

# Annals of Internal Medicine

## Oral Montelukast Compared with Inhaled Salmeterol To Prevent Exercise-Induced Bronchoconstriction

### A Randomized, Double-Blind Trial

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**Background:** Montelukast, an oral, once-daily leukotriene receptor antagonist, provides protection against exercise-induced bronchoconstriction.

**Objective:** To evaluate the effect of 8 weeks of therapy with salmeterol aerosol or montelukast on exercise-induced bronchoconstriction in adults with asthma.

**Design:** 8-week multicenter, randomized, double-blind study.

**Setting:** 17 asthma treatment centers in the United States.

**Patients:** 191 adults with asthma who had documented exercise-induced bronchoconstriction.

**Intervention:** Qualified patients were randomly assigned to double-blind treatment with montelukast (10 mg once in the evening) or salmeterol (50  $\mu$ g [2 puffs] twice daily).

**Measurements:** Changes in pre-exercise and post-exercise challenge values; percentage inhibition in the maximal percentage decrease in FEV<sub>1</sub>; the area above the FEV<sub>1</sub>-time curve; and time to recovery of FEV<sub>1</sub> at days 1 to 3, week 4, and week 8 of treatment.

**Results:** By day 3, similar and statistically significant reductions in maximal percentage decrease in FEV<sub>1</sub> were seen with both therapies. Sustained improvement occurred in the montelukast group at weeks 4 and 8; at these time points, the bronchoprotective effect of salmeterol decreased significantly. At week 8, the percentage inhibition in the maximal percentage decrease in FEV<sub>1</sub> was 57.2% in the montelukast group and 33.0% in the salmeterol group ( $P = 0.002$ ). By week 8, 67% of patients receiving montelukast and 46% of patients receiving salmeterol had a maximal percentage decrease in FEV<sub>1</sub> of less than 20%.

**Conclusions:** The bronchoprotective effect of montelukast was maintained throughout 8 weeks of study. In contrast, significant loss of bronchoprotection at weeks 4 and 8 was seen with salmeterol. Long-term administration of montelukast provided consistent inhibition of exercise-

induced bronchoconstriction at the end of the 8-week dosing interval without tolerance.

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Exercise-induced bronchoconstriction is common in patients with chronic asthma (1). Airway cooling or desiccation during exercise may trigger activation of mast cells and release of such mediators as histamine and cysteinyl leukotrienes, resulting in bronchospasm (1, 2). Cysteinyl leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>), synthesized from arachidonic acid through the 5-lipoxygenase pathway, are potent bronchoconstrictors, with an effect greater than 1000 times that of histamine (3–5). Several researchers have demonstrated an increase in urinary concentrations of LTE<sub>4</sub> after exercise (6, 7). Prophylaxis against exercise-induced bronchoconstriction with inhaled mast cell-stabilizing agents and short-acting  $\beta$ -agonists must be administered 15 to 30 minutes before exercise. The long-acting inhaled  $\beta$ -agonist salmeterol protects against exercise-induced bronchoconstriction for up to 12 hours, thus providing more flexibility in the dosing schedule for active patients with asthma (8, 9). However, in some patients, tolerance to salmeterol develops with long-term use, and the level of bronchoprotection diminishes by 6 to 9 hours (10–12).

Montelukast sodium, a leukotriene receptor antagonist, is a potent oral medication for the treatment of asthma. The leukotriene receptor antagonists have demonstrated a significant bronchoprotective effect with exercise after one or two doses (13, 14). In patients with exercise-induced bronchoconstriction, short-term treatment with montelukast (Singu-

lair, Merck & Co., Inc., Whitehouse Station, New Jersey) given once daily diminished the postexercise response, as described by the area under the FEV<sub>1</sub>-time curve (AUC<sub>0-60 min</sub>), by more than 50%, even at the end of the dosing interval (20 to 24 hours after administration) (15, 16). Furthermore, tolerance to the bronchoprotective effects of montelukast did not occur with long-term administration (17).

We sought to test the hypothesis that the bronchoprotective effects of montelukast were greater than those of salmeterol in patients with chronic asthma who experienced exercise-induced bronchoconstriction.

## Methods

### Design

We conducted a randomized, parallel-group study consisting of a 2-week, single-blind placebo baseline period followed by an 8-week, double-blind treatment period with montelukast sodium (10-mg tablet taken orally once in the evening) or inhaled salmeterol (50- $\mu$ g aerosol formulation [2 puffs] taken twice daily). Seventeen clinical study sites participated in the trial. To mask formulation differences, a double-dummy treatment regimen was used. Each patient received one tablet daily (active agent or matching placebo) or one inhaler twice daily (active agent or matching placebo) for both the single-blind and double-blind treatment periods. A computer-generated allocation schedule with a blocking factor of 4 was produced by the statistician. Each center was given a block of allocation numbers that were assigned sequentially to consecutive randomly assigned patients.

Spirometric measurements were obtained before and after standardized exercise challenges at the beginning and end of the baseline period, within the first 3 days of the double-blind treatment period, and at weeks 4 and 8 of the treatment period. Additional measurements were physical examination, vital signs, electrocardiography, chest radiography, and laboratory tests (hematology, chemistry profile, and urinalysis). At each visit, all spontaneously reported adverse events were recorded. The protocol was approved by the institutional review board of each site, and written informed consent was obtained from each patient.

### Inclusion Criteria

Male and female patients 15 to 45 years of age with a history of chronic asthma were enrolled. All patients had an FEV<sub>1</sub> of at least 65% of the predicted value at rest and a decrease in FEV<sub>1</sub> of at least 20% after a standardized exercise challenge on two occasions during the baseline period. All pa-

tients had been nonsmokers for at least 1 year and had a smoking history of less than 15 pack-years.

### Exclusion Criteria

Persons who had upper respiratory infection or exacerbation of asthma requiring emergency care within the past month or were hospitalized for asthma in the past 3 months were excluded. Use of oral or inhaled corticosteroids, theophylline, cromolyn sodium, nedocromil, oral  $\beta$ -agonist, and long-acting antihistamines was prohibited before and during the study. Use of inhaled albuterol for symptomatic relief of asthma and use of short-acting antihistamines were permitted.

### Evaluations

A standard spirometer (Puritan-Bennett PB100/PB110, Puritan-Bennett, Wilmington, Massachusetts) was used to obtain all spirometric measurements according to American Thoracic Society standard criteria (18). Patients had to have discontinued use of inhaled short-acting  $\beta$ -agonists for 6 hours before the visit. Exercise testing was done in the early afternoon near the trough of effect for both drugs according to a method described elsewhere (17). Measurements were obtained 20 and 5 minutes before exercise (prechallenge period). Exercise challenge was performed only if the average FEV<sub>1</sub> in the prechallenge period was greater than 65% of predicted; otherwise, the test was rescheduled.

Patients exercised on a treadmill while inhaling room temperature, compressed, dry air. During the first test, the speed and gradient of the treadmill were adjusted to achieve 80% to 90% of the patient's age-predicted maximum heart rate. The settings were maintained for a total of 6 minutes; the same settings were used for future tests. This level of exercise has been used to quantify the level of bronchoconstriction associated with regular exercise (19). Serial spirometric measurements were obtained at 0, 5, 10, 15, 30, 45, and 60 minutes after exercise (postexercise period). Additional measurements were carried out at 15-minute intervals for up to 90 minutes if the patient's FEV<sub>1</sub> had not returned to within 5% of the prechallenge value by 60 minutes. If the patient's FEV<sub>1</sub> did not return to the prechallenge value by 90 minutes after exercise, a rescue dose of inhaled  $\beta$ -agonist was administered at the discretion of the study investigator.

### Statistical Analysis

An all-patients-treated analysis, which included patients with a baseline visit and at least one post-randomization visit, was performed. The change from baseline in the maximal percentage decrease in FEV<sub>1</sub> after exercise at the end of 8 weeks of treatment was the primary end point. Analysis of

variance was used to compare the two treatment groups. The analysis of variance model included terms for treatment, center, and the interaction of treatment and center. Ninety-five percent CIs for within-group means and the difference between groups were constructed to assess the magnitude of the treatment effect. Analysis of variance on the ranked data was used to analyze percentage inhibition for all end points. In the event of early termination of the exercise challenge because of administration of rescue medication, the largest percentage decrease in FEV<sub>1</sub> achieved before administration of rescue medication was used in the analysis.

Secondary end points were change from baseline for maximal percentage decrease in FEV<sub>1</sub> at days 1 to 3 and week 4, the time required after maximal decrease in FEV<sub>1</sub> to return within 5% of prechallenge values (time to recovery), and the AUC<sub>0-60 min</sub> at all visits. The mean of the 20- and 5-minute prechallenge measurements was used as the pre-exercise FEV<sub>1</sub> value. If a patient required rescue with inhaled  $\beta$ -agonist during the postexercise period, the last recorded FEV<sub>1</sub> value was used and carried forward for all subsequent readings and 100 minutes was entered for the end point of time to recovery. The AUC<sub>0-60 min</sub> was calculated by using the trapezoidal method. If a patient's FEV<sub>1</sub> did not decrease below 95% of the prechallenge value, the time to recovery was assigned a value of zero.

The persistence of effect over time was assessed by using a repeated-measures fixed-effects model with terms for center, treatment group, time, and the interaction of treatment group and time to calculate the rate of change over the treatment period. Persistence of effect was defined as a slope of zero. The magnitude of the slopes for each treatment group was estimated, and 95% CIs were calculated. An overall test of equal slopes between the treatment groups was examined, and a 95% CI on the difference in slopes between treatment groups was provided.

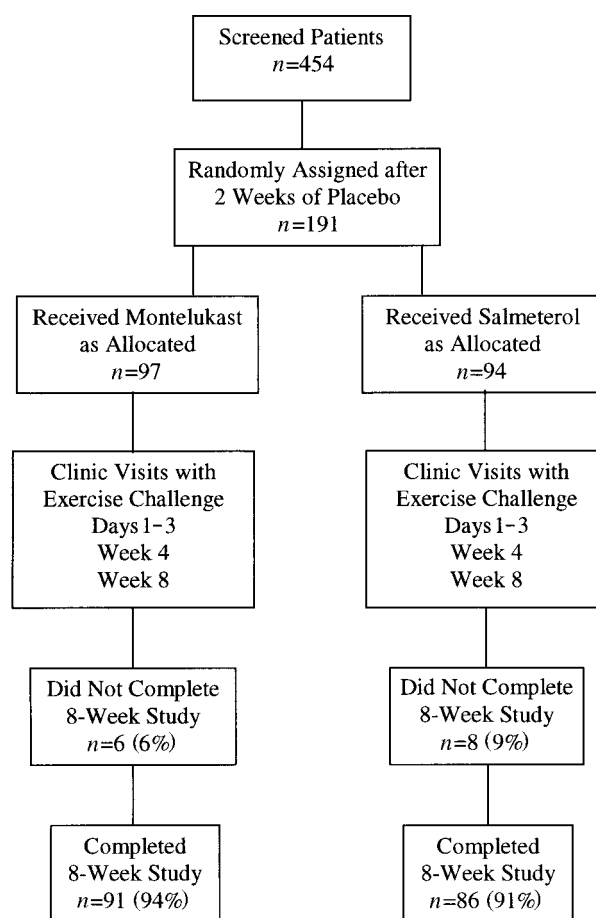
The number and percentage of patients requiring rescue medication during or at the end of the exercise test were summarized by treatment group at each time point. In addition, the number and percentage of patients whose decrease in FEV<sub>1</sub> from pre-exercise levels was less than 10%, 10% to 20%, 20% to 40%, and greater than 40% were summarized by treatment group for each visit.

The overall incidence of adverse events and laboratory abnormalities was assessed by using the Fisher exact test, and within-group changes in the number of laboratory abnormalities were assessed by using the McNemar test. Descriptive statistics were provided by treatment group for patient demographic characteristics, clinical characteristics, and baseline profile.

The study was designed with a sample size of 160 patients (80 patients per treatment group) to have 95% power (two-sided test at  $\alpha = 0.05$ ) to detect a 7% difference in the mean change in maximal percentage decrease in FEV<sub>1</sub> between treatments. All statistical analyses were performed by using SAS software, version 6 (SAS Institute, Inc., Cary, North Carolina).

### Role of the Funding Source

Funding for this trial was provided by Merck & Co., Inc., Whitehouse Station, New Jersey. Personnel from Merck U.S. Human Health, Clinical Development department played a significant role in the design, conduct, and analysis of the trial. The trial was conducted in accordance with guidelines for clinical trials of investigational agents established by U.S. regulatory authorities.



**Figure 1. Study profile.** Of the 454 patients screened, 263 (58%) did not meet protocol inclusion criteria: Ninety-nine (38%) did not meet exercise challenge inclusion criteria (postexercise decrease in FEV<sub>1</sub> < 20%), 102 (39%) did not meet pulmonary function inclusion criteria, 20 (8%) had disqualifying medical conditions or use of concomitant medications, and 42 (16%) were excluded for nonclinical reasons (they were lost to follow-up, withdrew consent, or had a scheduling conflict). Qualified patients (n = 191) were randomly allocated to receive montelukast (10 mg once every evening) or salmeterol (2 puffs [50  $\mu$ g] twice daily). Ninety-three percent of the patients completed the study.

**Table. Baseline Demographic and Clinical Characteristics\***

Characteristic	Montelukast Group (n = 97)	Salmeterol Group (n = 94)
Mean age (range), y	26.5 (15–46)	26.0 (15–45)
Women, n (%)	51 (53)	40 (43)
Men, n (%)	46 (47)	54 (57)
Mean duration of asthma $\pm$ SD, y	14.76 $\pm$ 8.87	14.91 $\pm$ 9.10
Mean prechallenge FEV <sub>1</sub> $\pm$ SD, L	3.42 $\pm$ 0.75	3.50 $\pm$ 0.77
Mean percentage predicted prechallenge FEV <sub>1</sub> $\pm$ SD	87.14 $\pm$ 11.24	87.95 $\pm$ 13.48
Mean postexercise maximal percentage decrease in FEV <sub>1</sub> $\pm$ SD	36.99 $\pm$ 11.49	36.58 $\pm$ 12.31
Mean postexercise AUC <sub>0–60 min</sub> $\pm$ SD	1411.4 $\pm$ 902	1298.5 $\pm$ 819
Mean time to recovery $\pm$ SD, min	62.23 $\pm$ 32	57.19 $\pm$ 32
Patients with symptoms on several, most, or all days in the past month, n (%)		
Wheezing	45 (46)	40 (43)
Shortness of breath	39 (40)	41 (44)
Coughing	32 (33)	25 (27)
Patients with nighttime awakening > 1 night/wk in the past month, n (%)	29 (30)	22 (23)
Patients with moderate to severe limitation of activity in the past month, n (%)	61 (63)	52 (55)
Patients with $\geq$ 5 d of oral corticosteroid use, n (%)	14 (14)	11 (12)

\* AUC<sub>0–60 min</sub> = area under the FEV<sub>1</sub>-time curve.

## Results

### Patients

One hundred ninety-one patients (97 in the montelukast group and 94 in the salmeterol group) from 17 centers were randomly assigned to double-blind treatment; of these, 177 patients (93%) completed all 8 weeks of the study (**Figure 1**). The discontinuation rate was similar between groups (6 patients [6%] in the montelukast group and 8 patients [9%] in the salmeterol group). In the montelukast group, 2 patients were lost to follow-up, 1 withdrew because of a clinical adverse event, 1 was excluded because of noncompliance, and 2 withdrew for other nonclinical reasons. In the salmeterol group, 4 patients withdrew because of clinical adverse events, 2 were lost to follow-up, and 2 withdrew for other nonclinical reasons.

No statistical differences were observed between treatment groups for patient demographic characteristics or baseline clinical characteristics (**Table**). Despite having near-normal pre-exercise spirometric values, many patients reported symptoms, nighttime awakenings, and exercise limitations frequently enough to be considered to have moderate asthma (**Table**) according to the guidelines of the National Asthma Education and Prevention Program (20). Approximately 35% of patients had visited an emergency department, and 14% of patients had taken oral corticosteroids for asthma during the past year. Twenty-three percent of patients reported losing

time from work or school because of asthma in the past year.

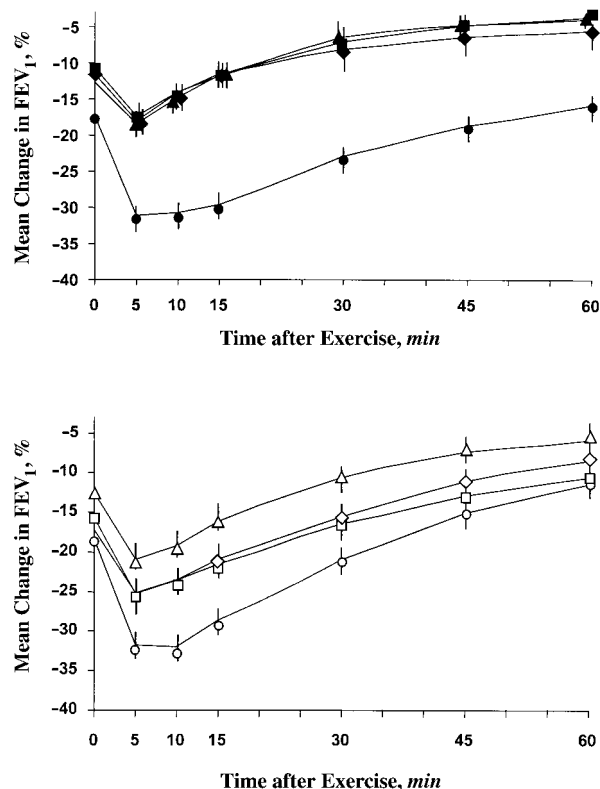
### Efficacy

#### Bronchodilatory Effect

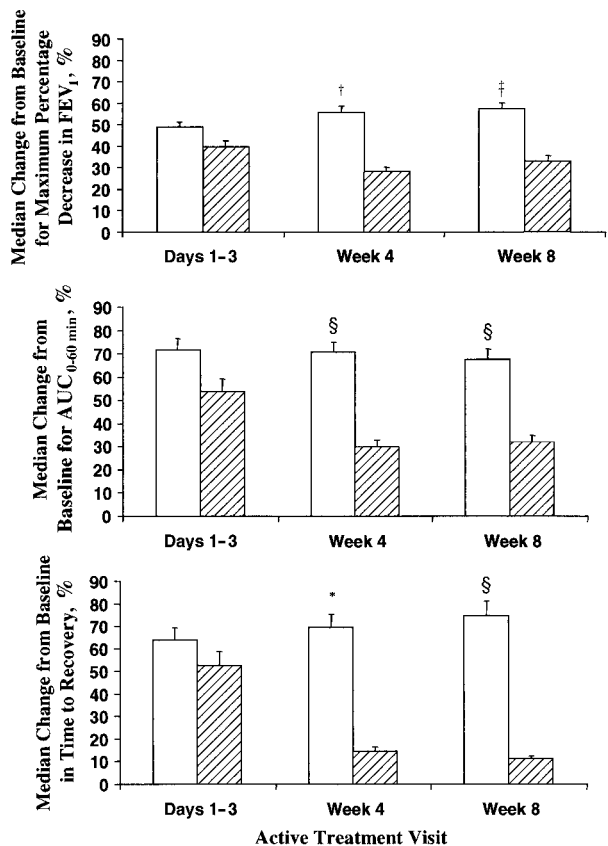
In both treatment groups, spirometry performed before exercise showed a small but nonsignificant change from baseline pre-exercise FEV<sub>1</sub> at the first post-treatment visit (0.14 L for the montelukast group and 0.17 L for the salmeterol group). This increase persisted for both groups at weeks 4 and 8 (0.09 L and 0.07 L, respectively, for the montelukast group and 0.14 L and 0.15 L for the salmeterol group). The groups did not differ statistically for this effect.

#### Exercise Challenge Response

At baseline, exercise spirometry showed no statistically significant differences between the montelukast and salmeterol groups in maximal percentage decrease in FEV<sub>1</sub> (37.0% and 36.6%), postexercise AUC<sub>0–60 min</sub> (1411% · min and 1299% · min), or time to recovery to within 5% of pre-exercise FEV<sub>1</sub> (62.2 minutes and 57.2 minutes) (**Table**). Exercise challenge was performed near the end of the dosing interval for both drugs throughout the study (mean



**Figure 2.** The FEV<sub>1</sub> after exercise in patients who received montelukast (top) and salmeterol (bottom). The mean response curves are shown for percentage change in FEV<sub>1</sub> from prechallenge FEV<sub>1</sub> at baseline (circles), days 1 to 3 (triangles), week 4 (squares), and week 8 (diamonds) after study treatment.



**Figure 3. Bronchoprotection over time.** Effect of treatment with montelukast (white bars) and salmeterol (striped bars) on percentage change from prandomization baseline values in maximal percentage decrease in FEV<sub>1</sub> (top), area under the FEV<sub>1</sub>-time curve (AUC<sub>0-60 min</sub>) (middle), and time to recovery (bottom). Data are presented as the median ± SE. \**P* = 0.010; †*P* = 0.015; ‡*P* = 0.002; §*P* ≤ 0.001.

postdose time range, 9.1 to 9.6 hours for salmeterol and 21.4 to 21.8 hours for montelukast). Exercise responses at each visit (mean percentage change from prechallenge FEV<sub>1</sub> over time) are shown in **Figure 2**. The degree of bronchoprotection (expressed as the median percentage change from the prandomization baseline value) for each end point at each visit is shown in **Figure 3**.

Within 3 days of initiation of therapy, both treatments provided significant and similar attenuation of exercise-induced bronchoconstriction for all study end points. The improvement in maximal percentage decrease in FEV<sub>1</sub> observed for the montelukast group was maintained at weeks 4 and 8. In contrast, a loss in bronchoprotective effect was noted in the salmeterol group; as a result, the reduction in maximal percentage decrease in FEV<sub>1</sub> represented a significantly greater bronchoprotective effect for montelukast than for salmeterol at weeks 4 and 8 (*P* = 0.015 and *P* = 0.002, respectively) (**Figure 3**).

Similar observations for time to recovery and AUC<sub>0-60 min</sub> were seen between treatment groups at all time points. The effect of salmeterol diminished after the initial visit, whereas the effect of

montelukast was maintained (**Figure 3**). In addition, after 8 weeks of treatment, 62 of 93 (66.7%) patients receiving montelukast achieved bronchoprotection sufficient to have a less than 20% decrease from pre-exercise FEV<sub>1</sub> levels after exercise challenge; in contrast, this effect was seen in only 41 of 90 (45.6%) patients receiving salmeterol (**Figure 4**).

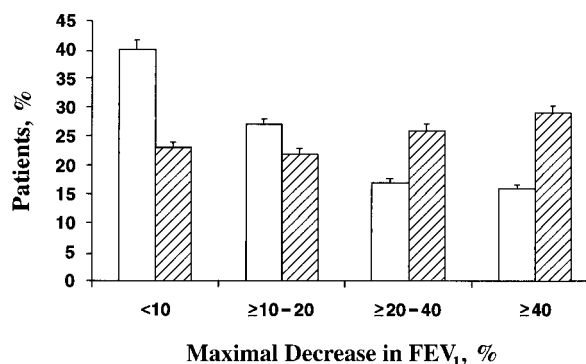
### Persistence of Effect

Over the 8-week treatment period, the slope of the maximal percentage decrease in FEV<sub>1</sub> for the montelukast group was -0.02% per day (95% CI, -0.08% to 0.03%); the CI does not include zero, indicating that tolerance did not occur. The slope for the salmeterol group was 0.06% per day (CI, 0.01% to 0.12%), indicating that tolerance to the bronchoprotective effect had developed. Similar results were noted for time to recovery and AUC<sub>0-60 min</sub>.

For each end point, the difference between the first measurement (obtained within 3 days of study initiation) and the measurement obtained after 8 weeks of therapy was calculated. The maximal decrease in FEV<sub>1</sub> between these two time points did not differ in the montelukast group (-1.60%), indicating persistence of effect, but differed significantly in the salmeterol group (3.98%) (*P* = 0.017), confirming tolerance. The difference between treatment groups was significant (5.58 percentage points; *P* = 0.017). Significantly fewer patients in the montelukast group than in the salmeterol group required rescue doses of β-agonist after exercise challenge at any post-treatment visit (25 of 96 patients [26%] compared with 37 of 93 patients [40%]; *P* = 0.044).

### Safety

Both montelukast and salmeterol were well tolerated. Five patients were withdrawn from the study because of a clinical adverse event (four in the



**Figure 4. Distribution of maximal percentage decrease in FEV<sub>1</sub>.** The percentage of patients achieving <10%, ≥10% to 20%, ≥20% to 40%, and ≥40% maximal decrease in FEV<sub>1</sub> from pre-exercise baseline values after 8 weeks of montelukast therapy (white bars) or salmeterol therapy (striped bars). *P* = 0.028 for overall distribution of maximal percentage decrease at week 8 between the montelukast group and the salmeterol group.

salmeterol group and one in the montelukast group). Of the patients who received salmeterol, one was withdrawn because of insomnia, two were withdrawn because of worsening asthma, and one died as a result of bronchial asthma. The investigator reported that this patient had mild persistent asthma and met all inclusion and exclusion criteria for the study. The death was classified as probably unrelated to study therapy. The patient who received montelukast was withdrawn because of exacerbation of asthma and allergic conjunctivitis. No patient was withdrawn because of laboratory adverse events.

Forty patients (41%) treated with montelukast and 38 patients (40%) treated with salmeterol experienced a clinical adverse event. The most common events (occurring in >5% of patients) in the montelukast and salmeterol treatment groups were upper respiratory infection (14% and 10%), headache (5% and 6%), and asthma (3% and 7%). No significant between-group differences were seen in the frequency of clinical or laboratory adverse events.

## Discussion

In our study, montelukast provided significantly greater inhibition of exercise-induced bronchoconstriction compared with salmeterol at 4 and 8 weeks of therapy, as demonstrated by the mean change from baseline in maximal percentage decrease in FEV<sub>1</sub>, AUC<sub>0-60 min</sub>, and time to recovery of FEV<sub>1</sub> to within 5% of prechallenge values.

With montelukast therapy, bronchoprotection persisted near the end of the once-daily dosing and was of similar magnitude after the initial dose and at 4 and 8 weeks of treatment; this result confirms previous findings for montelukast therapy (15, 16). In contrast, the bronchoprotective effect of salmeterol, which was effective initially, decreased significantly at 4 and 8 weeks, indicating that tolerance had developed. This finding is consistent with previous observations about salmeterol (10, 11).

Tolerance to exercise bronchoprotection after long-term therapy has been reported for other agents. The bronchoprotective effect of short-acting inhaled albuterol significantly decreased after 1 week of regular use (21), and in a clinical study of children (22), the bronchoprotection seen after 1 and 2 months of therapy with inhaled beclomethasone was lost at 3 months.

One important consideration in interpreting the clinical importance of our findings is the timing of the exercise challenge. In our study, exercise challenges were performed near the trough of the dosing interval for both drugs (mean time after administration, 21 hours for montelukast and 9 hours for

salmeterol). This time point was chosen for several reasons. First, both montelukast and salmeterol have been shown to inhibit exercise-induced bronchoconstriction at the end of their dosing intervals with short-term administration. Second, by making the measurement in the afternoon, we hoped to evaluate the duration of protective effect over time for these drugs. We did not evaluate the relative level of bronchoprotection shortly after drug administration. It is of interest to consider whether performing exercise challenge closer to the time of administration of both drugs would have provided different results. Because montelukast is administered at bedtime, it was not practical to make the comparison within a few hours of the dose. Nelson and colleagues (11) reported that protection against exercise-induced bronchoconstriction with long-term salmeterol use diminished with increasing time after administration (11). In that study, the level of bronchoprotection 2 hours after administration on days 14 and 29 was also less than that on day 1, although it was still significantly greater than that seen with placebo. Tolerance to the effects of salmeterol on bronchoprotection against methacholine challenge has been shown after only two doses (23).

The bronchoprotective effects of leukotriene receptor antagonists have been demonstrated 20 minutes after a single intravenous dose (13) and 2 hours after a single oral dose (14). We are unaware of data that compare the level of protection throughout the dosing interval for this class of drugs. We suspect that bronchoprotection at the time of peak effect of montelukast (approximately 4 hours after administration) would be no less than that observed at the end of the dosing interval.

Despite the development of some degree of tolerance for salmeterol, a persistent, mild bronchodilatory effect was seen throughout the study, suggesting that the time-dependent decrease in effectiveness of salmeterol was not due to differences in patient compliance. Our findings are consistent with previous observations that the bronchoprotective and bronchodilatory actions of long-acting  $\beta$ -agonists are affected differently by long-term administration (24).

It is noteworthy that neither montelukast nor salmeterol provided complete bronchoprotection at any time point. In some patients, prophylactic use of a short-acting  $\beta$ -agonist may therefore still be necessary. In a previous study, administration of a short-acting  $\beta$ -agonist to patients receiving montelukast showed additional bronchodilatory effect (25). In contrast, evidence suggests that salbutamol provides limited additional effect when it is given with salmeterol (26). It remains controversial whether long-term administration of salmeterol may induce  $\beta$ -receptor subsensitivity, thereby decreasing responsiveness to  $\beta$ -agonist therapy (23, 27). In our study,

patients who required rescue after exercise had improvement in FEV<sub>1</sub> with inhaled albuterol. However, substantially more patients receiving montelukast were able to maintain airway function with a decrease of less than 20% from pre-exercise levels compared with patients who received salmeterol, and fewer patients receiving montelukast required rescue with  $\beta$ -agonist after exercise.

The patients in our study all had substantial asthma that limited their ability to exercise (average decrease in FEV<sub>1</sub> with exercise, 37%) but had near-normal airway function at rest (FEV<sub>1</sub> > 86% of the predicted value). Despite this observation, the intensity and frequency of symptoms, sleep disturbance, oral corticosteroid use, and office or emergency department-based asthma care reported by the patients at study entry suggest that their disease burden is substantial. These findings serve as a reminder that exercise is a common trigger of asthma in patients with all levels of disease severity and that many of the typical features of asthma are present in patients with exercise-induced bronchoconstriction even when they are not exercising.

In conclusion, long-acting  $\beta$ -agonists are currently recommended as concomitant therapy to a controller drug for asthma, especially to prevent nocturnal awakenings. In addition, they are often used to attenuate predictable exercise-induced bronchoconstriction (20, 28). Like salmeterol therapy, montelukast therapy is effective when added to inhaled corticosteroids and diminishes exercise-induced bronchoconstriction (29, 30). Our results suggest that for long-term rather than intermittent treatment of exercise-induced bronchoconstriction, once-daily therapy with montelukast may provide greater bronchoprotection at the end of the dosing interval than twice-daily inhaled salmeterol.

## Appendix

The following persons were participating investigators for the Exercise Study Group: Dr. Edwin Bronsky, Intermountain Clinical Research, Salt Lake City, Utah; Dr. Robert Dockhorn, International Medical Technical Consultants, Inc., Lenexa, Kansas; Dr. David Dobratz, College Park Clinical Research, IMTCI, Overland Park, Kansas; Dr. David Goodman, Clinical Research Group of Colorado, Englewood, Colorado; Dr. Jay Grossman, VIVRA Research Partners, Tucson, Arizona; Dr. Leslie Hendeles, University of Florida, Gainesville, Florida; Dr. Craig Jacobson, Allergy and Asthma Research Group, Eugene, Oregon; Dr. James Kemp, Allergy & Asthma Medical Group and Research Center, San Diego, California; Dr. Robert Lapidus, Rocky Mountain Pulmonary Medicine, Wheat Ridge, California; Dr. William Mullican, Medisphere Medical Research Center L.L.C., Evansville, Indiana; Dr. David Pearlman, Colorado Allergy & Asthma Clinic, P.C., Aurora, Colorado; Dr. Jacob Pinnas,

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