Medicines Evidence Commentary
commentary on important new evidence from Medicines Awareness Weekly

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Asthma in children and young people: effects of inhaled corticosteroids on growth

A Cochrane review found that, in children and young people with persistent asthma, during the first year of treatment, low-to-moderate doses of inhaled corticosteroids were associated with a statistically significant reduction in linear growth velocity* (mean difference −0.48 cm/year) and a lower increase in height from baseline (mean difference −0.61 cm) compared with placebo or non-steroidal asthma drugs. The difference appeared less pronounced in subsequent years. A second Cochrane review found that, compared with lower doses, linear growth velocity was reduced by 0.20 cm when higher doses of inhaled corticosteroids were used in children aged less than 12 years with persistent asthma. These findings support the recommendations in the current British guideline on the management of asthma to use the lowest dose of inhaled corticosteroid that maintains disease control in children with asthma, and to monitor height and weight annually.

Overview and current advice

The British guideline on the management of asthma (SIGN guideline 141, October 2014: accredited by NICE) advises that inhaled corticosteroids (ICS) are the first-choice regular preventer therapy for adults and children with asthma for achieving overall treatment goals.

The guideline highlights that, in children, administration of ICS at or above 400 micrograms of beclometasone dipropionate a day or equivalent may be associated with systemic side effects including growth failure and adrenal suppression. The guideline recommends that growth (height and weight centile) of children with asthma should be monitored on an annual basis, and the lowest dose of ICS compatible with maintaining disease control should be used.

See the Clinical Knowledge Summary on asthma for a general overview of this condition. The NICE pathway on asthma brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. High-dose inhaled corticosteroids in asthma is one of the therapeutic areas in the Key therapeutic topics - Medicines management options for local implementation document produced to support the QIPP medicines use and procurement work stream.
New evidence

Two Cochrane reviews have investigated the effect of ICS on growth suppression in children and young people up to 18 years old with mild-to-moderate persistent asthma.

The first Cochrane review (Zhang et al. 2014)\(^1\) included 25 randomised controlled trials (RCTs; n=8471) investigating 6 ICS (beclometasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate and mometasone furoate). These were given at low or medium daily doses (up to around 400 micrograms beclometasone dipropionate or equivalent) for between 12 weeks and 6 years. Control groups included placebo and non-steroidal asthma drugs such as long-acting beta-2 agonists (LABAs), sodium cromoglicate, nedocromil, leukotriene receptor antagonists (LTRAs), and theophylline.

In the first year of treatment, ICS were associated with a statistically significant reduction in linear growth velocity\(^*\) (the primary outcome) compared with placebo or non-steroidal asthma drugs (14 trials, n=5717; mean difference [MD] −0.48 cm/year, 95% confidence interval [CI] −0.65 cm/year to −0.30 cm/year, \(p<0.0001\)). ICS were also associated with a lower increase in height from baseline compared with controls (15 trials; n=3275; MD −0.61 cm, 95% CI −0.83 cm to −0.38 cm, \(p<0.00001\)).

Subgroup analyses based on indirect comparisons found a statistically significant difference between the ICS drugs and their effect on linear growth velocity, but no statistically significant difference was found for ICS dose, inhaler device, or age.

In the second year of treatment, there was no statistically significant difference between the ICS and control groups for difference in linear growth velocity (\(p=0.22\)) or increase in height from baseline (\(p=0.74\)).

Four trials examined the effect on growth when ICS were stopped. During a 12-month off-treatment follow-up period (1 trial; n=285), there was statistically significantly greater linear growth velocity in favour of the ICS (fluticasone propionate) group compared with the placebo group (MD 0.60 cm/year, 95% CI 0.40 cm/year to 0.80 cm/year, \(p<0.00001\)). However, there remained a statistically significant difference in height of 0.7 cm in favour of the placebo group at the end of the 3-year trial. The other 3 trials (n=810) did not find a statistically significant difference between the ICS and placebo groups in catch-up growth 2 to 4 months after stopping treatment. Another trial (n=658) followed participants until adulthood and found that prepubescent children treated with budesonide 400 micrograms/day for a mean duration of 4.3 years had a mean reduction in adult height of 1.20 cm (95% CI −1.90 cm to −0.50 cm) compared with those receiving placebo.

The second Cochrane review (Pruteanu et al. 2014)\(^2\) investigated whether increasing doses of ICS were associated with slower linear growth, weight gain and skeletal maturation in children and young people with persistent asthma. The review included 10 RCTs reporting 17 comparisons (n=3394) between 2 or more different doses of ICS (as monotherapy or in combination with non-steroidal asthma drugs such as LABAs or LTRAs) for between 12 and 52 weeks.

Over 12 months, higher dose ICS were associated with a statistically significant reduction in linear growth velocity (the primary outcome) compared with lower dose ICS (4 comparisons; n=728 prepubescent children; MD 0.20 cm/year, 95% CI 0.02 to 0.39 cm/year, \(p=0.03\)). However, there was no statistically significant difference between the groups in change in height over time periods longer than 3 months. Change in height comparisons were not adjusted for important covariates such as age, sex, puberty, and baseline height. No statistically significant difference between the higher and lower dose ICS groups was found in change in weight, body mass index and skeletal maturation from 0 to 12 months.
Commentary

These Cochrane reviews reinforce the knowledge that regular ICS use can be associated with a reduction in linear growth velocity and lower increase in height in children and young people with mild to moderate persistent asthma.

In the first review (Zhang et al. 2014)\(^1\), regular use of low or medium daily doses of ICS were associated with an overall mean reduction in linear growth velocity of 0.48 cm/year and a reduction in change from baseline in height of 0.61 cm during the first year of treatment. The results may not be applicable to children and young people with more severe asthma who are taking higher doses of ICS. The reduction in growth seemed to be most pronounced during the first year of treatment, and the authors report that the effect size seemed to be associated more strongly with the particular ICS rather than with the device or dose. However, these findings were based on indirect comparisons and the authors note that further studies are needed to assess the effects of different ICS, doses, inhalation devices and ages, and to determine the effects of ICS on growth over several years in children with persistent asthma. A further Cochrane review (Axelsson et al. 2013) is investigating the effects of different ICS drugs and delivery devices on growth in children and young people with persistent asthma.

The second review (Pruteanu et al. 2014)\(^2\) found a small difference in effect on growth between lower and higher doses of ICS in children aged under 12 with mild to moderate persistent asthma. While higher dose ICS were associated with a reduced growth velocity compared with lower dose ICS, there were no differences in change in height over time periods longer than 3 months. However these findings were not adjusted for important confounders such as age, sex, puberty, and baseline height.

The benefits of using ICS as regular preventer therapy in children and young people with persistent asthma are well established. The findings of these Cochrane reviews should serve as a reminder for clinicians about the risk of growth suppression in children when regular ICS are used. Clinicians should continue to follow the current British guideline on the management of asthma and prescribe the lowest dose of ICS compatible with maintaining disease control. Growth (height and weight centile) of children with asthma should be monitored on an annual basis as recommended by the guideline.

Study sponsorship

The majority of the included studies in both Cochrane reviews were sponsored by related pharmaceutical manufacturers.

References


* Linear growth velocity is obtained by measuring height at a number of time points during the study and performing linear regression of height against time
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