

Response of preschool children with asthma symptoms to fluticasone propionate

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Background: Many uncertainties remain in the diagnosis and treatment of preschool children with asthma symptoms.

Objective: We sought to determine the subgroups of preschool children (aged 12-47 months) with recurrent asthma symptoms most likely to respond to inhaled fluticasone propionate (200 µg/d).

Methods: Subgroups of pooled data from 2 similar 12-week multicenter studies were analyzed.

Results: Children with frequent symptoms (symptoms on ≥ 3 days per week and a total of $\geq 75\%$ days with symptoms during the 4-week run-in period; $n = 169$) showed a significantly greater increase in days without symptoms after fluticasone propionate treatment (0% to 45%) compared with after placebo treatment (0% to 25%, $P = .005$). Children with a family history of asthma ($n = 213$) also had a significantly greater increase in days without symptoms after fluticasone propionate (11% to 54%) compared with after placebo (7% to 35%, $P = .002$) and a significantly higher proportion of exacerbation-free patients (61% to 76%, $P = .02$). Children with less frequent symptoms, no family history of asthma, or both showed no significant treatment effect. There seemed to be no association between response to fluticasone propionate and history of rhinitis or eczema or the number of previous exacerbations.

Conclusions: Children with frequent symptoms, a family history of asthma, or both showed the greatest response to fluticasone propionate treatment. These findings may help to predict treatment outcome and guide the management of preschool children with recurrent asthma symptoms. (*J Allergy Clin Immunol* 2001;108:540-6.)

Key words: Asthma, fluticasone propionate, Babyhaler spacer, preschool children, placebo

Children less than 4 years of age with wheeze or asthma symptoms are a difficult population to study because of the variable nature of the symptoms and limited out-

Abbreviation used

pMDI: Pressurized metered-dose inhaler

come measures.¹ Consequently, many uncertainties still remain in the diagnosis and treatment of preschool children with asthma symptoms.

Up to 40% of children in this age group may experience recurrent cough, wheeze, or breathlessness.² Such symptoms may be transient and benign in around 60% of cases, probably reflecting congenitally narrow airways or bronchospasm that predisposes to wheeze associated with viral infections.^{3,4} However, in other children recurrent wheeze and cough in the preschool years may persist into later childhood, when asthma may be diagnosed. Family history of asthma, positive skin test reactivity to allergens, and high serum IgE levels are all suspected to be risk factors for symptoms to persist.⁵ It is not clear whether these 2 groups of preschool children with asthma symptoms respond differently to treatment. Young children with persistent moderate-to-severe asthma symptoms may benefit from an inhaled corticosteroid.^{1,6-9} Intermittent high-dose inhaled corticosteroids have elicited modest improvement in preschool children with episodic viral wheeze.^{10,11} Regular prophylactic treatment in such children has not proved useful, although the evidence is limited to a few studies.¹²

Two large, multicenter, parallel-group, double-blind, placebo-controlled studies recently examined the dose-related response in preschool children to inhaled fluticasone propionate, which is effective in older children.¹³ Preschool children included in these studies had a history of recurrent wheeze or asthma symptoms and were symptomatic on entry. We have analyzed pooled data from these studies to characterize the subgroups of children most likely to benefit from this treatment. Such insight may help predict treatment response and guide the management of preschool children presenting with recurrent wheeze or asthma symptoms.

METHODS

Two multicenter, double-blind, randomized, placebo-controlled, parallel-group studies used for the analysis were similar in design but differed only in the range of fluticasone propionate doses investigated. Both studies involved a 4-week run-in period with placebo,

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followed by 12 weeks of treatment with either placebo or fluticasone propionate delivered from a pressurized metered-dose inhaler (pMDI) through a Babyhaler spacer device. The studies were conducted at 67 centers in 15 countries. Regulatory and ethics committee approval was obtained before the start of both studies, which were performed according to the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from the parent or guardian of each child before participation.

Study population

Children (aged 12-47 months) with a documented history of recurrent wheeze or asthma symptoms were eligible for entry; inclusion and exclusion criteria were identical for both studies. Patients were also eligible if, in the opinion of the investigator, they were considered to benefit from inhaled corticosteroids for their airway disease management. Patients were randomized to treatment if, on at least 7 of the last 14 days of the 4-week run-in period, they had symptoms of wheeze, cough, or shortness of breath during the day or night or had required symptomatic use of albuterol (salbutamol). Patients were excluded from the studies if, in the 2 weeks before the run-in period or during the run-in period, they received inhaled or systemic corticosteroids or methylxanthine therapy, had been hospitalized for asthma, had any changes in their asthma medication, or had received antibiotics for chest infection. Patients were also excluded if they were unable to use the Babyhaler device correctly.

Study design

During the run-in period, patients received 2 puffs twice daily of placebo pMDI through the Babyhaler spacer device, allowing at least 5 tidal breaths (or 15 seconds) for inhalation. Patients discontinued their usual bronchodilator at the start of the run-in period. This was replaced with albuterol (Ventolin inhaler, Ventodisks, Nebules, or Ventolin syrup as appropriate) for use on an as-required basis to relieve asthma symptoms during the run-in and treatment periods. Inhaled or systemic corticosteroids, anticholinergic agents, nedocromil sodium, methylxanthines, or β_2 agonists (other than the albuterol provided) were not permitted, unless for treatment of an exacerbation. All other regular medications for asthma (including sodium cromoglycate and ketotifen) or other conditions were continued, providing the dose regimens remained constant throughout.

At the end of the run-in period, patients were randomized to receive 2 puffs of either placebo twice daily, 50 μ g of fluticasone propionate twice daily, or 100 μ g of fluticasone propionate twice daily in study 1 or placebo twice daily, 100 μ g of fluticasone propionate twice daily, or 250 μ g of fluticasone propionate twice daily in study 2. Data from individual studies indicated the 100- μ g twice daily regimen to be optimal.

Assessments

Clinic assessments were performed at the beginning and end of the run-in period and thereafter every 3 weeks for the 12-week treatment period. Parents completed a daily diary of their child's symptoms, recording daytime and nighttime scores for wheeze, cough, and shortness of breath on a scale of 0 to 3. Daytime and nighttime use of rescue albuterol was also recorded. The primary measure of efficacy for both studies was the percentage of symptom-free days and nights over weeks 1 to 12 of the treatment period. At each clinic visit, adverse events and asthma exacerbations were recorded, inhalation technique and compliance with the protocol were checked, and a swab of the oropharynx was taken if there was visual evidence of fungal infection. Asthma exacerbations were defined as a worsening of the child's asthmatic symptoms that required either a change in medication (other than rescue albuterol), medical attention, or both. In both studies patients were withdrawn if they experienced more than one exacerbation

TABLE I. Patient demographics and baseline characteristics

	Placebo	FP 200 μ g/d
No. of patients	152	153
No. of male/female patients	99/53	101/52
Age (mo), mean $\pm$ SD	28 $\pm$ 10	29 $\pm$ 12
Height (cm), mean $\pm$ SD	89 $\pm$ 8	91 $\pm$ 10
Weight (kg), mean $\pm$ SD	13 $\pm$ 3	14 $\pm$ 3
Ethnic origin (white)	91%	92%
Family history of asthma	75%	67%
Personal history of seasonal rhinitis	27%	26%
Personal history of eczema	44%	39%
Duration of asthma		
1-12 mo	42%	50%
13-24 mo	36%	30%
25-36 mo	20%	16%
>36 mo	2%	3%
No. of prior asthma exacerbations		
0	16%	10%
1-3	37%	51%
4-6	26%	29%
7-10	13%	5%
>10	8%	5%
Number of prior hospitalizations for asthma		
0	69%	67%
1	17%	16%
2	11%	7%
>2	3%	10%

FP, Fluticasone propionate.

tion requiring oral or additional inhaled corticosteroids or if symptoms became unacceptable despite rescue medication.

Subgroup analysis

Data were analyzed for the following subgroups: symptom frequency (defined below) during the run-in period; family history of asthma and personal history of eczema or rhinitis (each elicited through questioning or case notes); and exacerbation rate (frequent, >3; less frequent, $\leq$ 3) in the year before study entry. The frequent symptoms subgroup comprised patients with symptoms on 3 or more days per week and for 75% or greater of the 4-week run-in period; the less frequent symptoms subgroup comprised patients with symptoms on less than 3 days per week and less than 75% of the 4-week run-in period.

Statistical analysis

A nonparametric method (the Van Elteren extension to the Wilcoxon rank sum test) was used for each variable to assess pairwise differences between the treatment groups in each subgroup over weeks 1 to 12 of treatment. Median treatment differences and 95% CIs for the differences were calculated by using the Hodges Lehmann method.¹⁴ Exacerbation rates between subgroups were compared by using the Fisher exact test. A 2 $\times$ 1-sided *P* value at the 5% level is presented. All analyses presented were carried out on the intent-to-treat population. In the derivation of percentage of symptom-free days, missing data were imputed. If one of the 3 symptoms was missing on any day, that was defined as "not symptom free."

RESULTS

The population for analyses from the 2 studies comprised 305 patients whose demography and baseline respiratory disease characteristics are described in Table I.

TABLE II. Response to fluticasone propionate, 200 µg/d, according to baseline frequency of symptoms

Median values	Frequent symptoms (n = 169)						Less frequent symptoms (n = 127)					
	Placebo		FP 200 µg/d		Treatment difference		Placebo		FP 200 µg/d		Treatment difference	
	Week 0	Weeks 1-12	Week 0	Weeks 1-12	% (95% CI)	P value	Week 0	Weeks 1-12	Week 0	Weeks 1-12	% (95% CI)	P value
Days and nights with no overall symptoms	0%	25%	0%	45%	13.1% (3.6-22.0)	.005	29%	50%	36%	64%	8.7% (-1.2-19.3)	.097
Days with no cough	14%	42%	8%	56%	11.4% (2.0-21.1)	.011	50%	61%	50%	70%	8.2% (-0.5-17.6)	.073
Days with no wheeze	71%	80%	71%	92%	8.5% (2.0-16.9)	.002	93%	92%	86%	95%	0% (-1.2-3.5)	.639
Days with no relief medication	36%	71%	36%	80%	7.1% (0.0-15.7)	.048	64%	74%	50%	77%	2.1% (-5.0-11.6)	.624

FP, Fluticasone propionate.

The use of permitted concurrent antiasthma medication (18% sodium cromoglycate, 12% ketotifen, and 5% other) and as-required albuterol was small and similar between the treatment groups. After randomization, 16 patients receiving placebo and 14 receiving fluticasone propionate withdrew. Adverse events were the most common cause for withdrawal (8 and 5 patients, respectively); the overall rate was small and not considered to have affected the results.

Overall response

Fluticasone propionate (200 µg/d) significantly increased the percentage of days and nights with no overall symptoms (Table II), from 11% at baseline to 54% (weeks 1-12), compared with placebo (8% to 36%; median difference, 11.2%; 95% CI, 3.6-22.0; $P = .002$).

Symptom frequency

During the run-in period, 169 children were defined as having frequent symptoms and 127 as having less frequent symptoms. Six children were excluded from analysis: 3 for incomplete data and 3 for receiving both fluticasone and placebo through erroneous dispensing of the randomized study pMDIs.

For patients with frequent symptoms, fluticasone propionate significantly increased the days and nights without symptoms from 0% at baseline to 45% over weeks 1 to 12 compared with placebo (0% to 25%, $P = .005$; Fig 1, A). Furthermore, there was a significant increase in the days with no cough, days with no wheeze, and days with no relief medication during weeks 1 to 12 compared with placebo (Table II).

For patients with less frequent symptoms, the increase in days and nights without symptoms with fluticasone propionate (36% to 64%) was not significantly different from that with placebo (29% to 50%; Fig 1, B). There were no significant differences for other measured symptoms (Table II).

Family history of asthma

Patients with a family history of asthma experienced a significant increase in days without symptoms with fluti-

cane propionate compared with placebo (Fig 1, C). Those without a family history of asthma failed to show a significant response (Fig 1, D).

Combination of symptom frequency and family history of asthma

In patients with frequent symptoms and a family history of asthma, fluticasone propionate significantly increased the days and nights with no overall symptoms compared with placebo (Fig 2, A). The difference between fluticasone propionate and placebo for patients with less frequent symptoms and a family history of asthma, however, did approach significance ($P = .061$; Fig 2, C), but the interpretation is complicated because of an imbalance in the baseline values for the 2 treatment groups. No significant treatment effects were observed in the remaining subgroups (Fig 2, B and D).

Personal history of rhinitis or eczema

There was a significant difference in the number of days and nights without symptoms with fluticasone propionate compared with placebo in both subgroups with and without eczema, in the subgroup without rhinitis, and in both the subgroups with and without a family history of asthma in combination with a personal history of eczema (Table III).

Prior exacerbation rate

There was a significant increase in the days and nights with no overall symptoms after treatment with fluticasone propionate, 200 µg/d, in both patients presenting with a history of 3 or fewer exacerbations and patients presenting with a history of more than 3 exacerbations in the year before study entry (Table III).

Effect of treatment on exacerbations

The proportion of exacerbation-free patients increased from 64% with placebo to 75% with fluticasone propionate ($P = .033$, Table IV). Categorization on the basis of symptom frequency showed no significant improvement. However, on the basis of a family history of asthma, fluticasone propionate provided a significantly greater

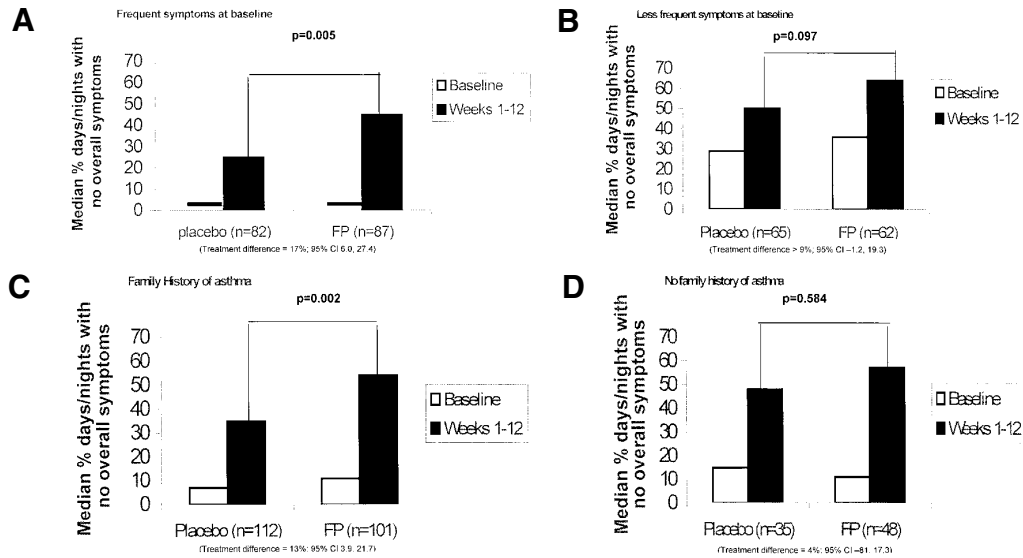


FIG 1. Response to fluticasone propionate (FP), 200 µg/d, measured by median percentage of days and nights with no overall symptoms in subgroups of patients with frequent symptoms at baseline (**A**), less frequent symptoms at baseline (**B**), a family history of asthma (**C**), and no family history of asthma (**D**).

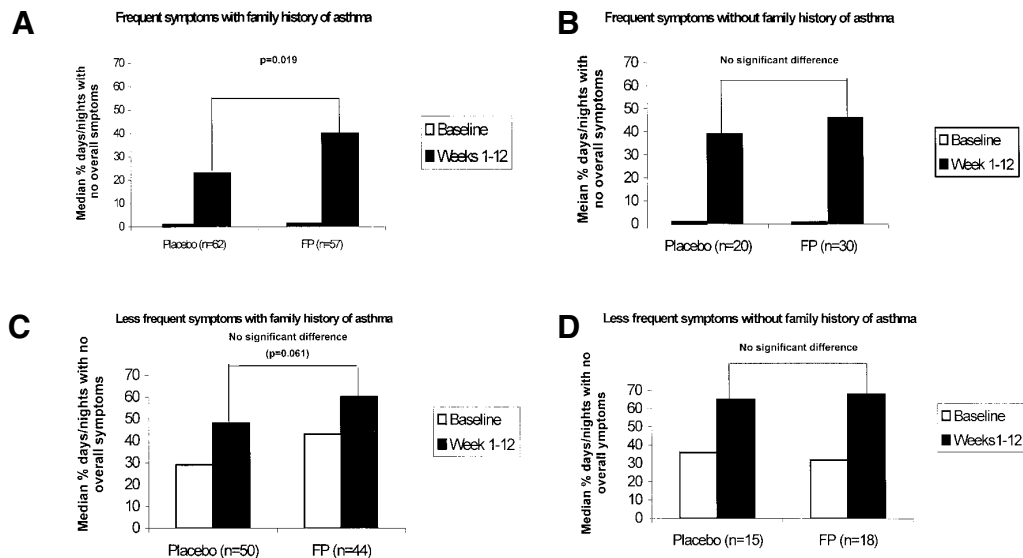


FIG 2. Response to fluticasone propionate (FP), 200 µg/d, measured by median percentage of days and nights with no overall symptoms in patients with frequent symptoms at baseline with (**A**) and without (**B**) a family history of asthma and in patients with less frequent symptoms at baseline with (**C**) and without (**D**) a family history of asthma.

improvement in the proportions of exacerbation-free patients (76% vs 61% on placebo, $P = .021$). Results of the remaining subgroup are detailed in Table IV.

Effect of age

Analyses of the total population showed that the percentage of days with no symptoms was significantly greater for patients aged 2 years or greater and treated with fluticasone propionate (median difference vs placebo, 15.7; 95% CI, 6.5-25.8; $P < .001$) than for patients aged less than

2 years (median difference vs placebo, 1.3; 95% CI, -10.7 to 15.5; $P = .763$). This was similar for patients with less frequent symptoms (≥ 2 years: median difference vs placebo, 13.1; 95% CI, 1.5-27.4; $P = .041$; < 2 years: median difference vs placebo, -3.7; 95% CI, -24.1 to 15.0; $P = .518$). However, fluticasone propionate was more effective than placebo in children aged less than 2 years presenting with frequent symptoms (< 2 years: median difference vs placebo, 11.9; 95% CI, -2.8 to 25.0; $P = .120$; ≥ 2 years: median difference vs placebo, 14.7; 95% CI, 2.4-28.5; $P < .015$).

TABLE III. Reduction in overall symptoms with fluticasone propionate, 200 µg/d, over weeks 1 to 12 in patients analyzed in accordance with family history of asthma, personal history of eczema or rhinitis, and prior exacerbation rate

Subgroup*	Days and nights with no overall symptoms						
	Placebo		FP 200 µg/d		Treatment difference		
	Week 0	Weeks 1-12	Week 0	Weeks 1-12	%	95% CI	P value
Personal history of rhinitis (n = 79)	11%	29%	4%	50%	13%	-1.2 to 26.2	.084
No personal history of rhinitis (n = 214)	7%	38%	14%	55%	11%	2.4-19.3	.009
Personal history of eczema (n = 123)	7%	32%	14%	55%	12%	0-23.5	.036
No personal history of eczema (n = 172)	14%	42%	8%	54%	10%	0-20.2	.039
Family history of asthma and personal history of eczema (n = 90)	7%	28%	7%	51%	13%	0-27.4	.040
No family history of asthma or no personal history of eczema (n = 205)	14%	42%	14%	55%	9%	0-18.3	.040
Frequent exacerbations in last year (n = 126)	14%	29%	14%	53%	13%	2.4-25.0	.020
Less frequent exacerbations in last year (n = 165)	14%	42%	7%	54%	9%	0-19.0	.043

*n = number of patients with relevant recorded data.

FP, Fluticasone propionate.

TABLE IV. Reduction in exacerbation rate with fluticasone propionate, 200 µg/d, analyzed in accordance with baseline symptom frequency, family history of asthma, personal history of eczema or rhinitis, and prior exacerbation rate

Subgroup*	Patients free of exacerbations			Treatment difference		
	Placebo	FP 200 µg/d	%	95% CI	P value	
All patients (n = 296)	64%	75%	11%	1%-23%	.033	
Frequent symptoms during run-in period (n = 169)	67%	77%	10%	-4% to 25%	.13	
Less frequent symptoms during run-in period (n = 127)	60%	73%	13%	-4% to 31%	.138	
Family history of asthma (n = 213)	61%	76%	15%	2%-28%	.021	
No family history of asthma (n = 83)	72%	75%	3%	-19% to 24%	.806	
Personal history of rhinitis (n = 79)	62%	75%	13%	-10% to 35%	.335	
No personal history of rhinitis (n = 214)	64%	76%	12%	-1% to 25%	.055	
Personal history of eczema (n = 123)	60%	76%	16%	-1% to 34%	.058	
No personal history of eczema (n = 172)	66%	75%	9%	-6% to 23%	.244	
Family history of asthma and personal history of eczema (n = 90)	55%	79%	24%	3%-45%	.026	
No family history of asthma or personal history of eczema (n = 205)	67%	74%	7%	-7% to 20%	.292	
Frequent exacerbations in last year (n = 126)	62%	78%	16%	-2% to 33%	.082	
Less frequent exacerbations in last year (n = 165)	64%	74%	10%	-5% to 26%	.182	

*n = number of patients with relevant recorded data.

FP, Fluticasone propionate.

DISCUSSION

Pooled analyses of data from 2 controlled studies show that fluticasone propionate treatment of preschool children presenting with frequent symptoms significantly increased the numbers of days and nights when the children remain symptom free. The effectiveness of treatment was apparently similar whether children were less than 2 or 2 or more years of age. In addition, a family history of asthma appeared to be a good predictor and substantiated the response to fluticasone propionate. Although patients with less frequent symptoms and no family history of asthma did not show a significant response, children 2 or more years of age with less frequent symptoms appeared to benefit. Similar subgroup analyses on the basis of a personal history of eczema, rhinitis, or both or a prior history of exacerbations failed to predict an unequivocal response.

In both controlled studies entry and randomization criteria were stringent and excluded children recovering

from an acute exacerbation of asthma or those with self-limiting respiratory symptoms caused by infection. Also, patients had to demonstrate symptoms on 50% of days in the last 2 weeks of the placebo run-in period. Despite these criteria, there was a high placebo response rate during the treatment period. This has been observed in other studies in asthmatic children under the age of 4 years,¹⁵⁻¹⁷ possibly because of the difficulty of accurate definitions and diagnoses of asthma in this age group. Future study designs should include age stratification at entry and for analyses.

Subgrouping and analysis of the pooled population was undertaken to better understand which asthmatic children might benefit most from regular treatment with an inhaled corticosteroid, such as fluticasone propionate. The definitions of symptom frequency were based on the 4-week run-in period and therefore extended the criteria required for randomization (symptoms on 50% of days in the last 2 weeks). The definition of frequent symptoms required patients to demonstrate a level of symptoms on

each week of the run-in period, and therefore these patients had more persistent and more frequent symptomatology than patients in the less frequent category. The purpose of subgrouping was to identify patients with chronic persistent symptoms (frequent symptom group) from those with intermittent or episodic symptoms (less frequent symptom group). We realize that classification according to symptoms and a primary outcome measure on the basis of symptoms could result in a methodological bias whereby the benefits of treatment on symptom levels might be more readily demonstrable in patients with frequent symptoms than in those children with less frequent symptoms. However, this would not preclude benefits of treatment for those patients with less frequent symptoms had different measures been studied (eg, time interval between episodes or duration of episodes) or more objective data used, such as pulmonary function tests. Indeed, there was no significant difference between the effect of fluticasone propionate and placebo on the number of patients with at least one exacerbation in either of the 2 symptom frequency subgroups, although there was a significant reduction in the exacerbation rate for the total population. Post hoc analyses have shown that the presence of chronic persistent symptoms remains a good predictor of response to fluticasone propionate in children aged less than 2 and those aged 2 or more years.

The categorization of patients according to family history of asthma may reflect differences in the underlying pathology of the child's asthma symptoms. The analysis showed that patients with a family history of asthma derived a significant benefit from treatment with fluticasone propionate in terms of reduction in overall symptoms relative to placebo, whereas those without a family history of asthma did not. Furthermore, the presence of a family history of asthma also appeared to be important in the significant reduction in the rate of exacerbations observed with fluticasone propionate. Further subgrouping showed that patients with both frequent symptoms and a family history of asthma also derived most benefit from fluticasone propionate, although interpretation of the effect in patients with less frequent symptoms and family history of asthma is complicated by an imbalance at baseline in symptom levels between the 2 treatment groups. Interestingly, a history of eczema or rhinitis failed to be as strong a predictor of fluticasone response. This may have been due to younger children with eczema or rhinitis being predisposed to having asthma or allergic rhinitis-hay fever at an older age.

The management of preschool children with asthma symptoms is still a subject of considerable discussion. Children aged less than 3 to 4 years presenting with symptoms of cough, wheeze, and shortness of breath may have either viral-associated respiratory problems that may not persist into later childhood or may be experiencing an asthmatic pattern of airways inflammation that may subsequently develop into asthma.¹⁸ The nature of symptoms in these groups does not appear to differ during earlier years of life.

Persistent wheezing in the first 3 years of life, as well as a maternal history of asthma, have been linked with

subsequent development of asthma.³ The present findings suggest that young children with frequent symptoms and those with a family history of asthma may particularly benefit from early prophylactic treatment with fluticasone propionate because it has been suggested that inhaled steroids may be of particular benefit to patients commencing treatment at a younger age. However, longitudinal studies are necessary to test this hypothesis. It may also be of value to keep a record of symptoms before the introduction of any prophylactic treatment.

In conclusion, fluticasone propionate was effective and well tolerated for the management of asthma symptoms in children less than 4 years of age. Subgroup analyses indicate that children displaying frequent symptoms are most likely to benefit in terms of symptom reduction with an inhaled steroid. Patients with a family history of asthma, irrespective of personal history of eczema or rhinitis, showed significant reduction in symptoms and exacerbations after fluticasone propionate treatment. These findings may help to predict treatment outcome and guide the management of preschool children presenting with a history of recurrent wheeze or asthma symptoms.

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