Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: Effects after controlled ragweed pollen challenge in an environmental exposure unit

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Background: Allergic rhinitis affects nearly one in 10 Americans. Cetirizine is a newer once-daily selective H_1-antagonist. In traditional clinical trials, cetirizine has been shown to be safe and effective for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria.
Objective: To better characterize the efficacy and onset of action of cetirizine in a more controlled but clinically relevant setting, this agent was compared with loratadine and placebo in patients with symptomatic seasonal allergic rhinitis undergoing controlled pollen challenge in an environmental exposure unit (EEU).
Methods: This was a double-blind, randomized, parallel-group study. After screening, patients were exposed to ragweed pollen (primed) in the EEU (up to six exposures), and those with qualifying symptom scores were randomized to controlled pollen exposure (two periods of 5.5 to 6.5 hours over 2 days) and once-daily treatment with 10 mg cetirizine ($n = 67$), 10 mg loratadine ($n = 67$), or placebo ($n = 68$). The mean ragweed pollen level was 3480 ± 350 grains/m^3 (standard deviation). The primary efficacy variables were the total symptom complex (TSC) and the major symptom complex (MSC) scores. Symptoms were evaluated every half hour in the EEU throughout the study.
Results: Cetirizine produced a 36.7% mean reduction in TSC scores overall versus 15.4% with loratadine and 12.0% with placebo ($p \leq 0.01$). Cetirizine also produced a 37.4% mean reduction in MSC scores overall versus 14.7% with loratadine and 6.7% with placebo ($p \leq 0.01$). Onset of action as assessed by reductions in TSC and MSC scores versus placebo was evident within 1 hour with cetirizine ($p \leq 0.02$) and 3 hours with loratadine ($p \leq 0.03$). The incidence of treatment-related side effects was similar among groups, with headache reported most commonly in each group.
Conclusion: Cetirizine is well tolerated and effective in reducing symptoms of seasonal allergic rhinitis in patients undergoing controlled pollen challenge. (J Allergy Clin Immunol 1998;101:638-45.)

Key words: *Allergic rhinitis, cetirizine, environmental exposure unit, loratadine, placebo, pollen challenge, seasonal allergic rhinitis*

Antihistamines are commonly used for the treatment of allergic rhinitis, a condition that is estimated to affect 10% of the population in the United States (not including those with concomitant asthma) and accounts for 9.4 million office visits to physicians and $1.8 billion in direct and indirect costs each year.[1-4] Cetirizine is a new once-daily antihistamine with high specificity for the H_1-receptor.[5] This agent, characterized by a rapid onset of activity and a 24-hour duration of effect, has proved useful in the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in adults and in children 6 years of age or older.[6-9] Cetirizine is minimally metabolized, crosses the blood-brain barrier with difficulty, and has a low incidence of adverse effects.[5, 10, 11] Loratadine is also a once-daily antihistamine, with high specificity for the H_1-receptor and a reported 24-hour duration of effect.[12]

Clinical trials comparing cetirizine with other antihistamines have revealed at least comparable efficacy in reducing symptoms as measured in typical outpatient settings.[13-24] These studies have, for the most part, incorporated traditional designs. These studies are useful and necessary in characterizing the efficacy and safety of allergy drugs; however, they have the potential for considerable variability in allergen exposure, reliability of symptom assessments, and dosing compliance. Several studies have demonstrated that both cetirizine and loratadine have effectively reduced rhinitis symptoms. In a recent outdoor park study that employed novel design elements and data collection technology, cetirizine was found to produce significantly greater symptomatic relief among patients with seasonal allergic rhinitis when compared with loratadine or placebo.[24]

This study was designed to further explore the clinical characteristics of cetirizine and loratadine in a rigorously controlled, yet clinically relevant setting. That is, all participating subjects were evenly exposed in an environmental exposure unit (EEU) to predetermined levels of ragweed pollen comparable to those experienced in the outdoors during peak ragweed season in many localities in the United States.[25-29] The onset and duration of symptomatic response to 10 mg once daily

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Abbreviations used
EEU: Environmental exposure unit
MSC: Major symptom complex
TSC: Total symptom complex

cetirizine versus that of 10 mg once daily loratadine or placebo were assessed in patients with seasonal allergic rhinitis who were uniformly exposed to predetermined levels of ragweed pollen for two 6-hour periods over the course of 2 days in an EEU. Pollen levels were consistent with those observed during the peak of a typical ragweed season. By conducting the study in an EEU, much of the considerable variability encountered in traditional outpatient studies with regard to symptom assessment and levels of pollen exposure could be reduced.

METHODS

Study design

This was a 2-day, randomized, double-blind, parallel-group study conducted in the EEU at Queen's University (Kingston, Ontario, Canada) during August 1995. After a screening visit (Phase I), eligible patients participated in one or more priming sessions in the EEU (Phase II). Those with qualifying rhinitis symptom scores were then assigned in randomized fashion in accordance with a computer-generated randomization code to receive 10 mg once daily cetirizine, 10 mg once daily loratadine, or placebo for 2 days in blocks of six patients, with symptoms assessed by the patients during two 6-hour periods of controlled exposure to ragweed pollen in the EEU (Phase III). Patients completed the protocol in two groups of approximately 100 different individuals seated together in the EEU at one time. The study protocol and patient consent forms were approved by the appropriate institutional review board.

Patients

Written informed consent to participate was obtained from each study patient; such consent was provided by a parent or guardian for patients under the age of 21 years. The study included men and women, 16 years of age or older, with a history and diagnosis of seasonal allergic rhinitis caused by ragweed pollen and serious enough to require pharmacologic treatment each year for at least 2 years. Prevalent seasonal allergy had to have been documented by a recognized skin prick test of at least moderate reaction at Phase I or within the past year.

Patients were excluded from the study if, on physical examination, history, or laboratory evaluation, they were found to have serious diseases, significant disorders of the major organ systems, or other abnormalities except those related to underlying allergic rhinitis. Patients also excluded were those with clinically significant nasal anatomic deformities causing more than 50% obstruction (e.g., septal defects and polyps) and those who had experienced a recent episode of acute sinusitis or acute respiratory infection (including the common cold). Patients treated with chronic asthma medication, except β-agonist inhalers used in conjunction with exercise, were excluded from the trial. Likewise, patients were not enrolled if they were initiating or advancing immunotherapy during the course of the study or used H_1-receptor antagonists, decongestants or saline nasal sprays; allergic ophthalmic treatments; inhaled and/or topical corticosteroids; intranasal or optical cromolyn; monoamine oxidase inhibitors; reserpine; β-blockers; systemic corticosteroids; or astemizole within prespecified relevant periods of time. They were also excluded if they had an intolerance to antihistamines, had used an investigational drug within 1 month of the study, or had participated in a previous cetirizine study.

Women participating in the study were either not pregnant as verified by a negative serum pregnancy test at period 1, not of child-bearing potential, or using approved methods of contraception during the study. Nursing mothers could not participate.

Study sequence

At the screening visit (Phase I), medical and medication histories were obtained, a physical examination was conducted, and laboratory tests (hematology, serum chemistry, urinalysis, and serum pregnancy) and skin tests with prevalent allergens were performed. In Phase II, patients eligible to participate were primed to ragweed pollen during one or more exposure sessions in the EEU (for up to 6 sessions, typically lasting 2 to 2.5 hours, as needed to produce qualifying symptoms). At the beginning of each visit in Phase II, concomitant and allergy medications taken since the last assessment were recorded, as were any adverse events. Patients were instructed regarding completion of the symptom diary cards, and initial ratings of rhinitis symptoms were obtained. While in the EEU, patients rated rhinitis symptoms every 30 minutes during exposure until the criteria for a positive response to priming had been met or until 3 hours of exposure had elapsed. After each rating, patients moved to an adjacent position within the EEU. Adverse events and intervals when patients had to leave the EEU (maximum of two times) were also recorded. After pollen exposure, patients were transferred to a pollen-free room for follow-up and were observed for up to 1 hour.

On the first day of Phase III, patients continuing in the study returned to the EEU, reported adverse experiences and concomitant medications used since the last visit, and rated symptoms in scoring diaries at 8:30 AM, 9 AM, and 9:30 AM before administration of study medication (baseline). Those with qualifying symptom scores (total symptom rating score sum of $\geq$ 18 for the three half-hourly pretreatment evaluations) received the first dose of study medication in blinded fashion at 10 AM, and proceeded to rate symptoms every half hour up to 3 PM in the diaries provided (period 1). Patients were transferred to a pollen-free room for up to 1 hour of observation and returned to the EEU the next day at 7:30 AM for questioning concerning adverse events and concomitant drug use. Symptoms were rated again at 9 AM, 9:30 AM, and 10 AM before administration of the second dose of study medication (period 2) and at half-hour intervals until 2:30 PM (period 3). At a follow-up visit the next day, patients reported adverse experiences and concomitant medication use and underwent a physical examination and clinical summary evaluation.

EEU

The EEU is a modified room housed within the Kingston General Hospital in which up to 150 subjects may be seated comfortably at one time and exposed to uniform concentrations of ragweed pollen for periods of up to 14 hours. The design and operation of the EEU have been described in detail previously.[25-27] In this study the predetermined exposure target concentration was 3500 pollen grains/m^3 (3.5 grains/L), an amount comparable to that found in some environments during peak ragweed season.[28-37] Air conditioning afforded comparable lev-

TABLE I. Demographic characteristics at baseline

	Cetirizine	Loratadine	Placebo
No. of patients	67	67	68
Gender (no. [%])			
M	31 (46.3)	29 (43.3)	26 (38.2)
F	36 (53.7)	38 (56.7)	42 (61.8)
Ethnicity (no. [%])			
White	62 (92.5)	65 (97.0)	61 (89.7)
Black	0	0	2 (2.9)
Asian	2 (3.0)	1 (1.5)	3 (4.4)
Hispanic	0	1 (1.5)	1 (1.5)
Other	3 (4.5)	0	1 (1.5)
Mean age (yrs [range])	32.0 (16.2-71.8)	30.9 (16.2-80.0)	31.3 (16.6-69.1)
Mean weight (kg [range])	73.8 (44-129)	74.0 (50-175)	72.0 (45-124)
Mean duration of rhinitis history (yrs)	15.0 (3-50)	15.4 (2-55)	17.1 (2-40)

els of humidity (50% to 80%) and temperature (18° C to 22° C) during exposure sessions. A modified laser counter measured the ragweed pollen grains emitted into the room and recorded the concentrations on a microcomputer. Rotorods (Sampling Technologies, St. Paul, Minn.) positioned around the room were used to measure ragweed pollen concentrations during the exposure sessions, sampling at a rate of 47.3 L air/min. Feedback at 20-minute intervals the first hour and at 30-minute intervals thereafter allowed adjustment of pollen emission to maintain pollen levels within the desired range. Of note, particles other than ragweed pollen grains that could have been shed by patients during exposure sessions, such as hair and clothing fiber, were not seen when the rotorods were examined under the microscope after routine cleaning between study sessions.

Commercially available short ragweed pollen (*Ambrosia elatior;* Greer Laboratories Inc., Lenoir, N.C.) with an antigen E content of 3891 U/gm was used. The pollen was stored at a temperature of −22° C before use.

Study medication

During study Phase III, patients were administered once daily in blinded fashion either one tablet containing 10 mg cetirizine and one placebo capsule, one capsule containing 10 mg commercially available loratadine and one placebo tablet, or one placebo capsule and one placebo tablet. The dissolution of the encapsulated loratadine tablet was equivalent to that of the loratadine tablet alone.

Symptom assessments

Patients were required to rate symptoms every half hour in diaries provided in the EEU. With the exception of nose blows, sneezes, and stuffiness, symptoms were rated on a scale of 0 (none, no symptoms whatsoever) to 5 (very severe, bothersome and disabling). An 8-point scale was used to measure severity of nose blows and sneezes (0 to 5 = actual number; 6 to 9 = 6, 10 to 15 = 7, and >15 = 8). Stuffy nose (left and right sides) was assessed on a scale of 0 (clear, fully open with no obstruction of air passage) to 4 (blocked, cannot move any air through nostril). At the end of the study, patients were asked to assess their global satisfaction with the efficacy of treatment on a scale of 1 (excellent) to 5 (poor), and their personal satisfaction with treatment on a scale of 1 (exceptionally satisfied) to 5 (unsatisfied).

Safety

The incidence and severity of all observed and volunteered adverse experiences were recorded by the investigator as was use of concomitant medications. A physical examination and laboratory testing were performed at screening and at the final visit.

Outcome measures

Two predetermined composite variables (the total symptom complex [TSC] and the major symptom complex [MSC] scores) were used as the primary efficacy end points of clinical effectiveness. Six individual symptoms most dominant in the rhinitis-symptom profile (runny nose, sniffles, itchy nose, nose blows, sneezes, and watery eyes) formed the MSC severity score. These symptoms combined with four additional symptoms (itchy eyes and ears, itchy throat, cough, and postnasal drip) formed the TSC severity score. Secondary efficacy parameters included changes in TSC scores plus nasal congestion, changes in individual rhinitis symptoms, and subject global and satisfaction evaluations. Baseline measures were obtained by averaging the three half-hourly measures recorded before dosing in the EEU. For symptom assessments, three evaluation periods were compared: the average of the first 10 half-hourly postdose measures on day 1 (10:30 AM to 3 PM, period 1); the average of 23-, 23.5-, and 24-hour first postdose measures on day 2 (period 2); and the average of the second nine half-hourly postdose measures on day 2 (10:30 AM to 2:30 PM, period 3).

Statistical analysis

Because this study was conducted in a controlled setting, the variability in efficacy response between treatment groups was assumed to be smaller than that observed in an outdoor park setting. The sample size was based on the variability observed in a previous study, allowing a detection of 20% difference between cetirizine and placebo (standard deviation [SD] of the difference = 35%) in the mean percent reduction from baseline in either TSC or MSC at $\alpha = 0.05$, with an 80% power. With these assumptions, the number of patients required was 65 to 67 per treatment group.

For comparison of demographic characteristics, categorical variables (sex and race) were summarized by frequency distributions, and continuous variables (age, weight, and rhinitis history) were summarized by means and ranges. The chi-squared test[38] was used for categorical data, and a one-way

analysis of variance,[39] including terms for treatment, was used for the continuous data.

For TSC and MSC severity scores, the change from baseline was assessed, with a decrease in scores denoting reduction in symptoms. Analyses were performed for both the percentage change and the absolute change from baseline. Because these results were virtually identical, only percentage changes are reported herein. Baseline scores for both primary and secondary parameters were assessed by a one-way analysis of variance, including effects for treatment. Treatment effects at each evaluation period were analyzed. An intention-to-treat analysis, which included overall and end-point analyses, was conducted to minimize possible bias caused by the omission of early dropouts. End-point analyses were conducted on the basis of the second period mean over the first 24-hour period to assess the sustained effect of the first dose of treatment (end point 1) and the last observed period change noted for each patient (end point 2). Because the magnitude of changes could be a function of the baseline values, comparability of treatment groups was analyzed with an analysis of covariance model, including treatment effects with baseline value as a covariate. For TSC and MSC severity scores, because the necessary underlying assumptions had been met, efficacy was assessed with parametric analysis of covariance. However, a confirmatory nonparametric analysis (rank transform) was also performed and was found to be in agreement. A similar analysis was performed for TSC plus nasal congestion scores, and analyses were also run for absolute change in each of the individual rhinitis symptoms by using the same parametric model as used for TSC and MSC. Global improvement ratings for each of the treatment groups were summarized and analyzed with the Mantel-Haenszel[40] mean score test.

For safety assessments, all patients receiving at least one dose of study medication were included, and the duration of exposure and number of patients exposed to study drugs were summarized by treatment group. Treatment-emergent adverse experiences were summarized by body system and World Health Organization preferred terms. The proportion of patients with the most frequently reported individual adverse experiences were compared among the treatment groups by chi-squared tests.

Statistical significance was defined for all tests at p values of 0.05 or less. All comparisons were based on two-sided tests. The p values for drug effects were based on comparisons of adjusted or least-squares means obtained from the statistical analyses. Statistical analyses were performed with SAS,[41] release 6.10 (SAS Institute Inc., Cary, N.C.).

RESULTS

Patients

Of the 304 patients screened, 202 patients were eligible to participate and were randomized to treatment, including 67 patients each in the cetirizine and loratadine groups and 68 patients in the placebo group. Of these, 194 completed the trial; three patients in the cetirizine group and two patients in the placebo group discontinued therapy because of an insufficient clinical response, one patient each in the cetirizine and loratadine groups withdrew due to side effects, and one patient in the placebo group withdrew consent.

Demographic characteristics according to treatment group are presented in Table I; no significant differences in these characteristics were observed between groups. Slightly more than half of the patients (57%) were women. The mean age was 31 years (range, 16 to 80 years), and the mean weight was 73 kg (median, 69 kg; range, 44 to 175 kg). Patients had an average 16-year history of seasonal allergic rhinitis (range, 2 to 55 years). Baseline TSC and MSC severity scores were comparable between groups (Table II).

TABLE II. TSC and MSC severity scores at baseline according to treatment group

Variable	Treatment	*N*	Mean	SD	*p* Value*
MSC	Cetirizine	67	12.03	6.21	
	Loratadine	67	12.55	5.64	0.88
	Placebo	68	12.28	5.59	
TSC	Cetirizine	67	18.95	8.81	
	Loratadine	67	19.00	8.18	0.82
	Placebo	68	19.76	7.92	

*Overall treatment comparison.

Pollen counts

Summary data for ragweed pollen counts in the EEU overall and during each period are provided in Table III. The mean ragweed pollen level was 3480 ± 350 grains/m^3. Pollen counts were consistent throughout the study.

TSC severity scores

Cetirizine produced a 36.7% mean reduction in TSC scores overall versus 15.4% with loratadine and 12.0% with placebo (Table IV). Mean percent reductions with cetirizine were consistently greater than those for loratadine and placebo overall and in all three evaluation periods ($p \leq 0.01$). The end-point analysis of the percent reduction from baseline in TSC severity scores for the last period mean over the first 24 hours of treatment revealed reductions of 27.1% with cetirizine, 4.4% with loratadine, and 4.7% with placebo ($p \leq 0.01$, cetirizine versus loratadine and placebo). The end-point analysis based on data obtained in the last period also showed greater reductions with cetirizine (44.8%) compared with either loratadine (24.7%, $p \leq 0.01$) or placebo (22.5%, $p \leq 0.01$).

The onset of action with cetirizine was prompt, with significant reductions in TSC severity scores versus placebo evident 1 hour after the first dose ($p \leq 0.02$) and sustained throughout the dosing interval (Fig. 1). The onset of action of loratadine was evident by hour 3 ($p \leq 0.02$). The reduction in TSC score achieved with cetirizine differed significantly from that achieved with loratadine and placebo at hour 1 and throughout the first 24 hours, with the exception of hour 5, at which time the differences between cetirizine and loratadine were not statistically significant. Loratadine produced statistically significant reductions compared with placebo from hours 3 to 5 after the first dose ($p \leq 0.03$). Significant reductions in TSC scores were also evident with cetirizine compared with loratadine and placebo after the second dose ($p \leq 0.05$) except for cetirizine versus placebo at hour 24.5 ($p = 0.06$). The reductions observed in the loratadine group did not differ

TABLE III. Summary data for ragweed pollen (grains per cubic meter) in the EEU at baseline and each treatment period in phase III

Period	Group I (August 25-26, 1995)		Group II (August 27-28, 1995)	
	Mean	SD	Mean	SD
Baseline (−1.5-0 hrs)	3430	220	3860	190
Period 1 (0-5 hrs)	3160	310	3650	350
Period 2 (23-24 hrs)	3760	210	3520	290
Period 3 (24.5-28.5 hrs)	3650	270	3250	220
Overall	3440	360	3510	350

significantly from those of the placebo group after the second dose at any measure.

MSC severity scores

Cetirizine produced a 37.4% mean reduction in MSC scores overall versus 14.7% with loratadine and 6.7% with placebo (Table IV). Overall and at each period, the mean percent reduction in MSC scores for the cetirizine group was greater than corresponding loratadine and placebo means ($p \leq 0.01$). For the end-point analyses, as was the case with TSC scores, the percent reduction in MSC severity scores was significantly greater with cetirizine compared with loratadine or placebo ($p \leq 0.01$) for both end points.

Hourly mean percent reductions in MSC severity scores are shown in Fig. 2. The onset of action as assessed by reductions in MSC scores versus placebo was evident within 1 hour with cetirizine ($p \leq 0.01$) and 3 hours with loratadine ($p \leq 0.02$), patterns consistent with those observed for hourly TSC scores. The duration of action was maintained for 24 hours with cetirizine. With second dosing, cetirizine treatment also produced greater mean reductions ($p \leq 0.05$) in MSC scores versus loratadine and placebo at all postdose measures, except at hour 24.5 versus loratadine ($p = 0.14$).

Secondary efficacy parameters

The effects of therapy on the TSC plus nasal congestion scores were similar to those on TSC scores alone. Cetirizine produced a 33.7% mean reduction in TSC plus nasal congestion scores overall versus 13.7% with loratadine and 11.1% with placebo. Mean percent reductions with cetirizine were consistently greater than those for loratadine and placebo overall and in all three evaluation periods ($p \leq 0.01$).

Assessment of effects of therapy on individual symptoms revealed statistically significant ($p \leq 0.05$) greater reductions with cetirizine versus loratadine overall at both end points and at all three periods for nose blows, runny nose/sniffles, itchy nose, watery eyes, and postnasal drip; overall and at period 1 for sneezes; overall and at end-point 1 and period 2 for itchy eyes/ears; at end-point 1 and period 2 for itchy throat; and overall and at end-point 2 and periods 1 and 3 for stuffy nose. Statistically significant reductions ($p \leq 0.05$) for cetirizine versus placebo were observed overall and for all three periods for nose blows, sneezes, runny nose/sniffles, itchy nose, and postnasal drip; overall and at period 1, for watery eyes and itchy eyes/ears; and at period 1 for itchy throat and stuffy nose.

TABLE IV. Mean percent reduction from baseline in TSC and MSC severity scores overall and at each study period

	Treatment	Least-square mean percent reduction	
		TSC score	MSC score
Period 1	Cetirizine	38.3*†	36.8*†
	Loratadine	17.4	13.6
	Placebo	8.9	2.4
Period 2	Cetirizine	26.6*†	30.0*†
	Loratadine	4.5	7.3
	Placebo	5.6	0.5
Period 3	Cetirizine	45.1*†	45.6*†
	Loratadine	24.8	23.8
	Placebo	24.3	19.9
Overall	Cetirizine	36.7*†	37.4*†
	Loratadine	15.4	14.7
	Placebo	12.0	6.7

*$p \leq 0.01$ versus placebo.
†$p \leq 0.01$ versus loratadine.

For global assessment of efficacy, treatment with cetirizine resulted in a larger percentage of improved patients (60.9%) compared with loratadine (50.0%) and placebo (43.1%), but the differences between groups were not statistically significant. For appraisal of personal satisfaction with therapy, treatment with cetirizine resulted in a larger percentage of satisfied patients (64.1%) compared with loratadine (45.5%) and placebo (41.5%); the difference between cetirizine and placebo was significant ($p = 0.04$).

Adverse experiences

Both active study medications were well tolerated. The incidence of treatment-related side effects was similar among groups, with headache reported most commonly in each group. Headache occurred in 27% of patients receiving cetirizine, 33% of patients receiving loratadine, and 28% of patients receiving placebo. Fatigue occurred in 3% of patients receiving cetirizine, 1.5% of patients receiving loratadine, and 0% of patients receiving placebo. Other events occurring in 2% or more of patients included abdominal pain in 4% of patients receiving placebo; back pain, dyspepsia, and migraine, each occurring in 3% of the placebo group; and chest pain and fever, each occurring in 3% of the loratadine group. Two patients withdrew from the study because of adverse experiences. One patient given cetirizine 5 hours

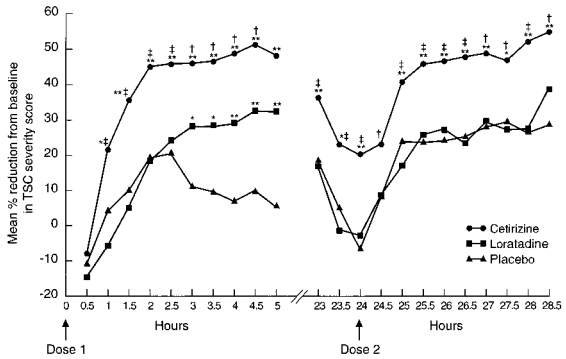

FIG. 1. Mean hourly percent reduction from baseline in TSC severity scores. $*p \leq 0.05$, $**p \leq 0.01$ versus placebo. $\dagger p \leq 0.05$, $\ddagger p \leq 0.01$ versus loratadine.

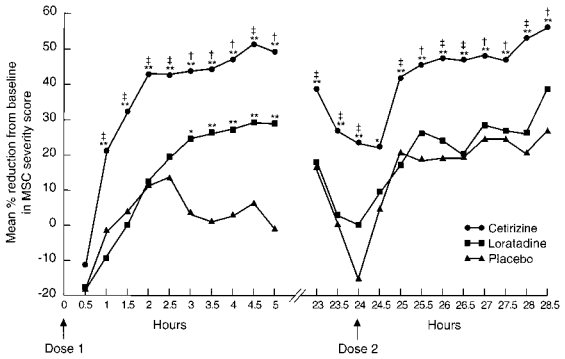

FIG. 2. Mean hourly percent reduction from baseline in MSC severity scores. $*p \leq 0.05$, $**p \leq 0.01$ versus placebo. $\dagger p \leq 0.05$, $\ddagger p \leq 0.01$ versus loratadine.

previously developed asthmatic symptoms. The other patient, given loratadine 23.5 hours previously, complained of nausea and some chest discomfort. In neither of these subjects were the symptoms believed to be related to study drugs. No significant differences were observed among groups for vital signs, body weight, findings on physical examination, or with regard to use of concomitant medications.

DISCUSSION

Among this large group of patients with seasonal allergic rhinitis who underwent carefully controlled ragweed pollen challenge over the course of 2 days in an EEU, the selective H_1-antagonist cetirizine produced reductions in TSC and MSC severity scores that were significantly greater than those achieved with placebo or loratadine overall and at each treatment period. Significant reductions in symptom scores were realized within 1 hour in patients administered cetirizine and were sustained throughout the study. Although loratadine did not produce changes in symptom scores overall or at the aggregate treatment periods that were significantly different from placebo, significant differences were observed from hours 3 to 5 after the first dose, indicating some level of therapeutic effect. The incidence of treatment-related side effects was similar among groups, with headache reported most commonly in each group.

The EEU is a large room into which is delivered uniform predetermined levels of ragweed pollen over the time periods required by a particular study. Not only is the pollen exposure consistent and evenly distributed among participating subjects, but also subject response to these levels is more accurately determined. These advantages make the EEU especially useful in determining precise information such as onset of action of medications, along with efficacy. The system is not intended to supplant multicenter field studies, which assess efficacy over a wide range of localities, but, rather, it obtains the kind of information not readily amenable to such field studies. Information about the comparability of activity of the several medications available for rhinitis assists prescribing physicians in their therapeutic choices.

The effects of cetirizine and loratadine on symptoms observed in this study are consistent with those reported by Meltzer et al.[24] in a park study comparing these two agents in patients with seasonal allergic rhinitis. In that randomized, double-blind, parallel group, 2-day study of 279 patients conducted during spring allergy season, 10 mg once daily cetirizine produced significantly greater mean reductions in TSC and MSC severity scores compared with 10 mg once daily loratadine and placebo. A more rapid onset of action was also observed with cetirizine. In that study loratadine had an overall efficacy profile similar to that of placebo. Two control features of the study are particularly notable. First, patients had been gathered at the same time at one of two outdoor park sites and remained in the park for significant portions of the day while rating symptoms. Thus patients were likely exposed to fairly consistent pollen levels within each site. Second, the patient diary cards used were scanned into the computer on site and were returned immediately for clarification or completion, increasing the reliability of the data collected.

The onset of action and efficacy of cetirizine observed in this study are also consistent with those observed in another multidrug comparative study conducted in the EEU.[25] In that placebo-controlled, randomized, double-blind study of 111 pollen-sensitive subjects, cetirizine and terfenadine, but not astemizole or loratadine, performed significantly better than placebo. Significant differences among groups occurred with regard to time of onset of definitive relief of symptoms, and a pairwise analysis revealed a rank order of cetirizine first, followed by terfenadine, loratadine, astemizole, and placebo. With the exceptions of the study by Cave and Billardon,[23] a randomized, double-blind, parallel-group of 41 patients with seasonal or perennial rhinitis, and the study by Meltzer et al.,[24] other clinical trials demonstrate no differences between cetirizine and loratadine.[20-22] In a 2-week, multicenter, double-blind study of 108 patients with seasonal allergic rhinitis conducted by Herman et

al.,[21] cetirizine and loratadine reduced global nasal and eye symptom scores at days 7 and 14 to a similar degree. Likewise, Braun et al.,[20] in a randomized, double-blind, 12-week study of 163 patients, found both agents to provide comparable symptomatic relief, as did Tarchalska-Krynska and Zawisza[22] in an open cross-over study of 56 patients with allergic rhinitis.

In this study both cetirizine and loratadine were well tolerated. There were no significant differences among treatment groups with regard to adverse experiences. Headache was the most frequently occurring side effect in each group. Unlike some other studies comparing these agents, somnolence did not occur in patients receiving cetirizine. In clinical studies the incidence of somnolence with cetirizine has been found to be dose-related, occurring in 6% of patients receiving placebo, 11% of patients receiving 5 mg cetirizine, and 14% of patients receiving 10 mg cetirizine; discontinuations caused by somnolence were not significantly different from placebo (1% vs 0.6% receiving placebo). A similar number of patients in each active treatment group withdrew from this study because of adverse events.

In general, traditional outpatient studies in patients with seasonal allergic rhinitis can provide useful information concerning the effects of therapy in a clinical setting more closely aligned to situations of daily living, but these studies are subject to considerable variability with regard to symptom assessment and levels of pollen exposure. Innovations in outdoor park study design and methodology have been successful in eliminating much of this variability. Even so, the timing of these and more traditional studies is restricted to periods of naturally occurring pollen exposure. Variability in pollen effects and levels from year to year and annual differences in concentration (which are dependent upon short-term and long-term weather conditions) introduce inconsistency in rhinitis symptoms, rendering results difficult to interpret within and between studies. Variations in personal habits and habitats, particularly time spent in air-conditioned environments, can also affect results as can emergent medical problems, including respiratory tract infections. Finally, the dynamics of the allergic state itself can result in enrollment of asymptomatic patients who, in previous years, experienced symptoms and had positive skin test responses.

In this study the EEU provided a reproducible exposure environment for testing the effects of cetirizine and loratadine on ragweed-induced symptoms in patients with seasonal allergic rhinitis. The absence of symptoms in nonallergic subjects indicates important evidence that the EEU environment itself does not produce nasal or ocular symptoms.[26] The concentration of pollen in the EEU was comparable to that found in many environments during peak ragweed season, and this was achieved with control over the many variables usually encountered in other or less rigorously controlled testing situations. The advantage of this method over direct nasal and ocular application techniques includes the ability to provide reproducible uniform exposure to a large number of patients simultaneously in a situation comparable to natural exposure.

This study demonstrates that in a tightly controlled setting of consistent reproducible pollen challenge, cetirizine was well tolerated and highly effective in reducing symptoms of seasonal allergic rhinitis, providing clinical efficacy greater than that of placebo or loratadine in this setting.

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REFERENCES

1. Naclerio RM. Allergic rhinitis. N Engl J Med 1991;325:860-9.
2. Centers for Disease Control and Prevention: Vital and Health Statistics, Current Estimates From the National Health Interview Survey, 1994. US Dept of Health and Human Services, Public Health Service, National Center for Health Statistics; DHHS Publication PHS 96-1521; December 1995. p. 82.
3. Centers for Disease Control and Prevention: Vital and Health Statistics, National Ambulatory Medical Care Survey: 1991 Summary. US Dept of Health and Human Services, Public Health Service, National Center for Health Statistics; DHHS Publication PHS 94-1777; May 1994. p. 24.
4. McMenamin P. Costs of hay fever in the United States in 1990. Ann Allergy 1994;73:35-9.
5. Sheffer AL, Samuels LL. Cetirizine: antiallergic therapy beyond traditional H_1 antihistamines. J Allergy Clin Immunol 1990;86: 1040-6.
6. Lockey RF, Findley S, Mitchell DQ, Woehler T, Lieberman P, Nicodemus CF. Effects of cetirizine versus terfenadine in seasonal allergic rhinitis. Ann Allergy 1993;70:311-5.
7. Mansmann HC, Altman RA, Berman BA, Buchman E, Dockhorn RJ, Leese PT, et al. Efficacy and safety of cetirizine therapy in perennial allergic rhinitis. Ann Allergy 1992;68:348-53.
8. Kalivas J, Breneman D, Tharp M, Bruce S, Bigby M, et al. Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. J Allergy Clin Immunol 1990;86:1014-8.
9. Spencer CM, Faulds D, Peters DH. Cetirizine: a reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. Drugs 1993;46:1055-80.
10. Wood SG, John BA, Chasseaud LF, Yeh J, Chung M. The metabolism and pharmacokinetics of ^{14}C-cetirizine in humans. Ann Allergy 1987;59:31-4.
11. Snyder SH, Snowman AM. Receptor effects of cetirizine. Ann Allergy 1987;59:4-8.
12. Dockhorn RJ, Bergner A, Connell JT, Falliers CJ, Grabiec SV, Weiler JM, et al. Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. Ann Allergy 1987;58:407-11.
13. Simons FER, McMillan JL, Simons KJ. A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo: suppressive effects on histamine-induced wheals and flares during 24 hours in normal subjects. J Allergy Clin Immunol 1990;86:540-7.
14. Backhouse CI, Renton R, Fidler C, Rosenberg RM. Multicentre, double-blind comparison of terfenadine and cetirizine in patients with seasonal allergic rhinitis. Br J Clin Pharmacol 1990;44:88-91.
15. Caiaffa MF, Iudice A, Macchia L, Tursi A, Vergallo G, Sacerdoti G, et al. Multicenter double-blind comparative study of terfenadine and cetirizine in hay fever. J Invest Allergol Clin Immunol 1992;2:162-6.
16. Lockey RF, Widlitz MD, Mitchell DQ, Lumry W, Dockhorn R, Woehler T, et al. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996;76:448-54.
17. Rijntjes E, Ghys L, Rihoux J-P. Astemizole and cetirizine in the treatment of seasonal allergic rhinitis: a comparative double-blind, multicentre study. J Int Med Res 1990;18:219-24.
18. Harcup JW, Hawkes G, Saul PA. The efficacy and sedative profile of

astemizole and cetirizine in the treatment of grass pollen hayfever in general practice. Br J Clin Pharmacol 1993;47:131-5.
19. Berkowitz RB, Dockhorn R, Lockey R, Findlay S, Howland WC, Mitchell DQ, et al. Comparison of efficacy, safety, and skin test inhibition of cetirizine and astemizole. Ann Allergy Asthma Immunol 1996;76:363-8.
20. Braun JJ, Conraux C, Bebear JP, Pignat JC, Haguenauer JP, Dubreuil C, et al. Evaluation of the effectiveness and tolerability of loratadine in seasonal allergic rhinitis [in French]. C R Ther Pharmacol Clin (France) 1992;10/98:19-24.
21. Herman D, Arnaud A, Dry J, Latil G, Pauli G, Perrin-Fayolle M, et al. Clinical effectiveness and tolerance of loratadine versus cetirizine in the treatment of seasonal allergic rhinitis [in French]. Allerg Immunol (Paris) 1992;24:270-4.
22. Tarchalska-Krynska B, Zawisza E. A 6-week, cross-over study comparing cetirizine and loratadine in seasonal allergic rhinitis [in Polish]. Pneumonol Alergol Pol 1994;62:573-7.
23. Cave J-P, Billardon M. Comparaison de l'efficacité de la cétirizine à celle de la loratadine sur la rhinite saisonnière ou per-annuelle. Immunologie Médicale 1991;8:87-90.
24. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. J Allergy Clin Immunol 1996;97:617-26.
25. Day JH, Briscoe M, Clark RH, Ellis AK, Gervais P. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. Ann Allergy Asthma Immunol 1997;79:163-72.
26. Donovan JP, Buckeridge DL, Briscoe MP, Clark RH, Day JH. Efficacy of immunotherapy to ragweed antigen tested by controlled antigen exposure. Ann Allergy Asthma Immunol 1996;77:74-80.
27. Day JH, Buckeridge DL, Clark RH, Briscoe MP, Phillips R. A randomized, double-blind, placebo-controlled, controlled antigen delivery study of the onset of action of aerosolized triamcinolone acetonide nasal spray in subjects with ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1996;97:1050-7.
28. Frenz DA, Palmer MA, Hokanson JM, Scamehorn RT. Seasonal characteristics of ragweed pollen dispersal in the United States. Ann Allergy Asthma Immunol 1995;75:417-22.
29. Buck P, Levetin E. Weather patterns and ragweed pollen production in Tulsa, Oklahoma. Ann Allergy 1982;49:272-5.
30. Solomon WR. Volumetric studies of aeroallergen prevalence. I. Pollens of weedy forbs at a Midwestern station. J Allergy Clin Immunol 1976;57:318-27.
31. Ogden EC, Hayes JV, Raynor GS. Diurnal patterns of pollen emission in ambrosia, phleum, zea, and ricinus. Am J Bot 1969;56: 16-21.
32. Arbesman CE. Buffalo and Western New York State. In: Samter M, Durham OC, editors. Regional allergy of the United States, Canada, Mexico, and Cuba. Springfield: Charles C. Thomas Publisher; 1955. p. 31-8.
33. Connell JT. A novel method to assess antihistamine and decongestant efficacy. Ann Allergy 1979;42:278-85.
34. Habenicht HA, Burge HA, Muilenberg ML, Solomon WR. Allergen carriage by atmospheric aerosol. II. Ragweed-pollen determinants in submicronic atmospheric fractions. J Allergy Clin Immunol 1984;74: 64-7.
35. Solomon WR. Aerobiology of pollinosis. J Allergy Clin Immunol 1984;74:449-61.
36. Driessen MNBM, Quanjer PH. Pollen deposition in intrathoracic airways. Eur Respir J 1991;4:359-63.
37. Solomon WR, Matthews KP. Aerobiology and inhalant allergens. In: Middleton E, Reed CE, Ellis EF, editors. Allergy: principles and practice. 2nd ed. St. Louis: Mosby, Inc.; 1983. p. 1143-202.
38. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley & Sons; 1973. p. 14-22.
39. Winer BJ. Statistical principles in experimental design. 2nd ed. New York: McGraw-Hill Book Company; 1971. p. 205-10, 228-32, 240-4, 752-65.
40. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22: 719-48.
41. SAS Procedures Guide. Version 6. 3rd ed. SAS/STAT User's Guide, Version 6. 4th ed. Vol I and II. Cary (NC): SAS Institute Inc.