Comparison of the efficacy and safety of inhaled fluticasone propionate 200 μg/day with inhaled beclomethasone dipropionate 400 μg/day in mild and moderate asthma

P Gustafsson, J Tsanakas, M Gold, R Primhak, M Radford, E Gillies

Abstract

This study was designed to compare the efficacy and safety of a new inhaled corticosteroid, fluticasone propionate at a total daily dose of 200 μg, with beclomethasone dipropionate 400 μg/day in childhood asthma. A total of 398 asthmatic children (aged 4–19 years) were randomised to receive either fluticasone propionate 200 μg daily or beclomethasone dipropionate 400 μg daily for six weeks inhaled via a spacer device from a metered dose inhaler. During the study the patients recorded morning and evening peak expiratory flow rate (PEFR), symptom scores, and use of β2 agonist rescue medication. In addition, clinic visit PEFR and forced expiratory volume in one second were measured. Safety was assessed by recording all adverse events and by performing routine biochemistry and haematology screens including plasma cortisol concentration before and after treatment. For the purposes of analysis the diary card data were grouped into three periods: week 3 (days 15–21), week 6 (days 36–42), and weeks 1–6 (days 1–42). The results showed no significant difference between treatments on most efficacy parameters. However, there were significant differences in changes from baseline in favour of fluticasone propionate for ½ predicted morning PEFR, both at week 3 (fluticasone propionate 6-1%, beclomethasone dipropionate 3-9%) and at week 6 (fluticasone propionate 8-3%, beclomethasone dipropionate 5-9%) and ½ predicted evening PEFR at week 6 (fluticasone propionate 7-3%, beclomethasone dipropionate 4-9%) and over weeks 1–6 (fluticasone propionate 5-5%, beclomethasone dipropionate 3-6%). Comparison between groups showed that the group receiving fluticasone propionate had a lower ½ of days with symptom-free exercise at week 6 (fluticasone propionate 87%, beclomethasone dipropionate 81%) and ½ days without rescue medication at week 6 (fluticasone propionate 87%, beclomethasone dipropionate 80%) and over weeks 1–6 (fluticasone propionate 80%, beclomethasone dipropionate 73%). Except for a higher incidence of sore throat in the fluticasone propionate group, the two treatments did not differ with regard to safety. There was no evidence of adrenal suppression with either treatment. In conclusion, fluticasone propionate 200 μg daily was at least as effective and as well tolerated as beclomethasone dipropionate 400 μg daily in childhood asthma.

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Asthma is one of the commonest diseases of childhood, affecting between 11% and 20% of all schoolchildren.1–3 Asthma reduces the quality of life for children as it leads to growth retardation,4 inability to exercise,5 and nocturnal bouts of wheezing resulting in loss of sleep that may also impair daytime concentration at school. In addition, children with more severe disease may be disadvantaged by frequent absences from school. Asthma symptoms experienced by children can exert a psychological stress not only in the affected child but can also be a source of stress for parents.6 Indeed, because of its prevalence, asthma is one of the most costly items for the public health budget of many countries7,8 and is likely to cost even more in the future as the incidence is on the increase.9–10 Therefore, emphasis must be placed on more effective preventative treatment that will improve management of the disease and so the well being of the asthma sufferer.

Inhaled glucocorticosteroid therapy is the recommended treatment for moderate to severe forms of childhood asthma.11 The systemic side effects commonly associated with oral glucocorticosteroids are largely absent with inhaled corticosteroids at doses up to 400 μg/day. But at doses greater than 400 μg/day, which may be required for the more severe patients, the incidence of systemic side effects is likely to increase.12 These include suppression of the hypothalamic-pituitary-adrenal axis and the possibility of growth retardation. The use of long term or high dose inhaled corticosteroid treatment is therefore regarded with some caution by parents and paediatricians alike.

Fluticasone propionate is a new inhaled glucocorticosteroid possessing high topical potency and negligible bioavailability.13 Preliminary studies have shown that fluticasone propionate has approximately twice the potency of beclomethasone dipropionate both as an anti-inflammatory agent14 and in improving lung function.15 Furthermore, studies have shown that fluticasone propionate
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has negligible oral bioavailability.\textsuperscript{13} The lack of systemic action with high oral doses has been demonstrated in healthy volunteers who were treated for 14 days with fluticasone propionate 20 mg/day.\textsuperscript{16} These results suggest that fluticasone propionate has a greater local to systemic ratio than beclomethasone dipropionate.

This present study was designed to evaluate fluticasone propionate in the management of childhood asthma by comparing the efficacy and safety of fluticasone propionate 100 \(\mu\)g twice a day with beclomethasone dipropionate 200 \(\mu\)g twice a day.

**Patients and methods**

**PATIENTS**

This study involved 398 children aged between 4 and 19 years selected from outpatient clinics at 32 centres in 11 countries worldwide. Each centre obtained ethical permission and patient consent. All children had a history of childhood asthma and were either receiving an inhaled glucocorticosteroid, up to 400 \(\mu\)g/day, or were receiving treatment with a bronchodilator, ketotifen, or sodium cromoglycate but were inadequately controlled. Furthermore, patients who were included had not changed their asthma treatment nor had been admitted to hospital for their respiratory condition during the previous month.

Patients who were not using an inhaled corticosteroid, or who were receiving less than 400 \(\mu\)g daily of their current inhaled corticosteroid, had to demonstrate a need for 400 \(\mu\)g daily based on one of the following criteria established during the run-in period: either, night time symptoms on at least one out of seven consecutive days; or, asthma symptoms on at least three out of seven consecutive days; or, a peak expiratory flow rate (PEFR) <80\% of predicted out on at least three out of seven consecutive days; or, >15\% reversibility of forced expiratory volume in one second (FEV\(_1\)) or PEFR after a bronchodilator dose of salbutamol. All patients had to be able to use the pressurised inhaler with a Volumatic (Glaxo) spacer device and a mini-Wright peak flow meter correctly and were able to keep accurate record cards. Patients were excluded if they had received oral corticosteroids in the four weeks before or during the run-in period or on more than three occasions in the preceding three months. Patients were also excluded if they had a lower respiratory tract infection within 14 days of the run-in or if their asthma became unstable during the run-in period.

**ASSESSMENTS**

Using the mini-Wright peak flow meter, patients measured their PEFR three times, morning and evening, before taking study medication or using salbutamol. They entered these measurements on a daily record card on which they also noted the severity of their asthma symptoms by day, at night, and on exercise, using four point rating scales. Symptoms during the day were rated from 0=no symptoms to 3=unable to carry out daily activities; symptoms during the night were rated from 0=slept through the night to 3=awake most of the night; and on exercise were scored from 0=not breathless to 3=very breathless, tight chested, and wheezy when walking: unable to run or play games. Patients also recorded their use of the study medication and of the salbutamol inhaler.

Patients attended the clinic on five occasions: at the start of the run-in, at the beginning, middle, and end of treatment, and two weeks after study treatment had finished. At the first clinic visit a full clinical history was documented and a physical examination performed. This was repeated at the end of the treatment period.

At each clinic visit, three measurements of PEFR and FEV\(_1\) were taken before, and 15 minutes after, inhalation of a bronchodilator dose of salbutamol. Where possible, these measurements were made at the same time of day for each visit, preferably in the morning, and the highest value being recorded for each parameter. Patients were asked not to use their bronchodilators for at least four hours before a clinic visit. If this proved impossible, then the use and time of use of the inhaled \(\beta_2\) agonist was to be recorded on the clinical record form.

The oropharynx was routinely examined at each clinic visit and swabs taken to determine the presence of *Candida albicans* if necessary.

At the beginning and end of the treatment period blood samples were taken for routine haematology and biochemistry and basal plasma cortisol concentration was measured. Where possible, blood samples were taken between 8 am and 10 am and before food.

**STUDY DESIGN**

This was a double blind, parallel group study. The treatment period lasted six weeks, preceded by a two week run-in period and followed by a two week follow up period. During the two week run-in period, patients continued taking their usual asthma medication at a regular dose with the exception of \(\beta_2\) adrenoceptor agonist (\(\beta_2\) agonist) treatment that could be taken at any time to relieve symptoms.

At the end of the run-in, patients discontinued inhaled corticosteroids but all other antiasthma medication was kept constant throughout the study. Eligible patients were randomly allocated to receive treatment with either fluticasone propionate 100 \(\mu\)g twice a day or beclomethasone dipropionate 200 \(\mu\)g twice a day, both administered via a pressurised inhaler and Volumatic spacer device.

**ANALYSIS**

It was estimated that 360 patients providing evaluable data would be required to give the study a power of 90\% to detect a mean difference in PEFR of 15 l/min between any two groups. This assumed that significance would be declared at the two sided 5\% level. In fact, 398 patients were randomised to treatment. A retrospective analysis performed at the end of
the study showed that for % PEF the study had a statistical power of 99% of detecting a 3% difference between treatments.

A baseline was established using data from the daily record cards completed during week 2 of the run-in period. For the treatment period, data were analysed for weeks 1–6 (days 1–42), week 3 (days 15–21), and week 6 (days 36–42). Patients recorded three PEF measurements every morning and at bedtime before taking study medication. The maximum of the readings was used in the analysis. The mean morning and evening PEF was then calculated over each period for each patient, and expressed as absolute values and as percentage of predicted values. Predicted lung function values were calculated from sex, age, and height using standard formulas. All statistical analyses were carried out using SAS programs and procedures.

Changes from baseline in diary card PEFs and changes from baseline in clinic lung function values together with plasma cortisol concentrations (which were previously log transformed) were analysed by analysis of covariance, adjusting for baseline, age, and country. The changes from baseline in percents of symptom-free days/nights and symptom-free exercise, the median symptom scores and the changes from baseline in use of rescue inhaled β2 agonist medication and median usage were analysed using the Wilcoxon rank sum test, adjusting according to country using the van Elteren method.

### Results

**Patients**

Table 1 shows the demographic details of the patients randomised to treatment, 197 received fluticasone propionate 100 μg twice a day and 201 received beclomethasone dipropionate 200 μg twice a day. There were no apparent differences between the two treatment groups. The population was predominantly male, white, and atopic (95%) with a mean age of approximately 10 years. Concurrent illnesses and medications were very similar between groups with a large proportion of patients suffering from atopic related diseases.

The two treatment groups were similar with regard to prestudy asthma medication. All patients were using β2 agonists and over 60% in each group using inhaled corticosteroids. Approximately, 29% of patients in each group were receiving sodium cromoglycate but there were more patients in the beclomethasone dipropionate group receiving methylxanthine preparations (16%) than in the fluticasone propionate group (9%). This pattern of treatment continued into the study period with approximately 22% of patients in both groups taking sodium cromoglycate whereas methylxanthines were taken by 8% and 14% of the fluticasone propionate and beclomethasone dipropionate groups, respectively. No effect of this difference on the results of the study could be determined.

A total of nine patients were withdrawn from the study, four from the fluticasone propionate group and five from the beclomethasone dipropionate group. Reasons for withdrawal were: exacerbations (six patients, three in each group), ineffectiveness of treatment (one patient), and failure to attend (one patient).

### DIARY CARD DATA

Mean morning PEF increased with each week of treatment for both the fluticasone propionate and beclomethasone dipropionate treatment groups (figure). By the sixth week, there was mean improvement of 24 l/min in the beclomethasone dipropionate group and 19 l/min in the fluticasone propionate group. When converted to percentage predicted values, the changes from baseline were statistically significantly different in favour of fluticasone propionate at weeks 3 (p=0.044) and weeks 6 (p=0.043; table 2).

Mean evening PEF showed a similar improvement for both treatment groups (figure). By week 6 patients in the fluticasone propionate group had an increase of 21 l/min above baseline (326 l/min) and patients in the beclomethasone dipropionate group 16 l/min above baseline (340 l/min). When converted to percentage predicted values, the changes from baseline in evening PEF were statistically significantly higher in the fluticasone propionate group than in the beclomethasone dipropionate group at week 6 and over the whole study period (weeks 1–6), p=0.041 and p=0.034 respectively (table 2).

Both treatments were similarly effective in reducing diurnal variation in PEF which was 9 l/min and 10 l/min during the baseline for the fluticasone propionate and beclomethasone dipropionate groups, respectively. The mean change from baseline for week 6 was –4 l/min in the fluticasone propionate group and –3 l/min in the beclomethasone dipropionate group.

There were no statistically significant differences between treatments in the percentage of symptom-free days or nights. During week 6, 83% patients in the fluticasone propionate group, and 81% in the beclomethasone dipropionate group either had no deterioration in daytime asthma symptoms or showed an

### Table 1  Demographic details of the patients randomised to treatment with fluticasone propionate 100 μg twice a day or beclomethasone dipropionate 200 μg twice a day

<table>
<thead>
<tr>
<th></th>
<th>Fluticasone propionate n=197</th>
<th>Beclomethasone dipropionate n=201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>111/86</td>
<td>114/87</td>
</tr>
<tr>
<td>White</td>
<td>192</td>
<td>191</td>
</tr>
<tr>
<td>Mean (range) age in years</td>
<td>46 (4–19)</td>
<td>10 (4–18)</td>
</tr>
<tr>
<td>Mean (SD) height in cm</td>
<td>142 (13)</td>
<td>144 (13)</td>
</tr>
<tr>
<td>Mean (SD) weight in kg</td>
<td>39 (16)</td>
<td>41 (17)</td>
</tr>
<tr>
<td>Duration of asthma (years)</td>
<td>1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>No (%) on pre study asthma medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled β2 agonist</td>
<td>186 (94)</td>
<td>190 (95)</td>
</tr>
<tr>
<td>Oral β2 agonist</td>
<td>11 (6)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>17 (9)</td>
<td>32 (16)</td>
</tr>
<tr>
<td>Inhaled steroids</td>
<td>142 (72)</td>
<td>125 (62)</td>
</tr>
<tr>
<td>Sodium cromoglycate</td>
<td>57 (29)</td>
<td>59 (29)</td>
</tr>
</tbody>
</table>
Fluticasone propionate in asthma

The daily mean change from run-in PEFR recorded in the morning (A) and evening (B) while taking fluticasone propionate 200 μg daily or beclomethasone dipropionate 400 μg daily for six weeks.

Table 2 Diary card PEFR data

<table>
<thead>
<tr>
<th>No</th>
<th>Fluticasone propionate</th>
<th>Adjusted mean change from baseline*</th>
<th>Fluticasone propionate</th>
<th>Adjusted mean change from baseline*</th>
<th>Beclomethasone dipropionate</th>
<th>Adjusted mean change from baseline*</th>
<th>Difference in adjusted means (95% CI)</th>
<th>Level of significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning PEFR % predicted normal value</td>
<td>Baseline 196 100-8</td>
<td>201 100-7</td>
<td>3 9</td>
<td>2 2 (0 1 to 4 4)</td>
<td>0 044</td>
<td>3 9</td>
<td>2 4 (0 1 to 4 7)</td>
<td>0 043</td>
</tr>
<tr>
<td>Week 3 193 106-8</td>
<td>6-1</td>
<td>198 104-6</td>
<td>5-9</td>
<td>2 4 (0 1 to 4 7)</td>
<td>0 043</td>
<td>2 2</td>
<td>(0 1 to 4 4)</td>
<td>0 044</td>
</tr>
<tr>
<td>Week 6 185 108-8</td>
<td>8-3</td>
<td>195 106-5</td>
<td>5-9</td>
<td>2 4 (0 1 to 4 7)</td>
<td>0 043</td>
<td>2 2</td>
<td>(0 1 to 4 4)</td>
<td>0 044</td>
</tr>
<tr>
<td>Weeks 1-6 196 106-8</td>
<td>6-2</td>
<td>201 105-0</td>
<td>4-5</td>
<td>1 7 (0 1 to 3 5)</td>
<td>0 069</td>
<td>2 2 (0 1 to 4 4)</td>
<td>0 044</td>
<td>3 9</td>
</tr>
<tr>
<td>Evening PEFR % predicted normal value</td>
<td>Baseline 196 103-6</td>
<td>201 103-9</td>
<td>3-0</td>
<td>1 9 (0 2 to 4 1)</td>
<td>0 080</td>
<td>3-9</td>
<td>2 4 (0 1 to 4 7)</td>
<td>0 041</td>
</tr>
<tr>
<td>Week 3 194 108-5</td>
<td>5-0</td>
<td>198 106-9</td>
<td>4-9</td>
<td>2 4 (0 1 to 4 7)</td>
<td>0 041</td>
<td>3 9</td>
<td>2 4 (0 1 to 4 7)</td>
<td>0 043</td>
</tr>
<tr>
<td>Week 6 183 110-6</td>
<td>7-3</td>
<td>193 108-4</td>
<td>4-9</td>
<td>2 4 (0 1 to 4 7)</td>
<td>0 041</td>
<td>3 9</td>
<td>2 4 (0 1 to 4 7)</td>
<td>0 043</td>
</tr>
<tr>
<td>Weeks 1-6 196 109-0</td>
<td>5-5</td>
<td>201 107-2</td>
<td>3-6</td>
<td>1 9 (0 2 to 4 1)</td>
<td>0 034</td>
<td>3 9</td>
<td>2 4 (0 1 to 4 7)</td>
<td>0 043</td>
</tr>
</tbody>
</table>

*Means adjusted for baseline, age, and country. CI = confidence intervals.

improvement. Similarly, at week 6, 83% of patients receiving fluticasone propionate and 82% of patients receiving beclomethasone dipropionate had no deterioration or showed an improvement in night time asthma symptoms. There was however, a significant difference between treatments in the percentage of days with symptom-free exercise. At week 6, more patients on fluticasone propionate showed no deterioration or enjoyed more symptom-free exercise days (87%) than patients using beclomethasone dipropionate (81%; p=0.04, scores stratified by region).

Daytime and night time asthma scores were comparable. A total of 90% of patients receiving fluticasone propionate and 93% of patients receiving beclomethasone dipropionate had a median daytime symptom score of 0 or 1 during the run-in and at week 6; and 93% of patients receiving fluticasone propionate and 96% of patients receiving beclomethasone dipropionate had a median night time symptom score of 0 or 1 during the run-in and at week 6. Exercise asthma symptom scores were also comparable, 91% of patients using fluticasone propionate and 94% of patients using beclomethasone dipropionate had a median asthma symptom score of 0 or 1 during the run-in at week 6.

A greater number of patients in the fluticasone propionate group than in the beclomethasone dipropionate group had an increase in the percentage of rescue β₂ agonist free days. This was statistically significant at week 6 (fluticasone propionate 87%, beclomethasone dipropionate 80%; p=0.01) and over the whole treatment period (fluticasone propionate 80%, beclomethasone dipropionate 73%; p=0.046). Use of rescue medication per day also varied at week 6 when a greater number of patients in the fluticasone propionate group (87%) showed an improvement over baseline compared to beclomethasone dipropionate (84%; p=0.044).

CLINIC LUNG FUNCTION

For both treatments, the adjusted mean change from baseline in clinic lung function...
was similar before and after bronchodilator usage. At the end of the treatment period for patients using fluticasone propionate, the change from baseline in PEFR was 20 l/min and for those using beclomethasone dipropionate, 21 l/min. The change from baseline in FEV₁ was 0-12 l for the fluticasone propionate group and 0-15 l for the beclomethasone dipropionate group (table 3). After bronchodilator the PEFR increased from baseline by 15 l/min for the fluticasone propionate group and 12 l/min for the beclomethasone dipropionate group and the FEV₁ increased from baseline by 0-07 l for the fluticasone propionate group and 0-10 l for the beclomethasone dipropionate group.

**SAFETY ASSESSMENT**

During the six week treatment period 99 patients (50%) reported 155 adverse events with fluticasone propionate and 95 patients (47%) reported 153 adverse events with beclomethasone dipropionate. Three patients on fluticasone propionate and two patients on beclomethasone dipropionate had serious adverse events, and three patients in each treatment group withdrew because of adverse events (exacerbation of asthma).

The most commonly occurring (>5%) adverse events were upper respiratory tract infection, asthma and related events, rhinitis, and sore throat (table 4). Apart from the incidence of sore throat reported by 16 patients (8%) on fluticasone propionate but only by two patients (<1%) on beclomethasone dipropionate, there were no significant differences between the groups. Although there was a significant (p<0.001) difference in the incidence of sore throat between the groups, the majority of reports were related to pharyngitis and tonsillitis and were not linked to hoarseness. The incidence of hoarseness and oral candidiasis, which are pharmacologically predictable adverse events common to inhaled corticosteroid treatment, was low. Hoarseness was reported by two patients in each treatment group and oral candidiasis was reported by three patients on beclomethasone dipropionate and none on fluticasone propionate.

**CORTISOLS**

There was no significant difference between the two treatments in the effect on hypothalamic-pituitary-adrenal axis function; ratio of fluticasone propionate/beclomethasone dipropionate was 1-00, 95% confidence interval 0-91 to 1.09, p=0.989. The geometric mean cortisol concentration was 196 nM during the run-in and 214 nM on fluticasone propionate treatment (n=182) and 217 nM during run-in and 228 nM on beclomethasone dipropionate (n=181). There was no apparent difference in the numbers of patients who had a cortisol value below the lower normal limit before and after treatment. In the fluticasone propionate group 19/191 (10%) had a low cortisol concentration at baseline and 16/188 (9%) after treatment and in the beclomethasone dipropionate group 12/191 (6%) had a low cortisol value at baseline and 8/191 (4%) after treatment.

**VITAL SIGNS**

No significant changes in weight, pulse rate, or systolic or diastolic blood pressure were detected.

**Discussion**

Current international guidelines from paediatricians recommend the use of prophylactic treatments such as inhaled corticosteroids in moderate childhood asthma. However, there is still reluctance to use these drugs in children because of the possibility of serious adverse effects even with conventional doses. This 'corticosteroid fear' is supported by the fact that only about 20% of an inhaled dose of the drug reaches the airways, the rest is swallowed. After it is swallowed this large fraction of drug (approximately 80%) may contribute to systemic steroid effects. The use of spacer devices with metered dose inhalers do enhance lung deposition while lessening oropharyngeal deposition and systemic absorption. Nevertheless, an ideal inhaled corticosteroid should have a wide margin between local and systemic activity.
Fluticasone propionate in asthma

Studies so far, suggest that fluticasone propionate is such a compound.13-16,25 Due to very low oral absorption and extensive first pass hepatic metabolism to an inactive metabolite, fluticasone propionate has been shown to have negligible oral bioavailability.13 Moreover, in preclinical and clinical studies in adults, when compared with beclomethasone dipropionate, fluticasone propionate is approximately twice as potent.14 15

This present study confirms the previous findings. The results presented here have demonstrated that fluticasone propionate 100 µg twice a day is at least as effective as beclomethasone dipropionate 200 µg twice a day in childhood asthma. Similar improvements in lung function were seen on both treatments and when converted to percentage predicted values, PEF R was statistically significantly greater on fluticasone propionate than on beclomethasone dipropionate treatment. Asthma symptoms were reported by few patients and there were statistically significantly more patients who enjoyed symptom-free exercise days in the fluticasone propionate group than the beclomethasone dipropionate group. Patients using fluticasone propionate also required less relief bronchodilator medication than those using beclomethasone dipropionate.

There were no unexpected findings in the adverse event profile of fluticasone propionate, the most commonly reported events being related to the patients' asthma. The incidence of all adverse events was low, and with the exception of sore throat, there was no difference between the treatments. There were more reports of sore throat (8%) during fluticasone propionate treatment than during beclomethasone dipropionate treatment (<1%). This may be related to tinnitus and pharyngitis as it has not been reported in any other studies. In fact, the incidence of expectedly pharmacologically predictable adverse events, that is candida and hoarseness, was not marked and not different between the two treatments. This may have been as a consequence of the use of spacer devices which limits oropharyngeal deposition. However, a study using high doses (750-1500 µg/day) of fluticasone propionate in adults has shown that the majority of adverse events reported were unrelated to the inhaled corticosteroid.25

Analysis of haematological and biochemical variables in this study revealed no clinically significant abnormalities during either treatment. Furthermore, there was no evidence of hypothyroidism in this study. Nevertheless, the confirmation of the 2:1 potency relationship between fluticasone propionate and beclomethasone dipropionate in childhood asthma is valid as all differences in efficacy found were in favour of fluticasone propionate.

To conclude, at the doses chosen, fluticasone propionate is approximately twice as potent as beclomethasone dipropionate in the management of mild to moderate childhood asthma with a similar safety profile.

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