Effects of 2 Inhaled Corticosteroids on Growth

Results of a Randomized Controlled Trial

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Objective: To compare the long-term effect of treatment with fluticasone propionate or beclomethasone dipropionate on growth in asthmatic children.

Design: Prospective, multicenter, randomized, double-blind, parallel-group study.

Setting: Children requiring regular treatment with inhaled corticosteroids and with a sexual maturity rating of Tanner stage 1 (prepubertal).

Patients: Three hundred forty-three children aged 4 to 11 years with asthma. The growth population (excluding patients with protocol violations likely to affect growth measurements) included 277 patients.

Interventions: Fluticasone propionate or beclomethasone dipropionate, both at a dosage of 200 µg administered twice daily via a dry powder inhaler (Diskhaler) for 12 months.

Main Outcome Measures: Growth velocity, lung function, and serum and urinary cortisol levels.

Results: The adjusted mean growth velocity in the fluticasone group was significantly greater than that in the beclomethasone group (5.01 [SE, 0.14] vs 4.10 [SE, 0.15] cm/y; difference, 0.91 cm; 95% confidence interval, 0.63-1.20 cm; P<.001). Both treatments improved lung function, with significant differences in favor of fluticasone. Adverse events were similar in both groups, and there were no significant differences in effect on serum and urinary cortisol levels.

Conclusions: The more favorable risk-benefit ratio of fluticasone indicates that this agent is preferable to beclomethasone for the long-term treatment of children with asthma, especially if moderate doses are required.


Asthma is characterized by symptoms of wheeze, cough, and tightness of the chest resulting from an inflammatory response in the airways. Anti-inflammatory drugs such as inhaled corticosteroids are recommended in all age groups if inhaled, short-acting β-agonists are required more than once a week. Beclomethasone dipropionate and budesonide have similar efficacy profiles, but fluticasone propionate is at least as effective and as well tolerated as beclomethasone and budesonide at half the dose.

Short-term studies have indicated that inhaled beclomethasone dipropionate and budesonide (≥400 µg/d) can affect lower-leg growth rates in children, but these data do not accurately predict long-term growth. One year of treatment with beclomethasone dipropionate, 400 µg/d, has been shown to cause significant slowing of growth, compared with placebo or non-corticosteroid control drug. In contrast, a 12-month, placebo-controlled study showed that prepubescent children treated with fluticasone propionate, 50 or 100 µg twice daily, grew at the expected velocity for their age. Furthermore, a significant difference in growth rate was found during a period of 20 months in steroid-naive asthmatic children treated with fluticasone propionate, 200 µg/d (5.75 cm/y), compared with beclomethasone dipropionate, 400 µg/d (4.94 cm/y).

There are, however, limited data on the effect of fluticasone propionate at doses of greater than 200 µg/d on growth rates. This study was therefore designed to compare the effects on growth of fluticasone propionate with that of beclomethasone dipropionate, both at a dosage of 400 µg/d administered via a dry powder inhaler (Diskhaler; GlaxoSmithKline, Greenford, England) in children with a history of chronic asthma. Lung function was also evaluated, to provide an indication of the risk-benefit ratio of the treatments.
POPCULATION, MATERIALS, AND METHODS

We conducted the study in Holland, Hungary, Italy, Poland, Argentina, Chile, and South Africa under the conditions described in the Declaration of Helsinki. Approval from the Ethics Committee of each participating center and prior written informed consent from the appropriate child, parent, and/or guardian were obtained.

STUDY POPULATION

Boys (aged 4-11 years) or girls (aged 4-9 years) with a sexual maturity rating of Tanner stage 1 were eligible for entry into the study if they required treatment with inhaled fluticasone propionate, 100 to 200 µg/d, or beclomethasone dipropionate or budesonide, 200 to 500 µg/d, for at least the previous 8 weeks, at a constant dosage for at least 4 weeks before the run-in period. Patients with intermittent asthma or disorders that could affect growth, patients receiving oral or parenteral steroids, and patients admitted to a hospital with respiratory disease in the 4 weeks before the run-in period were excluded from the study.

During the 2-week run-in period, patients continued to receive their existing inhaled corticosteroid treatment and albuterol sulfate from a metered-dose or dry-powder inhaler on an as-needed basis. Patients were randomized to treatment if they demonstrated a mean morning peak expiratory flow (PEF) during the last 7 days of the run-in period of no greater than 85% of their maximum achievable response after inhalation of albuterol sulfate, 400 µg, via a metered dose inhaler. Patients also had to have an asthma symptom score of at least 1 or require albuterol at least once daily on at least 4 of the last 7 days of the run-in period.

Patients were permitted to continue with the following antiasthma treatments, providing that the dose remained constant during the course of the study: cromolyn sodium, nedocromil sodium, methylxanthines, ketotifen fumarate, anticholinergics, and oral or long-acting β-agonists. In addition, the following treatments were permitted for use as needed: oral corticosteroids for asthma exacerbations, intranasal corticosteroids, decongestants, antihistamines, and antibiotics.

STUDY DESIGN

The study was a prospective, multicenter, randomized, double-blind, parallel-group design. The 2-week run-in period was followed by 52 weeks of treatment with fluticasone propionate or beclomethasone dipropionate, both administered at a dosage of 200 µg twice daily using a dry powder inhaler (Diskhaler). No specific instructions were given with respect to mouth rinsing. This was left to the investigators’ discretion, according to local practice. Both formulations looked the same because of the predominance of lactose in the formulation, and any taste associated with the products would be attributable to the lactose. Treatment randomization was generated by computer using a validated computer program (Patient Allocation for Clinical Trials; GlaxoSmithKline). Each investigator was given a block of treatment (minimum block size, 4 treatments) and provided with individually sealed envelopes containing details of the medication that corresponded to each patient’s treatment number. Treatment was assigned in ascending order, starting with the lowest number.

Patients visited the clinic after 2 and 4 weeks of treatment, and then at 12-week intervals for the next 48 weeks. A follow-up visit was arranged at 2 weeks after completion of treatment. No detailed assessments of compliance were made during the study. Although compliance with inhaled corticosteroid therapy is generally considered to be poor, the purpose of this study was to compare 2 inhaled corticosteroids for which it was assumed that compliance rates would be similar. However, investigators were asked to confirm whether patients were taking their medication correctly at each clinical visit.

OUTCOME MEASURES

The primary end point was growth velocity, measured by means of stadiometry during the 52-week treatment. Secondary end points included asthma symptom scores, β-agonist use, asthma exacerbation rate, and lung function measurements.

The study was powered to detect a difference in growth of 1 cm/y between the treatments. Based on data from a previous study,13 if the SD of growth velocity was 2.7 cm/y, it would be necessary to recruit 240 patients, ie, 120 per treatment group, to ensure a power of 80% to detect a difference of 1 cm/y at the 5% significance level.

On a daily basis, each patient recorded their daytime and nighttime asthma symptom score (0 indicates no symptoms; 1, mild; 2, moderate; and 3, severe), morning and evening PEF, the number of doses of as-needed albuterol administered, and concurrent medication on a diary card. This information was entered throughout the run-in period.

RESULTS

Of the 403 enrolled patients, 343 were randomized to treatment (170 to fluticasone and 173 to beclomethasone) (intent-to-treat population). The treatment groups were generally balanced with respect to age, sex, race, duration and severity of asthma, and use of corticosteroids before the study (Table 1). For the analyses of growth velocity, the intent-to-treat population excluded 3 patients treated with fluticasone and 4 patients treated with beclomethasone for whom there were insufficient height measurements. Sixty-six patients were excluded from the growth population, which therefore consisted of 277 patients (137 in the fluticasone group and 140 in the beclomethasone group) (Figure 1). Eight patients (3 receiving fluticasone and 5 receiving beclomethasone) required oral corticosteroid treatment and were excluded from the growth population.

The mean (SD) baseline height in both treatment groups for the growth population was comparable (fluticasone group, 123.8 [9.7] cm; beclomethasone group, 124.3 [10.8] cm), and there was a gradual increase in height over time in both groups (Figure 2). Adjusted mean (SE) growth velocity was significantly greater in
period and the first 4 weeks of treatment, and on the 14 days before subsequent clinic visits.

Height and lung function were recorded at each clinic visit. Height was measured on a standard calibrated, wall-mounted stadiometer (Harpenden; Holtain Ltd, Crymych, Wales) that was supplied to each participating center. Staff were trained in its use to ensure standardization of the measuring technique. The same operator collected all height measurements in triplicate at the same time (±4 hours) for an individual subject throughout the study. The PEF was measured using a mini–Wright peak flowmeter (Clement Clark International Ltd, Harlow, England). Optional spirometer measurements of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and forced expiratory flow from 25% to 75% of the FVC measurement (FEF25%-75%) were also obtained. Patients were asked to stop β-agonist use (4 hours for short-acting and 12 hours for long-acting agents) before the spirometry measurements.

Adverse events, including exacerbations of asthma, were recorded at each clinic visit. An asthma exacerbation was predefined as any worsening of asthma symptoms requiring a change or addition to the patient’s asthma medications, other than an increased use of as-needed albuterol.

Nonfasting venous blood samples were taken at the start and the end of the treatment period for determination of standard hematologic and biochemical variables. Urine and blood samples were collected at the start of treatment and after 16 and 52 weeks for the measurement of morning serum cortisol level and overnight 12-hour urinary cortisol excretion. Samples were analyzed using a fluororescent polarization antibody technique.

STATISTICAL ANALYSIS

Thirty-two centers from 7 countries were involved in the study, and all centers within a country constituted a single subgroup for the purposes of statistical analysis. All analyses were performed on the intent-to-treat population except growth velocity, which was performed on the growth population. Treatment differences were tested using a 2-sided significance test at the 5% level.

Growth velocity was calculated for each patient during the 52-week study using linear regression of all the available clinic visit means of the triplicate height measurements. Only patients with at least 2 data points, one at randomization and the other on or after 16 weeks of treatment, were included in the growth population. Tanner staging assessments were performed by a physician at each visit, and patients were excluded from the growth population if they reached a Tanner stage of 2 or more at any time during the study. Patients were also excluded from the growth population if there were other factors likely to affect the measurement of growth (such as poor compliance or use of systemic corticosteroids). Growth velocity was investigated using analysis of covariance, with the patient’s height and age at randomization, country grouping, sex, and ethnic origin taken as covariates in the model. The difference between treatment groups was tested, and the associated P value and 95% confidence interval (CI) were produced. The primary end point (growth velocity) was also analyzed for the intent-to-treat population, excluding only those patients with no height measurements at baseline and/or during treatment.

Individual country-specific growth charts were not available for this international multicenter study conducted in 7 countries. However, we compared individual patients’ growth velocities against the North American growth charts to calculate the number of patients with a growth velocity below the 3rd, 10th, 25th, and 50th percentiles. Percentiles were determined using the mean age for the time in which the patient was in the study. We compared the proportion of patients in each treatment group below the specified percentile using the Fisher exact test.

Clinic lung function variables (PEF, FEV1, FVC, and FEF25%-75%) were also analyzed using an analysis of covariance with pretreatment lung function, age, sex, and country grouping included as covariates.

Diary card lung function variables (morning and evening PEF) were investigated using a similar method to that used for clinic lung function variables, with baseline taken as the mean of the last 7 days of the run-in period. Diary-card symptom data were analyzed using the van Elteren extension to the Wilcoxon rank sum test, which allowed possible imbalances between countries to be taken into account in the analysis.

The frequency of asthma exacerbations for each patient was also analyzed using the van Elteren extension to the Wilcoxon rank sum test. The number of patients with exacerbations in each treatment group were compared using the Fisher exact test.

Logarithm-transformed serum and urinary cortisol measurements were analyzed using an analysis of covariance similar to that used for clinic lung function variables. The difference between treatments was expressed as a ratio, and the corresponding P value and 95% CI for this ratio were calculated.

the fluticasone than in the beclomethasone group (5.01 [0.14] vs 4.10 [0.15] cm/y; difference, 0.91 cm; 95% CI, 0.63–1.20 cm; P<.001). The growth velocity frequency distribution for both treatment groups is displayed in Figure 3. The results of the analyses for the intent-to-treat population were similar. The adjusted mean growth velocity was greater in the fluticasone group than in the beclomethasone group (4.76 [0.28] vs 4.06 [0.29] cm/y; difference, 0.70 cm; 95% CI, 0.13–1.26 cm; P<.02). The SEs for the intent-to-treat population analyses (0.28 and 0.29), however, were nearly twice those for the growth population analyses (0.14 and 0.15), indicating that the patients removed from the analyses were contributing to a large proportion of the variation. The difference in growth velocity between the fluticasone group (n=127; adjusted mean, 5.04 [SE, 0.15] cm/y) and the beclomethasone group (n=135; adjusted mean, 4.05 [SE, 0.16] cm/y) remained significant (P<.001) when excluding those patients who received intranasal corticosteroids during the study.

Table 2 shows the number of patients with a growth velocity below the specified North American standard percentiles. As expected from the study population, most patients in each treatment group were below the 50th percentile. However, there was a significant difference between treatment groups, whereby...
patients treated with beclomethasone were more likely to be below a specific percentile than patients treated with fluticasone ($P < .001$).

The mean change from baseline in morning percentage of predicted PEF was higher at all weekly time points for patients receiving fluticasone than those receiving beclomethasone (Figure 4). During the 52-week treatment, the adjusted mean morning PEF was significantly higher in the fluticasone group (percentage of predicted, 105.6% vs 102.0%; difference, 3.6%; 95% CI, 1.2%-6.0%; $P = .003$) (mean PEF, 251.3 vs 242.8 L/min; difference, 8.6 L/min; 95% CI, 3.0-14.1 L/min; $P = .004$). Results for evening PEF were similar, with a higher mean value in the fluticasone group during the entire treatment period (255.1 vs 246.5 L/min; difference, 8.6 L/min; 95% CI, 3.0-14.1 L/min; $P = .003$). Both treatments produced significant improvements from baseline in clinic lung function assessments, with a significantly greater benefit in the fluticasone group compared with the beclomethasone group for all measured variables at week 52 (adjusted mean PEF, 282.5 vs 267.3 L/min [P < .001]; FEV₁, 1.8 vs 1.6 L [P < .001]; FVC, 2.0 vs 1.9 L [P = .008]; FEF₂₅₋₇₅%, 2.2 vs 2.0 L/s [P = .02]).

There were no significant differences between treatment groups for any assessment period with respect to diary-card symptoms or the as-needed use of albuterol. There was no significant difference between treatments in the total number of exacerbations (47 in the fluticasone group vs 52 in the beclomethasone group) and the percentage of patients who experienced at least 1 exacerbation (16% of patients in the fluticasone group vs 19% of patients in the beclomethasone group). The incidence of exacerbations was similar in the small group of patients ($n = 35$) who were previously receiving a daily dose of inhaled corticosteroids greater than 400 µg/d (11% of the fluticasone group vs 18% of the beclomethasone group).

Both treatments were well tolerated, and the numbers and types of adverse events were similar in both treatment groups (Table 3).
Figure 3. Growth velocity frequency distribution during 52 weeks of treatment with fluticasone propionate or beclomethasone dipropionate, both at a dosage of 400 µg/d (growth population). During the 52-week study, there was a significant difference between treatment groups in adjusted mean growth velocity (P<.001).

Table 2. Patients With Growth Velocity Below the Specified Percentiles

<table>
<thead>
<tr>
<th>Growth Velocity Percentile†</th>
<th>Fluticasone Propionate Group (n = 137)</th>
<th>Beclomethasone Dipropionate Group (n = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3rd</td>
<td>39 (28.5)</td>
<td>76 (54.3)</td>
</tr>
<tr>
<td>&lt;10th</td>
<td>52 (38.0)</td>
<td>102 (72.9)</td>
</tr>
<tr>
<td>&lt;25th</td>
<td>76 (55.3)</td>
<td>120 (85.7)</td>
</tr>
<tr>
<td>&lt;50th</td>
<td>102 (74.5)</td>
<td>131 (93.6)</td>
</tr>
</tbody>
</table>

*Percentiles are based on Tanner and Davies.14 Data are given as number (percentage) of patients. Groups are described in the “Study Population” subsection of the “Population, Materials, and Methods” section. For all growth velocity percentiles, patients in the beclomethasone group were significantly more likely to be below the percentile (P<.001).

†Measured during the 52-week study.

During the treatment period, there were no significant changes from baseline in morning serum cortisol levels in either treatment group, despite a trend toward reduced levels in both groups. A significant reduction from baseline in overnight urinary cortisol levels was found in the beclomethasone group; however, the differences between treatments were not statistically significant (Table 4).

Table 3. Most Common Adverse Events During Treatment

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Fluticasone Propionate Group (n = 170)</th>
<th>Beclomethasone Dipropionate Group (n = 173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with adverse events</td>
<td>136 (80.0)</td>
<td>140 (80.9)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>43 (25.3)</td>
<td>20 (11.6)</td>
</tr>
<tr>
<td>Asthma</td>
<td>26 (15.3)</td>
<td>33 (19.1)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>24 (14.1)</td>
<td>20 (11.6)</td>
</tr>
<tr>
<td>Ear, nose, and throat infection</td>
<td>24 (14.1)</td>
<td>16 (9.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>23 (13.5)</td>
<td>25 (14.5)</td>
</tr>
<tr>
<td>Pharyngitis/throat infection</td>
<td>21 (12.4)</td>
<td>25 (14.5)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>20 (11.8)</td>
<td>13 (7.5)</td>
</tr>
<tr>
<td>Viral respiratory infection</td>
<td>16 (9.4)</td>
<td>18 (10.4)</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>11 (6.5)</td>
<td>17 (9.8)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>10 (5.9)</td>
<td>11 (6.4)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (5.3)</td>
<td>14 (8.1)</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (4.7)</td>
<td>11 (6.4)</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>7 (4.1)</td>
<td>10 (5.8)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients. Groups are described in the “Study Population” subsection of the “Population, Materials, and Methods” section.

Analysis of growth velocity using SD scores was considered, to compare the results with the equivalent healthy population. However, this comparison would not have been conclusive for 2 main reasons. First, children with moderate to severe asthma have been shown to have slower growth rates and later onset of puberty than non-asthmatic children.15 Thus, the differences between the growth rates measured in this study from reference values could be attributable to the treatment used or to the patients’ asthma. Second, reference growth values are not available for all the countries where this study was conducted, and comparison with data from England or the United States could be confounded by factors such as nutritional or ethnic differences.16,17 This problem might have been avoided if a control group had been included in the study, but the use of placebo would not be ethical in a population with asthma requiring long-term therapy. Inclusion of a control group taking active, nonsteroidal...
therapy would have caused problems with multinational approval and would also have led to difficulties with treatment blinding.

The comparison of the data against North American percentiles clearly illustrates these problems. Most patients in both treatment groups had a growth velocity below the 50th percentile. This could be attributable to the influence of asthma, the influence of treatment, and/or the inapplicability of the North American standards.14 Nevertheless, in the comparison of both treatment groups, which was the objective of the study, the results of this analysis were entirely consistent with primary outcome data. Patients treated with beclomethasone were significantly more likely to have a growth velocity below a specified percentile than were patients treated with fluticasone.

A potential criticism of this study design is that intranasal corticosteroids were permitted for use as required. There is evidence that intranasal beclomethasone can affect growth in children,18 but other intranasal corticosteroids have lower systemic bioavailabilities and so may not have the same effect on growth. There was, however, no change in the outcome of this study when excluding those patients who received treatment with an intranasal corticosteroid during the course of the study.

To our knowledge, this is the first large, prospective, long-term study on the comparative effects of 2 inhaled corticosteroids on growth of asthmatic children. In a recent study of 333 children with moderate to severe asthma, Ferguson et al19 demonstrated a significant difference in growth rate in favor of fluticasone propionate (400 µg/d) compared with budesonide (800 µg/d) during a 20-week period. However, that study was not specifically designed to critically assess growth as an outcome factor, and height was measured by means of stadiometry only in a subgroup of patients.

The finding that children treated with fluticasone propionate, 200 µg twice daily, grew at a faster rate than those treated with beclomethasone dipropionate, 200 µg twice daily, was unexpected. The dose of fluticasone was twice the therapeutic equivalent dose of beclomethasone,9 and it could therefore be predicted that the systemic effects of the drugs would be similar.

Although the mean growth velocity in the fluticasone group was significantly greater than that in the beclomethasone group, an effect on growth velocity with fluticasone cannot be excluded. Although the growth velocity of prepubertal children treated with fluticasone propionate at doses of 100 and 200 µg/d for 1 year was not different from that of children treated with placebo,11 a trend for slower growth velocity compared with children treated with placebo was evident. Furthermore, an effect of budesonide on growth velocity in children has been observed.20,21 However, it has been demonstrated recently that these initial reductions in growth velocity are not correlated with attained adult height.22 Indeed, the difference between attained adult height and target adult height after treatment with budesonide (mean dose, 412 µg/d for a mean of 9.2 years) was not different from that of children with asthma not receiving inhaled corticosteroids or that of healthy siblings of the budesonide-treated children.

Fluticasone and beclomethasone improved lung function, but there was a significantly greater improvement with fluticasone in all efficacy assessments, both in morning and evening PEF and in results of clinic visit spirometry. This finding is not surprising considering the at least 2-fold greater clinical potency of fluticasone compared with beclomethasone, and is in keeping with other studies of inhaled corticosteroids in asthmatic children9,23 and adults.1,24

There was no difference between treatment groups for morning serum and overnight urinary cortisol levels, although there were trends toward greater reductions in the beclomethasone group. This does not contradict the results of previous studies, which showed that fluticasone is much less likely to produce endogenous cortisol suppression than beclomethasone at equipotent doses.9,23,25-27 Finally, both drugs were well tolerated. The incidence of rhinitis was lower in the beclo-
methasone group than in the fluticasone group. This may reflect a beneficial effect on rhinitis through the more systemically active beclomethasone.

The results of this study are not necessarily transferenceable to all formulations of fluticasone and beclomethasone. The systemic bioavailability of inhaled corticosteroids in adults is known to depend on the inhalation device. For fluticasone, the systemic bioavailability via the Diskus (GlaxoSmithKline) and Diskhaler dry powder inhalers is 16.6% and 11.9%, respectively, in healthy volunteers, and for the metered-dose inhaler containing a chlorofluorocarbon or hydrofluoroalkane propellant, the corresponding values are 26.4% and 28.6%, respectively. Together with the elimination of the traditional coordination problems associated with metered-dose inhalers, this finding provides further evidence that a powder inhaler may be more appropriate for use in children with asthma than a metered-dose inhaler.

The 12-month growth rate of children treated with fluticasone propionate, 200 µg twice daily, was greater compared with that for children treated with beclomethasone dipropionate, 200 µg twice daily. Lung function was improved to a significantly greater extent with fluticasone than with beclomethasone. On the grounds of this study, fluticasone should be chosen in preference to beclomethasone in children with asthma, especially if moderate doses are required.

Accepted for publication May 25, 2001.

This study was funded by grant FLTB 3015 from GlaxoSmithKline, Uxbridge, England.

The results of this study were presented at the European Respiratory Society 8th Annual Congress, Geneva, Switzerland, September 19-23, 1998.

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