

## Increased urinary excretion of LTE<sub>4</sub> after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist

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### Abstract

**Background** – A study was undertaken to determine whether montelukast, a new potent cysteinyl leukotriene receptor antagonist, attenuates exercise-induced bronchoconstriction. The relationship between the urinary excretion of LTE<sub>4</sub> and exercise-induced bronchoconstriction was also investigated.

**Methods** – Nineteen non-smoking asthmatic patients with a forced expiratory volume in one second (FEV<sub>1</sub>) of  $\geq 65\%$  of the predicted value and a reproducible fall in FEV<sub>1</sub> after exercise of at least 20% were enrolled. Subjects received placebo and montelukast 100 mg once daily in the evening or 50 mg twice daily, each for two days, in a three-period, randomised, double blind, crossover design. In the evening, approximately 20–24 hours after the once daily dose or 12 hours after the twice daily dose, a standardised exercise challenge was performed. Data from 14 patients were available for complete analysis.

**Results** – The mean (SD) maximal percentage decrease in FEV<sub>1</sub> after exercise was 29.6 (16.0), 17.1 (8.2), and 14.0 (9.4) for placebo, once daily, and twice daily regimens, respectively. The mean (95% CI) percentage protection was 37 (15 to 59) for the group who received 50 mg twice daily and 50 (31 to 69) for those who received 100 mg once daily. Active treatments were not different from each other. The mean (SD) plasma concentrations of montelukast were higher after the twice daily regimen (1.27 (0.81)  $\mu\text{g/ml}$ ) than after the once daily regimen (0.12 (0.09)  $\mu\text{g/ml}$ ); there was no correlation between the percentage protection against exercise-induced bronchoconstriction and plasma concentrations. After exercise urinary excretion of LTE<sub>4</sub> increased significantly during placebo treatment (from 34.3 to 73.7  $\text{pg/mg creatinine}$ ;  $p < 0.05$ ) but did not correlate with the extent of exercise-induced bronchoconstriction.

**Conclusions** – Montelukast protects similarly against exercise-induced bronchoconstriction between plasma concentrations of 0.12 and 1.27  $\mu\text{g/ml}$ . The increase in the urinary excretion of LTE<sub>4</sub> after exercise and the protection from exercise-induced bronchoconstriction with a cysteinyl

leukotriene receptor antagonist provide further evidence of the role of leukotrienes in the pathogenesis of exercise-induced bronchoconstriction.

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Keywords: leukotriene receptor antagonist, exercise-induced bronchoconstriction, montelukast.

Cysteinyl leukotrienes, synthesised from arachidonic acid through the 5-lipoxygenase pathway, have an important role in asthma.<sup>1</sup> Leukotriene C<sub>4</sub> (LTC<sub>4</sub>) is the dominant metabolite of arachidonic acid released in lung tissue but it is very unstable and quickly converted to leukotriene D<sub>4</sub> (LTD<sub>4</sub>). In turn, LTD<sub>4</sub> is converted to a less potent metabolite, leukotriene E<sub>4</sub> (LTE<sub>4</sub>), which is excreted in the urine.<sup>2</sup> These leukotrienes are released from eosinophils, mast cells, and other inflammatory cells in the airways of patients with asthma and are highly potent constrictors of bronchial smooth muscle.<sup>3</sup> Observations in experimental animal models also suggest that they stimulate airway mucus secretion, impair mucociliary clearance, and increase vascular permeability.<sup>3</sup>

There is increasing evidence of the importance of the cysteinyl leukotrienes as mediators of exercise-induced bronchoconstriction. Although the mechanism of exercise-induced bronchoconstriction is controversial, one theory suggests that loss of heat and water from the respiratory mucosa during exercise results in a hyperosmolar stimulus of mast cell degranulation releasing bronchospastic mediators such as leukotrienes.<sup>4</sup> Previous studies have shown that cysteinyl leukotriene receptor antagonists attenuate airway responsiveness to exercise, suggesting that the pathogenesis of exercise-induced bronchoconstriction, at least in part, involves the release of leukotrienes.<sup>5,6</sup> If leukotrienes are involved in exercise-induced bronchoconstriction, then urinary excretion of LTE<sub>4</sub> should increase after exercise. However, the evidence is conflicting<sup>7,8</sup> and increases have only been seen in children with more severe asthma.<sup>8</sup>

Montelukast (MK-0476) is an orally bioavailable, selective, and potent cysteinyl leukotriene receptor antagonist capable of significant blockade of airway cysteinyl leukotriene receptors over a 24 hour dosing interval.<sup>9</sup>

Since cysteinyl leukotriene receptor antagonists differ in potency, the present study was

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conducted to determine whether montelukast attenuates exercise-induced bronchoconstriction and whether there is a relationship between plasma concentration and effect by testing two dosage regimens producing different plasma concentrations. In addition, it was the aim of this study to determine whether a sensitive assay could detect an increase in the urinary excretion of  $\text{LTE}_4$  after exercise.

## Methods

### SUBJECTS

Nineteen men aged 18–46 years with exercise-induced bronchoconstriction were selected for study. Each subject had at least a one year history of typical recurring symptoms of asthma including dyspnoea, wheezing, and cough. Furthermore, during the prestudy evaluation each subject had a forced expiratory volume in one second ( $\text{FEV}_1$ ) of at least 65% of the predicted value for age, height, and sex. A 20% decrease in  $\text{FEV}_1$  in response to standardised exercise bronchoprovocation was required on two prestudy (qualifying) visits. All of the subjects were non-smokers for at least a year, with a smoking history of no more than one pack per day for five years. Subjects were excluded if they had other illnesses based upon history, physical or laboratory examination, or had a respiratory infection within six weeks of the prestudy visit. Asthma medications were limited to rapidly acting inhaled  $\beta$  agonists and inhaled corticosteroids (maintained at a constant dose beginning four weeks before and throughout the study). All inhaled  $\beta$  agonists were withheld for at least six hours and inhaled corticosteroids for at least one hour before the exercise challenges. None of the subjects were taking antihistamines or salmeterol prior to the study. The protocol was approved by the institutional review board and written informed consent was obtained from each subject.

### STUDY DESIGN

The study was a double blind, randomised, three period, crossover trial. Treatments consisted of either 100 mg of montelukast with the evening meal and placebo with breakfast, 50 mg of montelukast with the evening meal and breakfast, or placebo twice daily for two days (to achieve steady state plasma concentration). Thus, all subjects received a total of 100 mg/day of montelukast or placebo in the 48 hour period prior to the test exercise challenge.

All subjects returned to the pulmonary function laboratory on the third day between 15.00 and 17.00 hours when the exercise challenge was performed 10–12 hours after the last dose of the twice daily regimen or 22–24 hours after the last dose of the once daily regimen. In addition, routine physical examinations were performed, vital signs and electrocardiographic changes were measured, and blood and urine were collected for laboratory tests of safety and measurement of montelukast plasma concentration and urine concentration of  $\text{LTE}_4$ . Adherence was monitored by capsule counts, telephone contact by the study coordinator,

and plasma concentrations of montelukast. The interval between treatment periods was at least four days.

### EXERCISE CHALLENGE

For each subject exercise was performed on a treadmill for six minutes. The gradient and speed of the treadmill was adjusted to achieve a work load of more than 80% of that subject's age-predicted maximum heart rate. Minor adjustments in work load were allowed in order to achieve the heart rate obtained in the prestudy visits. Pre-exercise spirometric values were measured in accordance with ATS guidelines<sup>10</sup> 20 and five minutes before the challenge. The best of three attempts at each time point were recorded and had to be at least 65% of the predicted value five minutes before exercise for the challenge to proceed. During the exercise the subject wore a nose clip and breathed room air (constant ambient environment in air conditioned laboratories).  $\text{FEV}_1$  was measured immediately after exercise and at five, 10, 15, 30, 45, 60, 75 and 90 minutes. After exercise a  $\beta$  agonist was administered to the patient if the  $\text{FEV}_1$  fell by  $\leq 40\%$  of the predicted value, if it was requested by the patient, or if the investigator thought it was clinically indicated.

### MONTELUKAST PLASMA CONCENTRATION

For the analysis of plasma drug concentration blood samples were collected from all subjects on the second prestudy visit and three minutes before exercise on day 3 (study day) of each treatment period. The plasma specimens were analysed for montelukast by high performance liquid chromatography (HPLC). The limit of detection was 30 ng/ml. The intraday precision values (percentage Relative Standard Deviation, %RSD) were in the range of 0–5.7% and the interday precision values (%RSD) at concentrations of 51 and 2040 ng/ml were 10% and 3%, respectively.

### URINE $\text{LTE}_4$ AND CREATININE

A separate objective of this study was to determine whether exercise challenge in asthmatic patients with exercise-induced bronchoconstriction is associated with increases in urinary concentrations of  $\text{LTE}_4$ . Urine was collected one hour before and one and two hours after exercise. Urinary  $\text{LTE}_4$  concentrations (pg/ml) were expressed as the ratio of creatinine (mg/ml) to correct for differences in urinary volume. Urinary  $\text{LTE}_4$  was measured by a modified HPLC/radioimmunoassay originally described by Tagari *et al*<sup>11</sup> and used clinically to demonstrate increases in urinary  $\text{LTE}_4$  levels after antigen challenge in allergic asthmatic patients.<sup>12</sup> HPLC separation was carried out as described previously<sup>13</sup> and fractions were assayed in a competitive-binding radioimmunoassay using a commercially available peptidyl leukotriene antibody (Cascade Biochem Ltd, Berkshire, UK).

The between day precision of the radioimmunoassay, expressed as coefficient of vari-

ation (CV), was 6.0%, 8.5%, and 13.6% for radioimmunoassay samples containing 104.2, 35.1, and 10.0 pg LTE<sub>4s</sub>, respectively. Overall recovery of <sup>3</sup>H-LTE<sub>4</sub> used as internal standard was 63%. Interday assay precision determined from analysis of pooled urine from healthy subjects was 13.3% and 11.4% for urine samples containing 54.5 and 20.2 pg LTE<sub>4</sub>/mg creatinine, respectively. The limit of reliable quantitation (LLRQ) was 5.24 pg LTE<sub>4</sub>/mg creatinine (based on a creatinine concentration of 142.5 mg/dl). LTE<sub>4</sub> values below this were reported as 2.5 pg LTE<sub>4</sub>/mg creatinine.

The urine creatinine assay is based on a modified Jaffe reaction as described by Chason.<sup>14</sup> The between day precision at 150.1, 70.5, and 13.8 mg/dl were 5.6%, 3.4%, and 5.6%, respectively.

#### DATA ANALYSIS

##### *Exercise end points: general*

The ability of montelukast to attenuate exercise-induced bronchoconstriction was determined by comparing three study end points among treatments: the maximum percentage decrease in FEV<sub>1</sub> after exercise, the time required after maximal decrease for FEV<sub>1</sub> to return to within 5% of the pre-exercise baseline value (recovery time), and the area above the post-exercise FEV<sub>1</sub>/time curve (AUC<sub>0-60 min</sub>). The mean of the 20 minute and five minute pre-exercise measurements was used as the pre-exercise FEV<sub>1</sub> value. End points were calculated for each individual and then averaged. If a patient required a bronchodilator during the post-exercise period or the FEV<sub>1</sub> value was not available, the last recorded FEV<sub>1</sub> was used at all subsequent time points.

##### *Maximal decrease in FEV<sub>1</sub>*

The maximum percentage decrease in FEV<sub>1</sub> after exercise was defined as:

$$\frac{\text{pre-exercise FEV}_1 - \text{lowest FEV}_1 \text{ (after exercise)}}{\text{pre-exercise FEV}_1} \times 100$$

The ability of the two montelukast dosage regimens to attenuate airway responsiveness to exercise relative to placebo was defined as percentage protection from exercise-induced bronchoconstriction and calculated as follows:

$$\% \text{ protection} = \frac{\text{maximum \% fall on placebo} - \text{maximum \% fall on drug}}{\text{maximum \% fall on placebo}} \times 100$$

##### *Time to recovery*

The time to recovery was defined as the time required after maximum decrease in FEV<sub>1</sub> for the FEV<sub>1</sub> to return to within 5% of the pre-exercise baseline value. If the exercise-induced bronchoconstriction was completely blocked (maximal decrease in FEV<sub>1</sub> ≤ 5%) the time to recovery was assigned a value of zero minutes. Additionally, if the post-exercise FEV<sub>1</sub> did not return to within 5% of baseline within 90 minutes the recovery time was assigned a value of

100 minutes minus the time required for the maximum decrease in FEV<sub>1</sub> from baseline to occur.

##### *Area under the curve (AUC)*

The area under the post-exercise FEV<sub>1</sub> percentage decrease through 60 minutes (AUC<sub>0-60</sub>) was also determined. This parameter provides a single number that summarises the extent and duration of bronchoconstriction. The trapezoidal method was used to calculate the AUC<sub>0-60</sub>. Only areas below the pre-exercise baseline were included when computing the AUC<sub>0-60</sub>.

##### URINARY LTE<sub>4</sub>

The ability of exercise to increase urinary LTE<sub>4</sub> levels (pg/mg creatinine) was determined by analysing the change between the pre-exercise baseline and the value two hours after exercise during the placebo period using the Wilcoxon signed rank test.

#### STATISTICAL ANALYSIS

The analysis of variance (ANOVA) model for a crossover study<sup>15</sup> was used to compare treatments for the three end points. The model included terms for subject, treatment, and period. Carryover effects were assessed by adding a carryover factor in the ANOVA model. Pairwise comparisons of the treatment means were made using linear contrasts. 95% confidence limits on differences or changes from baseline were provided when appropriate with p values of ≤ 0.05 (with a two-tailed test) being considered significant.

The study was designed to have 80% power (for 12 completing patients) to detect (α = 0.05, two-sided) a mean difference between treatment groups of 8.1 percentage points for maximal percentage decrease in FEV<sub>1</sub>.

## Results

### DEMOGRAPHIC DATA

Nineteen subjects qualified and received allocation numbers. Three subjects discontinued before completing the three study periods –

Table 1 Demographic data

Subject no.	Age (years)	Prestudy FEV <sub>1</sub> (% predicted)	Maximal decrease in FEV <sub>1</sub> after exercise (%)*
1	22	81.3	23.5
2	22	89.3	28.0
3	19	78.2	43.6
4	20	101.6	37.0
5	18	81.2	19.9
6	27	74.0	24.6
7	36	71.8	36.6
8	46	80.3	24.5
9	25	80.7	24.9
10	30	80.9	25.9
11	30	70.2	31.3
12	31	65.6	61.8
13†	33	84.6	31.9
14	21	91.6	62.3
Median	26	80.8	29.7
Range	18–46	65.6–101.6	19.9–62.3

\* Average of two pre-exercise challenges.

† Patient was using inhaled corticosteroids at a constant dose throughout the study.

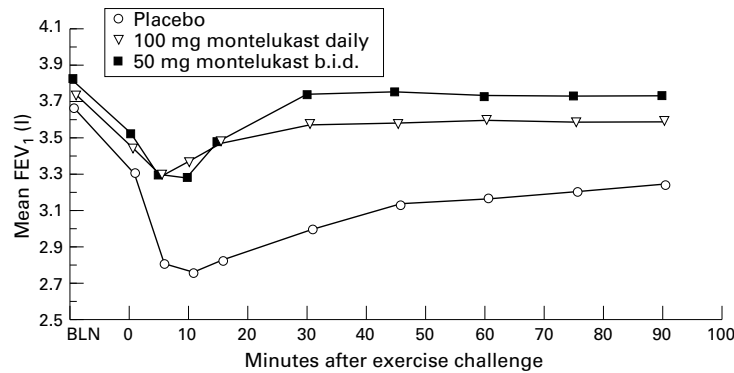


Figure 1 Mean forced expiratory volume in one second (FEV<sub>1</sub>) before and after exercise challenge among 14 subjects with data available from all treatments. Subjects received placebo, montelukast 50 mg twice daily or 100 mg daily for two days. Exercise challenge was performed 12 hours after the last dose on the twice daily regimen or placebo and 24 hours after the last dose of the once daily regimen. At the time of the exercise challenge the mean montelukast trough plasma concentrations were 1.27 µg/ml on the twice daily regimen and 0.12 µg/ml on the once daily regimen. There was no significant correlation between plasma concentration and the extent of protection for exercise-induced bronchoconstriction.

one because of a urinary tract infection and two because of asthma exacerbations unrelated to the exercise challenge (one each during 50 mg twice daily and placebo periods). Of the 16 subjects who completed the three study periods, data from two subjects were unavailable for complete analysis. In one of these patients maximal exercise was not achieved due to chest tightness (thought to be caused by bronchoconstriction) in one period, and in the second patient a technical problem with the spirometric measurement (moisture on the diaphragm of the pneumotachometer) prevented appropriate interpretation of the exercise challenge. The analysis was therefore based upon data from 14 subjects, only one of whom used concomitant inhaled corticosteroids (table 1).

There were no important differences in airway calibre before each exercise challenge for each treatment period with mean pre-exercise baseline FEV<sub>1</sub> values ranging from 3.67 to 3.83 l. Additionally, there was no significant treatment or carryover effect.

#### RESPONSE TO EXERCISE

The mean (SD) maximal percentage decrease in FEV<sub>1</sub> from the pre-exercise baseline value was 29.6 (16.0)%, 17.1 (8.2)%, and 14.0 (9.4)% for the placebo, twice daily and once daily regimens, respectively (fig 1, table 2). The decrease in FEV<sub>1</sub> was significantly ( $p < 0.05$ ) attenuated during both montelukast treatment regimens compared with placebo (mean protection of 37% (95% CI 15 to 59) for the group who received 50 mg twice daily and 50% (95% CI 31 to 69) for those who received 100 mg once daily, but there was no significant difference between the active treatments. Montelukast provided a mean protection against exercise-induced bronchoconstriction of 37% (95% CI 15 to 59) during the twice daily regimen and 50% (95% CI 31 to 69) during the once daily regimen ( $p < 0.05$ ).

The mean time to recovery to within 5% of the pre-exercise baseline FEV<sub>1</sub> value after the maximum decrease in post-exercise challenge was 67.1 (30.1), 20.7 (23.3), 25.7 (33.4) minutes for the placebo, twice daily, and once daily regimens, respectively (table 2). The recovery time was significantly shorter with both active treatments ( $p < 0.001$ ) than with placebo but did not differ between themselves.

The mean AUC<sub>0-60</sub> was 1166 (980)%, 368 (218)%, and 387 (316)% (table 2) for the placebo, twice daily and once daily regimens, respectively. Both active treatments were significantly ( $p < 0.001$ ) smaller than placebo but did not differ between themselves.

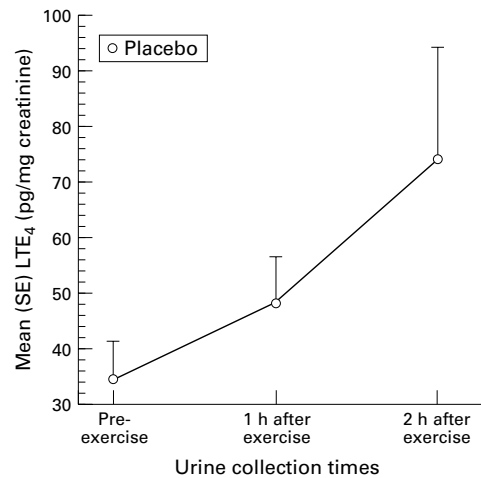
Beta agonist was administered to five patients while receiving placebo, three patients while receiving montelukast 100 mg once daily, but to no patients receiving montelukast 50 mg twice daily.

#### MONTELUKAST PLASMA CONCENTRATIONS

Plasma concentrations from 11 patients were available for analysis. The pre-exercise mean (SD) plasma concentration of montelukast was 1.27 (0.81) µg/ml during the 50 mg twice daily regimen and 0.12 (0.09) µg/ml for the 100 mg

Table 2 Response to exercise challenge

Subject no.	Maximal decrease in FEV <sub>1</sub> (% change from pre-exercise baseline)			Time to recovery (min) (FEV <sub>1</sub> to 5% of pre-exercise baseline)			AUC <sub>0-60</sub> minutes (min × %)		
	Placebo	Montelukast 50 mg twice daily	Montelukast 100 mg once daily	Placebo	Montelukast 50 mg twice daily	Montelukast 100 mg once daily	Placebo	Montelukast 50 mg twice daily	Montelukast 100 mg once daily
1	13.0	16.9	9.3	61.8	30.0	5.0	609	494	340
2	21.1	14.8	3.9	32.5	9.5	0.0	632	334	12
3	54.1	31.5	33.2	95.0	95.0	41.7	3166	823	802
4	19.5	24.5	19.2	90.0	13.6	25.0	833	366	867
5	17.8	7.7	5.3	95.0	3.0	0.0	675	210	50
6	35.4	22.4	13.4	40.0	19.0	4.4	1123	373	105
7	21.6	26.3	22.5	77.5	36.3	32.5	798	727	572
8	35.6	16.9	7.2	63.0	16.0	2.5	1180	304	196
9	15.0	7.2	14.7	4.6	12.5	90.0	105	137	521
10	8.9	0.4	0.7	85.0	0.0	0.0	427	0	1
11	29.1	16.1	16.8	25.0	12.5	55.0	630	309	606
12	60.0	19.2	26.4	90.0	14.4	95.0	3482	290	867
13	32.8	16.9	5.3	85.0	12.5	0.0	1240	264	237
14	50.4	19.5	19.0	95.0	15.0	8.3	1429	525	238
Mean	29.6	17.1	14.0	67.1	20.7	25.7	1166	368	387
SD	16.0	8.2	9.4	30.1	23.3	33.4	980	218	316
Difference from placebo (95% CI)		12.6 (6.5 to 18.8)	15.8 (9.7 to 22.0)		46.6 (69.5 to 23.8)	43.1 (65.9 to 20.3)		800 (371 to 1229)	779 (350 to 1208)



**Figure 2** Mean (SE) urinary concentration of LTE<sub>4</sub> (pg/mg creatinine) before and one and two hours after exercise in 13 subjects while receiving placebo. Patients received placebo, montelukast 50 mg twice daily or 100 mg for two days before exercise in a double blind, randomised, crossover design. There was no significant correlation between severity of exercise-induced bronchoconstriction and urinary concentration of LTE<sub>4</sub>.

**Table 3** Clinical adverse events\*

Placebo	Montelukast 100 mg once daily	Montelukast 50 mg twice daily
Back pain	Asthma	Dry mouth
Nausea	Fatigue	Diarrhoea
Headache		Epistaxis
Upper respiratory infection		Asthma
Urinary tract infection		

\* Each listing represents a single episode.

once daily dose. There was no correlation between the plasma concentration and the extent of protection from exercise-induced bronchoconstriction, as measured by either the AUC or the maximal percentage fall in FEV<sub>1</sub>.

#### LTE<sub>4</sub> IN URINE

The urine concentration of LTE<sub>4</sub> increased significantly ( $p < 0.05$ ) two hours after exercise challenge during placebo treatment from a mean (SD) of 34.3 (6.9) pg/mg creatinine to 73.7 (20.4) pg/mg creatinine (fig 2). Neither the pre-exercise LTE<sub>4</sub> nor the change in LTE<sub>4</sub> after exercise correlated with the maximal decrease in FEV<sub>1</sub> after exercise.

#### ADVERSE EFFECTS

Clinical adverse events were infrequent and there were no significant differences in frequencies between the three treatments (table 3). There were no significant changes in laboratory measurements of blood haematology and chemistry or urinalysis with montelukast treatments.

#### Discussion

The results of this study provide further evidence that cysteinyl leukotrienes are involved in the pathogenesis of exercise-induced bron-

choconstriction. This conclusion is based upon the observation that the concentration of LTE<sub>4</sub> increased after exercise challenge and montelukast, a potent and specific inhibitor of cysteinyl leukotrienes, attenuated the characteristic decrease in FEV<sub>1</sub> following exercise.

This study shows that urinary concentrations of LTE<sub>4</sub> increase after exercise in adults with mild asthma. Previous studies have shown an increase in urine concentrations of LTE<sub>4</sub> during severe episodes of worsening asthma and after bronchoprovocation with allergen or aspirin.<sup>16</sup> However, results from exercise studies have been conflicting. Previous adult studies were unable to detect increases in urinary levels of LTE<sub>4</sub> after exercise<sup>17</sup> while others detected increases after exercise in children with asthma but not in normal children.<sup>18</sup> A possible explanation for the differences between studies in the recovery of LTE<sub>4</sub> may be the timing of sample collection and/or the sensitivity of the assay employed.

The protection from exercise-induced bronchospasm was similar 24 hours after montelukast 100 mg once daily and 12 hours after 50 mg twice daily. On average, the plasma concentrations were almost 10 times higher at the trough of the twice daily regimen than at the trough of the once daily regimen, yet the protection was no greater. This indicates that the response after the 100 mg once daily regimen (0.12 µg/ml) is at or near the top of the concentration-response curve. A subsequent large clinical trial has shown the clinical benefit of montelukast in chronic asthma at a lower dose of 10 mg once daily at bedtime.<sup>19</sup>

If a β agonist was administered after exercise the last value before its administration was used at all subsequent time points. This decision rule tends to underestimate the true end point values (maximal FEV<sub>1</sub> % fall, time to recovery, and AUC). Because rescue occurs more frequently with placebo, the true difference between active treatment and placebo will also be underestimated.

Exercise challenges were generally reproducible – for example, between prestudy and placebo treatments – providing internal validation to the conclusions of this study.

Using the parameters of the maximal fall in FEV<sub>1</sub> after exercise, previous studies have shown that β<sub>2</sub> selective sympathomimetics may provide about 70% protection from exercise-induced bronchospasm immediately after administration which dissipates within six hours with short acting agents and within 12 hours with long acting agents.<sup>20</sup> Cromolyn provides about 50% protection within the first two hours after administration.<sup>21</sup> In the present study montelukast produced about 50% protection 24 hours after dosing. The magnitude of inhibition is consistent with similar studies with cysteinyl leukotriene receptor antagonists<sup>22</sup> or a 5-lipoxygenase inhibitor.<sup>23</sup> Since leukotriene modifiers (5-lipoxygenase inhibitors or receptor antagonists) incompletely block the response to exercise, it is probable that other mediators released in response to exercise are also involved in the pathogenesis of exercise-induced bronchospasm.

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# Increased urinary excretion of LTE<sub>4</sub> after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist.

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