

Profile of ragweed hay fever symptom control with terfenadine started before or after symptoms are established

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Summary

Forty-two ragweed hay fever patients participated in a study which examined the profile of symptom relief provided by terfenadine, and the relative adequacy of symptom control with the drug given from the beginning of the season compared with treatment started after symptoms were well established. Compared with placebo, terfenadine effectively relieved sneeze, itch and eye symptoms. It had no effect on running, blowing and drainage. Subjectively perceived congestion benefited marginally. When the drug was begun after symptoms were well established, sneezing responded quickly and maximally. Eye discomfort lessened but not to the level experienced by those dosed from the beginning of the season. The pattern in other symptom categories was less clear. Overall, terfenadine improved all rhinitis symptoms except those related to hypersecretion. Some symptoms appeared to respond better when drug dosing commenced at the beginning of the season.

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Introduction

Antihistamines are conventional first-line therapy for allergic rhinitis [1–3]. They are effective, but the relief they provide does not span all the symptoms of nasal allergy. Itch and sneeze, for example, seem to benefit more from antihistamines than does congestion [1]. A principal liability of these drugs has been unwanted sedation; several newer agents are free of this side-effect [4,5].

With most older antihistamines now available over the counter, patients have the means for self-medicating mild and moderate nasal allergic processes. Many patients will use these drugs intermittently, treating themselves only when symptoms are severe. This may not be an optimum therapeutic strategy for most antihistamines, but to our knowledge the overall effectiveness of continuous therapy started at the beginning of the season has not been compared to that begun after symptoms were established.

In this study we contrasted the effect of an H₁-blocking antihistamine, terfenadine, dosed from the beginning of the ragweed pollination season with the same drug begun 1 week after the appearance of significant pollen levels. We examined the profile of drug activity on different

classes of symptoms experienced by hay fever sufferers and looked for differences in responses in these classes of symptoms in the two times of drug dosing.

Subjects and methods

The study enrolled 42 volunteers with strongly positive weal-and-flare responses on ragweed prick testing and histories of seasonal symptoms suggesting ragweed sensitivity. Twenty-seven had participated in previous hay fever studies. None were allergic to mould. All lived within a 30-mile radius of the study site; no subject travelled outside this area during the study. Subjects could receive immunotherapy but had to have a constant dose while on the study.

None of the volunteers had complicating disease (including asthma) which required medication or which might compromise subject safety or study integrity. Before being enrolled, all prospective volunteers were informed concerning the study intent, design, risks and benefits, and all signed their consent to participate. The study protocol and consent documents were reviewed and approved by our hospital Institutional Review Board.

The study ran for 3 weeks beginning on 9 August. Significant levels of ragweed pollen typically occur in the study locale after 15 August. We obtained pollen counts

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Please rate all of the symptoms below (except sneezing) according to their severity in the hour before recording.

Which is the best description of your nasal

Congestion? (Evaluate the more congested side only)

- 1 - My nose is completely open and air flows easily.
- 2 - I am aware of congestion, but air flows satisfactorily.
- 3 - My nose is about half closed; it requires some effort to move air.
- 4 - I can move air, but my nose is so congested it requires great effort.
- 5 - My nose is completely blocked; I can't move air through it with any amount of effort.

Which is the best description of

Mucus/post-nasal drainage/sore throat?

- 1 - **None.**
- 2 - **Minimal.** Barely aware of one or more.
- 3 - **Modest.** One or more are present but no problem.
- 4 - **Moderate.** One or more are causing discomfort.
- 5 - **Severe.** One or more are a major problem.

Which is the best description of

Running nose/blowing?

- 1 - My nose isn't running.
- 2 - I am aware of my nose running, but don't need to blow or sniff to control it.
- 3 - I have to blow my nose a few times or sniff occasionally to control running.
- 4 - I have to blow my nose many times to control running.
- 5 - My running nose can't be controlled.

Which best describes your

Sneezing since your last diary entry?

- 1 - I didn't sneeze at all.
- 2 - My sneezing was mild or infrequent.
- 3 - I had one or more episodes of sneezing. It did not interfere with my activity.
- 4 - I sneezed frequently and it interfered with normal activities.
- 5 - My sneezing was constant and disabling.

Which is the best description of your

Itching?

- 1 - I have no itching that is related to my hay fever.
- 2 - I have mild itching, but do not need to rub.
- 3 - My itching is annoying. I sometimes need to rub.
- 4 - I have troublesome itching. It requires frequent rubbing and scratching.
- 5 - I have uncontrollable itching. It requires constant rubbing and scratching.

Which is the best description of your

Hay fever-related eye symptoms?

- 1 - I have no hay fever-related eye symptoms.
- 2 - My eyes are a little irritated, red, or watery.
- 3 - My eyes are definitely irritated, red, and watery.
- 4 - My eyes are irritated, red, watery, and swollen.
- 5 - My eyes are severely irritated, red, watery, and swollen; my vision is affected.

Fig. 1. Hay fever diary symptom severity scores.

using a Rotorod sampler (Ted Brown Associates, Los Altos Hills, U.S.A.) located on a downtown rooftop. These counts were superimposed on the symptom severity plots.

Treatment was randomly assigned and blind-labelled. All subjects weighing 130 pounds or more took three capsules per day; those weighing less took two. Fourteen subjects took placebo capsules during the first 2 weeks and capsules containing 60 mg of terfenadine each during the final week. This group was designated PT (placebo-terfenadine). Twenty-eight took terfenadine throughout (group TT, terfenadine-terfenadine). Other medications which might affect hay fever symptom severity were prescribed.

A symptom diary provided clinical data. The symptoms scored and scales used are presented in Fig. 1. The diary asked for symptom assessments twice a day, generally at breakfast and bedtime. There were five gradations of severity for all symptoms; we scored all according to current severity except for sneezing which was based on experience during the period since the last diary entry.

We saw the subjects twice each week during the study. At these visits we checked the study drug to verify consumption and issued new supplies as required. During the visit the volunteers blew their noses on weighed paper tissues every 2 min for a total 10-min collection period. The weight of the aggregate collection gave an indication of the amount of nasal secretion for that subject. We also checked diary entries for completeness, clarity and accuracy.

Data analysis

We analysed mean daily symptom diary scores for each subject using a repeated-measures analysis of variance model. The results were analysed by study week. The statistical model included the following effects: treatment group, subjects nested within groups, study day and group by study day interaction. The error for the group effect was the nested term. All other effects in the model were tested using the within-subject error term. The GLM procedure in SAS (SAS Institute, Inc., Cary, U.S.A.) was used to fit the model to the data. In no instance was the interaction term significant ($P < 0.08$).

We examined group differences in nasal secretion weights as well as certain population characteristics by means of the *t*-test. Means and standard deviations are reported. Secretion weight analyses were done by study day; there were no statistically significant group differences.

Results

As the study design precluded comparing baseline symptom severity in the two treatment groups, we contrasted these groups using a number of other measures. Group PT had five men and nine women; in group TT the ratio was 12 men and 16 women. Ages for Group PT were 34.7 ± 8.9 (mean $\pm$ s.d.) and for group TT 35.4 ± 9.3 . Duration of disease was 23.2 ± 7.85 yr (Group PT) and 23.0 ± 11.8 (Group TT). Body weight was 153.7 ± 26.3 pounds (Group PT) and 157.8 ± 32.2 (Group TT). Mean

ragweed RAST scores were 6.6 ± 6.8 (Group PT) and 7.5 ± 6.6 (Group TT).

After the ragweed season, skin-test titrations were made to elicit cutaneous late-phase responses. Thirty-six of the 42 who had contributed clinical data returned for this measurement. We did not look specifically for a weal/flare threshold but started all series at 1:1 000 000. All subjects had a definite flare, and all apart from three (one Group PT, two Group TT) had a weal area at least twice that seen with the control injection at the 1:1 000 000 injection site.

To analyse the late-phase results the threshold was defined as that concentration which produced a reaction where the greatest diameter (mm) and the diameter at right angles gave a product of 100 or more. The threshold concentrations were assigned numbers, 1:1 000 000 = 1, 1:300 000 = 2, 1:100 000 = 3, etc. Calculating basic statistics on the numbers gave means and standard deviations of 3.9 ± 1.5 for Group PT and for Group TT 3.5 ± 1.4 ; *t*-tests on all of the group comparisons showed no differences. The measures of central tendency suggested similarity.

Results of the diary end-points are in Figs 2 and 3. The figures show mean daily scores for the two treatment groups omitting days 1 and 22 for which we had only a single diary entry. As we were most concerned with week-to-week changes, we analysed the results by week using the repeated-measures analysis of variance model described earlier. The probability levels associated with the week-by-week treatment differences are included on the figures.

Congestion. This was perceived as slightly greater in the placebo recipients during the first two weeks (Fig. 2). Probability that the treatment groups were different was 0.083 in the first week and 0.051 in the second. Means were closer in the third week, when both groups were getting the same treatment, and were essentially identical in two of the last 3 days.

Drainage and running/blowing. These were nearly identical in the third week and differed slightly though insignificantly during weeks 1 and 2 (Fig. 2). Terfenadine treatment did not appear to have much impact on the subjects' perceptions of these problems. Table 1 contains complementary data derived from secretion collections at the clinic visits. There was a great deal of variation in these values and never a significant intergroup difference. Diary results and weights of collected secretions were mutually confirmatory.

Itching. This showed a substantial benefit from terfenadine treatment. In week 3 when both treatment groups were receiving antihistamine, mean itch scores ap-

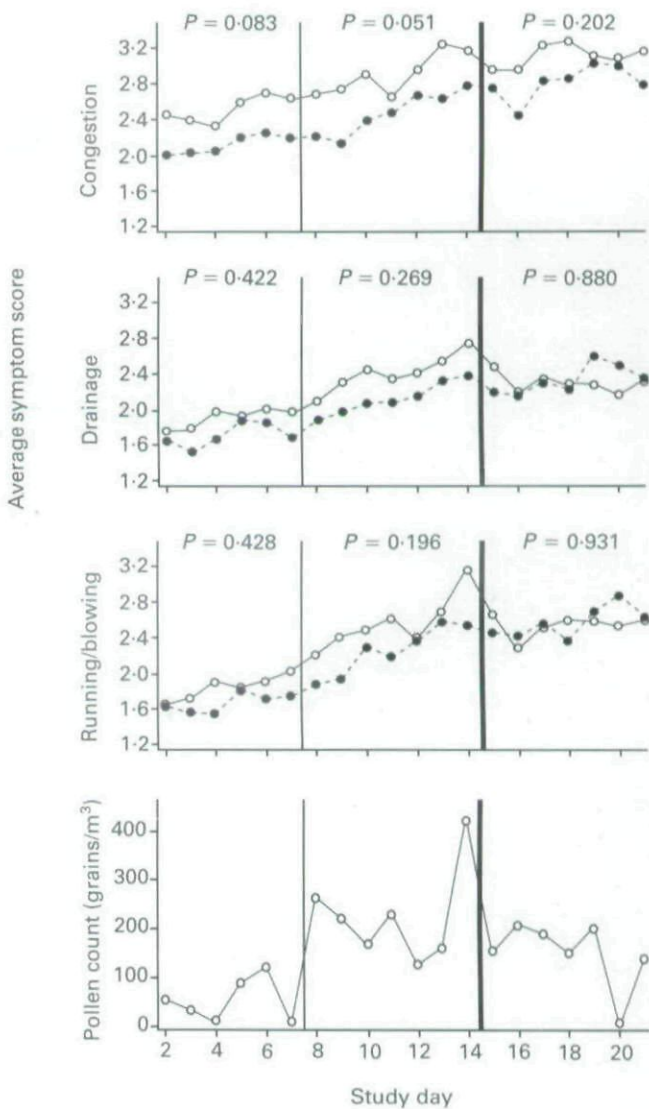


Fig. 2. Mean daily severity scores for symptoms minimally influenced by treatment—congestion, running and blowing, and drainage. Probabilities are for intertreatment differences by week using a repeated-measures analysis of variance model. Vertical lines separate study weeks. (○) Marks the switch to active drug in Group PT (○); Group TT (●). Community ragweed pollen count is included for comparison.

proached each other but did not overlap (Fig. 3). They tended to be closer in the later part of the week. The statistical probability of difference for the third week overall was 0.186.

Sneezing. This was less severe in active drug recipients during the first 2 weeks. In the third week when all were on active drug, sneezing scores for the former placebo recipients fell immediately into the range of those who had been on drug throughout.

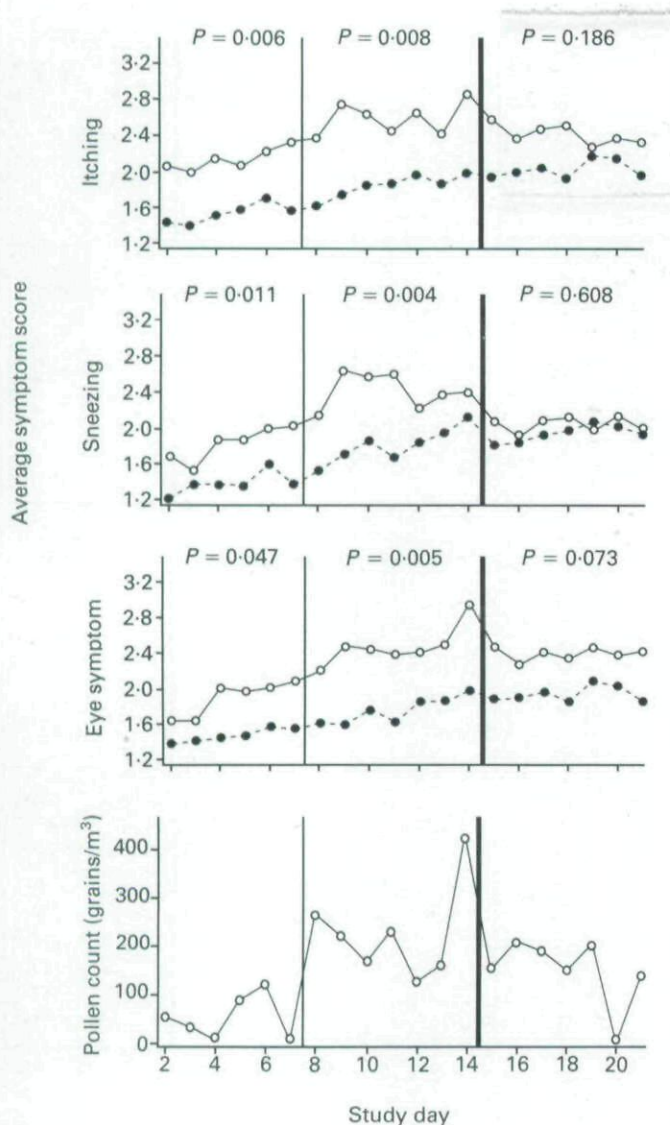


Fig. 3. Mean daily severity scores for symptoms significantly affected by treatment—sneezing, itching and eye symptoms. Probabilities are for intertreatment differences by week using a repeated-measures analysis of variance model. Vertical lines separate study weeks. (■) Marks the switch to active drug in Group PT (○); Group TT (●). Community ragweed pollen count is included for comparison.

Eye symptoms. These were less severe during terfenadine treatment. There were significant intergroup differences during week 1 ($P=0.047$) and week 2 ($P=0.005$). Starting terfenadine in former placebo recipients at the beginning of week 3 eased their eye symptoms slightly. However, Fig. 3 still shows a separation in the means through the third week. The probability that the two groups were different during that week was 0.073.

Table 1. Mean weight of recovered secretions at clinic visits on the indicated days

Study day	Secretion weight (Means $\pm$ s.d.)		P value
	Terfenadine	Placebo	
1	0.19 $\pm$ 0.38	0.17 $\pm$ 0.30	0.82
4	0.11 $\pm$ 0.06	0.15 $\pm$ 0.13	0.27
8	0.20 $\pm$ 0.52	0.42 $\pm$ 0.67	0.24
11	0.24 $\pm$ 0.44	0.34 $\pm$ 0.45	0.54
15	0.31 $\pm$ 0.56	0.39 $\pm$ 0.51	0.66
19	0.42 $\pm$ 0.63	0.37 $\pm$ 0.65	0.84
22	0.17 $\pm$ 0.18	0.15 $\pm$ 0.21	0.77

Discussion

There was an apparent variation in response of the different symptoms when antihistamine was started after hay fever was well established. Mean severity scores for running and drainage, and congestion were slightly closer in the third week of the study but had differed little in weeks 1 and 2. The subtle changes in these symptoms do not allow one to conclude much regarding the relative effectiveness of antihistamine treatment started in mid-season.

The other diary end-points (itching, sneezing, and eye symptoms) had shown highly significant intergroup differences, especially during the second week (Fig. 3). In the third week when both groups were taking terfenadine, sneezing scores quickly achieved similarity. This suggests that terfenadine treatment at any time in the course of the process can suppress sneeze effectively. It also suggests that the two treatment groups were similar with regard to disease severity.

The pattern with eye symptoms was different. Group PT and TT showed substantial differences during the first 2 weeks. When placebo was replaced with terfenadine there was an improvement in symptom severity but mean severity scores remained well apart; the probability of significant intergroup difference was still 0.073. These results would be compatible with the existence of a residue of eye symptoms not responsive to treatment started after they were well established.

Figure 3 shows that terfenadine significantly suppressed itch during the first 2 weeks. When terfenadine replaced placebo, the mean severity scores approached each other gradually. On day 15, the two groups were still different ($P=0.047$). Thereafter they were not, and the probability of difference for the entire week was 0.186. This pattern suggests a less immediate response to antihistamine with itch than with sneeze.

Table 2. Survey of terfenadine clinical trials—symptom relief profiles

Author	Reference	Relative symptom suppression					Treatment comparison	Comment
		Congestion, blockage	Sneeze	Itch	Run, rhinorrhea	Eye symptoms		
Backhouse <i>et al.</i>	[6]	+	++		++	++	Chlorpheniramine	Multicentre, 1-week
Brewster	[7]	+	++		+	++	Placebo Chlorpheniramine	Summation of four trials
Brooks <i>et al.</i> [Present study]		+	++	++	0	++	Placebo	
Buckley <i>et al.</i>	[8]	+	++		++	++	Chlorpheniramine	Six clinics. One week study.
Buckley <i>et al.</i>	[9]		++	++	+		Placebo Chlorpheniramine	Multiclinic, 7 days
Dugue <i>et al.</i>	[10]	+	++	++	++	++	Placebo	Multiclinic, 8 days duration
Girard <i>et al.</i>	[11]	++	++		++	+	Astemizole	Emphasis on onset of drug action, 8 days.
Gutkowski <i>et al.</i>	[12]	+	+	+	0	++	Placebo	End-point measures.
Horak <i>et al.</i>	[13]	+	++	++	+	++	Loratidine	Many dropouts
Howarth and Holgate	[14]	—	+		0	0	Placebo	Multiclinic. Two week study
Hugonot <i>et al.</i>	[15]	+	++	+	++	++	Astemizole	Clemastine rescue medication
Johansen <i>et al.</i>	[16]	0	0	+	0	0	Mequitazine	Seven day duration
Juniper <i>et al.</i>	[17]	+	+		0	+	Dexchlorpheniramine	Low pollen counts.
Kagan <i>et al.</i>	[18]	++	0		0	++	Astemizole	Mild symptoms
Kemp <i>et al.</i>	[19]	+	++	++	+	++	Placebo	Steroid spray prn.
Melillo <i>et al.</i>	[20]	+	++	0	+	++	None—open trial	End-points confounded
							Chlorpheniramine	Most patients used escape medication, chlorpheniramine
							Placebo	Multicentre
								period before and after

Most therapeutic studies have concentrated on demonstrating a difference between the drug of interest and a placebo or standard drug comparator. Different effects on different parts of the syndrome have received less emphasis. We surveyed published clinical studies on terfenadine for those which separated control of various symptoms (Table 2). The values assigned reflect an interpretation of the relative effectiveness of the drug in alleviating severity of the indicated symptom compared to other symptoms in that study. These values are not suitable for comparisons across studies.

Patterns were not entirely consistent among the several studies but a few generalizations seem warranted. Sneeze and eye symptoms showed substantial benefit most often. Congestion or blockage appeared to be improved by antihistamine in most of the studies, but typically the degree of benefit was modest. Running or rhinorrhea showed the greatest variation in response. Of the 15 studies surveyed, five reported substantial benefit, five indicated no benefit and five modest response. Itch was measured in only eight of the surveyed studies; drug effect was variable.

An anticongestive effect of terfenadine was unexpected. Our study showed marginal improvement in subjectively perceived blockage ($P=0.051$ in week 2), so agreed with the majority of the studies surveyed. In acute challenge studies terfenadine did not protect against rises in nasal airway resistance [21]. This is consistent with results seen with other antihistamines [22,23]. Several interpretations are possible. Congestion in the chronically dosed patient experiencing seasonal pollinosis may include a histamine-dependent mechanism which contributes little to the obstruction which follows acute challenge. Alternatively, the antihistamine may favourably influence the patients' perceptions of congestion more than it does the obstruction *per se*, or might act through a non-histamine-related mechanism.

Terfenadine's apparent lack of antisecretory effect in this study, and its inconsistent record in those surveyed, again does not agree with results of acute challenge studies. Here terfenadine appeared to inhibit secretion [21] as did other antihistamines [22]. A possible explanation for this paradox may lie in terfenadine's lack of anticholinergic effect [24,25]. In the chronically stimu-

lated allergic rhinitis patient, hypersecretion may be a cholinergic phenomenon influenced little by presence or absence of histamine.

Overall these findings show antihistamine treatment with variable levels of effectiveness against the several symptoms of allergic rhinitis. This allows us to infer, in real disease, parts of the syndrome attributable to histamine or to another mediator or mechanism. In this study terfenadine protected significantly against ragweed pollen-induced sneezing, itching, and eye symptoms. The drug also provided a marginal anticongestive effect but did not benefit hypersecretion. When antihistamine treatment was started in the presence of well-established hay fever symptoms, sneezing responded rapidly. Eye symptoms responded incompletely, while itch seemed to improve gradually. These results would justify a recommendation that antihistamine dosed continuously from the beginning of the season should provide better symptom control than intermittent dosing begun after symptoms are severe.

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