Inhaled corticosteroid and children's growth

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No one ever died because they fell 1 cm short of their potential final height, but many families understandably worry about the side effects of inhaled corticosteroids (ICS), and may stop ICS treatment in consequence. It is important to state at the outset that reduced linear growth in a child with asthma should not uncritically be attributed to ICS, but should rather lead to a critical re-evaluation of the child. Atopy per se may lead to delay in puberty and a more prolonged prepubertal growth deceleration[1]; poorly controlled asthma, as with any chronic disease, may lead to growth failure[2]; and coincidental disease such as growth hormone deficiency should be considered. Indeed, it has been argued that accurate height measurement, with the results plotted on an appropriate centile chart is an essential part of the paediatric asthma clinic.[3] Children still do die of asthma attacks, which may result from non-adherence to treatment.[4] So it is essential that all professionals treating children with asthma understand the risks of side effects of ICS, and also their benefits, and are able to give balanced and credible reassurance to families.

Among the more common family worries about ICS are their effects on final height. There have been numerous ultrashort-term studies measuring tibial length as a surrogate for change in height over time using knemometry, and short-term studies using direct measurement of height, usually using stadiometry.[5 6] They all illustrate the dictum of the late Professor David Flenley that you cannot do a 5 year study in less than 5 years. However, at long last, and the nearest we are likely to get to a definitive answer, has come from the Children's Asthma Management Program (CAMP) study in the USA. The original question that the CAMP study was set up to address[7] has long ceased to have any interest, but the many spin-off data are still compelling. The initial aim of the CAMP study was to compare asthma treatment with 400 mcg budesonide, 16 mg nedocromil or placebo daily for 4–6 years in children with asthma aged 5–13 years. In a recent report, an impressive 90.3% (943/1041) of the original study group had their adult height measured at a mean age of 24.9 years.[8] In the budesonide but not the nedocromil group, there was a deficit in adjusted mean adult height compared with placebo of 1.2 cm; the deficit was greater for women (−1.8 cm, $p<0.001$) than for men (−0.8 cm, $p=0.10$) but a test for interaction did not confirm a gender effect on adult height in the budesonide group ($p=0.10$). Importantly, the deficit developed in the first 2 years of treatment, and growth velocity thereafter was similar in all three groups. Reduction in growth velocity was predominantly seen in prepubertal children, although age at entry into the study did not affect final adult height. There was a dose effect, with a decrement of 0.1 cm for each mcg/kg daily dose of ICS. There was no effect of cumulative prednisolone dosage. Longer duration of asthma at trial entry and atopy (any positive skin test) were also risk factors for reduced adult height, implying that asthma itself and possibly the treatment for other atopic conditions (see below) are probably not innocent of effects on final height.

This is the only randomised controlled study of this nature ever likely to be done, and thus the best source of information. The only other really long-term study was observational and not randomised, had problems of attrition, was confounded by asthma severity and looked at predicted adult height rather than a comparison of treated versus untreated, so the conclusion of these investigators of no effect of ICS on final adult height is not as strong as CAMP.[9] Of course there are issues with the CAMP data. The most important are the initial and subsequent doses of ICS. There is increasing evidence that 400 mcg/day of budesonide (if considered to be equivalent to 200 mcg/day fluticasone) is at the top of the ICS dose response curve,[10] and therefore some of these children received a higher dose than they needed. Second, the dose was fixed for a period of years, rather than tapered to a lower dose when symptoms were controlled, as mandated by modern guidelines. This is important, because there is at least some evidence that systemic bioavailability of ICS relates to excessive doses, rather than the absolute dose used.[11] Also, perhaps the effects would have been less if the investigators had minimised systemic absorption by using metered dose inhalers and spacers rather than a dry powder device. Hence it is probably fair to say that the CAMP findings represent a worst case scenario, and perhaps in real life, when modern guidelines are followed, a lesser effect will be seen.

What are the implications of these data for intermittent use of ICS at the time of respiratory viral infections? Will there be a period of growth slowing after each burst of ICS? We know that intermittent high dose ICS (fluticasone 750 mcg twice daily) used at the time of viral colds in preschool children led to a decrement of −0.24 Z scores in height over 40 weeks,[12] but whether this would have been cumulative if the strategy had been used over several years is not known, nor is it likely to be in the foreseeable future. However, intermittent as well as continuous ICS must be subject to the same precautions (below).

Also important is to consider the relevance of CAMP to the increasing range of novel and ever more potent ICS coming on the market.[13] Once daily therapy is a laudable aim, but ever increasing topical potency may not be. It cannot be assumed that CAMP data can be applied uncritically to novel steroids, and the onus will be on manufacturers to prove safety. Perhaps not germane to growth, but well worth pointing out in this context, are the increasing data implicating topically potent ICS in increasing susceptibility to respiratory infections[14–16]; this should not be surprising. Systemic steroids are immunosuppressive, so why should not ICS adversely affect the innate airway defences as well?

So where does CAMP leave the paediatrician? What has not changed is the importance of getting the basics right. First, does the child have asthma at all, and if asthma is the correct diagnosis, is there really a need for the prescription of ICS? For example, the evidence that the preschool child with mild episodic viral wheeze has eosinophilic inflammation and benefits from ICS is tenuous in the extreme. An intermittent ICS strategy with viral colds should only be used if there is real evidence of benefit.[17] Next, the use of an appropriate medication

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delivery device, usually a large volume, valved spacer is mandatory, and the fact that even teenagers usually do not use pressurised metered dose inhalers correctly should be stressed. The dose of ICS must be minimised, and consideration given to an add-on therapy rather than increasing the ICS dose if symptoms persist. Unfortunately the use of inflammatory markers to titrate ICS dose has not been shown to be beneficial in children.[18 19] It should also be noted that steroid exposure in atopic asthmatic children may not solely be through the airway; nasal steroids for allergic rhinitis, and steroid creams for eczema, may significantly add to exposure, and should also be minimised.[20 21] Above all, if asthma treatment is not apparently working, rather than reflexly escalating treatment, reasons should be sought—adherence, allergen and tobacco smoke exposure, and psychosocial factors should all be considered.[22]

Also unchanged by CAMP is the need for excellent communication with families. Fears about side effects should be heard; in terms of height, assurances should be given that height will be measured carefully and plotted on a growth chart and *shown to the family* at each visit, and that of course ICS dose will be minimised. CAMP allows us to tell families that (A) final adult height will at worst be about 1 cm less than the child's potential; and (B) any early decrement in growth is followed by normal growth thereafter. But it is also essential to stress the benefits of ICS to families. Asthma is a killing disease, and there is cogent evidence that ICS treatment is associated with reduction in asthma attacks. Also, that the bedrock of the success of the Finnish programme in reducing asthma morbidity and mortality was to get the basics right and increase the appropriate use of ICS should never be forgotten.[23] Finally, perhaps we should think 'old is beautiful' (a comforting thought for this author) and stick with tried and tested ICS, about which CAMP is reassuring.

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