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Commentary

Cochrane in context: Inhaled corticosteroids in children with persistent asthma: effects on growth and dose–response effects on growth

Cochrane Review: Inhaled corticosteroids in children with persistent asthma: effects on growth Zhang L, Prietsch SOM, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: effects on growth. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD009471. DOI: 10.1002/14651858.CD009471.pub2

Cochrane Review: Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth Pruteanu AI, Chauhan BF, Zhang L, Prietsch SOM, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: dose–response effects on growth. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD009878. DOI: 10.1002/14651858.CD009878.pub2

This companion piece to the reviews, "Inhaled corticosteroids in children with persistent asthma: effects on growth" and "Inhaled corticosteroids in children with persistent asthma: dose–response effects on growth," contains the following pieces:

- The abstract of each review
- A commentary from one or more of the review authors, explaining why the review team felt both reviews were important to produce
- A review of clinical practice guidelines
- Some other recently published references on this topic

Abstract—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 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 the effects on linear growth.

Objectives To assess the impact of ICS on the linear growth of children with persistent asthma and to explore potential effect modifiers such as characteristics of available treatments (molecule, dose, length of exposure and inhalation device) and of treated children (age, disease severity and compliance with treatment).

Search methods We searched the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including CENTRAL, MEDLINE, EMBASE, CINAHL, AMED and PsycINFO; we handsearched respiratory journals and meeting abstracts. We also conducted a search of ClinicalTrials.gov and manufacturers' clinical trial databases to look for potential relevant unpublished studies. The literature search was conducted in January 2014.

Selection criteria Parallel-group randomised controlled trials comparing daily use of ICS, delivered by any type of inhalation device for at least 3 months, versus placebo or nonsteroidal drugs in children up to 18 years of age with persistent asthma.

Data collection and analysis Two review authors independently performed study selection, data extraction and assessment of risk of bias in included studies. We conducted meta-analyses using the Cochrane statistical package RevMan 5.2 and stata version 11.0. We used the random-effects model for meta-analyses. We used mean differences (MDs) and 95% confidence intervals as the metrics for treatment effects. A negative value for MD indicates that ICS have suppressive effects on linear growth compared with controls. We performed a priori planned subgroup analyses to explore potential effect modifiers, such as ICS

molecule, daily dose, inhalation device and age of the treated child.

Main results We included 25 trials 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 during a period of 3 months to 4–6 years. Most trials were blinded and over half of the trials had dropout rates of over 20%.

Compared with placebo or nonsteroidal drugs, ICS produced a statistically significant reduction in linear growth velocity (14 trials with 5717 participants, MD -0.48 cm year^{-1}, 95% confidence interval -0.65 to -0.30, moderate quality evidence) and in the change from baseline in height (15 trials with 3275 participants; MD -0.61 cm year^{-1}, 95% confidence interval -0.83 to -0.38, moderate quality evidence) during a 1-year treatment period.

Subgroup analysis showed a statistically significant group difference between six molecules in the mean reduction of linear growth velocity during 1-year treatment ($\chi^2 = 26.1$, d.f. $= 5$, $p < 0.0001$). The group difference persisted even when analysis was restricted to the trials using doses equivalent to 200 μg day^{-1} hydrofluoroalkane–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 1-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^{-1}, 95% confidence interval -0.48 to 0.11, $p = 0.22$). 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 vs. 5.34 cm year^{-1}), and another trial involving 1974 participants showed lower growth velocity in the budesonide group compared with the placebo group (MD -0.33 cm year^{-1}, 95% confidence interval -0.52 to -0.14, $p = 0.0005$). Among four trials reporting data on linear growth after treatment cessation, three did not describe statistically significant catch-up growth in the ICS group 2–4 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 3-year trial.

One trial with follow-up into adulthood showed that participants of prepubertal age treated with budesonide 400 μg day^{-1} for a mean duration of 4.3 years had a mean reduction of 1.20 cm (95% confidence interval -1.90 to -0.50) in adult height compared with those treated with placebo.

Authors' conclusions Regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm year^{-1} in linear growth velocity and a 0.61-cm change from baseline in height during a 1-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 seems to be maximal during the first year of therapy and less pronounced in subsequent years of treatment. However, additional studies are needed to better characterise the molecule dependency of growth suppression, particularly with newer molecules (mometasone and 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.

Abstract—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.

Objectives To assess whether increasing the dose of ICS is associated with slower linear growth, weight gain and skeletal maturation in children with asthma.

Search methods We searched the Cochrane Airways Group Specialised Register of trials and the ClinicalTrials.gov website up to March 2014.

Selection criteria Studies were eligible if they were parallel-group randomised trials evaluating the impact of different doses of the same ICS using the same device in both groups for a minimum of 3 months in children 1–17 years of age with persistent asthma.

Data collection and analysis Two review authors ascertained methodological quality independently using the Cochrane Risk of bias tool. The primary outcome was linear growth velocity. Secondary outcomes included change over time in growth velocity, height, weight, body mass index and skeletal maturation.

Main 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

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therapy with a long-acting beta2-agonist and generally compared low (50–100 μg) versus low to medium (200 μg) doses of hydrofluoroalkane–beclomethasone equivalent over 12–52 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^{-1} compared with 5.94 cm year^{-1} on lower-dose ICS ($N = 728$ school-aged children; MD 0.20 cm year^{-1}, 95% confidence interval 0.02–0.39; high-quality evidence). No statistically significant heterogeneity was noted between trials contributing data. The ICS molecules (ciclesonide, fluticasone and mometasone) used in these four comparisons did not significantly influence the magnitude of effect [$\chi^2 = 2.19$ (2 d.f.), $p = 0.33$]. 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 0–3 months (nine comparisons; $N = 944$ children; MD 0.15, 95% confidence interval −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.

Authors' conclusions In prepubescent school-aged 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 hydrofluoroalkane–beclomethasone equivalent, favouring the use of low-dose ICS. No apparent difference in the magnitude of effect was associated with three molecules reporting 1-year growth velocity, namely, 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 more than 86% (19/22) 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.

Authors' Commentary

Linjie Zhang*[1] Aniela I. Pruteanu[2,3] Sílvio O. M. Prietsch[1] Bhupendrasinh F. Chauhan[4] and Francine M. Ducharme[2,3]

[1]Faculty of Medicine, Federal University of Rio Grande, Porto Alegre, Brazil
[2]Research Centre, CHU Sainte-Justine, Montreal, Canada
[3]Department of Pediatrics, University of Montreal, Montreal, Canada
[4]Clinical Research Unit on Childhood Asthma, CHU Sainte-Justine Research Centre, Montreal, Canada

*Correspondence to: Linjie Zhang, Faculty of Medicine, Federal University of Rio Grande, Rio Grande, Brazil. E-mail: zhanglinjie63@yahoo.com.br

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ICS are widely used as first-line treatment in children with asthma, however, parents and physicians always remain concerned about the potential negative effect of ICS on growth. One previous Cochrane systematic review with five randomized trials (1) suggests that moderate doses of inhaled beclomethasone and fluticasone cause a decrease in linear growth velocity of 1.51 and 0.43 cm year^{-1}, respectively. Over the last 10 years, several new randomized trials have been undertaken using various new and old inhaled corticosteroid molecules (2–11). We therefore decided to conduct a series of Cochrane reviews to evaluate the adverse effects of all currently available ICS on growth in children with asthma. The first review shows that regular use of ICS at low or medium daily doses is associated with statistically significant growth suppression during a 1-year treatment period in children with mild to moderate persistent asthma. Growth suppression appears neither progressive nor regressive, and it is not cumulative beyond the first year of therapy. The second review shows a small but statistically significant group difference in growth velocity between low doses and low to medium doses, favouring the use of low-dose ICS. The evidence derived from the two reviews suggests that, although the well-established benefits of regular use of ICS may outweigh the potential risks of growth suppression in children with persistent asthma, one would argue that ICS should be prescribed at the lowest effective dose, and linear growth should be regularly monitored in children treated with ICS. These two reviews highlight the evidence gap on this topic and point out the directions for further research.

Guidelines

Canadian Paediatric Society, 2012 (12)	ICS in appropriate doses are safe and efficacious. Long-term studies have demonstrated that ICS use does not impair growth or affect final adult height.
National Guideline Clearinghouse, 2012 (13)	Potential harms: The height of individuals on corticosteroids should be monitored over time. The potential effect on linear growth in children is important because these drugs tend to be used over long periods of time. Cumulative data in children suggest that low-to-medium doses of inhaled corticosteroids may have the potential of decreasing growth velocity, but this effect is not sustained in subsequent years of treatment, is not progressive, and may be reversible.
National Institute for Health and Care Excellence, 2007 (14)	Comparisons of low-dose (200–400 μg) corticosteroids: 4.1.4 … three studies were identified in the submission from GlaxoSmithKline that suggested a statistically significant difference favouring the use of fluticasone propionate for growth outcomes when compared with budesonide and beclometasone dipropionate. However, this difference was not demonstrated in the low-dose studies included in the assessment report. Comparisons of high-dose (>400 μg) corticosteroids: 4.1.6 … two studies identified a statistically significant difference in growth rates favouring fluticasone propionate compared with budesonide. Comparisons of ICS/Long-acting beta-agonists and higher dose ICS 4.1.7 One randomized clinical trial was included in the assessment report that compared budesonide/formoterol fumarate 80/4.5 μg daily plus short-acting beta agonists (SABA), as required, with higher dose budesonide 320 μg daily plus SABA, as required. The study identified statistically significant higher growth rates in children receiving budesonide/formoterol fumarate. 4.3.9 The Committee considered the adverse event profiles of the ICSs. It was aware that parents were often concerned about possible adverse events associated with ICSs, including growth and adrenal suppression. The Committee noted that some studies had suggested that, in the short term, fluticasone propionate may be associated with less impact on growth than other ICSs. However, the Committee did not consider that this effect had been shown to be consistent across studies. In addition, the Committee heard from clinical specialists that they considered that such adverse events were more frequently associated with higher than licenced doses and that the long-term evidence for an impact on growth and final height was inconclusive. The Committee heard from clinical specialists that, in clinical practice, other factors such as choosing the most appropriate device were considered to be more important when selecting an ICS than the possible differences in the impact on growth, so this was not seen as an overriding factor in considering which product to use. The Committee concluded it was not appropriate to distinguish between the different ICSs on the basis of adverse events.
Scottish Intercollegiate Guidelines Network, 2008 (15)	4.2.3 Safety of inhaled steroids: Children Administration of inhaled steroids at or above 400 μg beclomethasone dipropionate a day or equivalent may be associated with systemic side effects. These may include growth failure and adrenal suppression. Isolated growth failure is not a reliable indicator of adrenal suppression and monitoring cannot be used as a screening test of adrenal function. While the use of inhaled corticosteroids may be associated with adverse effects (including the potential to reduced bone mineral density) with careful inhaled steroid dose adjustment this risk is likely to be outweighed by their ability to reduce the need for multiple bursts of oral corticosteroids. • Monitor growth (height and weight centile) of children with asthma on an annual basis. • The lowest dose of inhaled steroids compatible with maintaining disease control should be used.

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Some other recent systematic reviews

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