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Comparison of mizolastine with loratadine in the treatment of perennial allergic rhinitis*

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SUMMARY

Mizolastine is a new, non-sedating antihistamine providing satisfactory symptomatic relief in seasonal allergic rhinitis. The purpose of this study has been to compare mizolastine to loratadine in perennial allergic rhinitis. This multicentre, double-blind study has involved 68 patients, randomly allocated, after a one-week placebo run-in, to 10 mg mizolastine or 10 mg loratadine, both given on a once-daily basis, for four weeks. Comparable symptom relief occurs in both groups resulting, respectively for mizolastine and loratadine, in a 66.6% and a 61.3% decrease in total nasal score, to a 74.8% and a 76.4% decrease in total ocular score, and to a 69.0% and a 64.8% decrease in global total score. Safety is satisfactory in both groups. Mizolastine is at least as effective as loratadine in relieving perennial allergic rhinitis symptoms and its safety profile allows its use in the treatment of this disease.

Key words: mizolastine, loratadine, H_1-receptor antagonists, perennial allergic rhinitis

INTRODUCTION

Mizolastine (SL 85.0324), a benzimidazole derivative, is a new second-generation, selective and peripherally acting antagonist of H_1-receptors, effective in allergic rhinitis and urticaria. Mizolastine lacks affinity for any other known pharmacologically relevant receptor (Arbilla et al., 1990; Danjou et al., 1992) and, in addition, inhibits histamine release from rat mast cells at doses similar to that of cromoglycate (Levrier et al., 1995). Inhibition of the wheal-and-flare response to histamine is dose-dependent, significant from the dose of 2 mg; the onset of action is rapid (1 h) and persists for more than 24 h after a 10-mg dose (Rosenzweig et al., 1992). Neither impairment in psychomotor performances and cognitive functions (Danjou et al., 1990; Schaffler et al., 1990; Vuurman et al., 1993; Kerr et al., 1994) nor sedative effects or detrimental effects on memory in the elderly (Schaffler et al, 1990; Patat et al., 1994) have been observed at the 10-mg recommended therapeutic dose.

Mizolastine is readily absorbed, but the plasma half-life is approximately 14 h. The therapeutic benefit of mizolastine has been confirmed in seasonal allergic rhinitis in a placebo-controlled study involving 256 patients (Stern et al., 1992); the once-a-day 10-mg dose has been shown to provide a 24-h protection with convincing symptomatic relief.

The low occurrence of adverse events accounts for a good safety profile, making mizolastine an excellent candidate for prolonged use in perennial allergic rhinitis. Loratadine was chosen as a reference compound for comparison, as it has been shown to be highly effective and well-tolerated in perennial allergic rhinitis (Clissold et al., 1989; Frolund et al., 1990; Cua-Lim et al., 1991; Carlsen et al., 1993). The purpose of this study was to compare efficacy and safety of mizolastine and loratadine in this allergic condition.

MATERIAL AND METHODS

This multicentre (five Italian centres), double-blind, randomized study was to compare mizolastine (10 mg) and loratadine (10 mg), both given on a once-a-day basis. Treatment lasted four weeks, during which visits were scheduled at days 0, 14, and 28. The comparative phase was preceded by a 7-day placebo run-in period (day -7 to day 0), aimed at assessing the stability of the disease. The protocol was approved by the Ethics Committee of each investigator's Department in accordance with national

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legislation, and informed oral witnessed consent was obtained from each participant before entering the study.

Patients' selection

Patients 18 to 60 years old, and suffering from perennial allergic rhinitis for at least 12 months were considered for the study. Diagnosis was confirmed by a positive skin-prick test to house dust mites; doubtful results had to be confirmed either by a RAST test or by a nasal provocative challenge. The presence of prevailing nasal symptomatology was required with at least three of the six nasal symptoms (i.e., snoring, pruritus, rhinorrhoea, congestion, post-nasal discharge, sneezing) scored at least "2" on the 0-3 severity scale where "0" is none, "1" is mild, "2" is moderate, and "3" is severe (minimum score required: 6), both at the pre-inclusion and inclusion visits. Patients were not eligible in case of any other form of rhinitis or of a structural defect, such as polyps or deviated septa. Oral corticosteroids and ketotifen were to be withdrawn four weeks prior to the pre-inclusion visit, delayed-action ones, six months before; moreover, the following compounds were to be stopped at the beginning of the placebo run-in period: antihistamines (except astemizole, six weeks), sodium cromoglycate, acetylsalicylic acid, non-steroidal anti-inflammatory drugs, anticholinergics, and sedatives.

Evidence of major systemic disease and alcohol or substance abuse were reasons for non-inclusion. 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

After the one-week placebo run-in period, patients were consecutively and randomly assigned to receive either mizolastine (10-mg tablets) or loratadine (10-mg capsules), using the double-placebo technique. Treatments were taken once-daily in the morning. Packages were numbered according to a random distribution table; patients were identified with a number corresponding to their 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

Physicians' evaluations were done on days -7, 0, 14, and 28 using the 0-3 severity scale. In addition to the six nasal symptoms listed above, ocular (lacrimation, pruritus, conjunctival hyperaemia), auricular (pruritus) and pharyngeal (pruritus, throat-clearing acts) variables were assessed. Anterior rhinoscopy was carried out at every visit to rate nasal conchae swelling, nasal secretion and pharyngeal inflammation using the same severity scale. Patients were asked to assess overall discomfort on a 100-mm visual analogue scale ranging from 0 mm (i.e., absence of any symptom) to 100 mm (i.e., intolerable symptomatology). Also, the Clinical Global Impression was rated at the end of study by the investigator.

Assessment of safety

Adverse events, spontaneously reported by the patients and/or observed by the investigators were documented, regardless of relationship to therapy and in accordance with standard procedures. Blood pressure and health rate were monitored at each visit, as well as body weight. Standard laboratory tests were carried out upon pre-selection and final visit.

Statistical analysis

The statistical analyses have been carried out on an "intention-to-treat" basis. Homogeneity of the two treatment groups was checked by means of an unpaired t-test and chi-square for quantitative and qualitative variables, respectively. For each sign and symptom, the proportions of "improved" or "not changed or worsened" patients were compared by means of the chi-square test. Differences between baseline and the last visit for the total nasal score, the total ocular score and the global total score (nasal plus ocular) were compared using Wilcoxon's test. Frequencies of responders to these combined scores, i.e. presenting an at least 25% reduction from baseline values at day 14, were calculated. All statistical tests were two-sided at a significance level of 5%. Data are shown as mean±S.D.

RESULTS

Patients' characteristics

A total of 68 patients were recruited between October 1991 and April 1992, of whom 30 were randomized to mizolastine and 38 to loratadine. Patients (mean age: 35.7 years) presented perennial allergic rhinitis of a mean duration of 97 months, the current episode lasting for 2.7 days; nasal and ocular symptomatology was significantly more severe in the mizolastine-treated group upon enrollment (Table 1). Three patients were lost to follow-up after day 0 (one in the mizolastine group, two in the loratadine group), leading to a sample size of 65 for efficacy and safety analyses.

Table 1. Patients' characteristics.

	mizolastine n=30	loratadine n=38	total n=68	p value
males/females	12/18	20/18	32/36	NS
age (years)*	35.2±15.6	36.1±15.2	35.7±15.2	NS
duration of disease (months)*	100.4±83.1	94.7±84.1	97.2±83.0	NS
duration of present eipisode (days)*	3.8±8.0	1.8±5.0	2.7±6.5	NS
concomitant allergic disease (% of patients)	13.3	10.5	11.8	NS
known disease-awaking factors (% of patients)	50.0	44.7	47.1	NS
total nasal score*	9.7±1.8	8.6±2.1	9.1±2.0	0.026
total ocular score*	4.0±2.4	2.7±2.2	3.3±2.3	0.026
global total score*	13.6±3.9	11.3±3.6	12.3±3.9	0.013

*: mean value±SD.

Results

Both mizolastine and loratadine showed their ability in improving perennial allergic rhinitis symptomatology (Table 2). The total nasal score (i.e., the sum of nasal pruritus, rhinorrhoea,

Table 2. Changes from baseline in total symptom scores.

	mizolastine n=29	loratadine n=36	p value
total nasal score			
baseline*	9.7±1.8	8.6±2.2	0.026
end-point*	3.2±1.5	3.3±2.0	
percent decrease	66.6%	61.3%	0.09
total ocular score			
baseline*	4.0±2.5	2.6±2.1	0.026
end-point*	1.0±1.8	0.6±0.9	
percent decrease	74.8%	76.4%	0.07
global total score			
baseline*	13.7±3.9	11.1±3.7	0.013
end-point*	4.2±2.7	3.9±2.5	
percent decrease	69.0%	64.8%	0.04

*: mean value±S.D.

congestion, and sneezing) showed a 66.6% and a 61.3% decrease with mizolastine and loratadine (p=0.09), respectively; the total ocular score a 74.8% and a 76.4% decrease (p=0.07, respectively). A statistically significant difference in favour of mizolastine was observed for the global total score (nasal plus ocular) with a 69.0% decrease as compared to a 64.8% decrease with loratadine (p=0.04). Changes in ear and pharyngeal symptoms scores yielded comparable "improved" patients rates in both groups. Changes in individual symptoms were consistent with those of total symptom scores; for the nasal symptoms, percentages of improved patients were above 80% for pruritus, rhinorrhoea, congestion and sneezing, 63% for post-nasal discharge, and 47% for snoring. Results were comparable for loratadine-treated patients, with no statistically significant differences between both groups (Figure 1). For ocular symptomatology, percentages of improved patients were 70% or above for all three symptoms, yielding a trend in favour of mizolastine for pruritus (p=0.04) and lacrimation (p=0.06; Figure 2). Percentages of responders for each of the above total scores showed satisfactory and comparable results in both treatment groups, ranging from 82.8% to 86.2% of responders in the mizolastine group and from 77.8% to 84.6% in the loratadine group. The three objective signs assessed by anterior rhinoscopy led in both groups to

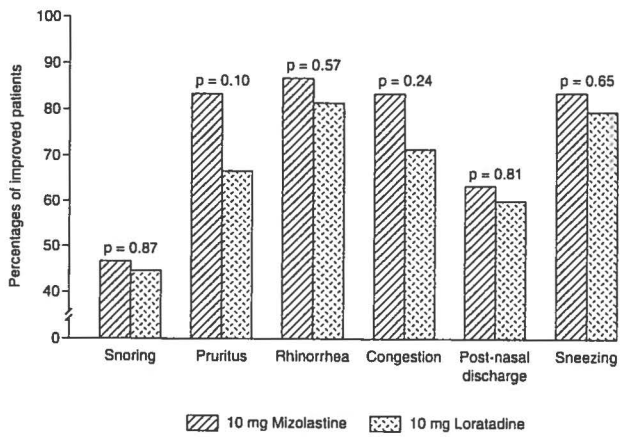

Figure 1. Percentages of improved patients for each individual nasal symptom.

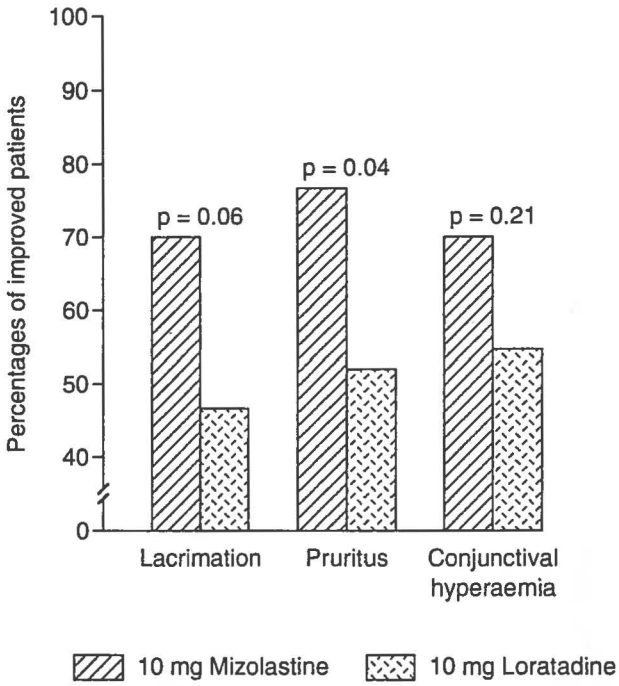

Figure 2. Percentages of improved patients for each individual ocular symptom.

a 57% improvement of total scores. Patients' own assessments on the visual analogue scales were consistent with investigators' findings, leading to a 42.0% decrease in the scale result in the mizolastine group and to a 56.4% decrease in the loratadine group (p=0.54). At Clinical Global Impression, the percentages of patients with at least "moderate therapeutic efficacy" assessment were also similar (86.2% in the mizolastine group, and 82.9% in the loratadine group). Safety results revealed no clinically relevant changes in blood pressure or heart rate, nor in laboratory data; no change was noticed in body weight. Three patients reported an adverse event: one mizolastine-treated patient described symptoms likely to be due to influenza, the second one suffered from two spontaneously resolving nausea episodes. One patient in the loratadine group complained of mild drowsiness lasting two days.

DISCUSSION

The ability of mizolastine in relieving perennial allergic rhinitis symptoms was at least as satisfactory, after four weeks of treatment, as with the widely used reference drug, loratadine. In particular, nasal symptomatology, which is generally more pronounced in perennial than in seasonal allergic rhinitis, showed a satisfactory improvement; the percent decrease in total nasal score was 66.6% with mizolastine and 61.3% with loratadine. These results can be interestingly compared with those reported by Bruttman et al. (1989), where the maximum improvement in symptom scores was 61% with loratadine, 63% with terfenadine, and 40% with placebo, in 228 patients treated for four weeks. Antihistamines are often effective with regard to sneezing and secretion, but with no or poor effect on nasal congestion, the reason for which antihistamines are usually combined with other medications, decongestants or steroids (Mygind, 1986). In the current study, 83% of the mizolastine-tre-

ated patients experienced improvement in nasal stuffiness, and 71% with loratadine; rhinoscopy data confirmed this effect with 83% and 71% of the patients having improved with regard to membrane swelling, and 77% and 71% with regard to nasal secretion, respectively with mizolastine and loratadine.

Bruttmann et al. (1989) found that loratadine was particularly effective in relieving nasal discharge, nasal obstruction, and post-nasal drainage, as compared with terfenadine and placebo. In comparing loratadine and clemastine, Frolund et al. (1990) found loratadine to be superior to clemastine in relieving nasal itching and nasal blockade. However, Carlsen et al. (1993) found no such difference with regard to nasal symptomatology, when comparing loratadine and terfenadine. For the global total score decrease, a statistically significant difference was seen in favour of mizolastine, in parallel with an absolute score reduction greater with mizolastine as baseline symptomatology was significantly more severe in this same treatment group. Symptom relief reported here with mizolastine and loratadine is slightly higher than in the few other double-blind trials involving loratadine (Table 3). For the Clinical Global Impression, the percentages of patients with an at least moderate therapeutic efficacy were 86.2% in the mizolastine group and 82.9% in the loratadine one. Some comparisons are available: Bruttmann et al. (1989) treated 228 patients for four weeks and reported a good or excellent response to treatment in 63% of the loratadine-treated patients, in 57% of the terfenadine-treated patients, and in 26% of the patients taking placebo. Similarly, in 215 patients treated during four weeks, approximately 50% of cetirizine-treated patients achieved good or excellent responses to treatment, whereas 25% of the placebo group achieved a similar response (Mansmann et al., 1992). The overall effectiveness was of the same order of magnitude with a one-week terfenadine treatment in 30 patients; 60–66% of the patients showed a marked to total relief (Rosario, 1989). Overall, the decrease in perennial allergic rhinitis symptoms after treatment with mizolastine compares favourably with that of loratadine. The safety of both drugs was very good; in particular, no case of drowsiness was reported with mizolastine. In conclusion, mizolastine is of pronounced efficacy in the treatment of patients with perennial allergic rhinitis. This convenient once-daily dosage regimen and satisfactory safety profile allow for its use in the therapy of this condition.

Table 3. Percent decrease in total symptom score in studies involving loratadine for perennial allergic rhinitis treatment.

author (year)	sample size	loratadine 10 mg daily	mizolastine 10 mg daily	terfenadine 120 mg daily	clemastine 2 mg daily
current study	68	64.8%	69.0%		
Carlsen et al (1993)	76	42.8%		42.1%	
Clissold et al (1980)	228	52%		50.0%	
Frolund et al (1990)	155	53.8%			51.6%

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