
Efficacy of loratadine-montelukast on nasal congestion in patients with seasonal allergic rhinitis in an environmental exposure unit

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Background: Nasal congestion is considered to be one of the most bothersome symptoms of allergic rhinitis (AR) and often the most difficult to treat. Oral therapies providing safe, effective, and reliable relief of AR symptoms, including nasal congestion, are limited.

Objective: To evaluate the efficacy of a single dose of loratadine-montelukast (10 mg/10 mg) vs placebo and phenylephrine (10 mg) in relieving nasal congestion over 6 hours after ragweed pollen exposure in the environmental exposure unit at the Kingston General Hospital.

Methods: After a screening visit and up to 6 priming visits, patients who met minimum symptom requirements during ragweed pollen exposure were randomized to receive loratadine-montelukast, phenylephrine, or placebo. Patients evaluated nasal congestion and other symptoms of AR and measured peak nasal inspiratory flow before dosing and at 20-minute intervals during the subsequent 8 hours of pollen exposure.

Results: During the first 6 hours after treatment (primary end point), loratadine-montelukast treatment resulted in greater improvement in the mean nasal congestion score vs placebo ($P = .007$) and phenylephrine ($P < .001$). Loratadine-montelukast was more effective than placebo ($P \leq .02$) and phenylephrine ($P \leq .002$) in relieving total symptoms, nasal symptoms, and nonnasal symptoms and in improving peak nasal inspiratory flow. There were no statistically significant differences between phenylephrine and placebo for any measures. Fewer patients in the loratadine-montelukast group (3.9%) reported adverse events than in the phenylephrine (7.9%) and placebo (7.1%) groups; most adverse events were mild or moderate.

Conclusions: Loratadine-montelukast was more effective than placebo and phenylephrine in relieving nasal congestion and other nasal and nonnasal symptoms resulting from ragweed pollen exposure. There was no statistically significant difference between phenylephrine and placebo.

Ann Allergy Asthma Immunol. 2009;102:328–338.

INTRODUCTION

Numerous surveys and clinical studies indicate that nasal congestion is one of the most bothersome symptoms of seasonal allergic rhinitis (AR).^{1–4} Nasal congestion is also specifically linked to disturbances in sleep, decreased work productivity, and emotional disturbances in patients with AR.^{1,4–9} The complex pathogenesis of nasal congestion includes overlapping inflammatory pathways and mediators of early- and late-phase allergic reactions, particularly cysteinyl leukotrienes.^{8,10–12}

Because of the importance of nasal congestion in AR, its relief is a desired objective of AR treatments. Single-agent

treatment with antihistamines, the current mainstay of AR therapy, results in inconsistent, limited relief of AR-associated nasal congestion,^{13,14} which is likely attributable to the involvement of multiple mediators, including histamine and leukotrienes in the allergic response and, specifically, nasal congestion.^{13,15,16}

Although the traditional outpatient trial is the most commonly used model for examining AR medications, these medications are associated with several limitations.¹⁷ Properly conducted allergen challenge chamber (ACC) studies control variability in allergen concentrations and ensure that all study participants are exposed to the same levels and type of allergen.¹⁷ The environmental exposure unit (EEU) at the Kingston General Hospital circulates fresh, filtered outdoor air throughout a specially designed room with accurately monitored concentrations of pollen dispersed into the airflow and distributed by fans throughout the allergen exposure sessions.^{17,18} The EEU can accommodate up to 160 study participants at one time and allows for considerable objective and subjective data to be collected under controlled conditions, including onset and duration of action, which are recommended by the Allergic Rhinitis and its Impact on Asthma/European Academy of

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Disclosures: Authors have nothing to disclose.

Funding Sources: Funding for this study was provided by Schering-Plough/Merck Pharmaceuticals.

ClinicalTrials.gov number, NCT00423995.

Received for publication July 31, 2008; Received in revised form December 23, 2008; Accepted for publication December 27, 2008.

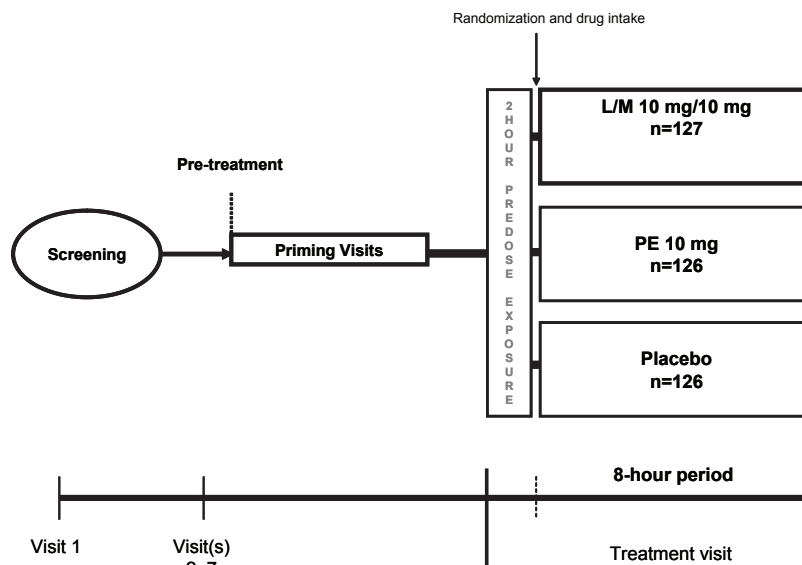


Figure 1. Study design. L/Mg loratadine-montelukast; PE, phenylephrine

Allergy and Clinical Immunology workshop as important properties of antiallergic medications.^{17,18}

Loratadine-montelukast is a fixed-dose single tablet containing loratadine (10 mg), a nonsedating, selective peripheral antagonist of the histamine type 1 receptor, and montelukast (10 mg), a selective antagonist of the cysteinyl leukotriene receptor. The primary objective of this study was to evaluate and compare the efficacy of loratadine-montelukast with that of placebo in relieving nasal congestion in patients with AR exposed to ragweed pollen in the EEU. This study also sought to estimate the onset of action of loratadine-montelukast based on change in total symptom score (TSS) from baseline and to evaluate the efficacy of phenylephrine (a nasal decongestant) on nasal congestion relative to placebo.

METHODS

Study Design

This was a phase 3, single-dose, double-blind, double-dummy, randomized, placebo-controlled, 3-arm, parallel-group, single-center study of loratadine-montelukast and phenylephrine in patients with seasonal AR exposed to ragweed pollen in the EEU (Fig 1). Patients completed a screening visit, up to 6 priming visits, and 1 treatment visit. During the priming visit(s), patients were exposed to ragweed pollen for up to 3 hours to stimulate symptoms. They completed evaluations of 4 nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) and 3 nonnasal symptoms (itching/burning eyes, tearing/watery eyes, and itching of ears/palate) using a severity scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) at 30-minute intervals. To qualify to attend the treatment visit, patients were required to meet minimum symptom scores (≥ 2 for nasal congestion, ≥ 7 for combined nasal

symptoms, ≥ 3 for combined nonnasal symptoms, and ≥ 10 for total symptoms) at the 90-minute time point of at least 1 priming visit.

At the treatment visit, patients were initially exposed to ragweed pollen in the EEU to produce adequate symptoms. Patients who met the minimum symptom scores after exposure to ragweed pollen at 90 minutes were randomized to receive a single dose of loratadine-montelukast, phenylephrine, or placebo at 120 minutes. Randomized patients then evaluated their AR symptoms and performed peak nasal inspiratory flow (PNIF) measurements at 20-minute intervals after treatment for 8 hours.

Before study initiation, the protocol and the written informed consent form were reviewed and approved by the Health Sciences and Affiliated Teaching Hospital Research Ethics Board of Queen's University; written informed consent was obtained from all the patients before any study-related procedure.

Patients

Eligible patients were men or women 18 years and older with a history of seasonal AR due to ragweed for at least 2 consecutive ragweed seasons. Patients were required to have a positive skin prick test reaction (wheal diameter ≥ 3 mm larger than diluent control within 15 to 30 minutes) to ragweed at screening or in the previous 12 months. Women of childbearing potential had to have a negative urine pregnancy test result at screening and before dosing at the treatment visit and to be using a medically accepted method of birth control throughout the study. All the patients were in good health and were free of any clinically significant disease that would have interfered with the study schedule or procedures or compromised the patient's safety.

Table 1. Demographic and Baseline Characteristics of the Treatment Groups

Characteristics	Treatment group		
	L/M (n = 127)	PE (n = 126)	Placebo (n = 126)
Sex, No. (%)			
F	78 (61)	67 (53)	75 (60)
M	49 (39)	59 (47)	51 (40)
Race, No. (%)			
White	127 (100)	120 (95)	119 (94)
Nonwhite	0	6 (5)	7 (6)
Asthma history, No. (%)			
No	113 (89)	104 (83)	106 (84)
Yes	14 (11)	22 (17)	20 (16)
Perennial AR history, No. (%)			
No	77 (61)	65 (52)	60 (48)
Yes	50 (39)	61 (48)	66 (52)
Age, mean (SD), y	33.6 (11.3)	32.8 (10.9)	33.4 (10.6)
Weight, mean (SD), kg	78.34 (18.31)	77.59 (18.85)	81.32 (20.03)
Height, mean (SD), cm	169.83 (8.67)	170.26 (9.60)	169.38 (9.16)
TSS, mean (SD)	17.49 (2.30)	17.19 (2.36)	17.30 (2.37)
Nasal congestion score, mean (SD)	2.81 (0.41)	2.75 (0.44)	2.83 (0.39)
PNIF, mean (SD), L/min	67.36 (30.89)	68.69 (34.10)	64.76 (24.34)
TNSS, mean (SD)	10.36 (1.43)	10.38 (1.50)	10.47 (1.40)
TNNSS, mean (SD)	7.13 (1.48)	6.81 (1.60)	6.83 (1.74)

Abbreviations: AR, allergic rhinitis; L/M, loratadine-montelukast (10 mg/10 mg); PE, phenylephrine (10 mg); PNIF, peak nasal inspiratory flow; TNNSS, total nonnasal symptom score; TNSS, total nasal symptom score; TSS, total symptom score.

Potential patients were excluded if they were pregnant, intended to become pregnant, or were lactating. Additional reasons for exclusion were any situation or any condition that, in the opinion of the investigator, might have interfered with optimal participation in the study; use of any investigational drugs within 30 days of screening and for the duration of the study; current participation in any other clinical trial; dependence on nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal corticosteroids; nasal structural abnormalities resulting in greater than 50% obstruction of nasal airflow; previous enrollment in this study; history of rhinitis medicamentosa or anaphylaxis or severe reactivity to skin testing; known potential for hypersensitivity, allergy, or idiosyncratic reaction to the study drugs or excipients; narrow-angle glaucoma, increased intraocular pressure, urinary retention, hypertension, severe coronary artery disease, ischemic heart disease, diabetes mellitus, hyperthyroidism, renal impairment, or prostatic hypertrophy; current treatment with monoamine oxidase inhibitors; an upper or lower respiratory tract infection within 28 days of priming and thereafter; positive test results for human immunodeficiency, hepatitis B, or hepatitis C virus or tuberculosis; or asthma that required more than occasional (≤ 3 uses per week) use of an inhaled short-acting β_2 -agonist.

Study Medications

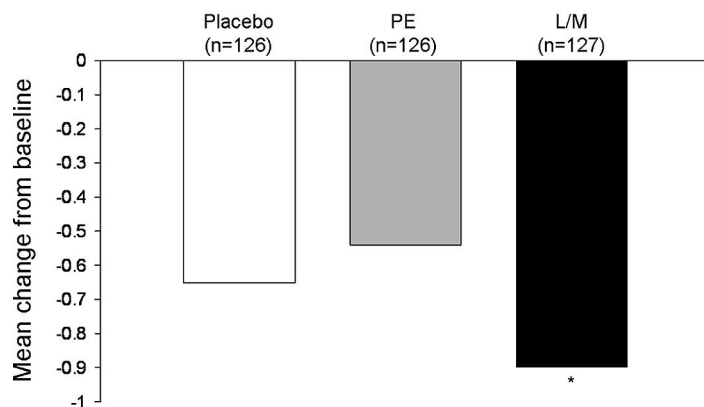
Eligible patients were randomized to receive a single dose of 1 of 3 treatments: loratadine-montelukast, 10 mg/10 mg; phenylephrine, 10 mg; or placebo. Loratadine-montelukast was administered as an immediate-release, fixed-dose single

pill. Phenylephrine (10 mg) was administered as an immediate-release, quick-dissolving strip (Sudafed PE Quick Dissolve Strips; Myderm Medical Supply, Norristown, Pennsylvania) that was dissolved in 50 mL of sugar-free Ora-Sweet (Paddock Laboratories Inc, Minneapolis, Minnesota). The placebo for loratadine-montelukast was a matching placebo tablet, and the placebo for phenylephrine was Ora-Sweet with red coloring to match the appearance of the active drug. Each patient received a tablet and a liquid (double-dummy) as follows: 1 loratadine-montelukast tablet and 50 mL of Ora-Sweet, or 1 placebo tablet and 50 mL of phenylephrine in Ora-Sweet, or 1 placebo tablet and 50 mL of Ora-Sweet. The randomization was performed by a third-party packager and was maintained by the study sponsor so that neither the investigator nor the study participants knew which treatment was being administered.

End Points

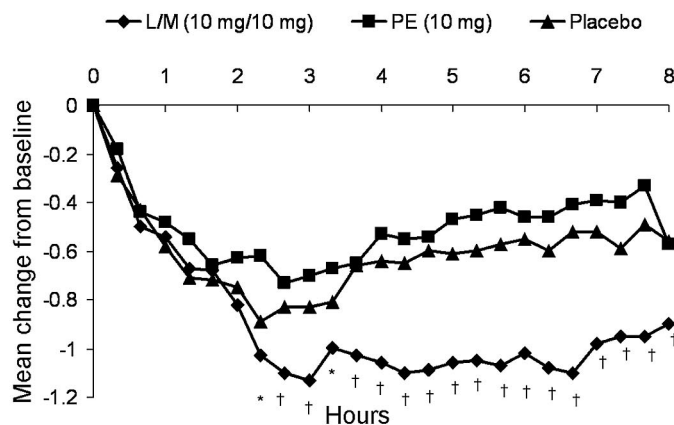
Efficacy determinants (4 nasal symptoms, 3 nonnasal symptoms, and PNIF assessments) were collected every 20 minutes after treatment for 8 hours. The primary efficacy variable was nasal congestion, expressed as a mean change from baseline averaged across all time points during the first 6 hours of the evaluation period. Baseline was defined as the PNIF rate and symptom scores as recorded by patients immediately before dosing. The primary comparison for this variable was loratadine-montelukast vs placebo. Secondary end points included onset of action (defined as the first time point at which a consistent statistically significant reduction was achieved relative to

A.



* $P=0.007$ vs placebo, $P<0.001$ vs PE.
0 = none; 1 = mild; 2 = moderate; 3 = severe.

B.



* $P<0.01$ L/M vs PE. † $P<0.01$ L/M vs PE and placebo.

Figure 2. Mean change from baseline during the first 6 hours after treatment (A) and across time (B) in nasal congestion scores for the loratadine-montelukast (L/M), phenylephrine (PE), and placebo groups.

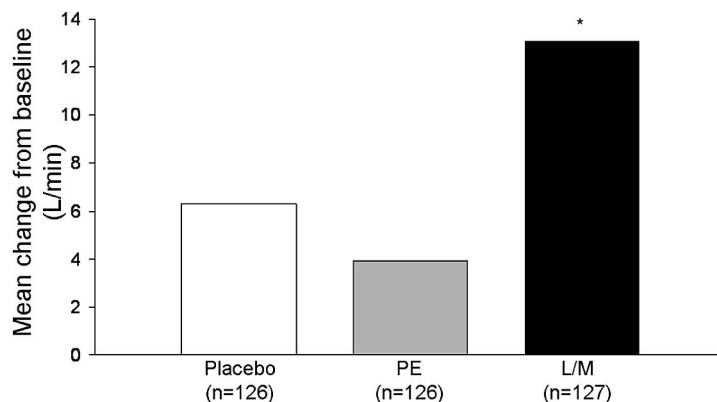
baseline symptom score) for loratadine-montelukast vs placebo; changes from baseline in nasal congestion, TSS, total nasal symptom score (TNSS), total nonnasal symptom score (TNNSS), and each individual symptom score; and the mean change from baseline in PNIF. Additional secondary end points included the estimate of the effect of phenylephrine vs placebo on nasal congestion during the first 6 hours of the evaluation period and the comparison of PE vs loratadine-montelukast for all end points. These end points were analyzed at each posttreatment time point, the mean across all time points of the first 6-hour period, and across all time points of the entire

8-hour period. Safety was evaluated by recording adverse events (AEs) and measuring vital signs.

Statistical Analysis

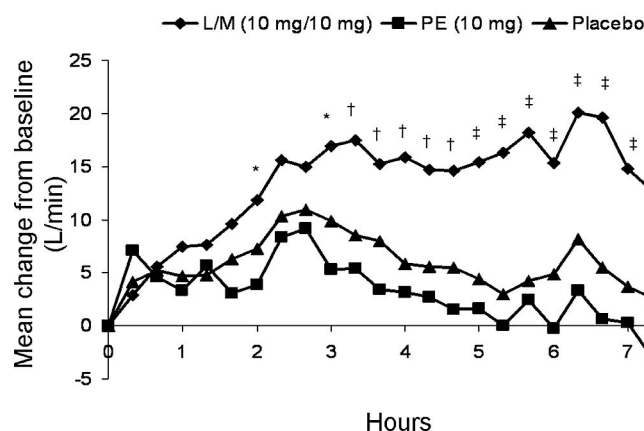
The primary comparison for nasal congestion (loratadine-montelukast vs placebo) was performed using a 1-way analysis of variance model (2-sided $\alpha = .05$). Estimates of the relative efficacy of loratadine-montelukast and phenylephrine vs placebo were derived from the least squares means from the analysis model, and 95% confidence intervals around this difference were constructed. For secondary efficacy vari-

A.



* $P=0.024$ vs placebo, $P=0.002$ vs PE.

B.



* $P<0.05$ L/M vs PE. † $P\leq 0.05$ L/M vs PE and placebo. ‡ $P<0.01$ L/M vs PE and placebo.

Figure 3. Mean change from baseline during the first 6 hours after treatment (A) and across time (B) in peak nasal inspiratory flow for the loratadine-montelukast (L/M), phenylephrine (PE), and placebo groups.

ables, pairwise comparisons were made using linear contrasts of the treatment means obtained from the same 1-way analysis of variance. The onset of action was defined as the first time point during the 4-hour postdosing period at which a reduction in TSS relative to baseline reached and maintained significance compared with placebo ($P \leq .05$). The number of patients reporting any AEs, the occurrence of specific AEs, and discontinuations due to AEs were tabulated.

The statistical plan for this study required that approximately 360 patients (120 per treatment group) be randomized in a 1:1:1 ratio to receive loratadine-montelukast, phenyleph-

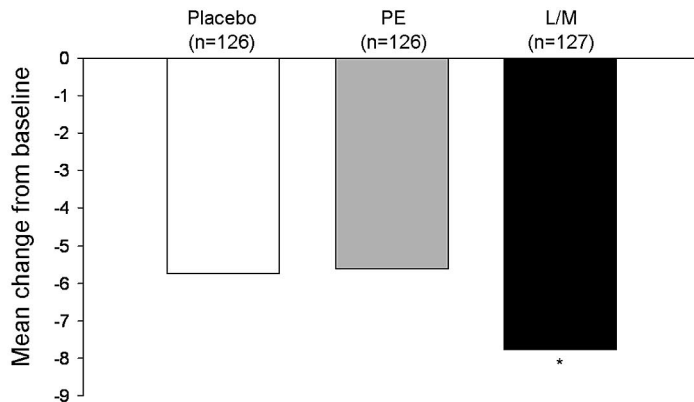
rine, or placebo to ensure 90% power to detect a difference of at least 0.3 point in change from baseline in nasal congestion score between loratadine-montelukast and placebo with an $\alpha = .05$, 2-sided test, assuming a pooled SD of 0.70.

RESULTS

Patients

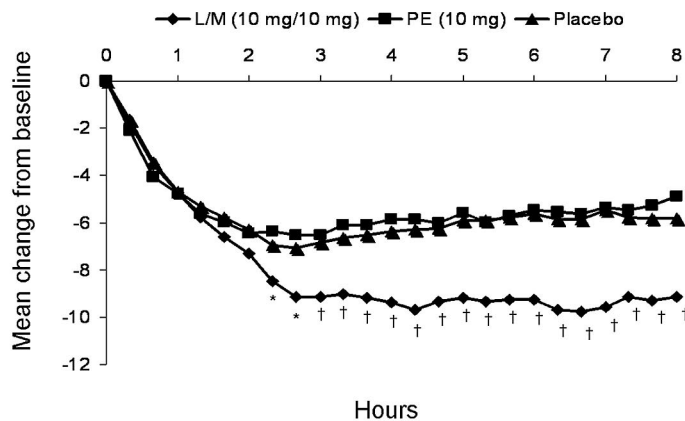
A total of 379 patients (159 men and 220 women aged 18–72 years) were randomized to treatment (127 in the loratadine-montelukast group and 126 in each of the phenylephrine and

A.



* $P < 0.001$ vs placebo and PE.
0 = none; 1 = mild; 2 = moderate; 3 = severe.

B.



* $P < 0.01$ L/M vs PE and placebo. † $P < 0.001$ L/M vs PE and placebo.

Figure 4. Mean change from baseline during the first 6 hours after treatment (A) and across time (B) in total symptom scores for the loratadine-montelukast (L/M), phenylephrine (PE), and placebo groups.

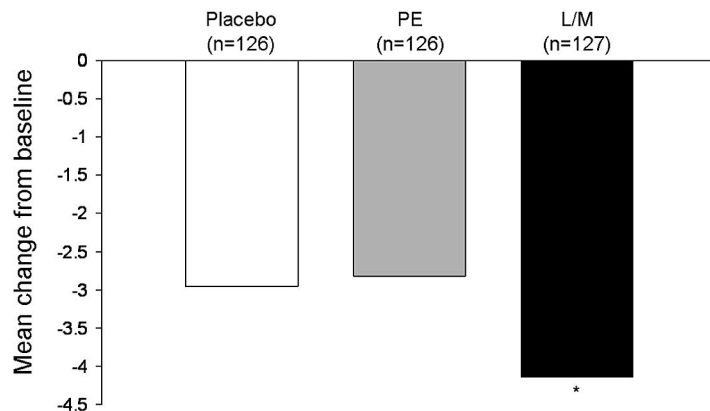
placebo groups). All the patients completed the study, and demographic and clinical characteristics were similar across treatment groups, with no statistically significant differences noted for any outcome measures (Table 1).

Efficacy

During the first 6 hours after treatment, loratadine-montelukast had a greater impact than did placebo on the primary efficacy variable, the mean change from baseline in nasal congestion score ($P = .007$) (Fig 2A). Phenylephrine was not different from placebo ($P = .23$). Compared with phenylephrine, loratadine-montelukast also had a greater effect on the mean change from baseline nasal congestion score during the

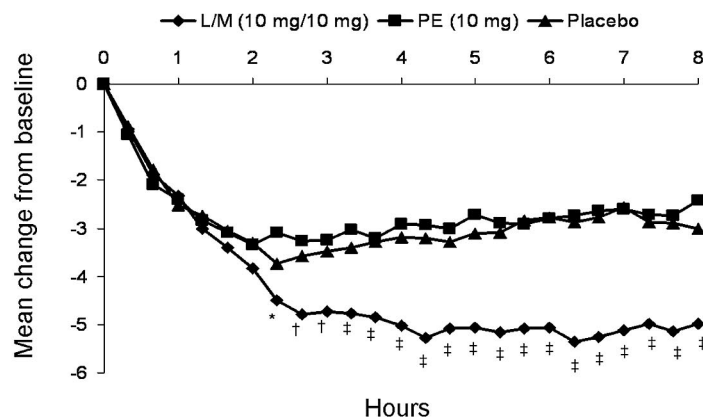
first 6 hours of the evaluation period ($P < .001$). The mean changes in nasal congestion scores averaged across all time points in the first 6 hours after treatment for the loratadine-montelukast, phenylephrine, and placebo groups were -0.90 , -0.54 , and -0.65 , respectively. Loratadine-montelukast was also more effective than placebo in reducing mean nasal congestion during the 8-hour posttreatment period ($P = .001$). Phenylephrine was not different from placebo ($P = .21$), and loratadine-montelukast was more effective than phenylephrine ($P < .001$) during the 8-hour posttreatment period (Fig 2B). A significant difference in treatment effect between loratadine-montelukast and placebo was first ob-

A.



* $P < 0.001$ vs placebo and PE.
0 = none; 1 = mild; 2 = moderate; 3 = severe.

B.



* $P < 0.05$ L/M vs PE and placebo. † $P < 0.01$ L/M vs PE and placebo. ‡ $P < 0.001$ L/M vs PE and placebo.

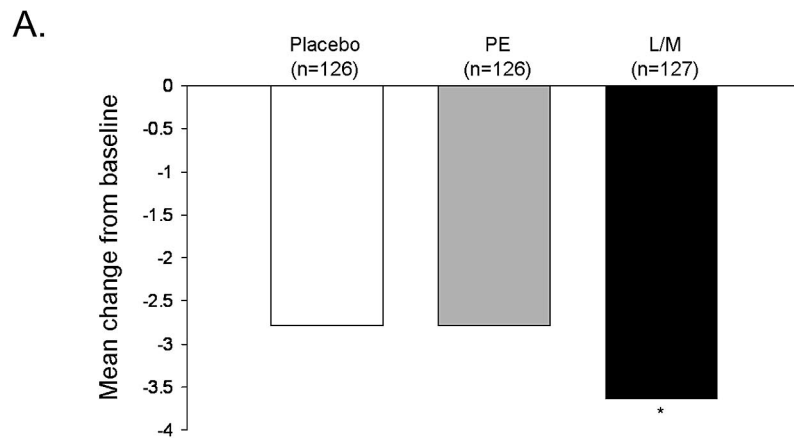
Figure 5. Mean change from baseline during the first 6 hours after treatment (A) and across time (B) in total nasal symptom scores for the loratadine-montelukast (L/M), phenylephrine (PE), and placebo groups.

served at the 2-hour, 40-minute time point, whereas that between loratadine-montelukast and phenylephrine was obtained at the 2-hour, 20-minute time point. Both differences in efficacy were maintained through the 8-hour study observation period (Fig 2B).

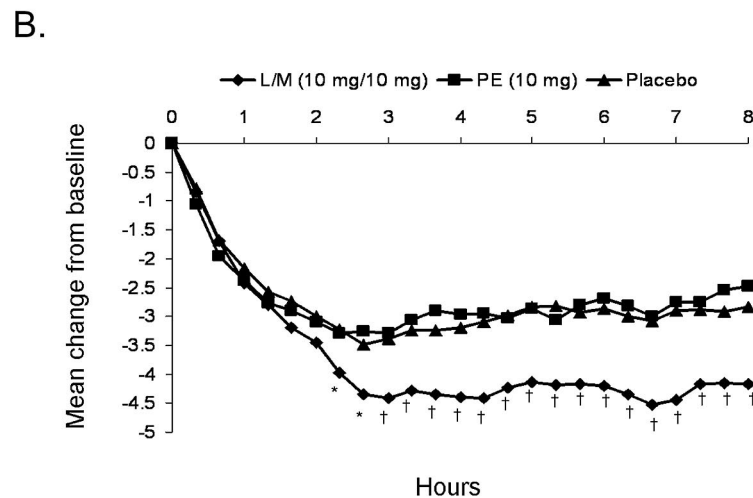
Loratadine-montelukast was also more effective than placebo in mean improvement in nasal obstruction as measured by PNIF during the first 6 hours after treatment ($P = .02$) (Fig 3A). No difference was observed between the phenylephrine and placebo groups ($P = .43$), and loratadine-montelukast was more effective than was phenylephrine ($P =$

.002) during the first 6 hours after treatment. During the 8-hour posttreatment period, similar results were observed; loratadine-montelukast was more effective than placebo in improving mean PNIF ($P = .01$), whereas phenylephrine was not different from placebo ($P = .33$) (Fig 3B). Loratadine-montelukast was more effective than was phenylephrine ($P < .001$) during this period. The superior efficacy of loratadine-montelukast over phenylephrine and placebo was maintained throughout the 8-hour study observation period (Fig 3B).

Loratadine-montelukast was more effective than placebo in relieving total symptoms (Fig 4), nasal symptoms (Fig 5), and



* $P < 0.001$ vs placebo and PE.
0 = none; 1 = mild; 2 = moderate; 3 = severe.



* $P < 0.01$ L/M vs PE and placebo. † $P < 0.001$ L/M vs PE and placebo.

Figure 6. Mean change from baseline during the first 6 hours after treatment (A) and across time (B) in total nonnasal symptom scores for the loratadine-montelukast (L/M), phenylephrine (PE), and placebo groups.

nonnasal symptoms (Fig 6) over 6 and 8 hours after treatment ($P \leq .002$). There was no difference between phenylephrine and placebo for any of the other secondary efficacy variables ($P \geq .35$), and loratadine-montelukast was more effective than was phenylephrine in relieving these symptoms during this period ($P \leq .05$). The onset of action for loratadine-montelukast for TSS, TNSS, and TNNSS, as indicated by a consistent, significant reduction in each score relative to baseline, occurred 2 hours 20 minutes after treatment for all 3 outcome measures.

Safety

Loratadine-montelukast was well tolerated in patients with AR. Fewer patients in the loratadine-montelukast group ($n = 5$; 3.9%) reported AEs than in the phenylephrine ($n = 10$; 7.9%) and placebo ($n = 9$; 7.1%) groups. Epistaxis (3 patients in the phenylephrine group) was the only individual treatment-emergent AE that occurred in more than 2 patients in any treatment group (Table 2). Most treatment-emergent AEs were considered unlikely to be related to the study drug. Most AEs were mild or moderate, and no

Table 2. Overview of Adverse Events (AEs)

AE	Patients, No. (%)		
	L/M (n = 127)	PE (n = 126)	Placebo (n = 126)
Any AE	5 (3.9)	10 (7.9)	9 (7.1)
Treatment-related AEs ^a	3 (2.4)	3 (2.4)	5 (4.0)
Deaths	0	0	0
Serious AEs	0	0	0
Severe AEs	0	2 (1.6)	0
Severe treatment-related AEs	0	0	0
Discontinuations due to AEs	0	0	0
AEs in >2 patients			
Epistaxis	0	3 (2.4)	0

Abbreviations: L/M, loratadine-montelukast (10 mg/10 mg); PE, phenylephrine (10 mg).

^a Treatment-related AEs were abdominal distention, abdominal pain, epigastric discomfort, headache, and somnolence for the L/M group, diarrhea, sinus headache (n = 2), and rash for the PE group, and abdominal pain, flatulence (n = 2), nausea, hypoesthesia, disorientation, and urticaria for the placebo group.

life-threatening AEs were reported. Only 2 severe AEs were reported during the posttreatment observation period (both in the phenylephrine group): 1 patient had a severe headache resolving within 1 day, and 1 patient had a severe sinus headache lasting 2 days, with associated severe nausea and vomiting lasting 1 day. These AEs were deemed unlikely to be related to study drug treatment. There were no deaths or discontinuations due to AEs and no clinically relevant changes in vital signs.

DISCUSSION

This study, which examined the efficacy and safety of loratadine-montelukast compared with that of placebo and phenylephrine during the first 6 hours after treatment demonstrated the clear benefit of loratadine-montelukast over phenylephrine and placebo, with no differences observed between phenylephrine and placebo. This period was selected for the primary comparisons because dosing of phenylephrine is recommended at 4- to 6-hour intervals. Patients were monitored for 8 hours to allow for the possible effect of phenylephrine lasting longer than the expected 6 hours.

The results of this study reinforce the previously demonstrated benefits of studying the treatment effects of AR therapies in the controlled environment of an ACC.^{17,19} Studies performed in the park or field setting are commonly used to evaluate the effectiveness of AR medications, but they have significant limitations, including variability in pollen levels during a study and between study sites and across allergy seasons.^{17,19} Furthermore, patient variability, bias, and noncompliance affect the ability of a study to detect differences between treatments.¹⁷ Onset of action, duration of action, and the effect of dosing on treatment outcomes, all of which require precise measurements, are best evaluated using an ACC.¹⁷ Thus, the EEU provides an environment in which variables, including the allergen, its concentration, and airflow, can be carefully regulated and protocols strictly adhered to.¹⁷ Studies per-

formed in the EEU are especially suited to generate onset-of-action data; this information is critical to patients with AR and their physicians given the importance of quick onset of symptom relief to patients with AR.¹⁸ The data generated in an EEU have clinical relevance, because the symptoms provoked in this setting are consistent and similar to those reported in clinical field studies and in allergen provocation tests.¹⁸

The onset of action in the relief of total AR symptoms with loratadine-montelukast was determined to be 2 hours 20 minutes in this EEU study. Furthermore, loratadine-montelukast treatment resulted in the rapid and significant reduction of nasal congestion (PNIF and subjective symptom score), total AR symptoms, TNSS (nasal congestion, rhinorrhea, nasal itching, and sneezing), and TNNSS (ocular itching or burning, ocular tearing, and itching of the ears and palate). These results are consistent with those of previous trials^{20,21} in which loratadine-montelukast was shown to effectively relieve the symptoms of AR. Findings from other studies comparing loratadine-montelukast with different antiallergic treatments have been variable. Loratadine-montelukast was shown to be equivalent to fexofenadine monotherapy,²² loratadine monotherapy, or montelukast monotherapy.²³ Another comparison showed that loratadine-montelukast was equivalent to fluticasone for relief of daytime symptoms but not nighttime symptoms, whereas both were better than montelukast alone.²⁴ Loratadine-montelukast compared with twice daily fexofenadine-pseudoephedrine showed equal efficacy for nasal congestion,²⁵ which was supported by another study²⁶ that showed no differences between sustained-release pseudoephedrine and montelukast monotherapy. Further study will help us better understand possible advantages of the loratadine-montelukast combination.

Decongestant agents are often added to antihistamine formulations for improved nasal congestion relief. However, safety and availability issues have led many manufacturers to substitute pseudoephedrine with phenylephrine

in these preparations because the Combat Methamphetamine Epidemic Act of 2005 bans the over-the-counter sale of products containing pseudoephedrine and requires that such products be moved "behind the counter."^{27,28} Furthermore, pseudoephedrine has been associated with small but significant increases in systolic blood pressure and heart rate, so physicians need to monitor patients with cardiovascular disease carefully if they intend to use pseudoephedrine-containing products.²⁹ Although data supporting the efficacy of phenylephrine in relieving nasal congestion have recently been questioned, phenylephrine was approved for this indication and is still used as a treatment for nasal congestion associated with AR.^{27,28,30} The results reported herein, which show that loratadine-montelukast is more effective than phenylephrine and that there are no differences between phenylephrine and placebo, are consistent with a study by Horak et al.³¹ That study further demonstrated that the difference in mean change in nasal congestion scores resulting from phenylephrine treatment compared with placebo was not statistically significant and that pseudoephedrine improved mean congestion scores compared with placebo and phenylephrine.³¹

Taken together, these data support the efficacy and tolerability of loratadine-montelukast as a viable treatment for AR and validate the approach of targeting 2 major mediators of the allergic cascade for rapid relief of symptoms, including nasal congestion. Dual-mediator inhibition of histamine and leukotrienes offers an important alternative treatment for AR with the potential to relieve a broad range of symptoms. Furthermore, the efficacy of loratadine-montelukast was shown to be clearly superior to that of phenylephrine in the relief of nasal congestion, with a favorable tolerability profile. These features make loratadine-montelukast an important treatment alternative for AR because 2 inflammatory pathways are targeted in a single medication.

ACKNOWLEDGMENTS

We thank Christina McManus, PhD, from The Scienomics Group for editorial assistance in the preparation of this manuscript.

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