

Short communication

Can an antihistamine delay appearance of hay fever symptoms when given prior to pollen season?

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Mizolastine is a new, nonsedating antihistamine providing satisfactory symptom relief in allergic conditions. The purpose of this study was to determine whether the onset of hay fever symptoms could be delayed in patients known to suffer seasonal allergic rhinoconjunctivitis symptoms if mizolastine was given before the pollen season. This double-blind study involved 342 patients, randomly allocated to once-daily 10 mg mizolastine ($n=115$), once-daily 120 mg terfenadine ($n=116$), or placebo ($n=111$) groups. All patients started treatment on 1 May, before the onset of the grass pollen season. The prophylactic effect of test drugs was assessed on their ability to delay the time to the first hay fever crisis of the season, which was defined by the occurrence of one of the following events: use of rescue medication, study withdrawal because of treatment failure, or total diary symptom score over 18. Active treatments prolonged the time to the first crisis by approximately 1 week (mizolastine 55 days, terfenadine 57 days) in comparison with placebo (50 days) (survival curve analysis: Logrank test, $P=0.01$; Wilcoxon test, $P=0.03$). Tolerability was satisfactory and comparable between groups. Thus, mizolastine can be safely used to delay and to treat symptoms of seasonal allergic rhinitis.

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The idea of using H₁ antihistamines as prophylactic treatment of seasonal allergic rhinitis arose recently, with the development of the second-generation, nonsedating compounds. Their clinical usefulness in relieving signs and symptoms of allergic rhinitis is well established, and the low incidence of adverse events allows their administration while patients are still asymptomatic. As these agents appear to exert their effect by acting as competitive inhibitors of histamine, the rationale for prophylaxis is to start their administration before pollen-induced histamine release. Studies with terfenadine (1–4), cetirizine (3, 5, 6), loratadine (7), and astemizole (8) have been carried out in patients recruited during the month of May. All these studies aimed at limiting allergic symptoms during the forthcoming pollen period, and the authors concluded that there was a benefit of antihistamine therapy in the prophylactic management of seasonal allergic rhinitis.

Mizolastine, a benzimidazole derivative, is a new, potent, selective, and peripherally acting histamine H₁-receptor antagonist. In healthy volunteers, mizolastine inhibits the histamine-induced wheal and flare response up to 24 h after a 10-mg dose (9), and with a similar order of magnitude as terfenadine 120 mg and cetirizine 10 mg (10). No impairment in psychomotor performance and cognitive function tests was observed (11–13), nor were sedative or detrimental effects on memory (13, 14), at doses up to 20 mg. Recent clinical studies have demonstrated that once-daily 10 mg mizolastine is effective in relieving symptoms of rhinoconjunctivitis (15), perennial allergic rhinitis (16, 17), and chronic idiopathic urticaria (18, 19). The aim of this study was different from those of studies on other antihistamines in preventive hay fever therapy (1–8); specific prophylactic assessment criteria were defined, which determined

whether the onset of allergic symptoms could be delayed when mizolastine therapy was started before the pollen season. Comparison was made with terfenadine (20) and placebo.

Material and methods

This double-blind, parallel-group study was carried out in the UK during the 1991 pollen season. The protocol was approved by the local ethics committees, and written informed consent was obtained from each participant before admission to the study.

Patients at least 18 years old were eligible if they had a well-documented history of seasonal allergic rhinoconjunctivitis, supported by positive skin prick test results to grass pollen. Patients were not included in cases of immunotherapy, or of antihistamine or delayed corticosteroid treatments. All medications that could influence symptoms were discontinued before the start of study treatment.

Screening visits took place in March and April; medications were dispensed at this time, according to randomization. Patients were asked not to take treatment at once, but to begin on 1 May. Visits were scheduled on days 15, 30, 60, and 90. The double-placebo technique ensured double-blindness. Rescue medications were not provided, but their use, although not permitted, was monitored. Pollen counts were recorded daily.

The prophylactic effect of the study drugs was assessed on their ability to delay the time to the first hay fever crisis of the season. A patient was considered to have had a crisis if at least one of the following events occurred: use of rescue medication, study withdrawal because of treatment failure, and total diary symptom score over 18.

Patients were to fill in daily diary cards for nasal (itch, rhinorrhea, sneezing, blockage) and ocular symptoms (itch, watering) on a 0–9 scale where 0 = absent, 1–3 = mild, 4–6 = moderate, and 7–9 = severe.

The statistical analysis was conducted on an intention-to-treat basis; the between-groups comparison with respect to the time to the first crisis was performed by survival curve analysis, resulting in two tests, Logrank and Wilcoxon. Comparisons were two-sided, with a significance level of 5%.

Results

A total of 342 patients participated in the study; 115 received mizolastine, 116 terfenadine, and 111 placebo. All groups were comparable at baseline with respect to demographic and disease characteristics (Table 1).

Assessment of antihistamine prophylactic efficacy

Both active treatments significantly delayed the onset of the first symptom crisis. In the mizolastine-treated patients, the first hay fever crisis of the season appeared after 55 ± 2 days, and after 57 ± 2 days with terfenadine. This delay was significantly greater than that observed in the placebo group, 50 ± 2 days ($P = 0.01$, Logrank test; $P = 0.03$, Wilcoxon test). The use of rescue medication and the number of study withdrawals due to treatment failure were numerically lower in the mizolastine and terfenadine groups than in the placebo group; the mean delay until the first appearance of a total symptom score over 18 was prolonged by both active treatments (Table 2). The daily average of total symptom scores over the peak pollen period (21 June–P27 July) is illustrated by Fig. 1.

Assessment of safety

The frequency of patients reporting at least one adverse event during the 3-month study period was comparable between groups (Table 3). The most common complaint recorded during the study was headache, which, in association with other

Table 1. Patient baseline characteristics

	Placebo <i>n</i> = 111	Mizolastine <i>n</i> = 115	Terfenadine <i>n</i> = 116	Total <i>n</i> = 342
Men/women	70/41	67/48	71/45	208/134
Age (years)*	34 ± 11	33 ± 11	36 ± 11	34 ± 11
History of allergy (months)*	241 ± 146	236 ± 130	221 ± 119	233 ± 132
Family history of allergy (<i>n</i>)	49	54	51	154 (45%)
Concomitant allergic disease (<i>n</i>)	45	40	43	128 (37.4%)
Total diary score* on 1 May	2.2 ± 3.6	2.9 ± 5.3	2.7 ± 4.9	2.6 ± 4.7

* Mean $\pm$ SD.

Table 2. Description of three events defining hay fever crisis in each therapeutic group

	Placebo	Mizolastine	Terfenadine
Use of rescue medication (<i>n</i>)	34	25	24
Withdrawal due to treatment failure (<i>n</i>)	37	32	28
Delay until symptom score > 18 (days)*	54 ± 2	57 ± 2	57 ± 2

* Mean $\pm$ SD.

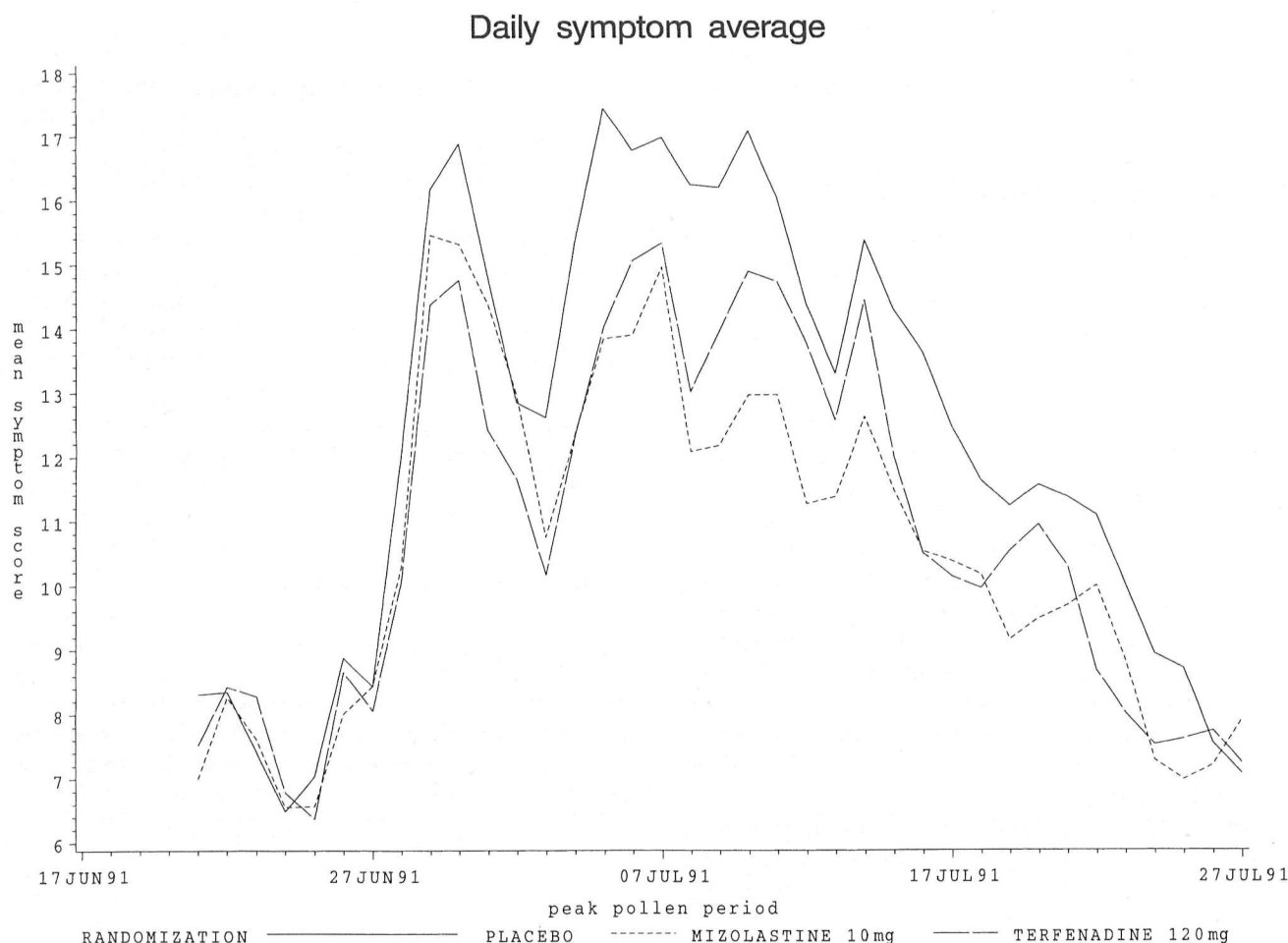


Fig. 1. Daily average of total symptom scores during peak pollen period.

Table 3. Most common adverse events

	Placebo	Mizolastine	Terfenadine
Patients with at least one adverse event (n) (%)	90 (81.1)	88 (76.5)	89 (76.7)
Withdrawals due to adverse event (n) (%)	8 (7.2)	14 (12.2)	10 (8.6)
Predominant* adverse events (n) (%)			
Central nervous system-related disorders			
Headache	48 (43.2)	53 (46.0)	50 (43.1)
Asthenia	5 (4.5)	11 (9.6)	5 (4.3)
Respiratory disorders			
Pharyngitis	24 (21.6)	20 (17.4)	12 (10.3)
Rhinitis	25 (22.5)	19 (16.5)	20 (17.2)

* Total frequency of adverse events reported at least 20 times.

complaints, led to study withdrawal in four mizolastine patients and in two placebo patients. Asthenia was reported slightly more often by the mizolastine-treated patients; however, these frequencies were comparable across treatment groups (chi-square test: $P=0.171$). Study withdrawal because of asthenia

occurred in four mizolastine patients and in one placebo patient. Respiratory disorders were suggestive of an underlying disorder (rhinitis) or of an intercurrent disease (pharyngitis), and tended to be more frequently reported in the placebo group. No evidence of a tendency to weight gain was noticed.

Discussion

Traditional study designs used in the treatment of hay fever involve the recruitment of patients already suffering symptoms. The question of the prophylactic effect of preseasonal therapy with an antihistamine is theoretically relevant, and the enrollment of patients before significant pollen count is accepted (1–8). Studies with various drugs, terfenadine, cetirizine, loratadine, and astemizole, aimed to determine whether severity of symptoms during the pollen period could be limited (Table 4); antihistamines were usually compared one to another, a placebo arm being used only twice (6, 7). Treatments were usually started during the

Table 4. Use of antihistamines as preventive treatment in seasonal allergic rhinitis

Author(s), year (reference)	Compounds		Use of placebo	Sample size	Study duration
Backhouse & Rosenberg, 1987 (1)	Terfenadine	Chlorpheniramine		138	6 weeks
Backhouse et al., 1986 (2)	Terfenadine	Terfenadine plus flunisolide		99	11 weeks
Davies, 1991 (3)	Terfenadine	Cetirizine		487	8 weeks
Schoel et al., 1993 (4)	Terfenadine	Levocabastine		115	8 weeks
D'Souza et al., 1990 (5)	Beclomethasone	Beclomethasone plus cetirizine		490	8 weeks
Grant et al., 1993 (6)	Cetirizine		Yes	186	6 weeks
Dolovich et al., 1994 (7)	Loratadine		Yes	118	6 weeks
Juniper et al., 1989 (8)	Astemizole	Beclomethasone and their combination		90	6 weeks
Present study	Mizolastine	Terfenadine	Yes	342	3 months

month of May, and follow-up lasted 6–11 weeks; efficacy, assessed as in traditional studies (i.e., decrease in symptom score), led to overall positive conclusions concerning the use of antihistamines before and during the pollen period.

The time to the onset of a crisis is probably a more accurate evaluation of prophylaxis, and the current study is presumably the first one to consider this approach in assessing the preventive effect of antihistamines. Patients commenced dosing on 1 May while symptoms were absent or minimal, in geographically close investigating centers where pollen counts showed similar trends. Pollen counts were low during the month of May, and high pollen counts appeared from 21 June. Patients were regularly monitored until the occurrence of the first hay fever crisis of the season. Mizolastine 10 mg and terfenadine 120 mg both prolonged by approximately 1 week the time to the onset of a hay fever crisis. A lower occurrence of rescue medication use and of patient study withdrawal due to lack of efficacy was observed in the mizolastine and terfenadine groups, as well as a prolonged time before the appearance of severe symptoms, leading to a statistically significant delay in the occurrence of the first hay fever crisis.

Even though reports of adverse events were frequent, their incidence was similar across treatment groups. The very thorough safety screening comprised allergy symptoms, which contributed, in part, to the high number of complaints. Headache was the side-effect most often reported, but the incidence was comparable across treatment groups. Asthenia was slightly more frequent with mizolastine. In the current study, the incidence of adverse events was higher than that reported in all perennial allergic rhinitis studies comparing placebo and mizolastine, which yielded respectively, 11.8% and 13.8% headaches, and 2.1% and 1.4% asthenia (data on-line).

In conclusion, mizolastine can be safely used both to delay the onset and treat the symptoms of

seasonal allergic rhinoconjunctivitis. A future study should investigate whether a similar prophylactic effect can be obtained when treatment is taken only a few days before theoretically high pollen counts.

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