Long-Term Safety of Fluticasone Propionate and Nedocromil Sodium on Bone in Children With Asthma

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ABSTRACT. Objective. Inhaled corticosteroids are recommended as first-line therapy for pediatric asthma. However, few controlled long-term studies have investigated their effect on bone mineral density (BMD) and growth.

Methods. Children who were aged 6 to 14 years and had persistent asthma were randomized to 24 months’ treatment with fluticasone propionate (FP) 200 μg/d or nedocromil sodium (NS) 8 mg/d (if uncontrolled, maximum doses of 400 μg/d and 16 mg/d, respectively). BMD was assessed blind and analyzed at a central facility on the basis of dual-energy x-ray absorptiometry measurements of the lumbar spine and femoral neck at months 0, 6, 12, and 24. Height was measured at months 0, 12, and 24. Efficacy parameters (lung function, asthma control, occurrence of exacerbations) were measured every 3 months.

Results. In total, 174 children were randomized to treatment (87 received FP, and 87 received NS). At month 24, the adjusted mean percentage increase in lumbar spine BMD was 11.6% in the FP group compared with 10.4% in NS-treated children (95% confidence interval for treatment difference: –0.7% to 3.1%). The corresponding increases in femoral neck BMD were 8.9% and 8.5%, respectively. There was no significant difference in growth between the 2 groups: adjusted mean growth rates were 6.1 cm/y with FP and 5.8 cm/y with NS. FP was significantly superior for every efficacy parameter investigated and was similarly well tolerated as NS.

Conclusions. The long-term effects of FP and NS on BMD accrual and growth are similar among children with asthma. The benefit:risk ratio of FP may be considered superior to that of NS. Pediatrics 2003;111:e706–e713. URL: http://www.pediatrics.org/cgi/content/full/111/6/e706; bone mineral density, fluticasone propionate, long-term safety, height.

ABBREVIATIONS. ICS, inhaled corticosteroid; BMD, bone mineral density; FP, fluticasone propionate; NS, nedocromil sodium; PEFR, peak expiratory flow rate; FEV₁, forced expiratory volume in 1 second; BHR, bronchial hyperreactivity; DXA, dual-energy x-ray absorptiometry; CI, confidence interval; ITT, intention-to-treat.

Inhaled corticosteroids (ICSs) are established as the most effective anti-inflammatory therapy for asthma. Thus, internationally endorsed treatment guidelines recommend the use of these agents for long-term control of asthma, in both adults and children.¹

Long-term treatment with oral corticosteroids may cause bone loss and reduce growth in children.²⁻³ In contrast, lower doses and lower systemic exposure with ICS has been shown to minimize the risk of such systemic effects.⁴⁻⁵ Nevertheless, concerns persist in relation to the potential effects of long-term therapy on bone in adults⁶ and on childhood growth.⁷ Complicating this issue is the knowledge that asthma also has the potential to reduce childhood growth and bone mineral density (BMD) accrual, mainly through reduced physical activity.⁸ Optimal asthma control therefore would facilitate normal growth and bone development, and clinical trials investigating the effects of ICS must account for this.

Inhaled fluticasone propionate (FP) has equivalent efficacy when used at half the dose of older-generation ICS (eg, beclomethasone dipropionate, budesonide) and has a comparable safety profile.⁹–¹¹ Numerous studies have investigated the safety of FP in children at doses up to 400 μg/d by measuring biochemical markers, most commonly relating to adrenal function.¹¹⁻¹⁵ In addition, biochemical markers of bone metabolism have been studied for up to 20 months.¹³,¹⁶,¹⁷ These studies indicate that although FP treatment may be associated with reduced cortisol levels compared with placebo, it is more favorable than therapeutically equivalent doses of budesonide or beclomethasone dipropionate and no different from nonsteroidal therapy in terms of bone markers.

Although biochemical markers may provide a sensitive short-term measurement of the effects of ICS therapy, long-term studies are required to show the consequences of these effects on bone and growth, with 24 months suggested as the minimum duration for bone density studies.¹⁸ Few such data showing the effects of FP on BMD and growth in children have been published. The present study was undertaken to compare the increase in BMD among children with asthma treated with FP or nedocromil sodium (NS).
METHODS

This was a randomized, open, multicenter, parallel-group, 2-year comparison of the safety and efficacy of FP and NS. All assessments of the main safety criterion (BMD) were performed blind. The study protocol was designed in accordance with the Declaration of Helsinki and was approved by a French ethics committee (Consultative Committee for the Protection of Persons Enrolled in Biomedical Research of Boulouge Ambroise-Paré). The parents of every child who participated in the study provided written informed consent; the consent of the patient was also sought when he or she was old enough to express his or her opinion. Respiratory care clinicians from 52 specialist clinics in France recruited study participants.

Patients

Children who were aged 6 to 14 years, weighed at least 13 kg, and experienced persistent asthma that was treated with a short-acting β2-agonist were eligible for inclusion. The defining criteria for persistent asthma were exacerbations occurring at least once a week but less often than daily, or chronic symptoms requiring daily treatment. The main exclusion criteria were treatment during the previous month with an oral, inhaled, or intranasal corticosteroid, a chromone theophylline, or a long-acting β2-agonist; or an uncontrolled serious concurrent disease.

The study included a run-in period of 1 to 4 weeks, during which previous bronchodilator therapy was replaced as required by salbutamol and patients completed daily record cards. Peak expiratory flow rate (PEFR) was measured twice daily using a Mini-Wright peak flow meter. Patients entered the study if the following 3 criteria were fulfilled: 1) clinic forced expiratory volume in 1 second (FEV1) or PEFR was at least 80% predicted; 2) FEV1 or PEFR reversibility was at least 15% from baseline (at clinic visit or during the previous year) or bronchial hyperresponsiveness (BHR) during the previous year; and 3) daily variability of PEFR was 20%–30% on at least 2 days, salbutamol was required >3 times during the previous week, or nocturnal symptoms were noted more than twice during run-in. Menstrual status was assessed at inclusion and at subsequent clinic visits, allowing classification of subjects according to whether menstruation commenced before, during, or later than the study.

Treatment

Eligible children received 24 months’ treatment with FP at an initial dose of 200 µg/d (100 µg twice daily, via the Diskus/Accuhaler dry powder inhaler; Glaxo-Wellcome CSU, Ware, United Kingdom) or NS at an initial dose of 8 mg/d (two 2-mg inhalations twice daily, via a metered-dose inhaler). Treatment was allocated by balanced, block randomization with gender stratification; investigators dialed into a central voice mail system to ensure correct synchronization. All patients used salbutamol as required throughout the study; persistent inadequately controlled asthma (defined below) was treated by doubling the dose of study medication, then by adding salmeterol (50 µg twice daily), and, when necessary, systemic corticosteroids. Previously used H1 antihistamines and ketotifen were permitted throughout the study. Use of vitamin D was limited to a maximum of 1000 IU/d, and treatments known as having an impact on bone metabolism were not allowed. When used, they had to be reported in the case report form.

Bone Safety

Dual-energy x-ray absorptiometry (DXA) examinations were performed at clinic visits during the run-in period and at months 6, 12, and 24. The lumbar spine and femoral neck were examined, with strict adherence to the equipment manufacturer’s recommendations for positioning the patient. Every patient was scanned using the same device (Hologic [Hologic, Waltham, MA] or Lunar [Lunar GE, Madison, WI]) throughout the study. Cross-calibration was achieved by scanning a European Spine Phantom 10 times on each device, whereas device stability was evaluated regularly during the study using the manufacturer-supplied phantom. All patient scans were analyzed blind in a central facility.

Secondary Endpoints

Lung function was assessed at clinic visits every 3 months, with measurements of FEV1, and PEFR. Asthma control (see definition in Table 1) was judged over the last 2 weeks before each clinic visit: a patient was declared as controlled if he or she was receiving FP 200 µg/d or NS 8 mg/d and if all the criteria were fulfilled. Height was measured at the end of the run-in period and at months 12 and 24, using the standard methods in place at each center. Adverse events were recorded at each clinic visit.

Statistical Methods

The primary endpoint was the percentage change from baseline in lumbar spine BMD, and the sample size was calculated to establish noninferiority of FP compared with NS. Noninferiority was declared when the lower bound of the 90% confidence interval (CI) for treatment difference (FP – NS) was greater than or equal to –2%, a threshold chosen according to our opinions on the basis of clinical practice and relevant literature. Assuming a standard deviation for the percentage change from baseline of 4%, the required sample size was 53 assessable patients in each treatment group (90% power). The analysis was originally based on 90% CIs. However, as 95% CIs have since become preferable for expressing noninferiority results, the data were reanalyzed accordingly.

Primary analysis of BMD outcomes was based on the intention-to-treat (ITT) population, defined as all patients who were randomized and received at least 1 dose of study medication. Secondary analysis was performed on the per-protocol population (ie, the ITT population, excluding patients with serious protocol violations). Efficacy analyses were performed on the ITT population. Adverse events were described for all patients who received at least 1 dose of study medication.

For patients with missing BMD or growth data, predicted values were derived from a linear regression model based on predictive covariates, baseline, and subsequent values. This was used instead of last observation carried forward, as last observation carried forward assumes that measurements remain constant over time and therefore would not be a conservative approach. A sensitivity analysis using alternative methods was performed to give robustness to the conclusion.

Percentage change in BMD was analyzed by analysis of covariance, with treatment as the main effect; adjustments were made for age, height, weight, and BMD at baseline, as well as gender and the make of device used to measure BMD (Hologic or Lunar). Interaction of treatment with these covariates was assessed separately. Secondary analyses were performed to assess the impact of systemic corticosteroid use and menstruation status. Growth (cm/y) was also analyzed by analysis of covariance, with adjustments for age, gender, and baseline measurement. Lung function parameters and asthma control at each visit were analyzed using a repeated measures model.

RESULTS

A total of 207 children were screened, 174 of whom were randomized to treatment: 87 with FP and 87 with NS (Fig 1). One additional patient received FP but was not randomized and was included in the adverse event but not in the ITT population. Baseline characteristics of the 2 treatment groups were well matched (Table 2); 94% were white in both groups.

Fifty-one patients withdrew early from the study, 13 from the FP group and 28 from the NS group (Fig 1). Adverse events caused 1 discontinuation in the FP group and 4 in the NS group, whereas lack of efficacy led to 0 and 8 discontinuations, respectively. The proportion of female patients who reported menstruation

TABLE 1. Definition of Asthma Control

During the last 2 weeks before each clinic visit
- No occurrence of asthma symptoms
- Salbutamol use ≤4 times a week
- No hospitalization or emergency visit as a result of asthma
- No limitation of physical activity
- Daily PEF variability <20% (data from diary, first 3 mo only)
- PEF >80% predicted
- No drug-related adverse event
ation onset during the study (additional to baseline) was 23% in the FP group and 27% in the NS group. Only 3 patients (2 in the FP group) used vitamin D during the study.

Bone Safety

At month 24, the adjusted mean increase in lumbar spine BMD from baseline (±standard error) was 11.6 ± 0.7% among children who received FP compared with 10.4 ± 0.7% among NS-treated patients. The treatment difference (FP − NS) was 1.2% (95% CI: −0.7% to 3.1%), indicating that FP was noninferior to NS. This finding was supported by the increase in lumbar spine BMD in the per-protocol population (95% CI for treatment difference: −0.7% to 3.5%).

Gender-specific increases in lumbar spine BMD are shown in Fig 2; larger increases were reported among female patients in both treatment groups. In addition to gender, the increase in lumbar spine BMD was significantly affected by baseline height, baseline BMD, and device used to measure BMD. However, none of these covariates had a significant interaction with treatment effect and hence did not affect the noninferiority of FP compared with NS.

The secondary analysis showed that after adjustment on baseline characteristics, the use of systemic corticosteroids had no significant impact on BMD (P = .778). Furthermore, the treatment effect was similar whether patients received corticosteroids or not, as showed by the lack of interaction between systemic corticosteroids and study treatment (P = .847). Onset of menstruation was associated with increased BMD (P < .001) but did not interfere with treatment effect (P = .544).

Femoral neck BMD outcomes were similar to those observed for lumbar spine (Fig 2). At month 24, the adjusted mean increase from baseline was 8.9 ± 0.6% among children who were treated with FP and 8.5 ± 0.6% among children who were treated with NS (ITT population). The treatment difference was 0.5% (95% CI: −1.2% to 2.1%).

Fig 1. Flow chart showing patients’ progress through the study.
Secondary Safety Outcomes and Tolerability

Height increased throughout the study in both groups, with no significant treatment effect (Table 3). The adjusted mean growth velocity over 2 years in the FP group was 6.1 cm/y, compared with 5.8 cm/y in the NS group (95% CI for treatment difference: −0.2 to 0.8 cm/y). During the first 12 months, the mean growth velocities in the 2 groups were 6.0 and 6.2 cm/y, respectively (95% CI for treatment difference: −0.9 to 0.5 cm/y).

Both FP and NS were well tolerated, with drug-related adverse events affecting 23% and 20% of patients, respectively. The most common adverse events are shown in Table 4; asthma was the most common drug-related adverse event in both treatment groups. Serious adverse events occurred in 4 patients in the FP group (5%) and 5 children in the NS group (6%); 1 of these was a traumatic fracture, occurring in the FP group. All of these events were resolved and considered unrelated to study medication.

Efficacy

More patients in the FP group had well-controlled asthma throughout the study: the mean proportion of patients with asthma controlled at initial dosage was 82% in the FP group, compared with 51% in the NS group (P < .001). No medication change was required in 45% of FP-treated patients compared with 34% of patients who received NS.

Figure 3 shows the difference between the 2 treatment groups for a number of efficacy parameters during the study. The mean proportion of children who experienced asthma exacerbations during the study was 8% in the FP group, compared with 16% in the NS group (P < .001). Both PEFR and FEV$_1$ (percentage predicted) were significantly higher among children who received FP (between-group differences of 6.9% and 4.1%, respectively).

Doubling of medication for patients with insufficient control was required by 38% of patients who were treated with FP compared with 61% of patients who were treated with NS and addition of a long-acting β$_2$-agonist was required by 15% and 39% of patients, respectively. Systemic corticosteroids were required by 26% of patients who were treated with FP, compared with 43% of those in the NS group.

The overall requirement for systemic corticosteroids to treat exacerbations was significantly lower in the FP group (P < .001), and just 3% of patients in this group required 3 or more courses (compared with 16% in the NS group). Mean cumulative doses of systemic corticosteroids were 193 mg in the FP group and 330 mg in the NS group, and the mean course durations were 3.9 days and 5.0 days, respectively.

DISCUSSION

This constitutes the largest controlled study yet reported to assess skeletal development in children who have asthma and are treated with ICS. Patients who received FP for 2 years demonstrated lumbar spine BMD increases that were no different from those of patients who were treated with NS. This was supported by the lack of between-group differences in femoral neck BMD and growth and, although not presented in this article, also by analyses using different imputation methods for missing data. Moreover, lung function and symptom control during treatment with FP were significantly superior to NS.

Owing to its speed, precision, and low radiation dose, DXA is widely accepted as the method of choice for measuring BMD, assuming that steps are taken to ensure correct positioning of patients and rigorous calibration of the DXA device.20 With such a quality control, the precision of the BMD measurements in children is 1% on average.21 BMD measurement provides the only direct measure of fracture risk relating to bone fragility, although this relationship is not as well-established in children as in adults.

The gender-specific increases in lumbar spine BMD with FP were comparable with increases previously observed among healthy children of a similar age. In the FP group (mean age: 9.1 year), the 24-month increase in lumbar spine BMD was 16.0% in female patients and 9.5% in male patients. In healthy children, the 2-year increase from 9 years onward has been reported as 10.5% in girls and 7.7% in boys.22 The likely reason for the higher increase in the present study was the wide age range of our subjects and the inclusion of pubertal subjects, in whom BMD increases at a faster rate (~12.5%/y for
14- to 16-year-olds). Although the inclusion criteria would ideally have been limited to prepubertal children, this would have led to recruitment difficulties and perhaps reduced the overall clinical impact and relevance. However, close matching of patients’ age and the proportion of girls beginning menstruation in the 2 treatment groups indicates that similar proportions of patients reached puberty, minimizing any potential effect on the comparison the study was intended to perform.

These findings are also consistent with other long-term pediatric safety studies of anti-asthma medication. For example, a 20-month comparison of FP 200 μg/d with beclomethasone dipropionate 400 μg/d indicated that BMD increased at normal rates in both treatment groups.16 In terms of growth, FP has previously been shown to have no significant inhibitory effect compared with placebo or chromones24 and to be more favorable than therapeutically equivalent

**TABLE 3.** Gender-Specific Height Change During the Study (ITT Population, Missing Data Imputed by Expected Values)

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean Height (cm)</th>
<th>Increase in Height From Baseline (cm)</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females (n = 31)</td>
<td>Baseline 138.3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Month 12 143.8</td>
<td>5.5 (2.4)</td>
<td>0–9</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Month 24 149.8</td>
<td>11.5 (4.5)</td>
<td>2–20</td>
<td>—</td>
</tr>
<tr>
<td>Males (n = 56)</td>
<td>Baseline 134.9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Month 12 141.2</td>
<td>6.3 (2.7)</td>
<td>2–16</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Month 24 147.5</td>
<td>12.6 (3.1)</td>
<td>8–24</td>
<td>—</td>
</tr>
<tr>
<td><strong>NS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females (n = 30)</td>
<td>Baseline 138.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Month 12 143.8</td>
<td>5.4 (2.3)</td>
<td>1–13</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Month 24 148.3</td>
<td>9.9 (3.5)</td>
<td>2–18</td>
<td>—</td>
</tr>
<tr>
<td>Males (n = 57)</td>
<td>Baseline 134.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Month 12 140.9</td>
<td>6.5 (2.1)</td>
<td>1–15</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Month 24 146.7</td>
<td>12.4 (3.1)</td>
<td>6–20</td>
<td>—</td>
</tr>
</tbody>
</table>

**TABLE 4.** Incidence of Drug-Related Adverse Events Affecting at Least 2% of Children Who Were Treated With Either FP or NS

<table>
<thead>
<tr>
<th></th>
<th>FP (n = 87)*</th>
<th>NS (n = 88)+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>8 (9%)</td>
<td>15 (17%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Lower respiratory infection</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Ear, nose, and throat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal inflammation</td>
<td>4 (5%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Throat and tonsil pain/discomfort</td>
<td>4 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Ear, nose, and throat infection</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (1%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Upper respiratory inflammation</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Any drug-related adverse event</td>
<td>20 (23%)</td>
<td>18 (20%)</td>
</tr>
</tbody>
</table>

* Includes 1 patient who was not randomized but received FP.  † Includes 1 patient who was randomized to FP but received NS.
Fig 3. Efficacy differences between FP and NS. A, Percentage of patients with asthma controlled at initial dosage. B, Mean FEV₁. C, Mean PEFR.
doses of budesonide and beclometasone dipropionate.\textsuperscript{16,25,26} Although growth was a secondary parameter in the present study, no differences in growth rates between FP and NS were found during 2 years of therapy, and there was no evidence of an early transient effect. This is in contrast to the controlled comparison of budesonide with NS, which showed significantly reduced growth with budesonide during the first year of treatment, although the effect was not sustained during subsequent years.\textsuperscript{27}

Only 1 previous bone safety trial with an ICS was of a longer duration and contained a larger number of patients than the present study, but this was neither randomized nor blinded.\textsuperscript{28} That study found no significant differences in BMD between patients who were treated with inhaled budesonide for 3 to 6 years and age-matched, steroid-naïve control subjects; however, lack of randomization could have confounded the results for reasons such as poorly matched disease severity.

Comparison of FP with a chromone can be considered more ethical than administering placebo as a control, while still providing a true measure of the effect of the ICS because chromones have no direct effect on BMD or childhood growth. The choice of NS as a comparator is also compatible with international treatment guidelines for asthma, as chromones are a recognized treatment option for mild persistent asthma in children.\textsuperscript{1} The allowance of an increase in the dose of study medication (up to the maximum licensed doses of FP and NS) for patients with uncontrolled asthma increases the clinical relevance of this study: as in clinical practice, systemic corticosteroids were administered only after the failure of the higher dose of FP or NS combined with a long-acting \(\beta_2\)-agonist. The proportion of patients who discontinued as a result of insufficient efficacy was low (no patients withdrew from the FP group for this reason), which is probably attributable to the treatment strategy put in place in case of insufficient control. Treatment was not blinded, to avoid the use of multiple inhalers—a complicated dosing regimen would not be feasible for a study of this duration.

Several confounding factors must be considered in studies that assess the effects of inhaled glucocorticosteroids on bone metabolism. Oral corticosteroid consumption had the potential to complicate the results of this study, because their use could have a negative impact on BMD accrual and growth. However, despite their proportionately greater use in the NS group, oral corticosteroids did not interfere with the study results as shown by the absence of effect on BMD. This may be attributable to the relatively low number of courses of oral corticosteroids and moderate doses received during the study. Another confounding factor is dietary calcium intake or use of drugs that are known to have an influence on bone metabolism or growth. It seemed difficult to ask patients (or their parents) to complete diary cards for the 2-year duration of the study and to try to estimate the amount of calcium absorbed. We assumed that, on average, because of randomization, the 2 groups would probably be similar. However, drugs that are known to have an effect on bone metabolism and growth were prohibited, and investigators were asked to check carefully their possible use and to report it in the case report form. Use of vitamin D was limited to a maximum of 1000 U1/d; only 3 patients took vitamin D during the study.

ICs are recognized in international treatment guidelines as a highly effective mainstay of asthma prophylaxis. Our study has demonstrated that FP treatment for up to 2 years had a similar effect on BMD and growth as a chromone, while providing a greater degree of disease control. Consequently, it may be possible to conclude that the long-term benefit:risk ratio of FP is superior to that of NS.

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**REFERENCES**


trial in asthmatic children using powder devices at a dosage of 400 microg x day(-1). Eur Respir J. 1996;9:2263-2272


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