

Efficacy of continuous treatment with astemizole (Hismanal) and terfenadine (Seldane) in ragweed pollen-induced rhinoconjunctivitis

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Astemizole (Hismanal; Janssen Pharmaceutica Inc., Mississauga, Ontario, Canada) and terfenadine (Seldane; Merrell Dow Pharmaceuticals [Canada], Inc., Concord, Ontario, Canada) were compared for clinical efficacy in a double-blind randomized trial during the ragweed pollen season. Sixty adults, with a history of ragweed-induced rhinoconjunctivitis, were matched according to sensitivity to ragweed pollen. Half took astemizole, 10 mg/day, and the rest took terfenadine, 60 mg twice daily. Medications were started 1 week before and continued daily until 1 week after the ragweed pollen season (7 weeks). If the trial medication was insufficient to keep symptoms well controlled, a steroid nasal spray and/or eye drops were used in the minimum dose that would ensure symptoms were not troublesome. Subjects completed a diary of nocturnal and daytime nasal and eye symptoms and recorded the amount of concomitant medications used. Astemizole showed greater efficacy than terfenadine in controlling rhinorrhea; in addition, the astemizole group used less nasal spray. Other nasal symptoms, eye symptoms, and use of eye drops were similar in the two groups. Skin test sensitivity to serial dilutions of histamine and ragweed extract was determined 1 and 7 weeks after the start of the trial medication. More tachyphylaxis to histamine was shown by the subjects taking terfenadine, as demonstrated by a larger increase in skin sensitivity over the study period. However, a similar change was not observed for ragweed skin sensitivity. These results suggest that when the medication is started before and continued daily throughout the pollen season, astemizole is more efficacious than terfenadine in controlling nasal symptoms, but there is little difference for eye symptoms. Over a 7-week period of continuous treatment, slightly more tachyphylaxis to histamine skin sensitivity may occur with terfenadine. (J ALLERGY CLIN IMMUNOL 1988;82:670-5.)

Antihistamines have been used for many years to help alleviate symptoms of allergic rhinitis. For some patients, the therapeutic potential of ingested antihistamines could not be realized, mainly due to central nervous system sedative side effects. Two new H₁ antihistamines, astemizole and terfenadine, have both been shown to have good therapeutic efficacy^{1,2} with

very few side effects,^{3,4} most notably a lack of drowsiness. The two previous comparisons between astemizole and terfenadine for the treatment of allergic rhinoconjunctivitis have suggested that astemizole is more effective than terfenadine. However, in one study,⁵ subjects were permitted to use another antihistamine "freely" for symptom breakthrough, which may explain why placebo was found to be more effective than terfenadine. In the second, a single-blind study,⁶ subjects were enrolled during the hay fever season after they had become symptomatic. Such an approach may be optimal for terfenadine, which reaches peak serum levels within hours,⁷ but less appropriate for astemizole, which does not reach steady-state plasma levels for 1 to 2 weeks.⁸ In the present study, we compared the prophylactic efficacy of astemizole (Hismanal; Janssen Pharmaceutica, Inc., Mississauga, Ontario, Canada) and terfenadine (Seldane; Merrell Dow Pharmaceuticals, [Canada] Inc.,

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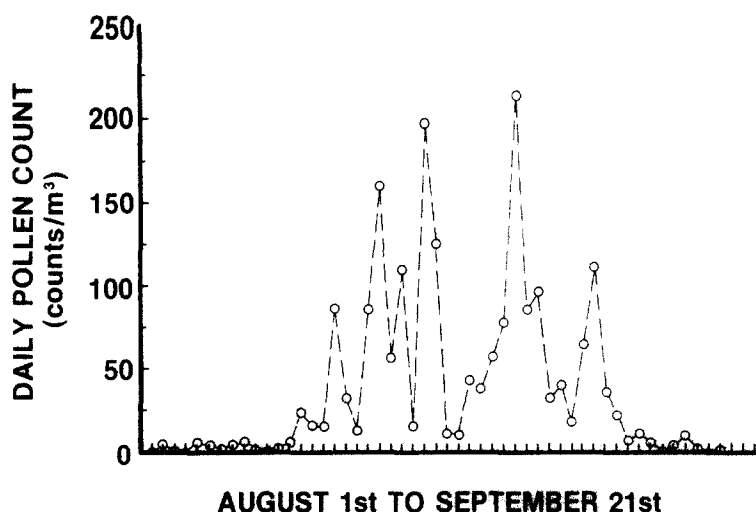


FIG. 1. Daily ragweed pollen count during study.

Concord, Ontario, Canada) by starting medication when the subjects were still asymptomatic, 1 week before ragweed pollen was first expected in the air. Subjects were permitted to use concomitant steroid nasal spray and eye drops for symptom breakthrough, and the amounts needed were recorded and included in the estimation of efficacy.

Tolerance has been reported to occur after 7 to 20 days of continuous treatment with some antihistamines.⁹ In this study we examined whether there was any difference in tachyphylaxis between astemizole and terfenadine after 7 weeks of treatment by evaluating changes in skin sensitivity to histamine and ragweed-pollen extract.

MATERIAL AND METHODS

Subjects

Sixty subjects, who were either attending the Firestone Regional Chest and Allergy Clinic or who responded to an article in a local newspaper, were enrolled in the study. All gave a history of rhinoconjunctivitis that had required treatment during the two previous ragweed pollen seasons, and all had positive allergy skin prick test results with ragweed-pollen extract. None had perennial rhinitis or illnesses other than seasonal rhinitis and asthma and none had received hyposensitization therapy during the previous 12 months. Pregnant and nursing mothers and subjects with more than a mild sensitivity to fungal spores were excluded. No subject had used either of the trial medications for at least 6 weeks before enrollment in the study. All participants signed an informed consent form approved by the St. Joseph's Hospital Ethics Committee.

Study design

The study was designed as a double-blind, randomized comparison of astemizole and terfenadine in two parallel groups. Three weeks before the ragweed pollen season,

subjects had duplicate skin prick tests with tenfold serial dilutions of ragweed-pollen extract (25 to 25,000 Noon units; Bencard Allergy Service, Weston, Ontario, Canada), histamine acid phosphate in 50% saline/glycol solution (2.0, 4.0, 8.0, and 16.0 mg/ml), and single dilutions of mixed tree pollen, mixed grass pollen (Bencard Allergy Service), *Alternaria tenuis*, and *Hormodendrum* (Hollister-Stier Labs of Canada, Rexdale, Ontario). Each wheal was measured in millimeters, 10 minutes after test agent application, across its widest diameter and across the axis at right angles to this. Allergy history was taken by questionnaire and weight was measured. Subjects were matched on the basis of skin sensitivity to ragweed-pollen extract, severity of ragweed-induced rhinoconjunctivitis the previous year, *Alternaria* and *Hormodendrum* sensitivity, history of asthma, and gender. One of each pair was randomly assigned to astemizole, 10 mg/day, while the other took terfenadine, 60 mg twice daily. A double-dummy technique was used to achieve blinding. Each subject took one tablet each morning, 1 hour before or 2 hours after food (astemizole or astemizole placebo), and one capsule each morning and evening (terfenadine or terfenadine placebo).

All subjects started taking trial medication on the morning of Monday, August 4, approximately 1 week before atmospheric ragweed pollen starts to cause symptoms (Fig. 1). They continued with daily medication until their final clinic visit during the fourth week in September, by which time pollen counts were negligible. During the season, if symptoms became troublesome, subjects were instructed to take concomitant medications in a standardized manner and in the minimum dose that would keep symptoms controlled. For nasal symptoms, they took beclomethasone dipropionate nasal spray, one puff (50 µg) into each nostril every 4 hours until symptoms were controlled and then when needed, up to a maximum of eight puffs per nostril per day. Eye symptoms were treated with naphazoline HCl anazoline ophthalmic drops, one drop into each eye when needed, up to four times per day. If this was insufficient, medrysone drops were used four times per day. Subjects were instructed to

TABLE I. Subject characteristics

	Astemizole (n = 30)	Terfenadine (n = 30)
Gender		
Male	15	17
Female	15	13
Mean age (yr)	42.9	43.2
Skin sensitivity to ragweed pollen (mean wheal diameter)		
>4.5 mm	6	5
3.8 – 4.5 mm	6	7
3.4 – 3.8 mm	6	6
2.8 – 3.4 mm	7	6
<2.8 mm	5	6
Severity of ragweed rhino- conjunctivitis during pre- vious season*		
Mild	9	7
Moderate	16	20
Severe	5	3
Skin sensitivity to <i>Alter- naria</i> and/or <i>Cladosporium</i> †	6	7
Skin sensitivity to grass pollen†	22	20
History of asthma	8	8

*Mild, symptoms well controlled by antihistamines or nasal spray/eye drops; moderate, symptoms well controlled by antihistamines and nasal spray/eye drops; severe, symptoms not well controlled by antihistamines and nasal spray/eye drops.

†>3 mm wheal on skin prick testing.

stop using concomitant nose and eye medications as soon as symptoms were not troublesome. Those with asthma used salbutamol aerosol, 200 µg when needed, up to four times per day. Subjects were instructed not to use other antihistamines.

Each morning and evening, subjects completed a diary of their symptoms.¹⁰ Sneezing, stuffy nose, runny nose, and eye symptoms were scored according to severity (0 = nil, 1 = mild, 2 = moderate, 3 = severe) and duration (0 = nil, 1 = a few short episodes, 2 = several episodes, 3 = continuous). Each evening subjects recorded the amount of nasal spray, eye drops, and salbutamol used during the previous 24 hours.

Subjects attended the clinic 1 week after starting medication, once during the last week of August when pollen counts were at their peak, and once during the fourth week of September. At each visit, diaries were reviewed, tablets and capsules counted for compliance, symptoms assessed to make sure they were well controlled, weight measured, and side effects documented. Duplicate skin prick tests with serial dilutions of ragweed-pollen extract and histamine acid phosphate were repeated 1 week after starting and on the

last day of trial medication dosing. In each subject, tests were performed at the same time of day so that the length of time after the morning medication was constant.

Daily mean ragweed pollen counts were measured throughout the pollen season with a Hirst volumetric spore trap (Burkard Manufacturing Co., Ltd., Rickmansworth, Hertfordshire, England),¹¹ located on the roof of the Hamilton Regional Laboratory at a height of 6 m above the ground.

Analysis

Daily symptom scores were expressed as the mean of the nocturnal and daytime severity and duration scores. For each of the 7 weeks of the study, mean daily symptoms scores and concomitant medication use were calculated. At the time of analysis, it was found that all variables showed instability of variance across the time periods. This was due to many subjects having zero symptoms scores and no concomitant medication use during the first and last weeks of the study. Therefore, a square root transformation was used to improve the statistical properties of the data. The two trial medications over the 7 weeks were compared by repeated-measures analysis. Skin sensitivity to the four serial dilutions of ragweed-pollen extract and the five serial dilutions of histamine acid phosphate were expressed as mean wheal diameter. Changes in sensitivity were determined by the paired *t* test. Results were considered significant at *p* < 0.05 (two tailed).

RESULTS

Sixty subjects entered the trial; one subject taking terfenadine did not complete it. Initial subject characteristics and matching criteria are listed in Table I. Subjects were well balanced between the two groups, with no evidence of any statistical differences for any of the variables.

Astemizole showed greater efficacy than terfenadine in controlling rhinorrhea (*p* = 0.046) (Fig. 2), but there was little difference between the two medications for sneezing, stuffy nose, eye symptoms, or cough (Figs. 2 and 3). Nine subjects taking astemizole and six taking terfenadine did not require any additional nasal spray; among those requiring nasal spray, considerably less per subject was used by the astemizole group (Fig. 4). These findings also suggest greater control of nasal symptoms by astemizole, but the numbers were small and the difference did not quite reach statistical significance (*p* = 0.13). Eye drop and salbutamol use were similar in the two groups.

Initial skin sensitivity to ragweed-pollen extract and histamine acid phosphate was similar in the two groups (Fig. 5). After 1 week of treatment, sensitivity was significantly reduced in both groups, with a significantly greater decrease in sensitivity to ragweed in

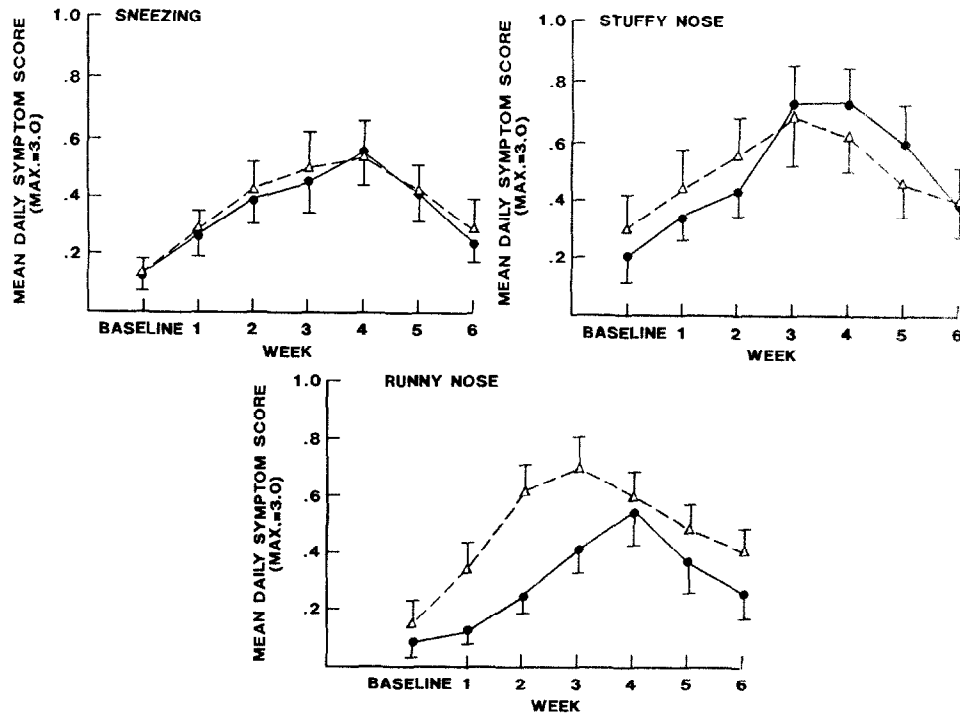


FIG. 2. Mean ($\pm$ SEM) daily nasal symptom scores of subjects taking astemizole (●) or terfenadine (Δ). Runny nose was better with astemizole ($p = 0.046$), but differences for sneezing and stuffy nose were not significant.

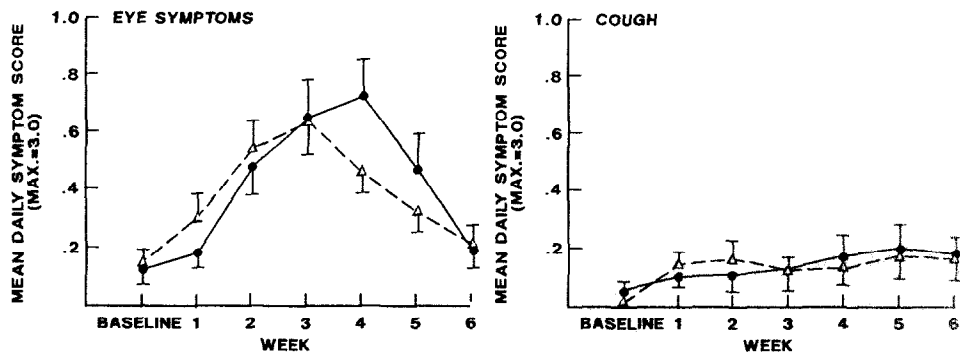


FIG. 3. Mean ($\pm$ SEM) daily eye symptom and cough scores of subjects taking astemizole (●) or terfenadine (Δ).

the astemizole group ($p = 0.04$). Tachyphylaxis to the two medications was examined by comparing the change in skin sensitivity between the first and seventh weeks of treatment. Sensitivity to histamine in the subjects taking astemizole remained very constant ($p > 0.3$), but those subjects receiving terfenadine demonstrated a small but significant increase in sensitivity ($p < 0.005$). The small difference in change in sensitivity between astemizole and terfenadine (approximately 10%) was also significant ($p = 0.047$).

In contrast, both medication groups showed an in-

crease in sensitivity to ragweed over the 7 weeks, but there was no evidence of any difference between the two medications ($p = 0.55$).

One subject taking terfenadine developed troublesome gastrointestinal symptoms that necessitated withdrawal from the study after 2 weeks. All other side effects in both groups were mild or transient. Increased appetite was reported by 11 subjects taking astemizole and 4 taking terfenadine, and there was a mean increase in weight of 1.1 kg in both groups, but this was not statistically significant. Dryness of the

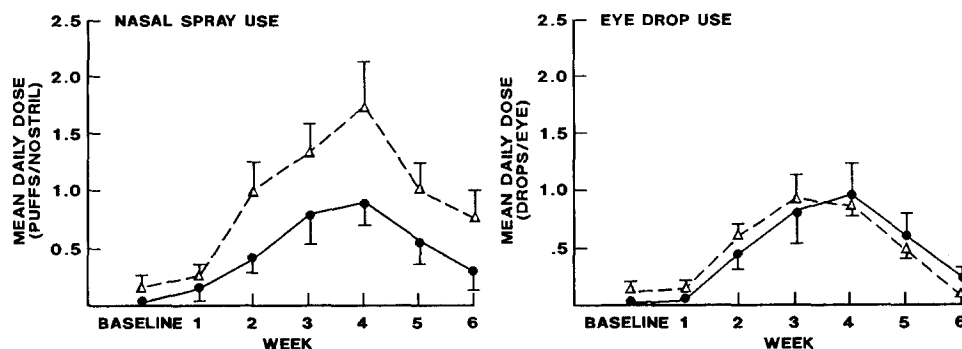


FIG. 4. Mean ($\pm$ SEM) daily concomitant medication use of subjects taking astemizole (●) or terfenadine (Δ).

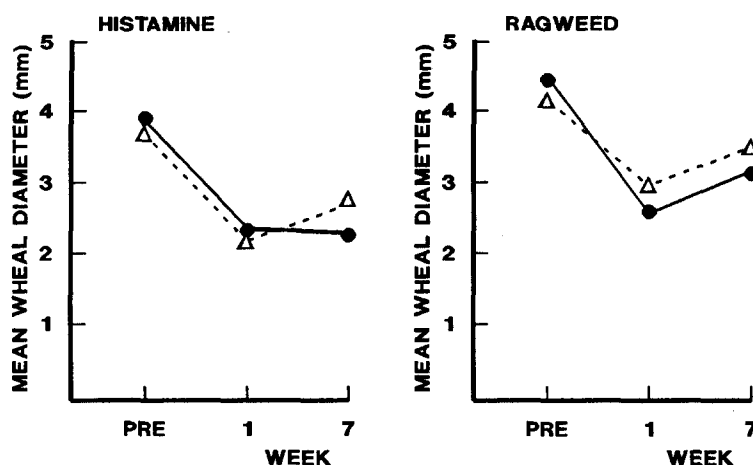


FIG. 5. Skin sensitivity to histamine and ragweed-pollen extract measured before treatment and 1 and 7 weeks thereafter of subjects taking astemizole (●) or terfenadine (Δ).

nose or mouth was reported by seven subjects receiving terfenadine and nausea was reported by three subjects taking astemizole and one taking terfenadine. Drowsiness occurred in six subjects taking astemizole and two taking terfenadine. Other single-subject events included, in the astemizole group, mild depression, increased frequency of nocturnal voiding, thirst, and headache, and in the terfenadine group, joint pain ($\times 2$), mental confusion, heavy menstruation, and headache.

Compliance with taking study medications was very good. Tablets were taken slightly more regularly (mean $\pm$ SD, 99% $\pm$ 5%) than capsules (97% $\pm$ 4%); the difference was due to the occasional omission of an evening capsule.

DISCUSSION

These results suggest that both astemizole (10 mg/day) and terfenadine (60 mg twice daily), when started before and continued daily through pollen ex-

posure, effectively control symptoms of rhinoconjunctivitis. In these doses, subjects who took astemizole had less rhinorrhea, fewer subjects required additional nasal spray, and, in those who did require additional nasal spray, the mean daily dose was lower. Although these differences were not large, they were statistically significant and consistent, suggesting that astemizole is more effective in controlling nasal symptoms than terfenadine. The results also demonstrate that the two medications have similar potency for eye symptoms. The skin test data suggest that more tachyphylaxis to histamine skin sensitivity may occur with terfenadine when the medications are taken on a continuous basis.

A placebo control group was not included in this study, because the individual efficacy of the two drugs in seasonal rhinoconjunctivitis has already been established.^{1,2} In one of the two previous comparisons between the two medications,⁵ it was observed that terfenadine showed less efficacy than placebo; how-

ever, in view of that study design, this was not really surprising. When symptoms were not controlled by study medications (astemizole, terfenadine, or placebo), subjects were "freely" treated with another antihistamine, clemastine. Symptom scores alone were then used to estimate efficacy, and the amount and effect of the additional medication were not taken into account. Unequal use of additional antihistamine by the three study groups probably masked the therapeutic effect of terfenadine and interfered with the comparison of the active medications. Nonetheless, our results agree with their observation that astemizole is more effective for the control of nasal symptoms. However, we differ in that we were unable to show any difference between the two medications for eye symptoms. In a single-blind comparison of terfenadine and astemizole, Wood⁶ enrolled subjects throughout the pollen season. Eye and nasal symptoms were not examined separately, but the overall symptom scores were better with astemizole.

One subject who received terfenadine was withdrawn from the study due to gastrointestinal symptoms. Otherwise, side effects in both treatment groups were mild or transient. In keeping with other studies, more subjects taking astemizole reported increased appetite, but weight gain in the two groups was similar. The other symptoms reported as possible side effects, such as drowsiness and mucosal dryness, were in comparable proportions to those observed in subjects receiving placebo in controlled trials of astemizole¹² and terfenadine.¹

After 7 weeks of continuous treatment with the study medications, there was a small but statistically significant increase in skin sensitivity to serial dilutions of histamine acid phosphate in the terfenadine group, but histamine sensitivity remained almost unaltered in those taking astemizole. This suggests that patients may build up a small amount of tolerance to terfenadine. However, a similar difference was not observed with the skin sensitivity to serial dilutions of ragweed-pollen extract. These data are more difficult to interpret, because both IgE and IgG ragweed-specific antibody levels change during the ragweed season, resulting in a change in the skin response to ragweed pollen extract. If tachyphylaxis were occurring with terfenadine, it would be expected that symptom scores and concomitant medication use would be greater in the terfenadine group toward the end of the study. However, there appeared to be no trend in the data supporting this (Figs. 2 and 3). Therefore, further placebo-controlled studies will be required to clarify whether tolerance to these medications develops.

In this study, the trial medications were used prophylactically; they were started before the ragweed

pollen season, when the subjects were virtually asymptomatic, and then used continuously throughout the season. This is the recommended treatment approach for astemizole, because stable serum levels are achieved only after 1 to 2 weeks of daily treatment.⁷ Terfenadine, on the other hand, is shorter acting⁶ and may be more suitable for a "when needed" approach to treatment. Because patients are often delinquent in starting to take medications before seasonal symptoms occur, and because some get caught by unexpected exposures to nonseasonal allergens, the two medications should also be compared based on a "when needed" approach to treatment.

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