Randomized Double-Blind Comparison of Cetirizine and Fexofenadine after Pollen Challenge in the Environmental Exposure Unit: Duration of Effect in Subjects with Seasonal Allergic Rhinitis

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ABSTRACT

There is published evidence that cetirizine has a longer duration of effect than fexofenadine. This study compared duration of effect and other measures of efficacy of cetirizine,10 mg; fexofenadine, 180 mg; and placebo in allergic subjects exposed to pollen in the Environmental Exposure Unit. Eligible subjects (n = 575) were exposed to ragweed pollen (day 1, 7 hours; day 2, 5 hours) and randomized in double-blind fashion to once-daily cetirizine, 10 mg; fexofenadine, 180 mg; or placebo. The total symptom severity complex (TSSC) score, the primary efficacy variable, was based on four rhinoconjunctivitis symptoms rated at 20-minute intervals. Treatment evaluation was divided into three periods: period 1 TSSC, average of 15 scores obtained 0–5 hours after the first dose; period 2 TSSC, average of 9 scores obtained 21–24 hours after the first dose; and period 3 TSSC, average of 6 scores obtained 0–2 hours after the second dose. The primary efficacy end point was the change from baseline TSSC at period 2. Baseline TSSC was the final pretreatment score on day 1 and was 9.7 for cetirizine, 9.8 for fexofenadine, and 9.7 for placebo. For the primary efficacy end point, the reduction in baseline TSSC at period 2 was greater for cetirizine (−3.6) compared with fexofenadine (−2.7; $p < 0.001$) and placebo (−2.0; $p < 0.001$), representing a 33% greater reduction for cetirizine versus fexofenadine. Cetirizine continued to reduce TSSC more than fexofenadine (−5.2 versus −4.6; $p = 0.017$) and placebo (−3.9; $p < 0.001$) (period 3). Similar efficacy was observed in period 1 for both active treatments. Treatment-related adverse events were similar in all groups with an incidence of somnolence of 1.3% for both active medications. In conclusion, cetirizine produced a 33% greater reduction in SAR symptoms over the 21- to 24-hour interval after the first dose and for 40 minutes after the second dose, indicating a superior and longer duration of effect, which is relevant because both are once-daily medications. Onset of action was comparable and both treatments were safe and well tolerated.
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Seasonal allergic rhinitis (SAR) is characterized by a clustering of nasal and ocular symptoms triggered by dispersion of grass, weed, and tree pollen. Antihistamines specific for the H_1-receptor are used commonly to treat SAR but few studies evaluate key aspects of efficacy, including onset of action and 24-hour duration of effect. Many of the newer antihistamines such as cetirizine and fexofenadine are approved for once-daily use, particularly to enhance patient convenience and compliance. Therefore, pa-

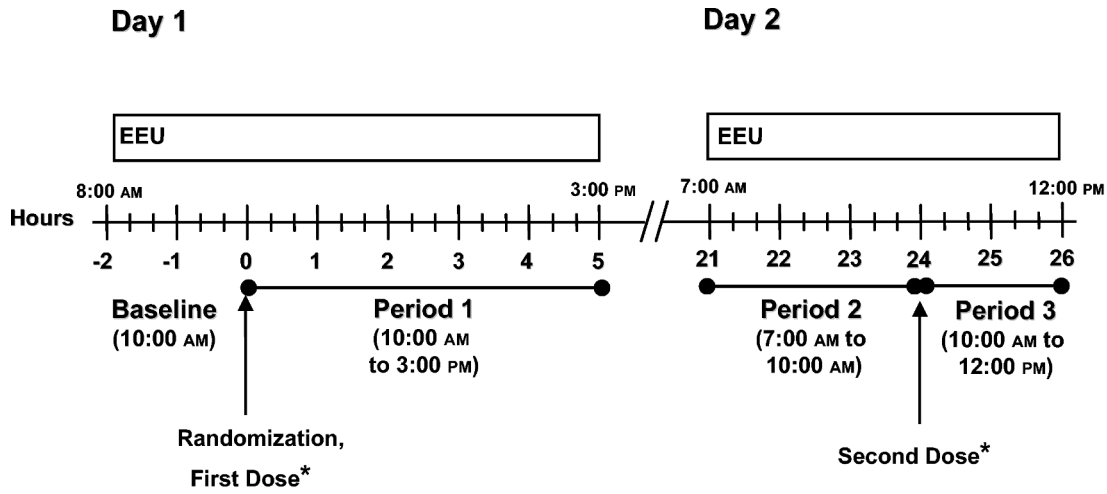

Figure 1. *Double-blind treatment schedule in the EEU. *Cetirizine, 10 mg; fexofenadine, 180 mg; or placebo (2.5:2.5:1).*

tients expect early onset of action and full 24-hour effect evident at the end of the dosing interval. Accordingly, we believe that information relative to the 24-hour duration of effect of antihistamines is important in their use for the treatment of SAR.

Cetirizine is indicated, in the United States, for the relief of SAR symptoms in adults and children ≥2 years of age and for perennial allergic rhinitis and chronic idiopathic urticaria in adults and in infants ≥6 months of age as well as older children. The recommended initial dose of cetirizine in adults and children ≥6 years is 5 or 10 mg once daily; in children 2–5 years of age, 2.5 or 5 mg once daily, and in infants 6–23 months, 2.5 mg once daily. Fexofenadine is indicated for the treatment of SAR and chronic idiopathic urticaria in adults and children ≥6 years of age. The recommended initial dose of fexofenadine for SAR in adults and children ≥12 years of age is 60 mg twice daily or 180 mg once daily; in children 6–11 years of age, it is 30 mg twice daily.

The antihistaminic activity of cetirizine is well described,[1] and its clinical benefits and safety profile for SAR versus placebo and other agents have been characterized in multicenter studies,[2–5] a park study,[6] and studies in the Environmental Exposure Unit (EEU).[7–9] Likewise, numerous multicenter studies[10–14] and an EEU study[15] have characterized the efficacy and safety profile of fexofenadine. However, there are relatively few well-controlled comparative studies that evaluate key aspects of efficacy, including onset of action and 24-hour duration of effect. In wheal-and-flare studies, cetirizine produced greater inhibition of histamine effects in the skin than fexofenadine and exhibited a longer duration of action.[16–18] A 2-week multicenter study of subjects with SAR by Howarth *et al.* revealed similar symptom relief with cetirizine, 10 mg once daily, and fexofenadine, 120 or 180 mg once daily, based on an average of two daily symptom diary measures.[19] However, a shorter but more controlled comparison of cetirizine, 10 mg once daily, and fexofenadine, 120 mg once daily, in the Vienna Challenge Chamber found both agents provided comparable symptom relief for the first 4 hours after the initial dose but greater reductions in symptom scores with cetirizine by the end of the dosing interval, indicating a better duration of action with this agent.[20]

It is apparent that adequate well-controlled studies directly comparing cetirizine and fexofenadine are needed to help clarify the relative duration of effect of these agents, because both are administered once daily to relieve symptoms of SAR. This requires a model that would specifically address this important component of antihistamine performance. The EEU is a self-contained, rigorously controlled system in which cohorts of up to 160 subjects at a time are uniformly exposed to predetermined levels of pollen that are consistent over the course of a study, without many of the commonly encountered confounding factors associated with multicenter studies.[21] We conducted a large, randomized, double-blind, placebo-controlled 2-day study of cetirizine, 10 mg once daily, and fexofenadine, 180 mg once daily, in the EEU located at the Kingston General Hospital in Kingston, Ontario. This is the first head-to-head placebo-controlled study comparing cetirizine and fexofenadine in the controlled setting of the EEU.

METHODOLOGY

Study Design and Conduct

This was a randomized, double-blind, placebo-controlled, parallel-group EEU study of the effects of cetirizine and fexofenadine in ragweed-sensitive subjects with SAR. After unblinded screening and priming phases, five cohorts of eligible subjects entered a third randomized, double-blind 2-day phase of symptom assessment during pollen exposure and study treatment (Fig. 1). Each cohort was studied for a 2-day period between July 21 and September 30, 2001 in the EEU at Kingston General Hospital

(Kingston, Ontario, Canada). The study was completed according to the guidelines of Good Clinical Practice and conducted in full compliance with the World Medical Assembly Declaration of Helsinki and its most recent amendments. The study was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. All participants provided written informed consent or parental consent/assent and if individuals were <18 years of age.

Participants

All randomized subjects were outpatients ≥16 years of age. The study included men, and women either not of childbearing potential or agreeing not to become pregnant (and using defined effective methods of contraception). Participants had documented SAR to ragweed pollen severe enough to require pharmacologic treatment for the past 2 consecutive years. The diagnosis was confirmed by skin-prick test to ragweed antigen at or within 1 year of screening. Individuals with known allergies to study medications or excipients were not eligible to participate. Subjects with clinically significant nasal anatomic deformities causing >50% obstruction also were excluded, as were those with acute or chronic sinusitis, otitis media, or upper-respiratory tract infections (including coryza) within 30 days of priming and asthma requiring medication beyond occasional use of inhaled short-acting β2-agonists. Subjects could not be initiating or advancing immunotherapy or using corticosteroids, leukotriene modifiers/antagonists, cromolyn, ipratropium bromide, monoamine oxidase inhibitors, reserpine, β-blockers, astemizole, norastemizole, monoclonal anti-immunoglobulin E antibody, or other miscellaneous antiallergy/decongestant treatments within prespecified periods. Subjects taking agents with a potential for interactions with study medication or potential effects on symptoms were disqualified, as were those who had recently donated blood or participated in other studies. Subjects were required to be free of other predefined illnesses or disorders, which in the judgment of the investigator were determined to be clinically significant and/or alter the subject's ability to participate in the clinical trial.

Study Sequence

The study sequence was divided into three phases (phases I-III). Potential subjects were screened in phase I according to prespecified study inclusion and exclusion criteria. Subjects satisfying study entrance criteria were invited to return to the EEU for phase II, the priming phase, to activate specific allergic reactivity. During this phase, subjects' unmedicated responses to up to six controlled ragweed pollen exposures for up to 3 hours per session were determined by self-assessment, performed at 30-minute intervals, of five rhinoconjunctivitis symptoms: runny nose, sneezing, itchy nose/palate/throat, itchy/watery eyes, and stuffy nose, though the first four symptoms, excluding stuffy nose, were used to determine eligibility. Symptoms were rated on a diary score card on a scale of 0 (absent) to 3 (severe). Subjects with minimum total symptom severity scores of ≥5 were eligible for randomization to double-blind treatment in phase III.

Eligible subjects returned to the EEU in phase III (Fig. 1) in one of five cohorts, each assessed over a 2-day period, with all members of a particular cohort seated at the same time in the EEU during uniform pollen exposure. During day 1 of phase III, subjects entered the EEU at 8:00 A.M. and began rating rhinoconjunctivitis symptoms every 20 minutes in their diaries according to the established rating system. Subjects with total qualifying symptom scores ≥5 (the four symptoms, as in priming, excluding stuffy nose) recorded at the 9:40 A.M. evaluation were randomized to double-blind once-daily treatment at 10:00 A.M. with cetirizine, 10 mg; fexofenadine, 180 mg; or placebo in double-dummy fashion in a 2.5:2.5:1 ratio by means of a single computer-generated randomization scheme. Symptoms were assessed every 20 minutes in the EEU during pollen exposure for an additional 5 hours. Subjects returned the next day at 7:00 A.M. for a 5-hour period of pollen exposure, with symptoms rated every 20 minutes. The second dose of study medication was administered at 10 A.M., allowing for 2 hours of symptom assessment after the dose during pollen exposure on day 2.

EEU

The EEU located at the Kingston General Hospital has been described in detail[21] and is well established and validated as an appropriate and reproducible environment in which to assess onset of action and other measures of efficacy including duration of effect of antihistaminic therapy in large groups of subjects simultaneously during controlled pollen exposure.[7–9,21] As in previous EEU studies, ragweed pollen was dispersed to achieve target exposure of 3500 grains ($\pm$500)/m^3 at each session, a level consistent with that occurring in nature during peak allergy season in many regions, and producing the full spectrum of clinical symptom responses from minimal to severe, which is typical for SAR subjects.

Study Medication

A double-dummy technique was used whereby cetirizine, 10-mg tablets, and overencapsulated fexofenadine, 180-mg tablets, and their placebo equivalents were administered in the EEU at 10:00 A.M. each day of phase III, for a total of two doses. Prior dissolution studies confirmed that overencapsulation did not alter the bioavailability of fexofenadine.

Symptom Evaluation

The rhinoconjunctivitis symptoms of runny nose, sneezing, itchy nose/palate/throat, itchy/watery eyes, and stuffy nose were individually self-rated on a scale of 0

(absent), 1 (mild), 2 (moderate), and 3 (severe) in subject diaries. One diary was completed for each specified assessment interval (at 30-minute intervals in phase II and at 20-minute intervals in phase III). At the conclusion of the final treatment day, subjects also completed a subject global evaluation assessment of treatment effectiveness, rated on a 7-point scale ranging from 1 (major improvement) to 7 (severe worsening). In addition, subjects rated personal satisfaction with treatment on a 5-point scale ranging from 1 (very satisfied) to 5 (very unsatisfied). They also rated their willingness to take the study medication again for SAR on a scale of 1 (definitely would) to 5 (definitely would not).

General Medical/Safety Assessments

A limited physical examination and laboratory assessments were performed at screening, and the physical examination was repeated at withdrawal or at the end of the study for randomized subjects. Adverse events and concomitant medication use were recorded before entering the EEU each day of phases II and III and at the end of the study and whenever adverse events were observed and/or reported in the EEU. In addition, all subjects were contacted by phone at least 1 week after the final visit to assess adverse events that might have occurred for the week after the final dose of study medication was received.

Outcomes Measures

The primary efficacy end point was the change in total symptom severity complex (TSSC) score from baseline at period 2, a measure of treatment duration of effect after the first dose. Secondary efficacy end points included change from baseline TSSC score at periods 1 and 3 and at each 20-minute interval measured on days 1 and 2 for all three periods; changes from baseline in TSSC score + stuffy nose at periods 1, 2, and 3 and at each individual 20-minute interval of days 1 and 2 for each period; changes from baseline in individual symptoms at periods 1, 2, and 3; and, at the end of the study, subject global evaluation and personal satisfaction ratings and subjects' willingness to take study medication again.

The TSSC score was used to measure rhinoconjunctivitis symptoms during the course of the study. The TSSC score was defined as the sum of self-assessed severity scores for the four symptoms of runny nose, sneezing, itchy nose/palate/throat, and itchy/watery eyes. For analysis of efficacy data, the baseline evaluation was defined as the final pretreatment symptom assessment on day 1 of phase III (*i.e.*, at 9:40 A.M.) and treatment evaluations were divided into three predefined periods, allowing for closer examination of onset and duration of effects: period 1, the average of the 15 postdose symptom scores on day 1 of phase III; period 2, the first nine assessments on day 2 of phase III before administration of the second dose; and period 3, the average of the 6 postdose symptom scores on day 2 of phase III.

Safety was assessed by reporting the incidence and severity of adverse events that occurred. Results from measurements of vital signs and physical examinations were also used. Treatment-emergent adverse events were those events occurring for the first time in a subject during the active treatment period (phase III) or those begun before active treatment but increasing in severity during treatment. Adverse events judged by the investigators most likely to have been caused by study drug or for which causality was unknown were categorized as treatment related.

Statistical Analysis Plan

The sample size of the study was determined based on the primary efficacy end point, TSSC change from baseline to period 2, with the comparison of interest being that between the cetirizine-treated and fexofenadine-treated groups. A total of 225 subjects in each active treatment group were needed for the study to have at least 80% power for a two-sided test to detect a 1.06-point difference in the primary efficacy end point between the active treatment groups. A 2.5:2.5:1 randomization ratio was used, providing a planned placebo group sample size of 90 subjects. The secondary comparison of either active treatment versus placebo had at least 80% power to detect a 1.4-point difference in the primary end point. All tests were two-sided at the 5% significance level, assuming a pooled SD = 4.0.

The primary end point was assessed in the intent-to-treat population, which included all subjects who took one or more doses of study medication and who had efficacy data at baseline and one or more postbaseline time points. Analysis of covariance models with terms for treatment group and baseline as covariate were used to compare the three treatment groups with respect to changes from baseline for primary and secondary efficacy end points that were continuous variables. Pairwise testing was performed on efficacy end points using Fisher's protected least significant difference. An analysis of variance model was used to compare primary efficacy data for the three treatment groups at baseline.

Global/satisfaction response ratings and willingness to take medication again were tested using the Mantel–Haenszel statistic for row mean scores. If significant differences among the three treatments emerged, a second test using only the cetirizine and fexofenadine groups was performed.

Safety analysis was undertaken on subjects who took at least one dose of study medication and had any follow-up safety data. Incidence and severity of treatment-emergent and treatment-related adverse events, discontinuations due to adverse events, dose reductions or temporary discontinuations due to adverse events, and serious adverse events were summarized.

SAR and non-SAR medications used for the 3-month period before the study and non-SAR medications taken during the study were summarized. Laboratory data were listed, with abnormal values noted. Vital signs were sum-

TABLE I

Demographic Characteristics at Baseline According to Treatment Group

	Cetirizine	Fexofenadine	Placebo
No. of subjects	240	239	96
Gender [no. (%)]			
Men	115 (47.9)	103 (43.1)	37 (38.5)
Women	125 (52.1)	136 (56.9)	59 (61.5)
Ethnicity [no. (%)]			
White	223 (92.9)	231 (96.7)	89 (92.7)
Black	7 (2.9)	3 (1.3)	2 (2.1)
Asian	7 (2.9)	2 (0.8)	3 (3.1)
Other	3 (1.3)	3 (1.3)	2 (2.1)
Mean age (yr)*	30.6 (16–73)	32.7 (16–86)	33.6 (16–68)
Mean weight (kg)*	76.6 (40–128)	75.6 (43–143)	79.1 (40–160)
Mean duration of rhinoconjunctivitis (yr)*	16.2 (2.7–54.6)	16.7 (1.9–61.6)	17.7 (1.9–50.1)

** Values in parentheses are ranges.*

marized. Physical examination findings were noted as normal or abnormal.

RESULTS

Participant Disposition

Among the 836 subjects screened, 575 subjects were randomized to treatment in phase III and 574 of these subjects were eligible for the intent-to-treat analysis, including 240 subjects in the cetirizine group (100%), 238 subjects in the fexofenadine group (99.6%), and 96 subjects in the placebo group (100%). One subject randomized to fexofenadine was not eligible for the intent-to-treat analysis because she discontinued at the time of the first dose because the overencapsulated pill lodged in her throat; however, this subject was included in the safety analysis. Five hundred sixty-three subjects completed the study: there were 236 subjects in the cetirizine group (98.3%), 232 subjects in the fexofenadine group (97.1%), and 95 subjects in the placebo group (99.0%).

Demographics/Allergy History

Demographic characteristics and disease history were comparable among treatment groups (Table I). Prestudy use of medications for allergic disorders was similar, ranging from 25.0 to 28.5% across groups.

Pollen Counts

Consistent pollen exposure in the EEU was achieved throughout the study. The mean ragweed pollen concentrations recorded in the EEU for the five cohorts studied (two cohorts in July, two cohorts in August, and one cohort in September of 2001) ranged from 3493 ± 535 grains/m^3 to 3758 ± 371 grains/m^3.

TSSC Scores

Mean baseline TSSC scores were comparable among treatment groups: 9.7 for cetirizine, 9.8 for fexofenadine, and 9.7 for placebo. The least square mean change from baseline in TSSC at each study period according to treatment is presented in Fig. 2. For the primary efficacy end point, change from baseline in mean TSSC score in period 2 (21–24 hours after the first dose), cetirizine produced a greater reduction (−3.6) compared with fexofenadine (−2.7; $p < 0.001$) and placebo (−2.0; $p < 0.001$). Subjects on cetirizine realized a 33% greater reduction in TSSC score than subjects on fexofenadine at this period. Fexofenadine provided a greater reduction in TSSC score from baseline at period 2 compared with placebo ($p = 0.025$).

Cetirizine and fexofenadine afforded greater symptom relief compared with placebo for the secondary end points of changes from baseline at periods 1 and 3 as well. Symptom score reductions were comparable between active treatment groups (−4.3 and −4.4, respectively) and better than placebo (−3.3; $p < 0.001$ for both) for period 1, which encompassed the first 5 hours after dosing. Greater TSSC score reductions also were evident with cetirizine (−5.2; $p < 0.001$) and fexofenadine (−4.6; $p = 0.017$) versus placebo (−3.9) at period 3, the 2-hour period after the second dose. The symptom score reduction observed with cetirizine at period 3 was significantly greater than that seen with fexofenadine ($p = 0.017$).

Figure 3 shows the absolute value of the least square mean changes from baseline in TSSC score at 20-minute intervals for each treatment group during each treatment period. A similar onset of effect for each active treatment was observed, with significant reductions in symptom

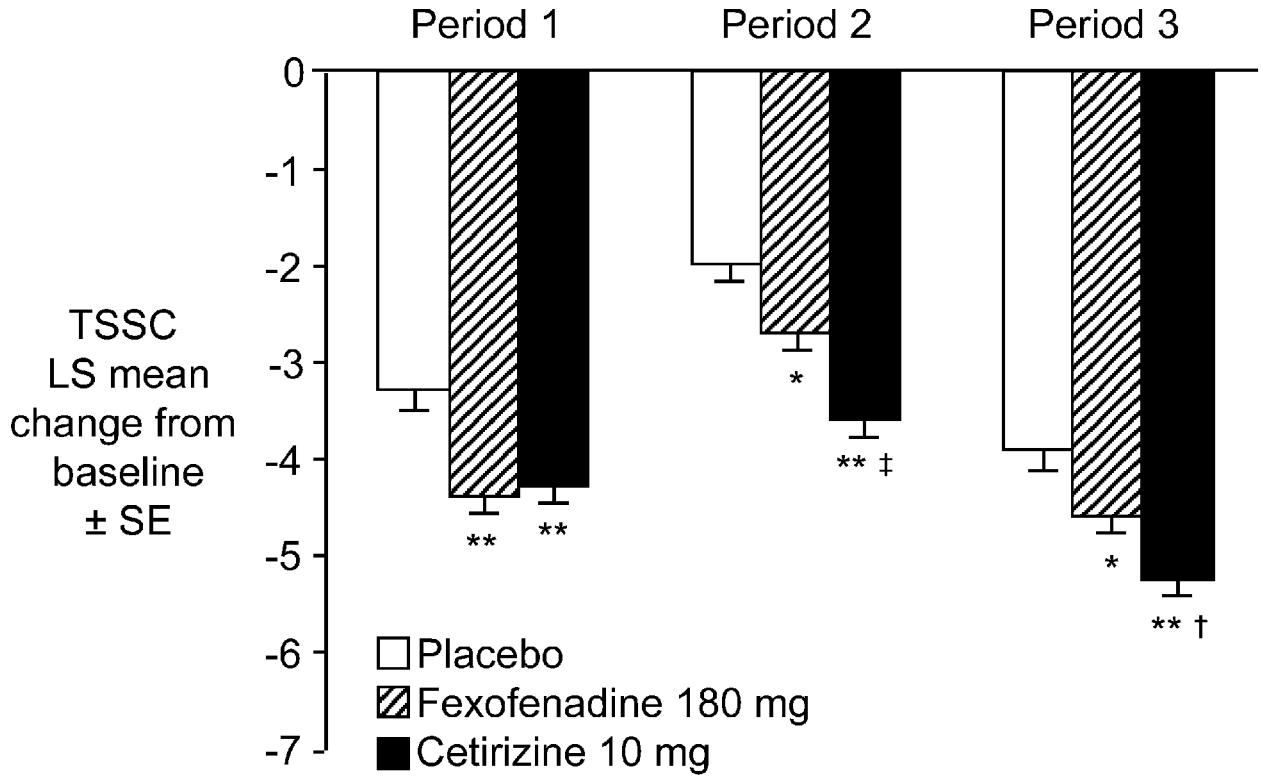

Figure 2. *Least-square (LS) mean change (±SE) from baseline in TSSC score to the end of periods 1, 2, and 3 during double-blind treatment with cetirizine, fexofenadine, or placebo. Intent-to-treat population. *$p < 0.05$ and **$p < 0.001$ versus placebo; †$p < 0.05$, and ‡$p < 0.001$ versus fexofenadine.*

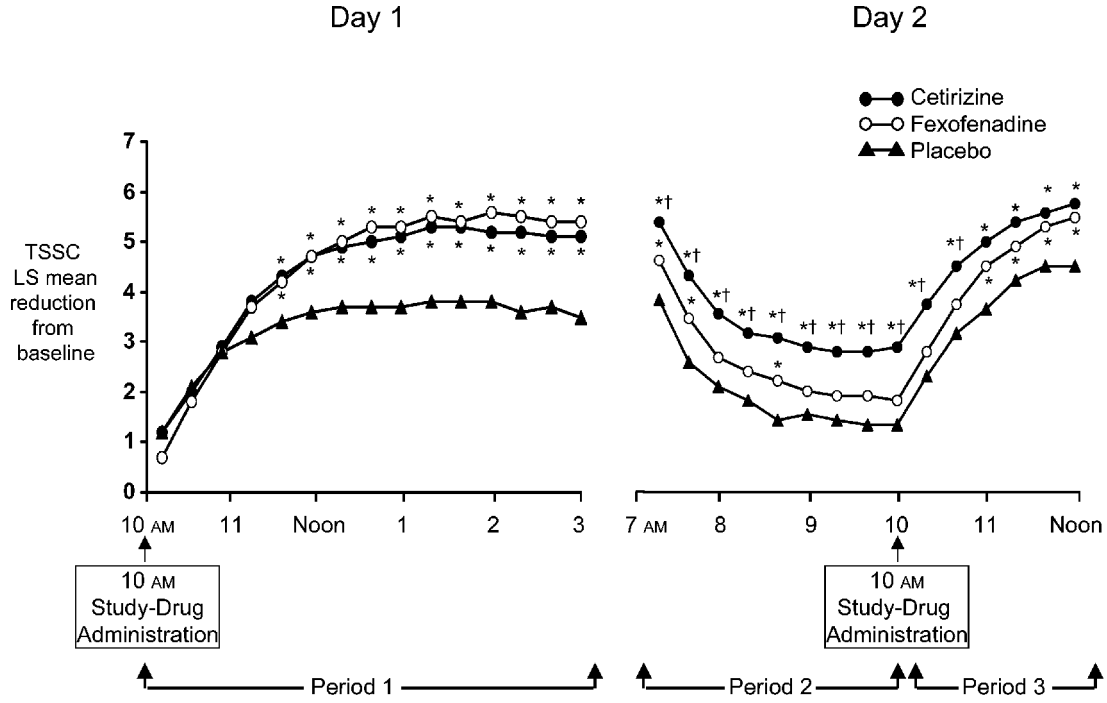

Figure 3. *Least-square (LS) mean changes from baseline in TSSC score at each 20-minute interval measured during double-blind treatment with cetirizine, fexofenadine, or placebo. Intent-to-treat population. *$p < 0.05$ versus placebo; †$p < 0.05$ versus fexofenadine.*

scores evident at 1 hour and 40 minutes for both agents. However, differences in duration of effect between active treatments were detected. Cetirizine was associated with significantly greater reductions in TSSC scores than placebo at every interval measured from 1 hour and 40 minutes and thereafter to the end of the study. In contrast, waning of symptom relief was observed with fexofenadine in period 2 at the end of the first dosing interval. No significant differences between fexofenadine and placebo were detected from 23 hours after the first dose until an hour after the second dose in period 3. Cetirizine produced significantly greater reductions than fexofenadine at each interval measured in period 2 and for the first 40 minutes of period 3, with the greatest difference between active treatments observed at 24-hours after the dose.

TSSC + Stuffy Nose

The effects of therapy on the composite of TSSC + stuffy nose scores were consistent with those noted for TSSC scores alone. Changes in TSSC + stuffy nose score from baseline at periods 1 and 2 and at each 20-minute time point were similar to the changes from baseline observed for TSSC scores alone.

Individual Rhinoconjunctivitis Symptoms

Cetirizine and fexofenadine were both significantly more effective than placebo in alleviating all four individual rhinoconjunctivitis symptoms comprising the TSSC during period 1 ($p < 0.05$). During period 2, cetirizine was significantly more effective than placebo and fexofenadine for all individual symptoms in the TSSC score, and fexofenadine was significantly more effective than placebo for sneezing ($p < 0.05$). Cetirizine produced significantly greater reductions than placebo for each individual symptom and significantly greater reductions than fexofenadine for runny nose and itchy nose/palate/throat at period 3 ($p < 0.05$). During this period, fexofenadine was significantly better than placebo for sneezing and itchy/watery eyes ($p < 0.05$). There were no statistical differences between treatment groups for stuffy nose.

Summary Evaluations

The distribution of responses for subjects' global evaluations of allergy symptom improvement, satisfaction with treatment, and willingness to take study medication were statistically different among the three treatment groups ($p = 0.002$, $p < 0.001$, and $p < 0.001$, respectively). Both active treatments were better than placebo: for the pairwise comparison of cetirizine versus fexofenadine the differences numerically favored cetirizine but did not reach statistical significance ($p = 0.181$, $p = 0.062$, and $p = 0.085$, respectively). For cetirizine-treated subjects, 17.1% reported being "very satisfied" and 20.0% reported that they "would definitely take [study medication] again," versus 13.4 and 14.7% for these respective categories in the fexofenadine-treated group.

Adverse Experiences

Cetirizine and fexofenadine were equally well tolerated in this study. One subject taking cetirizine (0.4%) and four subjects taking fexofenadine (1.7%) discontinued the study because of adverse events related to study medication. The cetirizine subject discontinued due to dizziness, headache, nausea, and vomiting. The four subjects taking fexofenadine who discontinued the study had experienced, respectively, flu-like symptoms; headache and nausea; back pain; and lodging of the overencapsulated pill in the esophagus, esophageal spasm, and soreness. The lowest percentage of subjects reporting treatment-emergent, all-causality adverse events was in the cetirizine-treated group: 93 events occurred in 71 cetirizine-treated subjects (29.6%); 140 events occurred in 93 fexofenadine-treated subjects (38.9%); and 45 events occurred in 34 placebo-treated subjects (35.4%). Treatment-emergent adverse events occurring in ⩾2% of subjects for any treatment group are listed in Table II. The most common adverse events (*i.e.*, occurring in ⩾2% of subjects) were headache and respiratory tract infection in the cetirizine group; headache, pharyngitis, respiratory tract infection, asthenia (includes fatigue), dizziness, rhinitis, nausea, and diarrhea in the fexofenadine group; and headache, back pain, nausea, chest pain, dyspepsia, pharyngitis, respiratory tract infection, and rhinitis in the placebo group. Somnolence occurred in 1.3% of subjects in each active treatment group and in 1% of subjects on placebo. Asthenia occurred in 3.8% of patients on fexofenadine, 1.3% on cetirizine, and 1.0% on placebo. Dry mouth occurred in 1.3% of patients on cetirizine, 0.8% on fexofenadine, and 1.0% on placebo. A total of 40 treatment-related adverse events occurred in 32 cetirizine subjects (13.3%); 59 such events occurred in 43 fexofenadine subjects (18.0%); and 20 such events occurred in 16 placebo subjects (16.7%).

The majority of treatment-emergent all-causality adverse events were mild to moderate in severity, with a similar frequency across groups except for higher occurrence of pharyngitis with fexofenadine (5.4%). One subject on fexofenadine, one subject on cetirizine, and one subject on placebo experienced a serious treatment-emergent adverse event. One serious adverse event was determined to be treatment-related: a fexofenadine subject had an overencapsulated pill lodged in her throat. This subject, who was eventually able to swallow the pill on her own, was found on subsequent evaluations to have a congenital or acquired esophageal web along with biopsy-confirmed eosinophilic esophagitis, which could have contributed to the pill lodging. Two other serious adverse events not considered related to treatment occurred during the study. A 20-year-old

TABLE II

Treatment-Emergent (All-Causality) Adverse Events with Incidence ≥2%*

Preferred Term	Cetirizine (n = 240)		Fexofenadine (n = 239)		Placebo (n = 96)	
	n	%	*n*	%	*n*	%
Headache	24	10.0	23	9.6	13	13.5
Pharyngitis	2	0.8	13	5.4	2	2.1
Respiratory tract infection	9	3.8	12	5.0	2	2.1
Asthenia	3	1.3	9	3.8	1	1.0
Nausea	4	1.7	5	2.1	3	3.1
Back pain	1	0.4	4	1.7	3	3.1
Rhinitis	1	0.4	6	2.5	2	2.1
Dizziness	2	0.8	6	2.5	0	0
Dyspepsia	3	1.3	4	1.7	2	2.1
Chest pain	0	0	1	0.4	2	2.1
Diarrhea	0	0	5	2.1	0	0

** Subjects with one or more event in a body system were counted only once for that body system.*

woman developed pyelonephritis before receiving cetirizine and a 51-year-old woman treated with placebo experienced an asthmatic episode on the second treatment day after completing the study. The asthmatic subject was treated in the clinic associated with the EEU and the event resolved the same day.

DISCUSSION

This large, randomized, double-blind study conducted in the EEU comparing cetirizine, 10 mg, with fexofenadine in the 180-mg formulation showed a similar onset of action and comparable relief of SAR symptoms for the first 5 hours after the initial dose. However, cetirizine had a longer duration of action and better symptom relief than fexofenadine as evidenced by 33% better symptom response from 21 to 24 hours after the initial dose, with the greatest difference between the active treatments observed at 24 hours after the dose. Superior symptom relief of cetirizine compared with fexofenadine continued for 40 minutes after the administration of the second dose. The frequency of treatment-emergent adverse events associated with cetirizine was similar to that of fexofenadine and to that of placebo, including somnolence.

The EEU lends itself to accurate assessment of duration of response by having subjects return to the facility at a predetermined time in the latter portion of the postdosing period when they are again exposed to the same levels of pollen and record symptoms once more at set intervals. The importance of duration of effect of these medications in the treatment for SAR is relevant considering the approval for once-daily dosing. The EEU has been established as a particularly suitable setting to evaluate efficacy of antiallergic medications.[7–9,15] A target ragweed pollen concentration of 3500 ± 500 grains/m^3 is representative of peak pollen exposure in the out-of-doors[22–24] and produces the full spectrum of symptom severity in allergic individuals. The reproducibility of pollen exposure that is attainable between cohorts and within individuals in the EEU creates conditions required for an accurate assessment of efficacy measures. Furthermore, the ability to assess symptoms precisely at 20-minute intervals in this study enabled an added sensitivity to detect differences throughout the dosing interval.

A single dose of cetirizine has a duration of effect lasting over the 24-hour period, an effect not observed with fexofenadine. This superior effect extends for at least 40 minutes beyond this 24-hour dosing interval after the second dose. This 24-hour duration of effect is especially relevant to the expectation of therapeutic efficacy by physicians and patients for once-daily medications used on an as-needed basis, a practice common to patients taking these medications. Two studies comparable in design with this study but using different symptom categories and rating scales comparing cetirizine to loratadine and placebo also showed a similar onset of action and duration of effect for cetirizine as in this study.[8,9]

This study also corroborates findings about individual characteristics of onset of action and duration of effect for SAR reported in earlier studies in other controlled systems offering consistent pollen exposure in which cetirizine or fexofenadine were compared with placebo and/or other agents.[7–9,15] In the only direct comparison in such a setting, Horak *et al.*, using the Vienna Challenge Chamber, conducted an investigator-blinded crossover study of cetirizine, 10 mg once daily, and fexofenadine, 120 mg once daily, in 40 subjects with SAR exposed to grass pollen for 6 hours on 2 consecutive days.[20] Both active medications were significantly more effective than placebo and displayed similar onset of symptom relief and comparable efficacy for the first 4 hours after the dose on both study days. However,

22–24 hours after the dose, symptom relief with cetirizine was superior to that of fexofenadine, suggesting a longer duration of action with cetirizine. Those findings are consistent with observations in the present EEU comparison of cetirizine, 10 mg, and fexofenadine, 180 mg. Although the fexofenadine dose was different between this EEU study and the study conducted by Horak *et al.*, efficacy comparability of both doses *(i.e.*, 120 and 180 mg) has been determined previously by Casale *et al.*[11] Earlier results of pharmacodynamic studies also support the current study's results by showing similar onset of action for cetirizine and fexofenadine but a more prolonged duration of effect for cetirizine.[16,18]

Our results differ somewhat from that of Howarth *et al.*, who conducted a multicenter, double-blind, placebo-controlled 2-week study comparing the effects of cetirizine, 10 mg, with fexofenadine, 120 and 180 mg (administered in multiples of 60-mg capsules), on total symptoms scores in 821 subjects with SAR.[19] They observed comparable efficacy among all active treatment groups including estimates of 24-hour efficacy. However, a comparison of that study with the current investigation is limited by the differences in methodology and study setting along with different symptom score criteria for entry, the grouping of symptoms for efficacy and safety analysis, and the way in which data were analyzed, especially for trough symptom scores. It is noteworthy that subjects with severe symptoms were excluded.

In this study, cetirizine and fexofenadine were equally well tolerated. The incidence of side effects overall and by type was similar across treatment groups. The incidence of somnolence was 1.3% for cetirizine, 1.3% for fexofenadine, and 1.0% for placebo. The safety profiles are consistent with previous observations in 2-day studies undertaken in the EEU.[9]

CONCLUSIONS

In this large study comparing two well-recognized antihistamines, cetirizine, 10 mg once daily, had a longer duration of effect than fexofenadine, 180 mg once daily, producing a 33% greater reduction of SAR symptoms from 21 to 24 hours after the first dose, the primary end point, and extending for 40 minutes after the second dose was administered at 24 hours. This finding is especially relevant because both medications are approved for once-daily dosing. Cetirizine and fexofenadine had the same time to onset of action and provided comparable symptom relief over the first 5 hours after initial dosing compared with placebo, and both were equally safe and well tolerated, with treatment related-adverse events including somnolence similar to placebo.

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REFERENCES

1. Sheffer AL, and Samuels LL. Cetirizine: Antiallergic therapy beyond traditional H_1 antihistamines. J Allergy Clin Immunol 86:1040–1046, 1990.
2. Backhouse CI, Renton R, Fidler C, et al. Multicentre, double-blind comparison of terfenadine and cetirizine in patients with seasonal allergic rhinitis. Br J Clin Pract 44:88–91, 1990.
3. Rijntjes E, Ghys L, and Rihoux JP. Astemizole and cetirizine in the treatment of seasonal allergic rhinitis: A comparative double-blind, multicentre study. J Int Med Res 18:219–224, 1990.
4. Falliers CJ, Brandon ML, Buchman E, et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. Ann Allergy 66:257–262, 1991.
5. Lockey RF, Findley S, Mitchell DQ, et al. Effects of cetirizine versus terfenadine in seasonal allergic rhinitis. Ann Allergy 70:311–315, 1993.
6. Meltzer EO, Weiler JM, and 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 97:617–626, 1996.
7. Day JH, Briscoe M, Clark RH, et al. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. Ann Allergy Asthma Immunol 79:163–172, 1997.
8. Day JH, Briscoe M, and Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: Effects after controlled ragweed pollen challenge in an environmental exposure unit. J Allergy Clin Immunol 101:638–645, 1998.
9. Day JH, Briscoe M, Rafeiro E, et al. Comparative onset of action and symptom relief with cetirizine, loratadine, or placebo in an environmental exposure unit in subjects with seasonal allergic rhinitis: Confirmation of a test system. Ann Allergy Asthma Immunol 87:474–481, 2001.
10. Bronsky EA, Falliers CJ, Kaiser HB, et al. Effectiveness and safety of fexofenadine, a new nonsedating H_1-receptor antagonist, in the treatment of fall allergies. Allergy Asthma Proc 19:135–141, 1998.
11. Casale TB, Andrade C, and Qu R. Safety and efficacy of once-daily fexofenadine HCl in the treatment of autumn seasonal allergic rhinitis. Allergy Asthma Proc 20:193–198, 1999.
12. Bernstein DI, Schoenwetter WF, Nathan RA, et al. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 79:443–448, 1997.
13. Van Cauwenberge P, and Juniper EF, for the Star Study Investigating Group. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. Clin Exp Allergy 30:891–899, 2000.
14. Simpson K, Jarvis B. Fexofenadine: A review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. Drugs 59:301–321, 2000.
15. Day JH, Briscoe MP, Welsh A, et al. Onset of action, efficacy, and safety of a single dose of fexofenadine hydrochloride for ragweed allergy using an environmental exposure unit. Ann Allergy Asthma Immunol 79:533–540, 1997.
16. Grant JA, Danielson L, Rihoux JP, et al. A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo: Suppression of histamine-induced wheal and flare response for 24 h in healthy male subjects. Allergy 54:700–707, 1999.
17. Ballmer-Weber BK, Gex-Collet C, and Wüthrich B. Inhibition of histamine or allergen-induced wheals by a single dose of acrivastine, fexofenadine or cetirizine. J Investig Allergol Clin Immunol 9:351–355, 1999.
18. Purohit A, Duvernelle C, Melac M, et al. Twenty-four hours of activity of cetirizine and fexofenadine in the skin. Ann Allergy Asthma Immunol 86:387–392, 2001.

19. Howarth PH, Stern MA, Roi L, et al. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. J Allergy Clin Immunol 104:927–933, 1999.
20. Horak F, Stübner P, Zieglmayer R, et al. Controlled comparison of the efficacy and safety of cetirizine 10 mg o.d. and fexofenadine 120 mg o.d. in reducing symptoms of seasonal allergic rhinitis. Int Arch Allergy Immunol 125:73–79, 2001.
21. Day JH, and Briscoe MP. Environmental exposure unit: A system to test anti-allergic treatment. Ann Allergy Asthma Immunol 83:83–93, 1999.
22. Solomon WR. Volumetric studies of aeroallergen prevalence. I. Pollens of weedy forbs at a midwestern station. J Allergy Clin Immunol 57:318–327, 1976.
23. Donnelly A, and Casale TB. Nedocromil sodium is rapidly effective in the therapy of seasonal allergic rhinitis. J Allergy Clin Immunol 91:997–1004, 1993.
24. Habenicht HA, Burge HA, Muilenberg ML, et al. Allergen carriage by atmospheric aerosol. II. Ragweed-pollen determinants in submicronic atmospheric fractions. J Allergy Clin Immunol 74:64–67, 1984. □