Allergy, 1990, 45, 254–261

A multicentre study of loratadine, clemastine and placebo in patients with perennial allergic rhinitis

L. FRØLUND,[1] B. ETHOLM,[2] K. IRANDER,[3] T. A. JOHANNESSEN,[2] L. ÖDKVIST,[3] B. OHLANDER[4] & B. WEEKE[1]

[1]State University Hospital, Copenhagen, Denmark, [2]Central Hospital of Vestfold, Tønsberg, Norway, [3]University Hospital, Linköping, Sweden, and [4]Växjö Hospital, Växjo, Sweden

This multicentre, double-blind, randomized parallel-group study compared 3 weeks' treatment with either loratadine (Clarityn®) 10 mg once daily, or clemastine (Tavegyl®) 1 mg twice daily, and placebo in outpatients with active perennial allergic rhinitis. 155 patients were evaluated for efficacy and safety. Grading of four nasal and three non-nasal symptoms, rhinoscopy signs, and therapeutic response was performed on treatment days 6, 13, and 20. Patients recorded daily symptoms and possible adverse experiences in a diary, also indicating when symptoms of active rhinitis were relieved. Loratadine and clemastine were statistically significantly superior to placebo throughout the study ($P < 0.05$), based on assessment of patients' nasal and eye symptoms, patients' diary scores, rhinoscopy signs of symptoms, and onset of relief. The loratadine group showed a statistically significantly ($P < 0.05$) faster onset of relief of symptoms compared with the group treated with clemastine. Concerning nasal stuffiness, loratadine was significantly ($P < 0.05$) superior to clemastine after 1 week's treatment. Reports of adverse reactions showed that significantly ($P < 0.05$) more patients complained of sedation in the clemastine than in the loratadine group. Regarding other adverse experiences and laboratory tests, the three treatment groups were statistically comparable ($P < 0.05$). The study showed that compared with placebo both loratadine and clemastine were effective in relieving nasal and eye symptoms in patients with perennial allergic rhinitis. Loratadine was safe and well tolerated and was significantly less sedative than clemastine; loratadine may therefore possess an advantage in clinical use in the treatment of perennial allergic rhinitis.

Key words: clemastine; loratadine; non-sedating antihistamines; perennial allergic rhinitis.

Accepted for publication 19 October 1989

Allergic rhinitis is an IgE-mediated response to airborne allergens mediated primarily by histamine release from basophils and mast cells, acting either directly on cellular histamine receptors, this being the main cause of oedema and persistent blockage in the nose, or indirectly via reflexes which account for sneezing and hypersecretion (11). The nose symptoms are often associated with symptoms from the eyes: itching, tearing, and redness of conjunctivae. The allergic rhinitis has been classified as *seasonal allergic rhinitis,* a generally accepted term for hayfever or pollinosis, usually triggered by tree pollen in spring, grass pollen in early summer, and wheat pollen in late summer, or as *perennial allergic rhinitis* with symptoms which may be daily, periodic, or occasional, the allergenic aetiology often being house dust mite, animal dander and mould (12). The efficacy of conventional antihistamines in alleviating such signs and symptoms of allergic rhinitis is well established (13). However these agents have the potential to produce undesirable side effects, particularly sedation. A new generation of

antihistamines almost devoid of unwanted sedative effects has been manufactured (14). Among these, is a selective peripheral histamine$_1$-receptor antagonist, loratadine, which has been described in pre-clinical and clinical studies as having essentially no sedative liability (1, 5). Moreover, a 10 mg dose of this antihistamine given once daily has proved efficacious in patients with allergic rhinitis (5).

Loratadine is completely absorbed after oral administration, and maximal plasma concentration is achieved after 60–90 min (7, 15). Loratadine undergoes a first-pass metabolism in the liver, and an active metabolite, descarboxyaethoxyloratadine (DCL), has been demonstrated, which is 25 % of loratadine after achievement of equilibrium (15). The half-life by equilibrium measured after 5 days' treatment is 14.4 h (15), and clearance 202±175 ml/min/kg (n = 12) (7), the kinetics of loratadine and DCL not being dependent on repeated administration (15). *In vivo* investigations in man have shown that loratadine inhibits skin reaction after intradermally injected histamine (2 μg) within 1 h with the maximal inhibition 2–4 h after administration (2, 8, 16). The skin reaction to histamine is normalized 3 days after discontinuation of oral loratadine administration (10 mg/day) (8).

The present 3-week multicentre study was conducted to evaluate the efficacy and safety of loratadine 10 mg given once daily (morning dose) in comparison with clemastine 1 mg twice daily, and placebo as oral therapy for outpatients in the treatment of perennial allergic rhinitis.

The multicentre, randomized, double-blind, placebo-controlled, parallel-group study was designed to compare the efficacy and safety of loratadine 10 mg once daily, clemastine 1 mg twice daily, and placebo, in outpatients with perennial allergic rhinitis. All patients gave informed consent to participation and the study was approved by the local ethics committee for each centre participating.

PATIENTS AND METHODS

Patients participating were between 18–65 years, of either sex with an unequivocal history of perennial allergic rhinitis, and with intermittent or continuous nasal symptoms for at least 1 year. During 1987, 155 patients were enrolled in this study and 130 completed it: 48 in the loratadine group, 44 in the clemastine group, and 38 in the placebo group. The separate form on which the patients were to monitor onset of relief of symptoms was delivered by only 127 patients to the investigator at visit 2. Concerning sex, age, weight at baseline, no systematic deviation was observed either from a random allocation of patients or treatments or between centres. The diagnosis was confirmed by a positive standard skin prick test.

Excluded from the trial were patients with a history of idiosyncratic reactions to antihistamines or multiple drug allergies. Patients were not accepted if they had any concurrent disease that would interfere with study results or require treatment, if pregnant, or lactating. Further, patients should not have nasal polyps, deviated septa or any structural defect which might cause nasal obstruction or interfere with clinical evaluation. Patients should not have any ongoing seasonal allergic rhinitis during the study period. Further exclusion criteria were: pre-seasonal or co-seasonal immunotherapy with antigen extracts started within the 12 months prior to the study, or any maintenance doses of these preparations during the last 12 months before entering the study. Similarly, enrolment was not allowed for patients who had received the following specified type of medication prior to the study start: therapy with loratadine within 3 months, systemic or topical corticosteroids, sodiumcromoglycate (cromolyn-sodium) within 2 weeks prior to the study, decongestants within 24 h, astemizole within 4 weeks, and antihistamines other than astemizole 3 days prior to the study. Patients with clinically significant, abnormal laboratory test results were also excluded. The severity of signs and symptoms of perennial allergic rhinitis was assessed for each patient. The patient scored four nasal symptoms (discharge, stuffiness, itching, and sneezing) and non-nasal signs (itching, tearing, and redness of eyes) on a 4-point scale (0 = none, to 3 = severe). For inclusion in the study, the combined symptom score had to be at least 4.

Allergy skin testing

The skin prick test was performed on the volar side of the forearm using a Dome/Hollister-Stier needle. The allergen extracts were used in the potency of 10 HEP (histamine equivalent prick) purchased from Allergologisk Laboratorium A/S, Copenhagen, Denmark) (Soluprick®). The standard panel included the following allergens: birch (*Betula verrucosa*), grass (*Phleum pratense,* timothy), wheat (*Artemisia vulgaris*), animal dander (horse, dog, cat), house dust mite (*Dermatophagoides pteronyssinus*), mould (*Alternaria alternata* and *Cladosporium herbarum*). To be eligible for enrolment, a patient had to develop an antigen-induced wheal (for antigens other than pollen) of at least half the size of the positive control (histamine 10 mg/ml) and larger than the negative control.

Drug administration

According to a computer generated randomization code, patients were assigned to oral treatment with loratadine 10 mg once daily combined with placebo once daily, clemastine 1 mg twice daily, or placebo twice daily. The test medication was provided as identical opaque capsules, supplied in strips labelled with Patient No., Week No., and Prescribed time of administration. The commercial formulation of the two drugs was not in any way changed by the blinding procedure so that it could affect the known pharmacokinetics of the two drugs (Schering Corp.). Medication sufficient for 1 week of treatment was given to patients on days 0, 7, and 14. Those assigned to the loratadine group took the active agent in the morning and placebo in the evening. The ingestion of other investigational or antihistamine-containing agents or any other medication liable to affect the cause of rhinitis or interact with the test medication was not permitted, unless essential for patients' welfare, and was then to be recorded in the case report form.

Evaluation of efficacy

Medical histories were obtained on Day 0. At baseline (Day 0) and on Days 7, 14, and 21 (visits 1, 2, 3, and 4, respectively), four nasal symptoms (discharge, stuffiness, itching, and sneezing), and three non-nasal symptoms (itching, tearing, and redness of eyes) were graded with regard to severity (0 = no symptoms, to 3 = severe symptoms). Rhinoscopy was made at each visit to assess nasal membranes, secretion and patency (0 = normal, 3 = abnormal). Blood pressure and body weight were recorded at each visit. The rhinitis evaluation for each patient was performed by the same person throughout the study. The patients recorded daily symptom scores 0–3 listing the above-mentioned symptoms, and were to monitor onset of relief in a separate form delivered at visit 1. A new diary card for symptom score recording during the forthcoming treatment period was distributed to the patient at each visit.

Evaluation of safety

Adverse experience information was obtained by asking the same general question at each evaluation. Details of all adverse experiences were recorded in the case report form with the date and time of onset, duration, severity, action taken, and outcome. Laboratory tests including complete blood counts and chemistry were made before starting treatment and at the final visit. Any laboratory test with a clinically significant, abnormal result was to be repeated, and an explanation for the abnormality was sought. At each visit to the clinic, the patients' weights were recorded.

Statistics

Mean values have been used for calculations. T-test and χ^2-test have been used for comparison of data. Least square regression was used for analysis of linear relationship. $P < 0.05$ was considered statistically significant.

Table 1

Distribution of antigens

Antigens	Loratadine	Clemastine	Placebo
1			
2			
3			
4		3	1
5		2	4
6	18	8	14
7	28	25	18
8			1
9		2	
1 + 7		1	
2 + 8	1		
4 + 6			1
5 + 6	1	2	1
5 + 7			1
6 + 5		1	
6 + 7	2	4	3
4 + 5 + 6			1
5 + 6 + 7	1	2	3
6 + 7 + 8 + 9	1		
Missing	1	1	3
Total = 155	53	51	51

1: *Betula ver.*
2: *Plenum prat.*
3: *Artemisia vulgaris*
4: Horse
5: Dog
6: Cat
7: *Dermatophagoides pter.*
8: *Alternaria alt.*
9: *Cladosporium herb.*

RESULTS

Table 1 shows the distribution of antigen data. By far the most common antigens were cat and *Dermatophagoides pteronyssinus*. Their distribution showed no significant differences between treatment groups.

Table 2

Total number of patients discontinuing treatment

Loratadine:	5 patients totally - all due to no return to clinical visits/other reason not related to treatment.
Clemastine:	7 patients totally 1 treatment failure + adverse reaction 2 treatment failures 4 no return to clinical visits/other causes unrelated to treatment.
Placebo:	13 patients totally 9 treatment failures 4 no return to clinical visits/other causes unrelated to treatment.

Table 3

Number of adverse effects

	Loratadine (n = 53)	Clemastine (n = 51)	Placebo (n = 51)	Total (n = 155)
Tiredness	2	18	10	30
Gastrointestinal	3	3	3	9
Headache	1	3	2	6
Dizziness		2	1	3
Dry mouth		1	1	2
Somnolence		1	1	2
Oedema			1	1
"Heavy"	1			1
Heartburn			1	1
Vertigo		1		1
Eczema			1	1
Asthenia			1	1
Common cold			1	1
Depression		1		1
Hunger	1			1
Itching			1	1
Swollen eyes			1	1

Rhinoscopy data

Rhinoscopy findings were statistically comparable at baseline between the three treatment groups and study centres. During the treatment, the loratadine and clemastine groups showed a statistically significant effect ($P < 0.05$) when compared with the placebo group with regard to assessment of nasal membranes, secretion, and patency.

Nasal and eye symptom scores

Total nasal symptoms and total eye symptoms are shown in Figs. 2 and 3. At visit 1, baseline, there were no statistically significant differences between treatment groups or study centres. However, at each of the subsequent visits, both loratadine and clemastine significantly reduced patients' symptoms compared with placebo

($P < 0.05$). A similar reduction was seen for all four nasal symptoms (discharge, stuffiness, itching, and sneezing). Concerning eye symptoms, this decrease was found for redness and itching ($P < 0.05$), but no significant decrease was observed for tearing. When comparing the loratadine and clemastine treatments with regard to differences in total symptoms scores, the general pattern was most pronounced ($P < 0.05$) at visit 2, which is in accordance with the faster onset of relief observed in the loratadine group. A significant difference was found between the two active medications with regard to nasal itching (Table 4) and nasal stuffiness (Table 5) at visit 2, when loratadine was superior to clemastine ($P < 0.05$). For all figures there is a decrease in the placebo group at visits 2, 3, and 4 in total nasal and eye symptom scores. Fig. 1 shows the mean values of total symptoms (nasal and eye symptoms) for the three treatment groups according to patient diaries. A significant difference between active treatments and placebo) is seen ($P < 0.05$) at Day 1.

Onset of relief

The diary cards (Fig. 1) show that there is a statistically significant onset of relief in the loratadine and clemastine groups within the first day of treatment compared with placebo. When evaluating the separate forms for onset of relief of symptoms, a statistically significantly faster onset was seen in the loratadine group compared with the clemastine group ($P < 0.05$) within the first day.

Safety

Table 2 shows the number of patients discontinuing treatment during the study. Table 3 shows the types and number of adverse reactions experienced during the study. Significantly fewer events, especially sedation, were found in the loratadine group compared with the clemastine group ($P < 0.05$) and with placebo ($P < 0.05$). No statistically significant differences were found between the three groups with regard to laboratory tests, blood pressure, and weight change at any subsequent time (Table 6).

DISCUSSION

This multicentre trial compared the efficacy and safety of loratadine 10 mg once daily, clemastine 1 mg twice daily, and placebo, administered orally for 21 days to outpatients with perennial allergic rhinitis. The demographic and disease characteristics were comparable between treatment groups and between the four different centres participating. Loratadine and clemastine were statistically significantly superior to placebo throughout the study, based on assessments of patients' nasal and eye symptoms, patients' diary scores, rhinoscopy signs of symptoms, and onset of relief. These evaluations were made at weekly visits by the same doctor throughout the study, and by the patients who reported daily symptom score in at diary. Comparing loratadine with clemastine, there was a statistically significantly faster onset of relief of symptoms in the loratadine group than in the group treated with clemastine. Moreover, this study showed that concerning nasal stuffiness, loratadine was significantly superior to clemastine after 1 week's treatment. Reports of adverse reactions showed that there was a significantly higher number of patients in the clemastine group than in the loratadine group complaining of sedation; for other adverse experiences mentioned (Table 3) the three treatment groups were statistically comparable.

Few detailed studies investigating the efficacy of loratadine in perennial allergic rhinitis have been published, whereas several studies have shown the beneficial effect of loratadine in alleviating symptoms in patients suffering from seasonal allergic rhinitis (5). In a multicentre study, Lockey et al. found that loratadine 10 mg once daily and clemastine 1 mg twice daily were equally efficacious in relieving symptoms over a 6 months' period in patients suffering from perennial rhinitis (10). In another study, loratadine 10 mg o.d., and terfenadine 60 mg b.i.d. were comparable, and both statistically significantly more effective in improving the symptoms of perennial allergic rhinitis com-

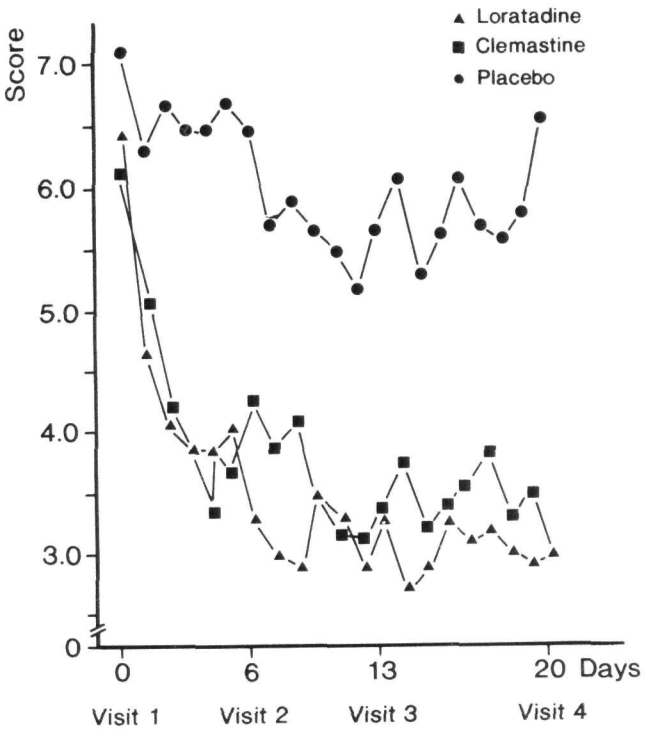
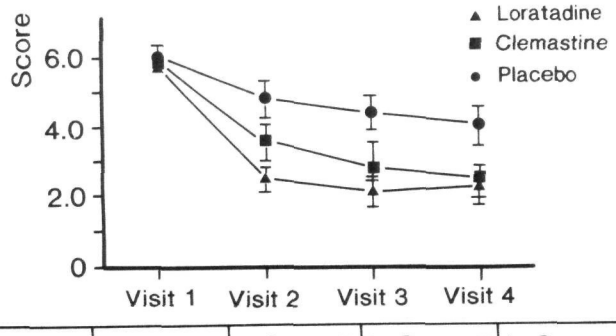


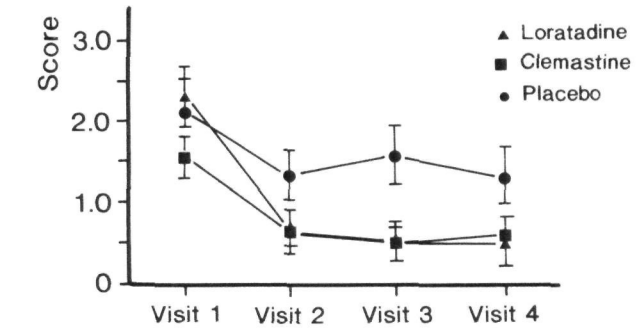
Fig. 1. Total symptoms from patient diary cards (nasal and eye symptoms). Significant difference between active treatments and placebo ($P < 0.05$).

pared with placebo in a total of 215 patients (4). Symptoms of perennial allergic rhinitis may be daily, periodic or occasional, and in the present study, all patients had to show a certain symptom score before inclusion, and, moreover, intermittent or continuous nasal symptoms over the last year. Therefore the decrease in total nasal and eye symptom score in the placebo group at visits 2, 3, and 4 could be due to this fluctuation or to the significantly



	L-C	L-P	L-C	L-P	L-C	L-P	L-C	L-P
P-values	0.91	0.76	0.04	0.00	0.19	0.00	0.78	0.01

Fig. 2. Total nasal symptoms from patient diary cards. Significant difference between loratadine and placebo (L and P) ($P < 0.05$). L = loratadine, C = clemastine, P = placebo.



	L-C	L-P	L-C	L-P	L-C	L-P	L-C	L-P
P-values	0.12	0.74	0.88	0.05	0.95	0.01	0.90	0.02

Fig. 3. Total eye symptoms from patient diary cards. Significant difference between active treatments (L, C) and placebo (P) ($P < 0.05$). L = loratadine, C = clemastine, P = placebo.

larger number of patients discontinuing treatment in this group (Table 2), or the event might be reflecting a placebo effect. The continued efficacy of loratadine over the period of this study suggests that patients did not develop tolerance to the medication over the 3 weeks' course of therapy, although this was a short treatment period with regard to evaluating this aspect. Treatment of perennial allergic rhinitis with antihistamines is often effective with regard to symptoms of sneezing and secretion, but with no or very poor effect on nasal stuffiness, for which reason antihistamines are usually combined with other medication, decongestant preparations, or steroids (11). In this study, a statistically significant difference was seen in symptom scores between loratadine and clemastine concerning nasal stuffiness, and rhinoscopy data confirmed this effect by an improvement of nasal membranes, secretion and patency when loratadine was compared with placebo. This latter event was not statistically significant when comparing the two active treatment regimens. This is an unexpected finding for an antihistaminic drug having an effect on nasal stuffiness, and it might by partly explained by the antiallergic action of loratadine previously reported (9). Brostoff (3) compared two antihistamines, terfenadine, chlorpheniramine maleate, and placebo in patients with perennial allergic rhinitis during a 2 weeks' treatment and found no statistically significant difference in response between active treat-

Table 4

Nasal itching from patient diary cards

	Visit 1		Visit 2		Visit 3		Visit 4	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Loratadine	1.11	0.12	0.40	0.10	0.28	0.09	0.41	0.11
Clemastine	1.12	0.13	0.73	0.12	0.47	0.11	0.45	0.12
Placebo	1.29	0.14	1.02	0.14	0.72	0.12	0.85	0.15
	L-C	L-P	L-C	L-P	L-C	L-P	L-C	L-P
P-values	0.98	0.31	0.04	0.00	0.19	0.00	0.82	0.02

L = loratadine; C = clemastine; P = placebo.

ments and placebo after evaluation of total nasal symptom score including nasal stuffiness. The number of patients in this study was less than 20 in each treatment group, and probably therefore too small to reveal any differences.

Loratadine was less effective on tearing compared with placebo, but very low symptom scores had been reported on this symptom at baseline, and thus no statistically significant reduction could be expected, whereas a significant improvement ($P < 0.05$) was reported on itching and redness, for which a higher symptom score at baseline was found.

The incidence of sedation with loratadine was significantly lower than with clemastine, and lower than placebo. This is not an unexpected finding, since clemastine is a conventional antihistamine known to cause sedation in some patients, also seen in other studies (6). The higher incidence of sedation reported in the placebo group compared with loratadine might be explained by no symptom relief in the placebo group. The incidence of anticholinergic side effects was also low, which is in accordance with observations previously reported (6), and no such side effects were observed in the loratadine group.

Conclusion

This 21-day study showed that both loratadine and clemastine were effective compared with placebo in relieving nasal and eye symptoms in patients with perennial allergic rhinitis. Furthermore, loratadine was superior to clemastine in relieving nasal stuffiness, and gave a faster onset of symptom relief within the first treatment day. Loratadine was safe and well tolerated, and was significantly less sedative than clemastine. Therefore, loratadine may possess an advantage in clinical use in the treatment of perennial allergic rhinitis.

Table 5

Nasal stuffiness from patient diary cards

	Visit 1		Visit 2		Visit 3		Visit 4	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Loratadine	1.91	0.12	1.06	0.12	0.94	0.14	0.86	0.14
Clemastine	1.92	0.11	1.53	0.13	1.27	0.13	1.02	0.14
Placebo	1.94	0.11	1.49	0.15	1.58	0.14	1.45	0.14
	L-C	L-P	L-C	L-P	L-C	L-P	L-C	L-P
P-values	0.92	0.83	0.01	0.03	0.08	0.00	0.42	0.00

L = loratadine; C = clemastine; P = placebo.

Table 6

Weight change recorded during study

	Visit 1	Visit 4	
Loratadine kg	67.9±1.8	68.4±1.9	$P > 0.05$
Clemastine kg	71.6±1.9	72.3±2.0	$P > 0.05$
Placebo kg	69.8±1.8	68.5±1.9	$P > 0.05$
	(mean±SEM)		

ACKNOWLEDGEMENT

We thank Knud Conradsen, Institute of Mathematical Statistics and Operation Analyses, The Danish Technical University, Copenhagen, for performing the statistical analyses, and Anne Larsen for secretarial assistance.

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Address:
Lars Frølund, M.D.
Medical Department TTA
Allergy Unit 7511
State University Hospital
Tagensvej 20
DK-2200 Copenhagen N
Denmark