

# Short term growth during treatment with inhaled fluticasone propionate and beclomethasone dipropionate

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## Abstract

Short term lower leg growth was investigated with twice weekly knemometry measurements in 19 schoolchildren with mild asthma during treatment with daily doses of 200 µg fluticasone propionate, 400 µg, and 800 µg beclomethasone dipropionate from a dry powder inhaler. The design was a randomised, double blind, crossover trial. After a run in period of four days (period 1) the children were allocated to a sequence of active treatments in periods 2, 4, and 6. In periods 3 and 5 (wash out) placebo was given. All periods except the run in were two weeks long.

The mean lower leg growth velocities during the wash out periods were 0.61 and 0.80 mm/week. Mean growth velocities during treatment with fluticasone propionate and low and high doses of beclomethasone dipropionate were 0.34, 0.09, and 0.06 mm/week respectively. Compared with fluticasone propionate, treatment with beclomethasone dipropionate 400 and 800 µg/day was associated with a statistically significant reduction in growth velocity.

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As inhaled glucocorticosteroids are becoming increasingly used for prophylaxis in childhood asthma, renewed attention is drawn to the risk of adverse systemic effects such as suppression of linear growth.<sup>1</sup> Knemometry has been established as an integral part of the available measures of systemic activity of topical steroids in children.<sup>2,3</sup> By measuring changes in lower leg length with an accuracy of 0.09-0.11 mm<sup>4,5</sup> the knemometer provides a powerful tool for investigating the influence of exogenous glucocorticosteroids on linear growth in children.<sup>6</sup>

Fluticasone propionate is a potent topically active synthetic glucocorticosteroid currently in clinical development as an inhaled steroid preparation for the treatment of asthma.<sup>7</sup> Beclomethasone dipropionate is an inhaled glucocorticosteroid widely used for many years.<sup>8</sup> The aim of this study was to compare short term linear growth measured by knemometry in children with mild asthma during treatment with these two inhaled glucocorticosteroids.

## Patients and methods

When planning the study we estimated the SD of the mean lower leg growth rate to be 0.20 mm/week.<sup>3,6</sup> On this assumption we calculated that 12 patients would be sufficient for a power of >0.90 to detect a 50% reduction in growth rate, which

was considered a clinically relevant difference.<sup>9</sup> As some withdrawals were to be expected the study population was increased by seven patients.

Nineteen children, outpatients in a secondary referral centre, entered the study. All had mild asthma requiring only treatment as needed with inhaled β<sub>2</sub> stimulants. None had received treatment with glucocorticosteroids either inhaled or by mouth for two months before the study and no other drug was taken during the study period. Two girls and one boy were stage 2 according to Tanner's rating of puberty.<sup>10</sup> The other children were preadolescents without any signs of puberty. Table 1 gives the patient data. The study was approved by the local ethics committee and informed consent was obtained from all children and their parents.

The study design was a double blind, crossover trial with three active treatment periods and two wash out periods. After a run in period of four days (period 1) during which the children took no treatment except inhaled β<sub>2</sub> agonists they were randomised to treatment with fluticasone propionate 200 µg/day and beclomethasone dipropionate 400 and 800 µg/day in periods 2, 4, and 6. Treatment order was allocated by a computerised randomisation scheme prepared in balanced blocks. In periods 3 and 5 (wash out periods) placebo was given. Periods 2-6 were each 15 days long. The drug was taken in the morning and in the evening as one blister from a dry powder Diskhaler (Glaxo). The Diskhalers, identical in size and appearance, were delivered in identical boxes labelled with case number, period number, and prescription. During the run in period a placebo Diskhaler was used by the children so that they would become used to inhaling from the device. The inhalation technique was checked at each visit. To ensure optimum compliance the number of consumed blisters was counted at every visit.

Table 1 Characteristics of the study group

Patient characteristic	Value
Sex	
Male	15
Female	4
Ethnic origin	
Asian	1
White	18
Mean (range) age (years)	10.7 (7-14)
Mean (range) height (cm)	142.7 (116-160)
Mean (range) height SD score	-0.39 (-3.58 to +2.76)
Mean (range) statural growth velocity (cm/year)*	6.0 (4.0-9.5)
Mean (range) weight (kg)	33.7 (21-48)
Mean (range) body surface area (m <sup>2</sup> )	1.16 (0.87-1.39)
Mean (range) duration of asthma (years)	4 (2-8)

\*Calculated for the year before enrolment in the study.

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Table 2 Sequences of treatment (number of children) with 200 µg/day fluticasone propionate, 400 and 800 µg/day beclomethasone dipropionate, and mean (SD) growth velocities in 17 children with asthma

Treatment period	Fluticasone propionate 200 µg	Beclomethasone dipropionate		Mean (SD) growth velocity (mm/week)
		400 µg	800 µg	
2	7	4	6	0.24 (0.31)
4	6	6	5	0.25 (0.29)
6	4	7	6	0.00 (0.24)

Knemometry of the right lower leg was scheduled twice a week using a knemometer manufactured by the inventor.<sup>11</sup> All measurements were performed by the same trained observer with no reference to the recordings of the previous day. The children were measured at roughly the same time (that is, within 30 minutes) in the afternoon (between 1 and 5 pm) as recommended for knemometry.<sup>4</sup> At each visit four estimations of the length of the lower leg were made, the mean of the last three measurements being used for analysis.<sup>4,5</sup> In addition, height (Harpenden stadiometer) and weight (electronic beam analyser) were also recorded.

Forced expiratory volume in one second was measured with a dry wedge spirometer (Vitalograph) at the two visits during run in and then at days 6 and 15 in each period, the best of three measurements being used for analysis. Throughout the study peak expiratory flow rate was measured at home in the morning and evening (best of three) with a Mini-Wright peak flow meter. In addition, the use of inhaled β<sub>2</sub> stimulants and asthma symptoms during the night and day were recorded in diaries. To minimise the risk of a possible suppressive effect of reduced pulmonary function on growth only data from children showing less than 15% variation in pulmonary function between various periods were analysed.

At each visit inquiries were made about the emotional wellbeing of the children and a thorough physical examination was carried out to detect any intercurrent illness or disorder which might interfere with linear growth.<sup>4,12</sup>

#### ANALYSIS

Knemometry data from the run in period were excluded from analysis as only two measurements were performed in this period.<sup>4,12</sup> The purpose of this period was to let the children become familiar with the measurement technique.

On the basis of all measurements in the wash out and active treatment periods lower leg

growth velocities were calculated for each period by linear regression analysis and expressed as mm/week. As the wash out periods were not randomised they were not formally compared with the active treatment periods. Growth velocities during active treatment periods were compared using analysis of variance techniques adjusting for subject, period, and treatment effects.<sup>13</sup> The effect of carryover and treatment by period interaction was assessed. Significant changes were analysed by paired *t* test.

#### Results

Seventeen children completed the study according to the protocol. Table 2 gives the treatment sequences. Two boys were withdrawn during the first wash out period because of a deterioration of pulmonary function.

The technical error of the knemometer (that is, the mean SD of three successive estimations of lower leg length) was 0.09 mm.

No significant variations were seen in pulmonary function or symptom severity between the various treatments (table 3).

The figure shows the individual and mean lower leg growth velocities during wash out periods, treatment with fluticasone propionate and low and high doses of beclomethasone dipropionate. Independent of the treatment given, the growth velocities were significantly lower during period 6 than during periods 2 and 4 (table 2). We adjusted for the period effect in the comparison of the three active treatments (table 4). Compared with treatment with 200 µg/day fluticasone propionate a statistically significantly lower growth velocity was seen during treatment with 400 and 800 µg/day beclomethasone dipropionate ( $p=0.003$ ,  $t=3.2$ , 95% confidence interval 0.08 to 0.3 mm/week; and  $p<0.001$ ,  $t=3.8$ , 95% confidence interval 0.1 to 0.4 mm/week respectively).

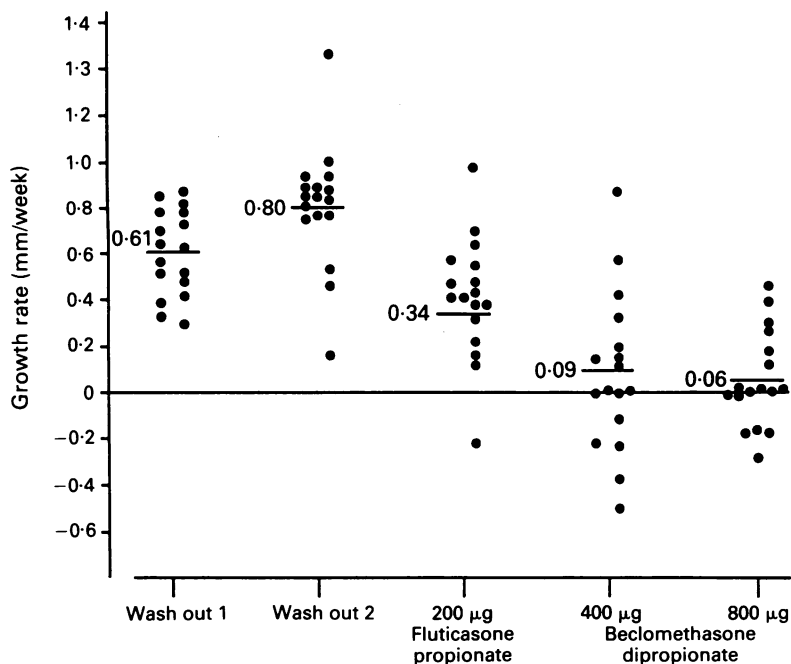
Two children presented with non-febrile sore throats, one during treatment with placebo and the other during treatment with fluticasone propionate. One child had a common cold during treatment with fluticasone propionate. No side effect attributable to any of the treatments was recorded.

#### Discussion

Efficacy studies have suggested that fluticasone propionate 200 µg/day is clinically equivalent to beclomethasone dipropionate 400 µg/day in controlling pulmonary symptoms (E A Gillies, Glaxo, personal communication). Therefore we decided to compare these doses, which should be

Table 3 Pulmonary function at hospital and at home and symptom severity in 17 children with mild asthma during run in and treatment with fluticasone propionate and beclomethasone dipropionate

Treatment	Mean (SD) forced expiratory volume (l)			Mean (SD) morning peak expiratory flow (l/min)		Mean (SD) evening peak expiratory flow (l/min)		Mean (SD) percentage of symptom free days (%)		Mean (SD) percentage of symptom free nights (%)	
	Treatment period			Run in	Treatment period	Run in	Treatment period	Run in	Treatment period	Run in	Treatment period
	Run in	Day 6	Day 15								
Fluticasone propionate 200 µg	2.08 (0.50)	2.08 (0.45)	2.13 (0.50)	311 (66)	334 (63)	318 (74)	335 (63)	73 (33)	75 (37)	89 (15)	91 (16)
Beclomethasone dipropionate 400 µg	1.90 (0.37)	2.03 (0.41)	2.13 (0.47)	322 (58)	336 (59)	324 (58)	336 (58)	74 (39)	78 (34)	88 (19)	92 (17)
Beclomethasone dipropionate 800 µg	1.98 (0.45)	2.09 (0.44)	2.08 (0.46)	319 (78)	333 (72)	324 (73)	336 (72)	71 (34)	76 (35)	90 (14)	92 (15)



Lower leg growth rates in 17 children during wash out periods and double blind treatment with fluticasone propionate 200 µg/day, beclomethasone dipropionate 400 µg/day, and beclomethasone dipropionate 800 µg/day.

regarded as standard paediatric doses capable of controlling asthma in most children. In addition, we added a period of treatment with beclomethasone dipropionate 800 µg/day because we wanted to include a dose which we expected would cause a significant reduction in growth rate.<sup>2,3</sup> We felt that it was important to show that the study design would allow us to demonstrate statistically significant changes.

The observed mean lower leg growth velocities during the placebo wash out periods were similar to those observed during run in and wash out periods in earlier trials of steroids given by mouth or inhaled in similar patient groups studied in similar study designs.<sup>2,6</sup> This confirms the reproducibility of the method used.

The growth rate during treatment with 200 µg/day fluticasone propionate was higher than during treatment with 400 µg/day beclomethasone dipropionate, indicating a significantly lower systemic effect of the former treatment. As the two doses may have an equipotent effect on asthma our data indicate that fluticasone propionate may be a therapeutic advance for the treatment of childhood asthma.

Previous knemometry studies have shown the systemic effect of inhaled budesonide to be dose related, reaching a significant level at a dose of 800 µg/day when taken from a conventional metered dose inhaler with a spacer.<sup>2,3</sup> Therefore the finding of similar growth velocities during treatment with 400 and 800 µg/day beclomethasone dipropionate in this study was surprising. The growth rate during treatment with 400 µg/day was so low, however, that a further reduction would be hard to detect. The suppressive effect of beclomethasone dipropionate seemed to be equivalent to that observed in children receiving 2.5 mg/day prednisolone.<sup>6</sup> Though no direct comparisons can be made these findings suggest

Table 4 Mean (SD) non-adjusted and adjusted growth velocities in 17 children with asthma during two weeks of treatment with 200 µg/day fluticasone propionate and 400 and 800 µg/day beclomethasone dipropionate

Treatment	Mean growth velocity (mm/week)	Adjusted mean growth velocity (mm/week)
Fluticasone propionate 200 µg	0.34 (0.29)	0.32
Beclomethasone dipropionate 400 µg	0.09 (0.34)	0.10
Beclomethasone dipropionate 800 µg	0.06 (0.21)	0.07

a more pronounced systemic effect of beclomethasone dipropionate delivered from a Diskhaler than of budesonide from a metered dose inhaler with a spacer.

There are no data evaluating long term growth in children treated with fluticasone propionate. Many reports have indicated that statural growth is unaffected during treatment with beclomethasone dipropionate in doses of 100–800 µg/day.<sup>14–18</sup> Most of these studies have been retrospective and uncontrolled and they all included children receiving the inhaled drug from a conventional metered dose aerosol. It is not known to what extent short term lower leg growth kinetics in children treated with exogenous glucocorticosteroids can be related to long term statural growth. Several workers have shown that short term growth rates are not good predictors of long term growth in normal children and in children with growth disorders.<sup>5,12,19,20</sup> This is probably due to the non-linearity of short term growth and to the diurnal and day to day variations in lower leg measurements. Age is another factor to consider when evaluating growth during long term treatment as some findings indicate that children in their teens may be less sensitive to the growth suppressive effect of glucocorticosteroids than children in the ages investigated in this study.<sup>21</sup> Finally, our study group consisted of children with mild asthma because we wanted to minimise any possible influence on growth due to a poorly controlled asthmatic disorder. These children would not normally receive treatment with inhaled glucocorticosteroids. In clinical practice this is restricted to children with moderate and severe asthma, a disorder which in itself has been suggested to retard growth.<sup>22,23</sup> Perhaps the growth suppressive effect of inhaled glucocorticosteroids in such children may be counterbalanced to some extent by the beneficial anti-inflammatory effect of the drug?

Considering the present findings fluticasone propionate may be an attractive alternative treatment to beclomethasone dipropionate in children with asthma. Dose response studies of topical and systemic activity are needed, however, before firm conclusions can be drawn.

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### Umbilical skin

Here's something else for you to measure in the newborn. The length of the skin of the umbilicus is slightly (2 or 3 mm) greater on the cranial surface than on the caudal. A paper from the Mayo clinic (Aengus S O'Marcaigh and colleagues, *Pediatrics* 1992; 90: 47-9) gives a normal range for cranial surface umbilical skin length measured from the junction of the abdominal wall and umbilicus to the junction of umbilical skin and gelatinous cord with gentle traction on the cord. In 104 babies of between 36 and 43 weeks' gestation and 2235 to 5490 g birth weight this measurement was not dependant on sex, gestation, weight, or body length. It did, however, slowly decrease between birth and 48 hours of age after which it remained constant up to 90 hours. Mean cranial surface umbilical skin length (95% confidence intervals) at birth was 13.5 mm (7.5 to 20.0) and at 48 hours 8.7 mm (2.5 to 16.0).

Why would you wish to measure umbilical skin length? It might help in the diagnosis of several dysmorphic syndromes especially Rieger's syndrome (autosomal dominant, goniodysgenesis, mid-face hypoplasia, variable hypodontia). Other syndromes with abnormal umbilical morphology include Aarskog's syndrome (X linked recessive, small stature, unusual facies, genital anomalies) and Robinow's syndrome (autosomal dominant, possibly recessive in some, 'fetal face', short forearms, genital hypoplasia, growth deficiency).

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