

Efficacy of acrivastine with pseudoephedrine in treatment of allergic rhinitis due to ragweed¹

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Background: Semprex-D capsules contain acrivastine 8 mg (a second generation H₁-antagonist) plus pseudoephedrine HCl 60 mg and were developed to satisfy the needs of allergy sufferers who prefer combination products designed to provide broader symptom relief. Approval of combination products by the US Food and Drug Administration requires demonstration that each component contributes to the overall effectiveness.

Objective: The objective of the study was to demonstrate that both acrivastine and pseudoephedrine share in the efficacy of the combination in relieving allergy symptoms in patients sensitive to ragweed pollen.

Methods: This was a double-blind, randomized, placebo-controlled, parallel groups, balanced design, multicenter (13 sites) study. Patients 12 years of age or older with skin test reactivity to ragweed were recruited. Patients who qualified for the study were dispensed either (1) acrivastine + pseudoephedrine, (2) acrivastine, (3) pseudoephedrine, or (4) placebo with instructions to take one capsule 4 times daily and to record allergy symptom scores in a symptom diary 3 times daily for 14 days. Assessments of health, global allergy symptoms, protocol compliance, adverse events, and vital signs were also documented.

Results: A total of 702 patients were enrolled in this study. Over the 2-week period, the combination of acrivastine + pseudoephedrine was significantly more effective than acrivastine, pseudoephedrine, and placebo for relief of all symptoms (P range .01 to .001); pseudoephedrine for treating symptoms responsive to antihistamines ($P = .003$); and acrivastine for treating symptoms responsive to nasal decongestants ($P < .001$). Relatively small increases in adverse experience rates were observed for the combination relative to placebo.

Conclusions: These findings in a large clinical trial demonstrate that each component of the combination of acrivastine 8 mg plus pseudoephedrine HCl 60 mg contributes to the overall efficacy, thereby supporting the conclusion that the combination is rational, safe, and effective for the treatment of allergic rhinitis.

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INTRODUCTION

Semprex-D capsules, containing 8 mg of the second generation H₁-antagonist acrivastine plus 60 mg of pseudoephedrine HCl, were developed to satisfy the needs of allergy sufferers who prefer combination products designed to provide broader symptom relief. At the time of the conduct of this study,

over 4,000 patients had received either acrivastine or acrivastine + pseudoephedrine in clinical trials.

Several second generation H₁-antagonists (including acrivastine, astemizole, azelastine, cetirizine, loratadine, and terfenadine) have been developed that have reduced anticholinergic effects and central nervous system penetration characteristics, thereby decreasing sedation compared with classical or first generation antihistamines.^{1–3}

Acrivastine 8 mg is effective in the treatment of allergic rhinitis^{4–6} and urticaria^{7,8} and has a rapid onset of action (30 to 60 minutes) when assessed by

inhibition of histamine-induced wheal and flare reaction,^{9,10} relief of allergy symptoms,¹¹ or inhibition of histamine bronchial challenge.¹²

Approval of combination products by the US Food and Drug Administration requires demonstration that each component of the combination contributes to the overall effectiveness. This study was designed to demonstrate that both acrivastine and pseudoephedrine share in the efficacy of the combination in relieving allergy symptoms in patients sensitive to ragweed pollen.

METHODS

Patient Inclusion and Exclusion

Patients 12 years of age or older with skin test reactivity to ragweed antigen and at least a 2-year history of seasonal allergic rhinitis symptoms during the ragweed pollen season were recruited. They were required to be in good health as demonstrated by physical examination and medical history.

Individuals who had diseases or conditions that contraindicated the use of antihistamines or pseudoephedrine or who had significant anatomic obstruction of the nasal turbinates, deviation of the nasal septum, or vasomotor rhinitis were excluded. Women who were pregnant or nursing a child or women of childbearing potential who were not practicing an acceptable method of contraception were eliminated from consideration. Also excluded were individuals who utilized antihistamines, nasal decongestants, monoamine oxidase inhibitors, cromolyn sodium, or corticosteroids within prescribed time limits prior to study entry according to the known duration of action of the respective drugs.

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Table 1. Diary Symptom Score*

Allergy Symptom Score	Nasal Congestion Score
1. Runny nose	5. Nasal congestion
2. Sneezing	6. Mouth breathing
3. Itchy nose/throat	
4. Tearing, itching or redness of eyes	

* Scale of severity: 0 = absent, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe.

Ethics

Institutional review and approval of the proposed research were received and informed consent was obtained from each patient in accordance with the US Food and Drug Administration regulations governing the use of investigational new drugs.¹³

Study Design

A 13-center, randomized, double-blind, placebo-controlled, parallel and balanced design was employed over a 2-week treatment period. An equal randomization to all study drugs was used. Individuals recorded their allergy symptoms three times in a diary during a 1-day baseline (day 0) phase prior to final qualification. Patients qualified at a clinic visit on day 1 by demonstrating a minimum baseline diary symptom score ≥ 9 and a nasal congestion score ≥ 3 . Patients were dispensed study medications and diaries weekly with instructions to take the medication 4 times each day and to record their allergy symptom scores within one hour of arising in the morning, at noon, and at bedtime for 14 days. Patients returned on days 8 and 15 to have evaluations of health, global allergy symptoms, and protocol compliance.

Study Medication

Patients took one of four identically appearing oral capsules containing either (1) acrivastine 8 mg + pseudoephedrine HCl 60 mg, (2) acrivastine 8 mg, (3) pseudoephedrine HCl 60 mg, or (4) placebo.

Efficacy Assessments

Patients evaluated their allergy symptoms three times daily for 14 days using the scales in Table 1.

The allergy symptom score (symptoms 1 to 4) measures the intensity of

symptoms attributable to histamine and likely to be responsive to acrivastine while the nasal symptom score (symptoms 5 and 6) measures the response to pseudoephedrine. The sum of scores for all six diary symptom scores reflects the overall intensity of the patient's allergy condition and measures the contribution of acrivastine + pseudoephedrine to symptom relief. Additionally, the investigators evaluated the patients' global allergy symptoms during physical examinations on days 8 and 15.

Safety Assessments

Safety was evaluated by spontaneous reports of adverse events and changes in vital signs.

Statistical Analyses

Analyses of covariance (ANCOVA) were used to compare mean values for diary symptom score, nasal congestion score, and allergy symptom score for each study medication with baseline

scores recorded the day before the start of drug administration used as covariates. The statistical comparisons used for each assessment type were as follows:

Diary symptom score: acrivastine + pseudoephedrine versus the other three study medications,

Nasal congestion score: acrivastine + pseudoephedrine versus acrivastine,

Allergy symptom score: acrivastine + pseudoephedrine versus pseudoephedrine.

Comparisons were one-sided at the .05 level of significance. Vital signs data were examined as individual and summary data. Standardized terms were assigned to each adverse event and these data were summarized by maximum reported severity within each study group. Additional statistical analyses were performed that excluded data from patients who used allergy medications other than study medications during the study or data from patients who used less than 75% of study medication during any week of the study. These analyses produced essentially identical results to those presented and consequently are not reported.

RESULTS

Patient Demographics

A total of 702 patients were enrolled in the study. The randomization scheme

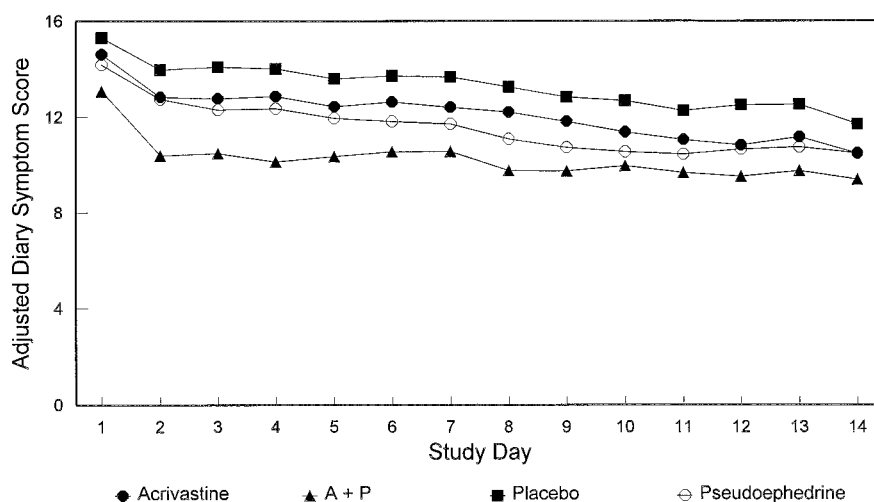


Figure 1. Mean diary symptom scores.

Table 2. Statistical Analysis of Mean Diary Symptom Scores Days 1–14

Treatment Days	Mean Diary Symptom Scores*				Comparisons <i>P</i> Values		
	A + P	A	P	Pla	A + P vs A	A + P vs P	A + P vs Pla
1–7	10.8	13.0	12.5	14.1	0.001	<0.001	<.001
8–14	9.7	11.3	10.8	12.1	0.005	0.050	<.001
1–14	10.3	12.3	11.8	13.4	<0.001	0.002	<.001

* A + P = acrivastine + pseudoephedrine, A = acrivastine, P = pseudoephedrine, and Pla = placebo.

resulted in assignment of 176, 175, 177, and 174 patients to the acrivastine + pseudoephedrine, acrivastine, pseudoephedrine, and placebo groups, respectively. All study medication groups were similar in mean age (approximately 32 years) and sex (53% to 60% female). The age range was 11 to 73 years. The majority (86% to 90%) of the patients in each group were white.

Fifty-six patients discontinued prematurely from the study, ranging from 5% of the patients in the acrivastine + pseudoephedrine group to 10% in the placebo group. Twenty patients discontinued due to adverse experiences, 19 due to worsening allergy symptoms (nine placebo, five acrivastine, four pseudoephedrine, and one acrivastine + pseudoephedrine), seven for protocol violations, six were lost to follow-up, and four withdrew consent.

Effcacy

Mean baseline diary symptom score values were similar, with values of 17.9, 18.2, 17.6, and 17.3 for acrivastine + pseudoephedrine, acrivastine, pseudoephedrine, and placebo, respectively.

Daily mean diary symptom score adjusted for baseline (day 0) values are illustrated in Figure 1. The rank order for reduction in diary symptom score values exhibited by the study medication groups was acrivastine + pseudoephed-

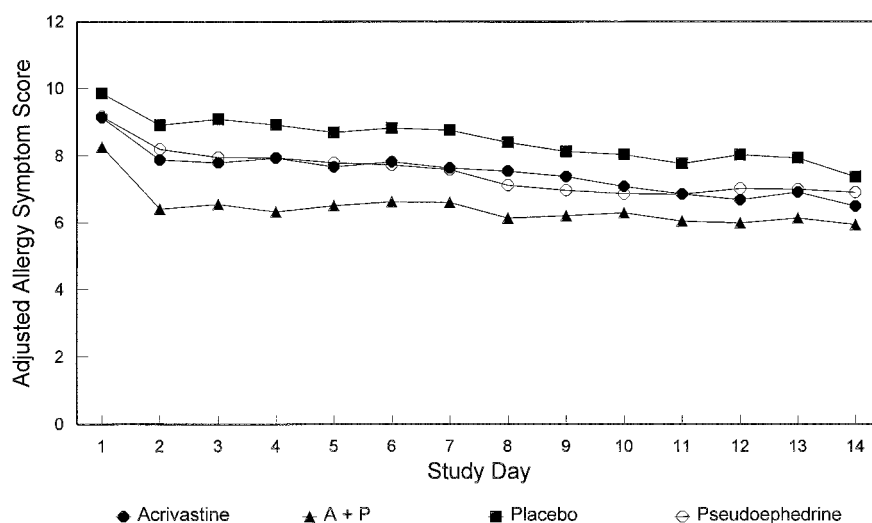


Figure 2. Mean allergy symptom scores.

rine > pseudoephedrine > acrivastine > placebo. Across the 2-week evaluation period, there was a consistent pattern of significant reductions in mean diary symptom score values for acrivastine + pseudoephedrine relative to acrivastine ($P < .001$), pseudoephedrine ($P = .002$), and placebo ($P < .001$) (Table 2). The number of days of significant differences over the 2 weeks between acrivastine + pseudoephedrine and the other test medications was 13 days relative to acrivastine, 9 days relative to pseudoephedrine, and 14 days relative to placebo.

Figure 2 illustrates the daily mean

nasal congestion score adjusted for baseline. The rank order for reduction in nasal congestion score values exhibited by the treatment groups was acrivastine + pseudoephedrine > pseudoephedrine > acrivastine placebo. Over the 2 weeks, there were significant reductions in mean nasal congestion score values for acrivastine + pseudoephedrine relative to acrivastine on all 14 days (2-week average $P < .001$, Table 3).

Daily mean allergy symptom score values adjusted for baseline are illustrated in Figure 3. The rank order for

Table 3. Statistical Analysis of Mean Nasal Congestion Score Days 1–14

Treatment Days	Mean Nasal Congestion Score Values*				Comparison <i>P</i> Values
	A + P	A	P	Pla	A + P vs A
1–7	4.0	5.0	4.4	5.1	<.001
8–14	3.6	4.3	3.7	4.7	.001
1–14	3.8	4.7	4.1	4.9	<.001

* A + P = acrivastine + pseudoephedrine, A = acrivastine, P = pseudoephedrine, and Pla = placebo.

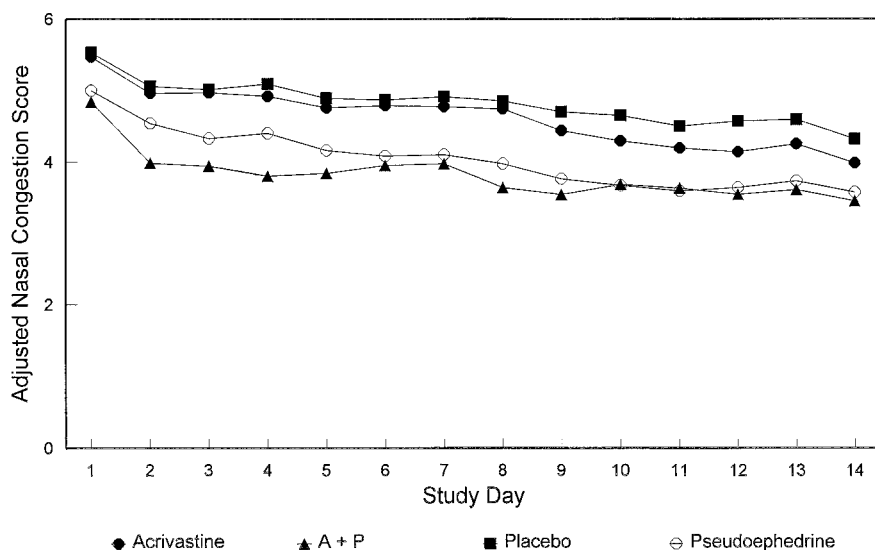


Figure 3. Mean nasal congestion scores.

reduction in allergy symptom score values exhibited by the study medication groups was acrivastine + pseudoephedrine > acrivastine = pseudoephedrine > placebo. Significant reduction in mean allergy symptom score values for acrivastine + pseudoephedrine relative to pseudoephedrine occurred on 13 of 14 evaluation days (2-week $P < .001$, Table 4).

Results of investigator-generated global assessments at both days 8 and 15 revealed significantly higher percentages of acrivastine + pseudoephedrine patients with some degree of improvement compared with the other study groups (data not shown). The results are consistent with the symptom scores above.

Safety

No clinically important changes in vital signs were observed in any of the

study groups. No patients were discontinued from the study because of changes in vital signs.

Eleven adverse events were reported at frequencies >1% for one or more of the study medication groups. The greatest increases in adverse event frequencies for acrivastine + pseudoephedrine relative to the placebo group were dry mouth (9%), somnolence (7%), nervousness (4%), and insomnia (4%). Severe adverse experiences included headache, insomnia, confusion, dry mouth, palpitation, or somnolence and were reported among all study groups at a frequency of 2% or less. Twenty patients discontinued from this study due to adverse events: six each associated with acrivastine + pseudoephedrine and pseudoephedrine, five with acrivastine, and three with placebo.

DISCUSSION

This study was conducted in a large study population to demonstrate that acrivastine + pseudoephedrine each make distinct and complementary contributions to the relief of allergic rhinitis symptoms over a 2-week time period. To demonstrate comparability among patients receiving the study medications at baseline and throughout the study, various study parameters were evaluated. These included baseline allergy scores, patient demographics, use of concomitant medications and study medications during the study, time of conduct of study in relation to ragweed season, and protocol compliance by the investigators and patients. Secondary study analyses to eliminate data from patients who used prohibited medications or less than 75% of study medication during the study revealed no effect upon the statistical outcome of the study. The available accountability data, therefore, indicate that the investigators and patients carried out their protocol-defined responsibilities and the four study groups were comparable in all major aspects.

Therapy with a combination antihistamine/nasal decongestant to treat seasonal allergic rhinitis represents the use of complementary pharmacologic agents: antihistamine to treat running nose, sneezing, etc and nasal decongestant to treat nasal congestion and mouth breathing. Allergic rhinitis typically involves this total complex of symptoms. Consequently, the antihistamine + nasal decongestant combination is expected to prove more effective in treating symptoms of allergic rhinitis than either ingredient used alone.

Table 4. Statistical Analysis of Mean Allergy Symptoms Score Days 1-14

Treatment Days	Mean Allergy Symptoms Score Values*				Comparison P Values
	A + P	A	P	Pla	A + P vs P
1-7	6.8	8.0	8.1	9.0	<.001
8-14	6.2	7.0	7.1	8.1	.017
1-14	6.5	7.6	7.6	8.6	<.001

* A + P = acrivastine + pseudoephedrine, A = acrivastine, P = pseudoephedrine, and Pla = placebo.

This study evaluated the contribution of the antihistamine, acrivastine, upon allergy symptom score, the contribution of pseudoephedrine upon nasal congestion score, and the contribution of acrivastine + pseudoephedrine upon the total symptom complex, diary symptom score in patients with seasonal allergic rhinitis over a 2-week period.

Acrivastine + pseudoephedrine was significantly superior across week 1, week 2, and week 1–2 with lower mean scores for diary symptom score, nasal congestion score, and allergy symptom score than the comparator study groups. Furthermore, daily comparisons for the same evaluations demonstrated significant superiority for acrivastine + pseudoephedrine in the vast majority of analyses. Overall symptom scores among acrivastine + pseudoephedrine patients improved by approximately 50% over the 2-week study. Data from the investigator-generated global assessments were entirely consistent with the patient-generated diary assessments.

In summary, this study provides substantial evidence that acrivastine + pseudoephedrine imparts complementary and sustained relief from the symptoms of seasonal allergic rhinitis throughout 14 days of treatment. Acrivastine + pseudoephedrine provides an alternative to the currently available antihistamines and antihistamine + nasal decongestant products. In a companion article, almost identical findings were determined for acrivastine + pseudosphedrine in patients experiencing seasonal allergic rhinitis due to mountain cedar.¹⁴ Given the results of

these two studies, the efficacy and safety of the combination product, acrivastine 8 mg + pseudoephedrine HCl 60 mg, are fully demonstrated.

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