Duration of growth suppressive effects of regular inhaled corticosteroids

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Abstract

The growth of 50 children receiving regular inhaled corticosteroids was segregated into divisions of six weeks from the start of treatment and compared with their growth when not receiving regular corticosteroids using a random effects regression model. Growth suppression was most marked during the initial six weeks after starting treatment, with most suppression occurring during the initial 18 weeks. Thereafter the children's growth was similar to their growth when not receiving treatment. These findings have important consequences for patterns of treatment of asthma in children.

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Regular treatment with inhaled corticosteroids may decrease growth in asthmatic children in the short^{1 2} and medium³⁻⁵ term. We have previously reported³ decreased growth in a group of prepubertal children regularly receiving an inhaled corticosteroid, beclomethasone dipropionate (BDP). The children's height was measured at least monthly during the study. Growth in those who received BDP was significantly decreased, with those randomised to receive BDP growing 1 cm less than the children given a placebo over a seven month period. Extrapolation of the degree of growth suppression we³ and others⁴ have reported is, however, inconsistent with long term historical data on asthma in children, which suggests essentially normal height attainment in adulthood.^{6 7}

The advent of computerised statistical packages enabling the analysis of complex longitudinal data such as that generated by our study prompted us to reanalyse growth in this group of children. We hypothesised that the growth suppressive effect of regular inhaled corticosteroids is non-linear, with the greatest effect at the start of treatment

Methods

Details of growth measurement are as reported elsewhere.³ The children were participating in

a randomised, double blind, placebo controlled study of BDP 200 µg twice daily via a Diskhaler as treatment for wheezing episodes associated with a viral infection. The treatment period was seven months, preceded by a two to six week run in period and followed by a wash-out period of four months. The children's height was measured using a Minimeter by a single observer before randomisation, at least monthly during the treatment period, and every alternate month during the washout period.

Analysis of growth in those children randomised to receive BDP used the STATA 5.0 (Stata Statistical Software, Stata Corporation, College Station, TX, USA) program using a random effects regression model to take account of clustering by subject. The random effects model thus allows valid regression estimates to be derived using more than one data point for each individual. Growth for the initial 30 weeks while receiving BDP was subdivided into six week blocks for each child and compared with growth when not receiving BDP.

Results

Fifty two children were randomised to receive BDP, of whom 50 had suitable growth data. Table 1 gives the growth details. Growth while not receiving BDP was 0.140 mm/week (95% confidence interval 0.136 to 0.144). Compared with their growth when not receiving BDP, growth in these children was significantly decreased during weeks 0-6. Although growth was decreased during weeks 7-18, this did not reach statistical significance. Growth during weeks 19-24 and 25-30 was similar to growth when not receiving treatment at 0.138 and 0.120 mm/day, respectively.

Discussion

Using a random effects regression model we have shown in this group of children that the growth suppressive action of inhaled corticosteroids is relatively short lived, with the most effect during the initial six weeks and most suppression occurring within 18 weeks of starting treatment. Growth was decreased by 50% during the first six weeks of treatment.

Table 1 Comparison of growth when not receiving BDP with growth during treatment segregated by six week divisions

Period	Growth (mm/week)	Difference between treatment/no treatment	95% confidence interval	p Value
No treatment	0.140	—		
Weeks 0-6	0.073	-0.067	-0.120 to -0.015	0.011
Weeks 7-12	0.094	-0.046	-0.098 to 0.005	0.076
Weeks 13-18	0.093	-0.047	-0.100 to 0.005	0.079
Weeks 19-24	0.138	-0.002	-0.054 to 0.051	0.935
Weeks 25-30	0.120	-0.02	-0.099 to 0.058	0.607

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Although the growth suppression was not statistically significant between weeks 7 and 18, the growth coefficients show a steady return to baseline, suggesting that our conclusions are valid. Thereafter growth was virtually identical to growth when not receiving treatment.

Unlike our previous work,³ we elected to include all 50 patients randomised to receive BDP in this analysis and did not exclude the four children who entered puberty during the study or the one child prescribed inhaled corticosteroids by his general practitioner. We felt this was justified as the comparisons were within subject, with each child acting as his or her own control. It is possible that the effects we observed reflect decreased compliance as the study progressed. Compliance with treatment, calculated by counting the used Diskhaler blisters, was, however, 75% in the group treated with BDP. Furthermore, the beneficial effect of BDP on lung function and bronchial responsiveness to methacholine was maintained over the course of the study.⁸

The growth suppressive effects of inhaled corticosteroids are poorly understood, although it is likely that they are mediated via an action on osteoblasts.⁹ Our findings suggest an ability to reset the growth suppressive effect and that a growth suppressive action is not observed after 18 weeks of treatment.

The current guidelines on the treatment of asthma in schoolchildren¹⁰ recommend that patients should double their dose of inhaled

corticosteroids at the first sign of an upper respiratory tract infection. In addition, many children only use inhaled corticosteroids when they have respiratory symptoms. In the absence of evidence in their favour, both these strategies could potentially magnify the growth suppressive effects of inhaled corticosteroids.

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