −0.50 cm) in adult height compared with those treated with placebo.

Conclusions

Regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm/year in linear growth velocity and a 0.61 cm change from baseline in height during a one-year treatment period in children with mild to moderate persistent asthma. The effect size of ICS on linear growth velocity appears to be associated more strongly with the ICS molecule than with the device or dose (low to medium dose range). ICS-induced growth suppression appears to be maximal during the first year of therapy and less pronounced in subsequent years of treatment. However, additional studies are needed to better characterize the molecule dependency of growth suppression, particularly with newer molecules (mometasone, ciclesonide), to specify the respective role of molecule, daily dose, inhalation device and patient age on the effect size of ICS, and to define the growth suppression effect of ICS treatment over a period of several years in children with persistent asthma.

The full text of the Cochrane Review is available in The Cochrane Library (1).

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INHALED CORTICOSTEROIDS IN CHILDREN WITH PERSISTENT ASTHMA: DOSE-RESPONSE EFFECTS ON GROWTH

Background

ICS are the first-line treatment for children with persistent asthma. Their potential for growth suppression remains a matter of concern for parents and physicians.

Methods

Selection criteria: Studies were eligible if they were parallel-group randomized trials evaluating the impact of different doses of the same ICS using the same device in both groups for a minimum of three months in children one to 17 years of age with persistent asthma.

Results

Among 22 eligible trials, 17 group comparisons were derived from 10 trials (3394 children with mild to moderate asthma), measured growth and contributed data to the meta-analysis. Trials used ICS (beclomethasone, budesonide, ciclesonide, fluticasone or mometasone) as monotherapy or as combination therapy with a long-acting beta$_2$-agonist and generally compared low (50 µg to 100 µg) versus low to medium (200 µg) doses of hydrofluoroalkane (HFA)-beclomethasone equivalent over 12 to 52 weeks. In the four comparisons reporting linear growth over 12 months, a significant group difference was observed, clearly indicating lower growth velocity in the higher ICS dose group of 5.74 cm/year compared with 5.94 cm/year on lower-dose ICS (n=728 school-age children; MD 0.20 cm/year [95% CI 0.02 to 0.39 cm/year]; high-quality evidence): No statistically significant heterogeneity was noted among trials contributing data. The ICS molecules (ciclesonide, fluticasone, mometasone) used in these four comparisons did not significantly influence the magnitude of effect (χ^2=2.19 [2 df]; P=0.33). Subgroup analyses on age, baseline severity of airway obstruction, ICS dose and concomitant use of nonsteroidal antiasthmatic drugs were not performed because of similarity across trials or inadequate reporting. A statistically significant group difference was noted in unadjusted change in height from zero to three months (nine comparisons; n=944 children; MD 0.15 [95% CI −0.28 to −0.02]; moderate-quality evidence) in favour of a higher ICS dose. No statistically significant group differences in change in height were observed at other time points, nor were such differences in weight, bone mass index and skeletal maturation reported with low quality of evidence due to imprecision.

Conclusions

In prepubescent school-age children with mild to moderate persistent asthma, a small but statistically significant group difference in growth velocity was observed between low doses of ICS and low to medium doses of HFA-beclomethasone equivalent, favouring the use of low-dose ICS. No apparent difference in the magnitude of effect was associated with three molecules reporting one-year growth velocity (mometasone, ciclesonide and fluticasone). In view of prevailing parents' and physicians' concerns about the growth suppressive effect of ICS, lack of or incomplete reporting of growth velocity in >86% (19 of 22) of eligible paediatric trials, including those using beclomethasone and budesonide, is a matter of concern. All future paediatric trials comparing different doses of ICS with or without placebo should systematically document growth. Findings support use of the minimal effective ICS dose in children with asthma.

The full text of the Cochrane Review is available in The Cochrane Library (2).

EXPERT COMMENTARY

Asthma continues to have a major impact on Canadian children, with preschool-age children outnumbering all other age groups combined in asthma-related emergency department visits (3). Canadian paediatric asthma guidelines recommend ICS for control (4); however, these Cochrane reviews confirm that ICS therapy is associated with an adverse effect that is contrary to the most fundamental tenet of paediatric care – the preservation of normal growth. Nevertheless, paediatricians should regard these reviews as good news: the glass is half-full, not half-empty. Since the first Cochrane review on this topic 15 years ago (5), many of us were understandably concerned because evidence suggested that long-term ICS therapy may suppress growth by 1.5 cm/year. The dread of creating a generation of well-controlled but stunted asthmatic adults was building as quickly as evidence supporting the use of ICS to control paediatric asthma. Thankfully, with the passage of time, it appears that the benefits of ICS therapy in children far outweigh the risks – but clearly there are risks.

We all wish we had 30-year studies documenting the unequivocal safety and efficacy of the ICS we tend to prescribe and in the exact dose and patient population that we serve – but that will simply never happen. We, therefore, must rely on the Herculean effort by the authors of these reviews to scrutinize the accumulated wisdom of dozens of well-designed but nevertheless imperfect and heterogeneous studies. So what have we learned?

- Treatment with any ICS has the potential to suppress growth. The full text of the Zhang et al (1) review reveals that the effect is greatest in the 'older' preparations, such as budesonide; less in the 'newer' ones, such as fluticasone; and smallest in the newest ICS, ciclesonide.
- Medium- to high-dose therapy (>200 µg/day budesonide equivalent) has more effect on growth than lower doses, which has more effect than intermittent therapy (6).
- It appears that most of this adverse effect occurs in the first year, after which the impact does not appear to be cumulative and/or there is some catch-up growth.
- Although only based on a single study, even the long-term use of high-dose 'older' ICS preparations (budesonide 400 µg per day for several years), only reduced final adult height by 1.2 cm (7). Furthermore, we can reasonably expect that this already minimal impact will be reduced with the use of newer ICS preparations as well as the potential role of intermittent therapy.

The management of paediatric asthma is challenged by the presence of several different wheezing phenotypes, the inability to measure airway inflammation or hyper-reactivity to help confirm a diagnosis in most children <6 years of age, and the dilemma that it is often "practically impossible" (8) to use an Asthma Predictive Index to distinguish a wheezing infant or toddler with the first of many subsequent episodes of viral-triggered asthma from one with their first and only episode of bronchiolitis. As a result, we often find ourselves using ICS preparations 'off label' and with equivocal clinical indications. We must not, however, become complacent; ICS therapy demands regular review with the goal of using the lowest effective dose possible. No pharmaceutical is without adverse effects, and these reviews help us to understand the measureable but, thankfully, minimal potential growth suppression from long-term ICS therapy in asthmatic children.

Tragically, mortality from paediatric asthma still occurs; however, as stated so eloquently by Professor Andrew Bush, "no one ever died because they fell 1 cm short of their potential final height" (9).

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