# Dose-related protection of exercise bronchoconstriction by montelukast, a cysteinyl leukotriene–receptor antagonist, at the end of a once-daily dosing interval

The dose-related protective effects of montelukast, a potent and selective cysteinyl leukotriene–receptor antagonist, against exercise-induced bronchoconstriction were investigated in a five-period, randomized, incomplete-block, crossover study with montelukast (0.4, 2, 10, 50 mg) and placebo. The study subjects were 27 nonsmoking, healthy stable patients with asthma (mean forced expiratory volume in 1 second [$FEV_1$], 82.0% predicted) who demonstrated a ≥20% decrease in $FEV_1$ while β-agonist was withheld for 6 hours before treadmill exercise. The standard exercise challenge was performed 20 to 24 hours, and again 32 to 36 hours, after the second of two once-daily doses. The effect of oral montelukast on exercise was measured by the area above the postexercise percentage decrease in $FEV_1$ versus time curve from 0 to 60 minutes [AUC(0-60)], the maximal percentage decrease in $FEV_1$ after exercise, and time after maximal decrease to recovery of $FEV_1$ to within 5% of the preexercise baseline. Twenty to 24 hours after administration, montelukast caused dose-related protection, while providing similar protection against exercise-induced bronchoconstriction at the two highest doses. The AUC(0-60) values (mean ± SD) were 637 ± 898, 715 ± 870, 988 ± 1147, and 927 ± 968 min · % for 50, 10, 2, and 0.4 mg montelukast, respectively, and 1193 ± 1097 min · % for placebo ($p = 0.003$). No important clinical effect was present 36 hours after dosing. Montelukast was generally well tolerated at all dose levels. In conclusion, montelukast caused dose-related protection against exercise-induced bronchoconstriction at the end of a once-daily dosing interval. Protection against exercise-induced bronchoconstriction can be used to determine appropriate dose selection. (Clin Pharmacol Ther 1997;62:556-61.)

**Edwin A. Bronsky, MD, James P. Kemp, MD, Ji Zhang, PhD, Debra Guerreiro, BS, and Theodore F. Reiss, MD** *Salt Lake City, Utah, San Diego, Calif., and Rahway, N.J.*

The cysteinyl leukotrienes are now known to be important mediators in the pathophysiology of asthma.[1] Derived from arachidonic acid by way of the 5-lipoxygenase pathway and released from inflammatory cells (mainly eosinophils, mast cells, and basophils), the cysteinyl leukotrienes are powerful bronchoconstrictors in both normal subjects and patients with asthma, and they have longer-lasting effects than inhaled histamine.[2] Cysteinyl leukotrienes also cause increased venopermeability and mucus secretion,[3] promote eosinophil migration into airway mucosa,[4] and may contribute to changes in airway structure by affecting factors such as proliferation of smooth muscle.[5]

The role of the cysteinyl leukotrienes in asthma has been shown in investigational studies of antileukotriene compounds. Pretreatment with MK-0571, a cysteinyl leukotriene–receptor antagonist, inhibited exercise-induced bronchoconstriction[6] and blocked both early and late bronchoconstrictor responses to inhaled allergens in patients with asthma.[7] A 6-week course of therapy with zafirlukast (ICI 204,219), another cysteinyl leukotriene–receptor antagonist, produced both objective and subjective improvement of asthma,[8] as did a 12-week course of zileuton, a 5-lipoxygenase inhibitor.[9]

From the AAAA Medical Research Group, Salt Lake City; the California Research Group, San Diego; and Merck Research Laboratories, Rahway.
Supported by a grant from the Merck Research Laboratories, Rahway, N.J.
Received for publication April 24, 1997; accepted July 28, 1997.
Reprint requests: Theodore F. Reiss, MD, Merck Research Laboratories, PO Box 2000, RY 33-648, Rahway, NJ 07065.

0009-9236/97/$5.00 + 0 **13/1/85059**

**Table I.** Characteristics at baseline of randomized patients

| *Patients (n = 27)* | *Age (yr)* | *Weight (lb)* | *Prestudy percentage predicted $FEV_1$** | *Maximal $FEV_1$ percentage fall after exercise†* |
|---|---|---|---|---|
| Median | 24 | 166 | 82.0 | 30.1 |
| Range | 18 to 45 | 114 to 260 | 60.5 to 109.2 | 19.5 to 68.1 |

$FEV_1$, Forced expiratory volume in 1 second.
*Average of 20- and 5-minute preexercise values at the second of two visits before randomization.
†Second of two exercise challenges before the randomization visit.

Montelukast (MK-0476), a potent and specific cysteinyl leukotriene–receptor antagonist,[10] has been shown to protect against leukotriene $D_4$[11] and exercise-induced bronchoconstriction 24 hours after dosing. Significant improvement in the signs and symptoms of chronic asthma have been reported.[12] To determine whether montelukast provides dose-related protection of exercise-induced bronchoconstriction at the end of a once-daily dosing interval, this study compared a range of doses in a double-blind, incomplete-block, crossover design. In addition, the persistence of effect 36 hours after dosing was determined.

## METHODS

### Patients

Twenty-seven healthy nonsmoking patients (Table I) with at least a 1-year history of typical recurring asthma symptoms (including exercise-induced symptoms) of dyspnea, wheezing, or cough that required only episodic bronchodilator treatment were entered into the study. Each patient demonstrated a preexercise forced expiratory volume in 1 second ($FEV_1$) ≥60% of predicted (withholding $\beta_2$-adrenergic agonist for 6 hours) and a ≥20% decrease in absolute $FEV_1$ after a standardized treadmill exercise challenge during each of two prestudy visits. Female patients of childbearing potential had a negative serum β-human chronic gonadotropin test at the prestudy visit and agreed to use appropriate contraceptive methods throughout the study.

Patients were excluded from study participation if they received oral, inhaled, or intramuscular corticosteroids, methylxanthines, cromolyn, oral or long-acting β-agonists, antimuscarinic agents, terfenadine or loratadine within 2 weeks, or astemizole within 3 months before the prestudy visit. Initiation or change in immunotherapy or emergency room treatment for asthma within 3 months before the prestudy visit were also causes for exclusion. Institutional Review Board (Western IRB, Olympia, Wash.) approval was obtained and all enrolled patients signed written informed consent agreements.

### Study design

This was a double-blind, incomplete-block, crossover study with patients receiving four of the five study treatments randomly according to a computer-generated schedule. (The number of patients in each period remained constant, whereas the number of patients receiving each treatment varied: 22, 21, 20, 23, and received 50, 10, 2, and 0.4 mg montelukast, respectively, and 22 patients received placebo during the four periods). During each period, oral montelukast was administered once daily in the evening for 2 days (achieving steady-state plasma levels),[13] and an exercise challenge was performed approximately 20 to 24 hours after the second dose (day 3) and again 32 to 36 hours after (day 4) the second dose. A 2- to 9-day washout interval occurred between treatment periods. Adherence was monitored by tablet counts and telephone contact by the study nurse. In addition, routine physical examinations (including vital signs), electrocardiograms, blood samples (for chemistry and hematology), and urine samples were collected as safety parameters.

### Exercise challenge

For each patient, exercise was performed on a treadmill for 6 minutes. The gradient and speed of the treadmill was adjusted to achieve a workload equal to or greater than 80% of the patient's age-predicted maximum heart rate. Once determined at the prestudy visit, the identical workload was provided during each subsequent exercise challenge, with minor adjustments in workload allowed to achieve the heart rate obtained in the prestudy visits. Preexercise spirometry was measured. A standard spirometer (Puritan-Bennett PB 100/PB110, Wilmington, Mass.) was used in accordance with American Thoracic Society acceptability and repro-

**Table II.** Preexercise $FEV_1$ (L) values

| | *Placebo* | *0.4 mg montelukast* | *2 mg montelukast* | *10 mg montelukast* | *50 mg montelukast* |
|---|---|---|---|---|---|
| Day 3 | 3.48 ± 0.74 | 3.67 ± 0.86 | 3.68 ± 0.52 | 3.61 ± 0.79 | 3.59 ± 0.66 |
| Day 4 | 3.60 ± 0.68 | 3.54 ± 0.70 | 3.52 ± 0.53 | 3.60 ± 0.85 | 3.59 ± 0.69 |

Data are mean values ± SD.

ducibility guidelines[14] 20 and 5 minutes before challenge, with the best of three attempts at each time point recorded; $FEV_1$ had to be at least 65% of the predicted value (5 minutes before exercise) for the challenge to proceed. $FEV_1$ was measured immediately after exercise and at 5, 10, 15, 30, 45, 60, 75, and 90 minutes. Postexercise β-agonist was administered to the patient if $FEV_1$ fell below 40% of the predicted value, if the patient requested treatment, or if the investigator thought it was clinically indicated. During the exercise, the patient wore a nose clip and breathed compressed dry air through a mask at constant ambient temperature. Heart rate was monitored continuously by a lead II electrocardiograph. Oxygen saturation was monitored by pulse oximetry.

### Study end points

The ability of montelukast to cause dose-related protection of exercise-induced bronchoconstriction 20 to 24 and 30 to 36 hours after dosing was determined by comparison of the five treatment groups in three study end points. These end points were the area above the postexercise decrease (from preexercise baseline) in $FEV_1$ versus time curve through 60 minutes [AUC(0-60)], the maximum postexercise percentage decrease in $FEV_1$ (maximal percentage fall), and the time required after maximal decrease for $FEV_1$ to return to within 5% of preexercise baseline (time to recovery).

The trapezoidal method was used to calculate the AUC(0-60). Only areas below the preexercise baseline were included when in the computation of the AUC(0-60) to capture only the extent and duration of the bronchoconstriction below the preexercise baseline. This parameter provides a single number that integrates intensity and duration of bronchoconstriction.

If a patient required a bronchodilator for asthma symptoms or low $FEV_1$ (or the $FEV_1$ value was not available), the last valid $FEV_1$ was used at all subsequent time points for analysis in that period. If the exercise-induced bronchoconstriction was completely blocked (maximal decrease in $FEV_1$ ≤5%), the time to recovery was assigned a value of 0 minutes. In addition, if the patient's postexercise $FEV_1$ did not return to within 5% of baseline in 90 minutes, the time to recovery was assigned a value of 100 minutes minus the time required for the maximum decrease in $FEV_1$ from baseline to occur.

### Statistical analysis

The ANOVA model for a crossover study was used to compare treatments in these three end points. The model included terms for patient, treatment, and period. Carryover effects were assessed by addition of the carryover factor to the ANOVA model. Comparisons of the treatment groups were made with use of stepwise linear contrasts (ordinal scale linear trend test); $p \leq 0.050$ (with use of a two-tailed test) was considered to be significant.

The study was designed to have 80% power (for 25 completing patients) to detect ($\alpha = 0.05$, two-sided) a mean difference between treatment groups of 8.1 percentage points for maximal percentage decrease in $FEV_1$.

## RESULTS

### Patient demographics

Twenty-seven patients (20 men and seven women) began the study, completed all periods, and were included in the analyses. Table I lists baseline characteristics. Table II lists the $FEV_1$ values before each exercise challenge. Other than β-agonists, no other asthma medications were used during the course of the study.

### Efficacy

***Day 3.*** Significant dose-related effects were observed for all end points. Montelukast, 10 and 50 mg, significantly and similarly protected against exercise-induced bronchoconstriction compared with placebo. Although small effects were noted, the 0.4 and 2 mg doses of montelukast were not significantly different from placebo (Fig. 1).

For AUC(0-60), a significant ($p = 0.003$) linear dose-response trend was detected among the five treatments (Fig. 1, *A*), as was the response on the mean maximal $FEV_1$ percent fall ($p = 0.005$) (from preexercise baseline, Fig. 1, *B*). In addition, the mean time to recovery to within 5% of baseline $FEV_1$ (after the maximum postexercise fall) also showed a significant linear trend among the five treatments ($p = 0.001$; Fig. 1, *C*). Albuterol (INN, salbutamol) was required after exercise for three patients receiving 50 mg montelukast (14%), five patients receiving 10 mg montelukast (24%), six patients receiving 2 mg montelukast (30%), eight patients receiving 0.4 mg montelukast (35%), and eight patients receiving placebo (36%).

***Day 4.*** For each end point, day 4 values for all treatment groups were smaller than those on day 3. Montelukast provided slight nondose-related effects compared with placebo 32 to 36 hours after dosing (Table III).

### Safety

Thirteen patients reported a total of 26 clinical adverse experiences that were randomly distributed among treatment groups. All of these adverse events were transient and self-limited (Table IV). One laboratory adverse experience was reported with montelukast treatment during the study: an elevated AST of 46 U/L (normal range, 11 to 36 U/L), which was believed to be the result of concurrent pharyngitis.

## DISCUSSION

Protection against bronchoconstricting challenges, such as exercise, is an important characteristic of any chronic asthma therapy and, as shown in this trial, is a key property of the anti-leukotriene drug montelukast. Because exercise-induced bronchoconstriction is clinically important, an asthma agent must be administered in a dose sufficient to maximize its protective effect throughout its dosing interval. Frequently, however, dose ranging is performed with only end points of the improvement in the chronic signs and symptoms of asthma, ignoring the need to determine dose-related protection against bronchoconstricting challenges. The utility of including exercise in the dose selection process has been described previously.[15]

In this trial, we have shown the ability of montelukast to provide dose-related protection against exercise-induced bronchoconstriction. These exercise challenges were performed at the end of a once-daily dosing interval, suggesting that protec-

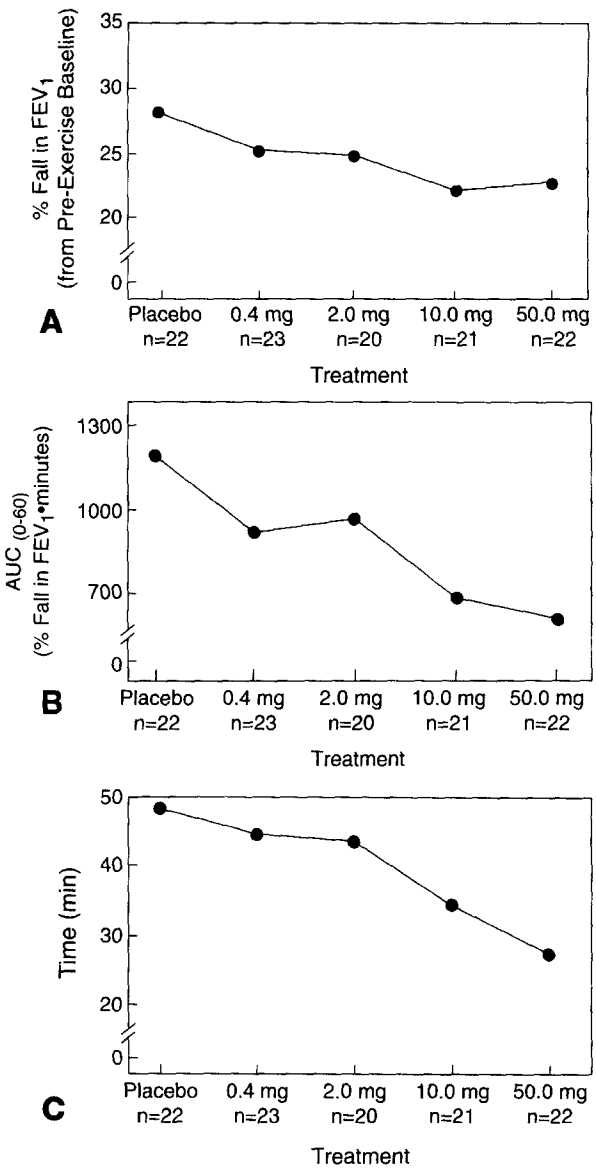


**Fig. 1. A,** Montelukast showed a dose-related inhibition of exercise-induced bronchoconstriction from 20 to 24 hours after oral dosing on the end points of the area under the postexercise decrease (from preexercise baseline) in $FEV_1$ time curve through 60 minutes [AUC(0-60); root mean square error (MSE) = 701]. **B,** The maximum postexercise percent decrease in forced expiratory volume in 1 second ($FEV_1$) (maximal percentage fall; root MSE = 10.9). **C,** The time required after maximal decrease for $FEV_1$ to return to within 5% of preexercise baseline (time to recovery; root MSE = 24.7). Significant ($p < 0.050$) and similar differences were observed for the 10 and 50 mg montelukast doses compared with placebo with use of the linear trend test.

**Table III.** Day 4: Mean postexercise challenge results

| *End point* | *Placebo* | *0.4 mg montelukast* | *2 mg montelukast* | *10 mg montelukast* | *50 mg montelukast* |
|---|---|---|---|---|---|
| AUC (min · %)* | 658.6 | 567.9 | 591.3 | 435.3 | 511.4 |
| Maximal percentage fall in $FEV_1$† | 20.4 | 16.9 | 17.3 | 14.4 | 17.1 |
| Time to recovery (min)‡ | 38.6 | 26.2 | 29.7 | 28.3 | 21.6 |

AUC, Effect of oral montelukast on exercise was measured by the area above the postexercise percentage decrease in $FEV_1$ versus time curve from 0 to 60 minutes.
*$p$ = 0.053, based on stepwise linear trend test with all treatments.
†$p$ = 0.072, based on stepwise linear trend test with all treatments.
‡$p$ = 0.006, based on stepwise linear trend test with all treatments.

**Table IV.** Clinical adverse experiences by treatment group

| *Placebo (n = 22)* | *50 mg montelukast (n = 22)* | *10 mg montelukast (n = 21)* | *2 mg montelukast (n = 20)* | *0.4 mg montelukast (n = 23)* |
|---|---|---|---|---|
| Fever | Fever | Arm pain | Hematoma | Heat exhaustion |
| Appetite increase | Abdominal pain | Foot pain | | Abdominal pain |
| Diarrhea | Diarrhea | Fasciculation | | Diarrhea |
| Diarrhea | Diarrhea | Headache | | Bite/sting, venomous |
| Asthma | Nausea | Headache | | |
| Pharyngeal discomfort | Vomiting | | | |
| Vesicle | Myalgia | | | |
| | Foot pain | | | |
| | Pharyngitis | | | |

tion is present throughout this schedule. Montelukast has previously shown the ability to block airway cysteinyl leukotriene–receptors for a 24-hour time period (inhalational leukotriene $D_4$ challenge in patients with asthma)[13] and to cause clinical benefit by improving the parameters of clinical asthma control (improvement in airways obstruction, patient-reported symptoms, and episodes of worsening asthma) with once-daily dosing.[13] In this trial, all of the parameters that measured the protection against exercise-induced bronchoconstriction were consistent in their demonstration of the dose-related response. In general, these results show that the effects of the 10 mg and 50 mg once-daily doses were similar (and probably maximal) in their protection, whereas the other lower doses were inferior in their effect. Consistent with the results of this trial, a separate dose-ranging study that investigated the effects of montelukast on asthma control end points (measurements of airway obstruction, symptoms, and asthma exacerbations), rather than the protective effects against exercise-induced bronchoconstriction, also found 10 mg to be the minimal dose to achieve the maximal clinical response.[16]

Although present, activity 30 to 36 hours after administration was minimal for all doses. At this time, the placebo effect was only 75% of the response noted 20 to 24 hours after dosing. This observation remains unexplained. The timing of this repeated exercise test is outside the known refractory period for bronchoconstriction caused by exercise[17]; there have been no published investigations of the circadian response of the airways to exercise challenge.

The protection provided by montelukast in this study was consistent with a previous report of the effect of montelukast with use of higher doses.[12] Studies of other leukotriene receptor antagonists in exercise-induced bronchoconstriction showed more complete protection[6]; however, the severity of the pretreatment exercise-induced bronchoconstriction in these studies was milder than that in the montelukast studies, which allowed protection, on a percentage basis, to be greater in the earlier studies.

In conclusion, montelukast provides dose-related protection against bronchoconstriction caused by exercise performed at the end of a once-daily dosing interval. Determination of the dose-related protection against an acute bronchoconstricting challenge,

such as exercise, provides critical information in the selection of an optimal clinical dose.

We thank Alise Reicin, MD, Trudy Noonan, and Susan Frank for their assistance in the development of the manuscript, Amy Ko for statistical analysis, and Judy Evans for editorial assistance.

### *References*

1. Lewis RA, Austen F, Soberman RJ. Leukotrienes and other products of the 5-lipoxygenase pathway [review]. N Engl J Med 1990;323:645-55.
2. Drazen JM, Austen KF. Leukotrienes and airway responses. Am Rev Respir Dis 1987;136:985-98.
3. Woodward DF, Wichmann BF, Gill CA, Wassermann MA. The effect of synthetic leukotrienes on tracheal microvascular permeability. Prostaglandins 1983;25:131-42.
4. Takafuji S, Bischoff SC, De Weck AL, Dahinden CA. IL-3 and IL-5 prime normal human eosinophils to produce leukotriene $C_4$ in response to soluble agonists. J Immunol 1991;147:3855-61.
5. Cohen P, Noveral JP, Bhala A, Nunn SE, Herrick DJ, Grunstein MM. Leukotriene $D_4$ facilitates airway smooth muscle cell proliferation via modulation of the IGF axis. Am J Physiol 1995;269:L151-7.
6. Manning PJ, Watson RM, Margolskee DJ, Williams VC, Schwartz JI, O'Byrne PM. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene $D_4$-receptor antagonist. N Engl J Med 1990;323:1736-9.
7. Margolskee D, Bodman SE, Dockhorn R, Israel E, Kemp J, Manamann H, et al. The therapeutic effects of MK-571 a potent and selective leukotriene $D_4$ receptor antagonist in patients with chronic asthma [abstract]. J Allergy Clin Immunol 1991;87:309A.
8. Spector SL, Smith LJ, Glass M, and the ACCOLATE Asthma Trialists Group. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene $D_4$-receptor antagonist, in subjects with bronchial asthma. Am J Respir Crit Care Med 1994;150:618-23.
9. Israel E, Cohn J, Dube L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. JAMA 1996;275:931-6.
10. De Lepeleire I, Reiss TF, Rochette F, Botto A, Zhang J, Kundu S, et al. Montelukast causes prolonged, potent leukotriene $D_4$-receptor antagonism in the airways of patients with asthma. Clin Pharmacol Ther 1997;61:83-92.
11. Jones TR, Labelle M, Belley M, Champion E, Charette L, Evans J, et al. Pharmacology of montelukast sodium (SINGULAIR$^{TM}$), a potent and selective leukotriene $D_4$-receptor antagonist. Can J Physiol Pharmacol 1995;73:191-201.
12. Reiss TF, Bronsky E, Hendeles L, Hill J, Haroon E, Guerreiro D, et al. MK-0476, a potent leukotriene $LTD_4$-receptor antagonist, inhibits exercise-induced bronchoconstriction at the end of a once-daily dosing interval [abstract]. Am J Respir Crit Care Med 1996; 151(4 pt 2):377.
13. Schoors DF, DeSmet M, Belley M, Reiss TF, Margolskee D, Cheng H, et al. Single dose pharmacokinetics, safety and tolerability of MK-0476, a new leukotriene $D_4$-receptor antagonist, in healthy volunteers. Br J Clin Pharmacol 1995;40:277-80.
14. Crapo RO, Hankinson JL, Irvin C. Standardization of spirometry. Am J Respir Crit Care Med 1995;152: 1107-36.
15. Silverman M, Konig P, Godfrey S. Use of serial exercise tests to assess the efficacy and duration of action of drugs for asthma. Thorax 1973;28:574-8.
16. Reiss TF, Chervinsky P, Noonan M, Prenner B, Zhang J, Hess J, et al. MK-0476, an $LTD_4$ receptor antagonist, exhibits a dose related improvement in the once daily treatment of patients with chronic asthma [abstract]. Eur Respir J 1995;8:19.
17. Gaddy NJ, Margolskee DJ, Bush RK, Williams VC, Busse WW. Bronchodilation with a potent and selective leukotriene $D_4$ ($LTD_4$) receptor antagonist (MK-571) in patients with asthma. Am Rev Respir Dis 1992;146:358-63.