Original Article

A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ebastine (20 mg and 10 mg) to loratadine 10 mg once daily in the treatment of seasonal allergic rhinitis

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Summary. Few randomized studies have compared the H1-receptor antagonists loratadine and ebastine in seasonal allergic rhinitis (SAR) patients. The objective of this study was to compare the efficacy and safety of ebastine 20 mg (E20), ebastine 10 mg (E10), loratadine 10 mg (L10), and placebo (P), once daily, in controlling symptoms of SAR over a 4-week period. This was a double-blind, placebo-controlled, randomized, parallel-group study. Efficacy was assessed in 749 patients (12 to 70 years old) by SAR symptom scores (nasal discharge, congestion, itching, sneezing, and total eye symptoms) entered on diary cards every morning and every evening over the previous 12 hours (reflective score) and at the time of recording (snapshot score). The E20 group showed greater reductions from baseline compared with the L10 group in 2 daily reflective composite scores (nasal index [with or without congestion]) and in all 4 daily snapshot composite scores. E10 and L10 groups showed no significant differences in either the daily reflective or snapshot scores overall although E10 showed a greater improvement of nasal discharge snapshot score than L10. The efficacy of E20 at controlling the symptoms of SAR was well sustained during the fourth week of treatment, with significant differences over placebo in 22/36 total rhinitis symptom scores, followed by E10 (6/36), whereas L10 showed no differences (0/36). Patient and physician global evaluations at the final visit were not statistically significant for any treatment group compared with placebo. There was no significant difference among all groups in the number of patients who reported adverse events. In conclusion, ebastine 20 mg given once daily for 4 weeks in the treatment of SAR showed larger mean reductions from baseline in most rhinitis symptoms scores than loratadine 10 mg. Sustained efficacy was most frequently observed with ebastine 20 mg over placebo, whereas loratadine 10 mg did not provide a statistically significant improvement in any individual or composite symptom score at the end of the fourth week. Both ebastine 20 and 10 mg were well tolerated and proved safe in the treatment of SAR.

Key words: Antihistamines - Clinical trial - Ebastine - Loratadine - Seasonal allergic rhinitis

Introduction

Ebastine (4-diphenylmethoxy-1-[3-(4-tert-butyl-benzoyl)propyl]piperidine) is a long-acting second generation H1-receptor antagonist approved in Spain in 1990 and now available for the first-line treatment of allergic rhinitis in more than 40 countries worldwide. The safety and efficacy of ebastine have been reported in placebo-controlled and comparative trials on the treatment of perennial [1, 2] and seasonal allergic rhinitis (SAR) [3-7]. Loratadine (4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-ylidene) -1-piperidinecarboxylic acid ethyl ester) is another H1-receptor antagonist available in most countries

worldwide for SAR. In large comparative trials of patients with SAR, short-term (2-3 weeks) therapy at the recommended adult dose of 10 mg once daily was significantly superior to placebo, and as effective as azatadine, cetirizine, clemastine, mequitazine, or terfenadine [8].

Few randomized studies have compared loratadine to ebastine in SAR patients. In one 2-week study including 306 patients, ebastine 20 mg once daily, but not loratadine 10 mg once daily, was significantly more effective than placebo both in the overall efficacy evaluation and in the individual evaluation of symptomatology; only the symptom "blocked nose" did not show significant improvement. Significant differences between both active treatments were found only for sneezing. In addition, ebastine 20 mg was found as safe as placebo, whereas loratadine 10 mg showed the higher rate of adverse events [6]. A second study assessed the efficacy and safety of ebastine 20 mg and 10 mg vs. loratadine 10 mg administered for a longer term (4 weeks) in 565 patients. This study reported larger mean reductions from baseline with ebastine 20 mg vs. loratadine 10 mg in all 4 daily reflective and morning snapshot composite scores, as well as in the individual scores of nasal discharge, nasal congestion and sneezing. Nevertheless, no differences were found for ebastine 10 mg vs. loratadine 10 mg and the rate of adverse events was similar among all treatment groups [7]. This second trial had a 4-week double-blind treatment duration, which is a good study design to provide enough duration of treatment for rhinitis symptoms throughout the ragweed season as well as to assess treatment tolerance. Unfortunately, the results found in that study could not be compared to other previous trials because of their different treatment duration. A difference was found for sustained efficacy after 4 weeks of treatment between ebastine 20 mg and loratadine 10 mg; however, this finding awaited further clinical trials to be confirmed. The aim of the present study was to compare the efficacy and the safety of ebastine 20 mg, ebastine 10 mg, loratadine 10 mg and placebo administered once daily in controlling symptoms of SAR over a 4-week period in a significant number of patients.

Materials and methods

The present study was a double-blind, placebo-controlled, randomized, parallel-group, comparative study of ebastine 20 mg (E20), ebastine 10 mg (E10), loratadine 10 mg (L10), and placebo (P), all administered once daily, in patients with a history of fall (ragweed) SAR. This study was conducted in compliance with local Ethical Committees and all patients gave their written informed consent before admittance to the trial.

Inclusion criteria were as follows: 1) patients of both genders aged 12 to 70 years; 2) at least a 2-year history of ragweed SAR characterized by the following symptoms: nasal congestion, rhinorrhea, sneezing, and nasal itching; 3) a positive skin prick test to ragweed allergen within 1 year before enrollment defined as a wheal and flare greater than or equal to that produced by histamine 1 mg/ml control or at least 5 mm greater in diameter than that produced by saline solution control; 4) a minimum baseline reflective total symptom score of at least 42 of 105 points (with at least one of the allergy symptoms present at a moderate or severe level) during at least 3 of the last 4 days of screening, including the morning of randomization; 5) normal electrocardiogram (ECG); 6) absence of medical conditions that could significantly interfere with the study; and 7) no history of hypersensitivity to antihistamines.

Exclusion criteria were as follows: 1) pregnant or lactating women; 2) patients who had received decongestants within 2 days, H1 antagonists (except astemizole) within 7 days, short-acting systemic or topical corticosteroids or intranasal cromolyn within 21 days, depot corticosteroids within 2 months, or astemizole within 12 weeks; 3) patients who had initiated immunotherapy within 1 month of the study initiation or were unable to maintain it at a stable dose; 4) patients who currently had an acute respiratory tract infection, otitis media, significant nasal polyps, acute asthma, or have had clinical signs of bacterial sinusitis; and 5) patients who had a significant concomitant illness that might affect the evaluation of the study medications. Patients were not permitted to take any other medication for the specific purpose of relieving the SAR symptoms nor any medication for another indication that could produce or relieve the symptoms of SAR (e.g., medications with anticholinergic activity, antihistaminic sleeping aids, anti-inflammatory agents, centrally acting cardiovascular drugs, or antidepressants). In addition, patients were not permitted to take any drug known to increase the Q-T interval corrected for heart rate > 444 milliseconds (QTc) or to inhibit CYP3A4 enzyme systems, such as azole antifungals and macrolide antibiotics. Steroids were not permitted in any form with the exception of contraceptives.

The study was conducted in 18 centers in the southern and southwestern United States from September 8 through December 2, 1999, coinciding with the ragweed pollen season in this region. The study consisted of a screening period of up to 28 days with the last 5 days as a baseline period, followed by a 28-day randomized double-blind treatment period (Fig. 1). Patient enrollment was completed within a 1-week period after verification of sufficient ragweed pollen present in the study site environment. At the first and final visits, patients underwent a full medical history, physical examination, standard laboratory panel, and an ECG. Eligible patients were randomized to receive one of four treatments: E20, E10, L10 or P. The treatments were blinded by inserting 1 or 2 ebastine 10 mg tablets, 1 loratadine 10 mg tablet, or no tablets (placebo) into

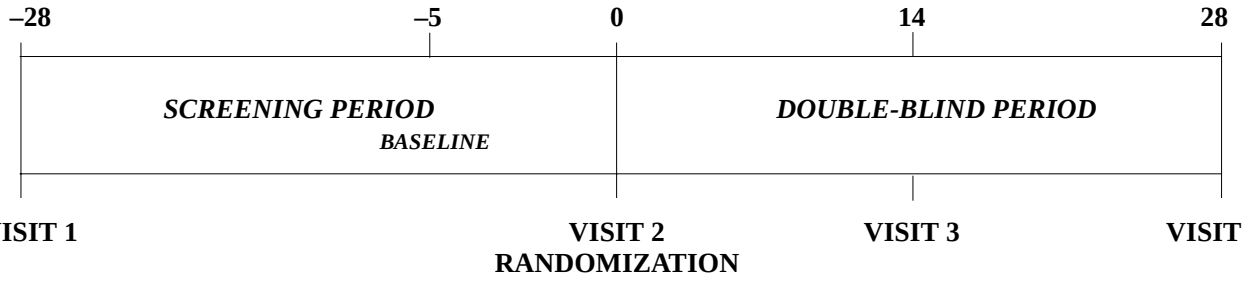

Figure 1. Flow-chart of the study.

an opaque capsule containing inactive excipients, and were to be taken on a once daily basis. Patients were instructed to take one capsule immediately after breakfast (which must include solids) with 8 ounces (240 ml) of water.

Patients were provided with a daily diary card and were instructed to score their rhinitis symptom scores every morning and every evening over the previous 12 hours (reflective score) and at the time of recording (snapshot score). Efficacy was assessed by means of SAR symptom scores entered on diary cards (nasal discharge [anterior and/or posterior], nasal congestion, nasal itching, sneezing, and total eye symptoms [itchy/watery eyes]), patient and physician global evaluation, and the number of withdrawals due to treatment ineffectiveness. The severity of symptoms was scored numerically on a scale of 0–3 with 0=absent, 1=mild, 2=moderate, or 3=severe. The patients and physician global evaluation of efficacy was scored numerically on a scale of 0=greatly improved, 1=somewhat improved, 2=no change, 3=somewhat worsened, and 4=greatly worsened. Patients also recorded any adverse events or concomitant medications throughout the study period.

Statistics

The study population size (200 patients/group) was determined to achieve a 90% power to detect a difference of 1 unit in the mean change from baseline in the daily reflective total symptom score between 2 treatments, assuming a SD of 2.9 units and a 10% discontinuation rate. The efficacy and safety analyses were performed on the intent-to-treat population, which comprised all randomized patients who took at least one capsule of study medication. The following 4 composite scores were calculated: total symptom score (sum of all 5 individual scores), total symptom score without congestion, nasal index (sum of the 4 nasal symptom scores), and nasal index without congestion. The primary efficacy variable was the change from baseline in mean daily (average of morning and evening) reflective symptom score over the whole treatment duration. The primary statistical analysis was the analysis of covariance (ANCOVA) with the primary variable as dependent, treatment and investigator as factors and important baseline variables as covariates. Treatment effect was evaluated using a 2-sided test and a p value <0.05 was considered significant. The primary comparison was between E20 and L10 groups; if this was significant, then comparisons of E10 to L10 groups were performed. Secondary comparisons were between each of the 3 active treatments vs. placebo. The patients' dropout rate due to treatment failure and the overall proportion of patients with adverse events was compared among treatment groups using the Cochran-Mantel-Hazel test.

Results

Study population

A total of 749 patients were enrolled in the study: 186 patients each in the E20 group and the P group, 188 patients in the E10 group, and 189 patients in the L10 group. A total of 649 patients (86.6%) completed the study. The number of patients who discontinued the study was lowest in the E20 group (19 patients) and similar among the other treatment groups: 30 in the E10 group, 26 in the L10 group, and 25 in the P group. The most frequent reason for discontinuation was treatment failure that occurred in 27 patients (3.6%): 5 patients (2.7%) in the E20 group, 6 patients (3.2%) in the E10 group, and 7 patients (3.7%) in the L10 group. No significant differences in dropout rate were found between any of the treatment groups and placebo. Twenty patients (2.7%) withdrew due to adverse events: the lower rates were found for the E20 group and the P group. Moreover, 25 patients (3.4%) discontinued the study due to protocol deviations. Patient disposition is summarized in Table 1.

Baseline characteristics

Table 2 summarizes the main demographic data of patients. The majority of patients were Caucasian (75.3%) and the larger proportion of patients (89.6%) was between the ages of 18 and 65 years. No significant differences were observed among the four treatment groups.

Table 1. Summary of patient disposition

Patient status	E10 N (%)	E20 N (%)	L10 N (%)	P N (%)	Total (N%)
Total enrolled	188	186	189	186	749
Completed entire study	158 (84.0)	167 (89.8)	163 (86.2)	161 (86.6)	649 (86.6)
Total discontinued	30 (16.0)	19 (10.2)	26 (13.8)	25 (13.4)	100 (13.4)
Reason for discontinuation					
Test drug ineffective	6 (3.2)	5 (2.7)	7 (3.7)	9 (4.8)	27 (3.6)
Protocol deviation	9 (4.8)	6 (3.2)	2 (1.1)	8 (4.3)	25 (3.3)
Adverse event	6 (3.2)	1 (0.5)	12 (6.3)	1 (0.5)	20 (2.7)
Lost to follow-up	4 (2.1)	5 (2.7)	3 (1.6)	4 (2.2)	16 (2.1)
Consent withdrawn	5 (2.7)	1 (0.5)	2 (1.1)	2 (1.1)	10 (1.3)
Other	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)

Table 2. Patient demographic data

	Treatment group				
Characteristic	**E10 N (%)**	**E20 N (%)**	**L10 N (%)**	**P N (%)**	**Total N (%)**
Patients enrolled	188	186	189	186	749
Gender (%)					
Male	99 (52.7)	85 (45.7)	87 (46.0)	93 (50.0)	364 (48.6)
Female	89 (47.3)	101 (54.3)	102 (54.0)	93 (50.0)	385 (51.4)
Age (years)					
Mean (±SD)	38.2±12.5	37.9±13.4	37.3±13.6	37.0±13.5	37.6±13.2
Range (min, max)	12,69	12,70	12,70	12,66	12,70
12-17 years, N (%)	14 (7.4)	15 (8.1)	18 (9.5)	18 (9.7)	65 (8.7)
(E 18-65 years, N (%)	172 (91.5)	167 (89.8)	167 (88.4)	165 (88.7)	671 (89.6)
66-70 years, N (%)	2 (1.1)	4 (2.2)	4 (2.1)	3 (1.6)	13 (1.7)
Weight (pounds)					
Mean (±SD)	176.3±39.9	167.9±37.7	168.7±42.8	173.9±45.7	173.9±45.7
Range (min, max)	95,304	99,283	82,400	84,375	84,375
Years with allergy					
Mean (± SD)	18.8±12.5	20.0±13.5	18.9±13.5	18.4±13.0	19.0±13.1
Range (min, max)	2,51	2,65	2,69	2,60	2,69

Overall efficacy

E20 vs. L10. The E20 group showed significantly greater mean reductions from baseline compared with the L10 group in two daily reflective composite scores (nasal index [with or without congestion]) (Table 3) and in all 4 daily snapshot composite scores (Table 4). Two individual reflective scores (nasal discharge (p=0.0048), and sneezing [p=0.0362]) and 3 individual snapshot scores (nasal discharge [p=0.428], nasal congestion [p=0.353], and sneezing [p=0.0210]) showed greater significant changes from baseline in the E20 group.

E10 vs. L10. The comparisons between the E10 and L10 groups showed a lack of significant differences in either the daily reflective or snapshot scores overall (Tables 3 and 4). Nevertheless, the difference between E10 and L10 was significantly different for nasal discharge snapshot score.

Active treatments vs. placebo. Overall, patients receiving E20, E10 or L10 showed significantly greater mean reductions than patients receiving placebo in 36, 29 and 12 of 36 rhinitis symptom scores, respectively. The 36 scores equal 9 daily reflective scores (9 = 4 composite + 5 individual scores) plus 9 daily snapshot scores plus 9 morning snapshot scores plus 9 evening snapshot scores. E20 and E10 showed significant differences vs. placebo in all snapshot rhinitis symptom scores, whereas L10 showed significant differences vs. placebo only for sneezing and nasal itching.

Table 3. Overall change from baseline in mean daily reflective composite scores

Variable	Treatment group	Baseline mean	Mean change from baseline (SE)	% mean change from baseline	*p* value Vs. L10	*p* value Vs. P
Total score	E20	9.83	–3.92 (0.20)	–39.3	NS	0.0003
	E10	10.21	–3.64 (0.20)	–35.9	NA	0.0083
	L10	10.25	–3.40 (0.20)	–33.3		NS
	P	9.72	–2.91 (0.20)	–28.2		
Total score w/o congestion	E20	7.55	–3.19 (0.16)	–41.7	NS	0.0001
	E10	7.89	–2.95 (0.16)	–37.4	NA	0.006
	L10	7.97	–2.80 (0.16)	–35.3		0.0407
	P	7.50	–2.34 (0.16)	–28.7		
Nasal index	E20	7.91	–3.11 (0.16)	–38.0	0.0426	0.0003
	E10	8.25	–2.88 (0.16)	–34.3	NS	0.0115
	L10	8.33	–2.66 (0.16)	–32.2		NS
	P	7.94	–2.32 (0.16)	–27.7		
Nasal index w/o congestion	E20	5.63	–2.39 (0.12)	–41.1	0.0478	0.0001
	E10	5.93	–2.19 (0.12)	–34.8	NS	0.0075
	L10	6.06	–2.06 (0.12)	–34.4		NS
	P	5.72	–1.74 (0.12)	–28.6		

E10: ebastine 10 mg; E20: ebastine 20 mg; L10: loratadine 10 mg; P: placebo. NS: not sifnificant: NA: analysis not performed since no significant difference between E20 and E10 was found.

Table 4. Overall change from baseline in mean daily snapshot composite scores

Variable	Treatment group	Baseline mean	Mean change from baseline (SE)	% mean change from baseline	*p* value Vs. L10	*p* value Vs. P
Total score	E20	9.32	–3.46 (0.20)	–35.8	0.0344	0.0001
	E10	9.72	–3.28 (0.20)	–33.5	NS	0.0015
	L10	9.69	–2.89 (0.20)	–29.8		NS
	P	9.19	–2.42 (0.20)	–24.4		
Total score w/o congestion	E20	7.11	–2.82 (0.16)	–38.4	0.0426	0.0001
	E10	7.49	–2.65 (0.16)	–34.5	NS	0.0010
	L10	7.48	–2.38 (0.16)	–30.7		0.0431
	P	7.05	–1.93 (0.16)	–22.0		
Nasal index	E20	7.44	–2.74 (0.16)	–32.9	0.0278	0.0001
	E10	7.85	–2.59 (0.16)	–31.9	NS	0.0017
	L10	7.85	–2.26 (0.16)	–29.1		NS
	P	7.48	–1.91 (0.16)	–24.1		
Nasal index w/o congestion	E20	5.24	–2.09 (0.12)	–36.4	0.0341	0.0001
	E10	5.62	–1.97 (0.12)	–32.8	NS	0.0010
	L10	5.63	–1.74 (0.12)	–30.4		NS
	P	5.34	–1.42 (0.12)	–22.1		

E10: ebastine 10 mg; E20: ebastine 20 mg; L10: loratadine 10 mg; P: placebo; NS: not sifnificant.

Weekly efficacy

The efficacy of E20 at controlling the symptoms of SAR was well sustained during the fourth week of treatment, with significant differences over placebo in 22/36 total rhinitis symptom scores. This was not equally observed with E10 or L10 groups at week 4, where significant differences vs. placebo were seen in 6/36 and 0/36 scores, respectively.

Patient and physician global evaluation

Patients and physician global evaluations at the final

visit were not statistically significant for any treatment group compared with placebo. Physicians reported no significant differences among the 3 active treatments but patients found E20 response significantly better than that of L10 (p=0.0052). The patient and physician global evaluations yielded similar ratings: 62.1% and 60.0% improved, 25.9% and 29.0% did not change, and 12.0% and 11.0% worsened according to patient and physician evaluations, respectively.

Safety

Overall, E20 and E10 once daily doses were found to be safe and well tolerated. Of all 749 patients enrolled, 223 patients (29.8%) reported 410 adverse events during the study period. There was no significant difference among the 4 study groups in the number of patients who reported one or more adverse events. Patients in all four treatment groups most frequently reported adverse events associated with the body as a whole system (E20, 11.8%; E10, 11.2%; L10, 15.3%; and P, 14.0%) followed by adverse events associated with the respiratory system (E20, 7.5%; E10, 8.5%; L10, 12.2%; and P, 10.2%). Of individual events reported, patients in all treatment groups experienced headache most frequently (E20, 3.2%; E10, 4.3%; L10, 5.8%; and P, 4.3%). Additionally, patients in the E20 group also reported dyspepsia (3.2%) and those in the placebo group reported pharyngitis (4.3%) as the other most frequent individual adverse event. Most of the adverse events reported were of mild to moderate intensity. Thus, 30 of 749 patients (4.0%) reported 40 severe adverse events during the study: 5 in the E20 group, 14 in the E10 group, 8 in the L10 group, and 13 in the P group. Most of the severe adverse events were considered by the investigators to be unrelated to treatment. No deaths occurred during the study. As mentioned above, 20 of 749 patients (2.7%) were prematurely discontinued from the study due to adverse events; most of these discontinuations were considered unrelated to the study drug.

Adverse events of special interest included those associated with the cardiovascular, nervous, and respiratory systems. These adverse events were reviewed extensively to determine any trends associated with the study drugs. In all active treatment groups, prolonged QTc interval was the most frequently reported cardiovascular adverse event. Prolonged QTc interval was reported by <3.5% of patients in the active treatment groups: E20, 2.2%; E10, 3.2%; and L10, 1.6%. Within the placebo group, prolonged QTc interval (0.011 sec) was reported in one patient (0.5%). All of the cases of prolonged QTc interval were mild and none resulted in premature discontinuation. The mean change ± SD from baseline in QTc interval was similar between E20 (0.026 ± 0.012 sec), E10 (0.022 ± 0.009 sec) and L10 groups (0.021 ± 0.004 sec). The maximum final QTc value for those patients who experienced QTc prolongation >0.444 sec at the end of the study was 0.452 sec (E20), 0.469 sec (E10), 0.463 sec (L10) and 0.450 sec (P). A slight increase in heart rate was observed in all 4 treatment groups, with the E20 group showing the highest mean increase from baseline (E20 7.7 bpm; E10 4.6 bpm; L10 4.9 bpm; and P 4.3 bpm). There was one report of palpitation in a patient receiving L10.

Thirty-three patients (4.4%) reported a total of 44 nervous system adverse events during the study; the highest number occurred in the E20 group (17 events) but most of them were mild to moderate. Somnolence appeared in 5 patients (2.7%) in the E20 group and in 3 patients (1.6%) in the E10 group. Three severe nervous system adverse events were reported: two cases of somnolence, one each in the E20 and E10 groups, and one case of dry mouth in the E20 group. Seventy-two patients (9.6%) reported a total of 101 respiratory system adverse events; the E20 group showed the lowest number (19 adverse events in the E20 group vs. 21 in the E10, 33 in the L10 and 28 in the P group). In all treatment groups, the respiratory system adverse events were mostly unrelated to the study drug, and 95 adverse events (94.1%) were mild to moderate. Pharyngitis was the most reported respiratory adverse event. No clinically significant adverse trends were observed in laboratory parameters, physical examination results, or vital signs.

Discussion

To date, this is the largest study performed comparing the efficacy and safety of ebastine 20 mg and ebastine 10 mg vs. loratadine 10 mg, an effective and safe second-generation H1 antihistamine, in relieving the symptoms of SAR; 749 patients were studied whereas the two previously published studies included 306 [6] and 565 patients [7]. Patients receiving the three active treatments showed significantly greater mean reductions from baseline than patients receiving placebo; this finding confirms the effectiveness of all three active therapies in relieving the symptoms of SAR already reported in previous studies [6, 7]. However, ebastine 20 mg in particular, as well as ebastine 10 mg, showed more significant symptom score differences vs. placebo than loratadine 10 mg.

Ebastine 20 mg showed significantly greater changes from baseline than loratadine 10 mg in 8 secondary efficacy variables (daily reflective nasal index, nasal index without congestion, nasal discharge and sneezing overall, and all 4 composite daily snapshot scores overall). The changes in the primary efficacy variable (daily reflective total score) were not significantly different between both therapies. Nevertheless, these changes were quantitatively higher with ebastine 20 mg (mean change from baseline, –3.92) or ebastine 10 mg (mean change from baseline, –3.64) than with loratadine 10 mg (mean change from baseline, –3.40) or placebo (mean change from baseline, –2.91) (Table 3). Overall,

the present data agrees with the results of previous studies although in one of these studies significant changes were found also in the primary efficacy variable "total symptom score" [7].

While H1-receptor antagonists are not commonly recognized as effective therapy for nasal congestion, we observed in this study that ebastine 20 mg, but not loratadine 10 mg, consistently and significantly improved the mean daily reflective and mean daily snapshot scores overall, compared to placebo. This finding was consistently observed in a previous comparative efficacy study in SAR [7] and it appears to be a unique, reproducible, and desirable characteristic of ebastine given at 20 mg once daily.

The efficacy of ebastine 20 mg at controlling the symptoms of SAR was well sustained during the fourth week of treatment, with significant differences over placebo in 26/36 rhinitis symptom scores. Ebastine 10 mg also showed significant differences over placebo at week 4 in 6/36 rhinitis symptom scores, whereas loratadine 10 mg showed no significant differences (0/36 scores). These findings confirm the results found in previous studies [7]; the authors suggested that changes in ambient pollen count over time could modify the efficacy of loratadine treatment since loratadine is not associated with the development of tolerance over time [9]. Accordingly, the present results add evidence on a possible maintenance of the efficacy of ebastine 20 mg and 10 mg over a wider range of ambient pollen counts and for a greater number of days during the SAR season.

Moreover, several previous studies reported circadian rhythms of allergic rhinitis: most patients had maximum intensity of symptoms in the morning [10, 11]. Consequently, all study medications were to be taken once daily in the early morning hours. Ebastine 20 mg achieved a significantly greater overall improvement from baseline over loratadine 10 mg in 7 of 9 morning snapshot scores but only in 1 of 9 evening snapshot scores. This result is very similar to that found in previous studies [7] and suggests that ebastine 20 mg given once daily is significantly more efficacious than loratadine 10 mg given once daily in controlling the symptoms of SAR at awakening in the morning.

Ebastine was safe and well tolerated at a dose of 10 mg or 20 mg once daily. The total incidence of adverse events was comparable to that found with loratadine 10 mg and placebo. Somnolence was reported in 2.6% of patients receiving the highest ebastine dose and only two cases of severe somnolence were reported, one in each of the ebastine groups. These results are consistent with previous data [7, 12] and support the non-sedating property of ebastine [13-15]. The data on QTc interval for those patients who had a prolonged QTc interval (>0.444 sec) in the two ebastine groups agrees with that obtained in an analysis of pooled cardiac data from a total of 842 patients treated with ebastine 1 to 30 mg/day and 360 placebo recipients in 5 multicenter studies, in which no patients recorded a QTc interval > 500 msec [16]. Data on heart rate changes obtained here and in previous studies [7] suggest that ebastine 20 mg may cause a small (around 3 bpm) increase in mean heart rate over placebo, which is unlikely to have any clinical relevance.

In conclusion, ebastine 20 mg given once daily for 4 weeks in the treatment of SAR showed larger mean reductions from baseline in most rhinitis symptoms scores than loratadine 10 mg. Improvement in rhinitis symptoms was observed throughout the day and at awakening. Moreover, sustained efficacy at the end of the 4-week treatment period was most frequently observed with ebastine 20 mg over placebo, although ebastine 10 mg also showed some significant changes, whereas loratadine 10 mg did not provide a statistically significant improvement in any individual or composite symptom score at the end of the fourth week. Finally, ebastine 20 and 10 mg were well tolerated and proved safe in patients 12 to 70 years old, with a total incidence of adverse events comparable to those of loratadine 10 mg and placebo.

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References

1. Davies, R.J. Efficacy and tolerability comparison of ebastine 10 and 20 mg with loratadine 10 mg: a double-blind, randomised study in patients with perennial allergic rhinitis. *Clin Drug Invest* 1998, 16:413-420.
2. Bousquet, J., Gaudano, E.M., Palma Carlos, A.G., Staudinger, H. A 12-week, placebo-controlled study of the efficacy and safety of ebastine, 10 and 20 mg once daily, in the treatment of perennial allergic rhinitis. Multicentre Study Group. *Allergy* 1999, 54(6):562-568.

3. De Molina, M., Cadahia, A., Cano, L., Sanz, A. Efficacy and tolerability of ebastine at two dose levels in the treatment of seasonal allergic rhinitis. *Drug Invest* 1989, 1:40-46.
4. Storms, W.W. Clinical studies of the efficacy and tolerability of ebastine 10 or 20 mg once daily in the treatment of seasonal allergic rhinitis in the US. *Drugs* 1996, 52(Suppl 1):20-25.
5. Gehanno, P., Bremard-Oury, C., Zeisser, P. Comparison of ebastine to cetirizine in seasonal allergic rhinitis in adults. *Ann Allergy Asthma Immunol* 1996, 76(6):507-512.
6. Luria, X., Robert, M., Antepara, I., Basomba, A., Castillo, J.A., Cisteró, A.M., Diaz, M., Fernandez, J., Nevot, S., Picado, C., Pinto, E., Raga, E. A double-blind placebo controlled study of the efficacy and tolerability of ebastine and loratadine in seasonal allergic rhinitis patients. *Allergy* 1995, 50(26 Suppl.):199 (Abst P-0350).
7. Ratner, P.H., Lim, J.C., Georges, G.C. Comparison of once-daily ebastine 20 mg, ebastine 10 mg, loratadine 10 mg, and placebo in the treatment of seasonal allergic rhinitis. *J Allerg Clin Immunol* 2000, 105(6):1101-1107.
8. Haria, M., Fitton, A., Peters, D.H. Loratadine. A reappraisal of its pharmacological properties and therapeutic use in allergic disorders. *Drugs* 1994, 48(4):617-637.
9. Claritin brand of loratadine tablets. In *Physician's Desk Reference.* Montvale (NJ): Medical Economics 1999, pp. 2825-2827.
10. Reinberg, A., Gervais, P., Levi, F., Smolensky, M., Del Cerro, L., Ugolini, C. Circadian and circannual rhythms of allergic rhinitis: an epidemiologic study involving chronobiologic methods. *J Allergy Clin Immunol* 1988, 81(1):51-62.
11. Smolensky, M.H., Reinberg, A., Labrecque, G. Twenty-four hour pattern in symptom intensity of viral and allergic rhinitis: treatment implications. *J Allergy Clin Immunol* 1995, 95(5 Pt 2):1084-1096.
12. Roberts, D.J., Gispert, J. The non-cardiac systemic side-effects of antihistamines: ebastine. *Clin Exp Allergy* 1999, 29 Suppl 3:151-155.
13. Wiseman, L.R., Faulds, D. Ebastine. a review of its pharmacological properties and clinical efficacy in the treatment of allergic disorders. *Drugs* 1996, 51(2):260-277.
14. Vincent, J., Sumner, D.J., Reid, J.L. Ebastine: the effect of a new antihistamine on psychomotor performance and autonomic responses in healthy subjects. *Br J Clin Pharmacol* 1988, 26(5):503-508.
15. Hurst, M., Spencer, C.M. Ebastine - An update of its use in allergic disorders. *Drugs* 2000, 59(4):981-1006.
16. Connell, L., Alderfer, V., García, J. Electrocardiographic evaluation of ebastine in double-blind allergic rhinitis clinical trials. *Allergy* 1995, 50(Suppl 26):105.

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