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Effects of inhaled corticosteroids on growth in children with persistent asthma: impact of drug molecules and delivery devices - an overview of Cochrane reviews

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BACKGROUND

Inhaled corticosteroids (ICS) are the cornerstone of treatment for persistent asthma [1]. Their potential for growth suppression in children remains a matter of concern for parents and physicians. A series of three Cochrane Reviews have assessed the effects of ICS on growth in children with persistent asthma. The first review [2] provided an overview regarding growth suppression of ICS, and showed that regular use of ICS at low or medium daily doses was associated with a mean reduction of 0.48 cm/year in linear growth velocity during a one-year treatment period. The post hoc subgroup analysis of trials that used similar doses of ICS (equivalence of 200 µg/day HFA-beclomethasone) showed a significant difference between five ICS molecules regarding the effect size on linear growth velocity, with mean reductions of: -1.0 cm/year with beclomethasone, -0.61 cm/year with budesonide, -0.15 cm/year with ciclesonide, -0.42 cm/year with fluticasone, and -0.67 cm/year with mometasone. The second review [3] aimed to examine the dose-response relationship of ICS on growth. 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

low-dose ICS. The drug molecules (ciclesonide, fluticasone, mometasone) did not significantly influence the magnitude of effect of ICS on growth. The effects of inhalation devices were not taken into account in the analyses of both reviews. The third review [4] compared the effects of different ICS drug molecules and delivery devices on growth. In this paper, we briefly summarise the main findings of the third review.

METHODS

We conducted a literature search (up to April 2019), study selection, data extraction and assessment of risk of bias according to the rigorous Cochrane methodology [5]. We selected parallel-group randomised controlled trials comparing the effects on growth between different inhaled corticosteroid molecules at equivalent doses, delivered by the same type of device, or between different devices used to deliver the same inhaled corticosteroid molecule at the same dose, in children up to 18 years of age with persistent asthma. We used mean difference (MD) and 95% confidence interval (CI) as the metrics for treatment effects, and the random effects model for meta-analyses.

MAIN RESULTS

We identified six randomised trials involving 1199 children (4 to 12 years old) with mild-to moderate persistent asthma. The duration of trials varied from six to 20 months. Four trials compared different ICS molecules. One compared fluticasone with beclomethasone, and showed that patients treated with fluticasone at an equivalent dose had a significant greater linear growth velocity (MD 0.81 cm/year, 95% CI 0.46 to 1.16; 23 participants; low certainty evidence). Three trials compared fluticasone with budesonide. Fluticasone given at an equivalent dose had a less suppressive effect than

budesonide on growth, as measured by change in height over a period from 20 weeks to 12 months (MD 0.97 cm, 95% CI 0.62 to 1.32; 2 trials, 359 participants; moderate certainty evidence) (**Figure 1**).

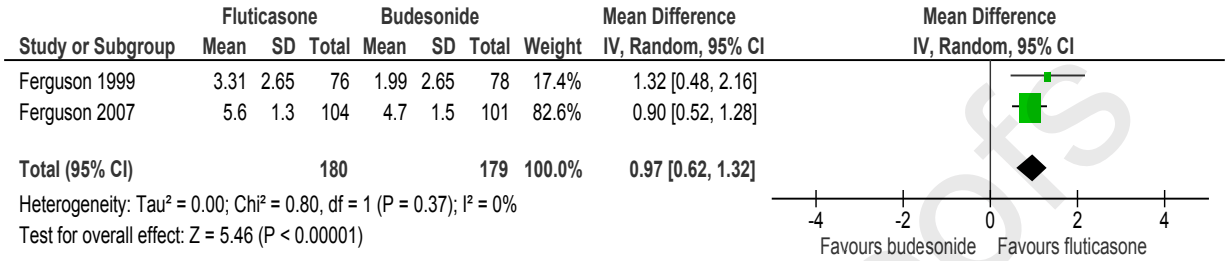

Figure 1. Comparison of fluticasone and budesonide: change in height (cm) over a period of time

We did not find significant difference in linear growth velocity between fluticasone and budesonide at equivalent doses (MD 0.39 cm/year, 95% CI -0.94 to 1.73; 2 trials, 236 participants; very low certainty evidence) (**Figure 2**).

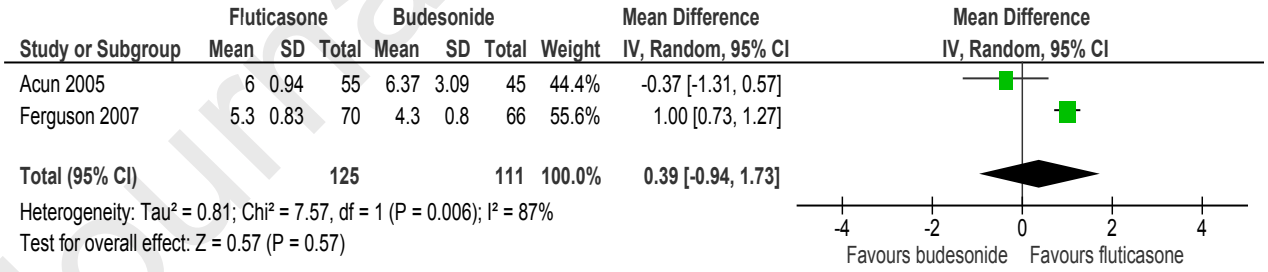

Figure 2. Comparison of fluticasone and budesonide: linear growth velocity (cm/year)

Two trials compared different inhalation devices. One reported a comparable linear growth velocity between beclomethasone administered via hydrofluoroalkane-metered dose inhaler and beclomethasone administered via chlorofluorocarbon-metered dose inhaler at an equivalent dose (MD -0.44 cm/year, 95% CI -1.00 to 0.12; 212

participants; low certainty evidence). Another trial showed a small but statistically significant greater increase in height over a period of six months in favour of budesonide via Easyhaler, compared to budesonide given at the same dose via Turbuhaler (MD 0.37 cm, 95% CI 0.12 to 0.62; 229 participants; low certainty evidence).

IMPLICATIONS FOR RESEARCH AND PRACTICE

This systematic review of head-to-head trials suggests that drug molecule and delivery device may impact the effect size of ICS on growth in children with persistent asthma. Fluticasone at an equivalent dose seems to inhibit growth less than beclomethasone and budesonide. Easyhaler is likely to have less adverse effect on growth than Turbuhaler when used for delivery of budesonide. However, the evidence from this review is not certain enough to make a definitive recommendation for clinical practice. The selection of inhaled corticosteroid and delivery device should be based on the efficacy, overall safety profile, ease of use, availability, cost of treatment, and preference of the child. Use of the lowest effective dose of ICS along with regular monitoring of growth are recommended for all asthmatic children who receive long-term treatment with ICS.

There is a limited number of head-to-head trials assessing the impact of drug molecule and delivery device on the effects of ICS on growth in children with asthma. There is probably little impetus for both pharmaceutical industries and researchers to conduct such further trials because of complexities in study design, limited clinical relevance, and concerns for conflict of interests. Pragmatic trials and real-world observational studies seem to be feasible options for further research.

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