

Twelve-Month Safety and Efficacy of Inhaled Fluticasone Propionate in Children Aged 1 to 3 Years With Recurrent Wheezing

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ABSTRACT. *Objective.* Our aim was to compare the 12-month safety and efficacy of fluticasone propionate (FP) and sodium cromoglycate (SCG) in children aged 1 to 3 years with mild to moderate recurrent wheeze.

Methods. The study was a randomized, parallel-group, open-label multicenter study of 625 children, aged 1 to 3 years, with recurrent wheeze randomized in a 3:1 ratio to treatment for 52 weeks with FP (100 µg twice daily) via metered-dose inhaler and Babyhaler spacer device or SCG (5 mg 4 times daily) via metered-dose inhaler and Nebuhaler spacer device, respectively.

Results. There was no significant difference in mean adjusted growth rates between the 2 groups: 84.0 mm/year in the FP group versus 86.4 mm/year in the SCG group (difference FP-SCG: -2.4 mm/year; 95% confidence interval: -6.6 to 1.8). Growth comparisons were independent of age, gender, previous use of steroid, or whether measured as length and/or height. Serum and urinary cortisol concentrations showed a statistically significant suppression of 10% and 14%, respectively, but the number of patients with serum cortisol levels below the lower normal limit was reduced during the trial. Both treatments were well tolerated. The most common drug-related adverse events were cough (2% FP vs 1% SCG) and hoarseness (1% FP vs 0% SCG). One incident of cataract was observed at baseline and 1 after FP treatment; the latter had resolved after 12 months. The efficacy of FP was superior to SCG with fewer cases of symptom worsening, exacerbations, and requirements for oral steroid treatment and more symptom-free days and days without use of rescue treatment.

Conclusions. Twelve months of treatment with inhaled FP (100 µg twice daily) in preschool children aged 1 to 3 years with recurrent wheeze has no effect on growth and no other clinically important side effects but is more efficacious than SCG. *Pediatrics* 2004;113:e87-e94. URL: <http://www.pediatrics.org/cgi/content/full/113/2/e87>; fluticasone propionate, sodium cromoglycate, asthma, wheeze, preschool children, growth velocity, cortisol.

ABBREVIATIONS. ICS, inhaled corticosteroid; FP, fluticasone propionate; BUD, budesonide; MDI, metered dose inhaler; SCG, sodium cromoglycate; DRC, daily record card; CI, confidence interval; OR, odds ratio.

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Received for publication May 27, 2003; accepted Oct 14, 2003.

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International treatment guidelines recognize the role of inhaled corticosteroids (ICSs) for the treatment of children who have asthma and are younger than 4 years.¹ In such children, ICSs have been shown to control symptoms,²⁻⁵ reduce markers of airway inflammation (eg, exhaled nitric oxide),⁶ improve lung function, and reduce bronchial hyper-reactivity.⁷ Fluticasone propionate (FP) in a 100- and 200-µg daily dose provides a dose-related reduction in the incidence of exacerbations and improvement of symptoms in children who have recurrent wheeze and are aged 1 to 3 years⁴ with a beneficial cost-effectiveness.⁸

The potential adverse effects of long-term corticosteroid treatment have been a concern. In school children, ICSs have been reported to affect short-term growth (2 weeks),⁹ intermediate-term growth (3-12 months),¹⁰⁻¹⁴ and long-term growth (4-6 years),¹⁵ although final adult height was not affected in 1 long-term observational study.¹⁶ In children aged 2 to 8 years, intermediate-term growth of 12 months was reduced during daily treatment with 1 mg of nebulized budesonide (BUD).¹⁷ Children who were 2 to 5 years of age and were treated for 24 weeks with FP (190-565 µg twice daily) also showed a significant decrease in height velocity compared with placebo, although at the end of treatment, height standard deviation scores did not differ significantly.¹⁸ Growth over a 3- to 5-year observation was unaffected in a retrospective, uncontrolled report of 15 children who were aged 2 to 7 years and had severe asthma that was treated with relatively low doses of BUD by metered-dose inhaler (MDI) and spacer (100 µg twice daily).¹⁹

Children under 3 years of age may respond to ICSs differently, because linear growth in the first years of life is still influenced by factors that are important for fetal growth (eg, nutrition) before the dominating influence of growth hormone for subsequent childhood growth. In studies of children of this age (1-3 years), short-term lower leg growth (2-4 weeks) was reduced after treatment with FP or BUD via MDI with spacer.^{20,21} We know of no randomized studies on growth rate over a longer term in such young children with asthma. Accordingly, we conducted a prospective, randomized comparison of the 1-year safety and efficacy of FP (100 µg twice daily) or sodium cromoglycate (SCG; 5 mg 4 times daily). SCG was selected as the comparator drug on the basis of previous guidelines for asthma management in

young children.¹ We report the results of this trial in a large pediatric population ($n = 625$), aged 1 to 3 years, who presented with mild to moderate recurrent wheeze.

METHODS

Study Design

This was a randomized, parallel-group, open-label study in a multicenter setting, designed to investigate the safety of FP in children younger than 4 years. The size and treatment duration fulfill guidelines issued by the International Committee on Harmonization²² and leading regulatory guidelines for design of growth studies. The treatment schedule comprised a 1-week run-in (visit 1), a 52-week treatment phase (visits 2–10), and a posttreatment follow-up 2 weeks after completion or withdrawal from the study (visit 11). The study protocol was approved by the investigational center Research Ethics Committees and conducted according to Good Clinical Practice guidelines and the declaration of Helsinki. The study was conducted between October 1999 and March 2001. Signed informed consent was obtained from parents before enrollment.

Patients

We recruited patients who were aged 12 to 47 months and had a documented history of recurrent cough or wheeze and were between the 5th and 95th centiles for height and weight on the growth charts provided for the study.²³ Patients were excluded when they had received systemic corticosteroid therapy for >5 days within 8 weeks or ICS at doses greater than FP 100 $\mu\text{g}/\text{day}$ or other ICS of 200 $\mu\text{g}/\text{day}$ within 4 weeks of visit 1. Patients were also excluded when they had been hospitalized or altered their medication within 4 weeks of visit 1 or had been hospitalized on >2 occasions for their recurrent wheeze within 12 months of visit 1. Patients with a systemic disease likely to affect growth were also excluded, as were patients who had a low birth weight (<1.5 kg) or were born before 32 weeks' gestation. Information on atopy, family history of atopy, and hospitalizations for asthma was also collected.

Treatment

Patients were randomly assigned to receive either FP ($2 \times 50 \mu\text{g}$ twice daily) via MDI and Babyhaler (GlaxoSmithKline, Stevenage, United Kingdom) spacer device or SCG ($1 \times 5 \text{ mg}$ 4 times daily) via MDI and Nebuhaler (AstraZeneca, Loughborough, United Kingdom) spacer device. Parents were instructed in the correct use of the Babyhaler and Nebuhaler spacer devices and only subjects whose parents could demonstrate correct use of the devices were randomized.

Treatment numbers were allocated in a 3:1 ratio using a blocked randomization stratified by age (<2 years, ≥ 2 years). The randomization code was computer generated, and treatment numbers were allocated centrally (ClinPhone Ltd, Nottingham, United Kingdom).

At the end of run-in, all usual asthma medication was discontinued (inhaled or intranasal corticosteroids [FP $\leq 100 \mu\text{g}/\text{day}$; other ICS $\leq 200 \mu\text{g}/\text{day}$], SCG, oral antileukotrienes, or β -agonists). Systemic corticosteroids were permitted for treatment of exacerbations (maximum 15 days). Patients continued to receive their usual relief medication on an "as required" basis for relief of recurrent wheeze.

Efficacy Parameters

Patients' parents completed daily record cards (DRCs) each morning to record patient wheeze symptoms and symptomatic use of relief medication during the previous 24 hours. DRCs were completed during run-in, for 2 weeks after each visit, and during the 2 weeks preceding visit 10 (week 52), a total of 21 weeks. Overall assessment of wheeze symptoms was scored using a rating scale of 0 to 3. A symptom-free day was defined as a symptom score of 0 for 1 day. Relief medication usage was recorded as a dichotomous variable. A mild exacerbation was defined as a worsening of symptoms requiring a change in the patient's asthma medication other than relief medication (theophyllins, anticholinergics, or antihistamines—not oral corticoste-

roids). A severe exacerbation was defined as a worsening of symptoms requiring treatment with oral or parenteral corticosteroids and/or an emergency or hospital visit.

Adherence

No formal assessment of treatment compliance was made. The dates on which patients started and stopped their medication were recorded. Protocol adherence was reinforced by clinic visits at short intervals (9 visits in 12 months), where the ability of the caregiver to complete DRCs and to use the spacer devices correctly was assessed, as well as their general adherence with the protocol.

Growth

Patients' height and/or length was measured at each visit in triplicate by the same observer (between 6:00 AM and 10:00 AM) using a calibrated stadiometer (Magnimeter; Raven Equipment, Great Dunmow, UK) and/or an infantometer (Kiddimeter; Raven Equipment). Height was measured in all children above 90 cm with the stadiometer, assuming that the child was able to stand unsupported with legs straight. Height was measured with patients barefoot (heels together and against the heel plate) standing upright with legs, buttocks, backs, shoulders, and occiput in contact with the measuring device. Length was measured in all children <100 cm and when the patient was unable to stand unsupported or stood unsupported but with legs bent. Infants were measured face up on a measuring board with head against the headpiece, knees together, and hips and legs extended. In infants of between 90 and 100 cm, both infantometry and stadiometry were measured. The mean of 3 height or length measurements were used for analysis. When both height and length were measured, all 6 measurements were used for analysis.

All investigators were instructed in device calibration before use, and training in the form of live demonstrations was given on measurement technique. A detailed description of the method for measuring height and length and positioning of the patient and a training video, prepared by the Child Growth Foundation, on the use of the stadiometer and infantometer were also provided to all investigators.

Hypothalamic-Adrenal Axis

At weeks 0 and 52, a blood sample was collected from the patients between 8:00 AM and 10:00 AM (not fasting) for measurement of serum cortisol concentrations. Blood was collected only from patients who were willing to provide a sample. At week 0, if there was any clinically significant abnormality, then the patient was withdrawn from the study at the discretion of the investigator. Serum samples were analyzed in duplicate in a blinded manner for serum cortisol using solid-phase extraction in combination with liquid chromatography tandem mass spectrometry.²⁴

Overnight 12-hour urine samples were collected at weeks 0, 28, and 52 for the measurement of urinary-free cortisol concentrations corrected for creatinine excretion. Urine was collected in urine bags for infants who were not toilet trained. Cortisol and creatinine concentrations were determined by Chiron ACS 180 chemiluminescence (Chiron Diagnostics, Walpole, MA) and Roche Hitachi alkaline/picric acid (Roche Diagnostics, Basel, Switzerland), respectively.

Eye Examination

The incidence of cataract formation was monitored carefully during the study. Slit-lamp examinations under sedation were performed at week 0, at week 52, or at withdrawal.

Statistical Analyses

As this was primarily a safety study examining the long-term effects of FP, a primary endpoint was not identified and no power calculations were performed for generating the sample size. Patient numbers were determined by International Committee on Harmonization requirements for the minimum population exposure to assess clinical safety.²² On the basis of experience, it was judged that approximately 450 patients should be randomized to receive FP to ensure that at least 300 and 100 patients completed weeks 28 and 52, respectively (minimum number for safety regu-

latory requirements). Similarly, ~150 patients should be randomized to receive SCG to ensure that at least 100 and 33 patients completed weeks 28 and 52, respectively. The intention-to-treat population consisted of all patients who entered the study, were randomized to treatment, and received at least 1 dose of study medication.

All analyses were performed using SAS software (version 8.01; SAS, Inc, Chicago, IL). All tests were performed at the 5% level of significance, with treatment differences and associated 2-sided 95% confidence intervals (CIs) constructed from the final model. Comparison of height velocity between the 2 treatment groups was done using a mixed-effects model.²⁵ The model included random effect terms for subject and the subject by time interaction, and fixed effect terms for center grouping, age, baseline weight, gender, baseline height and length, indicator variable during treatment data being length or height, treatment, time, and treatment by time interaction. The baseline factors described were found to have a significant impact (at the 10% level) on growth in this group of patients and were from a larger list of factors considered in the protocol. Additional comparisons of height velocity were performed for patients who recorded height only or length only throughout the study. As a confirmatory analysis, the height velocity for each subject derived using linear regression was compared between treatment groups using analysis of covariance including the same baseline factors as above. Serum cortisol concentrations (week 52) and overnight 12-hour creatinine-corrected urinary-free cortisol concentrations (weeks 28 and 52) were log-transformed to satisfy normality assumptions and analyzed using analysis of covariance allowing for effects as a result of baseline (visit 2 data) age, gender, center grouping, and treatment. All urine and serum data collected were included in the analysis. For efficacy parameters, the primary assessment period for statistical analysis was weeks 1 to 52. The percentage of symptom-free days and percentage of days with no rescue medication were calculated for each subject and assigned to 1 of the following 4 categories: 0% to 25%, >25% to 50%, >50% to 75%, and >75% to 100%. The numbers of subjects in each of the categories was compared between treatment groups using a proportional odds model allowing for effects as a result of age, gender, center grouping, and treatment. The overall incidence of withdrawals and the incidence of withdrawals as a result of lack of efficacy were examined using Fisher's exact test.

RESULTS

Study Population

A total of 625 patients were randomized to treatment: 471 patients to the FP group and 154 patients to the SCG group, with 25% ($n = 158$) of these patients aged 12 to 23 months. The number of patients who discontinued therapy was balanced between groups, 19% and 21% of patients in the FP and SCG groups, respectively, and was attributable mainly to protocol violation. Patients were discontinued when they fell beyond the 5th to 95th centiles for height and/or weight during the study. A total of

381 patients completed treatment in the FP group compared with 122 patients in the SCG group. Table 1 summarizes patient accountability during the study. Patients were recruited in Bulgaria (13%), Czech Republic (8%), Croatia (5%), Hungary (12%), Israel (4%), New Zealand (4%), Poland (16%), Russia (20%), Slovakia (9%), and South Africa (10%); however, 93% of the patients were white. The interaction between treatment and country was assessed and found not to be significant, indicating that there was no evidence of different effects between countries.

Treatment groups were well balanced with regard to anthropometric measures, socioeconomic status, and atopic history (Table 2). Fifty-six percent of patients had been hospitalized in the previous year for persistent wheeze; 40% had an atopic history, with 39% having a family history of asthma; and 36% had previously been on regular ICSs. During the 1-week run-in period, the mean percentage of symptom-free days was 60%, which equates to an average of 3 days per week with symptoms.

Adherence

The mean (\pm standard deviation) estimated exposure time was 322 ± 96 days versus 319 ± 102 days in the FP and SCG groups, respectively. The patient accountability shows the number who completed all measurements (Table 1). The percentage of patients who remained in the study over time is shown in Fig 1.

Safety Parameters

Stadiometry and Infantometry Measurements

There was no significant difference in the mean adjusted growth rates between the 2 groups after 52 weeks of treatment (Fig 2), and the estimate of treatment difference with associated 95% CI was small (FP-SCG difference: -2.4 mm/year; 95% CI: -6.6 to 1.8 ; $P = .259$). Regression slope analysis revealed a growth rate of 85.3 mm/year in both groups (FP-SCG difference: 0.0 mm/year; 95% CI: -5.2 to 5.2 ; $P = .993$). Growth rates did not differ when estimated separately for all measurements of length and all measurements of height (Fig 2). There was also no significant growth rate difference during the first 3 months of treatment, and estimates of growth rate were independent of country. Estimates of growth

TABLE 1. Summary of Patient Accountability

	FP	SCG	Total
Total population screened			668
ITT population	471	154	625
Withdrawal after randomization, n (%)	90 (19)	32 (21)	122 (20)
Adverse event*	2 (<1%)	2† (1%)	4 (<1%)
Consent withdrawn	9 (2%)	1 (<1%)	10 (2%)
Lack of efficacy	0	3 (2%)	3 (<1%)
Lost to follow-up	3 (<1%)	1 (<1%)	4 (<1%)
Nonadherence	2 (<1%)	1 (<1%)	3 (<1%)
Protocol violation	72 (15%)	21 (14%)	93 (15%)
Other	2 (<1%)	3 (2%)	5 (<1%)
Completed (n [%])	381 (81%)	122 (79%)	503 (80%)

ITT indicates intention to treat.

* Includes related to lack of efficacy and not related to lack of efficacy.

† Adverse event related to lack of efficacy for both patients.

TABLE 2. Baseline Characteristics of Children Aged 12–47 Months With Recurrent Wheeze

Characteristic	FP (<i>n</i> = 471)	SCG (<i>n</i> = 154)
Anthropometrics		
Mean age, mo (range)	31.1 (11–47)	30.7 (11–47)
<12 mo	<1%	<1%
12–23 mo	26%	23%
24–35 mo	37%	41%
36–47 mo	37%	35%
Male	64%	71%
White	93%	90%
Mean height ± SD, mm	926.6 ± 79.0	922.2 ± 75.8
Mean weight ± SD, kg	14.3 ± 2.4	14.1 ± 2.3
Body mass index, range	16.6 (13–22)	16.5 (13–20)
Socioeconomics		
Low socioeconomic status	19%	21%
Medium socioeconomic status	51%	50%
High socioeconomic status	30%	29%
Exposure to cigarette smoke	27%	25%
Atopic history		
Subject history of atopic eczema	38%	47%
Family history of asthma	38%	42%
Hospitalization due to asthma in previous year		
0	44%	44%
1	28%	32%
2	18%	15%
≥3	10%	10%
Steroid naïve	65%	61%
Baseline symptom-free days, % ± SD	60.1 ± 38.6	59.7 ± 38.7
Baseline days with no rescue medication, % ± SD	82.2 ± 29.6	83.1 ± 28.6

SD indicates standard deviation.

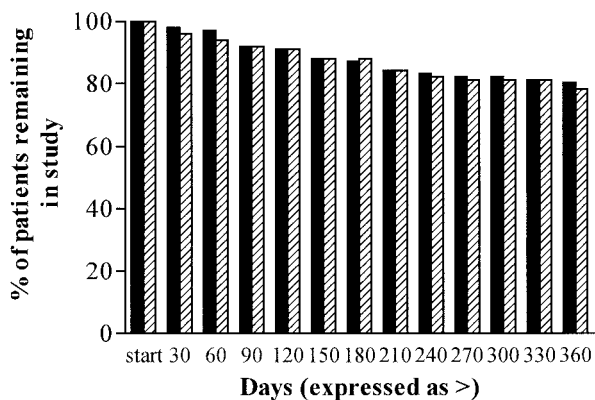


Fig 1. Percentage of patients who attended at each clinic visit. ■, FP (100 µg twice daily); ▨, SCG (5 mg 4 times daily).

rates were also independent of gender, age, previous use of corticosteroids, and measurement method (length and/or height; Table 3). Only a very small number of patients grew abnormally during this study, and numbers were similar between the 2 groups, indicating that this was unlikely to be a treatment effect. Eight (2%) patients in the FP group and 4 (3%) in the SCG group grew <20 mm/year, and 13 (3%) patients in the FP group and 4 (3%) in the SCG group grew >140 mm/year.

Cortisol Measurements

Serum-cortisol was significantly reduced in the FP-treated (*n* = 289) compared with SCG-treated

(*n* = 94) children at the end of the study: 240.8 nmol/L versus 267.9 nmol/L (odds ratio [OR]: 0.90; 95% CI: 0.81–1.00; *P* = .050). Eleven (3%) children in the FP treatment group had adrenal suppression at randomization shown by serum cortisol levels below the lower limit (83 nmol/L). This improved during the study as only 3 children (<1%) had this reported level after 52 weeks of treatment, compared with 4 (3%) and 0 children in the SCG group.

Twelve-hour urinary-free cortisol corrected for creatinine was significantly reduced after FP treatment (28.2 nmol/mmol) compared with SCG (33.0 nmol/mmol; OR: 0.86; 95% CI: 0.76–0.96; *P* = .008). Urinary cortisol concentrations decreased by ≥30% in 27% and 18% of children in the FP and SCG groups, respectively, and by ≥50% in 13% and 11% in the FP and SCG groups, respectively. During the study, oral corticosteroids were permitted for a maximum period of only 15 days and so were unlikely to have had an effect on cortisol concentrations. Table 4 summarizes mean serum and creatinine-corrected urinary cortisol concentrations.

Eye Examination

A total of 432 children and 358 children had an ophthalmic examination at week 0 and at week 52, respectively. Cataract was reported in 2 patients: 1 at baseline (steroid naïve), who was withdrawn before treatment, and 1 patient (male, 44 months) treated with FP was found on slit-lamp examination to have a pinhead-sized posterior capsule intraocular opacity in the left eye that had no effect on visual acuity (in

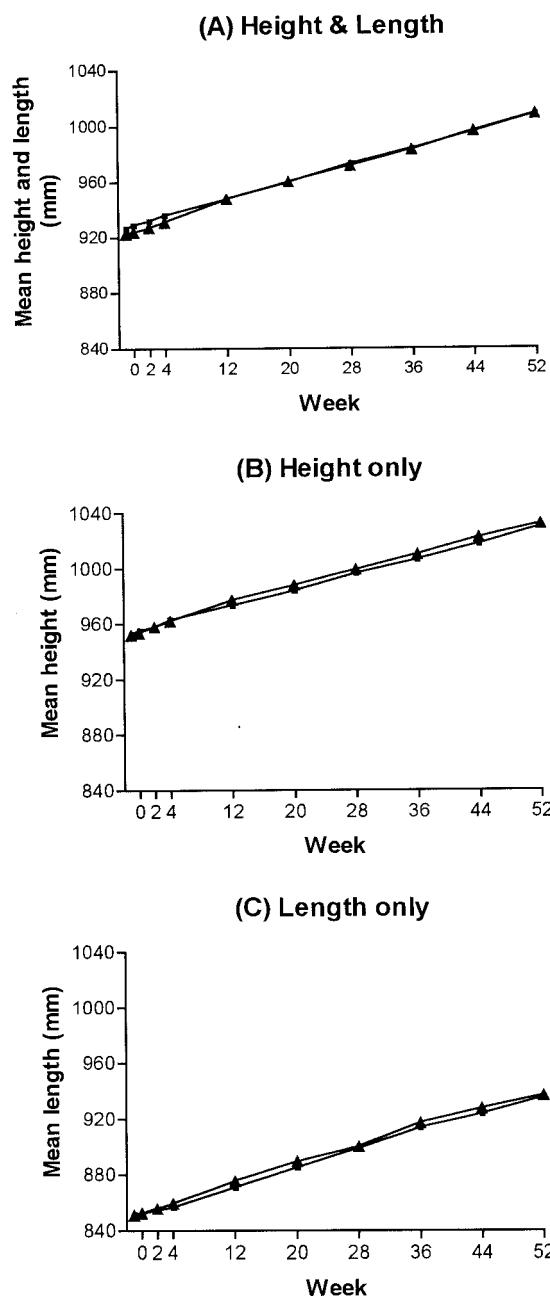


Fig 2. Effect of FP (■; 100 µg twice daily) or SCG (▲; 5 mg 4 times daily) on stadiometry and/or infantometry measurements of children with persistent/recurrent asthma-like symptoms. A, Height and length difference: -2.4 mm/year; 95% CI: -6.6 to 1.8 ; $P = .259$. B, Height-only difference: -2.4 mm/year; 95% CI: -6.7 to 2.0 ; $P = .288$. C, Length-only difference: -0.3 mm/year; 95% CI: -8.1 to 7.5 ; $P = .936$.

the opinion of the ophthalmologist). No raised intraocular pressures were detected. The child had a growth rate of 100 mm/year (above 97th centile) versus a mean of 83.9 mm/year for the whole study population. Baseline urinary cortisol concentration was higher in this child (48 nmol/L) than the group mean value (27 nmol/L) and fell to 12 nmol/L at week 52. He was taken off FP after the study. Follow-up visits showed that the size of the cataract seemed to have decreased 6 months posttreatment and had disappeared 1 year posttreatment.

Adverse Events

Any drug-related adverse event was reported by 4% on FP and 2% on SCG. The most common drug-related adverse events were cough (2% FP vs 1% SCG) and hoarseness (1% FP vs 0% SCG). Candida was seen in 3 children on FP and in 0 on SCG. Other drug-related events were seen only in single cases.

Five percent of patients in the FP group had a serious adverse event compared with 6% in the SCG group, although none of these events was considered by the investigators to be drug related and mostly consisted of asthma. Two subjects from both groups withdrew as a result of adverse events (not drug related).

Efficacy Parameters

FP demonstrated statistically significant superior efficacy to SCG in all comparisons, suggesting good compliance with therapy in the FP group. Fewer patients who were treated with FP experienced 1 or more mild exacerbation (30% vs 38%; OR: 1.60; 95% CI: 1.08–2.37; $P = .017$), severe exacerbation (7% vs 16%; OR: 2.41; 95% CI: 1.31–4.38; $P = .004$), and need for courses of oral corticosteroids for such exacerbations (6% vs 12%). Patients on FP had significantly more symptom-free days (OR: 0.49; 95% CI: 0.33–0.72; $P < .001$) and less use of rescue medication (OR: 0.56; 95% CI: 0.34–0.93; $P = .023$) compared with patients on SCG. This means that FP patients were twice as likely to be in a higher category of both symptom control and reduced use of rescue medication as SCG patients. The week by which the majority of patients reached 100% symptom-free days was week 5 to 6 for FP and week 13 to 14 for SCG. A total of 72% ($n = 340$) of patients in the FP group exhibited symptom-free days for $\geq 75\%$ of the whole treatment period compared with 61% ($n = 94$) of patients in the SCG group. Similarly, 88% ($n = 411$) and 79% ($n = 123$) of patients in the FP and SCG groups, respectively, did not use rescue medication for at least 75% of the treatment period. In the northern hemisphere, asthma symptoms improved throughout the summer with both treatments, but control was sustained during the subsequent winter only with FP (Fig 3). Symptom improvement on FP compared with SCG was independent of gender and previous use of ICSs.

The percentage of patients who withdrew was similar in both treatment groups, but significantly fewer patients withdrew from the FP group as a result of lack of efficacy (difference FP-SCG: -3% ; 95% CI: -6% to 0% ; $P = .002$), although the numbers in each treatment group was small (0 patients with FP and 5 patients with SCG).

DISCUSSION

The importance of early anti-inflammatory control even in young children is increasingly appreciated.^{1,26} Therefore, there is a clinical need for the evaluation of the safety of ICSs in children who are younger than 4 years and have asthma-like symptoms. In our study, we found that 1-year treatment with standard doses of inhaled FP in children who were aged 1 to 3 years and had mild to moderate

TABLE 3. Mean Growth Rate in Children Aged 12–47 Months With Persistent/ Recurrent Wheeze After Treatment With FP or SCG for 52 Weeks

Growth Rate (mm/y)	FP	SCG	Growth Rate Statistics
Mixed-model analysis			
Height and length	(<i>n</i> = 471) 84.0 ± 1.1	(<i>n</i> = 153) 86.4 ± 1.8	Diff: –2.4 mm/y CI: –6.6 to 1.8 <i>P</i> = .259
Height only	(<i>n</i> = 346) 78.9 ± 1.1	(<i>n</i> = 107) 81.3 ± 1.9	Diff: –2.4 mm/y CI: –6.7 to 2.0 <i>P</i> = .288
Length only	(<i>n</i> = 113) 100.8 ± 2.2	(<i>n</i> = 44) 101.1 ± 3.4	Diff: –0.3 mm/y CI: –8.1 to 7.5 <i>P</i> = .936
Height and length, first 3 mo	(<i>n</i> = 471) 85.8 ± 2.4	(<i>n</i> = 153) 90.9 ± 4.2	Diff: –5.1 mm/y CI: –14.5 to 4.3 <i>P</i> = .289
Regression slopes	(<i>n</i> = 466)	(<i>n</i> = 152)	Diff: –0.0
Height and length	85.3 ± 1.5	85.3 ± 2.4	CI: –5.2 to 5.2 <i>P</i> = 0.993
Growth rate by subgroup*			
Steroid history			
Steroid takers	(<i>n</i> = 167) 83.7 ± 1.8	(<i>n</i> = 60) 87.2 ± 3.0	Diff: –3.5 mm/y CI: –10.4 to 3.4
Steroid naïve	(<i>n</i> = 304) 84.2 ± 1.3	(<i>n</i> = 93) 85.8 ± 2.4	Diff: –1.6 mm/y CI: –7.0 to 3.7
Age			
<2 y	(<i>n</i> = 123) 101.4 ± 1.8	(<i>n</i> = 37) 106.7 ± 3.3	Diff: –5.4 mm/y CI: –12.7 to 2.0
≥2 y	(<i>n</i> = 348) 77.8 ± 1.1	(<i>n</i> = 116) 80.0 ± 1.9	Diff: –2.2 mm/y CI: –6.4 to 2.0
Gender			
Male	(<i>n</i> = 300) 83.1 ± 1.3	(<i>n</i> = 110) 84.3 ± 2.1	Diff: –1.3 mm/y CI: –6.2 to 3.7
Female	(<i>n</i> = 171) 85.7 ± 1.8	(<i>n</i> = 43) 92.3 ± 3.7	Diff: –6.6 mm/y CI: –14.7 to 1.4

* None of the treatment-by-time interactions with these covariates was significant.

TABLE 4. Mean Serum and Creatinine-Corrected 12-Hour Urinary-Free Cortisol Concentrations in Children Aged 12–47 Months With Persistent/Recurrent Wheeze After Treatment With FP or SCG for 52 Weeks

	FP	SCG
Serum cortisol (nmol/L), all samples		
Week 0	240.7 (56.9) <i>n</i> = 410	216.9 (73.0) <i>n</i> = 134
Week 52 geometric mean ratio	0.97 <i>n</i> = 289	1.09 <i>n</i> = 94
FP/SCG ratio	0.90; 95% CI: 0.81–1.00; <i>P</i> = .050	
12-h urinary cortisol adjusted for creatinine (nmol/mmol)		
Week 0	30.3 (73.7) <i>n</i> = 430	28.7 (58.7) <i>n</i> = 140
Week 28 geometric mean ratio	0.89 <i>n</i> = 358	1.15 <i>n</i> = 118
FP/SCG ratio	0.82; 95% CI: 0.73–0.92; <i>P</i> < .001	
Week 52 geometric mean ratio	0.91 <i>n</i> = 342	1.12 <i>n</i> = 110
FP/SCG ratio	0.86; 95% CI: 0.76–0.96; <i>P</i> = .008	

Results are expressed as geometric mean (coefficient of variation).

recurrent wheeze resulted in improved symptom control with no effect on growth rate compared with inhaled SCG. The large number of children recruited (*n* = 668) and treated (*n* = 625) far exceeds that in previous studies. The treatment difference for growth rates was small with a narrow CI (–6.6 to 1.8 mm/year) and was not influenced by age, gender, previous use of steroids, or measurement technique (height vs length). Although previous use of steroids can affect growth, this study contained a large num-

ber of steroid-naïve patients, indicating that the results seen were not influenced by previous use of steroids. A diagnosis of asthma is difficult in this young population. These children received a diagnosis of mild to moderate persistent wheeze with a documented history of persistent/recurrent cough, wheeze, and/or asthma-like symptoms. More than 50% had been hospitalized for the disorder in the previous year, and >30% had been on regular ICSs. The dose of FP (100 µg twice daily) was considered

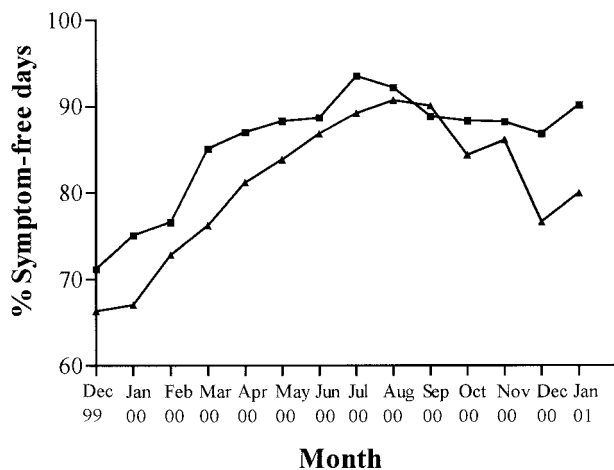


Fig 3. Effect of FP (100 µg twice daily) or SCG (5 mg 4 times daily) on the percentage of symptom-free days per month in a group of preschool children from the northern hemisphere with recurrent asthma-like symptoms. ■, FP; ▲, SCG.

appropriate on the basis of our earlier dose-response study.⁴

Measurement of urinary cortisol concentrations in this size and age of population for 1 year was a major achievement given the difficulty in using urine bags for children who were not toilet trained. Mean serum cortisol concentrations showed a statistically significant suppression of 10% but stayed within the normal range for age. Similarly, urinary cortisol concentrations were suppressed by 14%. Still, fewer subjects had serum cortisol levels below the normal range at the end of the study compared with baseline values. Thirteen and 11% on FP and SCG, respectively, exhibited >50% suppression with no significant difference between treatments. Changes in endogenous cortisol production reflected detectable systemic steroid activity from FP but did not indicate clinically relevant hypothalamic-adrenal axis suppression. Detectable steroid activity is inevitable for any topical steroid treatment of the airways, as steroids are not metabolized locally but have to pass via the systemic circulation to the liver for degradation. The systemic activity therefore is reflective of the route of elimination and is not a measure of a clinical side effect, which can be measured only through clinical measurements of the target organs such as growth measurements, ophthalmic examination, and test for adrenal responsiveness to stress (the first 2 of which were measured in this study and both of which provided reassuring safety data). It is recognized, however, that urinary-free cortisol concentration is a relatively insensitive marker of hypothalamic-pituitary-adrenal activity and that a better approach would be to estimate 24-hour secretion rates of total cortisol and cortisol metabolites²⁷ or a low-dose synacthen test.²⁸ Few recent case reports in children have indicated that high, nonlicensed doses of ICSs, particularly fluticasone propionate (500–2000 µg/day), can cause serious systemic side effects such as hypoglycemia, secondary to adrenal insufficiency.^{29–31} It is reassuring that in the present study, using a licensed dose of 200 µg/day, adrenal func-

tion tests gave reassuring results with no single child having urinary cortisol below the lower reference limit. Indeed, this finding of cortisol suppression is in keeping with our recent report on knemometry showing approximately 50% reduction on lower leg length growth during 2-week periods.²¹ Such findings are very sensitive measures of systemic steroid activity and useful for comparative purposes. However, it has no bearings on clinically relevant side effects that can be gauged only from direct measurements of the target organ.

Slit-lamp examination of the lenses was completed in 432 children at study entry and in 358 at completion. This provides the most powerful pediatric ophthalmic safety database in the public domain. A pin-head-sized posterior capsule intraocular opacity was seen in the left eye of 1 steroid-naïve child who withdrew before receiving treatment and another steroid-naïve child after 52 weeks of FP treatment. However, growth was not affected in this child. The incidence of congenital cataract in children aged 2 to 10 has previously been shown to be 4 to 6/10 000.^{32,33}

Both treatments were well tolerated. The most common drug-related adverse events were cough (2% FP vs 1% SCG) and hoarseness (1% FP vs 0% SCG).

The efficacy of FP was superior to SCG, with fewer cases of mild and severe exacerbations and requirements for oral steroid treatment and more symptom-free days and days without use of rescue treatment. Typically, there is a considerable spontaneous improvement of this highly variable condition observed in clinical trials.^{4,34} However, the effect of FP over the comparator was further illustrated by the sustained symptom control on FP treatment and worsening on SCG that coincided with the start of the viral season (Fig 3). The lower efficacy of SCG is probably in part attributable to low adherence to the required 4-times-daily regimen revealed in this long-term trial, although caregivers were reminded periodically of compliance.

The study was a randomized, parallel-group, open-label study. Although the study was designed predominantly as a safety study before regulatory authority guidelines on growth studies, it did comply with many of the recommendations with respect to study design, inclusion/exclusion criteria, treatment duration, method of height measurements, and statistical analyses. This study did not, however, contain either a 6-month run-in or a six-month follow-up period as specified in regulatory authority guidelines on growth studies. In view of the accumulated evidence of efficacy of ICSs in this age group,^{35–37} placebo control was not considered ethical in this 12-month study of young symptomatic children. Furthermore, placebo control would require a double-dummy technique that, in view of the 4-times-daily treatment regimen of SCG, would compromise patient recruitment, retention, and compliance. In addition, many of the key safety parameters were objective, reducing the potential for bias introduced by the open-label design. Adherence with study medication is suggested from the documented clinical efficacy even at the end of this 12-month study

period. Also, cortisol suppression at the last visit attests to the adherence to study treatment. The completion rate was good with 80% of patients attending all visits of the study, withdrawal rates being similar for both treatment groups.

Our study represents the first prospective, controlled, and randomized 1-year study of growth, urine cortisol, and slit-lamp examination of the lenses in toddlers who were younger than 4 years and had recurrent wheeze treated with ICSs. The recruitment of >600 young children provides a more precise estimate of treatment effects and thereby greater reassurance on the safety of inhaled FP in young children with recurrent wheeze. In conclusion, this study provides reassuring safety data permitting a strategy of early intervention with ICSs in young children with wheeze.

ACKNOWLEDGMENTS

Funding for this study (protocol no. FAS30009) was provided by GlaxoSmithKline.

We thank the following investigators: Paul Francis, Nicholas Freezer (Australia); Dimitre Petrov, Rumiana Ratcheva, Nina Markova, Vassilka Ilieva (Bulgaria); Vladimir Ahel, Eva Verona, Jasna Cepin-Bogovic, Darko Richter (Croatia); Petr Pohunek, Martin Fuchs, Ondrej Rybnicek, Hana Janickova, Ivan Drnek, Olga Skopkova (Czech Republic); Istvan Bittera, Bela Nagy, Maria Adonyi, Endre Cserhati, Kalman Gyurkovits, Lasalo Barkai, Tamas Dolinay (Hungary); Asher Tal, Elvan Tabachnik, Lea Ben-Tur, Haim Bibi (Israel); Jim Reid, John Gillies, Jeff Brown (New Zealand); Ryzard Kurzawa, Jerzy Alkiewicz, Andrzej Boznanski, Ewa Najberg, Krystyna Karczewska, Teresa Malaczynska (Poland); Boris Blokhin, Natalia Geppel, Evgeni Pashanov, Alexander Kharchev, Irina Makarova, Vera Afanaseran Reviakina, Natalia I. Iljina, Irina Sheveluk, Irina Sidorenko, Lubov Pushko (Russia); Zuzana Kukova, Anna Feketeova, Peter Banovcin, Ivan Hruskovic, Eva Mocova (Slovakia); Ahmed Ismail Manjra, Mervyn Ossip, Jan Vermeulen A. L., Heinrich Weber, Eugene Weinberg, Adrian Morison, Mike Greeff (South Africa).

REFERENCES

- Global Strategy for Asthma Management and Prevention. NHLBI/WHO Workshop Report. NIH Publication No. 95-3659, Bethesda, MD: National Institutes of Health; 2002
- Noble V, Ruggins N, Everard M, Milner A. Inhaled budesonide for chronic wheezing under 18 months of age. *Arch Dis Child.* 1992;67:285-288
- Connett G, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1-3 years. *Arch Dis Child.* 1993;69:351-355
- Bisgaard H, Gillies J, Groenewald M, Maden C. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med.* 1999;160:126-131
- Bisgaard H, Munck S, Nielsen J, Petersen W, Ohlsson S. Inhaled budesonide for treatment of recurrent wheezing in early childhood. *Lancet.* 1990;336:649-651
- Buchvald F, Bisgaard H. FeNO measured at fixed exhalation flow rate during controlled tidal breathing in children from the age of 2 yr. *Am J Respir Crit Care Med.* 2001;163:699-704
- Nielsen K, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year old asthmatic children. *Am J Respir Crit Care Med.* 2000;162:1500-1506
- Bisgaard H, Price M, Maden C, Olsen N. Cost-effectiveness of fluticasone propionate administered via metered-dose inhaler plus Babyhaler spacer in the treatment of asthma in pre-school aged children. *Chest.* 2001;120:1835-1842
- Agertoft L, Pedersen S. Short-term knemometry and urine cortisol excretion in children treated with fluticasone propionate and budesonide: a dose response study. *Eur Respir J.* 1997;10:1507-1512
- Doull I, Freezer N, Holgate S. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med.* 1995;151:1715-1719
- Verberne A, Frost C, Roorda R, vanderLaag H, Kerrebijm K. One year

- treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med.* 1997;156:688-695
- Simons F. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. *N Engl J Med.* 1997;4:1659-1665
- Tinkelman D, Reed C, Nelson H, Offord K. Aerosol beclomethasone dipropionate compared to theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics.* 1993;92:64-77
- Allen D, Bronsky E, LaForce C, et al. Growth in asthmatic children treated with fluticasone propionate. Fluticasone propionate Asthma Study Group. *J Pediatr.* 1998;132:472-477
- Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med.* 2000;343:1054-1063
- Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med.* 2000;343:1064-1069
- Skoner D, Szeffler S, Welch M, Walton-Bowen K, Cruz-Rivera M, Smith J. Longitudinal growth in infants and young children treated with budesonide inhalation suspension for persistent asthma. *J Allergy Clin Immunol.* 2000;105:259-268
- Turktas I, Ozkaya O, Bostanci I, Bideci A, Cinaz P. Safety of inhaled corticosteroid therapy in young children with asthma. *Ann Allergy Asthma Immunol.* 2001;86:649-654
- Volovitz B, Amir J, Malik H, Kauschanski A, Varsano I. Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. *N Engl J Med.* 1993;329:1731-1733
- Bisgaard H. Systemic activity from inhaled topical steroid in toddlers studied by knemometry. *Acta Paediatr Scand.* 1993;82:1066-1071
- Anhøj J, Bisgaard A, Bisgaard H. Systemic activity of inhaled steroids in asthmatic young children 1-3 years of age. *Pediatrics.* 2002;109(3). Available at: pediatrics.aappublications.org/cgi/content/full/109/3/e40
- Guideline for Industry: The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life threatening conditions. ICH-E1A. 95-4958, 11269-11271; 1995
- Boys and Girls Growth Charts.* London, UK: Child Growth Foundation; 1990
- Callejas S, Biddlecombe R, Jones A, Joyce K, Pereira A, Pleasance S. Determination of the glucocorticoid fluticasone propionate in plasma by automated solid-phase extraction and liquid chromatography tandem mass spectrometry. *J Chromatogr Biomed Sci Appl.* 1998;718:243-250
- Goldstein H. Multilevel statistical models, Kendall's Library of Statistics 3. 1995
- Martinez F. Present and future treatment of asthma in infants and young children. *J Allergy Clin Immunol.* 1999;104:169-174
- Hindmarsh P. Exogenous glucocorticoids influence adrenal function, but assessment can be difficult. *BMJ.* 2002;324:1083
- Crowley S, Hindmarsh PC, Honour JW, Brook CG. Reproducibility of the cortisol response to stimulation with a low dose of ACTH(1-24): the effect of basal cortisol levels and comparison of low-dose with high-dose secretory dynamics. *J Endocrinol.* 1993;136:167-172
- Drake AJ, Howells RJ, Shield JPH, Prendiville A, Ward PS, Crowne EC. Symptomatic adrenal insufficiency presenting with hypoglycaemia in children with asthma receiving high dose inhaled fluticasone propionate. *BMJ.* 2002;324:1081-1083
- Todd GRG, Acerini CL, Buck JJ, et al. Acute adrenal crisis in asthmatics treated with high-dose fluticasone propionate. *Eur Respir J.* 2002;19:1207-1209
- Patel L, Wales JK, Kibirige MS, et al. Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. *Arch Dis Child.* 2001;85:330-334
- Stewart-Brown S, Haslum M. Partial sight and blindness in children of the 1970 birth cohort at 10 years of age. *J Epidemiol Community Health.* 1988;42:17-23
- Stayte M, Reeves B, Wortham C. Ocular and vision defects in pre-school children. *Br J Ophthalmol.* 1993;77:228-232
- Knorr B, Franchi L, Bisgaard H, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics.* 2001;108:1-10
- de Blic J, Delacourt C, Le Bourgeois M, et al. Efficacy of nebulized budesonide in the treatment of severe infantile asthma: a double blind study. *J Allergy Clin Immunol.* 1996;98:14-20
- Roorda R, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol.* 2001;108:540-546
- Mellon M. Efficacy of budesonide inhalation suspension in infants and young children with persistent asthma. Budesonide Inhalation Suspension Study Group. *J Allergy Clin Immunol.* 1999;104:191-199

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Pediatrics 2004;113:e87
DOI: 10.1542/peds.113.2.e87

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