Mizolastine

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Efficacy and safety of mizolastine in seasonal allergic rhinitis
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Efficacy and safety of mizolastine 10 mg in a placebo-controlled comparison with loratadine in chronic idiopathic urticaria: results of the MILOR study
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Efficacy and safety of mizolastine in seasonal allergic rhinitis

Background: Mizolastine is a new, nonsedating antihistamine under clinical investigation for treatment of allergic rhinitis and urticaria.

Objective: The purpose of this study was to determine the optimally active dose of once-daily mizolastine in seasonal allergic rhinitis.

Methods: This multicenter, double-blind, parallel study involved 494 patients randomly allocated to mizolastine (5, 10, or 15 mg) or placebo for 2 weeks.

Results: Physicians' assessments indicated the superiority of 10 and 15 mg mizolastine to placebo in reducing total symptom scores (P= .002), nasal scores (P = .004), and ocular scores (P = .007) at day 7. Patients' diaries showed a significant change from baseline in daily symptom scores as early as day 2 (P = .01) in 10- and 15-mg mizolastine groups in comparison to placebo, but this was not maintained throughout the study. No additional benefits were demonstrated during the second week of treatment in terms of efficacy. Adverse events were slightly more frequent in the 15-mg mizolastine group.

Conclusion: This study confirms mizolastine is an effective and well tolerated antihistamine in the treatment of seasonal allergic rhinitis; 10 mg is the optimal dose.

INTRODUCTION

Mizolastine (SL 85.0324), a benzimidazole derivative, is a new potent, selective, and peripherally acting antagonist of histamine H_1 receptors currently under clinical investigation for treatment of allergic conditions. Mizolastine has high affinity for histamine H_1 and lacks affinity for H_2 and H_3, muscarinic and serotoninergic receptors.[1,2] Standard tests of antihistaminic and of antiallergic activities show at least as potent results as with astemizole, loratadine, and terfenadine.[3]

The apparent half-life for the pharmacologic activities of mizolastine ranges from 6 to 11 hours.3 In addition, mizolastine inhibits histamine release from rat mast cells at doses similar to those of cromoglycate.[4] Suppression of the wheal and flare response is dose-dependant, significant from 2 mg upwards; the onset of action is rapid, one hour, and persists up to 24 hours after a 10-mg dose.[5] Mizolastine 10 mg has an H1 antihistamic activity similar to that of terfenadine, 120 mg, and cetirizine, 10 mg, but appears to be more potent than loratadine, 10 mg, from three to eight hours after dosing.[6] No impairment of psychomotor performance and cognitive function,[7-9] nor sedative effects or detrimental effects on memory in the elderly[9-10] have been observed at doses less than 20 mg. Pharmacokinetic parameters, mainly a plasma half-life of approximately 14 hours, allow a single oral daily regimen. A preliminary clinical trial in seasonal allergic rhinitis was carried out in 256 patients suggesting 10 mg to be an adequate dose.[11]

The aim of this study was to determine accurately on a large sample the optimally active dose of mizolastine in seasonal allergic rhinitis and to provide information about its safety profile.

MATERIALS AND METHODS

This multicenter, double-blind, randomized, 4-parallel group study compared three dosages of mizolastine, 5, 10, and 15 mg daily and placebo. Treatment lasted 2 weeks and visits were scheduled at days 0, 7, and 14. The trial was conducted in seven European countries during the 1990 pollen season. The protocol was approved by Ethics Committees in accordance with national legislations, and informed consent was obtained from each participant before entering the study.

Patient Selection

Patients at least 15 years old, currently suffering from seasonal allergic rhinitis with predominantly nasal symptoms were considered for the study. Two of the four following nasal symptoms, itching nose, sneezing, runny nose, blocked nose, were to be scored at least 2 on the 0 to 3 severity scale, where 0 = none, 1 = mild, 2 =moderate, and 3 = marked (minimum score required =4 upon enrollment). The diagnosis was established on a documented clinical history of allergic rhinitis during the previous one or two pollen seasons; treatment had to be required and skin tests to grass pollen were to be positive.

Patients were not eligible in case of upper respiratory tract or eye infection, chronic rhinitis or conjunctivitis, even if partly allergic in nature, or nasal polyposis. Patients were also excluded if they had used topical steroids within the past 2 weeks, systemic steroids within the past 4 weeks, ketotifen within the past week, if desensitization had been started within the past 6 months and if hypersensitivity to antihistamine or benzimidazole derivatives had been demonstrated. The washout period for the following drugs was two days: antihistamines (except astemizole:6 weeks), nasal decongestants, sodium cromoglycate, anticholinergics, and sedatives. Evidence of major systemic disease, alcohol, or substance abuse were reasons for exclusion. Patients were not to work with dangerous machinery nor to drive vehicles as an integral part of their job. Female patients were excluded if they were pregnant, lactating, or not using effective methods of contraception.

Drug Administration

Patients were randomly assigned to receive one of the following four study drugs, 5, 10, or 15 mg mizolastine or placebo. The 5- and 10-mg tablets were 1 mm smaller than the 15 mg ones; therefore, the double-placebo technique was chosen to ensure double- blindness. Both tablets (ie, active drug and placebo for mizolastine groups or both sizes of placebo tablets for the placebo group) were taken once-daily in the morning, beginning on day 1, day 0 being the day of inclusion. The last tablets were taken on the morning of the final visit, on day 14. Packagings were numbered according to a random distribution table; each patient was identified with a number corresponding to the order of enrollment and received packaging with the same number. All medications were returned to the physician at the end of the study to verify compliance.

Assessment of Efficacy

Both the patient and the physician rated therapeutic activity. Patients were given diary cards on which they were to evaluate the severity of symptoms, each evening of the first week, beginning on the day of enrollment. The following symptoms, blocked nose, running nose,

itching nose, itching eyes, and watery eyes were scored using the 0 to 3 severity scale, sneezes were recorded as exact number. At each visit, patients were asked to assess overall discomfort on a 100-mm visual analogue scale ranging from 0 = no discomfort to 100 mm =worst possible discomfort. At each visit, the physician rated the severity of symptoms with the same 0 to 3 scale; in addition to the above listed symptoms, red eyes, itching throat, itching ears, and red ears were evaluated yielding the following ranges of scores: nasal symptom score (0 to 12), ocular symptom score (0 to 9) and total score (sum of the nasal, ocular, throat and ear scores) (0 to 30). At the final visit, the physician also noted the clinical global impression, ratio of the score for the therapeutic effect (4 = marked, 3 = moderate, 2 = minimal, 1 = unchanged) over that for adverse events (1 _=none, 2 = no significant interference, 3 =significant interference, 4 =overweighs), yielding results ranging from 0.25 to 4.

Table 1. Patient's Characteristics

	Placebo	Mizolastine			p value*
		5 mg	10 mg	15 mg	
Number of patients	122	118	130	124	-
Males	61	53	67	49	0.21
Females	61	65	63	75	-
Age,yr†	30.8±1.0	29.7±0.9	30.0±0.8	32.0±1.3	0.40
Race					
White	111	109	119	114	0.98
Other	11	9	11	10	-
Rhinitis duration,mo†	113.2±8.6	116.5±8.7	126.1±8.2	116.0±8.3	0.71

*Intergroup comparison.
† Mean value ± SEM

Assessment of Safety

Adverse events, spontaneously reported by the patients and/or observed by the investigator were documented regardless of relationship to therapy and in accordance with standards. Body weight measurements and standard laboratory tests were carried out upon enrollment and at the final visit. Blood pressure and heart rate were monitored at each visit.

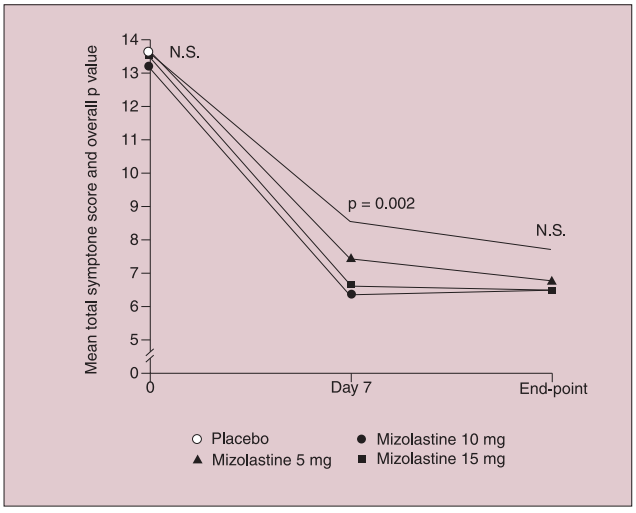

Figure 1. *Seasonal allergic rhinitis improvement assessed using the physician total score in patients who received 5, 10, and 15 mg mizolastine in comparison to placebo.*

Statistical Analysis

The statistical analyses have been conducted on an "intent-to-treat" basis. The primary efficacy criteria of treatment activity were the scores computed from the symptoms evaluated by the investigator: total score, nasal, and ocular scores. Comparisons between treatment groups at day 7 were tested by Hommel's method and the endpoint analysis performed using an analysis of variance.

Other criteria were secondary. Data from the patients' diaries were analyzed using an analysis of variance. Visual analogue scales were analyzed using the same methods as those described for the primary criteria, and percentage of responders (at least a 50% score improvement) were analyzed with the X^2 test. For the clinical global impression, a Kruskal-Wallis nonparametric analysis was performed. All comparisons were two-sided, with a significance level of 5%. Data are presented as mean ±SEM.

RESULTS

Patients' Characteristics

A total of 494 patients were recruited between mid-March and August 1990 at 35 sites, late summer inclusions having been made in the northern countries (investigators of the Rhinase study are listed under Acknowledgments). Patients, mean age 30.6 years old, presented seasonal allergic rhinitis of a mean duration of 118 months; 21% of them suffered from other concomitant allergic diseases (asthma, eczema, urticaria). At baseline, no differences were noted across treatment groups for demographic and clinical characteristics (Table 1). Symptoms were of comparable severity in all groups, the mean total score assessed by the physicians was 13.5 ±0.2, the mean total symptom score on the diary cards was 7.2 ±0.2, and the mean discomfort rated by the patients on the visual analogue scale was 60.5 ± 0.9.

A total of 77 patients discontinued treatment prior to scheduled study completion with an occurrence that was comparable across treatment groups, even though dropouts for adverse experiences were more frequent in the placebo group. Forty-five patients withdrew because of lack of efficacy (14 in the placebo group, 10 in the 5-mg, 15 in the 10-mg, and 6 in the 15-mg mizolastine group). Fourteen patients withdrew because of adverse events (seven in the placebo group, three in the 5-mg, one in the 10-mg and three in the 15-mg mizolastine group). A total of ten patients were lost to follow-up, three others did not wish to cooperate, and five left the study for unknown reasons. The majority of the patients who did not complete the study underwent one visit under test drug leading to "intent to treat" sample sizes of 464 patients on day 7 and of 484 on end-point for efficacy analysis; data from 491 patients were included in safety evaluations.

Efficacy Results

As shown in Figure 1 and Table 2, the mean physicians' rating of total symptom score was significantly lower with mizolastine, 10 and 15 mg

(53% and 51% improvement, respectively), at day 7 than with placebo (38% improvement) (P =.002); the decrease with the 5-mg dose level was intermediate (46% improvement), but not statistically different from the placebo. During the second week of treatment, no improvement was gained with the two highest mizolastine dose levels, whereas addidional 5% and 6% improvements were noticed in the 5-mg mizolastine and placebo groups, bringing results to be comparable in all groups at end-point.

Table 2. Mean Nasal, Ocular and Total Scores Assessed by the Physician

	Placebo	Mizolastine			P value*
		5 mg	10 mg	15 mg	
Nasal score					
Baseline	8.1±0.2	7.8±0.2	7.8±0.2	7.8±0.2	NS†
Day 7	5.3±0.3	4.6±0.2	4.1±0.2	4.2±0.2	.004
End-point	4.8±0.3	4.4±0.3	4.1±0.3	4.2±0.3	NS
Ocular score					
Baseline	4.1±0.2	4.2±0.2	3.9±0.2	4.1±0.2	NS
Day 7	2.5±0.2	1.9±0.2	1.7±0.2	1.7±0.2	.007
End-point	2.1±0.2	1.7±0.2	1.6±0.2	1.5±0.2	NS
Total score					
Baseline	13.6±0.4	13.7±0.4	13.2±0.4	13.5±0.4	NS
Day 7	8.5±0.5	7.4±0.5	6.3±0.4	6.6±0.4	.002
End-point	7.6±0.5	6.7±0.5	6.4±0.5	6.4±0.4	NS

* Intergroup comparison
† NS, not significant (P > .05)

Table 3. Mean Daily Global Symptom Score Assessed by the Patient, Change from Baseline

	Placebo	Mizolastine			P value*
		5 mg	10 mg	15 mg	
Baseline	7.3±0.3	7.5±0.3	7.0±0.3	6.7±0.3	NS†
Change from Baseline					
Day 1	-0.8±0.2	-1.2±0.3	-1.4±0.3	-0.9±0.3	NS
Day 2	-0.9±0.3	-2.2±0.3	-1.9±0.3	-1.3±0.3	.01
Day 3	-1.4±0.3	-2.5±0.3	-2.0±0.3	-1.4±0.3	.052
Day 7	-1.8±0.4	-2.2±0.4	-2.3±0.4	-1.9±0.4	NS

* Intergroup comparison
† NS, not significant (P > .05).

The decrease of the mean nasal and ocular scores assessed by the physicians (Table 2) were consistent with that of the total score, showing constantly better results with mizolastine than with placebo, results that reached statistical significance for 10- and 15-mg dose levels versus placebo at day 7 (P = .004 for the nasal score, P =.007 for the ocular score). The patients' ratings agreed with those of the physicians. Diaries showed an early improvement in symptoms, statistically significant as early as day 2 in the 10- and 15-mg groups (P =.01) (Table 3), remaining greater with mizolastine throughout the first week of treatment. Patients showing an improvement of at least 50% on the visual analogue scale score were considered responders. At day 7, significantly more patients responded to treatment with mizolastine, 10 and 15 mg, than with placebo (P = .014), results being intermediate with the 5-mg dose level but not statistically different from placebo (Fig 2). No or little improvement was gained with the two highest mizolastine dose levels during the second week of treatment, again leading to comparable results in all groups at end-point.

The clinical global impression ratio at end-point was constantly higher in the mizolastine groups, respectively 2.53, 2.60, and 2.51 for 5, 10, and 15 mg, than in the placebo group, 2.36. On the whole, efficacy was observed from the 5-mg mizolastine dose upwards, was maximum with both 10- and 15-mg dose levels, and was prompt to appear, as early as the second day of treatment.

Safety Results

The number of patients reporting adverse experiences was comparable across treatment groups (Table 4). Even though more events occurred in the 15-mg mizolastine group than in the other groups, withdrawals related to side effects were more frequent with placebo. The most common adverse events were drowsiness and fatigue, which occurred more often with mizolastine, and headache, more frequent with placebo. Fatigue was reported more frequently in the 15-mg mizolastine group (8.9%) than in the other groups. This complaint was usually observed during the first two days of treatment and was generally transient. Three patients withdrew because of fatigue (one receiving placebo; one, 5 mg; and one, 10 mg mizolastine). Headache was more often notified in the placebo group (7.3%) than in all mizolastine groups (2.7%). Increased appetite, reported in 2.3% to 3.2% of all groups of patients, did not induce weight gain. No changes were seen in blood pressure and heart rate. Laboratory tests revealed no clinically relevant abnormalities and no serious or unexpected adverse event was reported.

DISCUSSION

The results of this study confirm in a substantial number of patients the activity of mizolastine as an effective antihistamine in the treatment of seasonal allergic rhinitis, activity which had been

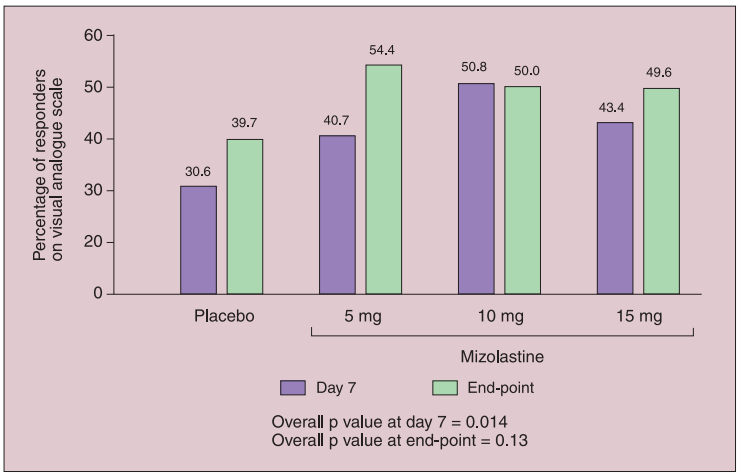

Figure 2. Percentage of responders (patients with at least a 50% improvement on the visual analogue scale) at day 7 and end-point among patients who received 5, 10, and 15 mg mizolastine in comparison to placebo.

foreseen in a preliminary clinical trial.11 From the dose of 5 mg upwards, mizolastine is more effective than placebo in alleviating nasal and non-nasal symptoms, maximum efficacy being obtained with the 10-mg dose level, and there being no tendency to greater efficacy with 15 mg.

Table 4. Most Common Adverse Events

	Placebo	Mizolastine		
		5 mg	10 mg	15 mg
Patients with at least one adverse events, n (%)	21(17.2)	25(21.4)	29(22.5)	35(28.5)
Withdrawals due to adverse events, n (%)	7(5.7)	3(2.6)	1(0.7)	3(2.4)
Predominant adverse events*, n(%)				
Drowsiness	1 (0.8)	4 (3.4)	9 (6.9)	9 (7.3)
Headache	9 (7.3)	5 (4.3)	1 (0.7)	4 (3.2)
Fatigue	2 (1.6)	3 (2.6)	3 (2.3)	11 (8.9)
Increased appetite	3 (2.4)	3 (2.6)	3 (2.3)	4 (3.2)
Abdominal pain	1 (0.8)	3 (2.6)	2 (1.5)	3 (2.4)
Dry mouth	–	1 (0.8)	3 (2.3)	2 (1.6)
Vertigo	2 (1.6)	–	2 (1.5)	1 (0.8)

* Number of adverse events reported more than three times by the whole study population

After 1 week of treatment, 10 and 15 mg mizolastine produced a significant reduction in total, nasal and ocular scores assessed by physicians; a significant number of patients responded favorably to treatment. The 53% and 51% improvements in total symptom scores obtained with the two highest mizolastine doses at day 7 are of the same order of magnitude as those reported with other second generation antihistamines studied for one week (Table 5). Peak relief with mizolastine, shown on daily diaries, was observed on the second day of treatment, and as early as the first day for certain symptoms. The 38% improvement obtained after 1 week of placebo treatment is consistent with values in other trials of the same duration: 23% to 40%.[12,17,19]

Table 5. Improvement in Seasonal Allergic Rhinitis Symptom Scores with Various H1 Antihistamines

Test drug (Dose)	Authors (references)	Patients (n)	Improvement in score(%)
Loratadine (10 mg)	Dockhorn[12]	330	49%
	Herman[13]	108	53%
	Bertrand[14]	75	53%
Cetirizine (10 mg)	Herman[13]	108	55%
	Lockey[15]	160	47%
	Backhouse[16]	285	50%
	Falliers[19]	419	61%
	Caiaffa[18]	136	52%
Terfenadine (120 mg)	Herman[14]	75	52%
	Lockey[15]	160	33%
	Backhouse[16]	285	50%
	Caiaffa[18]	136	58%
Clemastine (2 mg)	Dockhorn[12]	330	46%
Mizolastine (10 mg)	Present study	494	53%

The second week of this study did not demonstrate additional benefits in terms of efficacy as expected due to the short duration of seasonal allergic rhinitis episodes. This additional week, however, allowed an accurate evaluation of safety, mandatory for the first large scale clinical trial, and yielded positive information in terms of maintenance of efficacy and lack of tolerance over a 2-week period. Overall, no difference was observed between the frequencies of adverse events in the placebo, 5-, and 10-mg mizolastine groups (17.2%, 21.4%, and 22.5% respectively), whereas the percentage was slightly greater in the 15-mg mizolastine group (28.5%). Analysis of the incidence of emerging events, ie, excluding intercurrent diseases, events related to the indication and abnormal laboratory test results, confirms these conclusions. However, the number of dropouts related to adverse events was higher in the placebo group (5.7%) than in the 5-, 10- and 15-mg mizolastine groups (2.6%, 0.7%, and 2.4% respectively).

The most frequently reported adverse events were drowsiness, fatigue, and headache. The overall frequency in mizolastine-treated patients was 5.9% for drowsiness, 4.6% for fatigue, and 2.7% for headache. Reports for drowsiness were slightly more frequent from patients receiving mizolastine than from those on placebo (0.8%). In the 10- and 15-mg groups, only 7% reported drowsiness; that incidence is similar to that encountered with other nonsedating antihistamines, 5% to 23%.[12,13,15,17,19,20] The incidence of fatigue was the highest in the 15-mg mizolastine group (8.9%). Reports of all other adverse events were infrequent and of similar incidence in all four groups. No evidence of a tendency to weight gain was noticed and no significant or clinically meaningful changes in blood pressure and heart rate were reported. This study confirms mizolastine's efficacy as a potent antihistamine in the treatment of seasonal allergic rhinitis; 10 mg, given once daily, is the dosage with the best benefit/risk ratio, improving total symptom score by over 50% and presenting an acceptably low incidence of adverse events with no substantial sedative effects. Mizolastine should become a safe and effective alternative in the management of seasonal allergic rhinitis.

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Efficacy and safety of mizolastine 10 mg in a placebo-controlled comparison with loratadine in chronic idiopathic urticaria: results of the MILOR study

Abstract

Background Mizolastine is a novel histamine H_1-antagonist registered in Europe for the management of allergic rhinitis and urticaria.

Objectives To compare the clinical efficacy and safety of mizolastine with loratadine and placebo in patients with chronic idiopathic urticaria (CIU).

Methods A multicentre, double-blind, parallel group study was designed in which 247 patients with CIU were randomized after a 1-week placebo run-in period to 10 mg daily mizolastine (n = 88), 10 mg daily loratadine (n = 79), or placebo (n = 80) for a 4-week treatment period.

Results Mizolastine and loratadine both relieved symptoms of CIU. After 2 weeks' treatment, the severity of pruritus (visual analogue score (VAS) assessed by patients) decreased significantly in both the mizolastine and loratadine groups compared with placebo (mizolastine: -36.7 mm, P = 0.0001; loratadine: -29.8, P = 0.0071; placebo: -16.3); this improvement with both active treatments was maintained throughout the treatment period, the difference being significant only for the mizolastine group (P = 0.0090). Both active treatments were also associated with reduced weekly episodes of urticaria compared with placebo. which was significant after 2 weeks' treatment (mizolastine: 7.9 episodes, P = 0.0061; loratadine: 8.3, P = 0.0221; placebo: 13.3). Angioedema was improved to a clinically significant extent with mizolastine, and loratadine compared with placebo in those patients who had this symptom before treatment. Overall tolerability of both treatments was similar to placebo, and there were no clinically relevant effects on cardiac repolarisation with either mizolastine or loratadine.

Conclusion Mizolastine (10 mg daily) is confirmed as an effective and well tolerated agent, comparable to loratadine and superior to placebo, for the management of CIU. Mizolastine acted as rapidly as loratadine in improving urticarial symptoms from the first day of treatment.

1. Introduction

Chronic urticaria is idiopathic (CIU) in 70% of cases [1]. CIU is characterised by the appearance of episodic or persistent wheals with or without associated angioedema [2–4]. It may recur at frequent intervals over several months or years, with severe itching as a particularly troublesome symptom. The treatment of CIU represents a challenge to the physician because of the incidence of troublesome sideeffects and the recurrence of urticaria when therapy is stopped [4]. Although antihistamines are the treatment of choice for CIU, individual response to these agents is variable, can be incomplete and may be compromised by sedative and anti-cholinergic effects [5–7]. More recently, minimally sedating and long-acting antihistamines have become available, and some are just as effective as older agents [8–10].

Mizolastine, a benzimidazole derivative, is a novel, selective and peripherally acting antihistamine with high affinity for H_1-receptors [11]. The drug lacks affinity for histamine H_2 and H_3, muscarinic and serotoniergic receptors and has been shown to be more potent in terms of anti-allergic activity as astemizole, loratadine and terfenadine [12–14]. Mizolastine inhibits histamine release from rat mast cells at doses similar to those required with cromoglycate [14]. Suppression of the wheal and flare response is dosedependent, and is significant from dosages of 2 mg [15]. Onset of action is rapid (1 h) and persists for up to 24 h after a 10 mg dose [15]; mean plasma half-life is approximately 13 h [16]. Recent results of wheal and flare testing confirm that once-daily oral administration is effective[17]. A 10 mg dose of mizolastine H1-antagonistic activity similar to that of 120 mg terfenadine or 10 mg cetirizine, but appears more potent than 10 mg loratadine from 3 to 8 h after administration [18]. There have been no observations of impairment of psychomotor performance or cognitive function [19,20], nor are there reports of sedative effects or adverse on memory in the elderly [16]. In addition, mizolastine does not potentiate the adverse psychomotor effects of lorazepam [21] or ethanol [22]. Mizolastine has also been shown to have other anti-allergic effects at therapeutic doses in allergic patients, as demonstrated by its ability to inhibit the early (intracellular adhesion molecule-1) and late phases (protein exudation) of allergic inflammatory events [23].

The clinical efficacy of mizolastine, 10 mg once daily for up to 4 weeks, in CIU has already been demonstrated in placebo-controlled clinical trials [24–26]. Results are also available from a 4-week study of 61 patients with CIU that show equivalent efficacy of 10 mg daily mizolastine to 10 mg daily loratadine [27]. Loratadine is a non-sedating, secondgeneration selective antihistamine with a long duration of action compared with older agents, that has been shown to confer symptomatic relief in CIU [28–32]. Thus, this drug was chosen as the comparison agent for the large-scale multicentre, placebocontrolled trial of the efficacy and safety of mizolastine in CIU described in this paper.

2. Materials and methods

This 42-centre randomised, double-blind, parallelgroup study was carried out in France, Italy and Spain between July 1993 and September 1995. The study was conducted in accordance with the Declaration of Helsinki and with French law no. 90-86. Approval was obtained from the local ethics committee at each centre before inclusion of patients, and written informed consent was obtained from each subject before participation.

All subjects were at least 18 years old and had a documented history of CIU (with or without angioedema) of at least 6 weeks' duration and with a frequency of at least two episodes per week in the absence of treatment. Each episode of urticaria was defined as itching papular eruptions of varying size of no more than few hours' duration. During the 7-day run-in period at least two of the symptoms or signs of urticaria (pruritus, size and number of urticarial patches and/or wheals) were required to have a score of ≥2 on the three scales described below.

Severity of itching was assessed on a 4-point scale, where 0 = absent, 1 = present but mild with no discomfort, 2= moderate with slight disturbance of daily activities and/or sleep, 3= intense unbearable itching with marked disturbance of daily activities and/or sleep.

Maximum size of the largest wheals was scored as follows: 1 = ≤1.5 cm, 2 = .1.5 cm and ≤2.5 cm, 3 = .2.5 cm.

Number of wheals and/or patches were also scored on a scale of 4:0 = absent, 1 = ≤10 wheals and/or patches, 2 = .10 wheals and/or patches spread over the entire body, 3 = extensive wheals and/or patches all over the body.

Thus, patients were included with a score of at least 4 out of a possible total of 9. Washout periods were required for astemizole (6 weeks), systemic corticosteroids (4 weeks), parenteral sustained-release corticosteroids (3 months) and ketotifen (4 weeks). Aerosol formulations of corticosteroids, topical urticaria treatments, oral sodium cromoglycate, aspirin and non-steroidal anti-inflammatory drugs, and sedatives had to be stopped before the screening visit.

The following patient categories were excluded: pregnant or lactating women and those not using effective contraception, subjects operating dangerous machinery or for whom driving was an integral part of their occupation, persons with hereditary angioedema or isolated dermographism and/or with evidence of major systemic disease.

At the first visit (day −7) a complete medical history was taken for each patient. A clinical examination (including ECG) with a standard laboratory test was also carried out at inclusion and repeated after 2 and 4 weeks of treatment.

2.1. Drug administration

After a 7-day placebo run-in phase (day −7 to day 0) for baseline (d_0) evaluation of symptoms, patients were randomised to a 4-week double-blind treatment phase during which they took 10 mg mizolastine, 10 mg loratadine or placebo in a single dose each evening.

2.2. Efficacy criteria

The primary criterion assessed by patients was pruritus severity on a 100 mm visual analogue scale (VAS) (0 = no discomfort to 100 = extreme discomfort) for the 7 days preceding each visit. Secondary criteria recorded from daily diary cards were: (1) the weekly number of episodes of urticaria, (2) the total urticarial score (= severity of itching + size of lesions + number of urticarial lesions) and (3) the intensity of angioedema (worst episode). Angioedema was scored from 0 to 3 (0 = absent, 1 = mild, 2 = moderate with sensation of tension, 3 = severe, disfiguring).

2.3. Safety criteria

Blood pressure and heart rate were measured and 12-lead surface ECGs were performed on days −7 and 28. The RR, PR and QRS intervals were measured with an ECG ruler and compass by a single cardiologist. From these measurements the following were calculated: JT = QT − QRS; JTc = QTc − QRS, and heart rate (beats/min) = 60 000/RR. The corrected QT interval, QTc, was calculated using the Bazett and Fridericia formulae [33]. Wherever possible, each parameter was expressed as the mean of measurements from three complexes. Each parameter was taken from the same ECG lead in all cases (usually V2 − V3, with PR being measured in D2).

Adverse events were defined as clinical signs or symptoms that appeared or worsened during treatment. Abnormalities in laboratory parameters and vital signs that lead to withdrawal of treatment were also recorded.

2.4. Analysis of results

Analyses were performed using SAS software on an intention-to-treat basis. Quantitative variables were presented as means and standard deviations and categorical or dichotomous variables as absolute or relative frequency by class. Where global treatment effects were significant, two-by-two comparisons were performed at a significance level of 5%.

Pruritus VAS scores, as well as the number of episodes of urticaria per week and the mean total urticarial score were analysed using analysis of variance (ANOVA). Evolution of angioedema was analysed using the x^2-test. In addition, an analysis was also performed whereby changes in mean total scores were plotted graphically from days 0 to 7 to ascertain whether improvements were reported earlier with active treatment than with placebo.

2.4.1. ECG: statistical analysis

Descriptive statistics and comparisons between treatment groups (ANOVA) were performed at d_0 and at the last observed value in the study (d_{end}), and on the difference between these two values. The parameters measured were: RR, PR, QRS, QT, QTcF (using Fridericia's formula) and QTcB (using Bazett's formula).

3. Results

A total of 247 patients were enrolled, of whom 88 were randomised to mizolastine, 79 to loratadine and 80 to placebo. Of these patients, 243 (98%) were Caucasian. The main patient characteristics are shown in Table 1. There were no significant differences between the groups for age, weight, height or sex distribution. Histories of urticaria ranged from 6 weeks to 21 years, with a mean duration of 119.0 ± 162.1 weeks. The mean number of urticarial episodes per week at d_0 was 16.2 ± 18.4, mean pruritus severity (VAS score) was 64.4 ± 21.9 mm and the mean episode duration was 9.4 ± 10.1 h. Urticaria was most

Table 1. Baseline demographic and disease characteristics (mean±SD)

	Placebo *n*=80	Mizolastinene *n*=88	Loratadine *n*=79	All *n*=247
Age,years(range)	42±15 (18-76)	43±15 (19-74)	41±13 (19-73)	42±15 (18-76)
Male (%)	37.5	36.4	36.7	36.8
Female (%)	62.5	63.6	63.3	63.2
Patients with concomitant allergic disease(%)	13.7	19.3	17.7	17.0
Baseline disease severity				
Pruritus (VAS score) mm	65.1±20.6	65.2±22.89	62.9±21.9	64.4±21.9
Urticaria episodes per week	17.7±21.1	15.9±17	14.9±16.7	16.2±18.4
Patients with angioedema (%)	52.5	51.3	55.7	51.4

frequently localised on the trunk and limbs. Half the patients had angioedema. Overall, there were no significant differences between groups in disease characteristics at baseline. A total of 205 patients (83.0%) completed the study. Of the 42 patients (17%) who withdrew prematurely, 13 were in the mizolastine group, 10 in the loratadine group and 19 in the placebo group. Reasons for treatment discontinuation are given in Table 2.

Table 2. Reasons for discontinuation of treatment (number and percentage of patients)

	placebo	Mizolastine	Loratadine	All
Lost to follow-up	2(3)	2(2)	0	4(2)
Lack of efficacy[a]	11(14)	3(3)	5(6)	19(8)
Adverse events	0	4(5)	3(4)	7(3)
Non-compliance	4(5)	2(2)	0	6(2)
other	2(3)	2(2)	2(3)	6(2)

[a]The number of patients who withdrew from treatment because of lack of efficacy was significantly (P = 0.015) less in the mizolastine group than in the placebo group

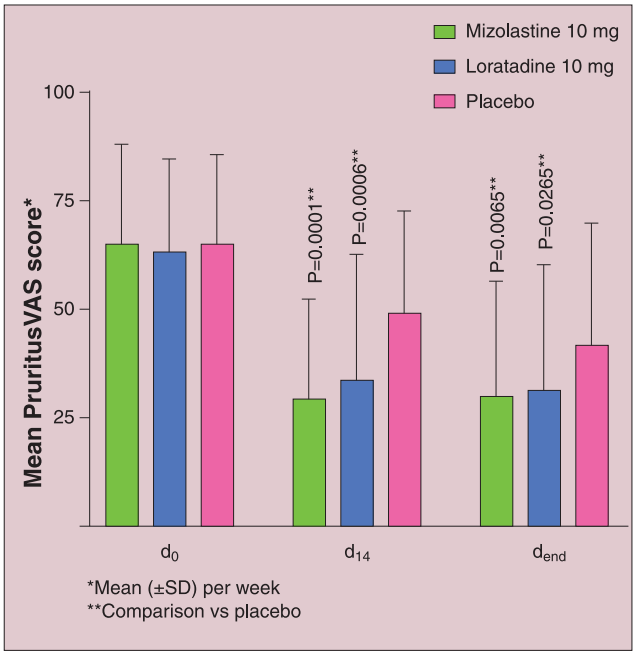

Fig. 1. Improvement in pruritus severity with mizolastine, loratadine and placebo treatment.

3.1. Efficacy assessments

Both mizolastine and loratadine were associated with relief of CIU symptoms. Pruritus (VAS score) was significantly less severe in both mizolastineand loratadine-treated patients after 2 weeks treatment (P = 0.0001 and 0.0006, respectively) and at d_{end} (P = 0.0065 and 0.0265, respectively) (Fig. 1). Similarly, after 2 week's treatment both active treatments significantly reduced the number of weekly urticarial episodes compared with placebo (P = 0.0061 and 0.0221, respectively) (Fig. 2). The loss of significance at the end of the study was due to a reduction in the number of urticarial episodes in the placebo group, rather than any decrease in the efficacy of mizolastine or loratadine. Indeed, both mizolastine and loratadine maintained greater clinically relevant improvement throughout the study compared with placebo (Fig. 2).

Mizolastine and loratadine also significantly reduced total urticarial score (sum of severity of itching, size and number of lesions) after 2 (P = 0.0022 and 0.0038, respectively) and 4 weeks' SD)(P = 0.0096and 0.0064, respectively) treatment compared with placebo (Fig. 3). In addition, there was a sharp decrease in total urticarial score after the first day with both active treatments, indicating that both mizolastine and loratadine had a rapid onset of action and gave prompt relief from symptoms (Fig. 4). Angioedema was improved to a clinically significant extent in the mizolastine and loratadine groups compared with placebo in the 127 patients who had this symptom before treatment. Percentages of patients with improvements in angioedema at d_{end} were: 77.5% with mizolastine, 77.3% with loratadine, and 63.4% with placebo (not significant).

Fewer patients withdrew from the study because of lack of efficacy in the mizolastine group than in the placebo group (3 vs. 11, P = 0.015) (Table 2). There was no significant difference between loratadine (5) and placebo (3) with respect to patient withdrawal because of lack of efficacy. Overall, there was no difference between the two antihistamines in terms of urticaria relief.

3.2. Safety assessments

Overall, the numbers of patients who experienced at least one adverse event were comparable in the three treatment groups (39% of mizolastine patients, 34% of loratadine patients and 26% of placebo patients). Of the 247 patients randomised, 245 received treatment and were eligible for the safety assessment. Incidences of the most prominent adverse events (≥5% incidence) are shown in Table 3. In the mizolastine group, 11 of the 12 cases of drowsiness and asthenia/fatigue were rated as mild, while in seven of these cases it was also transient. The one case rated as moderate was associated with overwork by the patient.

Two serious adverse events were reported; one was a diagnosis of pre-existing MacDuffie's syndrome, made during the study in a mizolastine patient who developed vasculitis; the other was a case of appendicitis in a loratadine patient. Both resulted in hospitalization and treatment withdrawal. Patient heart rates and mean supine systolic and diastolic blood pressures were stable throughout the study. No serious laboratory abnormalities were associated with either mizolastine or loratadine treatment.

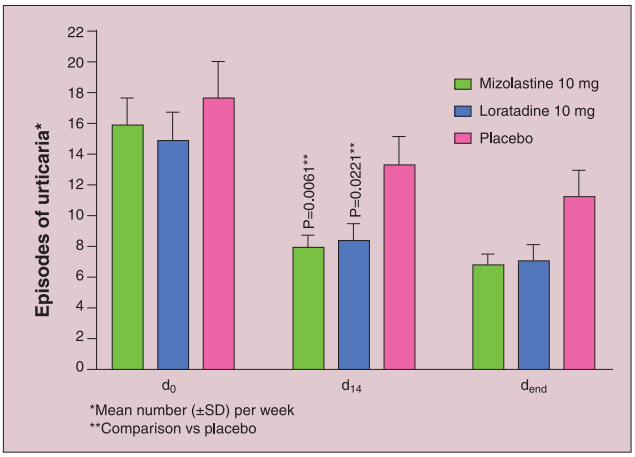

Fig. 2. *Improvement in urticarial episodes with mizolastine, loratadine and placebo treatment.*

Of the 184 patients who had complete ECG records, 66 were treated with mizolastine, 61 with loratadine and 57 with placebo. All the patients were in sinus rhythm. Mean QT duration, using Fridericia's formula, at d_0 and d_{end} and the change between these two time points are listed in Table 4. No clinically or statistically significant differences

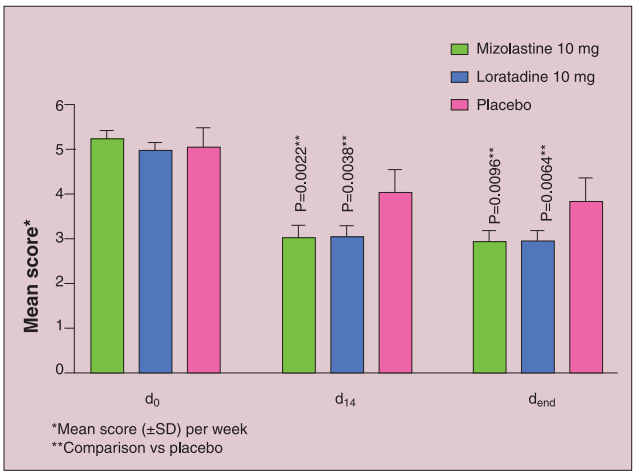

***Fig. 3**. Improvement in total urticarial score with mizolastine, loratadine and placebo treatment.*

were observed between the treatment groups at any time during the study When QT_cF >450 ms was considered there was one mizolastine patient with a lower value at dend compared with d_0. Two loratadine patients had QT_cB> 450 ms at the end of treatment. Among placebo patients, one had a 44 ms increase in QT_cF and another a 57 ms increase in QT_cB.

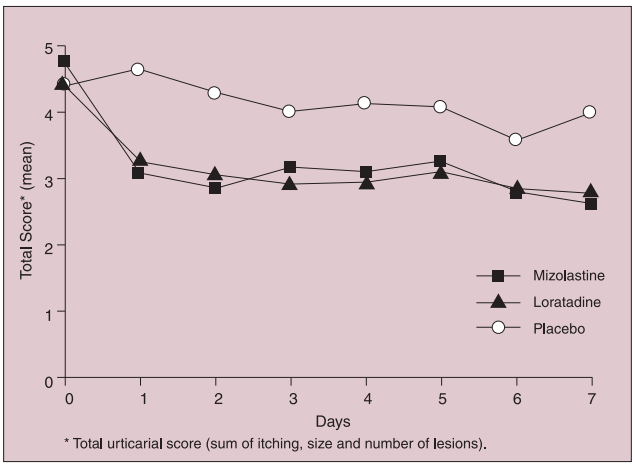

Fig. 4. Onset of therapeutic action, changes in total urticarial score during the first 7 days treatment with mizolastine, loratadine and placebo.

4. Discussion

Whereas the older, first-generation antihistamines, such as chlorpheniramine and hydroxyzine, are effective in the symptomatic relief of chronic urticaria in many patients, newer agents with comparable efficacy, superior tolerability (particularly with respect to sedation and anti-cholinergic effects) and the convenience of once daily administration have now become widely available. This study showed that the novel antihistamine mizolastine was at least as effective as loratadine and superior to placebo in the management of patients with CIU.

Mizolastine treatment was associated with a rapid onset of action (day 1), which resulted in a significant reduction in pruritus severity (VAS score) throughout the study. The effectiveness of mizolastine was also reflected by the reduction in the number of weekly urticarial episodes. Again, mizolastine was as effective as loratadine in this respect.

The statistically significant reductions in total urticarial scores (patient diary cards) with mizolastine and loratadine were also maintained throughout the study. Both mizolastine and loratadine produced more clinically relevant improvement in angioedema than placebo in those patients who had reported this symptom before treatment.

The prominent placebo response observed in this study is not altogether surprising, as similar effects have been documented in other placebo-controlled trials in urticaria. The placebo response most often reported is between 10 and 25% [34–36], but this figure

Table 3. The most common adverse events by treatment group

	Placebo *n*=57	Mizolastinene *n*=87	Loratadine *n*=79
Patients with at least one adverse event, n (%)	21 (27)	34 (39)	27 (34)
Withdrawals due to adverse events, n (%)	0	4 (5)	3 (4)
Adverse events[a], n (%)			
Drowsiness	0	6(7)	1(1)
Headache	5(6)	3(3)	5(6)
Asthenia/fatigue	0	6(7)	1(1)
Influenza-like symptoms	2(3)	5(6)	1(1)
Nausea	1(1)	1(1)	2(3)

[a]Adverse events with an incidence ≥5% in the exposed population.

can be as high as 40% [2]. Interestingly, a placebo response of 27% was reported in an earlier placebo- controlled double-blind study of mizolastine in 56 CIU patients [24]. This phenomenon is probably related to the variability of the disease. Thus, patients may be randomised at a time when their disease is at its worst and show improvement thereafter regardless of therapy.

Both mizolastine and loratadine showed no cardiac repolarisation effects in this study. No clinically relevant effects on heart rate, blood pressure, PR intervals, QRS duration, QT or QT_c intervals were noted. No increases in QT_cF were recorded in any of the mizolastine patients, even in the one who had a prolonged QT_cF at the start of the study. Indeed, QT_cF decreased by −4 ms in this patient over the course of the study (d_0 = 454 ms, d_{end} = 450 ms). One placebo patient experienced a 44 ms increase in QT_cF (vs. baseline) and another a 57 ms increase in QT_cB (vs. baseline), thus demonstrating that variation in the QT_c interval may occur in the general population.

Furthermore, mizolastine and loratadine were comparable to placebo in the overall incidence of adverse events. Statistical significance relative to placebo was attained only in the mizolastine group with a reduction in the number of treatment withdrawals due to lack of efficacy. A slightly higher number of reports of sedative events was noted in the mizolastine group than in the loratadine group. However, 11 of the 12 cases of drowsiness and asthenia/fatigue with mizolastine were rated as mild and the effects were transient in seven of these cases. The remaining case, rated as moderate, was associated with

overwork by the patient. These results are supported by the results from another double-blind comparative study of mizolastine and loratadine in 61 CIU patients, which reported slight drowsiness in two patients, one in each treatment group [27]. Placebo failed to cause sedation in any of the patients although placebo-associated sedation is a usual feature of controlled histamine trials; this finding is in contrast with the prominent placebo response in suppression of urticaria.

Table 4. ECG parameters QT interval using Fridericia's in the study population and description of patients with QT_c abnormalities(outliers)

	Placebo *n*=57	Mizolastinene *n*=66	Loratadine *n*=61
Fridericia QT duration (ms)			
d_0			
Mean±SD	394±20	391±19	392±19
(min;max)	(340;439)	(342;454)	(334;445)
d_{end}			
Mean±SD	392±18	392±20	389±19
(min;max)	(354;426)	(340;450)	(347;431)
d_{end} - d_0			
Mean±SD	-0.4±4.1	0.2±3.5	-0.5±4.4
(min;max)	(-10;12.1)	(-10.6;8.2)	(-13.9;7.2)
Outliers	n=2-	n=1	n=2
QT_cF[a]>450 ms		d_0 d_{end}	
Value (ms)	-	454 450	
Δ QT_cF[a]>40 ms value	44[aa]	-	-
QT_cB_c>450 ms value	-	-	d_0 d_{end} 431 453 440 458
ΔQT_cBc>40 ms value	57[aa]	-	-

[a]Using Fridericia's formula
[aa]Patients whose QTcF or QTcB was not >450 ms
cUsing Bazett's formula.

The results of this study therefore confirm the efficacy and safety of mizolastine at doses of 10 mg daily in patients with CIU. Mizolastine was as effective as loratadine and significantly more effective than placebo in these patients. Mizolastine had a rapid onset of action, with improved symptoms from the first day of treatment, which was maintained throughout the 4- week study. Mizolastine was well tolerated with a clinical safety profile similar to that of placebo and comparable to other second-generation antihistamines. Thus, mizolastine should be considered suitable for first-line therapy of CIU.

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