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Cochrane Corner

Effect of inhaled corticosteroids on linear growth in children with persistent asthma

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BACKGROUND

Inhaled corticosteroids (ICS) are widely used as first-line therapy in children with persistent asthma [1]. Although ICS are generally considered a safe treatment in pediatric patients, the potential systemic adverse effects related to regular use of these drugs have been, and continue to be a concern, especially the effects on linear growth [2,3]. One previous Cochrane systematic review with 5 randomised trials suggests that moderate doses of inhaled beclomethasone and fluticasone cause a decrease in linear growth velocity of 1.51 cm/year and 0.43 cm/year, respectively [4]. Over the last 10 years, several more randomised trials have been undertaken using various new and old inhaled corticosteroid molecules. We therefore conducted this new Cochrane review to evaluate the adverse effects of all currently available ICS on growth in children with persistent asthma and to explore potential effect modifiers such as molecule, dosage, inhalation devices, duration of exposure and patient's age. In this paper, we briefly summarise the main finding of this Cochrane review [5].

METHODS

We conducted a literature search (November 2011- January 2014), study selection, data extraction and assessment of risk of bias according to the rigorous Cochrane methodology. We included parallel group randomised controlled trials comparing daily use of ICS, delivered by any type of inhalation device for at least three months, with either placebo or non-steroidal drugs in children up to 18 years of age with persistent asthma. We used the random-effects model for meta-analyses. We used mean difference (MD) and 95% CI as the metrics for treatment effects. A negative value of MD indicates that ICS have suppressive effects on linear growth compared with the controls. We performed subgroup analyses and sensitivity analyses to explore potential effect modifiers.

RESULTS

We included 25 trials involving 8471 (5128 ICS-treated and 3343 control) children with mild to moderate persistent asthma. All but 5 trials included in the review are multicenter trials, and 5 of them are international multicenter trials conducted in both high-income and low-income countries across Africa, Asia-pacifica, Europe and the Americas. Twelve trials were specially designed to assess the effect of ICS on linear growth in children with 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 varying from 3 months to 4-6 years. Compared to placebo or non-steroidal drugs, ICS caused a statistically significant reduction in linear growth velocity (14 trials with 5717 participants, MD -0.48 cm/yr, 95% CI -0.65 to -0.30) (Figure 1), in the change from baseline in height (15 trials with 3275 participants, MD -0.61 cm, 95% CI -0.83 to -0.38) and in height standard deviation score (4 trials with 258 participants, MD -0.13, 95% CI -0.24 to -0.01) during a one-year treatment. The subgroup analysis showed a statistically significant group difference in the mean reduction of linear growth velocity during one-year treatment between 6 molecules ($\chi^2 = 26.1$, df = 5, $P < 0.0001$). The group difference persisted even when the analysis was restricted to the trials using equivalent dose of 200 μg/day hydrofluoroalkane HFA-beclomethasone. The subgroup analyses did not show a statistically significant impact of daily dose (low vs. medium), inhalation device and patient age on the magnitude of ICS-induced suppression of linear growth velocity during a one-year treatment. No statistically significant difference was found between ICS and controls in linear growth velocity in the second

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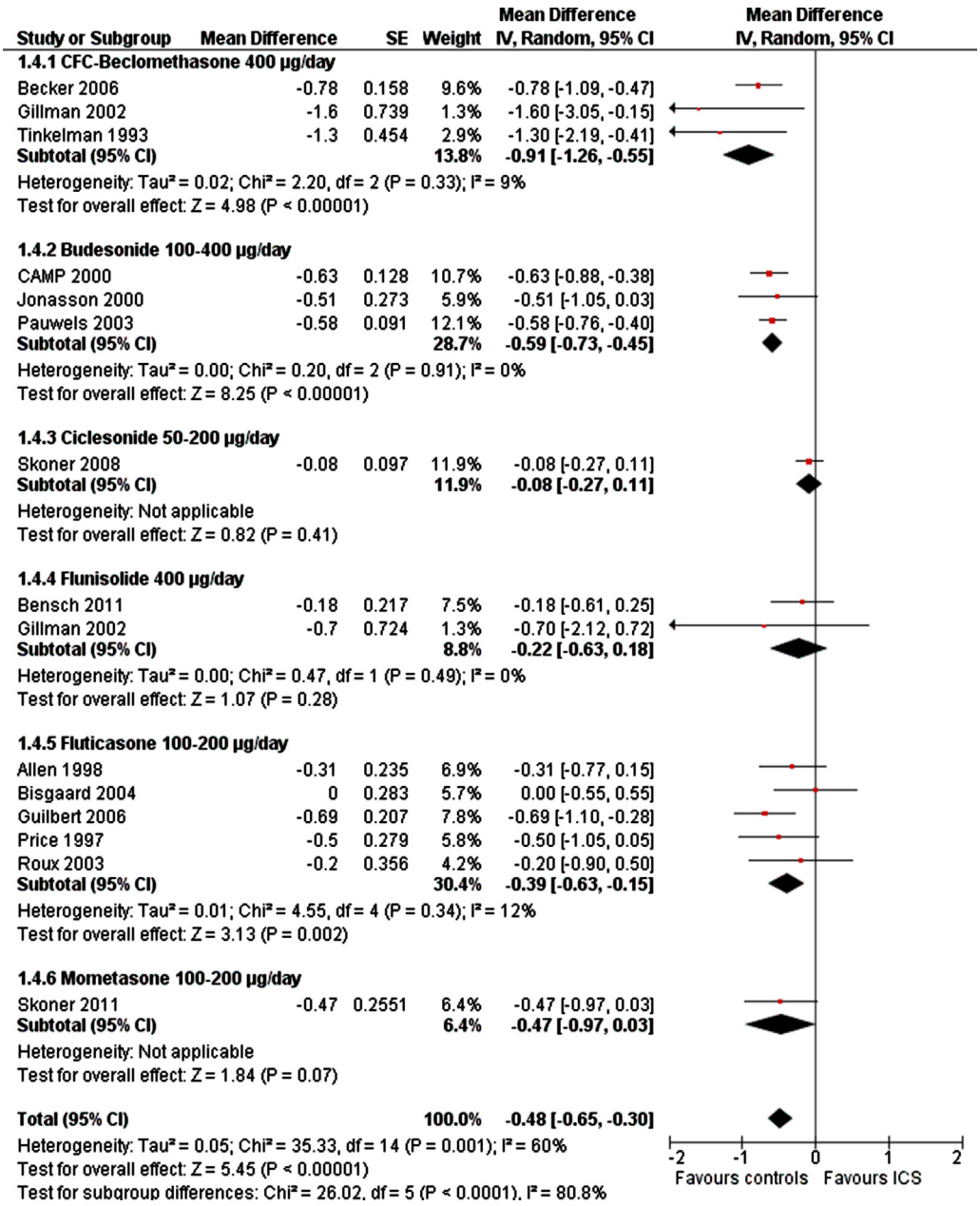

Figure 1. Inhaled corticosteroids vs. placebo or non-steroidal drugs: linear growth velocity (cm/yr) during a one-year treatment.

year of treatment (5 trials with 3174 participants, MD -0.19 cm/yr, 95% CI -0.48 to 0.11, p = 0.22) in contrast with a MD of -0.58 cm/yr (95% CI -0.71 to -0.44, p < 0.00001) in favour of placebo in the first year of treatment. Of 2 trials which reported linear growth velocity in the third year of treatment, one trial with 667 participants showed similar growth velocity between the budesonide and placebo groups (5.34 cm/yr vs. 5.34 cm/yr) and another trial with 1974 participants showed lower growth velocity in the budesonide group compared to the placebo group (MD -0.33 cm/yr, 95% CI -0.52 to -0.14, p = 0.0005), but the difference was less than that observed in the first year of treatment. Among 4 trials reporting the data of linear growth after treatment cessation, 3 trials did not find a statistically significant catch-up growth in the ICS group during 2 to 4 months after treatment cessation. One trial showed an 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 patients treated with budesonide 400 µg/day for a mean duration of 4.3 years in prepubertal age had a mean reduction of 1.20 cm (95% CI -1.90 to -0.50) in adult height compared to those treated with placebo.

DISCUSSION

Evidence derived from this meta-analysis of randomized trials shows that regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm per year in linear growth velocity and 0.61 cm in change from baseline in height during a one-year treatment 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 device or dose (low to medium dose range). The ICS-induced

growth suppression seems to be maximal in the first year of therapy and less pronounced in the subsequent years of treatment. However, additional studies are needed to better characterise the molecule dependancy of growth suppression, particularly with newer molecules (mometasone, ciclesonide), to specify the respective role of molecule, daily dose, inhalation device and patients' age on the effect size of ICS and to define the growth suppression effect of ICS treatment over period of several years in children with persistent asthma.

Given the considerable number of included trials did not report the methods of random sequence generation and allocation concealment, had high withdrawal rate, had open-label design and were sponsored by pharmaceutical-industry, selection bias, attrition bias, performance and detection bias and sponsorship bias might have occurred. However, the sensitivity analyses showed that these potential biases did not affect significantly the results of this review, underlying the robustness of the findings. We also conducted sensitivity analyses to assess the potential impact of compliance with treatment, previous use of ICS and missing data on the results, and no significant influence of these factors was found.

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