

Montelukast, a Leukotriene Receptor Antagonist, in Combination With Loratadine, a Histamine Receptor Antagonist, in the Treatment of Chronic Asthma

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Background: Montelukast sodium, a potent, oral, specific leukotriene-receptor antagonist, has demonstrated clinical efficacy in the treatment of chronic asthma. Loratadine, a selective histamine type 1 (H_1)-receptor antagonist, has demonstrated antiallergic properties. Leukotriene-receptor antagonists given concomitantly with H_1 -receptor antagonists have been shown to have additive effects in the prevention of bronchospasm in antigen-challenge models.

Objective: To determine whether montelukast plus loratadine provides improved efficacy to montelukast alone in the treatment of chronic asthma.

Methods: The efficacy of montelukast alone vs montelukast-loratadine was studied in a 10-week, multicenter, randomized, double-blind, 2×2 crossover study. After a 2-week placebo run-in period, patients received montelukast sodium (10 mg) plus loratadine (20 mg), or montelukast sodium (10 mg) plus placebo once daily for 2 weeks. After a 2-week placebo washout period, patients were crossed over to receive 2 weeks of the other

active treatment regimen, followed by another 2-week placebo washout period.

Results: Montelukast given concomitantly with loratadine caused significant improvement in percentage of change from baseline in forced expiratory volume in 1 second (FEV_1) compared with montelukast alone (13.86% vs 9.72%; $P = .001$). The average additional effect of loratadine (least square mean difference in percentage of change from baseline in FEV_1) was 4.15% (95% confidence interval, 1.65%-6.65%). Key secondary end points (mean daily β -agonist use, daytime and nighttime symptom scores, morning and evening peak expiratory flow rate, and the Patient Global Evaluation) all showed significant improvement with montelukast-loratadine ($P < .05$).

Conclusion: Montelukast-loratadine significantly improved end points of asthma control during a 2-week treatment period.

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ASTHMA IS a significant public health concern, with a 5% to 7% prevalence in adults worldwide.¹ In the United States alone, asthma affects an estimated 14 to 15 million persons.²

Leukotrienes are important mediators of asthma, and are produced and released from inflammatory cells, including eosinophils and mast cells. They induce bronchoconstriction, mucous secretion, and increased vascular permeability.³⁻⁵ Studies using leukotriene-receptor antagonists and 5-lipoxygenase inhibitors have demonstrated improvement in asthma control in patients with chronic asthma.⁶⁻¹² Montelukast sodium (Singulair) is a potent, oral, specific leukotriene D_4 -receptor agonist (cysteinyl leukotriene [$CysLT_1$]-receptor antagonist) recently approved for the treatment of chronic asthma

in patients aged 6 years and older. In recent studies in adults, montelukast sodium (10 mg) administered once daily at bedtime demonstrated improvement in variables of asthma control, including forced expiratory volume in 1 second (FEV_1), daytime and nighttime symptom scores, and as-needed β -agonist use.^{8,9,12-14}

Histamine type 1 (H_1)-receptor antagonists have been used extensively in the treatment of allergic diseases such as rhinitis and urticaria, but conventionally have not been used in the treatment of asthma. Histamine acts as a bronchoconstrictor in patients with asthma. It is considered a major mediator in the early allergic reaction, and may play a role in the late-phase reaction.¹⁵ Elevated histamine levels have been found in the bronchoalveolar lavage fluid, plasma, and urine of patients with asthma and patients undergoing inhaled-antigen provocation.¹⁶⁻¹⁸ Nevertheless, studies us-

PATIENTS AND METHODS

STUDY DESIGN

This multicenter, double-blind, randomized, 2 × 2 cross-over study compared the clinical effect of oral montelukast sodium (10 mg once daily at bedtime) given concomitantly with loratadine (20 mg once daily at bedtime) with that of montelukast sodium (10 mg once daily at bedtime) given concomitantly with placebo (matching loratadine image) in patients aged 15 to 64 years with chronic asthma. The 10-week study involved 2 active-treatment periods. Patients were given placebos for both drugs and were not told that the treatment would be broken into specific periods. After a 2-week single-blind placebo run-in period (period 1), patients entered a 2-week double-blind active-treatment period (period 2). Patients then entered another 2-week single-blind placebo washout period (period 3), followed by the second 2-week double-blind active-treatment period (period 4), where patients crossed over to the other active-treatment regimen. The study concluded with a single-blind placebo washout period (period 5) (**Figure 1**).

The study was conducted at 19 study centers in the United States from July 23 through December 19, 1996. All patients, study sites, and the coordinating center (Merck & Co, Inc, Rahway, NJ) were unaware of treatment sequence. The patients' treatment sequences during the active-treatment periods were determined by random allocation according to a computer-generated schedule in blocks of 4. Randomization of patients to treatment sequence was stratified according to the presence or absence of history of seasonal allergies. For the purposes of stratification, *seasonal allergies* were defined as having a positive reaction to a skin test for an allergen prevalent during the months the study was conducted and a history of asthma, rhinitis, or conjunctivitis that is active during the season of the study or is exacerbated by one of the seasonal allergens to which the patient had the positive skin test reaction. All patients used short-acting inhaled β -agonists, as needed, to treat asthma exacerbations.

Written informed consent approved by the respective institutional review boards was obtained from all patients.

INCLUSION CRITERIA

Nonsmoking male and female outpatients aged 15 to 65 years with at least a 1-year history of intermittent or persistent asthma symptoms were enrolled. Patients needed to demonstrate an FEV₁ from 50% to 80% of the predicted

value and an increase in FEV₁ of 15% or greater, 20 to 30 minutes after inhalation of a β -agonist at least twice during the prestudy visit and placebo run-in period. Patients were also required to have a minimum biweekly daytime asthma symptom score of 64 and to have required, on average, at least 1 puff per day of albuterol during the 2-week run-in period. At the prestudy visit, patients received a peak flow meter (Mini Wright; Clement Clark, Columbus, Ohio) and a practice diary card. Patients were required to demonstrate competence with these instruments and the ability to perform reproducible spirometry to become eligible for the active-treatment period.

EXCLUSION CRITERIA

Study exclusion criteria included active acute or chronic pulmonary disorder, acute sinus disease that had not resolved within 1 week (active hay fever and allergic rhinitis symptoms were allowed), and upper respiratory tract infection within 3 weeks, emergency department treatment of asthma within 1 month, and hospitalization for asthma within 3 months before the prestudy visit. Patients who received theophylline, β -agonists (oral or long-acting), or anticholinergics within 1 week, cromolyn sodium or nedocromil within 2 weeks, corticosteroids within 1 month, cimetidine hydrochloride, warfarin, digoxin, ketoconazole, itraconazole, clarithromycin, erythromycin, troleandomycin, terfenadine, loratadine, cetirizine hydrochloride, chlorpheniramine maleate, clemastine fumarate, diphenhydramine, or hydroxyzine within 2 weeks, azithromycin within 1 month, or astemizole within 3 months before the prestudy visit also were excluded. Patients receiving immunotherapy for at least 6 months had to maintain therapy at a constant dosage during the study. Corticosteroid therapy, if initiated at least 2 weeks before the prestudy visit and maintained at a constant dosage throughout the study, was permitted. Patients taking any new asthma medications other than short-acting inhaled β -agonists were discontinued from the study when the new therapy was instituted.

EVALUATIONS

Spirometry (FEV₁) was performed at each clinic visit between 6 and 9 AM. Inhaled β -agonists and all caffeinated beverages were withheld for at least 6 and 8 hours, respectively, before each clinic visit. The largest FEV₁ from a set of 3 acceptable maneuvers at each clinic visit was recorded as the true value in accordance with American Thoracic Society standards of acceptability and reproducibility.³⁴ Airway reversibility (evaluated by measuring

ing first-generation H₁-receptor antagonists demonstrated minimal benefit in asthma.¹⁹ Recent studies of newer, more potent, and selective H₁-receptor antagonists have shown limited benefit in the treatment of asthma.²⁰⁻²²

Loratadine is a selective H₁-receptor antagonist devoid of significant sedative or anticholinergic properties. In addition to its activity as an H₁-receptor antagonist, loratadine has demonstrated other antiallergic properties. In vitro, loratadine inhibits leukotriene C₄ synthesis. In vivo, it has been shown to inhibit histamine release and to decrease eosinophil counts in blood

and sputum.^{16,23,24} Loratadine also protects against histamine-induced bronchoconstriction in patients with asthma.^{24,25} A dose response has been demonstrated, with loratadine given in 20-mg doses demonstrating greater protection than in 10-mg doses.²⁵ Clinical trials evaluating the efficacy of loratadine in the treatment of chronic asthma, however, have generated conflicting results.²⁶⁻²⁹

To date, no large clinical trials have evaluated the clinical efficacy of a CysLT₁ antagonist and an H₁-receptor antagonist given concomitantly to patients with

FEV₁ 20-30 minutes after administration of 2 puffs of albuterol sodium) was tested during at least 2 visits during the run-in period, at the conclusion of both active-treatment periods, and at the end of the final washout period. Spirometry measurements were collected with a standard spirometer (model PB 100/PB110; Puritan Bennett, Lenexa, Kan).

A validated daily diary card³⁵ was used to record daytime and nocturnal symptoms, as-needed β -agonist use, morning and evening peak expiratory flow rate (AM and PM PEFR, respectively), and asthma attacks (defined as an unscheduled visit to a physician, emergency department, or hospital for asthma or treatment with oral corticosteroids). Patients completed the diary card in the evening at bedtime (daytime symptoms) and in the morning on awakening (nighttime symptoms). The daytime symptom score was the average of patient responses to 4 questions, each rated from 0 (best) to 6 (worst).³⁵ Nocturnal symptoms were evaluated by a single question.³⁵

Patients measured PEFR using a peak flow meter (Mini Wright) and recorded values on the daily diary card on arising in the morning (AM PEFR) and immediately before the evening dose of study medication (PM PEFR). The best of at least 3 maneuvers was recorded on the diary card.

At the completion of each treatment period, physicians and patients independently evaluated the overall change in the patient's asthma compared with the beginning of the treatment period on a 7-point scale that ranged from 0 (very much better) to 6 (very much worse).

Safety was assessed by clinical evaluation (physical examination, vital signs, and electrocardiograms), adverse experience reporting, and laboratory tests (hematology, serum biochemistry, and urinalysis).

END POINTS

The prespecified primary efficacy end point was the mean percentage of change from baseline in FEV₁ averaged during the 2 weeks of the active-treatment period. Prespecified secondary end points were changes or percentage of changes from baseline averaged during the active-treatment period in daytime symptom scores, AM and PM PEFR, and total daily β -agonist use. Baseline values for these end points were defined as the average values during the placebo run-in period.

Other prespecified end points included peripheral blood eosinophil counts, patient's and physician's global asthma evaluations, and nocturnal awakenings in those patients with predefined baseline nocturnal awakenings (average of ≥ 2 nights with nocturnal awakenings per week).

STATISTICAL METHODS

Analysis

The evaluation of efficacy was based on a modified intention-to-treat analysis. To evaluate treatment efficacy in this crossover study design, measurements were needed from both active-treatment periods (periods 2 and 4). Therefore, all patients with baseline values and at least 1 measurement during each active-treatment period were included in the analysis, regardless of compliance with study medications. The only patients excluded in this modified intention-to-treat analysis were the 11 patients who discontinued treatment before obtaining efficacy measurements in period 4. For all end points, the average responses during periods 2 and 4 were compared between treatments using an analysis of variance (ANOVA) model with factors for sequence, stratum (seasonal allergy status), patient within stratum-by-sequence, treatment, and study period. The assumption of the primary ANOVA model was tested using the Shapiro-Wilk test for normality and the Pitman-Morgan test for homogeneity of variances.²⁴ The treatment-by-subgroup interactions were evaluated for the subgroups of stratum, sex, age group, race, history of allergic rhinitis, and history of exercise-induced asthma by including the subgroup and treatment-by-subgroup factor in the ANOVA model. The carryover effect was further assessed in the analysis, including data from periods 1 to 4. All statistical tests were 2-tailed, and $P \leq .05$ was considered statistically significant.

The onset of action of montelukast alone and montelukast-loratadine was evaluated by examining the daytime symptom scores, AM PEFR, and total daily β -agonist use collected during the first week of each active-treatment period.

The percentage of patients demonstrating a greater response to montelukast-loratadine than to montelukast alone was evaluated by determining the proportion of patients with better responses during the montelukast-loratadine period than during the montelukast alone period.

All randomized patients received active treatment and were included in the safety evaluations. The number and percentage of patients reporting adverse experiences and clinical laboratory abnormalities were summarized by treatment. The incidences of the adverse experiences were compared using the McNemar test.

Power and Sample Size

The study was designed with a sample size of 90 patients to have 80% power (2-sided test at $\alpha = .050$) to detect a 5.13 percentage point difference in FEV₁ percentage of change from baseline between treatments.

chronic asthma. Studies of antigen-induced contraction of bronchial smooth muscle in isolated, sensitized lung tissue have shown that treatment with a combination CysLT₁ antagonist and H₁-receptor antagonist was more beneficial than by either agent alone.³⁰⁻³² In addition, the concomitant administration of a CysLT₁ and an H₁-receptor antagonist was significantly more effective than either agent alone in inhibiting allergen-induced late-phase airway obstruction in patients with asthma.³³ These observations suggest that, in the management of asthma, concomitant administration of CysLT₁ and H₁-receptor

antagonists may provide additional benefits to CysLT₁-antagonist monotherapy. We evaluated the effects of combination therapy using the previously demonstrated effective dose of montelukast sodium (10 mg) combined with loratadine (20 mg). The dose of loratadine was chosen based on previous studies that demonstrated that this dose provided maximal protection against histamine-induced bronchospasm²⁵ and showed synergistic inhibition of allergen-induced asthmatic responses when combined with a CysLT₁ antagonist.³³ In this double-blind, placebo-controlled, crossover study, the effect of con-

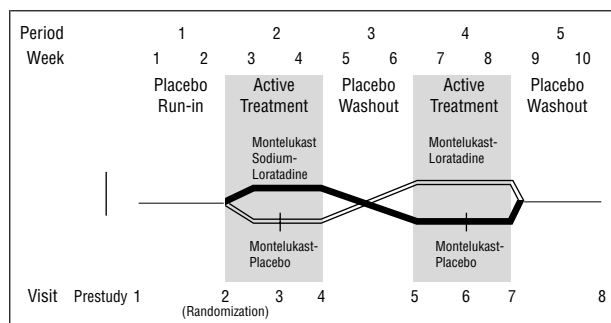


Figure 1. Study design. Two hundred twenty-nine patients underwent screening; 136 were randomized into the study; and 117 completed the study. Discontinuations secondary to adverse experiences occurred in 10 patients (7%). Three patients withdrew consent; 5 patients were discontinued due to protocol deviations; and 1 patient was unavailable for follow-up.

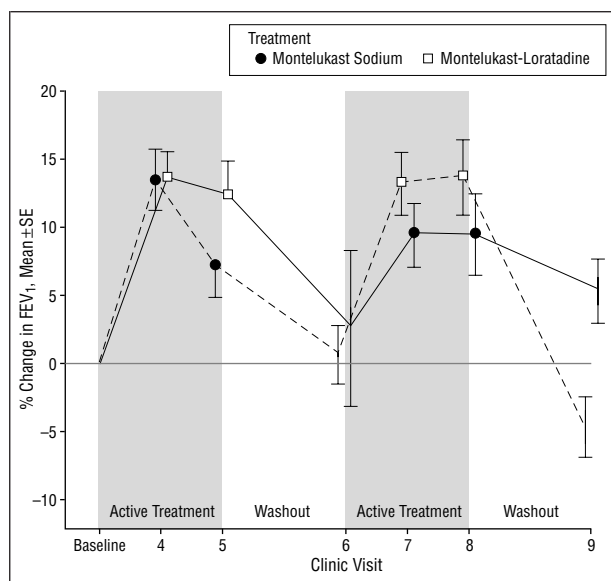


Figure 2. The effects of montelukast sodium given concomitantly with loratadine and montelukast alone on the primary end point (mean percentage of change from baseline in forced expiratory volume in 1 second [FEV₁]). The solid line represents patients who received montelukast-loratadine in period 2 and montelukast alone in period 4; the dashed line, patients who received montelukast alone in period 2 and montelukast-loratadine in period 4. Data points are shown for each clinic visit; however, only data points from active-treatment periods have symbols. Data points are shifted to maximize legibility.

Table 1. Analysis of Efficacy End Points Without Baseline Measurements*

End Point	Treatment Period†		P	Least Square Mean Difference (95% Confidence Interval)
	Montelukast Sodium Alone	Montelukast-Loratadine		
Patient Global Evaluation	1.75	1.46	.05	-0.29 (-0.58 to -0.00)
Physician Global Evaluation	1.95	1.73	.11	-0.22 (-0.49 to 0.05)

*Includes patients with data in both active-treatment periods.

†Values are least square means; a lower score implies greater improvement.

comitant therapy (montelukast-loratadine) was compared with montelukast monotherapy on variables of asthma control, including measurements of airway

obstruction and patient-reported end points, as well as safety.

RESULTS

PATIENTS

Two hundred twenty-nine patients underwent screening for the study. The most common reason for exclusion was failure to meet the spirometry criteria. One hundred thirty-six patients entered the first active, double-blind treatment period, and 117 (86%) patients completed the study. Mean age of patients was 34 years (range, 15-64 years); mean duration of asthma, 18 years (range, 1-56 years). Mean ($\pm$ SD) percentage of predicted FEV₁ was 67.0% $\pm$ 9.9%. Other baseline characteristics are shown in the following tabulation:

Demographics	No. (%) of Patients
Sex	
Male	64 (47.1)
Female	72 (52.9)
History of exercise-induced symptoms	117 (86.0)
History of allergic rhinitis	130 (95.6)
Seasonal allergy status positive	99 (72.8)

Nineteen patients (13.7%) were discontinued from the study because of clinical adverse experiences (n=10 [7%]), withdrawn consent (n=3 [2%]), deviation from the protocol (n=5 [4%]), and unavailability for follow-up (n=1 [0.7%]).

One hundred twenty-five patients (91.9%) underwent evaluation in the modified intention-to-treat analysis. Eleven patients were excluded from this analysis because they did not have any FEV₁ measurements during period 4, the second active-treatment period. Of the 11 patients who discontinued treatment, 7 patients discontinued due to adverse experiences (including 4 asthma exacerbations, 3 of which occurred during the placebo washout period in between active-treatment periods); 2 patients withdrew consent from the study; 1 patient was unavailable for follow-up; and 1 patient was discontinued due to a protocol deviation (error in study drug medication, ie, period 3 drug was given during period 2).

EFFICACY

Montelukast-loratadine, compared with montelukast alone, caused significant ($P=.001$) improvement in the primary end point, FEV₁ percentage of change from baseline. Averaged during the 2-week treatment period, the least square (LS) mean percentage of change from baseline in FEV₁ was 13.86% for montelukast-loratadine and 9.72% for montelukast alone, with a difference of 4.15% and a 95% confidence interval (CI) for the difference of 1.65% to 6.65% (**Figure 2** and **Table 1**). Sixty-five percent of the patients showed a greater response in FEV₁ while receiving montelukast-loratadine than while receiving montelukast alone. There was no apparent relation between response to loratadine; all patients, regardless of their response to montelukast alone, had similar potential for benefiting from the addition of loratadine. In ad-

Table 2. Analysis of Efficacy End Points With Baseline Measurements*

End Point	Baseline, Mean $\pm$ SD All Patients	Change From Baseline During Treatment†			
		Least Square Means		P	Least Square Mean Difference (95% CI)‡
		Montelukast Sodium Alone	Montelukast- Loratadine		
FEV ₁ , L‡	2.48 $\pm$ 0.60	9.72	13.86	.001	4.15 (1.65 to 6.65)
Predicted after β -agonist therapy, FEV ₁ ‡	84.94 $\pm$ 11.37	0.57	3.12	<.001	2.55 (1.12 to 3.99)
Daily β -agonist use, No. of puffs‡	5.07 $\pm$ 3.05	-27.41	-34.56	.02	-7.15 (-13.34 to -0.96)
Daytime symptoms§	2.58 $\pm$ 0.81	-0.48	-0.70	<.001	-0.22 (-0.34 to -0.09)
AM PEFR, L/min	394.53 $\pm$ 89.66	15.08	23.46	.002	8.38 (3.22 to 13.54)
PM PEFR, L/min	418.83 $\pm$ 89.64	15.27	21.53	.008	6.26 (1.64 to 10.88)
Nocturnal awakenings, nights/week	5.65 $\pm$ 1.56	-1.76	-2.22	.04	-0.46 (-0.91 to -0.01)
Peripheral eosinophil count, $\times 10^9/L$	0.27 $\pm$ 0.26	-0.04	-0.02	.29	0.02 (-0.02 to 0.05)

*Includes patients with data in both active treatment periods. FEV₁ indicates forced expiratory volume in 1 second; AM and PM PEFR, morning and nighttime peak expiratory flow rate; and CI, confidence interval.

†Mean of Montelukast-Loratadine minus mean of montelukast.

‡Prespecified analysis was percentage of change from baseline.

§Measured on a scale of 0 (best) to 6 (worst).

||Includes patients with baseline nocturnal asthma symptoms only (n=88).

dition, montelukast-loratadine resulted in significantly higher ($P<.001$) increases in FEV₁ percentage predicted after β -agonist treatment than montelukast alone (**Table 2**). Furthermore, the effect of montelukast-loratadine and montelukast alone on FEV₁ was persistent, with no loss of effect, during the 2-week treatment period (Figure 2). The study period and carryover effect were not statistically significant ($P>.99$ and $P=.33$, respectively).

Montelukast-loratadine, compared with montelukast alone, caused significant improvements in all secondary end points, ie, the daytime symptom score (**Figure 3** and Table 2), AM and PM PEFR (Table 2), and β -agonist use (Table 2). Averaged during the 2-week treatment period, the LS means for the change from baseline in the daytime symptom score were -0.70 for montelukast and loratadine and -0.48 for montelukast alone. The LS mean for the difference between the treatment effects was -0.22 ($P<.001$), with a 95% CI of -0.34 to -0.09.

In the prespecified group of 88 patients (64.7%) with nocturnal awakenings on at least 2 nights per week during the placebo run-in period, the number of nocturnal awakenings with asthma were significantly decreased during treatment with montelukast-loratadine, compared with montelukast alone ($P=.04$) (Table 2).

The addition of loratadine to montelukast treatment demonstrated no improvement in a single end point, change in eosinophil count from prerandomization baseline. Montelukast-loratadine and montelukast alone showed similar decreases in eosinophil counts from prerandomization baseline (Table 2).

The Patient Global Evaluation was significantly improved with montelukast-loratadine compared with montelukast alone (**Table 3**). Montelukast-loratadine caused a greater, but not statistically significant, improvement in the Physician Global Evaluation over montelukast alone (Table 1).

The onset of action of montelukast was analyzed using predefined patient-reported diary card variables, including daily symptom scores, β -agonist use, and PEFR measurements. Montelukast and montelukast-loratadine

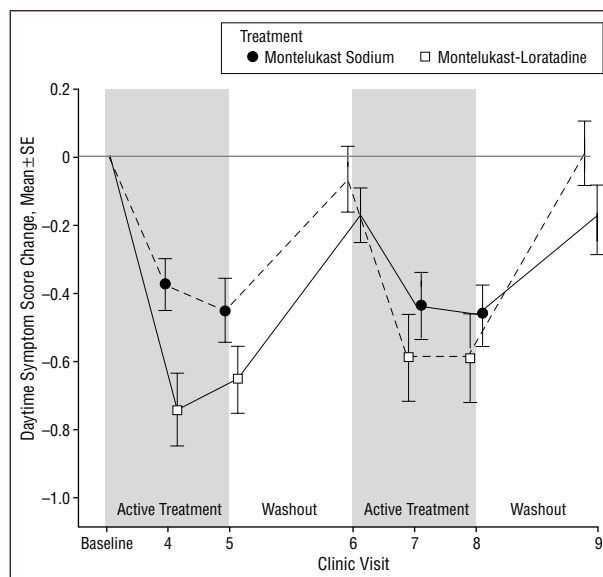


Figure 3. The effects of montelukast sodium given concomitantly with loratadine and montelukast alone on daytime asthma symptoms recorded on a daily diary at home (scale, 0-6). The solid line represents patients who received montelukast-loratadine in period 2 and montelukast alone in period 4; the dashed line, patients who received montelukast alone in period 2 and montelukast-loratadine in period 4. Data points are shown for each clinic visit; however, only data points from active-treatment periods have symbols. Data points are shifted to maximize legibility.

had rapid (within 1 day of dosing) onsets of action (**Figure 4**).

Notably, the effects of montelukast-loratadine and montelukast on FEV₁, total daily β -agonist use, PEFR, and daytime symptoms were consistent across sex, race, age group, history of allergic rhinitis, seasonal allergy status, and history of exercise-induced asthma. No subgroup interaction was found.

SAFETY

Table 3 summarizes the most common clinical adverse experiences reported after randomization. Adverse ex-

Table 3. Incidence of the Most Common Adverse Experiences*

	No. (%) of Patients		P
	Montelukast Sodium-Loratadine (n=130)	Montelukast Alone (n=132)	
Patients with >1 adverse experiences	53 (41)	64 (48)	.13
Headache	10 (8)	15 (11)	.28
Upper respiratory tract infection	8 (6)	14 (11)	.16
Asthma exacerbation	3 (2)	7 (5)	.21
Pharyngitis	3 (2)	5 (4)	.48
Dyspepsia	4 (3)	2 (2)	.41
Urinary tract infection	1 (0.8)	4 (3)	.18

*Includes adverse events occurring in more than 2% of patients receiving either treatment.

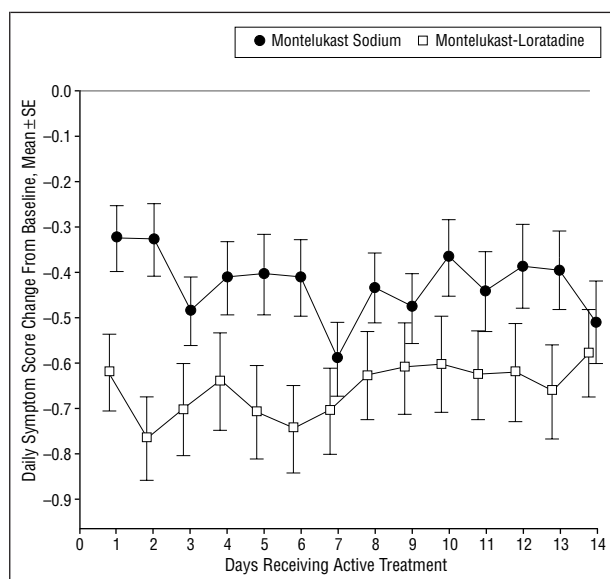


Figure 4. Onset of action of montelukast sodium alone and montelukast given concomitantly with loratadine. The effect of montelukast-loratadine and montelukast alone on change from baseline in the daytime symptom score during the 2-week active-treatment period, based on pooled treatment sequences.

periences were assigned to the treatment during which they began. Adverse experiences beginning during the placebo washout period were assigned to the previously administered treatment. The most common adverse experiences were headache, upper respiratory tract infection, and asthma exacerbations. Overall, montelukast-loratadine and montelukast alone treatment groups demonstrated no significant differences in the frequency of any adverse experiences (Table 3).

Ten patients discontinued from the study due to an adverse experience and were evenly distributed between the treatments (5 receiving montelukast-loratadine and 5 receiving montelukast alone). Six of the discontinuations due to adverse experiences occurred during the placebo washout periods (2 after montelukast-loratadine treatment and 4 after montelukast alone

treatment). Six discontinuations were due to asthma exacerbations requiring steroid administration (3 receiving montelukast-loratadine and 3 receiving montelukast alone); 4 of these occurred during the washout periods. The remaining 4 adverse experiences resulting in discontinuation included constipation and bronchitis (montelukast-loratadine treatment) and dry nose and sinusitis (montelukast alone treatment).

Fewer asthma exacerbations were reported during montelukast-loratadine treatment compared with montelukast alone treatment. There were 10 reported asthma exacerbations (3 during montelukast-loratadine treatment and 7 during montelukast alone treatment) (Table 3).

Somnolence, a side effect usually associated with the use of the first-generation H₁-receptor antagonists, was only reported in 2 patients receiving montelukast-loratadine. Adverse experiences of somnolence were transient and self-limited.

Laboratory adverse experiences were generally infrequent during both treatments and did not cause discontinuations. One patient (0.8%) receiving montelukast-loratadine and 4 patients (3%) receiving montelukast alone had laboratory abnormalities during treatment, most of which were transient and self-limited. The frequency of patients with elevated serum transaminase levels was similar between treatments. In addition, montelukast-loratadine did not cause any significant changes in the electrocardiogram QT intervals as assessed by measuring QTc values.

COMMENT

To our knowledge, this is the first study to demonstrate the therapeutic benefit of montelukast sodium (10 mg/d), a CysLT₁-receptor antagonist, given concomitantly with loratadine (20 mg/d), an H₁-receptor antagonist, in adults with chronic asthma. In this short-term pilot study, montelukast alone and montelukast-loratadine administered once daily at bedtime showed improvements in objective and subjective measurements of asthma control. The magnitude of the treatment effects demonstrated after 2 weeks of montelukast alone in this study is similar to that seen in previous placebo-controlled studies of longer duration.^{8,9,12-14} Montelukast-loratadine demonstrated significant improvements over montelukast alone in FEV₁ (primary end point), AM and PM PEF, daily β -agonist use, daytime symptom scores (secondary end points), nocturnal asthma symptom score, nocturnal awakenings, and the Patient Global Evaluation. Montelukast-loratadine showed a greater but not statistically significant improvement over montelukast alone in the Physician Global Evaluation. Since the global evaluations measured degree of improvement relative to the beginning of the treatment period, the data from period 4 might have been confounded with the residual effect of treatment administered in period 2, although the carryover effect was not significant statistically. A long-term, parallel-group, placebo-controlled trial is ongoing to define the long-term efficacy of combination montelukast-loratadine therapy for the treatment of chronic asthma.

The onset of action of montelukast-loratadine and montelukast alone was rapid. Maximal treatment effects occurred within 1 day after the first dose as assessed by diary card variables, ie, daytime symptoms, total daily β -agonist use, and patient-reported AM PEFR. These results compare favorably with other therapies that have a longer onset of action such as inhaled corticosteroids.³⁶ Montelukast-loratadine and montelukast alone not only demonstrated a rapid onset of action but their treatment effects were maintained over time. There was no evidence of tachyphylaxis in this or previous adult and pediatric long-term efficacy studies with montelukast.^{8,9,11}

A comparison of montelukast-loratadine and montelukast alone did not show any difference in effects in any subgroup evaluated (age, sex, race, history of allergic rhinitis, history of exercise-induced bronchoconstriction, or seasonal allergy status). A caveat of these analyses is that our study was not powered to detect treatment-by-subgroup interaction. However, our findings suggest that a broad range of patients with asthma may benefit from montelukast and montelukast given concomitantly with loratadine. Previous reports suggest that an improvement in allergic rhinitis can also improve asthma control.³⁷ Although rhinitis symptoms were not specifically measured, our results imply that loratadine has broader effects on asthma control. The additive efficacy of montelukast given concomitantly with loratadine was seen in patients with and without a history of active seasonal allergies, including rhinitis, suggesting that patients without active seasonal allergic rhinitis also benefited from combination therapy. The demonstrated efficacy of concomitant administration of an H_1 -receptor and CysLT₁ antagonist in the treatment of chronic asthma along with the finding that a combined regimen was significantly more effective than either agent alone in inhibiting allergen-induced early- and late-phase airway obstruction in patients with asthma³³ implies that histamine is an important mediator in allergen-induced bronchoconstriction and chronic asthma. Antihistamines have previously been shown to result in bronchodilation³⁸⁻⁴⁰ with effects additive to β -agonists.⁴¹ Demonstration of higher increases in FEV₁ percentages predicted after β -agonist administration in patients receiving montelukast-loratadine than observed in patients receiving montelukast alone may imply that H_1 -receptor and CysLT₁ antagonists have complementary airway dilatory effects.

The eosinophil is an asthma-inflammatory effector cell that plays a critical role in the pathogenesis of asthma. This cell and its mediators are found in increased quantities in bronchial tissue and are correlated with asthma severity.⁴² In our study, treatment with montelukast alone resulted in a decrease in peripheral blood eosinophil counts. The magnitude of the decrease was similar to that observed in previous studies after 2 weeks of treatment with montelukast, suggesting that montelukast may have significant effects on variables of asthmatic inflammation.^{8,12} Unlike β -agonists, inhaled corticosteroids have been shown to affect peripheral blood eosinophil counts similarly in patients with asthma.⁴³ In a previous

study, the effect of montelukast was additive to that of inhaled beclomethasone dipropionate in decreasing peripheral blood eosinophil count.⁴⁴ No additive effect was detected for montelukast-loratadine for this end point, despite previous evidence that loratadine given as a single agent can decrease peripheral blood eosinophil counts.²⁵

Montelukast-loratadine and montelukast alone demonstrated similar safety profiles. Overall, montelukast-loratadine and montelukast alone were generally well tolerated. Although the loratadine dose used in this study is twice that prescribed for allergic rhinitis, the incidence of somnolence was extremely low. The low incidence of somnolence may be due to the fact that dosing with both drugs occurred at bedtime. Laboratory adverse experiences were infrequent, mild, transient, and similar in frequency in both treatments. Future studies are needed to determine the long-term safety profile of the concomitant administration of montelukast-loratadine.

CONCLUSIONS

Our study demonstrated that montelukast sodium (10 mg) given concomitantly with loratadine (20 mg) provides additional benefit compared with montelukast alone in the treatment of patients with asthma. Montelukast alone and with loratadine was well tolerated. The results are consistent with and confirm the finding that montelukast is an effective treatment for asthma. Overall, our results suggest that montelukast-loratadine would be a well-tolerated and effective therapeutic regimen for patients with asthma that is not completely controlled with montelukast. A recent study demonstrated the efficacy of concomitant therapy with montelukast and loratadine in the treatment of allergic rhinitis,⁴⁵ implying that therapy with both agents may provide a new strategy for the treatment of upper and lower airway disease. Further studies will be needed, including a study with loratadine, 10 mg/d (the marketed dose), to confirm that the additional efficacy seen with the concomitant administration of montelukast with loratadine in this study is maintained over time and has a positive impact on asthma outcomes such as the number of asthma exacerbations and the number of asthma control days.

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