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# Lack of subsensitivity to mizolastine over 8-week treatment

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Mizolastine is a new, nonsedating antihistamine providing satisfactory symptom relief in allergic rhinitis and urticaria. The purpose of this study was to use the wheal and flare skin reactions model to assess the maintenance of the pharmacodynamic effect of mizolastine, administered for 2 months. This double-blind, parallel-group study involved 60 atopic patients randomly allocated, after a 1-week placebo run-in, to once-daily 10 mg mizolastine ($n=29$) or placebo ($n=31$) groups. Treatment continued for 8 weeks. Prick tests were performed in duplicate with histamine chlorhydrate (10 mg/ml), codeine phosphate (9%), and five increasing concentrations (1–500 reactivity index/ml) of standardized allergen extracts (grass pollen or mites) at days 0, 7, 28, 42, and 56. After 7 days of treatment, inhibition of histamine-induced wheal was −76% and +20%, respectively, with mizolastine and placebo ($P=0.0001$), in comparison with baseline; inhibition of flare was −86% and +5%, respectively, with mizolastine and placebo ($P=0.0001$). Suppression was maintained to a similar extent throughout the study. Results were consistent between histamine-, codeine-, and allergen-induced tests. Safety was satisfactory in both groups. This study confirms mizolastine as a potent antihistamine which does not induce subsensitivity when taken for 8 weeks, and which can be safely recommended in allergic conditions.

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Since the phenomenon of subsensitivity to antihistamines was first reported in the early 1950s by Monash with chlorpheniramine (1) and by Dannenberg & Feinberg with diphenhydramine (2), the possibility of a loss of efficacy in clinical use has been investigated for this class of drugs. Thorough studies undertaken with chlorpheniramine show that subsensitivity cannot be completely eliminated by doubling the dose after 3 weeks of treatment (3), and that unsatisfactory compliance may further contribute to poor clinical results during this same period of time (4). Mean serum chlorpheniramine levels (3) and chlorpheniramine serum half-lives (4) showed that changes in metabolism were not involved in these observations. Another study comparing six first-generation antihistamines (5) showed, after 3 weeks of treatment, that the suppressive effect of hydroxyzine, as well as that of the five antihistamines, was significantly reduced. In addition, hydroxyzine caused the development of partial tolerance, not only to its own effect, but to those chemically unrelated antihistamines.

The investigation of a similar phenomenon has been undertaken for the widely prescribed, second-generation antihistamines such as loratadine (6, 7), terfenadine (8, 9), and cetirizine (9, 10). Repeated assessments of inhibition of skin reactions to histamine, up to 12 weeks with loratadine, 8 weeks with terfenadine, and 5 weeks with cetirizine, concomitantly with closely monitored compliance, established the absence of subsensitivity with these three compounds. Nevertheless, subsensitivity has become a mandatory step in the clinical development of a new antihistamine and warrants investigation. Mizolastine, a benzimidazole derivative, is a new, potent, selective, and peripherally acting antagonist of histamine $H_1$-receptors, currently under clinical investigation in allergic conditions. Mizolastine is readily absorbed, a peak plasma concentration occurring 1.5 h after ingestion; its elimination half-life is approximately 12 h, allowing a once-daily regimen (11). No impairment in psychomotor performance and cognitive functions was observed, nor sedative effects or detrimental effects on memory in the elderly, at doses up to 20 mg

(12–15). Mizolastine inhibits the histamine-induced wheal and flare skin reactions from a dose of 2 mg upward, the effect lasting up to 24 h after a 10-mg dose (16), and with a similar order of magnitude as terfenadine 120 mg and cetirizine 10 mg (11). Recent clinical studies demonstrated that 10-mg, once-daily mizolastine therapy is effective in relieving symptoms of seasonal allergic rhinitis (17), perennial allergic rhinitis, and urticaria (data on line, Synthélabo Recherche).

The present trial was designed to assess the persistence during 2 months of the pharmacodynamic effect of mizolastine, using the widely accepted wheal and flare skin reaction model (18). Histamine, codeine, and allergen skin prick testing was carried out concomitantly with mizolastine plasma assays and assessment of compliance.

## Material and methods

This double-blind, parallel-group study compared the maintenance of the antihistaminic efficacy of 10 mg mizolastine over 8 weeks of treatment in comparison with placebo. The protocol was approved by the Nîmes Ethics Committee (France), and informed written consent was obtained from each participant before entering the study.

### *Patients*

Patients 18–45 years old, allergic to orchard grass pollen (*Dactylis glomerata*) or to house-dust mites (*Dermatophagoides pteronyssinus*), with elevated serum specific IgE antibodies, i.e., radioallergosorbent test (RAST) $\geq 2$ (Pharmacia Diagnostics, Uppsala, Sweden), were considered for the study. This test is a solid-phase immunoassay in which aliquots of the serum to be tested are added to each of the test allergens covalently bound to a paper disk. The amount of specific IgE that reacts to the antigen is then determined by adding $^{125}$I-labeled anti-IgE, washing the disk, and measuring the radioactivity bound to the disk. The amount of radioactivity in counts/min is compared with a standard reference curve using five dilutions of positive sera, and the test sera are scored as 0 (undetectable) through 4 (very high) (19). In addition, skin prick tests of histamine, codeine, and one of both allergens had to be positive on two successive visits, day 7 and day 0. Patients were not included in case of immunotherapy or delayed corticoid treatments. Histamine blockers were stopped for at least 2 weeks, imipramine was not to have been taken within 3 weeks, ketotifen and corticoids within 4 weeks, and astemizole within 6 weeks. Evidence of major systemic disease, or of alcohol or substance abuse were also 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. Patients who volunteered to participate in this study were paid to ensure satisfactory protocol compliance.

### *Study design*

Patients were randomly assigned, after a placebo run-in period, to receive 10 mg mizolastine or placebo in tablets of identical appearance. Tablets were to be taken each morning between 7:00 and 9:00 a.m. for 8 weeks. Remaining study medications were returned to the physician at each visit to verify compliance. Concomitant medications likely to interfere with the study were not allowed. Patients were seen a total of six times during the study. These visits were on days −7, 0, 7, 28, 42, and 56.

### *Skin prick testing*

The maintenance of mizolastine's antihistaminic activity was assessed by the extent of wheal and flare reaction inhibition. Skin prick tests were performed double-blind, at each visit, 2 h after test drug intake, on the volar surface of both of each patient's forearms. Challenge sites stood 3 cm apart in order to avoid interference from neighboring reactions. The values used in the analyses were the averages of the corresponding measurements from both areas. All punctures were given by the same investigator throughout the study, in a random order from the elbow to the wrist, and without causing bleeding. Each patient was tested with histamine chlorhydrate (10 mg/ml), codeine phosphate 9%, saline solution, and five increasing (biologically standardized to the index reactivity) concentrations of either orchard grass pollen (1, 5, 10, 50, and 100 IR/ml) or house-dust mites (5, 20, 50, 200, and 500 IR/ml). All punctures tests were performed with a hypodermic needle (Stallerpoint, Stallergène Laboratories, Fresnes, France). Allergen dilutions were prepared from lyophilized extracts; the diluant was phenol glycerosaline solution. The same batches were used throughout the study. Wheal and flare areas were recorded 15 min after the puncture by the same technician, outlined with ink, transferred onto transparent sheets, and measured by a computerized planimetry system (Canvas software, Macintosh).

### *Mizolastine plasma assays*

Blood samples were drawn on days 7, 28, 42, and 56, and mizolastine was assayed in plasma with

high-performance liquid chromatography; detection was carried out by UV spectrophotometry at 285 nm, and limited to 1 ng/ml.

*Safety*

Adverse events, spontaneously reported by the patients and/or observed by the investigator, were documented regardless of the relation to the therapy and in accordance with standard procedures. Blood pressure, heart rate, and weight were monitored at each visit; electrocardiogram and laboratory tests were performed upon enrolment and at the end of the study.

*Statistical analysis*

The statistical analyses (SAS) were conducted on an intention-to-treat basis. The primary efficacy criteria were the histamine- and codeine-induced tests performed in all participants. For the wheal sizes, corrected values were calculated by subtracting the area induced by the saline solution from that observed after histamine and codeine solutions, as the saline itself may have a whealing effect (20). This correction was not calculated for the flare areas. Relative differences from baseline, expressed as percentages, were generated. A univariate analysis of variance for repeated measurements (ANOVA with a single factor: treatment) was carried out to evaluate mizolastine's efficacy, and a multivariate analysis of variance (MANOVA with three factors: treatment, visit, and patient) was used to verify the absence of subsensitivity. The same methodology was applied to the secondary criteria, the allergen-induced tests. As no interaction between treatment and allergen species was shown, analysis was carried out with both types of allergens and all concentrations considered together. Descriptive data are given for compliance and pharmacokinetics. All comparisons were two-sided, with a significance level of 5%. Data are expressed as mean ± SD.

## Results

*Patient characteristics*

A total of 60 patients were recruited between September 1992 and April 1993. Both groups of patients, mean age 27 ± 6 years, were comparable at baseline with respect to demographic and disease characteristics (Table 1); 59 patients (98%) had a history of allergic rhinitis, 44 (73%) of conjunctivitis, and 21 (35%) of asthma. Allergy to pollen was present in 40 patients (67%) and to dust mites in 35 (58%); 15 (25%) were allergic to both allergens. Twenty-five patients (42%) had been treated with an antihistamine during the last 6 months. Of the 29 patients who were randomized to mizolastine, 15 were prick tested with pollen extract and 14 with house-dust mite extract. Of the 31 who received placebo, 15 were prick tested with pollen extract and 16 with dust mite extract. Baseline histamine-, codeine-, and allergen-induced wheal and flare areas were comparable in both groups (Table 1). Only one patient, in the mizolastine group, withdrew prematurely from the study (he left for military service).

Table 1. Baseline patient characteristics

| | Placebo $n=29$ | Mizolastine $n=31$ | Total $n=60$ | $P$ value* |
|---|---|---|---|---|
| Men/women | 16/13 | 17/14 | 33/27 | NS |
| Age (years) ± | 27.1 ± 6 | 26.8 ± 6 | 26.9 ± 6 | NS |
| History of allergy | | | | |
| Rhinitis | 30 | 29 | 59 | NS |
| Conjunctivitis | 22 | 22 | 44 | NS |
| Asthma | 7 | 14 | 21 | 0.037 |
| Allergies | | | | |
| Pollen | 22 | 18 | 40 | NS |
| Dust mite | 16 | 19 | 35 | NS |
| Both | 9 | 6 | 15 | NS |
| Histamine-induced ± | | | | |
| Wheal ■ | 18.3 ± 5.4 | 19.9 ± 7.3 | 19.1 ± 6.4 | NS |
| Flare ■ | 262 ± 106 | 284 ± 136 | 273 ± 121 | NS |
| Codeine-induced ± | | | | |
| Wheal ■ | 15.6 ± 4.4 | 16.9 ± 7.1 | 16.2 ± 5.9 | NS |
| Flare ■ | 202 ± 122 | 213 ± 131 | 207 ± 126 | NS |
| Pollen-induced ± ● | | | | |
| Wheal ■ | 27.1 ± 9.9 | 33.0 ± 17.1 | 30.0 ± 12.1 | NS |
| Flare ■ | 458 ± 140 | 486 ± 171 | 472 ± 156 | NS |
| Dust mite-induced ± ● | | | | |
| Wheal ■ | 30.1 ± 11.8 | 30.2 ± 13.1 | 30.1 ± 12.4 | NS |
| Flare ■ | 486 ± 171 | 374 ± 148 | 432 ± 160 | NS |

*Intergroup comparison; ± mean ± SD; ■ areas expressed in $mm^2$; ● at highest allergen concentrations.

*Wheal and flare skin reactions*

After the first week of treatment with mizolastine, the histamine-induced skin areas decreased by −76% and −85%, respectively, for the wheal and for the flare reactions. This suppression was highly significant in comparison with placebo, +20% and +14%, respectively, for the wheal and the flare formations (MANOVA, $P=0.0001$) (Table 2). This inhibition was maintained at the same level with mizolastine throughout the study, −70%, −70%, and −79% on the wheal reaction after 28, 42, and 56 days of treatment, and −81%, −82%, and −84% on the flare reactions on the same days (MANOVA, $P=0.0001$) (Table 2).

Codeine-induced reactions were inhibited by mizolastine to a similar extent: −71% for the wheal and −86% for the flare reactions after 1 week of treatment. This was highly significant in comparison

Table 2. Relative differences (%) from baseline in mean (±SD) histamine and codeine-induced wheal and flare areas

| | Histamine test | | Codeine test | |
|---|---|---|---|---|
| Differences in wheal areas[a,b] | Placebo | Mizolastine[a] | Placebo | Mizolastine[a] |
| Day 7 | 20±59 | −76±22 | 3±37 | −71±15 |
| Day 28 | 16±48 | −70±19 | 11±35 | −61±24 |
| Day 42 | 16±46 | −70±19 | 14±32 | −69±17 |
| Day 56 | 15±43 | −79±13 | 29±97 | −69±22 |
| Differences in flare areas[a,b,c] | | | | |
| Day 7 | 14±43 | −85±22 | 1±45 | −85±15 |
| Day 28 | 39±70 | −81±20 | 29±61 | −85±14 |
| Day 42 | 23±43 | −82±15 | 23±57 | −83±14 |
| Day 56 | 18±57 | −84±18 | 13±56 | −86±19 |

[a] Treatment effect in favor of mizolastine, MANOVA tests yield $P=0.0001$ for all relative differences, for wheal as well as for flare areas.
[b] No visit effect for wheal areas, MANOVA tests yield $P=$NS.
[c] Visit effect for flare areas, MANOVA tests yield $P<0.05$ due to fluctuations of values in placebo group; suppression is constantly maintained with mizolastine.

with placebo, +3% and +1%, respectively, for the wheal and flare formations (MANOVA, $P=0.0001$) (Table 2). Suppression was also maintained with mizolastine throughout the study, −61%, −69%, and −69% on the wheal reaction after 28, 42, and 56 days of treatment, and −85%, −83%, and −86% on the flare reaction on the same days (MANOVA, $P=0.0001$) (Table 2).

For the allergen prick tests, the analysis was carried out, taking into account both allergen types and all concentrations together, as no allergen/treatment interaction was revealed. Allergen-induced skin reactions, to both types of allergens considered together, were also constantly suppressed by mizolastine. Wheal inhibition ranged, throughout the study, from −60% to −66% with mizolastine and from −3% to +14% with placebo (MANOVA, $P=0.0001$). Flare inhibition ranged from −80% to −84% and from −2% to +14%, respectively, with mizolastine and placebo (MANOVA, $P=0.0001$). Allergen-induced wheal and flare reactions during placebo and mizolastine treatments are illustrated in Fig. 1.

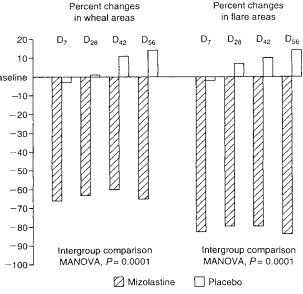



*Fig. 1.* Changes from baseline in allergen-induced skin reactions during placebo and mizolastine treatments, all concentrations of both types considered together (model incorporating factors treatment, allergen, and interaction).

### *Mizolastine assays and treatment compliance*

Mizolastine plasma concentrations were assayed upon each visit on the 29 patients of this treatment group, 2 h after drug intake and just after skin punctures. Results show similar mean concentrations throughout the 2-month treatment: 259±73 ng/ml after 7 days of treatment, 261±69 ng/ml after 28 days, 249±73 ng/ml after 42 days, and 269±83 ng/ml after 56 days. Patients were asked to bring back their remaining medication at the next visit so that compliance could be checked (placebo tablets on day 0, and mizolastine or placebo tablets on days 7, 28, 42, and 56). Medications were forgotten a total of five times. Over the 9-week period, a difference of more than ±1 tablet between the prescribed and taken tablets was recorded in 8.6% of verifications, and a difference of more than ±2 tablets, 2.3% of the time.

### *Safety*

The safety profile of mizolastine was satisfactory during the study, even though the incidence of adverse reactions was higher in the mizolastine group (17/29 patients reported at least one event), compared with placebo (10/31 patients). Increased appetite was reported by seven mizolastine-treated patients and by one placebo-treated patient. No evidence of a tendency to gain weight was noticed

in these patients, and mean weights were stable in both groups from the beginning to the end of the trial. Drowsiness of mild or moderate severity was noted five times in the mizolastine group and twice in the placebo group. Each of the following complaints was reported twice in the mizolastine treatment group, diarrhea, rhinitis, and asthenia, but not in the placebo group. Electrocardiogram parameters were not modified; in particular, no abnormal prolongation of Q-Tc value was revealed.

## Discussion

The goal of this study was to assess the maintenance during 2 months, and in comparison with placebo, of the antihistaminic effect of mizolastine on wheal and flare skin reactions. A thorough investigation was carried out, using cutaneous responses to different agents, histamine itself, a pharmacologic agent as a nonspecific antigen (codeine), and two specific allergens (grass pollen and dust mite). Prick tests were monitored regularly. With all agents, inhibition with mizolastine was highly significant in comparison with placebo ($P = 0.0001$). In the mizolastine group, the relative difference in wheal or flare inhibition ranged from −61% to −86% throughout the 2-month treatment, whereas relative differences ranged from −3% to +39% in the placebo group. The suppression measured after 1 week of mizolastine treatment was maintained to a similar extent up to the end of the study for both the wheal and flare reactions. Intermediate visits after 4 and 6 weeks of treatment also showed a strong and stable inhibition. The only fluctuations of inhibition levels, due to spontaneous changes, were seen in the placebo group, whereas suppression was constantly sustained with mizolastine. The use of a saline control at each time-point provided corrected wheal area values. This technique is recommended by Byrom et al. (20) for histamine assays in skin, and was previously used in a mizolastine pharmacodynamic study (11), enabling an accurate analysis of wheal formation. The closely verified pill count, in addition to stable mean mizolastine plasma concentrations, was in accordance with a very good treatment compliance, atopic volunteers having been recruited especially for this study. On the whole, the current results clearly indicate that there was no development of subsensitivity to mizolastine. Another recent study (data on line, Synthélabo Recherche) confirmed these findings; 32 patients suffering chronic urticaria were treated either with mizolastine or with loratadine. Skin prick tests with four concentrations of histamine (1.25–10 mg/ml), carried out after 2 and 4 weeks of treatment, indicated that subsensitivity did not develop with either compound. The sustained pharmacodynamic effect of mizolastine is in agreement with that of other second generation antihistamines (6–10) (Table 3): trials have been conducted in healthy volunteers or atopic patients, during 3–12 weeks, versus placebo or a competitor. All concluded the absence of a tolerance phenomenon. These observations are of primary importance, as $H_1$-blockers may be administered for weeks or months; therefore, it is not necessary to increase the dose to relieve symptoms in allergic patients.

In conclusion, this study confirms that mizolastine is a potent $H_1$ antihistamine which does not induce subsensitivity, and which can be safely recommended for a long-term period.

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Table 3. Studies investigating subsensitivity during second-generation antihistamine therapy

| Author, year, (reference no.) | Compound (daily dose) | Comparator | Study duration | Population | Sample size | Agent | Percent wheal inhibition |
|---|---|---|---|---|---|---|---|
| Roman et al. 1986 (6) | Loratadine (10–40 mg) | Chlorpheniramine and placebo | 4 weeks | Healthy volunteers | 60 | Histamine | L 10 mg ≃ −80% P ≃ −23% |
| Bousquet et al. 990 (7) | Loratadine (10 mg) | Placebo | 12 weeks | Atopic patients | 20 | Orchard grass, dust mite, histamine | L ≃ −50% P ≃ −12% |
| Simons et al. 1988 (8) | Terfenadine (120 mg) | None | 8 weeks | Healthy volunteers | 11 | Histamine | T: −44 to −52% |
| Rihoux et al. 1992 (9) | Cetirizine (10 mg) | Terfenadine (120 mg) | 3 weeks | Atopic patients | 24 | Histamine | C: −100% T: −60 to −80% |
| Watson et al. 1989 (10) | Cetirizine (5 mg) | Cetirizine (10 mg) | 5 weeks | Atopic children | 19 | Histamine | C: −85 to −100% |
| Present study | Mizolastine (10 mg) | Placebo | 8 weeks | Atopic patients | 60 | Histamine<br>Codeine<br>Pollen<br>Dust mite | M: −79% P: 15%<br>M: −69% P: 29%<br>M: −62% P: 19%<br>M: −68% P: 7% |

L = loratadine, P = placebo, T = terfenadine, C = cetirizine, M = mizolastine.

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