

Efficacy of acrivastine plus pseudoephedrine for symptomatic relief of seasonal allergic rhinitis due to mountain cedar

Benjamin O Williams; Heyward Hull, PharmD; Paul McSorley; Michael F Frosolono, PhD; and Ronald L Sanders, PhD

Background: Acrivastine is a second-generation H₁-antagonist chemically related to triprolidine, but more polar and with less central nervous system penetration than triprolidine.

Objective: The efficacy of the antihistamine-decongestant combination product (Semprex-D capsules) containing acrivastine 8 mg plus pseudoephedrine HCl 60 mg was evaluated for the treatment of seasonal allergic rhinitis symptoms.

Methods: A total of 676 patients sensitive to mountain cedar pollen was enrolled into a 6-center, randomized, double-blind, placebo-controlled, parallel, 4-group study designed to compare acrivastine + pseudoephedrine, acrivastine, pseudoephedrine, and placebo. Patients with demonstrable diary symptom scores at baseline took study medication (4 doses/day) and recorded symptom scores twice daily for 2 weeks. The effectiveness of the acrivastine + pseudoephedrine combination was examined relative to the individual components and placebo in terms of changes in diary symptom scores.

Results: Over the 2-week period, the combination of acrivastine plus pseudoephedrine was significantly more effective than (1) acrivastine, pseudoephedrine, and placebo ($P < .001$) for relief of all symptoms; (2) pseudoephedrine ($P < .001$) for relieving allergy symptoms, ie, running nose, sneezing, itchy nose/throat and tearing; and (3) acrivastine ($P < .001$) for reducing nasal congestion. Relative to placebo, small increases in adverse experience rates were observed with acrivastine + pseudoephedrine for dry mouth, insomnia, somnolence, and headache.

Conclusion: These findings in a large clinical trial demonstrate (1) the efficacy of acrivastine and (2) 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.

Ann Allergy Asthma Immunol 1996;76:432-8.

INTRODUCTION

The first generation H₁-antagonists (including diphenhydramine, triprolidine, and chlorpheniramine) are effective in relieving allergy symptoms, but an appreciable proportion of the patients taking these medications experience sedation that may interfere with daily

activities.^{1,2} Consequently, several second generation H₁-antagonists, including terfenadine, astemizole, loratadine, acrivastine, and azelastine, have been developed with reduced anticholinergic effects and reduced penetration of the central nervous system, thereby decreasing sedation.¹⁻³

Acrivastine (Fig 1) was synthesized by inserting an acrylic acid moiety onto the classical H₁-antihistamine, triprolidine. The addition of an acrylic acid moiety decreases the lipophilicity of the new compound, thus reducing the penetration of acrivastine into the central nervous system.⁴

Acrivastine 8 mg is effective in the treatment of allergic rhinitis⁴⁻⁶ 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,⁹⁻¹² inhibition of histamine bronchial challenge,¹³ or relief of allergy symptoms.¹⁴ Pseudoephedrine is a safe and effective nasal decongestant available singly and in numerous prescription and over-the-counter products. Acrivastine 8 mg plus pseudoephedrine HCl 60 mg was developed as Semprex-D capsules to satisfy the needs of a large population of allergy patients who want relief from allergy symptoms and nasal congestion in a single product. Prior to marketing approval of combination products, the FDA requires demonstration that each component of the combination contributes to the overall effectiveness. This study was conducted to determine whether both acrivastine and pseudoephedrine in the combination contribute to the relief of allergy symptoms in patients sensitive to mountain cedar pollen, *Juniperus sabi-noides*.

METHODS

Patient Inclusion and Exclusion

Patients 18 years of age or older with skin test reactivity to mountain cedar antigen and at least a 2-year history of seasonal allergic rhinitis symptoms during the mountain cedar pollen season were recruited. Patients were required to have good health as demonstrated by physical examination and medical history.

Individuals with diseases or conditions that contraindicated the use of antihistamines or pseudoephedrine or

From the Burroughs Wellcome Co, Research Triangle Park, North Carolina.

This study was funded by Burroughs Wellcome Co.

Received for publication April 5, 1995.

Accepted for publication in revised form August 30, 1995.

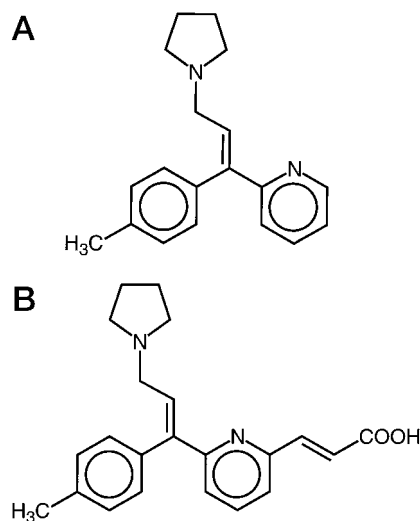


Figure 1. Chemical structures of (A) triprolidine and (B) acrivastine.

who had significant anatomic obstruction of the nasal turbinates, deviation of the nasal septum, or vasomotor rhinitis were excluded. Women who were pregnant or breast feeding or women of childbearing potential who were not practicing an acceptable method of contraception were excluded. Also excluded were individuals who utilized antihistamines, nasal decongestants, monoamine oxidase inhibitors, cromolyn sodium, or corticosteroids within specified times prior to study entry according to the known half lives of the respective drugs.

Ethics

An Institutional Review Committee approved this research and informed consent was obtained from each patient in accordance with the FDA regulations governing the use of investigational new drugs.¹⁵

Study Design

This study was conducted at six centers in south central Texas using a randomized, double-blind, placebo-controlled, parallel group design. Assignment to treatment groups was based upon a randomization scheme designed to assure a uniform gender representation within a 3:3:3:1 ratio for acrivastine + pseudoephedrine, acrivastine, pseudoephedrine and placebo. Individuals recorded their allergy

symptoms in a diary during a 1-day baseline phase on the day prior to the start of the study. Patients qualified at a site visit on day 1 by demonstrating a baseline (day 0) morning and evening average allergy diary symptom score ≥ 9 and nasal congestion score ≥ 3 (Table 1). 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 and at bedtime for 14 days. Patients returned on days 8 and 15 to have assessments made of their 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 assessed allergy symptoms twice daily for 14 days using the assessment scales in Table 1.

The allergy symptom score (symptoms 1–4) measures the intensity of symptoms attributable to histamine and likely to be responsive to acrivastine while the nasal congestion score (symptom 5) measures the response to pseudoephedrine. The sum of scores for all five diary symptoms scores reflects the overall intensity of the patient's allergy condition and measures the contribution of acrivastine + pseudoephedrine in symptom relief. Additionally, the investigators evaluated the patient's global allergy symp-

toms 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

Mean daily and weekly values for allergy symptom score, nasal congestion score, and diary symptom score for each study medication were compared by analyses of covariance (ANCOVA), with baseline scores recorded the day before the start of drug administration used as covariates. Comparisons were one-sided at the .05 level of significance. The primary statistical comparisons used for the mean daily scores 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

Vital signs data were examined as individual and summary data. Adverse experiences were listed using standardized terms and summarized according to maximum reported severity within each treatment group.

RESULTS

Patient Demographics

A total of 676 patients, 367 females and 309 males, were enrolled in the study over approximately a 6-week in-

Table 1. Diary Assessment Scales

Diary Symptom Score*	
Allergy Symptom Score	Nasal Congestion Score
1. Runny nose	5. Nasal congestion
2. Sneezing	
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.

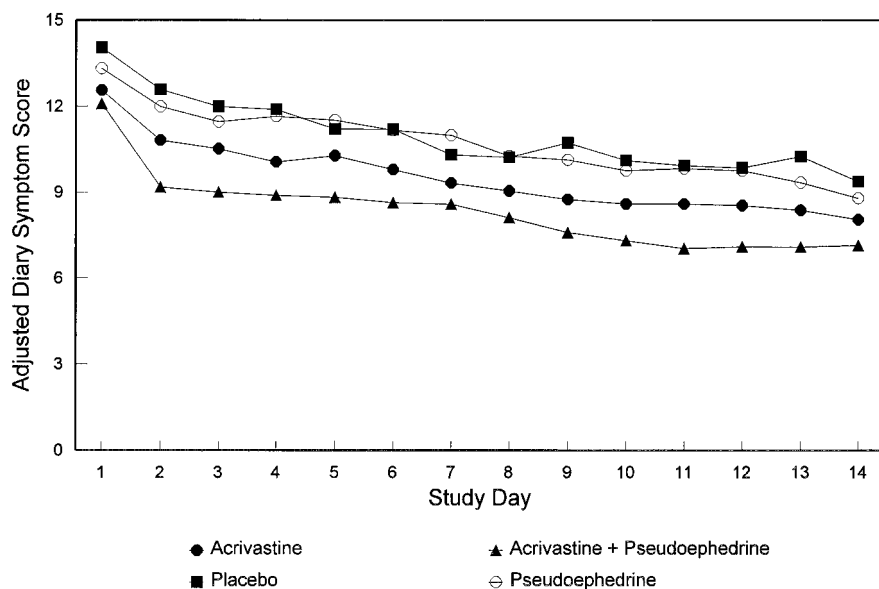


Figure 2. Mean diary symptom scores. Plot of mean diary symptom scores for each day of treatment.

terval. Each of the three active study medication groups contained 202 to 203 patients, while the placebo group consisted of 68 patients. All study medication groups were similar in mean age (36 to 37 years) and sex (54% to 55% female). The age range across all patients was 18 to 76 years. Most (81% to 91%) of the patients in each group were white.

Efficacy

Mean baseline diary symptom score values were similar across treatment groups, with 15.7, 16.1, 15.9, and 16.3 for acrivastine + pseudoephedrine, acrivastine, pseudoephedrine, and placebo, respectively, out of a maximum possible score of 25. Daily mean diary symptom score values adjusted for baseline (day 0) are illustrated in Figure 2. The rank order for reduction in

diary symptom scores exhibited by the treatment groups was acrivastine + pseudoephedrine > acrivastine > pseudoephedrine > 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 ($P < .001$), and placebo ($P < .001$) (Table 2). Over the 2 weeks, acrivastine + pseudoephedrine was significantly different from acrivastine on 13 days and from pseudoephedrine and placebo on 14 days.

Figure 3 illustrates the daily mean nasal congestion scores adjusted for baseline. The rank order for reduction in nasal congestion scores exhibited by the treatment groups was acrivastine +

pseudoephedrine > pseudoephedrine $\approx$ 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 treatment days (2-week average $P < .001$, Table 3).

Daily mean antihistamine-sensitive allergy symptoms scores adjusted for baseline are illustrated in Figure 4. The rank order for reduction in allergy symptom score exhibited by the study medication groups was acrivastine + pseudoephedrine > acrivastine > pseudoephedrine $\approx$ placebo. Significant reductions in mean allergy symptom score values for acrivastine + pseudoephedrine relative to pseudoephedrine occurred on all 14 treatment days (2-week $P < .001$, Table 4).

Results of investigator-generated global assessments on both days 8 and 15 revealed significantly higher percentages of acrivastine + pseudoephedrine patients with some degree of improvement compared with the other three study groups.

Safety

There were minimal differences in systolic and diastolic blood pressures, pulse and respiration rates, and temperature among the study groups at baseline and on days 1, 8, and 15.

Twelve adverse events were reported at frequencies >1% for one or more of the study medication groups. Of these 12 adverse events, increases in frequencies for acrivastine + pseudoephedrine relative to the placebo group were observed for dry mouth (8%), insomnia (7%), somnolence (7%), and headache (6%). The great majority of all 12 events were rated as mild or moderate by the pa-

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

Treatment Days	Mean Diary Symptom Score Values*				Comparison <i>P</i> Values		
	A+P	A	P	Pla	A+P vs A	A+P vs P	A+P vs Pla
1–7	9.3	10.6	11.7	12.1	.001	<.001	<.001
8–14	7.5	8.7	9.7	10.1	.005	<.001	<.001
1–14	8.5	9.8	10.8	11.3	<.001	<.001	<.001

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

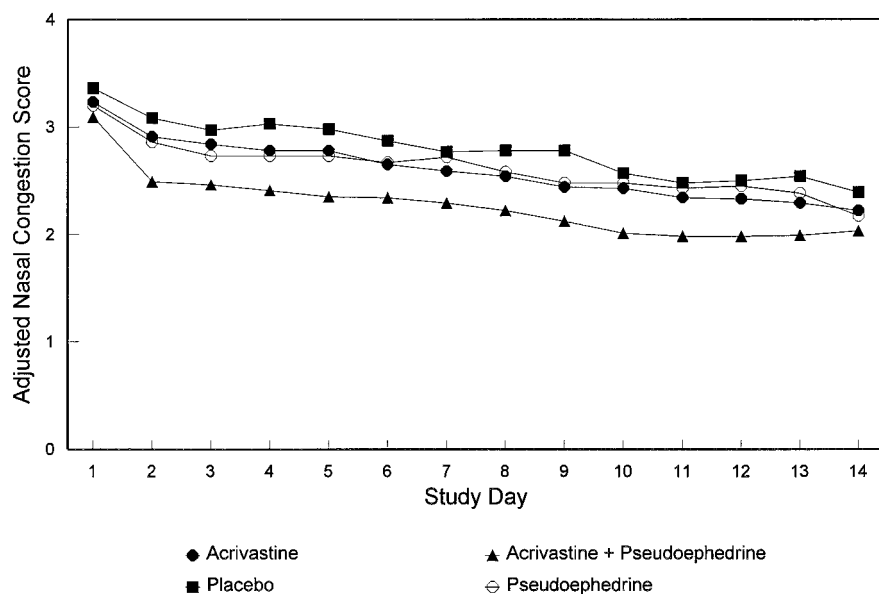


Figure 3. Mean nasal congestion scores. Plot of mean daily nasal congestion scores for each day of treatment.

tients. Adverse experiences rated as severe in intensity included headache, insomnia, nervousness, or somnolence and were reported in less than 1% of patients who received active study medications.

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 consumed 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.

DISCUSSION

This study was conducted in patients sensitive to mountain cedar because this pollen has a very predictable sea-

son, generally Christmas through February, and a large number of patients could be enrolled within a rather small geographic area (~100 mile radius) helping to ensure uniformity of allergy conditions between study sites. Additionally, mountain cedar produces a severe allergic reaction in the upper respiratory tract with typical histamine symptoms of runny nose, watery eyes, etc and also significant nasal congestion.

Pseudoephedrine is a widely used nasal decongestant available in numerous over the counter products. Acrivastine, an antihistamine effective in the treatment of allergic rhinitis and urticaria,⁴⁻⁹ was approved for marketing in the United Kingdom in 1988 as the single ingredient, and in combination with pseudoephedrine in 1993. Only

the combination product is approved in the United States. The present study, conducted in a large study population to determine whether acrivastine and pseudoephedrine each make distinct and complementary contributions to the relief of symptoms of allergic rhinitis over a 2-week period, was one of the pivotal efficacy studies for approval of Semprex-D by the Food and Drug Administration.

Patient diaries and physician global assessments were used to evaluate the relief provided by acrivastine upon allergy symptoms, pseudoephedrine upon nasal congestion, and acrivastine + pseudoephedrine upon the total symptom complex. Acrivastine + pseudoephedrine was significantly superior across week 1, week 2, and weeks 1-2 with lower mean scores for (a) diary symptom score, (b) nasal congestion score, and (c) allergy symptom score than the appropriate comparator study groups. Total diary symptom scores, allergy symptom scores and nasal congestion scores improved 55%, 57%, and 47%, respectively, from baseline among acrivastine + pseudoephedrine patients over the 2-week study. Data from the investigator-generated global assessments were entirely consistent with the patient-generated diary assessments. The improvements in allergy symptom scores seen in this study with acrivastine and acrivastine + pseudoephedrine are similar to the total improvements seen with terfenadine and astemizole when tested with the same diary system and the same mountain cedar allergen.¹⁴

The concept of complementary action may be more easily understood as depicted in Figure 5. In this idealized representation, a pure antihistamine reduces only allergy symptoms, whereas

Table 3. Statistical Analysis of Mean Nasal Congestion Across Days 1-14

Treatment Days	Mean Nasal Congestion Score Values*				Comparison P Values A+P vs A
	A+P	A	P	Pla	
1-7	2.5	2.9	2.8	3.1	<.001
8-14	2.1	2.4	2.4	2.6	.002
1-14	2.3	2.7	2.6	2.9	<.001

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

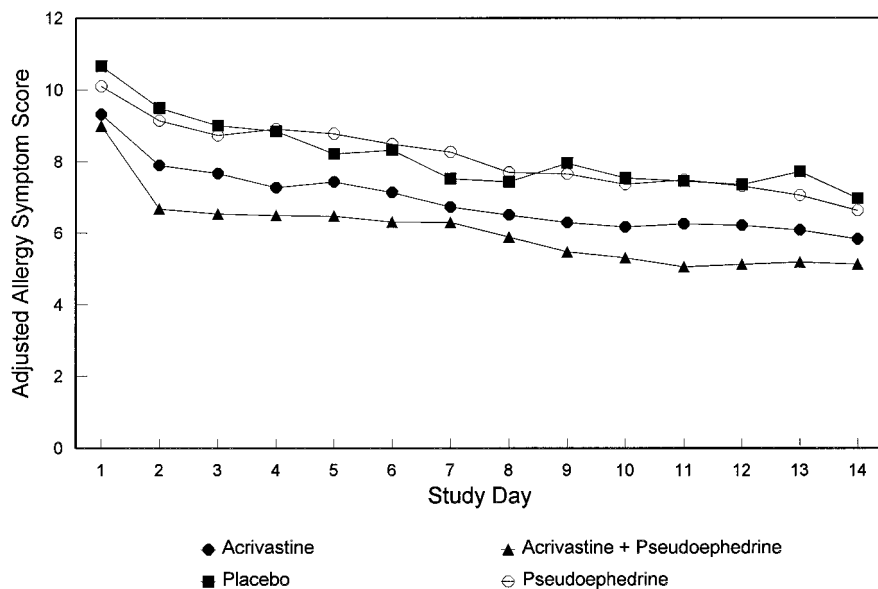


Figure 4. Mean allergy symptom scores. Plot of mean allergy symptom scores for each day of treatment.

a pure decongestant reduces only nasal congestion. The contributions of the single ingredients are additive in the combination. The 2-week nasal congestion scores and allergy symptom scores from this study are presented in Figure 6. In contrast to the idealized representation, pseudoephedrine behaved as a pure decongestant, acrivastine provided allergy and nasal congestion relief, and the effects of the combination appeared to be synergistic rather than additive. These findings demonstrate the superiority of the combination of acrivastine + pseudoephedrine over its single ingredients and placebo in treating the total symptoms profile of patients with allergic rhinitis.

Based upon inhibition of either dermal or bronchial histamine challenge, acrivastine has an onset of

action of 30 minutes or less, considerably faster than terfenadine, loratadine or clemastine.¹⁰⁻¹³ Rhinometric techniques demonstrate that pseudoephedrine relieves nasal congestion within 30 minutes.^{16,17} Acrivastine, singly and in combination with pseudoephedrine, begins to relieve allergic rhinitis symptoms within 40 minutes of oral administration.¹⁴ While the short half-life of acrivastine in the presently marketed immediate release formulation necessitates dosing every four to six hours, the rapid onset of action makes acrivastine well suited both for conventional antihistaminic therapy and prn or "on demand" use when allergy symptoms are intermittent.^{11,18}

The incidence of somnolence or sedation in this study due to acrivastine

was 7% greater than placebo. This is similar to the 6% rate reported for the across study database in the acrivastine + pseudoephedrine package insert. The 6% somnolence rate for acrivastine is significantly different from placebo, and presumably from terfenadine which has a rate equal to placebo, and less than clemastine.⁴ A somnolence rate 2% greater than placebo (no statistical difference) is reported in the 1995 package insert for loratadine; however, direct comparisons with acrivastine have not been reported. In contrast, classical antihistamines have somnolence rates generally of 15% to 25%,¹⁹ with reports as high as 50%.²⁰ Acrivastine may therefore be considered a low sedating antihistamine. While terfenadine and astemizole have label warnings regarding the potential for prolongation of QT_c intervals, neither loratadine nor acrivastine has such warnings. Loratadine 40 mg daily (4× dose) for 90 days²¹ and acrivastine 400 mg (50×) single doses²² or 2400 mg (75×) daily for six days²³ did not produce a prolongation of the QT_c interval.

In summary, this study demonstrates that acrivastine and pseudoephedrine impart 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. Similar findings were observed in a companion article describing another evaluation of acrivastine + pseudoephedrine in patients experiencing seasonal allergic rhinitis due to ragweed.²⁴

Table 4. Statistical Analysis of Mean Allergy Symptom Scores Across Days 1-14

Treatment Days	Mean Allergy Symptom Score Values*				Comparison P Values A+P vs P
	A+P	A	P	Pla	
1-7	6.9	7.8	8.9	9.0	<.001
8-14	5.4	6.3	7.3	7.5	<.001
1-14	6.2	7.1	8.2	8.4	<.001

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

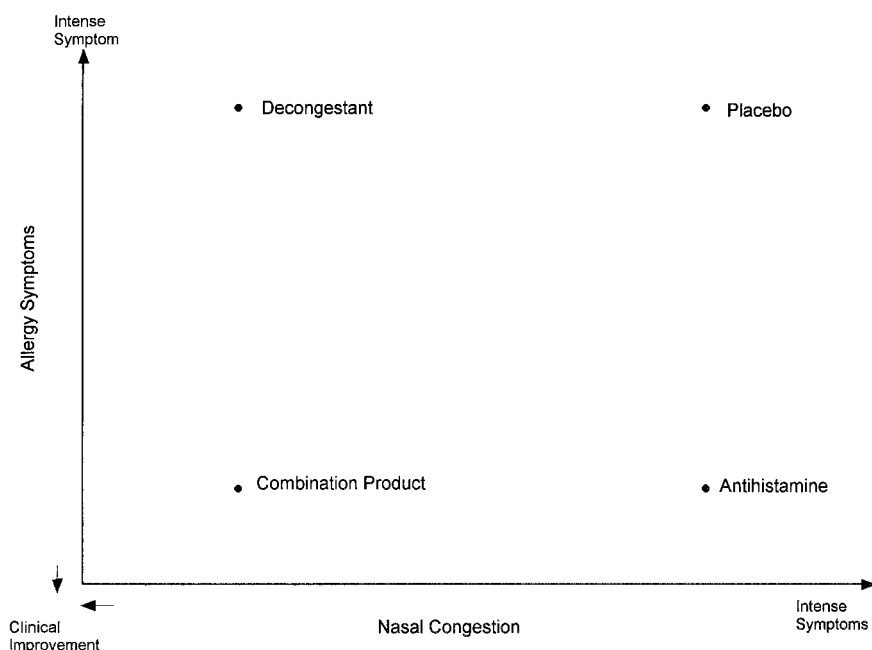


Figure 5. Idealized combination efficacy of an antihistamine-nasal decongestant product. Hypothetical reduction of allergy symptom scores and nasal congestion scores by a pure antihistamine, a pure nasal decongestant, and a combination of the two.

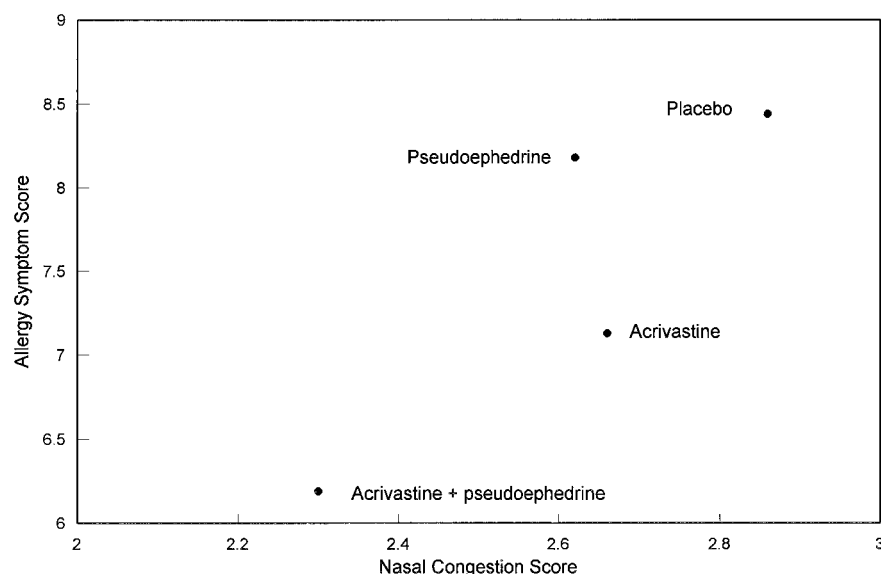


Figure 6. Demonstration of combination efficacy of acrivastine + pseudoephedrine. Plot of mean 2-week nasal congestion scores versus mean 2-week allergy symptom scores.

ACKNOWLEDGMENTS

The authors thank Drs. Stephen Findlay, Frank Hampel, Bruce Martin, Barry Paull, Paul Ratner, Jay van Bavel and their respective research

staff for their efforts in recruiting patients and collecting data for this study.

REFERENCES

1. Naclerio RM. Allergic rhinitis. *N Engl J Med* 1991;325:860–9.

2. Anonymous. Histamine and antihistamines. Section 16, Chapter 3, pgs 1–12 in Volume 3 of Drug Evaluations Subscription. American Medical Association 1990.
3. Simons FER, Simons KJ. The pharmacology and use of H_1 -receptor antagonist drugs. *N Engl J Med* 1994;330:1663–70.
4. Brogden RN, McTavish D. Acrivastine. A review of its pharmacological properties and therapeutic efficacy in allergic rhinitis, urticaria and related disorders. *Drugs* 1991;41:927–40.
5. Gervais P, Bruttman G, Pedrali P, et al. French multicentre double-blind study to evaluate the efficacy and safety of acrivastine as compared with terfenadine in seasonal allergic rhinitis. *J Intern Med Res* 1989;17:47B–53B.
6. Bojkowski CJ, Gibbs TG, Helstern KH, et al. Acrivastine in allergic rhinitis: a review of clinical experience. *J Intern Med Res* 1989;17:54B–68B.
7. van Joost T, Blog FB, Westerhof W, et al. A comparison of acrivastine versus terfenadine and placebo in the treatment of chronic idiopathic urticaria. *J Intern Med Res* 1989;17:14B–7B.
8. Leyh F, Harvey SG, Gibson JR, Manna VK. A comparison of acrivastine versus clemastine and placebo in the treatment of patients with chronic idiopathic urticaria. *J Intern Med Res* 1989;17:22B–5B.
9. Marks P, Manna VK, Gibson JR. Acrivastine—an evaluation of initial and peak activity in human skin. *J Intern Med Res* 1989;17:3B–8B.
10. Callaghan JM, Frosolono MF, Rolan P, Posner J. Onset of effect of products containing acrivastine, loratadine, or clemastine [Abstract]. *Ann Allergy* 1994;72:82.
11. Peterson LJ, Bindslev C, Poulsen LK, Malling HJ. Time of onset of action of acrivastine in the skin of pollen-allergic subjects. A double-blind, randomized, placebo-controlled comparative study. *Allergy* 1994;49:27–30.
12. Leynadier F, Murrieta M, Dry J, et al. Effects of acrivastine and terfenadine on skin reactivity to histamine. *Ann Allergy* 1994;72:520–4.
13. Rolan PE, Adams J, Posner J. Comparison of the onset of H_1 -antagonism with acrivastine and terfenadine by histamine bronchial challenge in volunteers. *J Intern Med Res* 1989;17:35B–9B.

-
14. Frosolono MF, Findlay S, van Bavel J, et al. A comparison of Prolert-D (acrivastine + pseudoephedrine HCl), Prolert (acrivastine), Seldane, Hismanal, and placebo for treatment of seasonal allergic rhinitis [Abstract]. *Ann Allergy* 1992;68:112.
 15. Anonymous. Protection of human subjects and institutional review boards. *Code of Federal Regulations* 1993;21:229–45.
 16. Roth RP, Cantekin EI, Bluestone CD, et al. Nasal decongestant activity of pseudoephedrine. *Ann Otol* 1977;86:235–42.
 17. Bickerman HA. Physiologic and pharmacologic studies on nasal airway resistance (R_N) in Current research in the evaluation of proprietary medicines. *Proc Proprietary Assoc*, New York, NY, 1971:61–72.
 18. Larsen KE, Dockhorn RJ, Yuen N. Improved safety and efficacy of acrivastine, a second-generation antihistamine, in combination with pseudoephedrine HCl in the treatment of allergic rhinitis. *Today's Therapeutic Trends* 1995;12(4):145–51.
 19. Meltzer EO. Performance effects of antihistamines. *J Allergy Clin Immunol* 1990;86:613–9.
 20. Garrison JC. Histamine, bradykinin, 5-hydroxytryptamine, and their antagonists. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *The pharmacological basis of therapeutics*. Pergamon Press, Elmsford, NY 1990:574–99.
 21. Affrime MB, Lorber R, Danzig M, et al. Three month evaluation of electrocardiographic effects of loratadine in humans [Abstract]. *J Allergy Clin Immunol* 1993;91:259.
 22. Dockhorn RJ, Alderman JL, Wenger TL, et al. Lack of acrivastine effects upon the electrocardiogram [Abstract]. *J Allergy Clin Immunol* 1992;68:108.
 23. Sanders RL, Wenger TL, Frosolono MF. Cardiac safety of high dose acrivastine in cancer patients [Abstract]. *Ann Allergy* 1993;70:64.
 24. Dockhorn RJ, Williams BO, Sanders RL. Efficacy of acrivastine + pseudoephedrine in treatment of allergic rhinitis due to ragweed. *Ann Allergy Asthma Immunol* 1996;76:204–8.
-

*Requests for reprints should be addressed to:
Ronald L Sanders, PhD
5120 Shagbark Dr
Durham, NC 27703*