

Comparison of Montelukast and Pseudoephedrine in the Treatment of Allergic Rhinitis

Samantha M. Mucha, MD; Marcy deTineo, BSN; Robert M. Naclerio, MD; Fuad M. Baroody, MD

Objective: To compare montelukast sodium and pseudoephedrine hydrochloride in the treatment of seasonal allergic rhinitis.

Design: A 2-week, parallel, randomized, double-blind study with rolling enrollment.

Setting: Tertiary care medical center.

Patients: A total of 58 adult subjects with ragweed allergic rhinitis as documented by positive findings on a skin test to ragweed and history of symptoms during previous seasons.

Interventions: After recording their own baseline nasal symptoms, nasal peak inspiratory flow (NPIF), and diurnal and nocturnal rhinoconjunctivitis quality of life (QOL) scores, subjects were randomized to receive daily morning oral doses of either pseudoephedrine hydrochloride (240 mg) or montelukast sodium (10 mg) for 2 weeks. They recorded their nasal symptoms and NPIF twice daily during this time, and at the end of the study, they completed another QOL questionnaire and 2 tolerability profiles.

Main Outcome Measures: Nasal symptoms, NPIF, QOL scores, and tolerability profiles.

Results: Both active treatments resulted in significant improvements from baseline in all symptoms of allergic rhinitis as well as in all the domains of the QOL questionnaires. When changes from baseline were compared between treatments, there were no significant differences except in the symptom of nasal congestion, for which pseudoephedrine was more effective than montelukast. Both treatments resulted in a significant increase in NPIF over baseline with no significant difference between treatments. Both drugs were well tolerated with no differences in the tolerability profiles between treatments.

Conclusions: Pseudoephedrine and montelukast are equivalent in improving symptoms and QOL and increasing nasal airflow in patients with seasonal allergic rhinitis. The lack of the usual adverse effects in the pseudoephedrine group is ascribed to morning dosing.

Arch Otolaryngol Head Neck Surg. 2006;132:164-172

APPROXIMATELY 40 MILLION people in the United States have allergic rhinitis.¹ Not only does allergic rhinitis cause the well-known symptoms of sneezing, rhinorrhea, itchy nose and throat, and nasal congestion, but it also leads to adverse effects on sleep, specifically daytime somnolence and decreased productivity, and has a negative impact on patients' quality of life (QOL).^{2,3} The most bothersome and most difficult to control symptom of allergic rhinitis is nasal congestion, which is due to pooling of blood in the cavernous sinusoids and a subsequent reduction in the airway lumen in response to allergic stimulation.

Blocking histamine has traditionally been the target of therapeutic intervention, and thus multiple antihistaminic

agents are available for the treatment of allergic rhinitis. Because these agents have not been especially successful in addressing the nasal congestive response of the allergic state, they have been coupled with α -adrenoceptor agonists to help control the symptom of stuffy nose. Other treatments, such as intranasal steroids, are also more effective in controlling nasal congestion than antihistamines. The only oral α -adrenoceptor agonist currently available is pseudoephedrine hydrochloride, which causes vasoconstriction, physiologically antagonizing the effects of multiple vasodilator mediators and resulting in decreased nasal congestion.⁴ Despite its welcome decongestant effect, pseudoephedrine has an undesirable adverse effect profile that includes insomnia and nervousness in a proportion of the patients who receive it.⁵

Author Affiliations: Section of Otolaryngology–Head and Neck Surgery, The Pritzker School of Medicine, The University of Chicago, Chicago, Ill.

Montelukast sodium, a cysteinyl leukotriene receptor antagonist, is approved for the treatment of seasonal allergic rhinitis. Leukotrienes are one of the main inflammatory mediators released during the body's reaction to allergen exposure. They are produced from arachidonic acid via the 5-lipoxygenase pathway and include LTC₄, LTD₄, and LTE₄.⁶ They are released by many inflammatory cells, including eosinophils, mast cells, monocytes, basophils, and neutrophils.⁷⁻⁹ Their importance in the nasal allergic response has been suggested because of several observations: (1) they are recovered in nasal secretions after nasal allergen challenge and during the occurrence of seasonal symptoms^{10,11}; (2) nasal challenge with LTD₄ in patients with allergic rhinitis was shown to lead to increased secretions and an increase in nasal airway resistance, to increase superficial blood flow as determined by laser Doppler flow cytometry, and to produce a stronger congestive response than histamine^{12,13}; (3) the cysLT1 receptor for leukotrienes has been identified in the nasal mucosa on a variety of inflammatory cells¹⁴; and (4) leukotriene receptor antagonists such as montelukast have been shown to be effective in relieving all the symptoms of seasonal allergic rhinitis (sneezing, itching, and rhinorrhea in addition to nasal congestion) when compared with placebo.¹⁵⁻¹⁷

The leukotrienes are thought to play a critical role in the development of nasal congestion by increasing vascular permeability and pooling of blood in the cavernous sinusoids and leading to narrowing of the nasal airway. Thus, we were interested in comparing 2 agents used for the treatment of allergic rhinitis and, in particular, nasal congestion associated with the disease. Montelukast would provide relief by specific mediator antagonism and possibly by decreasing the recruitment of inflammatory cells such as eosinophils, which can release additional inflammatory mediators; pseudoephedrine works by physiologic antagonism and constriction of the nasal vasculature.

We hypothesized that both montelukast and pseudoephedrine would be beneficial in the treatment of nasal congestion and would therefore be equivalent in the control of that symptom. We also hypothesized that montelukast would have additional beneficial effects, including relief from sneezing, rhinorrhea, and nasal itching. We were also interested in comparing the adverse effect profiles of these 2 treatments, presuming that pseudoephedrine would have undesirable effects on sleep, while montelukast would not. We, therefore, performed a study to compare montelukast with pseudoephedrine for the treatment of ragweed seasonal allergic rhinitis.

METHODS

STUDY DESIGN

We performed a 2-week, parallel, randomized, double-blind, single-center study in patients with ragweed seasonal allergic rhinitis. After an initial screening with a skin puncture test and a nasal symptom questionnaire, qualified volunteers were asked to complete the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)¹⁸ as well as the Nocturnal RQLQ

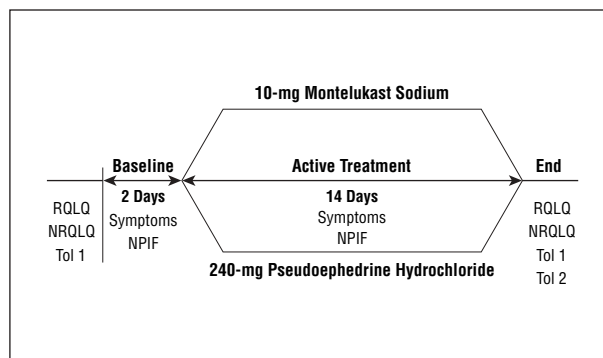


Figure 1. Schematic of study design and procedures performed during each portion of the study. Both treatments were daily oral doses given in the morning. RQLQ indicates rhinoconjunctivitis quality of life questionnaire; NRQLQ, nocturnal RQLQ; Tol, tolerability profile; NPIF, nasal peak inspiratory flow.

(NRQLQ)¹⁹ and a tolerability profile. Participants were then randomized to receive either of 2 active treatments for 2 weeks: 10 mg of montelukast sodium (Singulair; Merck & Co Inc, Whitehouse Station, NJ) or 240 mg of sustained-release pseudoephedrine hydrochloride (Sudafed 24 Hour; Pfizer Inc, New York, NY) once daily in the morning (**Figure 1**). All participants received a medication bottle containing white capsules to be taken each morning. The capsules contained either of the 2 agents and looked alike such that the patients were blinded to the study drug. The bottles were labeled with patient code numbers, and the investigator assigned patients in a sequential randomized fashion to a study code number in groups of 4.

Patients were instructed to keep a diary of daily symptoms, nasal peak inspiratory flow (NPIF) meter readings, and medication use during the study. They recorded the severity of sneezing, rhinorrhea, itchy eyes and/or nose, and nasal congestion for the past 12 hours twice daily, recorded in the morning before taking the study medication and in the evening before going to bed. They also recorded the best of 3 NPIF values taken at the time the symptoms were recorded and their intake of study medication. The patients returned after 2 weeks for their final visit, during which the diaries were collected and they were asked to complete another RQLQ and NRQLQ and 2 tolerability profiles. Baseline symptoms and NPIF measurements were recorded for 2 days at the beginning of the study before the patients started taking their assigned medications. Written informed consent was obtained from all participants before enrollment, and the study was approved by the institutional review board at the University of Chicago.

PATIENTS

Healthy adults between the ages of 18 and 45 years with ragweed seasonal allergic rhinitis were recruited between August 18 and September 12, 2003, the fall ragweed season in Chicago. All patients had a positive finding on a skin test to ragweed antigen extract and at least a 2-year history of allergy symptoms during the ragweed season. Patients requiring daily medications (with the exception of birth control pills, acetaminophen, and medroxyprogesterone acetate) and pregnant or lactating women were excluded from the study. A urine pregnancy test was performed on all female participants prior to enrollment. Patients were also excluded if they had used systemic glucocorticosteroids in the past 30 days, intranasal steroids in the past 2 weeks, oral antihistamines or decongestants in the past 7 days, or topical antihistamines or decongestants in the past 24 hours.

POLLEN COUNTS

Pollen counts for the Chicago area were obtained from the National Allergy Bureau Pollen and Mold Report Certified Counting Station in Melrose Park, Ill.

QOL QUESTIONNAIRES

The RQLQ is a research-validated measure of a patient's QOL. It includes domains that measure nasal and eye symptoms and domains that quantitate generic QOL measures such as activity, sleep, nonnose and noneye symptoms, and practical and emotional measures. Patient responses were recorded on a scale of 0 to 6, with lower scores indicating a better QOL. The overall domain score reflects the average of all domain scores. Changes of 0.5 or more in the overall domain score have been demonstrated by Juniper and Guyatt¹⁸ to be clinically relevant, as evaluated by a survey of patients with allergic rhinitis. The NRQLQ is recorded in the same manner as the RQLQ. The domains quantitate generic nighttime measures (sleep problems, sleep time problems, waking symptoms, and practical awake symptoms).¹⁹

SYMPTOM DIARY CARD

Patients recorded their symptoms twice daily, before taking their medication in the morning and before going to bed in the evening. Scores were reflective of symptoms over the previous 12 hours. Symptoms of sneezing, rhinorrhea, itchy eyes and/or nose, and nasal congestion were scored on a scale of 0 to 3 (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms). The morning and evening individual symptoms were analyzed separately. Furthermore, the morning individual symptoms were added to the evening individual symptoms on each of the baseline and treatment days, and these total scores were also analyzed. Total symptom scores consisted of the sum of all 4 individual symptom scores and were also evaluated separately for the morning and evening as well as the sum of the morning and evening recordings for each day. The highest possible combined total symptom score was 24.

NASAL PEAK INSPIRATORY FLOW

Nasal air flow was objectively measured in liters per minute by use of the In-Check Peak Inspiratory Flow Meter (Ferraris Medical Inc, Orchard Park, NY). Patients were instructed on using the flow meter at their first visit by laboratory personnel. They obtained 3 readings at the times they reported their symptoms and recorded the best flow measured in the diaries. Like for symptoms, the morning and evening values of NPIF were evaluated separately, and the sum of the flows obtained in the morning and evening of each day were also compiled and analyzed.

BASELINE MEASUREMENTS

The first RQLQ and NRQLQ results served as baseline values. Symptoms and NPIF measurements were recorded twice daily throughout the study. On the day of enrollment into the study, patients were given their medication and instructed not to start taking it until after recording symptoms and NPIF scores for 2 mornings and 2 evenings, which would serve as the baseline measurements. Patients were to start taking their study medication after recording the third set of morning symptoms and NPIF scores and to fill in the diaries throughout the 14 days of study medication intake.

TOLERABILITY PROFILES

Two types of tolerability profiles were administered in the form of questionnaires. In the first, patients were asked how much they were bothered by several symptoms over the past week, including headaches, insomnia, nausea, nervousness, dry cough, sweating more than usual, dizziness, dry mouth, agitation, anxiety, heartburn, tenseness, restlessness, upset stomach, swollen ankles, throat irritation, diarrhea, dryness of nose, fatigue, and heart palpitations or racing heartbeat. The possible responses were as follows: 0, not at all bothered; 1, a little bothered; 2, moderately bothered; 3, quite a bit bothered; and 4, extremely bothered. We arbitrarily divided the responders as having the symptom if their responses were 2, 3 or 4, and as not having the adverse effect if their responses were 0 or 1. This profile was administered at initiation and after 2 weeks of treatment.

The second tolerability profile consisted of a set of 4 questions and was administered once at the end of the study. The questions and respective response options were as follows:

1. Overall, how would you rate the level of bother that you experienced from side effects of your study medication?

Responses ranged from 1 (not bothered by adverse effects) to 10 (extremely bothered by adverse effects).

2. Overall, how would you rate your satisfaction with relief of nasal congestion (stuffy nose)?

Responses ranged from 1 (very dissatisfied—no relief of congestion) to 10 (very satisfied—complete relief of congestion).

3. Overall, how would you rate your satisfaction with relief of symptoms of allergic rhinitis (including runny nose, sneezing, and itchy eyes)?

Responses ranged from 1 (very dissatisfied—no relief of symptoms) to 10 (very satisfied—complete relief of symptoms).

4. Overall, considering the level of relief of symptoms as well as the bother from side effects, how satisfied were you with your study medication?

Responses ranged from 1 (very dissatisfied) to 10 (very satisfied).

STATISTICAL ANALYSIS

The RQLQ and NRQLQ data were normally distributed and analyzed by parametric statistics, with the data depicted as mean $\pm$ SEM. The symptom and NPIF data were not normally distributed and were analyzed by use of nonparametric statistics, with data depicted as medians.

The primary end point was NPIF, and secondary end points were symptom scores, QOL questionnaire findings, and tolerability profiles. The equivalence of the 2 drugs with respect to the end points was evaluated. To achieve that, we calculated changes over baseline for NPIF, symptom scores, and QOL domains and compared them between the 2 treatments. We also evaluated whether treatment with each of the agents resulted in a significant improvement from the pretreatment baseline after 2 weeks of therapy.

Each domain of the RQLQ and NRQLQ contained several questions, and the average score obtained for the responses was analyzed. The overall domain is the average of all individual domains for each patient. A paired *t* test was used to compare the scores for each domain between visit 1 (baseline) and visit 2 (after treatment) to evaluate the effect of treatment within each study group. A nonpaired *t* test was used to compare the

baseline and after-treatment scores of the RQLQ and NRQLQ between the 2 groups. The change from baseline in each domain (visit 2 minus visit 1 scores) between the 2 treatment groups was also compared with a nonpaired *t* test.

Daily median values (morning plus evening) were calculated for each of the 4 symptoms recorded and for total daily symptoms as well as for NPIF. A Wilcoxon signed-rank test was first used to compare the baseline symptoms and NPIF scores within groups. If there were no significant differences between the baseline measurements obtained at day 1 and day 2, the average of the 2 baseline days was used for further analysis. The Wilcoxon signed-rank test was then used to compare the average baseline symptoms and NPIF scores with those recorded during each day of treatment. Comparison of symptoms and NPIF scores between groups at each time point was performed with a Mann-Whitney *U* test. The same analysis was performed separately for the symptoms and NPIF measurements obtained in the morning and those obtained in the evening. For the equivalence analysis, we calculated the total change from baseline for the 14 days of each treatment and compared these by Mann-Whitney *U* test.

For the first tolerability profile, the number and percentage of subjects with and without each specified symptom was calculated, and the change in these percentages between visits 1 and 2 was evaluated by using the χ^2 test for each study drug. We then compared the proportion of subjects with and without symptoms on the exit visit between the 2 treatments using the same test. For the second tolerability profile, the median score was computed for the answer to each of the 4 questions obtained at the exit visit, and these scores were compared between drug treatments using the Mann-Whitney *U* test.

The χ^2 test was performed using the Georgetown University χ^2 calculator (http://www.georgetown.edu/faculty/ballc/webtools/web_chi.html), and all other statistical tests were performed using SPSS 12.0 for Windows (SPSS Inc, Chicago, Ill). For all statistical tests, $P \leq .05$ was considered significant.

We based our determination of sample size on a previous study by our research group in which the effects of an intranasal steroid (budesonide) on NPIF in seasonal allergic rhinitis were compared with those of an antihistamine (desloratadine).²⁰ In that study, 30 patients were enough to detect a significant difference in NPIF between the 2 treatments with a power of 0.8 with $\alpha = .05$. For the present study, we presumed that the same number of subjects would be appropriate to detect a difference, if present, between the 2 treatments compared herein.

RESULTS

The Chicago ragweed pollen count for the enrollment period of the study was typical for the fall allergy season (**Figure 2**). Patients were enrolled during active ragweed pollination. Sixty-one patients were enrolled in the study. Three patients from the pseudoephedrine group dropped out because of noncompliance with the study protocol. Thirty patients in the montelukast group and 28 patients in the pseudoephedrine group completed the study. The demographic characteristics of age, sex, and race, as well as skin-prick test reactivity as measured by wheal size, showed no significant differences between the 2 treatment groups (**Table 1**).

RHINOCONJUNCTIVITIS QOL

The RQLQ data analysis showed the 2 treatment groups to be similar at baseline for all domains. To assess equivalence

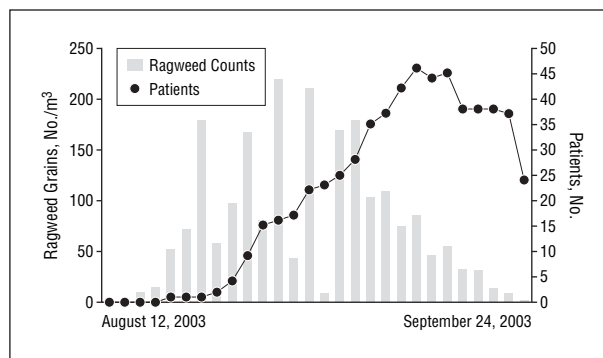


Figure 2. Ragweed pollen count for the 2003 season and the number of study patients enrolled on each study date.

Table 1. Patient Demographics*

Characteristic	Montelukast Sodium	Pseudoephedrine Hydrochloride
Race		
White	23	19
African American	5	6
Latino	0	1
Asian	1	2
Other	1	0
Sex, F/M	17/13	11/17
Age, mean $\pm$ SD, y	29.8 $\pm$ 7.2	30.1 $\pm$ 7.7
Wheal size, mean $\pm$ SD, mm	11.6 $\pm$ 2.9	11.1 $\pm$ 1.9

*Unless otherwise indicated, data are reported as number of patients.

lence of the treatments, we compared the change between the scores at visits 1 and 2 (visit 2 scores minus visit 1 scores) between the 2 agents. There were no significant differences between treatments for any of the RQLQ domains.

When visit 1 and visit 2 scores were compared within each treatment group, there was a significant decrease in scores after both treatments in all domains ($P < .02$), which suggests that both treatments had a positive impact on patients' QOL (**Figure 3**). When visit 2 scores were compared between the groups, only the nonnose/noneye and emotional domains showed a significant difference, with the pseudoephedrine group having a lower score than the montelukast group ($P < .02$). The overall QOL scores were significantly improved after both treatments and were similar at baseline and at visit 2 between the 2 groups. The improvement of the overall QOL scores after both treatments was more than 0.5, which suggests that the improvement was clinically relevant in addition to being statistically significant.

NOCTURNAL RHINOCONJUNCTIVITIS QOL

The NRQLQ data analysis showed the 2 treatment groups to be similar at baseline in all individual domains except for the practical awake symptoms domain, for which the group taking pseudoephedrine had a lower score (better QOL) than the montelukast group ($P = .05$). The treatments were equivalent because the change from base-

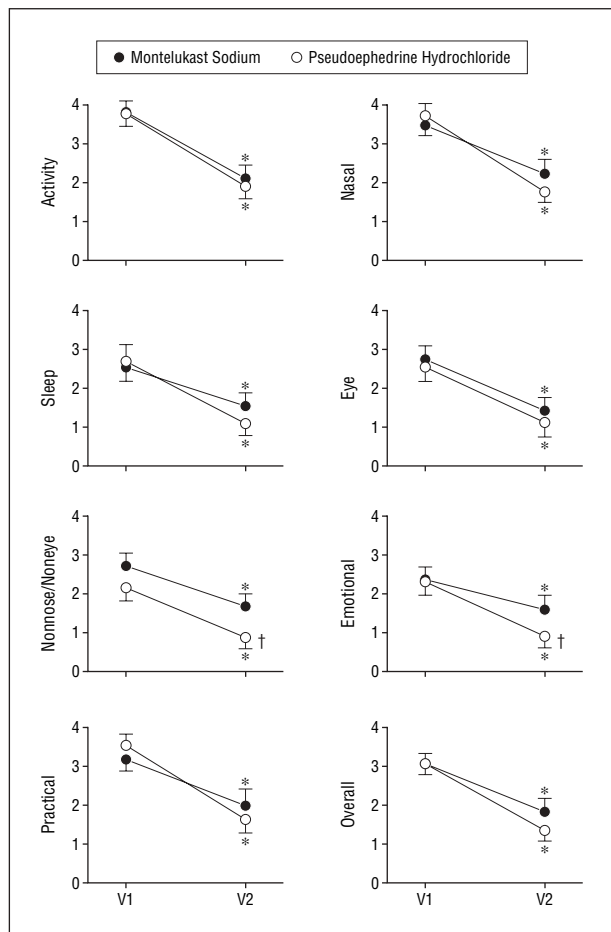


Figure 3. Mean $\pm$ SEM rhinoconjunctivitis quality of life questionnaire response scores. All domains showed significant improvement for both groups from visit 1 (V1) to visit 2 (V2). The asterisk indicates $P < .05$ vs visit 1; dagger, $P < .05$ on visit 2 between the 2 groups.

line in the overall nocturnal QOL domain was not different between the 2 treatments. Furthermore, when the changes between visits 1 and 2 were compared, there were no significant differences between the 2 treatment groups in any of the individual domains. When visit 1 scores were compared with visit 2 scores within each treatment group, there was a significant reduction of scores (and thus improvement in QOL) after both treatments for all individual domains ($P < .01$). When visit 2 scores were compared between groups, there were no significant differences between the 2 treatments except in the sleep time problems domain and the practical wake symptoms domain, with the pseudoephedrine group having a better score than the montelukast group ($P = .02$). When the overall nocturnal QOL domain was evaluated, both treatments had similar scores at baseline and led to significant reductions and thus improvements in QOL at visit 2 ($P < .01$). When comparing the visit 2 scores between treatments, we found that the pseudoephedrine group had better scores than the montelukast group ($P = .02$).

DAILY SYMPTOM SCORES

There were no significant differences between the average baseline scores in either treatment group. When com-

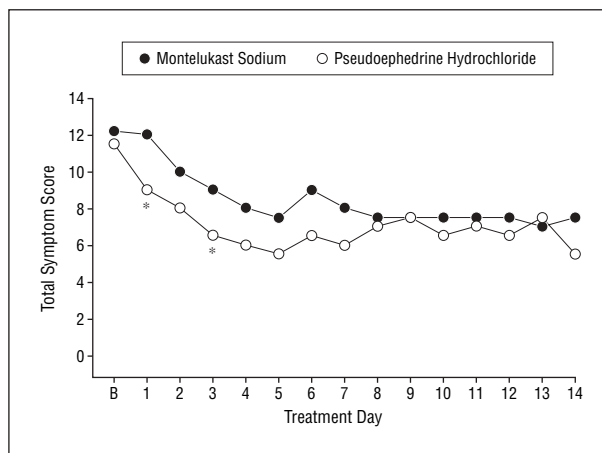


Figure 4. Total symptom scores by day of study. B indicates the average baseline measurement for the 2 baseline days. There was a significant reduction in symptom scores compared with baseline ($P \leq .05$) in both groups on all treatment days except for treatment day 1 in the montelukast sodium group. The asterisk indicates $P < .05$ for montelukast vs pseudoephedrine hydrochloride on days 1 and 3 of treatment.

paring the change from average baseline between the groups (the sum of the change from baseline for each active treatment day), we found no significant difference between montelukast (median score, -48 ; range, -254 to 72) and pseudoephedrine (median score, -63 ; range, -233 to 95) ($P = .10$). Total symptom scores on each treatment day were compared with the average baseline score within each treatment group (**Figure 4**). There was a significant reduction in total symptom score compared with baseline on all treatment days in the pseudoephedrine group ($P < .001$). For the montelukast group, all treatment days showed a significant decrease in total symptom score when compared with baseline, except for treatment day 1 ($P < .01$). When each treatment day was compared between groups, there was a significant difference between the 2 treatments at days 1 and 3, favoring pseudoephedrine ($P \leq .03$).

When individual symptoms of sneezing, rhinorrhea, itchy eyes and/or nose, and nasal congestion were evaluated separately, there were no significant differences between groups at baseline for any of the symptoms. When the total change from baseline was compared between groups to evaluate the equivalence of the 2 treatments, the only symptom to be significantly different between treatment groups was nasal congestion, with pseudoephedrine having a larger change from baseline, indicating a larger improvement in this symptom after treatment, as detailed in **Table 2** and illustrated in **Figure 5**. When comparing the scores on the different treatment days with the average of the baseline scores, we found that both treatments led to significant improvements over baseline in all individual symptoms on almost all treatment days with a few exceptions. There were no differences in sneezing or rhinorrhea between the 2 treatment groups for any treatment day. For itchy eyes and/or nose, there were significant differences between the groups for treatment days 1, 2, and 3, with the pseudoephedrine group having the lower symptom scores ($P < .05$). For nasal congestion, treatment days 5 and 7 were significantly different between the 2 treatment groups, with

Table 2. Change in Individual Symptoms During Active Treatment*

Symptom	Montelukast Sodium	Pseudoephedrine Hydrochloride	P Value
Sneezing	-13 (-58 to 25)	-16 (-64 to 21)	.79
Runny nose	-7 (-67 to 45)	-16 (-61 to 24)	.12
Itchy eyes and/or nose	-21 (-55 to 24)	-18 (-81 to 38)	.68
Nasal congestion	-9.5 (-81 to 14)	-24 (-53 to 15)	.01

*Values are expressed as median change from baseline (range).

pseudoephedrine having the lower symptom scores ($P<.05$).

NASAL PEAK INSPIRATORY FLOW

The total change from baseline was compared between the 2 treatment groups, and there was no significant difference between the patients treated with montelukast (median flow, 265 L/min; range, -1170 to 2690 L/min) and those treated with pseudoephedrine (median flow, 407.5 L/min; range, -1120 to 2285 L/min). The baseline NPIF was also compared with the NPIF obtained during each treatment day within each group (**Figure 6**). There was a significant increase in total NPIF (morning plus evening measurements) from baseline for all treatment days in the patients treated with pseudoephedrine, and for all treatment days except 1, 3, 4, and 7 in the montelukast group ($P\leq.05$). When the time points were compared between treatment groups, there were no significant differences at any time point, including baseline.

These results are for total symptoms and NPIF, that is, the sum of scores and nasal flows obtained during the morning (24 hours after intake of study medication and just before the next dose was administered) and at the end of the day, 12 hours after administration of treatment. When the symptoms and NPIF measures obtained in the morning and the evening of each day were analyzed independently, similar trends were seen with improvements at most treatment days over baseline for each of the treatments. However, the improvements tended to be slightly greater compared with baseline and more consistent for each of the treatment days in the scores obtained at the end of the day (12 hours after the medication intake) compared with those obtained in the morning, 24 hours after the treatment was administered.

TOLERABILITY PROFILES

The results of the first tolerability profile are summarized in **Table 3**. The percentages of subjects with any given symptom varied between the groups, but a trend for a decrease in symptoms after both treatments was seen. This decrease was significant between the visits for headache, insomnia, dry cough, dry mouth, anxiety, heartburn, restlessness, and throat irritation ($P\leq.05$) for the patients taking montelukast, and for restlessness and fatigue ($P\leq.05$) for the patients taking pseudoephedrine. Despite randomization, there was a tendency to have fewer patients with the described symptoms before initiation

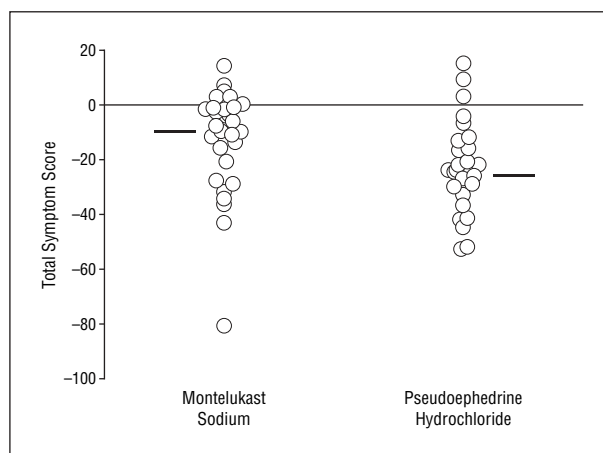


Figure 5. Total change from baseline in total nasal congestion symptom score. Individual data points are depicted with the horizontal bars representing medians. Pseudoephedrine hydrochloride led to more reduction of this symptom from baseline than montelukast sodium ($P=.01$).

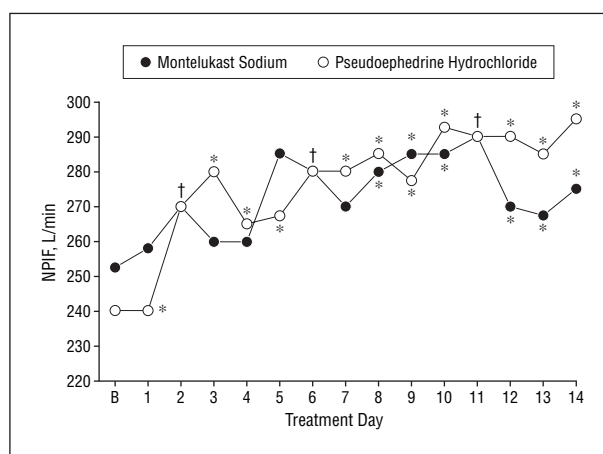


Figure 6. Nasal peak inspiratory flow (NPIF). B indicates the average baseline measurement for the 2 baseline days. Asterisk indicates $P\leq.05$ vs respective average baselines; dagger, both groups had a significant improvement on that treatment day ($P\leq.05$).

of treatment in the pseudoephedrine group. When the percentages of subjects in each group were compared, there were no significant differences.

The second tolerability profile included 4 questions. When the patients were asked how much they were bothered by the adverse effects of study medication, the median response was 1.5 (range, 1-7) for the patients taking montelukast and 2.0 (range, 1-7) for the patients taking pseudoephedrine, which suggests lack of bother by the adverse effects for both drugs. When they were asked to rate satisfaction with relief of nasal congestion, their median response was 6.0 (range, 1-10) for both groups, reflecting slightly above average satisfaction. When asked to rate satisfaction with the relief of the symptoms of allergic rhinitis, the median response was 5.0 (range, 1-10) for montelukast and 7.0 (range, 1-10) for pseudoephedrine, reflecting slightly more satisfaction with pseudoephedrine. Finally, in response to the question of overall satisfaction including relief of symptoms and bother from adverse effects, the responses were 6.0 (range, 1-10) for montelukast

Table 3. Results of Tolerability Profile 1*

Adverse Effect	Montelukast Sodium n = 30		P Value†	Pseudoephedrine Hydrochloride n = 28		P Value†
	V1	V2		V1	V2	
Headache	16 (53)	8 (27)	≤.05	11 (39)	6 (21)	NS
Insomnia	12 (40)	5 (17)	≤.05	11 (39)	6 (21)	NS
Nausea	3 (10)	2 (7)	NS	1 (4)	0	NS
Nervousness	8 (27)	3 (10)	NS	2 (7)	1 (4)	NS
Dry cough	9 (30)	2 (7)	≤.03	8 (29)	3 (11)	NS
Excess sweating	4 (13)	2 (7)	NS	4 (14)	4 (14)	NS
Dizziness	7 (23)	2 (7)	NS	1 (4)	1 (4)	NS
Dry mouth	16 (53)	8 (27)	≤.05	11 (39)	7 (25)	NS
Agitation	10 (33)	4 (13)	NS	4 (14)	2 (7)	NS
Anxiety	10 (33)	3 (10)	≤.05	4 (14)	1 (4)	NS
Heartburn	5 (17)	0	≤.03	3 (11)	2 (7)	NS
Tenseness	12 (40)	6 (20)	NS	5 (18)	1 (4)	NS
Restlessness	13 (43)	5 (17)	≤.03	13 (46)	2 (7)	≤.001
Upset stomach	6 (20)	5 (17)	NS	2 (7)	1 (4)	NS
Swollen ankles	0	0	NS	1 (4)	0	NS
Throat irritation	15 (50)	7 (23)	≤.05	10 (36)	5 (18)	NS
Diarrhea	3 (10)	2 (7)	NS	0	0	NS
Nasal dryness	11 (37)	11 (37)	NS	8 (29)	5 (18)	NS
Fatigue	14 (47)	8 (27)	NS	14 (50)	4 (14)	≤.01
Palpitations	2 (7)	2 (7)	NS	0	1 (4)	NS

Abbreviations: NS, not significant; V1, visit 1; V2, visit 2.

*Data are given as number (percentage) of patients reporting being moderately to extremely bothered by the adverse effect.

†Using the χ^2 test.

and 7.0 (range, 1-10) for pseudoephedrine, reflecting more than average overall satisfaction. None of the response scores were significantly different between study groups.

COMMENT

Leukotriene receptor antagonists are an effective treatment for the symptoms of seasonal allergic rhinitis. Pseudoephedrine is a potent decongestant that is often combined with antihistamines to treat seasonal allergic rhinitis. Pseudoephedrine has stimulant properties that can interfere with sleep.⁵ The present study was performed to investigate the hypothesis that both montelukast and pseudoephedrine would be beneficial in the treatment of nasal congestion but that montelukast would have additional beneficial effects including improvement of sneezing, rhinorrhea, and nasal itching. We also hypothesized that pseudoephedrine would have adverse effects on sleep while montelukast would not. We therefore compared these 2 treatments during the 2003 ragweed allergy season in Chicago using a randomized, double-blind, parallel study design. Contrary to our hypothesis, pseudoephedrine and montelukast were equivalent in improving daytime and nocturnal measures of QOL and all symptoms of allergic rhinitis, including nasal congestion, without much difference in the adverse effect profile.

If one examines the data obtained from measuring the total change from baseline in the objective measure of nasal airflow, NPIF, 30 patients are enough to detect a significant difference in NPIF between the 2 treatments with a power of 0.8 with $\alpha = .05$. This estimate is ob-

tained assuming normal distribution of the data and the use of parametric statistics. The NPIF data, however, are not normally distributed and are usually analyzed using nonparametric statistics. Similar power calculations are more difficult using nonparametric statistics but would likely yield similar results, thus making us confident that our conclusions are valid.

The improvement in the subjective measure of nasal congestion in the montelukast group parallels previous reports in the literature.^{16,17} These results suggest the utility of this agent in the relief of nasal congestion in keeping with the reported role of leukotrienes in the genesis of this symptom. The efficacy of pseudoephedrine in controlling nasal congestion was also expected because this agent exerts efficacy via its vasoconstrictor effect. When the nasal congestion score was analyzed, pseudoephedrine showed superior improvement over montelukast. When the objective measure of nasal congestion (NPIF) was examined, pseudoephedrine and montelukast were equivalent in controlling this parameter. The discrepancy between results obtained using subjective and objective measures of nasal congestion are not surprising in view of the often poor correlation between these 2 measures of the same symptom. This is the first report that we are aware of that shows an objective and significant improvement of NPIF over baseline in patients with seasonal allergic rhinitis treated with montelukast. This is probably related to the antagonism of leukotrienes, which are important contributors to the restriction of nasal airflow in allergic rhinitis.

We were surprised by the efficacy of pseudoephedrine in controlling symptoms such as sneezing, rhinorrhea, and

itching. Montelukast, on the other hand, has been shown to have efficacy related to these symptoms.^{16,17} In one study, pseudoephedrine was shown to decrease rhinorrhea during the common cold, presumably related to its vasoconstrictor properties.²¹ In the same study, pseudoephedrine had no effect on the symptom of sneezing.

In clinical studies using pseudoephedrine, some efficacy in controlling sneezing, rhinorrhea, and itch has been reported. These clinical studies primarily compared the efficacy of pseudoephedrine with that of an antihistamine and the combination product and were primarily designed to show superiority of the antihistamine-decongestant combination product compared with its individual components. In such a study, Bronsky and colleagues²² compared the combination of 10-mg loratadine and 240-mg pseudoephedrine given once daily to that of 10-mg loratadine given once daily, 120-mg pseudoephedrine given every 12 hours, and placebo in a double-blind, placebo-controlled study in subjects with seasonal allergic rhinitis. The results showed that the combination product was superior to each of its individual components and placebo in the control of symptoms. Of interest to the present findings is the efficacy of pseudoephedrine, when given alone, compared with placebo. When the mean reduction from baseline in mean total nasal symptoms (sum of rhinorrhea, stuffiness, itching, and sneezing) was examined, pseudoephedrine was significantly superior to placebo at all study time points, namely, day 4, end point, and overall. Thus, the study by Bronsky et al²² yielded results similar to our own in that pseudoephedrine significantly reduced nasal symptoms such as itching and sneezing.

In light of these reported beneficial effects of pseudoephedrine compared with placebo, it is not surprising that it was equivalent to montelukast in alleviating the symptoms of seasonal allergic rhinitis. Since the efficacy of montelukast in controlling these symptoms is, in general, comparable to that of loratadine, an H₁ antihistamine, we are assuming that pseudoephedrine is exhibiting some efficacy against sneezing, rhinorrhea, and itch. The reason for that effect is not obvious. A possible explanation could be that the subjects felt improvement in the most bothersome symptom of allergic rhinitis, nasal congestion, when using pseudoephedrine, and consequently had a globally positive impression of the treatment, and this affected the other individual symptom scores in a positive manner in favor of the drug.

We used 2 different tolerability questionnaires to assess potential adverse events associated with the treatments. The first tolerability profile was administered before and after treatment, and the responses obtained before treatment are probably reflective of the overall occurrence of these symptoms in the general population as well as a potential effect of the disease process, namely, seasonal allergic rhinitis, on these symptoms. It is interesting to note that the percentage of subjects who reported being bothered by these symptoms before treatment was quite high for some of the symptoms, with percentages ranging from 40% to 55% for headache, dry mouth, insomnia, tenseness, restlessness, throat irritation, and fatigue. Unfortunately, no comparative data are available in a matched sample of subjects without allergic rhinitis to allow us to make any conclusions as to the possible effects of the disease process itself in the genesis of these symptoms.

When evaluating the possible effects of the study drugs on the generation of these symptoms using the 2 different types of tolerability profile questionnaires, we found that both treatments were clearly rated as satisfactory by the patients and that there were no differences in the tolerability of the drug treatments. Indeed, when the percentage of subjects with specific symptoms before and after treatment with pseudoephedrine was analyzed, there was no increase in the symptoms typically associated with pseudoephedrine administration, such as insomnia, nervousness, dry mouth, agitation, anxiety, tenseness, restlessness, and palpitations. Furthermore, administration of pseudoephedrine did not lead to worsening in the QOL sleep domain or any of the domains of the nocturnal QOL questionnaire. In fact, all the domains showed significant improvement over baseline after 2 weeks of treatment with pseudoephedrine. This is in contrast with other clinical studies using this agent,^{22,23} most likely owing to its once-daily administration, which has been shown to have less stimulant adverse effects than more-than-once-daily dosing.^{24,25}

Indeed, in a study of the pharmacokinetics of loratadine and pseudoephedrine following administration as single vs multiple doses, Kosoglou et al²³ showed that after 10 days of administration to healthy male patients, lower plasma concentrations were observed from 16 to 24 hours after dosing with the once-daily formulation (10 mg of loratadine and 240 mg of pseudoephedrine sulfate in an extended release core) compared with the twice-daily formulation (5 mg of loratadine and 120 mg of pseudoephedrine sulfate with 60 mg in an immediate-release coating and 60 mg in the barrier-protected core). Thus, if there is a relationship between blood levels of pseudoephedrine and insomnia, the once-daily preparation could explain the insignificant effect observed in our study. In addition, the mean age of our subjects was approximately 30 years, and it is possible that an older cohort of subjects might have experienced more adverse effects related to the administration of pseudoephedrine.

In conclusion, our study shows equivalence in the control of seasonal allergic rhinitis of montelukast and pseudoephedrine administered once daily. In addition to efficacy in the control of nasal symptoms and QOL measures, montelukast provided similar improvement in NPIF when compared with the vasoconstrictor pseudoephedrine. Finally, both medications were well tolerated, and pseudoephedrine did not lead to any of its well-known stimulant adverse effects, likely owing to its once-daily administration in the morning and lower blood levels in the later hours of the day closer to bedtime. It would be interesting to design follow-up studies examining the pharmacokinetics of pseudoephedrine administration (once vs twice daily) and confirming the efficacy of this agent for the many symptoms of allergic rhinitis that were seen in this study. In sum, these agents appear equivalent for the treatment of seasonal allergic rhinitis. A larger study may have shown a difference in the adverse effect profile.

Submitted for Publication: May 28, 2005; final revision received August 7, 2005; accepted August 24, 2005.

Correspondence: Fuad M. Baroody, MD, Section of Otolaryngology–Head and Neck Surgery, The University of

Chicago, 5841 S Maryland Ave, MC1035, Chicago, IL 60637 (fbaroody@surgery.bsd.uchicago.edu).

Financial Disclosure: Drs Naclerio and Baroody belong to the Speakers Bureau of Merck & Co Inc, and Dr Baroody has received honoraria from Merck.

Funding/Support: This study was supported in part by a medical school grant from Merck & Co Inc (Dr Baroody), and Merck contributed editorial suggestions during the preparation of this article.

Previous Presentation: Material from this article was presented as a poster at the annual meeting of the American Academy of Allergy, Asthma, and Immunology; March 20, 2005; San Antonio, Tex.

REFERENCES

1. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol*. 2001;108:S2-S8.
2. McMenamin P. Costs of hay fever in the United States in 1990. *Ann Allergy*. 1994;73:35-39.
3. Bousquet J, Bullinger M, Fayol C, et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol*. 1994;94:182-188.
4. Wellington K, Jarvis B. Cetirizine/pseudoephedrine. *Drugs*. 2001;61:2231-2240.
5. McFadden EA, Gungor A, Ng B, et al. Loratadine/pseudoephedrine for nasal symptoms in seasonal allergic rhinitis: a double-blind, placebo-controlled study. *Ear Nose Throat J*. 2000;79:254-260.
6. Haberal I, Corey JP. The role of leukotrienes in nasal allergy. *Otolaryngol Head Neck Surg*. 2003;129:274-279.
7. Henderson WR Jr. The role of leukotrienes in inflammation. *Ann Intern Med*. 1994;121:684-697.
8. Naclerio RM, Baroody FM, Togias AG. The role of leukotrienes in allergic rhinitis: a review. *Am Rev Respir Dis*. 1991;143:S91-S95.
9. Bousquet J, Chané P, Michel FB. Pathophysiology and treatment of seasonal allergic rhinitis. *Respir Med*. 1990;84(suppl):11-17.
10. Volovitz B, Osur SL, Bernstein JM, Ogra PL. Leukotriene C4 release in upper respiratory mucosa during natural exposure to ragweed in ragweed-sensitive children. *J Allergy Clin Immunol*. 1988;82:414-418.
11. Creticos PS, Peters SP, Adkinson NF Jr, et al. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. *N Engl J Med*. 1984;310:1626-1630.
12. Okuda M, Watase T, Mezawa A, Liu CM. The role of leukotriene D4 in allergic rhinitis. *Ann Allergy*. 1988;60:537-540.
13. Bisgaard H, Olsson P, Bende M. Effect of leukotriene D4 on nasal mucosal blood flow, nasal airway resistance and nasal secretions in humans. *Clin Allergy*. 1986;16:289-297.
14. Shirasaki H, Kanaizumi E, Watanabe K, et al. Expression and localization of the cysteinyl leukotriene 1 receptor in human nasal mucosa. *Clin Exp Allergy*. 2002;32:1007-1012.
15. Chervinsky P, Philip G, Malice MP, et al. Montelukast for treating fall allergic rhinitis: effect of pollen exposure in 3 studies. *Ann Allergy Asthma Immunol*. 2004;92:367-373.
16. Philip G, Malmstrom K, Hampel FC, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy*. 2002;32:1020-1028.
17. Nayak AS, Philip G, Lu S, et al. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol*. 2002;88:592-600.
18. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy*. 1991;21:77-83.
19. Juniper EF, Rohrbach T, Meltzer EO. A questionnaire to measure quality of life in adults with nocturnal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2003;111:484-490.
20. Bhatia S, Baroody FM, deTineo M, Naclerio RM. Budesonide increases nasal airflow more than desloratadine during the allergy season. *Arch Otolaryngol Head Neck Surg*. 2005;131:223-228.
21. Sperber SJ, Turner RB, Sorrentino JV, O'Connor RR, Rogers J, Gwaltney JM. Effectiveness of pseudoephedrine plus acetaminophen for treatment of symptoms attributed to the paranasal sinuses associated with the common cold. *Arch Fam Med*. 2000;9:979-985.
22. Bronsky E, Boggs P, Findlay S, et al. Comparative efficacy and safety of a once daily loratadine-pseudoephedrine combination versus its components alone and placebo in the management of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1995;96:139-147.
23. Sussman GL, Mason J, Compton D, Stewart J, Ricard N. The efficacy and safety of fexofenadine HCl and pseudoephedrine, alone and in combination, in seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1999;104:100-106.
24. Kaiser HB, Banov CH, Berkowitz RR, et al. Comparative efficacy and safety of once-daily versus twice-daily loratadine-pseudoephedrine combinations versus placebo in seasonal allergic rhinitis. *Am J Ther*. 1998;5:245-251.
25. Kosoglou T, Radwanski E, Batra VK, et al. Pharmacokinetics of loratadine and pseudoephedrine following single and multiple doses of once- versus twice-daily combination tablet formulations in healthy adult males. *Clin Ther*. 1997;19:1002-1012.