

Asthma, rhinitis, other respiratory diseases

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

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Background: Fexofenadine hydrochloride (HCl) is a new H₁ antihistamine used twice daily in some countries.

Objective: A multicenter, double-blind, parallel-group, placebo-controlled trial compared the efficacy and safety of fexofenadine HCl (120 and 180 mg administered once daily) and cetirizine (10 mg once daily) in the treatment of seasonal allergic rhinitis.

Methods: After a 3- to 5-day run-in period, patients meeting entrance criteria were randomized to receive placebo, fexofenadine HCl 120 mg once daily, fexofenadine HCl 180 mg once daily, or cetirizine 10 mg once daily (active control) for 2 weeks. Eight hundred twenty-one patients comprised the intention-to-treat population and 722 patients completed the study. Symptom assessments were conducted 12 hours after the dose for the previous 12 hours and again at 24 hours after the dose for the previous 12 hours. In addition, assessment was made immediately before dosing in the morning for the previous 30 minutes. Total symptom score was calculated as the sum of scores for the 4 individual symptoms: (1) sneezing, (2) rhinorrhea, (3) itchy nose, palate, or throat, and (4) itchy, watery, or red eyes; the nasal congestion score was also recorded.

Results: Both doses of fexofenadine HCl were superior to placebo in reducing the total symptom score. Efficacy was maintained for the entire dosing interval (ie, for 24 hours). There were no differences in efficacy between the 2 doses of fexofenadine HCl or between either dose of fexofenadine HCl and cetirizine. There was no major side effect, but the combined incidence of drowsiness or fatigue was greater with ce-

tirizine (9%) than with placebo (4%) ($P = .07$) or fexofenadine (4%) ($P = .02$).

Conclusions: Once-daily fexofenadine is thus a valuable addition to the nonsedating group of H₁ receptor antagonists currently available for the treatment of seasonal allergic rhinitis. (*J Allergy Clin Immunol* 1999;104:927-33.)

Key words: Seasonal allergic rhinitis, efficacy, safety, fexofenadine hydrochloride, cetirizine, total symptom score, antihistamine, once daily

Allergic rhinitis is associated with the epithelial accumulation of effector cells, such as mast cells and basophils, and inflammation in the nasal mucosa.^{1,2} Immunologic activation of these effector cells induces the secretion of both newly generated and preformed mediators. Quantitatively, histamine is the most abundant mediator, and because nasal challenge with histamine mimics many of the features of allergic rhinitis, including nasal itch, sneeze, rhinorrhea, and nasal congestion,³ histamine has been implicated in the genesis of this disease. Because these effects are largely mediated through histamine H₁ receptors, H₁ receptor antagonists have become established as a primary therapy.

Fexofenadine is a long-acting antihistamine, highly selective for peripheral H₁ receptors, that is devoid of sedative effects.⁴ It is not metabolized by the liver and has no effect on the cytochrome P450 enzyme CYP3A4.⁵ In vitro electrophysiologic studies have demonstrated that fexofenadine does not affect the cardiac potassium rectifier current.^{6,7} In addition, studies in animals⁸ and rigorous clinical studies⁹⁻¹¹ have shown fexofenadine to be free of cardiotoxic effects, such as those that exist with a number of other nonsedating antihistamines.^{6-8,12,13}

Previous studies have demonstrated the efficacy and safety of fexofenadine hydrochloride (HCl) at twice-daily (BID) doses ranging from 60 to 240 mg.⁹ The half-life of fexofenadine is such, however, that it would also be applicable as a once-a-day (QD) medication. This study was thus designed to investigate the efficacy and safety of fexofenadine given at 120 mg and 180 mg QD,

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Abbreviations used

ANCOVA:	Analysis of covariance
BID:	Twice a day
HCl:	Hydrochloride
ITT:	Intention to treat
QD:	Once a day
SAR:	Seasonal allergic rhinitis
TSS:	Total symptom score
VAS:	Visual analog scale

compared with cetirizine 10 mg QD, in the treatment of seasonal allergic rhinitis (SAR).

METHODS

Study design

The study was a multicenter, double-blind, randomized, placebo-controlled, parallel-group design of 2 weeks' duration, preceded by a single-blind placebo run-in period of 3 to 5 days in symptomatic patients with SAR. To ensure entry at periods of pollen prevalence, the local pollen count was recorded in each region of entry with use of the local pollen count method and the study was conducted in the respective peak grass pollen seasons.

Patient population

Patients were eligible to participate in the study if they were 12 to 65 years old, had a history of SAR of at least 2 years, had a positive skin prick test response to mixed grass pollens (3 mm > negative control), and provided written informed consent. Patients were excluded from entry if they had received intranasal or oral prophylactic therapy that season; had received immunotherapy (unless the immunotherapy had been stable for at least 6 months); had had an upper respiratory tract infection within 30 days before the study; had known serious renal, cardiac, or hepatic disease; were pregnant or lactating; or had received oral or topical H_1 receptor antagonists within the last 48 hours (with the exception of astemizole, which had to be discontinued for a minimum of 6 weeks). Patients were also required to meet specific symptom severity criteria (see below).

Study protocol

Patients were assessed for symptom severity entry criteria at 2 screening visits. The screening visits were separated by a 3- to 5-day single-blind placebo lead-in phase. The placebo lead-in was used to reduce the number of placebo responders who would enter the double-blind phase of the study and to establish a baseline for allergy symptom severity. The following 5 individual symptoms were assessed and recorded in the patient symptom diaries: sneezing; rhinorrhea; itchy nose, palate, or throat; itchy, watery, or red eyes; and nasal congestion. Each symptom was scored by the patient on a 5-point scale, where 0 = absent (symptom not present), 1 = mild (symptom present but not annoying or troublesome), 2 = moderate (symptom frequently troublesome but not interfering with either normal daily activity or sleep), 3 = severe (symptom sufficiently troublesome to interfere with normal daily activity or sleep), and 4 = very severe (symptom so severe as to warrant an immediate visit to the physician). A total symptom score (TSS) was calculated as the sum of the first 4 individual symptom scores (ie, excluding nasal congestion).

At the first screening visit, before they entered the single-blind placebo lead-in, patients were required to meet the following criteria

for the previous 24-hour period: TSS ≥ 6 , 2 or more individual symptoms (excluding nasal congestion) rated as moderate or severe, and no symptom (including nasal congestion) rated as very severe. Patients having a very severe score for any of the individual symptoms were excluded from the study on the basis that they would not be able to tolerate placebo treatment.

Patients who entered the single-blind placebo phase of the study took single-blind placebo at 8 AM daily. They assessed their symptoms daily at 12 hours after dosing for the previous 12 hours (8 PM 12-hour reflective assessment) and again at 24 hours after dosing for the previous 12 hours (8 AM 12-hour reflective assessment), just before the next dose. The afternoon and morning 12-hour reflective assessments were averaged to give the 24-hour reflective individual symptom scores and the 24-hour reflective TSS. In addition, an instantaneous assessment (for the last 30 minutes) was made at 8 AM. The instantaneous assessment was obtained to determine efficacy at trough drug blood levels and thus address 24-hour control with once-daily medication.

At the second screening visit (after patients had completed the single-blind placebo lead-in) patients were required to meet the following criteria to qualify for randomization to the double-blind phase of the study: TSS ≥ 5 for at least 2 assessments; at least 2 symptoms, excluding nasal congestion, rated as moderate or severe at afternoon and morning assessments on those days in which the TSS was ≥ 5 ; and no symptom, including nasal congestion, rated as very severe at any morning or afternoon assessment.

Patients who qualified for randomization and entered the 2-week double-blind phase of the study took study medication and completed symptom diaries in a manner identical to that done during the placebo lead-in phase. Eligible patients were randomized to 1 of 4 double-blind treatments: placebo, fexofenadine HCl 120 mg QD (as 2 $\times$ 60 mg capsules), fexofenadine HCl 180 mg QD (as 3 $\times$ 60 mg capsules), or cetirizine 10 mg QD.

Patients were withdrawn from the study if they had any intolerable treatment emergent adverse event or any clinically significant abnormal laboratory tests or if they failed to return to the study site for a scheduled visit or if they elected to discontinue.

Safety

Adverse experiences were recorded daily together with symptom assessments. Patients also assessed sensation of somnolence on a visual analog scale (VAS). The scale consisted of a 100-mm line with one pole labeled "no drowsiness" and the other labeled "severe drowsiness." Patients assessed their drowsiness every evening, just before bedtime, for that day. Blood samples were taken at entry and again at completion of the study to measure standard hematologic and biochemical parameters.

Trial end points

The primary efficacy variable was the change in mean 24-hour reflective TSS during the treatment period in relation to the single-blind placebo lead-in phase. Secondary efficacy variables were the change in instantaneous TSS in comparison to baseline, the change in 24-hour reflective scores for individual symptoms, the incidence of adverse events, and VAS somnolence assessment.

Statistical analysis

Analysis was undertaken on an intention-to-treat (ITT) basis and also on a protocol-correct population. Symptom scores were analyzed between groups by an analysis of covariance (ANCOVA) with use of treatment, investigation site, and baseline score as predictor (independent) variables and the primary efficacy measure (change in symptom score) as the response (dependent) variable. The baseline score was included as a continuous covariate. The study was powered to detect a difference of 0.7 between active dose and placebo,

TABLE I. Baseline characteristics for ITT population (n = 821)

Baseline characteristics	Placebo (n = 201)	Fexofenadine 120 mg (n = 211)	Fexofenadine 180 mg (n = 202)	Cetirizine 10 mg (n = 207)
Sex (male/female [No.])	103/98	117/94	100/102	100/107
Age (y) (mean [range])	34 (12-66)	33 (13-66)	32 (12-64)	33 (13-62)
SAR history (y) (mean [range])	15 (0-50)	15 (0-46)	14 (0-61)	14 (0-53)
24-Hour reflective TSS (mean $\pm$ SD)	7.3 $\pm$ 2.0	7.2 $\pm$ 2.1	7.4 $\pm$ 1.9	7.3 $\pm$ 2.1
Morning instantaneous trough TSS (mean $\pm$ SD)	7.1 $\pm$ 2.3	7.0 $\pm$ 2.6	6.9 $\pm$ 2.4	7.1 $\pm$ 2.4

with an SD of 2.4. All tests were 2-tailed and a 5% level of significance was taken as being indicative of a group difference. ANCOVA or rank ANCOVA was used for analysis of all other efficacy variables. The chi-square test was used to test for differences in the incidence of drowsiness and/or fatigue for the different treatments.

For the primary efficacy end point (change in 24-hour reflective TSS), consistency of the treatment effect was assessed in subgroups of patients defined by investigative site, country, and baseline characteristics (baseline TSS, age, sex, and race). The subgroup analyses were made with an ANCOVA model that included terms for treatment, site, baseline 24-hour reflective TSS, subgroup, and treatment by subgroup interaction. A significant treatment by subgroup interaction was taken to indicate evidence of inconsistency in treatment effect across the patient subgroups defined by the subgroup factor.

Study conduct

The study was in accordance with the standards of good clinical practice. Before study initiation, ethical approval was obtained at each local site and patients were only entered into the study after they had been given a full explanation and provided written informed consent.

RESULTS

Number of patients studied

A total of 1094 eligible patients were screened for entry to the study. Of these, 842 fulfilled the entry criteria and were randomized to double-blind treatment at 49 investigation sites (33 in Europe, 15 in South Africa, and 1 in Australia). The mean ($\pm$ SD) number of patients per center was 17 ($\pm$ 25.1), with the number of patients at each center ranging from 1 to 68. There were 8 centers with fewer than 5 patients and 17 centers with 5 to 10 patients; country centers were pooled if they had 6 or fewer patients. Of the 842 randomized patients, 839 were exposed to double-blind medication (3 patients discontinued before taking study medication). All 839 patients were included in the safety analysis. A further 18 patients were excluded from the ITT population because they were missing either the 24-hour reflective baseline or the postbaseline TSS, leaving 821 in the ITT population. Of these 821 patients, 765 had no major protocol violations and were classified as protocol correct. Seven hundred twenty-two patients completed the 2-week study. Therefore a total of 117 patients (14% of the safety population) discontinued before study completion. The most common reasons for early discontinuation were lack of effect (5%) and failure to return to the study site for scheduled visits (3%). However, in all instances the frequency of withdrawals was similar across all treatment groups.

Demographic characteristics of the patients

There were no statistically significant differences among the 4 treatment groups with respect to gender, age, historical duration of disease, or baseline TSS (Table I).

Primary efficacy analysis: 24-hour reflective TSS

All active treatments were significantly superior to placebo in reducing the 24-hour reflective TSS ($P \leq .0001$) (Fig 1). The magnitude of the mean reduction in the placebo, fexofenadine HCl 120 mg, fexofenadine HCl 180 mg, and cetirizine 10 mg groups was -1.9 , -3.0 , -3.3 , and -3.3 , respectively. The SD was 2.34 (consistent with the sample size planning assumptions), whereas the difference in change from the baseline TSS versus placebo was 1.1, 1.4, and 1.4, respectively. There were no significant differences among the 3 active treatment groups. No inconsistency in treatment effect was found across subgroups of patients defined by investigative site, country, or baseline characteristics (baseline TSS, age, gender, and race).

Secondary efficacy analyses

Individual symptom scores. All active treatments were statistically more effective in reducing all 24-hour reflective individual symptom scores, including nasal congestion, compared with placebo (Table II).

Instantaneous TSS at trough. All active treatments were significantly superior to placebo ($P < .003$) in reducing the 24-hour instantaneous TSS, thus indicating full 24-hour protection with once-daily therapy (Fig 2). The magnitude of the mean reduction was -1.6 , -2.4 , -2.7 , and -2.8 , respectively, in the placebo, fexofenadine HCl 120 mg, fexofenadine HCl 180 mg, and cetirizine 10 mg treatment groups. There was no statistical difference among these active treatment groups.

Safety

Adverse events. Treatment-related adverse events (those considered by the investigator as possibly, probably, or definitely related to study medication) were reported for 23% (50/213) of patients given fexofenadine HCl 120 mg, 23% (47/208) given fexofenadine HCl 180 mg, 25% (52/209) given cetirizine 10 mg, and 25% (53/209) given placebo.

The type and incidence of adverse events were generally similar with the different treatments (Fig 3). The most commonly reported treatment-related adverse

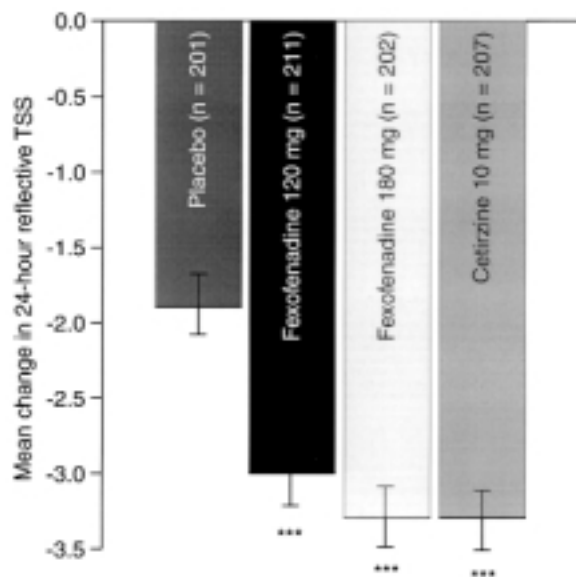


FIG 1. Mean ($\pm$ SE) change in 24-hour reflective TSS with use of ITT population. Three asterisks, $P \leq .0001$ versus placebo. Mean $\pm$ SE baseline scores were 7.3 ± 0.1 for patients who received either placebo or cetirizine (10 mg), 7.2 ± 0.1 for those who received fexofenadine (120 mg), and 7.4 ± 0.1 for fexofenadine (180 mg) group. There were no significant differences among active treatment groups.

events were headache and drowsiness. Headache occurred with similar frequency with all treatments: placebo (7%, 15/209), fexofenadine (8%, 35/421), and cetirizine (8%, 16/209). Drowsiness occurred more frequently with cetirizine (6%, 13/209) than with placebo (3%, 7/209) or fexofenadine (3%, 14/421). The incidence of fatigue was similar with both treatments (1%, 3/421 with fexofenadine; 2%, 5/209 with cetirizine) and was comparable to placebo (1% 2/209). However, the combined incidence of drowsiness or fatigue was greater for cetirizine (9%, 18/209) than for fexofenadine (4%, 17/421) or placebo (4%, 9/209) (Table III). This difference was statistically significant for cetirizine versus fexofenadine ($P = .018$) and near statistical significance for cetirizine versus placebo ($P = .073$).

The incidence of patients discontinuing study medication because of adverse events was similar for all treatments: 2% (4/209) for placebo, 2% (8/421) for fexofenadine, and <1% (1/209) for cetirizine. There were no deaths during the study.

Clinical laboratory and vital sign results were similar in active and placebo groups and did not change significantly with treatment.

Somnolence VAS. From the rank ANCOVA there were significant differences between cetirizine and the other treatments ($P = .0065$ vs placebo, $P = .0195$ vs fexofenadine HCl 120 mg, $P = .0256$ vs fexofenadine HCl 180 mg), with increased somnolence in the cetirizine group for weeks 1 and 2 combined (Table IV). However, the median changes from baseline of the VAS scale were all small (change of

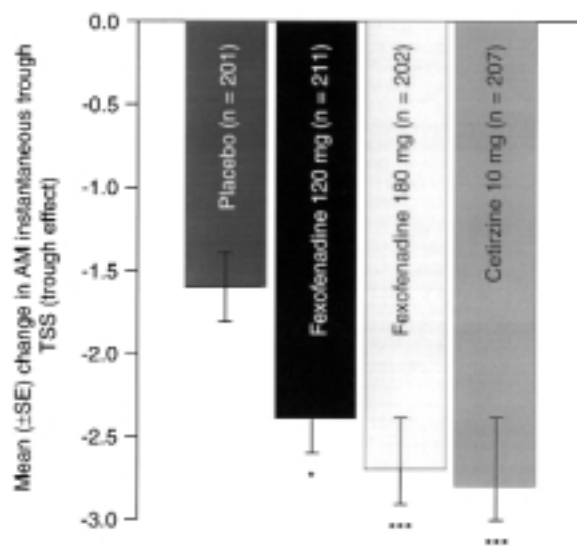


FIG 2. Mean ($\pm$ SE) change in morning instantaneous TSS (at trough drug levels before daily medication) with use of ITT population. Asterisks indicate level of significance versus placebo: one asterisk, $P < .003$, and three asterisks, $P \leq .0001$ versus placebo. Mean $\pm$ SE baseline scores were 7.1 ± 0.2 for patients who received either placebo or cetirizine (10 mg), 7.0 ± 0.2 for those who received fexofenadine (120 mg), and 6.9 ± 0.2 for fexofenadine (180 mg) group. There were no significant differences among active treatment groups.

0.04 mm for cetirizine, 0.0 mm for all other doses). In addition, there was evidence of inconsistency in treatment effect across centers (treatment by center interaction test, $P = .0994$). Therefore clear differences in VAS-assessed somnolence across treatments could not be established.

DISCUSSION

This study demonstrates that fexofenadine HCl 120 mg and 180 mg administered QD is an effective and safe treatment for SAR, with efficacy comparable to that of cetirizine for both doses. There were no statistical differences among any of the active treatments in any of the primary or secondary efficacy criteria. All active treatments were still effective at trough drug levels, just before repeat daily dosing, indicating 24-hour symptom relief. Analysis of individual symptoms identified significant improvement with all active treatments in non-rhinitic symptoms (itchy, watery, red eyes and itchy throat or palate) and all nasal symptoms associated with allergic rhinitis, including nasal congestion.

For all treatments of seasonal allergic rhinitis, including topical steroids, placebo effects occur in clinical studies, which can influence the TSS and often make it difficult to differentiate between clinically and statistically significant results. This study was designed to detect statistical treatment differences in 24-hour reflective TSS on the basis of previous studies with fexofenadine and terfenadine. The statistical differences observed between the active treatments and placebo were better than anticipated. In addi-

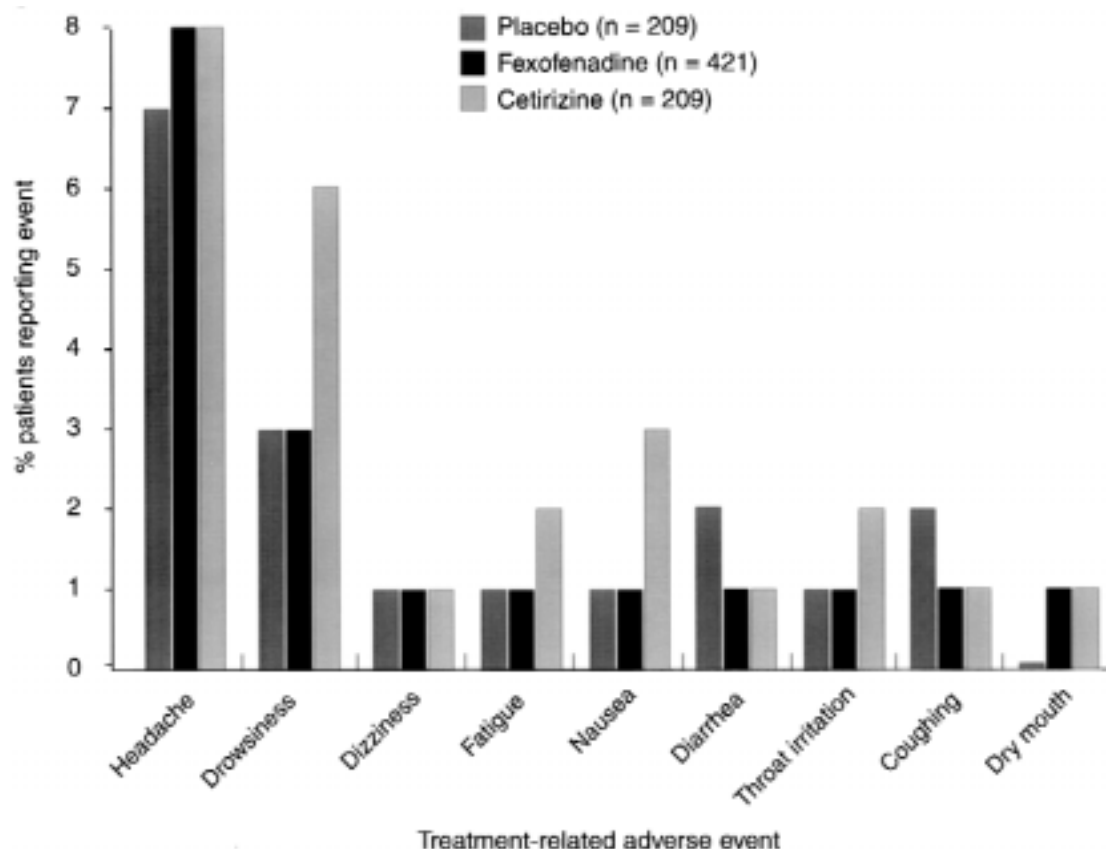


FIG 3. Incidence of most frequent treatment-related adverse events with placebo, fexofenadine HCl (120 and 180 mg), and cetirizine administered QD.

TABLE II. 24-Hour reflective individual symptom scores (ITT)

Symptom		Change from baseline treatment (once-daily)			
		Fexofenadine HCl			Cetirizine 10 mg (n = 207)
		Placebo (n = 201)	120 mg (n = 211)	180 mg (n = 202)	
Sneezing	Baseline (mean $\pm$ SE)	1.8 $\pm$ 0.0	1.8 $\pm$ 0.0	1.8 $\pm$ 0.0	1.8 $\pm$ 0.0
	Change from baseline (mean $\pm$ SE)	-0.5 $\pm$ 0.0	-0.7 $\pm$ 0.0 <i>P</i> = .0001	-0.8 $\pm$ 0.1 <i>P</i> = .0001	-0.8 $\pm$ 0.0 <i>P</i> = .0001
	Statistical significance*				
Rhinorrhea	Baseline (mean $\pm$ SE)	1.9 $\pm$ 0.0	1.9 $\pm$ 0.0	2.0 $\pm$ 0.0	1.9 $\pm$ 0.0
	Change from baseline (mean $\pm$ SE)	-0.5 $\pm$ 0.10	-0.7 $\pm$ 0.0 <i>P</i> = .0001	-0.8 $\pm$ 0.0 <i>P</i> = .0001	-0.8 $\pm$ 0.0 <i>P</i> = .0001
	Statistical significance*				
Itchy nose, palate, or throat	Baseline (mean $\pm$ SE)	1.9 $\pm$ 0.0	1.8 $\pm$ 0.0	1.9 $\pm$ 0.0	1.9 $\pm$ 0.0
	Change from baseline (mean $\pm$ SE)	-0.5 $\pm$ 0.1	-0.8 $\pm$ 0.0 <i>P</i> = .0001	-0.9 $\pm$ 0.0 <i>P</i> = .0001	-0.8 $\pm$ 0.0 <i>P</i> = .0001
	Statistical significance*				
Itchy, watery, or red eyes	Baseline (mean $\pm$ SE)	1.7 $\pm$ 0.1	1.8 $\pm$ 0.1	1.8 $\pm$ 0.1	1.8 $\pm$ 0.1
	Change from baseline (mean $\pm$ SE)	-0.4 $\pm$ 0.0	-0.7 $\pm$ 0.0 <i>P</i> = .0001	-0.8 $\pm$ 0.0 <i>P</i> = .0001	-0.8 $\pm$ 0.0 <i>P</i> = .0001
	Statistical significance*				
Nasal congestion	Baseline (mean $\pm$ SE)	1.8 $\pm$ 0.1	1.7 $\pm$ 0.1	1.8 $\pm$ 0.1	1.8 $\pm$ 0.1
	Change from baseline (mean $\pm$ SE)	-0.3 $\pm$ 0.0	-0.4 $\pm$ 0.0 <i>P</i> = .0052	-0.4 $\pm$ 0.0 <i>P</i> = .0076	-0.4 $\pm$ 0.0 <i>P</i> = .0199
	Statistical significance*				

*Pairwise comparison of treated group to placebo.

TABLE III. Treatment-associated fatigue or drowsiness

Treatment week	Patients with treatment-associated fatigue or drowsiness (%)		
	Placebo	Fexofenadine (120 and 180 mg)	Cetirizine (10 mg)
1	4 (8/209) <i>P</i> = .133*	3 (14/421) <i>P</i> = .030	7 (15/209)
2	1 (3/202) <i>P</i> = .082*	2 (9/414) <i>P</i> = .120*	4 (9/204)
1 and 2 combined	4 (9/209) <i>P</i> = .073*	4 (17/421) <i>P</i> = .018*	9 (18/209)

Statistical significance from chi-square test comparing placebo or 120 and 180 mg of fexofenadine with cetirizine.

tion, although the study was not powered to obtain statistical significance in individual symptoms, all 24-hour reflective individual symptom scores, including nasal congestion, are uniformly significant versus placebo.

For most H₁ blockers, dose-response efficacy is difficult to demonstrate both in clinical trials and with skin tests to histamine.¹⁴ No dose-response relationship has been shown with fexofenadine doses of 60 mg BID, 120 mg BID, and 240 mg BID in SAR.⁹ It is most likely that 120 mg QD and 180 mg QD have a similar effect in the majority of patients with seasonal allergic rhinitis and are close to the top of fexofenadine's dose-response curve. Therefore in these patients the increments in efficacy with any additional dose increase would be relatively small.

A 2-week study duration is required by regulatory authorities in the United States, Europe, and elsewhere in the world for the licensing of an antihistamine. Thus a 2-week study duration is common for antiallergy treatments in SAR,¹⁵ and indeed in some cases clinical efficacy is assessed after only 1 week. Although the entire pollen season usually lasts longer than 2 weeks, we could not assess treatment efficacy for more than 2 weeks because we wanted to study patients with sufficient symptoms and during the peak of the pollen season. ment.⁸ Thus this study allowed a new registration in most European Union countries and in many other countries. In the current study both doses of fexofenadine HCl were similarly effective and were as effective as cetirizine 10 mg QD. Fexofenadine 120 mg and 180 mg QD were effective on all symptoms of SAR, including ocular symptoms and nasal congestion.

Oral antihistamines alone generally are not effective, or are minimally effective, in relieving nasal congestion.¹⁷⁻¹⁹ In a previous study, the reduction in the nasal congestion score with doses of 60 to 240 mg BID fexofenadine HCl was statistically significantly greater than that produced by placebo.⁹ Nasal congestion is a vascular response arising from an interaction between mediators and end-organ receptors. In this respect mediators other than histamine are known to predominate.¹ The effect of fexofenadine HCl and cetirizine on nasal congestion could reflect an activity broader than just H₁

TABLE IV. Mean $\pm$ SE change from baseline VAS somnolence (0-100 scale)

Treatment week	Mean $\pm$ SE change from baseline (statistical significance)			
	Placebo	Fexofenadine (120 mg)	Fexofenadine (180 mg)	Cetirizine (10 mg)
1	-0.1 $\pm$ 1.1 (<i>P</i> = .1030)	-1.8 $\pm$ 1.1 (<i>P</i> = .2771)	-0.2 $\pm$ 1.2 (<i>P</i> = .0893)	2.1 $\pm$ 1.2
2	-1.7 $\pm$ 1.1 (<i>P</i> = .0098)	-4.1 $\pm$ 1.1 (<i>P</i> = .0413)	-1.4 $\pm$ 1.3 (<i>P</i> = .0330)	0.1 $\pm$ 1.3
1 and 2 combined	-1.2 $\pm$ 1.1 (<i>P</i> = .0065)	-2.9 $\pm$ 1.0 (<i>P</i> = .0195)	-0.6 $\pm$ 1.2 (<i>P</i> = .0256)	1.2 $\pm$ 1.2

P values compare placebo or fexofenadine group to cetirizine group with use of rank ANCOVA.

receptor antagonism.

Fexofenadine HCl was found to be free from adverse effects in this study, with no hematologic, biochemical, or clinical effects different from those of placebo. The incidence of drowsiness (3%) or fatigue (1%) was the same for fexofenadine as for placebo. Although the incidence of these adverse events was higher for cetirizine (6% and 2%, respectively), this was not statistically significant compared with either fexofenadine or placebo. However, the combined incidence of drowsiness and fatigue was significantly greater for cetirizine compared with fexofenadine (*P* = .018). As noted in the Results section, because the frequency of early discontinuation from the study was similar across all treatment groups and those patients who were withdrawn from treatment were included in the analysis of adverse events, there should not have been any appreciable effect on the efficacy and safety results.

The specific VAS somnolence assessment showed a trend for increased somnolence with cetirizine. These findings are in agreement with previous clinical studies that have indicated no sedative effect for fexofenadine^{9,10} and a sedative effect for cetirizine.²⁰ For most other H₁ antihistamines, the manufacturers' recommended doses appear to be optimal with regard to safety and should not be exceeded because the incidence of adverse effects may increase when higher doses are used.¹⁸ However, these considerations do not apply to fexofenadine HCl because there are no adverse effects described for doses far higher than 120 mg QD and 180 mg QD.⁹ Because tolerance to the sedative effects of classical antihistamines is well documented,^{21,22} we analyzed separately the 2 weeks of the study. The specific VAS somnolence assessment showed a trend for increased somnolence with cetirizine, compared with the other treatment groups, which reached statistical significance in week 2 and in weeks 1 and 2 combined. These findings are in agreement with previous clinical studies that have indicated no sedative effect for fexofenadine^{9,10} and a sedative effect for cetirizine.²⁰

In summary, fexofenadine HCl QD in doses of 120 and 180 mg is as effective as cetirizine 10 mg in the treatment of SAR. There was no statistical difference among

fexofenadine HCl treatment groups in the incidence of adverse events compared with placebo. Moreover, there was no increase in the frequency of reported adverse events with increased fexofenadine HCl doses. Once-daily fexofenadine is therefore a valuable H₁ receptor antagonist for the treatment of SAR.

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