

Mizolastine therapy also has an effect on nasal blockade in perennial allergic rhinoconjunctivitis

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Background Mizolastine is a new, non-sedating antihistamine with additional anti-inflammatory properties, providing relief in allergic rhinitis and urticaria. The aim of this study was to determine the efficacy and safety of 10 mg o.d. mizolastine given to patients with perennial allergic rhinoconjunctivitis.

Methods This double-blind, placebo-controlled study involved 257 patients suffering from the disease for more than 10 years. They were allocated, after a 1-week placebo run-in, to receive mizolastine ($n=133$) or placebo ($n=124$) for 4 weeks.

Results Mizolastine-treated patients showed significantly greater alleviation of nasal symptoms, with a mean decrease of 36% compared with pretreatment score, compared to a mean decrease of 10% in placebo patients ($P<0.001$). Nasal blockade responded favorably to mizolastine compared to placebo and was associated with a significant reduction in rhinoscopy findings ($P=0.030$). Likewise, the mean ocular symptom score decreased 40% in mizolastine-treated patients compared to 7% in the placebo group ($P<0.003$). The safety profile of mizolastine was satisfactory and similar to that of placebo.

Conclusions In patients suffering from perennial allergic rhinoconjunctivitis, mizolastine is a safe and potent treatment. Mizolastine's pronounced effect on nasal blockade could possibly be linked to its anti-inflammatory properties.

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Allergic rhinitis is one of the most common allergic conditions known to man. In particular, perennial allergic rhinitis (PAR) is not a trivial disease in its prevalence, impact on quality of life, and its effect on related respiratory disorders. It also produces a significant economic impact in terms of treatment costs and lost productivity. The prevalence of both PAR and asthma has risen over the last three decades; for example, PAR was found in 13% of patients in a London general practice survey in 1991 (1). As well as an increase in prevalence, both diseases often coexist. Approximately 75% of patients with allergic asthma have PAR, while 20% of patients with PAR have signs of asthma (2, 3).

Allergic rhinitis involves an early phase of inflammatory reactions, largely mediated through mast cells, and a late phase which involves cellular

infiltration and mediator release. In the early phase, mast cells release mediators as a result of antigen cross-linking immunoglobulin E molecules bound to their surfaces. This results in an accumulation of histamine which gives rise to the characteristic symptoms – sneezing, itching, rhinorrhea, and nasal blockade. At 3–12 h after allergen challenge, about 50% of allergic patients experience a recurrence of symptoms, most notably nasal blockade: this is the late-phase reaction (4). This late phase involves infiltration of the nasal epithelium by eosinophils, basophils, monocytes, and T cells which release mediators such as leukotrienes, kinins, and histamine. The most important part of the late phase is probably mediated via the production of cytokines by mast cells which, by complex reactions, results in adhesion molecule expression

and subsequent recruitment of inflammatory cells (5).

The late-phase response may be more important in PAR than in seasonal allergic rhinitis (SAR), where nasal blockade due to increased mucosal blood flow and increased mucosal thickness are the predominant symptoms (6).

Alleviation of nasal blockade remains a key issue, as treatment response to antihistamines is known to be poor, particularly in PAR (7–10).

Mizolastine, a benzimidazole derivative, is a new, potent, selective, and peripherally acting second-generation histamine₁-receptor antagonist (11) tested in allergic rhinitis and urticaria. It is readily absorbed after a standard meal and is eliminated with a plasma half-life of approximately 13 h, allowing once-a-day (o.d.) administration (12). It inhibits histamine-induced wheal and flare reactions at doses of 2 mg and above (11); onset of action is rapid (1 h) and lasts for up to 24 h after a 10-mg dose with a similar order of magnitude as 120 mg of terfenadine or 10 mg of cetirizine (13). A controlled trial involving 60 atopic patients, with inhibition of skin reactions to histamine and codeine extracts as the end point, confirmed that activity was not reduced when mizolastine was administered for 2 months (14). Mizolastine has also been described as having essentially no sedative side-effect (15–20). Two placebo-controlled clinical trials conducted on a total of 750 patients showed that mizolastine is effective and well tolerated in SAR, 10 mg o.d. being the optimal dose (19, 20). More recently, comparison of mizolastine and loratadine in the treatment of PAR showed that the decrease in symptoms in the mizolastine-treated patients was comparable to that reported by patients receiving loratadine (21). In the treatment of chronic idiopathic urticaria, mizolastine significantly reduced frequency and severity of symptoms and relieved global discomfort (22).

In addition to the profile of a potent and specific antihistamine, mizolastine has been shown to have additional antiallergic and anti-inflammatory properties. After antigen challenge in the guinea pig, mizolastine inhibits inflammatory cell (neutrophil and eosinophil) migration (23). Mizolastine also inhibits arachidonic acid-induced cutaneous inflammation in the rat, an effect not related to its H₁-antagonism, but possibly to 5-lipoxygenase inhibition (24). In contrast to terfenadine, mizolastine has anti-inflammatory and visceral antinociceptive properties in a model of experimental colitis in the rat (25). Finally, at therapeutic doses in sensitized patients, mizolastine decreases early- and late-phase events of inflammatory reactions (protein exudation, ICAM-1) (26).

The present study was undertaken to evaluate the efficacy and safety of 10 mg mizolastine o.d. in patients suffering from PAR and to assess whether the anti-inflammatory properties of mizolastine were beneficial in alleviating nasal blockade.

Material and methods

This multicenter, double-blind, placebo-controlled, randomized study was carried out in Germany (12 centers) and the UK (10 centers). The participating allergologists are listed in the Acknowledgments section. The trial lasted 5 weeks, the 4-week active-treatment phase being preceded by a 7-day run-in period during which all patients took a placebo tablet on an o.d. basis. Recruitment was interrupted during the grass-pollen season to avoid the inclusion of patients suffering from both SAR and PAR at a period when symptoms are related to hay fever. The protocol was approved by local ethics committees in accordance with national legislation. Written, informed consent was obtained from each participant, or from the parent or legal guardian if the patient was a minor, before entry to the study.

Patient selection

Patients at least 15 years of age qualified if they had a well-documented history of perennial allergic rhinoconjunctivitis requiring regular pharmacotherapy for at least 1 year, supported by positive skin tests and/or RAST to house-dust mite (*Der-matophagoides pteronyssinus* and/or *D. farinae*) or animal (cat or dog) dander. Tests were considered positive when the wheal area was at least 50% greater than that observed with the positive control (histamine) or the negative control (diluent). Skin testing had to be positive within the previous 3 years with no immunotherapy in the meantime.

On the first clinic visit (day 7 of the study), after questioning and examining the patient, the investigator scored the patient's nasal symptoms (itching, sneezing, rhinorrhea, and blockade) and ocular symptoms (itching, tearing and erythema) on a 0–9 scale of severity as follows: 0=none, 1–3=mild, 4–6=moderate, and 7–9=severe. Therefore, the sum of the scores of the four nasal symptoms could range from 0 to 36; that of the three ocular symptoms from 0 to 27. During the period from day 7 to the day of inclusion (day 0), the patients scored their symptoms on the same 0–9 scale, recording the scores on a daily diary card. For a patient to be included, the investigator must have scored at least two of six symptoms (ocular erythema being excluded here) in the mild or moderate range, and the patient must have had a summed score of at least 16 during the last 2 days

of the placebo period. The investigator also performed anterior rhinoscopy to assess nasal inflammation, secretion, and mucosal swelling, using a 4-point scale (ranging from 0=none to 3=severe) for each of these signs; the sum of these scores (ranging from 0 to 9) is referred to as the rhinoscopy score.

Patients were excluded if they had an ocular or an acute or chronic respiratory tract infection or nasal polyposis. Also excluded were patients who had taken oral corticosteroids during the previous 4 weeks as well as those who had received an intramuscular corticosteroid or allergen immunotherapy during the previous 6 months. Evidence of any major systemic disease and alcohol or drug abuse, and hypersensitivity to antihistamines or benzimidazole drugs were further reasons for exclusion. Female patients were excluded if they were pregnant, lactating, or not using effective methods of contraception. A washout period of 1 week (from day 7 through day 1) was required for the following drugs: all antihistamines (but 6 weeks for astemizole), sodium cromoglycate, ketotifen, nasal decongestants, corticosteroid aerosols, and drugs with antihistaminic, anticholinergic, or sedative properties. Patients were advised not to work with dangerous machinery or to drive vehicles as an integral part of their job.

Drug administration

After the 7-day placebo run-in period, patients were randomly assigned to receive either 10 mg mizolastine or an identical-appearing placebo tablet. Tablets were to be taken in the evening. The drug-containing bottles were numbered according to a random distribution table, and patients received the drug bottle having the corresponding number. Patients were to return drug bottles to the physician at the end of the study to verify compliance. Rescue medication was not provided.

Assessment of efficacy

Physicians' evaluations, by the scale described above, were done during the pretreatment visit and then again on the three subsequent clinic visits (those scheduled on days 0, 14, and 28). An anterior rhinoscopy was performed by the investigator at each of these visits before a thorough questioning of the patient.

Patients used daily diary cards (mentioned above) to record each morning during the treatment period the severity of their nasal symptoms (including blockade) and ocular symptoms (itching and tearing only). In addition, at each clinic visit, patients were asked to assess their overall level of discomfort on a 100-mm visual analog scale, with

ratings ranging from 0=no discomfort to 100=maximum discomfort.

Assessment of safety

In accordance with standard procedures, adverse events spontaneously reported by the patient and/or observed by the physician were documented, regardless of their potential relationship to the therapy. Standard laboratory tests were carried out at the first clinic visit and again after 2 and 4 weeks of treatment. Body weight was measured at the initial visit and at the 4-week visit. Blood pressure and heart rate were monitored at each visit.

Statistical analysis

Statistical analyses (by SAS software) were conducted on an intention-to-treat basis, including all randomized patients who had had at least one evaluation under double-blind treatment. The main efficacy criteria were the nasal symptom scores computed from the four symptoms evaluated by the physicians and the patients. In addition, nasal blockade scores recorded by the physicians were analyzed separately to evaluate the effect of mizolastine on this symptom. Secondary criteria included total ocular scores, the rhinoscopy scores, and the patient discomfort score (calculated on the visual analog scale). ANOVA was used for analyzing quantitative variables, and the Cochran-Mantel-Haenszel test for the qualitative variables. All comparisons were two-sided, with a significance level of 5%. Data are presented as mean $\pm$ the standard deviation.

Results

Patient characteristics

A total of 257 patients were included in the study, 177 in the UK and 80 in Germany. A total of 133 patients were randomized to mizolastine treatment and 124 to placebo. Five patients were excluded from the baseline characteristics and efficacy analyses when an internal audit revealed that their randomization code had been broken during the study for no relevant reason. Therefore, efficacy analysis was carried out on 252 patients. In addition, four of the 257 patients were lost to follow-up after inclusion, leading to a sample size of 253 patients for safety evaluation.

Demographic and disease characteristics are presented in Table 1. Patients had had perennial allergic rhinoconjunctivitis for an average of 11 years. Allergen tests (skin tests or RAST) showed that half of them had more than one positive result.

Table 1. Baseline demographic and disease characteristics (mean $\pm$ SD)

	Mizolastine (n=132)	Placebo (n=120)	All (n=252)
Sex, n (%)			
M	55 (42%)	42 (35%)	97 (38%)
F	77 (58%)	78 (65%)	155 (62%)
Race, n (%)			
White	122 (92%)	110 (92%)	232 (92%)
Age (years)	35 $\pm$ 15	35 $\pm$ 14	35 $\pm$ 15
Duration of illness (years)	10.4 $\pm$ 11	11.7 $\pm$ 11	11.0 $\pm$ 11
Concomitant allergic disease, n (%)	47 (36%)	39 (33%)	86 (34%)
Positive allergen tests			
House-dust mite (n)	113	100	213
Animal dander (n)	64	57	121
Nasal score+			
Physicians' rating	13.9 $\pm$ 6.5	13.9 $\pm$ 6.1	13.9 $\pm$ 6.3
Patients' rating	13.0 $\pm$ 6.0	13.8 $\pm$ 5.5	13.4 $\pm$ 5.8

* Sum of itching, sneezing, rhinorrhea, and nasal blockage: score limits 0–36.

Sensitivity to house-dust mites was found most frequently, in 213 patients, followed by animal dander sensitivity in 121. One-third of patients also complained of a concomitant allergic disease. Based on both the investigators' and the patients' assessments, allergic symptoms were of comparable severity in the two groups (Table 1).

Thirty-seven patients left the study prematurely, 20 in the mizolastine group and 17 in the placebo group (Table 2).

Efficacy

A 28-day treatment with mizolastine 10 mg o.d. resulted in significant improvement of the nasal and ocular symptoms of the patients' perennial rhinoconjunctivitis compared to placebo. In mizolastine-treated patients, total nasal symptom scores decreased by 30% at 2 weeks and 36% at 4 weeks according to the physicians' evaluations (Table 3). Patients' own assessments followed a similar pattern and showed a rapid onset of action (Fig. 1). Ocular symptoms improved to a similar extent with mizolastine with a 40% score decrease according to physicians' (Table 3) and patients' evaluations (Fig. 1), whereas there were only minimal changes in the placebo group.

Table 2. Premature patient withdrawals (n)

	Mizolastine	Placebo	Total
Treatment failure	5	5	10
Adverse event	4	5	9
Lack of cooperation	4	2	6
Lost to follow-up	3	2	5
Unknown reason	4	3	7
Total	20	17	37

Mizolastine treatment significantly improved nasal blockage in comparison with placebo (Table 3). This was associated with a significant reduction in the rhinoscopy findings (based on nasal inflammation, secretion, and mucosal swelling) compared to those of the placebo group after both 2 and 4 weeks' treatment (Table 3). These observations support the mizolastine-treated patients' rating of their discomfort, which was significantly less than that recorded in the placebo group at both the 2-week and the 4-week clinic visits (Table 4) (Fig. 1).

Safety

Fifty-six (42.7%) of the mizolastine-treated patients and 58 (47.5%) of the placebo-treated patients reported at least one adverse event during the study. Reports revealed a similar safety profile for both treatment groups (Table 4); the incidence of the most frequent side-effects was as follows: respiratory tract events (19.8%, 22.9%), central nervous system events (15.3%, 25.4%), and gastrointestinal events (9.1%, 9.8%) with mizolastine and placebo, respectively. The reasons for discontinuation due to an adverse event among patients receiving mizolastine (n=4; 3%) were drowsiness (n=1),

Table 3. Physicians' ratings of patients' response to treatment (mean $\pm$ SD)

	Mizolastine	Placebo	P value
Total nasal score*			
D0	13.9 $\pm$ 6.5	13.9 $\pm$ 6.1	NS
D14	9.7 $\pm$ 5.2	12.5 $\pm$ 6.8	<0.001
D28	8.9 $\pm$ 5.1	12.3 $\pm$ 6.4	<0.001
Change at D28 vs D0	-5.0 $\pm$ 7.1	-1.5 $\pm$ 6.5	<0.001
% change relative to D0	-36%	-10%	
Total ocular score**			
D0	5.2 $\pm$ 5.0	4.4 $\pm$ 4.6	NS
D14	3.4 $\pm$ 4.5	4.5 $\pm$ 4.6	0.056
D28	3.1 $\pm$ 4.2	4.1 $\pm$ 4.8	NS
Change at D28 vs D0	-2.1 $\pm$ 4.2	-0.3 $\pm$ 5.2	<0.003
% change relative to D0	-40%	-7%	
Nasal blockage***			
D0	4.5 $\pm$ 2.4	4.6 $\pm$ 2.6	NS
D14	3.7 $\pm$ 2.4	4.2 $\pm$ 2.5	NS
D28	3.4 $\pm$ 2.5	4.1 $\pm$ 2.5	0.049
Change at D28 vs D0	-1.1 $\pm$ 2.3	-0.5 $\pm$ 2.4	0.056
% change relative to D0	-24%	-10%	
Rhinoscopy score***			
D0	4.4 $\pm$ 2.0	4.5 $\pm$ 1.5	NS
D14	3.4 $\pm$ 2.0	3.9 $\pm$ 2.0	0.032
D28	2.9 $\pm$ 1.9	3.5 $\pm$ 2.1	0.030

* Score limits: 0–36; ** score limits: 0–27; *** score limits: 0–9; D: day.

Table 4. Most relevant adverse events

	Mizolastine (n=131)	Placebo (n=122)
Patients with at least one adverse event	56 (42.7%)	58 (47.5%)
Withdrawals due to adverse event	4 (3.0%)	5 (4.0%)
Relevant adverse events		
Headache	14	19
Drowsiness	5	4
Dizziness	—	3
Dry mouth	—	3

transient leukopenia in a patient treated concomitantly with a nonsteroidal anti-inflammatory drug, cellulitis of an elbow, and an asthma attack. Adverse events requiring discontinuation of treatment in patients given placebo ($n=5$; 4.0%) included asthma, upper respiratory tract infection, hypotension with dizziness, an influenza-like episode, and headache (one case of each). No clinically relevant changes were found in vital signs, including body weight, or in laboratory test results at any time during the study.

Discussion

This multicenter, double-blind, randomized clinical trial compared the efficacy and safety of 10 mg mizolastine administered o.d. for 4 weeks compared with placebo to patients with a long history of perennial allergic rhinoconjunctivitis. At baseline, patients were fairly symptomatic; however, it did appear that nasal blockade was the symptom that disturbed the patients most. This was confirmed by the rhinoscopy examinations, which yielded a mean score of 4.4 (range 0–9).

Consistently greater relief of both nasal and ocular symptoms and signs was obtained with mizolastine than placebo. Nasal blockade also responded to mizolastine treatment. These subjective improvements were supported by the rhinoscopy findings, which also showed statistically significant changes in favor of mizolastine. This observation might be partly explained by an inhibitory effect of mizolastine on the arachidonic acid-induced inflammation via the lipoxygenase pathway, as demonstrated in animals (24). Many mediators, including histamine and leukotrienes, are involved in nasal blockade (27).

Nasal blockade combined with associated symptoms can produce quite severe impairment of day-to-day functioning, and cause distress and sleep disturbances (28). In this aspect, mizolastine could offer a wide and thorough relief of PAR symptoms.

From the assessments at day 14 and at the last study day, it can be seen that the greatest improvement in most of the symptoms in patients on

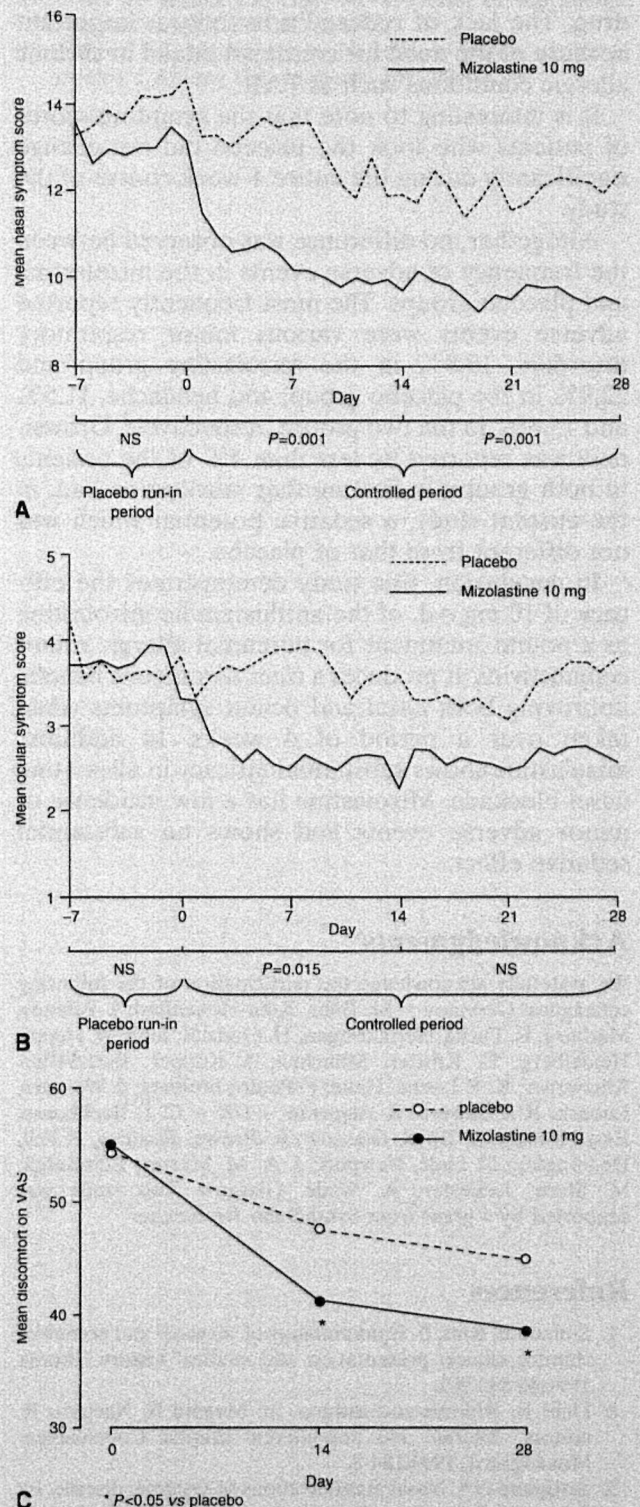


Fig. 1. Patients' rating of their own discomfort. A) Mean daily diary nasal symptom score (score limits: 0–36); B) mean daily diary ocular symptom score (score limits: 0–18); C) mean discomfort rated on visual analog scale (VAS) (score limits: 0–100).

mizolastine occurred during the first 2 weeks of treatment. During the following 14 days, there was slight additional improvement, indicating that these patients had continued to respond to the drug. The lack of reduced sensitivity is important because of the need for continual intake in chronic allergic conditions such as PAR.

It is interesting to note that the symptom scores of patients who took the placebo did not change significantly during the entire 4-week course of the study.

Altogether, no difference was observed between the frequency of adverse events in the mizolastine and placebo groups. The most frequently reported adverse events were various minor respiratory disorders, 19.8% in the mizolastine group and 22.9% in the placebo group; and headache, 11.5% and 15.6%, in the two groups, respectively. Drowsiness was reported by less than 4% of the patients in both groups, indicating that mizolastine had, in the current study, a sedative potential which was not different from that of placebo.

In conclusion, this study demonstrates the efficacy of 10 mg o.d. of the antihistamine mizolastine as a potent treatment for perennial allergic rhinoconjunctivitis. It produces a clear therapeutic benefit, improving both nasal and ocular symptoms when taken over a period of 4 weeks. In addition, mizolastine shows substantial efficacy in alleviating nasal blockade. Mizolastine has a low incidence of minor adverse events and shows no substantial sedative effect.

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