EDITORIAL

When will research measure up to our need to know how steroids affect childhood growth?

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"The efficacy of orally administered steroid preparations for the control of asthma is such that they would be universally used were it not for their undesirable side-effects when administered in pharmacological doses. These include manifestations of Cushing's syndrome, suppression of the pituitary-adrenal axis, and stunting of growth in children."

So begins the first published report of a randomised controlled trial of an inhaled steroid in children with asthma.[1] The observed clinical improvement on the children's asthma control was dramatic. Numerous studies since have established the effectiveness of inhaled corticosteroids (ICS) on a range of clinical outcomes in chronic asthma in children,[2] and ICS are now recommended in major asthma guidelines as first-line therapy for persistent asthma in children.[3] Surprisingly, there is no single Cochrane Review that pulls together the evidence comparing the effects of ICS molecules as a class versus placebo or non-steroid comparators in children with asthma for a range of important outcomes.

The clinical advent of ICS in 1973 marked a major step towards a therapy with the effectiveness of oral corticosteroids but without their associated side effects. However, there has been continuing concern about the undesirable steroid-related side effects of ICS on growth and, more recently, on pituitary-adrenal function.[4]

Two new Cochrane Reviews bring together the evidence about ICS in persistent childhood asthma and growth.[5][6] The first analysed 25 trials involving 8471 children (5128 ICS-treated and 3343 controls) with mild-to-moderate persistent asthma.[5] These children received a range of ICS (six different molecules) given at low or medium daily doses over a period of 3 months to 6 years. There was a highly significant but modest mean reduction in growth velocity (−0.48 cm/year) and mean change from baseline height during one year of treatment (−0.61 cm). There was evidence of a difference in the effects of the six ICS molecules, with first-generation drugs producing a slightly greater growth reduction than newer drugs, even at an equivalent dose. There was also evidence of a dose-response effect, with medium doses producing a statistically significant greater effect than low doses on the mean change from baseline in height, but not in linear growth velocity, during one year of treatment. There was no apparent effect of age or inhalation device on the magnitude of the effect. Strikingly, the reduction in linear growth velocity in ICS-treated children was most marked during the first year.

Only one trial followed children into adulthood.[7][8] This showed that prepubertal children treated with budesonide 400 µg/day for a mean duration of 4.3 years had a mean reduction of 1.20 cm in adult height compared with placebo-treated children. Again this growth deficit developed in the first two years of treatment, and growth velocity was similar between the ICS group and the comparators thereafter, without evidence of catch-up growth. In this study, longer duration of asthma at trial entry and atopy (any positive skin test) were also risk factors for reduced final height, suggesting that asthma and atopy may also effect linear growth. It is many years since Ninan and Russell noted that height velocity in children with asthma was maximal when the asthma was well controlled, both before and after starting ICS therapy, with growth poorest when asthma control was poorest.[9]

The second report reviewed the evidence for dose-response effects from ICS on linear growth, weight gain, and skeletal maturation in children with mild-to-moderate persistent asthma.[6] In the higher dose group, there was a small but statistically significant effect in growth, indicating a lower growth velocity equivalent to 0.2 cm/year. The effect on growth was only seen in the first 3 months, and was not influenced by the ICS molecule used. Evidence for other outcomes was considered of low quality. The review authors commented: "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 for concern."

Paediatricians and parents will in the main find the results reassuring. The studies included children from preschool though to puberty and from many different countries, so they are likely to have high generalisability. A reduction of 1.2 cm in final height may be a small price to pay when set against the asthma-associated morbidity experienced by many families.

However, parents and their physicians may be more concerned about how short term many of the studies are and how confusing their results are. The review authors conclude that additional studies are needed to: (i) better characterise the molecular dependency of growth suppression, particularly with respect to newer steroids; (ii) specify the respective role of molecule, daily dose, inhalation device, and patient's age on the effect size of ICS; and (iii) define the growth suppression over several years in children with persistent asthma.

One other area of concern for this author is the documentation of compliance. In nine studies treatment compliance was not measured, and in the other 16 studies compliance was measured by self-reporting or more objective methods, such as counting drug blisters or weighing canisters. The reported mean compliance was more than 75% in all but three studies and more than 90% (in both ICS and control groups) for a number of studies lasting a year, a figure that seems suspiciously high.

In two studies, treatment compliance declined over the first year of treatment,[10][11] and decline in treatment compliance with ICS over time has been observed in other studies.[12] It seems not unreasonable to speculate that greater growth suppression in the first year of ICS treatment, a consistent and unexplained observation, may reflect a decline in compliance with ICS over time. In this situation, the growth effects, especially over the long term, may be more dependent on the level of compliance than the effect of the drug. If high levels of compliance over the long term were to be achieved, the effects on final height might then be much more substantial.

If you had been writing about ICS in 1974 you would not have expected to be where we are now, still with so little unequivocal evidence about side effects. Concerns about side effects have been there from the beginning, and these drugs must by now have been given to millions of children. Yet, to take only one outcome, there has been only one randomised controlled trial in 658 children taking ICS for 4 years that provides final height data.[8] From studying the Cochrane Central Register of Controlled Trials, Sinha and colleagues reported that clinical trials of ICS for children with asthma were narrowly focused on short-term disease activity.[13] They recommended a core set of outcomes, developed using consensus techniques, that would standardise the measurement of important outcomes in randomised controlled trials. Such an approach is perhaps even more needed for evaluating long-term side effects. In the meantime, clinicians remain well advised to use ICS in the lowest doses necessary to achieve good asthma control.

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Declarations of interest

The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request) and declares no conflicts of interest.

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