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Official publication of the American College of Chest Physicians



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Chest 2007;132:1876-1881
DOI 10.1378/chest.07-1587

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
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Effects of Montelukast Treatment and Withdrawal on Fractional Exhaled Nitric Oxide and Lung Function in Children With Asthma*

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Background: Leukotriene receptor antagonists (LTRAs) reduce fractional exhaled nitric oxide (FENO) concentrations in children with asthma, but the effect of LTRA withdrawal on FENO and lung function is unknown. We aimed to study the effect of treatment and withdrawal of montelukast, a LTRA, on airway inflammation as reflected by FENO and lung function in children with asthma.

Methods: A double-blind, randomized, placebo controlled, parallel group study was undertaken in 14 atopic children with mild persistent asthma who were treated with oral montelukast (5 mg/d for 4 weeks) and 12 atopic children with mild persistent asthma who received matching placebo. A follow-up visit was performed 2 weeks after montelukast or placebo withdrawal.

Results: Montelukast reduced FENO concentrations by 17% ($p = 0.067$), an effect that was more pronounced (35%) [$p = 0.0029$] when children with seasonal atopy who were exposed to relevant allergens during the treatment phase were excluded from analysis ($n = 3$). Compared to those at the end of treatment, FENO concentrations were increased 2 weeks after montelukast withdrawal ($p = 0.023$) concomitant with a reduction in absolute FEV₁ values ($p = 0.011$), FEV₁ percentage of predicted values ($p = 0.006$), FEV₁/FVC ratio ($p = 0.002$), and forced expiratory flow at 25% to 75% of FVC values ($p = 0.021$). These changes were not observed in the placebo group.

Conclusions: LTRAs reduce FENO concentrations in children with asthma, and withdrawal can result in increased FENO values and worsening of lung function in children with asthma.

(CHEST 2007; 132:1876–1881)

Key words: airway inflammation; childhood asthma; fractional exhaled nitric oxide; leukotriene receptor antagonists; lung function

Abbreviations: FEF_{25%–75%} = forced expiratory flow at 25% to 75% of FVC; FENO = fractional exhaled nitric oxide; LTRA = leukotriene receptor antagonist; PEF = peak expiratory flow; ppb = parts per billion

Leukotriene receptor antagonists (LTRAs) are a therapeutic option for children with mild persistent asthma.^{1,2} LTRAs improve symptoms and lung function, and reduce asthma exacerbations and β_2 -agonist use in asthmatic children.^{3,4} Measurement of fractional exhaled nitric oxide (FENO) is a well-established method for assessing airway inflammation and the antiinflammatory effects of pharmacologic treatment in patients with asthma.⁵ FENO correlates with peripheral blood eosinophils and bronchial hyperresponsiveness in asthmatic children.⁶ In asthmatic children, montelukast, a LTRA,

reduces FENO concentrations with a size effect ranging from 20 to 65%.^{7,8} A large clinical trial⁹ has shown a mean reduction in FENO of approximately 20% after oral montelukast at a dose of 5 mg qd for 48 weeks. This effect occurs rapidly with a 15% decrease in FENO levels within 2 days.⁷

One open-label, uncontrolled study¹⁰ reported increased FENO in asthmatic children after LTRA withdrawal, but the effect of discontinuation of LTRAs on lung function in asthmatic children is mostly unknown.¹¹ In the present study, we investigated the effect of montelukast treatment and with-

drawal on lung function and FENO in atopic children with mild persistent asthma.

MATERIALS AND METHODS

Study Subjects

Thirty-six atopic children with persistent mild asthma were studied: 18 children were included in the montelukast group, and 18 children were included in the placebo group. Fourteen children in the montelukast group and 12 children in the placebo group completed the study (Table 1). Three children in the montelukast group and four children in the placebo group were excluded from the study because of asthma exacerbation; one child in the montelukast group and two children in the placebo group were excluded because of consent withdrawal. Three children with seasonal atopy in the montelukast group and three children with seasonal atopy in the placebo group were exposed to relevant allergens during the treatment phase.

Children were recruited from the Asthma and Allergy Clinic, Pediatric Hospital Bambino Gesù, Palidoro, Italy, and Azienda Sanitaria Locale Roma C, Rome, Italy. The diagnosis and classification of asthma were based on clinical history and examination and pulmonary function parameters according to guidelines issued by the National Heart, Lung, and Blood Institute of the National Institutes of Health.¹ Children had symptoms more often than twice a week but less often than once a day, FEV₁ ≥ 80% of predicted value and reversibility ≥ 12% to salbutamol, or a positive provocation test result with methacholine or exercise. They were not taking any regular medication, but used inhaled short-acting β₂-agonists as needed for symptom relief. Asthmatic children had FENO values > 20 parts per billion (ppb) at baseline. Children had no upper respiratory tract infections in the previous 3 weeks and were excluded from the study if they had used glucocorticoids or LTRAs in the previous 4 weeks. Children received inhaled glucocorticoids for not > 4 weeks in the previous year.

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This work was performed at the Catholic University of the Sacred Heart, Rome, Italy.

This work was supported by Merck, Sharp, and Dohme, Rome, Italy, and Catholic University of the Sacred Heart, Rome, Italy; academic grant from 2004 to 2007.

The authors have no conflicts of interest to disclose.

Manuscript received June 23, 2007; revision accepted August 20, 2007.

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DOI: 10.1378/chest.07-1587

Table 1—Characteristics of Children With Asthma at Baseline (Visit 1)*

Characteristics	Placebo Group	Montelukast Group
Patients, No.	12	14
Age, yr	10.5 ± 0.6	10.8 ± 0.5 (p = 0.71)
Female/male gender, No.	2/10	3/11
FEV ₁ , L	2.44 ± 0.25	2.46 ± 0.19 (p = 0.96)
FEV ₁ , % predicted	91.4 ± 3.2	95.3 ± 2.5 (p = 0.33)
FEV ₁ /FVC, % predicted	97.7 ± 2.5	100.3 ± 2.4 (p = 0.46)
Seasonal atopy†, No.	8	6
Perennial atopy†, No.	4	8
FENO, ppb	42.6 (28.0–66.4)	51.4 (37.2–59.1) [p = 0.94]

*Data are presented as mean ± SEM or median (interquartile range) unless otherwise indicated.

†Presence of atopy was confirmed by skin-prick testing for common aeroallergens (mixture for house dust mite [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*], grass pollen [cockfoot, timothy], tree pollen [birch, ash tree, olive tree, oak, cypress], weed pollen [*Ambrosia artemisiifolia*, *Parietaria officinalis*], animal danders [cat and dog allergens], fungal allergens [*Aspergillus*, *Alternaria alternata*]). A positive skin-prick test response was defined as a wheal with a mean diameter (mean of maximum and 90° midpoint diameters) of at least 3 mm greater than that produced with a saline solution control. All atopic children had a clinical history of atopy. Asthmatic children with seasonal atopy were allergic to grass pollen, tree pollen, and weed pollen. Asthmatic children with perennial atopy were allergic to house dust mite and animal danders.

Study Design

A double-blind, randomized, placebo controlled, parallel group study was undertaken in 14 asthmatic children treated with montelukast and 12 asthmatic who received placebo. Children attended on four occasions for clinical examination, measurement of FENO, and lung function tests. After a screening visit (visit 1) and 1-week run-in period (visit 2), children were administered either oral montelukast (5 mg qd as tablet) for 4 weeks or matching placebo. After treatment phase (visit 3) and after 2 weeks from montelukast or placebo withdrawal (visit 4), all these tests were repeated. Skin testing was performed on visit 1. Informed consent was obtained from parents, and the study was approved by the Ethics Committee of the Catholic University of the Sacred Heart, Rome, Italy.

Pulmonary Function

FEV₁, FVC, FEV₁/FVC, forced expiratory flow from 25% to 75% of FVC (FEF_{25%–75%}), and peak expiratory flow (PEF) were measured by spirometry (Pony FX; Cosmed; Rome, Italy), and the best of three consecutive maneuvers were chosen.

FENO Measurement

FENO was measured with the NIOX system (Aerocrine; Stockholm, Sweden) with a single-breath on-line method at constant flow of 50 mL/s according to American Thoracic Society guidelines.⁵ Exhalations were repeated after 1-min relaxation period until the performance of three FENO values that varied < 10%. FENO measurements were obtained before spirometry.

Skin Testing

Atopy was assessed by skin-prick testing for common aeroallergens (Stallergenes; Antony, France).¹²

The study sample was calculated¹³ considering posttreatment FENO values as the primary outcome. Sample size was calculated on the basis of a previous study¹⁴ and was estimated to be 18 children per group, after having considered a SD of 15 ppb, a dropout of 15%, and identified the minimal difference of biological significance (18 ppb corresponding to 31% reduction of mean FENO values) with a power of 90% ($\alpha = 5\%$, $\beta = 10\%$). Study power, recalculated on the basis of the number of children who completed the study, was 75%.

Statistical Analysis

FENO values were expressed as medians and interquartile ranges (25 to 75 percentiles). Friedman repeated-measures analysis of variance was used to compare FENO values within each treatment arm. Spirometry values were expressed as mean $\pm$ SEM. Newman-Keul repeated-measures analysis of variance was used to compare spirometry values within each treatment arm. Unpaired *t* tests and Wilcoxon signed-rank tests were used for comparisons of differences between treatments for normally distributed and nonparametric data, respectively. Correlation was expressed either as Spearman coefficient or Pearson coefficient on the basis of data distribution. Significance was defined at $p < 0.05$.

RESULTS

FENO

There was no statistically significant difference between pretreatment FENO concentrations in the montelukast and placebo groups ($p = 0.64$), although absolute pretreatment FENO was higher in the montelukast group (Table 2). There was no difference between FENO at baseline (visit 1) and before treatment (visit 2) [montelukast group, $p = 0.24$; placebo group, $p = 0.13$; Table 2].

Montelukast reduced FENO concentrations by 17%, although this reduction did not reach statis-

tical significance (pretreatment, 45.5 ppb [33.2 to 64.1 ppb]; posttreatment, 37.9 [25.6 to 62.5 ppb]; $p = 0.067$; Table 2).

When children with seasonal atopy who were exposed to relevant allergens such as grass pollen or tree pollen during the treatment phase were excluded from analysis ($n = 3$), there was a significant reduction in FENO concentrations by 35% after montelukast (pretreatment, 56.4 ppb [33.8 to 72.4 ppb]; posttreatment, 36.9 ppb [19.5 to 62.5 ppb]; $p = 0.0029$) [Table 3].

When all children were considered for analysis, FENO concentrations were increased after placebo (pretreatment, 37.5 ppb [28.2 to 66.5 ppb]; posttreatment, 46.3 ppb [33.6 to 86.1 ppb]; $p = 0.043$) [Table 2]. In contrast, when children who were exposed to relevant allergens during placebo treatment phase were excluded ($n = 3$), placebo had no effect on FENO ($p = 0.30$) [Table 3]. Posttreatment FENO concentrations were increased in the three children who were exposed to relevant allergens during placebo administration (pretreatment, 84.7 ppb [minimum to maximum range, 27.3 to 137.9 ppb]; vs posttreatment, 103.8 ppb [minimum to maximum range, 53.2 to 213.4 ppb]).

Compared to those at the end of treatment, FENO concentrations were increased 2 weeks after montelukast withdrawal (37.9 ppb [25.6 to 62.5 ppb] vs 52.2 ppb [36.0 to 72.9 ppb], $p = 0.023$, respectively) [Table 2]. Similar results were obtained when children exposed to relevant allergens were excluded (posttreatment, 36.9 ppb [19.5 to 62.5 ppb]; follow-up, 43.6 ppb [28.5 to 74.8 ppb]; $p = 0.032$) [Table 3].

There was no change in FENO after placebo discontinuation (posttreatment, 46.3 ppb [33.6 to 86.1 ppb]; follow-up, 40.6 ppb [26.8 to 82.5 ppb]; $p = 0.52$) [Table 2]. Similar results were observed when children who were recently exposed to relevant allergens were

Table 2—Effects of Treatment With Oral Montelukast (5 mg qd for 4 Weeks) or Matching Placebo on FENO Concentrations and Pulmonary Function Test Values in Atopic Children With Persistent Mild Asthma*

Variables	Visit 1	Visit 2	Visit 3†	Visit 4‡
Montelukast ($n = 14$)				
FENO, ppb	51.4 (37.2–59.1)	45.5 (33.2–64.1)	37.9 (25.6–62.5) [$p = 0.067$]	52.2 (36.0–72.9)§ [$p = 0.023$]
FEV ₁ , L	2.46 $\pm$ 0.19	2.43 $\pm$ 0.18	2.48 $\pm$ 0.22 [$p = 0.41$]	2.33 $\pm$ 0.19§ [$p = 0.011$]
FEV ₁ , % predicted	95.3 $\pm$ 2.5	94.3 $\pm$ 2.4	95.7 $\pm$ 2.9 [$p = 0.49$]	90.6 $\pm$ 3.1 [$p = 0.006$]
FEV ₁ /FVC, % predicted	100.3 $\pm$ 2.4	99.2 $\pm$ 2.4	99.8 $\pm$ 2.8 [$p = 0.70$]	96.4 $\pm$ 2.8 [$p = 0.002$]
Placebo ($n = 12$)				
FENO, ppb	42.6 (28.0–66.4)	37.5 (28.2–66.5)	46.3 (33.6–86.1)§ [$p = 0.043$]	40.6 (26.8–82.5) [$p = 0.52$]
FEV ₁ , L	2.44 $\pm$ 0.25	2.49 $\pm$ 0.26	2.28 $\pm$ 0.25 [$p = 0.69$]	2.44 $\pm$ 0.26 [$p = 0.30$]
FEV ₁ , % predicted	91.4 $\pm$ 3.2	93.1 $\pm$ 3.1	92.9 $\pm$ 3.0 [$p = 0.90$]	90.7 $\pm$ 2.8 [$p = 0.19$]
FEV ₁ /FVC, % predicted	97.7 $\pm$ 2.5	96.7 $\pm$ 2.2	95.9 $\pm$ 3.0 [$p = 0.67$]	94.7 $\pm$ 3.0 [$p = 0.33$]

*Data are presented as median (interquartile range) or mean $\pm$ SEM.

†Compared with pretreatment values (visit 2).

‡Compared with posttreatment values (visit 3).

§ $p < 0.05$.

|| $p < 0.01$.

Table 3—Effects of Treatment With Oral Montelukast (5 mg qd for 4 Weeks) or Matching Placebo on FENO Concentrations and Pulmonary Function Test Values in Asthmatic Children With Perennial and/or Seasonal Atopy Who Were Not Exposed to a Relevant Seasonal Allergen During the Treatment Phase*

Variables	Visit 1	Visit 2	Visit 3†	Visit 4‡
Montelukast (n = 11)				
FENO, ppb	52.7 (42.5–71.5)	56.4 (33.8–72.4)	36.9 (19.5–62.5) [p = 0.0029]	43.6 (28.5–74.8)§ [p = 0.032]
FEV ₁ , L	2.37 ± 0.22	2.34 ± 0.21	2.42 ± 0.27 [p = 0.32]	2.28 ± 0.23§ [p = 0.029]
FEV ₁ , % predicted	93.2 ± 2.8	92.4 ± 2.6	94.5 ± 3.7 [p = 0.36]	89.6 ± 3.7§ [p = 0.015]
FEV ₁ /FVC, % predicted	99.8 ± 2.9	99.1 ± 2.5	99.4 ± 3.5 [p = 0.87]	96.7 ± 3.5§ [p = 0.014]
Placebo (n = 9)				
FENO, ppb	32.2 (28.0–52.9)	35.2 (29.1–39.7)	41.2 (28.7–41.7) [p = 0.30]	38.9 (32.9–42.2) [p = 0.50]
FEV ₁ , L	2.60 ± 0.31	2.62 ± 0.32	2.59 ± 0.32 [p = 0.31]	2.57 ± 0.33 [p = 0.39]
FEV ₁ , % predicted	93.4 ± 3.3	93.8 ± 3.3	92.8 ± 3.4 [p = 0.27]	91.4 ± 3.4 [p = 0.23]
FEV ₁ /FVC, % predicted	96.6 ± 3.3	96.4 ± 2.9	94.2 ± 3.7 [p = 0.16]	92.9 ± 3.8 [p = 0.26]

*Data are presented as median (interquartile range) or mean ± SEM.

†Compared with pretreatment values (visit 2).

‡Compared with posttreatment values (visit 3).

§p < 0.05.

||p < 0.01.

excluded (p = 0.50) [Table 3]. Median absolute change in FENO concentrations in asthmatic children after montelukast was −7.6 ppb when all children were considered and −19.5 ppb when children who were recently exposed to relevant allergens were excluded.

There were no between-group differences in FENO concentrations at the end of treatment (p = 0.27) and 2 weeks after montelukast or placebo withdrawal (p = 0.79) [Table 2]. However, posttreatment FENO concentrations were lower in the montelukast group than in the placebo group (−8.4 ppb) [Table 2]. After treatment withdrawal, asthmatic children who were treated with montelukast had higher FENO concentrations than those who received placebo (+11.6 ppb) [Table 2]. There was no correlation between FENO and age, sex, and lung function in any study group.

Lung Function Tests

Lung function test values at baseline were similar in the two study groups (Table 1). Montelukast had no effect on lung function test results in asthmatic children (Fig 1, 2; Table 2, 3). FEV₁ (Fig 1), FEV₁/FVC (Fig 2, top, A), and FEF_{25%–75%} values (Fig 2, bottom, B) 2 weeks after montelukast withdrawal were lower than those at the end of treatment (Table 2). Clinical worsening was observed in four children.

Similar results were obtained when asthmatic children with seasonal atopy who were exposed to relevant allergens during the treatment phase were excluded (Table 3). Placebo treatment and withdrawal had no effect on lung function tests (Fig 1, 2; Table 2, 3).

Compared with posttreatment FEV₁ values, mean absolute change in FEV₁ in the montelukast group 2 weeks after stopping drug treatment was −150 mL when all children were considered for analysis (Table

2), and −140 mL in the subgroup of children (Table 3). This reduction in mean FEV₁ values corresponds to −5.1% and −4.9% of FEV₁ percentage of predicted values, respectively.

There were no between-group differences in posttreatment pulmonary function test values: absolute FEV₁ (p = 0.95) [Fig 1, bottom, B; Table 2], FEV₁ percentage of predicted (p = 0.70) [Fig 1, top, A; Table 2], absolute FVC (p = 0.85), FVC percentage of predicted (p = 0.51), FEV₁/FVC percentage of predicted (p = 0.43) [Fig 2, top, A; Table 2], FEF_{25%–75%} in liters (p = 0.56) [Fig 2, bottom, B], PEF in liters (p = 0.73), and PEF in percentage of predicted (p = 0.48). There were no between-group differences in pulmonary function test values 2 weeks after stopping treatment: FEV₁ in liters (p = 0.71) [Fig 1, bottom, B; Table 2], FEV₁ percentage of predicted (p = 0.78) [Fig 1, top, A; Table 2], FVC in liters (p = 0.69), FVC percentage of predicted (p = 0.36), FEV₁/FVC percentage of predicted (p = 0.64) [Fig 2, top, A; Table 2], FEF_{25%–75%} in liters (p = 0.56) [Fig 2, bottom, B], PEF in liters (p = 0.64), and PEF in percentage of predicted (p = 0.41).

DISCUSSION

In the present study, montelukast reduced FENO concentrations in atopic children with persistent mild asthma, with a median reduction of 17% over baseline values, close to statistical significance. However, a highly significant reduction in median FENO concentrations of 35% was observed in the montelukast group when children with seasonal atopy who were exposed to relevant allergens during the treatment phase were excluded from analysis. These findings indicate that the effect of montelukast on FENO levels in asthmatic

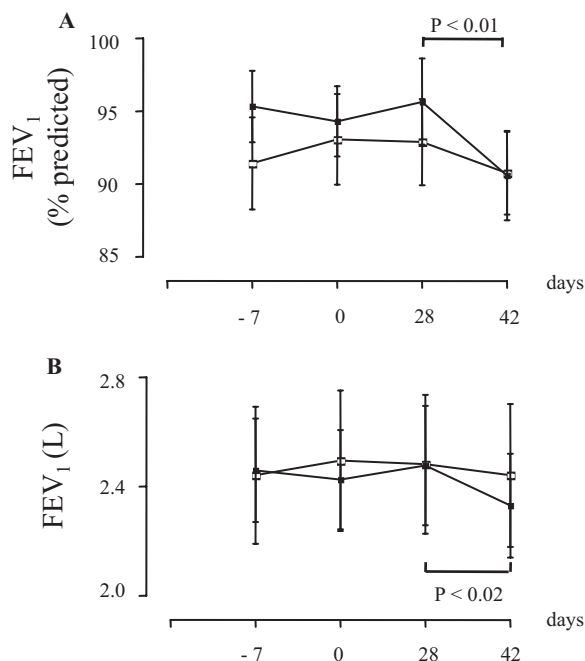


FIGURE 1. *Top, A:* FEV₁ percentage of predicted values in children with asthma at baseline (day 7), before treatment with montelukast (n = 14; filled squares) or placebo (n = 12; open squares; day 0), after treatment with oral montelukast (5 mg qd for 4 weeks) or matching placebo (day 28), and 2 weeks after montelukast or placebo withdrawal (day 42). *Bottom, B:* Absolute FEV₁ values in children with asthma at baseline (day 7), before treatment with montelukast (n = 14; filled squares) or placebo (n = 12; open squares; day 0), after treatment with oral montelukast (5 mg qd for 4 weeks) or matching placebo (day 28), and 2 weeks after montelukast or placebo withdrawal (day 42). Values are expressed as mean ± SD.

children can be masked by recent exposure to relevant allergens. This is further supported by elevated FENO levels after placebo when all children were considered, but not when children who were exposed to relevant allergens during placebo treatment phase were excluded. After placebo administration, FENO concentrations were increased in the three children with seasonal atopy who were exposed to relevant allergens consistent with previous studies.^{15,16} The present findings indicate that LTRAs reduce FENO concentrations in atopic asthmatic children who were not exposed to relevant allergens during the treatment phase; in those asthmatic children with seasonal atopy who were exposed to relevant allergens during the treatment phase, montelukast abolishes the increase in FENO due to allergen exposure. A similar effect of montelukast in preventing increase in FENO has been reported in asthmatic children allergic to house dust mite after exposure to relevant allergens.¹⁷

In contrast to a previous study,⁷ we were unable to detect any significant difference in posttreatment FENO concentrations between the montelukast-treated and placebo-treated groups. However, FENO differ-

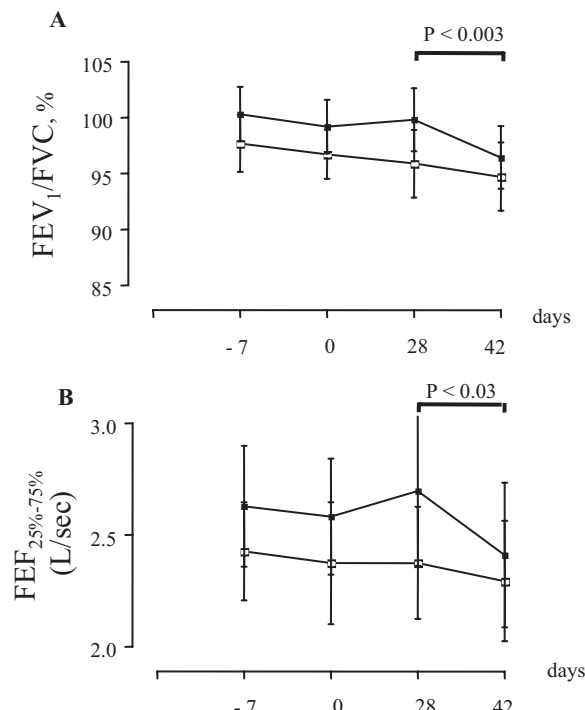


FIGURE 2. *Top, A:* FEV₁/FVC ratio values in children with asthma at baseline (day 7), before treatment with montelukast (n = 14; filled squares) or placebo (n = 12; open squares; day 0), after treatment with oral montelukast (5 mg qd for 4 weeks) or matching placebo (day 28), and 2 weeks after montelukast or placebo withdrawal (day 42). *Bottom, B:* FEF_{25%-75%} values in children with asthma at baseline (day 7), before treatment with montelukast (n = 14; filled squares) or placebo (n = 12; open squares; day 0), after treatment with oral montelukast (5 mg qd for 4 weeks) or matching placebo (day 28), and 2 weeks after montelukast or placebo withdrawal (day 42). Values are expressed as mean ± SD.

ence from placebo observed in our study (−8.4 ppb) was similar to that previously reported (−7.3 ppb).⁷ The lack of statistical significance in our study might be explained by the different study design (parallel groups vs crossover) and the smaller number of children included in our study (14 and 12 children per group vs 26 children). It is possible that our study was insufficiently powered to detect significant between-group differences as dropout rate (montelukast group, 22%; placebo group, 33%) was higher than that expected (15%); the size effect of montelukast on FENO concentrations in asthmatic children in the present study (−17%) was smaller than that observed in a similar group of asthmatic children (−27%)¹⁴; posttreatment differences in FENO concentrations between montelukast and placebo group could have been masked by higher (although not statistically different) pretreatment FENO values in the montelukast group compared with those in the placebo group, and the small size effect of montelukast on FENO concentrations (−17%). In our study, montelukast had no effect on lung function in asthmatic children, possibly due to the

normal lung function of the children included into the study, the insufficient duration of treatment, or the small number of children studied.

Consistent with previous studies,^{10,11} FENO in asthmatic children was increased 2 weeks after montelukast withdrawal. This increase is unlikely to be explained by the presence of the three asthmatic children with seasonal atopy who were recently exposed to relevant allergens because increased FENO was also observed when these children were excluded from analysis. Increased FENO 2 weeks after montelukast withdrawal was also observed in an uncontrolled open-label study¹⁸ in asthmatic children who were treated with inhaled glucocorticoids. By contrast, one study¹⁹ showed no increase in FENO concentrations 1 week after montelukast withdrawal in adults with mild asthma. This discrepancy might be explained by the different study populations (adults¹⁹ vs children^{10,11,18}) and duration of washout (1 week¹⁹ vs 2 weeks^{10,11,18}). Taken together, this evidence suggests that FENO measurement seems to be sensitive in detecting rebound of inflammation after LTRA withdrawal in asthmatic children.

In the present study, we show that LTRA withdrawal can result not only in increased FENO concentrations in asthmatic children, but also in worsening of lung function as indicated by decreased FEV₁, FEV₁/FVC, and FEF_{25%-75%} values over posttreatment values. Changes in FENO concentrations and lung function tests were likely caused by montelukast withdrawal because they were not observed in the placebo group and were not dependent on recent allergen exposure. These findings might be relevant for the management of asthmatic children who are treated with LTRAs as monotherapy. In contrast to our study, one study¹¹ has shown that increase in PEF after 2 weeks of montelukast treatment persists after 2 weeks of montelukast withdrawal. This discrepancy might be explained by the different study design (uncontrolled open-label¹¹ vs double-blind, placebo controlled), study population (children with mild to moderate asthma¹¹ vs children with mild asthma), and pulmonary function tests considered (PEF¹¹ vs FEV₁, FEV₁/FVC, and FEF_{25%-75%}).

In the present study, the lack of statistically significant between-group differences in FENO concentrations and lung function tests 2 weeks after withdrawal could be due to the fact that these were not primary outcomes and the number of children studied was small. Larger controlled trials to clarify the effect of LTRA withdrawal on airway inflammation and lung function in asthmatic children are required.

In conclusion, treatment with a LTRA has no effect on lung function test results in atopic children with persistent mild asthma, whereas it reduces FENO concentrations. LTRA withdrawal can result in increased FENO and worsening of lung function in children with asthma.

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Chest 2007;132;1876-1881
DOI 10.1378/chest.07-1587

This information is current as of December 18, 2007

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