

Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma

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ABSTRACT: The leukotrienes are known to be important mediators of bronchial asthma. The ability of montelukast, a potent and selective CysLT₁ leukotriene receptor antagonist, to cause a dose-related improvement in chronic asthma was investigated in a placebo-controlled, multicentre, parallel-group study.

After a two week placebo run-in period, chronic asthmatic patients with a forced expiratory volume in one second (FEV₁) 40–80% predicted with $\geq 15\%$ increase (absolute value) after β_2 -agonist were randomly assigned to one of four treatment groups (placebo or montelukast 2, 10, or 50 mg once daily in the evening) for a three week, double-blind treatment period.

For patient-reported end-points (daytime symptom score, use of as needed inhaled β_2 agonist, asthma-specific quality of life) and frequency of asthma exacerbations, montelukast 10 and 50 mg caused similar responses, superior to 2 mg and significantly ($p < 0.05$; linear trend test) different from placebo. All three doses caused improvements in FEV₁ and morning and evening peak expiratory flow rate (PEFR) that were significantly ($p < 0.05$) different from placebo. Differences (least square mean) between the pooled 10 and 50 mg montelukast treatment groups and placebo were: 7.1% change from baseline in FEV₁, 19.23 L·min⁻¹ in morning PEFR, -0.29 in daytime asthma symptom score (absolute value), and -0.82 in β_2 -agonist use (puff·day⁻¹). The incidence of adverse experiences was neither dose-related nor different between montelukast and placebo treatments.

We conclude that montelukast causes a dose-related improvement in patient-reported asthma end-points over the range 2–50 mg. Montelukast causes benefit to chronic asthmatic patients by improving asthma control end-points.

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The cysteinyl leukotrienes (LTC₄, D₄, E₄) are known to play an important role in the pathobiology of asthma. These compounds, derived from arachidonic acid via the 5-lipoxygenase pathway, are produced in cells of inflammation such as eosinophils, mast cells, monocytes, and basophils [1]. The leukotrienes have multiple effects that contribute to the airways obstruction and inflammation which characterize asthma, including constriction of small and large airways (effects up to a thousand-fold greater than histamine and methacholine) [2], and promotion of eosinophil migration into the airway mucosa [3]. *In vitro* studies with the cysteinyl leukotrienes have shown increased venous permeability [4], mucus secretion [5], and decreased activity of the respiratory cilia [6].

Clinical studies of antileukotriene agents have provided direct evidence of the role of the cysteinyl leukotrienes in clinical asthma. Early clinical studies with MK-0571, a leukotriene receptor antagonist, demonstrated protection against both early- and late-phase bronchoconstriction due to inhaled allergens [7] and exercise-induced bronchoconstriction [8], while demonstrating rapid bronchodilation in other studies [9]. A six week course of therapy with zafirlukast, a leukotriene receptor antagonist, produced both an objective and subjective improvement of asthma [10],

as did a three month course of zileuton, a 5-lipoxygenase inhibitor [11].

Montelukast (MK-0476, SINGULAIR®) is a potent and specific CysLT₁ receptor antagonist [12]. When given once daily to patients with asthma, montelukast protects against LTD₄-induced [13] and exercise-induced bronchoconstriction [14], 20–24 h after administration. Similarly, significant improvement in the signs and symptoms of chronic asthma have been observed after 6 weeks of double-blind treatment with montelukast dosed once daily between 10–200 mg [15].

The similarity of the response between a daily dose of 10–200 mg suggested that the evaluation of doses < 10 mg would be necessary to identify a dose-response relationship. Using a dose < 10 mg, this multicentre study had the objective of investigating the dose-related tolerability and efficacy of montelukast.

Materials and methods

Study design

This double-blind, randomized, three-period, parallel-group study comparing the clinical effect of three dosages

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of montelukast and placebo was conducted at 22 study centres in the United States. After a two week placebo run-in (period I), the active treatment period (II) was double-blind and 3 weeks in length; patients received either placebo, 2, 10, or 50 mg of montelukast administered once daily at bedtime. Eligible patients were randomly allocated to receive study medication according to a computer-generated schedule. After completion of the active treatment period, patients entered a single-blind, one week placebo washout period (III).

Patients

Healthy, nonsmoking chronic asthmatic patients (males and females of nonchildbearing potential), aged 18–65 yrs, were enrolled. Patients were required to demonstrate a forced expiratory volume in one second (FEV₁, measured in the morning, 8–10 h after the evening dose) 40–80% predicted (after withholding short acting, inhaled β_2 -agonist for 6 h) on two of the three clinic visits before the randomization. Eligible patients also twice demonstrated reversible airways obstruction (a 15% or greater increase in FEV₁ (absolute value) 20–30 min after inhalation of a short acting β_2 -agonist) and a weekly total daytime asthma symptom score of at least 32 (see below). Additionally, an average of at least 1 puff·day⁻¹ of a short-acting, inhaled β_2 -agonist was also required during the run-in period (I). Adequate study procedure performance was required for allocation to active treatment.

Patients were excluded for: an upper respiratory tract infection within three weeks, acute sinus disease requiring antibiotic therapy within one week, emergency room treatment for asthma within one month, or hospitalization for asthma within three months before the prestudy visit. Female patients had negative pregnancy tests (serum β_2 -human chronic gonadotropin) at the screening visit.

Beginning at period I, patients received three bottles of study medication containing montelukast 2, 10, or 50 mg or matching-image placebo tablets at each weekly visit. Patients were instructed to take one tablet from each bottle at bedtime. Patients also received a Mini-Wright™ peak flow meter (Mini-Wright, Columbus, OH, USA) and were instructed in its proper use. During the study, all patients used short acting inhaled β_2 -agonists "as needed". Additionally, the following concomitant medications were permitted (at a constant dose): twice-daily theophylline beginning one week prior to the prestudy visit, inhaled corticosteroids (limited to no more than 20% of cohort), short- or intermediate-acting antihistamines, cough suppressants, expectorants, and nasal decongestants in monosubstance formulations, nasal steroids and nasal cromolyn at constant doses, paracetamol (acetaminophen) and codeine in monosubstance formulations or brand name combinations, estrogen, and thyroid hormone. The use of new or changing doses of concomitant asthma medications by a patient (other than short-acting inhaled β_2 -agonists) resulted in discontinuation. Mild consumption of alcohol and caffeine was permitted.

Written informed consent, approved by the respective institutional review boards, was obtained from each patient.

Efficacy measurements

Spirometry. Morning spirometry was performed in the clinic weekly at approximately 07:00 h (± 1 h), 7–9 h after the previous evening dose of study medication, and at least 6, 24 and 48 h after inhaled β_2 -agonist, theophylline, and short- and intermediate-acting antihistamines, respectively. Inhaled corticosteroids were administered at least 1 h before the morning clinic visit. Afternoon spirometry was obtained twice (at the randomization visit and at the end of the study) at 17:00 h (± 1 h), approximately 17–19 h after the previous bedtime dose of study medication. The largest FEV₁ from at least three acceptable manoeuvres was recorded. A standard spirometer (Puritan-Bennett PB 100/PB110; Kansas City, KS, USA) was used at all clinical centres. All spirometry measurements were reviewed centrally to ensure uniform adherence to American Thoracic Society standards of acceptability and reproducibility [16]. When appropriate, feedback was given to individual clinical centres to enhance quality. β_2 -agonist reversibility was determined by measuring FEV₁ 20–30 min after administration of two 90 μ g puffs of β_2 -agonist.

Asthma symptoms and β_2 -agonist use. A daily diary card included four daytime symptom questions (0 (best) to 6 (worst)) and one nocturnal awakening question previously shown to have acceptable evaluative measurement properties [17]. The amount of "as needed" β_2 -agonist was recorded both in the morning and evening as the number of puffs inhaled.

Peak expiratory flow rate. Peak expiratory flow rate (PEFR) was measured by the patient immediately upon arising before any morning medication (*am* PEFR) and immediately before the evening dose of study medication (*pm* PEFR). The best of at least three manoeuvres was recorded on the diary card. PEFR measurements made within four hours of β_2 -agonist use were identified on the diary card.

Global evaluations. Upon completing the active treatment period, both physicians and patients independently evaluated the overall change in asthma. The question, "Compared to when I (the patient) entered the study, my (the patient's) asthma is now" was answered on a self-administered evaluation 7-point scale. Responses included: "very much better", "moderately better", "a little better", "unchanged", "a little worse", "moderately worse", "very much worse". When completing this questionnaire, the physician had access to the verbal history, physical examinations, and FEV₁ measurements. To increase clinical clarity, the 7-point scale was summarized by reducing the seven responses to three categories: "better" (three responses), "no change" (one response), and "worse" (three responses).

Asthma-specific quality-of-life questionnaire. At the randomization visit (before receiving study medication) and the final visit of active treatment, the patient completed a validated, self-administered, quality-of-life questionnaire [18]. The questionnaire was divided into four domains-activity, symptoms, emotions, and environment. In response to the questions, patients identified an answer on a 7-point scale which ranged from 0 (worst) to 6 (best).

Asthma exacerbation. The days with an asthma exacerbation were determined by the occurrence of any one change in patient-recorded diary card parameters: a decrease >20% from baseline in morning PEFr; PEFr <180 L·min⁻¹; an increase >70% from baseline in β_2 -agonist use (minimum increase, two puffs); an increase >50% from baseline in symptom score; "awake all night" because of asthma; or an unscheduled visit to a doctor or hospital.

Eosinophil and blood theophylline levels. Blood obtained at each visit was analysed for eosinophil counts (measured as a per cent of total cell count). Blood obtained at the last active treatment visit was analysed for theophylline levels. All analyses were performed in a central laboratory.

Safety evaluations

Patient-reported adverse experiences were recorded during each clinic visit. Clinical laboratory (haematology, serum chemistry, and urinalysis) and pregnancy tests were collected at the prestudy visit, before and at the end of the active treatment period. A complete physical examination and 12-lead electrocardiogram (ECG) were performed at prestudy and upon study completion.

Analysis

An intention-to-treat approach, including end-points from each patient with prerandomization values and at least one treatment period value was performed. For all end-points, the average treatment period response was analysed using an analysis of variance (ANOVA) model that included terms for treatment, study centre, stratum (inhaled corticosteroids and theophylline), and treatment-by-stratum interaction. Ordinal data were analysed using the Cochran-Mantel-Haenszel (CMH) test to corroborate the ANOVA results. Tukey's modified linear trend test (stepwise trend test) [19] was used to assess a dose-response. Baseline values were defined as the mean values during the placebo run-in period. Doses having similar and maximal responses across all end-points were pooled to estimate treatment effects compared to placebo with greater precision.

A 95% confidence interval (CI) for mean change or per cent change from baseline (within-group change) was calculated using the least square (LS) mean, as was the 95% CI for the difference between treatment groups and placebo. Assumptions of normality and homoscedasticity were assessed. All statistical tests were two-tailed, and a $p < 0.05$ was considered statistically significant.

All randomized patients were included in the tolerability assessment. Fisher's exact test was used to compare the frequency of clinical and laboratory adverse experiences among treatment groups.

Power and sample size. The study was designed *a priori* with a sample size of 50 patients per treatment group to have 80% power to detect (at $\alpha = 0.05$, two-tailed test) a mean difference between treatment groups in FEV₁ of 11% in mean per cent change from baseline.

Results

Patients

Four hundred and seventy-five patients were screened allowing 281 patients to enter the active, double-blind treatment period. Of these, 273 (99.2%) completed the active treatment period and 272 (96.8%) completed the placebo washout period. Of the nine patients who did not complete the trial, one patient (50 mg treatment group) was discontinued due to worsening asthma; two patients were discontinued due to other clinical adverse experiences (gastrointestinal haemorrhage, 2 mg treatment group; erythema multiforme, 10 mg treatment group); one patient (placebo) became pregnant and was discontinued; two patients (one 50 mg treatment group, one placebo) had protocol deviations; and three patients (2 mg, 10 mg, placebo treatment groups) discontinued due to personal reasons. There were no clinically meaningful differences between the treatment groups in demographic parameters or baseline characteristics (table 1).

Efficacy

Patient- and physician-reported end-points. Montelukast caused dose-related responses ($p < 0.05$) for the daytime asthma symptom score, β_2 -agonist use, frequency of asthma exacerbations (table 2) and the combined (as well as individual) quality-of-life domain scores (table 2, fig. 1).

Table 1. – Randomized patients - characteristics at baseline

	Placebo (n=69)	Montelukast		
		2 mg (n=72)	10 mg (n=68)	50 mg (n=72)
Median age yrs (range)	36 (18–63)	34 (18–61)	32 (19–60)	30.5 (18–63)
Sex				
Male	34	36	42	40
Female	35	36	26	32
Concomitant medication				
Inhaled corticosteroid	18	15	16	18
Theophylline	7	16	14	15
Neither	44	41	38	39
History of allergic rhinitis n	59	63	54	61
Baseline asthma measurements mean (\pm SD)				
FEV ₁ L	2 (1)	2 (1)	2 (1)	2 (1)
FEV ₁ % pred	61 (14)	60 (14)	59 (14)	64 (14)
<i>am</i> PEFr L·min ⁻¹	379 (97)	378 (82)	386 (81)	395 (82)
Daytime symptom score	3 (1)	3 (1)	3 (1)	3 (1)
β_2 -agonist use puffs·day ⁻¹	5 (3)	6 (3)	6 (3)	5 (3)
<i>pm</i> PEFr L·min ⁻¹	413 (93)	409 (80)	416 (75)	424 (83)
Nocturnal awakenings nights·week ⁻¹	4 (3)	4 (3)	5 (3)	4 (3)

FEV₁: forced expiratory volume in one second; % pred: percentage of predicted; PEFr: peak expiratory flow rate; *am*: morning; *pm*: afternoon.

Table 2. – Patient-reported end-points

End-point	Placebo n=69	Montelukast				Pooled 10–50 mg n=140	Pooled/Placebo difference [†] (CI) [#]
		2 mg n=72	10 mg n=68	50 mg n=72			
Daytime symptom scores [‡]	-0.1 (-0.3, 0.0)	-0.3 (-0.4, -0.1)	-0.4* (-0.5, -0.2)	-0.4* (-0.6, -0.3)	-0.4 (-0.5, -0.3)	-0.3 (-0.5, -0.1)	
β_2 -agonist use puffs-day ^{-1‡}	-0.2 (-0.6, 0.2)	-0.7 (-1.1, -0.3)	-1.1* (-1.5, -0.7)	-0.9* (-1.3, -0.6)	-1.0 (-1.3, -0.7)	-0.8 (-1.3, -0.4)	
Asthma-specific quality of life, all domains score [‡]	0.4 (0.1, 0.6)	0.5 (0.3, 0.7)	0.7* (0.5, 0.9)	0.8* (0.6, 1.0)	0.7 (0.6, 0.9)	0.4 (0.1, 0.6)	
Nocturnal awakenings nights-week ^{-1‡}	-0.3 (-0.7, 0.2)	-0.9* (-1.3, -0.5)	-1.4* (-1.9, -1.0)	-0.8* (-1.2, -0.4)	-1.1 (-1.4, -0.8)	-0.8 (-1.4, -0.3)	
Asthma exacerbations % patients	69.6	54.2	44.1 [‡]	50.0 [‡]	47.1	-	

Values are presented as mean and 95% confidence interval (CI). [‡]: change from baseline; *: p<0.05 compared with placebo based on stepwise linear trend test; [‡]: difference in least square (LS) means between placebo and pooled 10 and 50 mg montelukast; [‡]: p<0.05 compared with placebo based on pairwise comparison with placebo using Cochran-Mantel-Haenszel test; [#]: CI not containing zero indicates statistical significance.

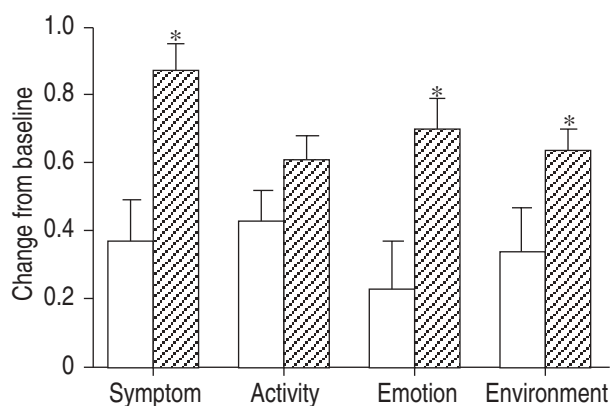


Fig. 1. – Values presented as mean \pm SE scores (change from baseline) of the four domains of the asthma-specific quality-of-life questionnaire in the placebo (□) and pooled (10 and 50 mg) (▨) montelukast treatment groups. Significant (p<0.05) improvement on symptom, environment and emotion domains was observed. *: p<0.05 compared with placebo.

For these parameters, both the 10 and 50 mg doses demonstrated similar and significantly better improvement than placebo, whereas the 2 mg dose did not (table 2). Nocturnal awakenings did not demonstrate a dose-response relationship (table 2). Physician's global evaluations demonstrated a significant (p<0.05) dose-related response (2.35, 1.96, 1.76, 1.69 for the placebo, 2 mg, 10 mg, and 50 mg, respectively, on the 0–6 point scale) with the 10 and 50 mg doses significantly different from placebo. Patient's global evaluation did not (p=0.370) demonstrate a dose-related response (2.07, 1.61, 1.40, 1.64 for the placebo, 2, 10, and 50 mg, respectively, on the 0–6 point scale) with all doses significantly different from placebo. These global evaluations (collapsed categories of pooled 10 and 50 mg doses compared with placebo) are illustrated in figure 2.

Measurements of airway obstruction. All doses of montelukast resulted in similar and significantly (p<0.05) greater improvements compared with placebo in morning FEV₁ and morning and afternoon PEFR (table 3).

Consistency of effects. Montelukast demonstrated consistent effects over the three week treatment period without

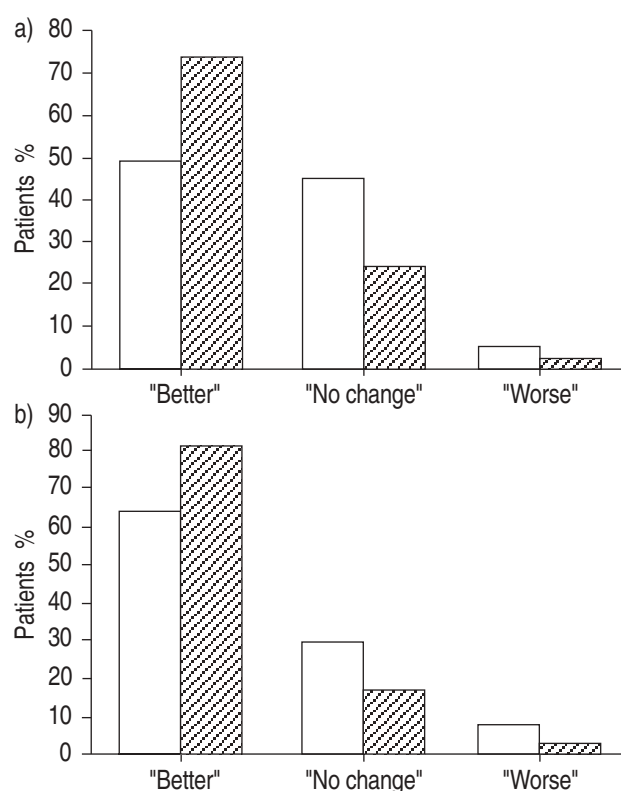


Fig. 2. – Mean percentage responses to a) physician and b) patient global evaluations where the 7-point scale global evaluation was collapsed to three responses: Better (0, 1, 2), No change (3), and Worse (4, 5, 6) for the placebo (□) and pooled 10 and 50 mg montelukast treatments (▨). Montelukast was significantly preferred by physicians and patients (p<0.05).

evidence for rebound worsening when patients were switched to placebo in a blinded manner (washout period). Figure 3 illustrates this observation for the end-points of daytime asthma symptom scores, β_2 -agonist use, morning FEV₁, and morning PEFR.

Onset of action. Clinical benefit was apparent within the first day of initiating treatment with montelukast. Figure 4 demonstrates this onset of action with daytime asthma symptom scores and β_2 -agonist use.

Table 3. – Measurements of airway obstruction

End-point	Placebo n=69	Montelukast				Pooled/Placebo difference† (CI)‡
		2 mg n=72	10 mg n=68	50 mg n=72	Pooled 10–50 mg n=140	
Morning FEV ₁ [‡]	6.2 (1.9, 10.6)	14.7* (10.6, 18.8)	13.5* (9.3, 17.7)	13.1* (9.0, 17.1)	13.3 (10.3, 16.3)	7.1 (2.1, 12.1)
Morning PEF _R L-min ⁻¹ §	-0.6 (-8.5, 7.3)	19.3* (11.8, 26.8)	21.5* (13.9, 29.2)	15.7* (8.3, 23.1)	18.5 (13.1, 24.0)	19.2 (10.1, 28.3)
Afternoon FEV ₁ [‡]	3.3 (-2.4, 9.0)	11.2 (5.9, 16.5)	6.3 (0.9, 11.7)	8.3 (3.1, 13.5)	7.3 (3.5, 11.2)	4.0 (-2.5, 10.5)
Afternoon PEF _R L-min ⁻¹ §	0.6 (-5.7, 6.9)	14.1* (8.1, 20.1)	22.2* (16.1, 28.3)	13.6* (7.7, 19.5)	17.8 (13.4, 22.1)	17.3 (10.1, 24.6)

Values are presented as mean and 95% confidence interval (CI). ‡: percentage change from baseline; morning forced expiratory volume in one second (FEV₁) was performed during a morning clinic visit, 8–10 h after dosing, afternoon FEV₁ was recorded in late afternoon. §: change from baseline: morning peak expiratory flow rate (PEFR) was performed in the morning upon arising, afternoon PEFR was performed immediately before bedtime administration at the end of the dosing interval. *: p<0.05 compared with placebo based on stepwise linear trend test; †: difference in least square (LS) means between placebo and pooled (10 and 50 mg) montelukast; ‡: CI not containing zero indicates statistical significance.

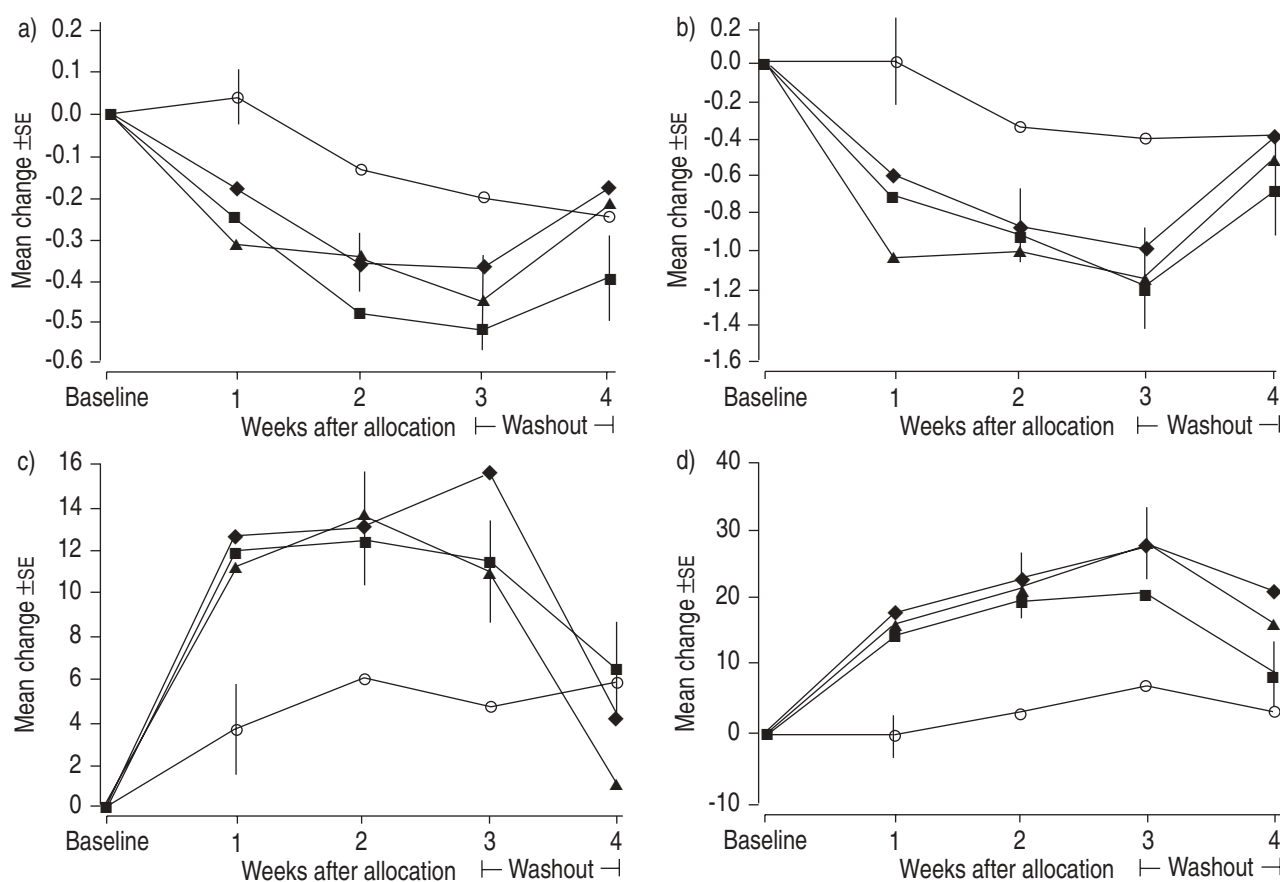


Fig. 3. – Comparison of once-daily at bedtime placebo (○) and montelukast (◆: 2 mg; ▲: 10 mg; ■: 50 mg) treatment groups during the active treatment and washout periods. a) Change from baseline in daytime symptom (scores); b) change from baseline "as needed" β_2 -agonist use (puffs·day⁻¹); c) percentage change from baseline morning forced expiratory flow in one second (FEV₁); d) change from baseline in morning peak flow rate (PEFR) (L·min⁻¹). Montelukast 10 and 50 mg caused significant (p<0.05), consistent improvement compared with placebo over the three-week, active period. There was no rebound worsening of asthma during the one-week placebo washout period. The values are reported as mean±SE.

Other end-points. Administration of montelukast was associated with a decrease in peripheral eosinophils. The mean decrease from baseline in peripheral eosinophil count approached significance (p=0.08) for the pooled montelukast group *versus* placebo (-0.97% confidence interval (CI) -1.72, -0.21 (as a difference in percentage points of the total peripheral blood leukocyte count)). There were

no dose-related responses. There were no differences in plasma theophylline levels among treatment groups, (mean $\mu\text{g}\cdot\text{mL}^{-1}$ 4.66, 5.05, 5.19, and 3.28 in the placebo, 2, 10, and 50 mg groups, respectively) indicating that theophylline was withheld as instructed. Additionally, the similarity of the plasma levels argues against theophylline influencing the observed treatment.

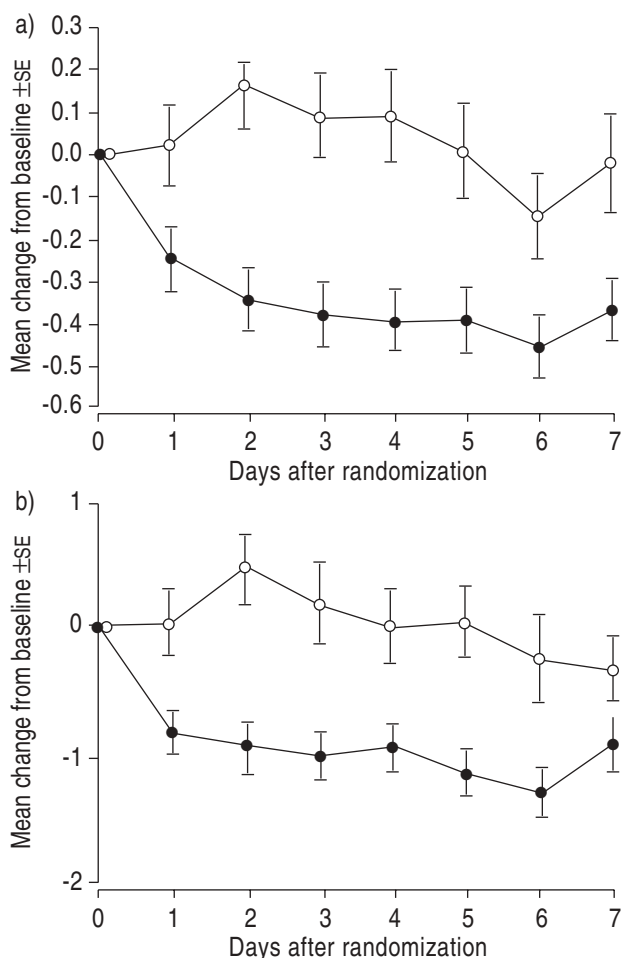


Fig. 4. – Time course of onset of action for a) daytime symptom (score) and b) β_2 -agonist use (puffs·day⁻¹) during the first seven days after randomization for pooled (10 and 50 mg) montelukast (●) and placebo treatments (○). Montelukast effects were evident during the first day of treatment. The values are reported as mean±SE.

Table 4. – Incidence of most common adverse experiences†

	Placebo n=69	Montelukast			
		2 mg n=72	10 mg n=68	50 mg n=72	Pooled* n=212
Headache	10 (15)	4 (6)	6 (9)	8 (11)	18 (8)
Upper respiratory infection	3 (4)	6 (8)	5 (7)	2 (3)	13 (6)
Pharyngitis	4 (6)	3 (4)	1 (2)	2 (3)	6 (3)
Diarrhoea	4 (6)	0	0	2 (3)	2 (1)
Nasal congestion	4 (6)	0	0	2 (3)	2 (1)

Values are presented as number (percentage) of patients. †: adverse experiences occurring in 6% or more patients in at least one treatment group; *: all montelukast treatment groups.

Effects with concomitant asthma therapies. The treatment effect of montelukast was consistent among all patients, irrespective of concomitant (inhaled corticosteroid, theophylline) asthma therapies (stratum interactions were not significant; mean effects were similar among subgroups for these end-points).

Safety

Headache, upper respiratory tract infection, and pharyngitis were the most frequently reported clinical adverse experiences (table 4). These events were not dose-related and there were no differences between montelukast (all groups pooled or each group separately) and placebo in incidence. Six patients (four placebo, two montelukast) had at least one laboratory adverse experience, all of which were transient and self-limited.

Discussion

This study demonstrated that montelukast, once daily at bedtime for three weeks, improved parameters of asthma control (airway obstruction, patient-reported end-points, and asthma outcomes) compared with placebo.

A dose-response relationship was evident in patient-reported end-points, including daytime asthma symptoms, β_2 -agonist use, asthma-specific quality of life, and frequency of asthma exacerbations. With these end-points, the 10 and 50 mg doses of montelukast were associated with similar improvements, while the 2 mg dose was less effective and not significantly different from placebo. The measurements of airway obstruction clinic spirometry (FEV₁) and home peak flow monitoring did not demonstrate a dose relationship; all three doses of montelukast were similarly and significantly different from placebo.

A dose-response relationship for clinical asthma therapies is often difficult to demonstrate [20]. For example, published dose-response studies with budesonide and beclomethasone have reported conflicting conclusions using spirometric and symptom end-points [21, 22]. Other authors have suggested that dose-response studies with inhaled corticosteroids should be performed using outcomes (worsening episodes of asthma or oral corticosteroid tapering) and have provided meta-analyses supporting this point of view [23]. Similarly, recent studies with a newer inhaled corticosteroid, fluticasone, have demonstrated modest, dose-related effects [24]. Dose-clinical response relationships with leukotriene blockers have also been difficult to demonstrate. For example, published studies of zafirlukast, a leukotriene receptor antagonist, have not shown consistent dose-related responses [10], while studies with zileuton, a 5-lipoxygenase inhibitor, did suggest a difference between doses of 2400 and 3200 mg·day⁻¹ [11]. The reason for the modest dose-related response [5] in all these studies remains speculative. Possibilities include selection of dose range, length of the observation period, or end-point selection. As an example of the latter, PEDERSEN and HANSEN [25] found that in children, PEFR and diary recordings were not sensitive parameters, but the protection against exercise-induced asthma was a sensitive parameter for detecting differences between budesonide doses.

The montelukast dose-response relationship observed in this study is consistent with the results of a complementary dose-response study demonstrating protection against exercise-induced bronchoconstriction at the end of a once daily dosing interval [26]. These two studies provide dose-related responses in the complementary clinical situations of improving chronic asthma (persistent presence of leukotrienes in the airway) and protecting against episodic worsening asthma (bolus release of leukotrienes) by

provocative challenge (exercise at the end of a once daily dosing interval). The results of the studies were consistent: the 10 and 50 mg doses were similar in their response, while lower doses had less effect, suggesting that these clinical situations require similar receptor occupancy with montelukast. The explanation for the difference in the dose relationship between classes of end-points also remains speculative. Because leukotriene receptor biology is in its infancy (to date, the CysLT₁ receptor has not been isolated or cloned), the possibility of receptors differing in sensitivity on airway cells causing asthmatic responses is a possible explanation.

Additionally, both studies demonstrate that montelukast provides activity throughout the once daily dosing interval, evidenced by its protection against exercise-induced bronchoconstriction [26] and the improvement in PEF_R at the end of the dosing interval.

The decreased peripheral eosinophil count associated with montelukast therapy in this study suggests that montelukast may modulate the parameters of inflammation. Eosinophils are typically increased in the circulation and airways of patients with asthma and are thought to play a central role in asthma pathogenesis [27]. In patients receiving inhaled corticosteroids, circulating eosinophils decrease [28]. The effect of long-term montelukast therapy on levels of eosinophils in airways and peripheral blood will require additional prospective studies.

In this study, the incidence of clinical and laboratory adverse events was similar between montelukast and placebo-treated patients, without evidence of a relationship to dose. Montelukast was similarly well tolerated in other studies in which higher doses were administered. For example, montelukast was dosed 600 mg·day⁻¹ for 10¹/₃ days [29] and 200 mg for 6 weeks [15] without adverse events in excess of placebo treatment. These safety and efficacy data suggest that 10 mg of montelukast provides a maximal clinical response with a tolerability profile generally similar to placebo. Studies of longer duration will be needed to confirm the tolerability profile of montelukast.

In conclusion, once daily therapy with montelukast 10 and 50 mg are equally effective and are associated with significant improvement in parameters of asthma control compared with placebo. Ten and 50 mg once daily bedtime doses are generally more effective than the 2 mg dose, consistent with a complementary exercise challenge study [26].

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