

Clinical advantages of dual activity in urticaria

Urticaria is a common disorder that adversely affects quality of life; work-related and recreational activities are restricted, while rest, sleep, and emotions are seriously disturbed in a significant proportion of patients. The pathogenic mechanisms vary, but cutaneous mast-cell activation with release of histamine and other vasoactive or proinflammatory mediators is thought to be the final common pathway for lesion induction in most cases. A subsequent, but incompletely understood, late-phase allergic reaction seems to prolong the inflammatory process, particularly in certain chronic forms of the disorder. Although histamine is considered an important mediator of urticaria, additional substances, including the cysteinyl leukotrienes (LTs), are putative mediators of the immediate urticarial responses and the inflammatory events that follow in some types of urticaria. A second-generation antihistamine, mizolastine, which exhibits dual activity with selective H₁-receptor antagonism and, as shown in animal studies, anti-5-lipoxygenase activity, represents an advance in the treatment of urticaria. It has rapid, potent and sustained action. At the recommended 10-mg dose, mizolastine suppresses the histamine-induced wheal reaction as early as 1 h after oral administration. Compared to placebo, mizolastine significantly reduces overall patient discomfort and pruritus in patients with chronic idiopathic urticaria. Double-blind, placebo-controlled studies have also shown mizolastine to be at least as effective as other second-generation antihistamines. Furthermore, with long-term use of mizolastine over 1 year, a reduction in pruritus and the number of urticarial episodes was maintained with no evidence of tachyphylaxis or tolerance. Mizolastine has also been shown to be an effective treatment for cold-induced urticaria, causing significant delay in the whealing response to the ice-cube test and also reducing the wheal diameter.

K. Kontou-Fili

Department of Allergology–Clinical Immunology,
Division of Internal Medicine, Laikon General District
Hospital of Athens, Athens, Greece

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K. Kontou-Fili, MD, PhD
Department of Allergology–Clinical Immunology
Division of Internal Medicine
Laikon General District Hospital of Athens
Agiou Thoma 17
Athens 115–27
Greece
Tel. +301 7716 920
Fax: +301 6010842 (7784 396)
E-mail: kontoufk@otenet.gr

Introduction

Urticaria is a common disorder affecting between one in six and one in four people, sometimes throughout their lives (1, 2). Furthermore, chronic urticaria persists for at least 1 year in more than 50% of those affected and for more than 20 years in 20% (3). Extrinsic causative or eliciting factors are identified more often in acute than in chronic urticarias (1, 4). The various types of urticaria constitute a diverse and nonuniform group of disorders that share some common characteristics, both pathogenically and morphologically.

Urticaria is characterized by the appearance of circumscribed, pruritic wheals, surrounded by variable erythema; occasionally, burning or painful angioedema is noted. Individual lesions usually last for minutes or a few hours and rarely for up to 48–72 h; the entire process may, however, recur over days, months, or even years. Urticarial episodes of up to 6 weeks' duration are classified as acute, whereas those lasting longer are considered to be chronic.

Pathogenesis of urticaria

In its pathogenesis, the common element of urticaria appears to be a "final pathway" involving dermal mast cells. This pathway is activated by various trigger factors through immunologic or nonimmunologic mechanisms. The end result is the release of preformed and newly synthesized mediators (e.g., histamine, kinins, arachidonic acid metabolites) with potent effects on the microvasculature. Vasodilatation and increased permeability of the postcapillary venules result in erythematous wheals of various shapes and sizes. In addition to their vasoactive properties, some mediators stimulate nerve endings, thus causing pruritus or more rarely a painful burning sensation. If the deeper layers of the dermis and subcutaneous or submucosal tissues are affected, angioedema results.

Activated mast cells may also release other substances, such as chemotactic factors, cytokines, enzymes, and neuropeptides, which recruit and activate various inflammatory cells (5). These cells enter the site

Table 1. Proinflammatory mediators and factors in urticaria

Type of urticaria	Mediators/factors
Chronic urticaria	Histamine, ECP, MBP, IL-3, TNF- α , LTs, adhesion molecules
Dermographism	Histamine, NP, ECP, tryptase, adhesion molecules
Cholinergic or solar urticaria	Histamine, tryptase, NCF, ECP, ECF, MBP, adhesion molecules
Cold urticaria	Histamine, kinins, ECF, NCF, PAF, LTE ₄ , PGD ₂ , IL-3, IL-6, TNF- α , adhesion molecules
Pressure urticaria	Histamine, LTB ₄ , LTC ₄ , TNF- α , IL-3, IL-6, ECP, MBP, adhesion molecules

ECP: eosinophil cationic protein; MBP: major basic protein; IL: interleukin; TNF- α : tumour necrosis factor-alpha; NP: neuropeptides; NCF: neutrophil chemotactic factor; ECF: eosinophil cationic factor; PAF: platelet-activating factor; LT: leukotriene; PG: prostaglandin.

of the allergic reaction and subsequently release secondary mediators, which may act on the target tissue (nerve endings and small vessels), and may also activate other inflammatory or resident cells. In this way, the allergic response may be perpetuated, leading to chronic inflammation.

Various investigators have found increased levels of inflammatory mediators and/or factors in the different types of urticaria (Table 1). Histamine is the single mediator always shown to be present, even in pressure urticaria, where it is not considered the major mediator. Additional proinflammatory mediators detected in increased amounts in the systemic circulation or in the venous blood draining affected cutaneous sites are kinins, neuropeptides, interleukins, prostaglandins, LTs, tryptase, adhesion molecules, tumour necrosis factor-alpha (TNF- α), eosinophil cationic protein (ECP), major basic protein (MBP), platelet-activating factor (PAF), eosinophil cationic factor (ECF), and neutrophil chemotactic factor (NCF). In some forms of urticaria, an intense inflammatory response may occur, as, for example, in delayed-pressure urticaria. Biopsies obtained at peak reaction time after application of a pressure stimulus (19 h in one patient) showed a mixed inflammatory response with a significant eosinophilic component (6).

Some mediators can act together additively or synergistically. For example, histamine and LTB₄ injected in low concentrations (both 1 μ M) into the skin of rats had little effect on leukocyte adhesion when injected alone, but adhesion increased more than

2000-fold when the substances were injected together (7). Maximal adhesion was almost reached; increasing the LTB₄ concentration 10-fold resulted in little further increase. When the animals were pretreated with effective doses of an H₁-receptor antagonist, leukocyte adhesion was abolished, indicating the importance of the interaction between the two mediators.

The need for aggressive treatment of urticaria

A comparative study of the impact of chronic urticaria on the quality of life showed that patients were almost as affected and stressed by their disease as those suffering from ischaemic heart disease (8). Urticaria had a negative effect on emotions and self-esteem; patients felt aggressive, anxious, and fearful. The same study showed that wheals and pruritus were judged to be the worst aspects of the disorder (59% and 42%, respectively); smaller percentages of patients ranked tiredness and weakness (22%), or the side-effects of previous pharmacotherapy (5%), as the most disturbing aspect of their disease (8). Thus, potent drugs, free of adverse effects, are needed for the treatment of patients with urticaria, particularly those suffering from the chronic forms of the disorder, in order to control symptoms effectively and improve the quality of life. Mizolastine, an H₁-histamine antagonist, which has also been shown to possess anti-5-lipoxygenase activity in animal studies (9), appears to be one such drug.

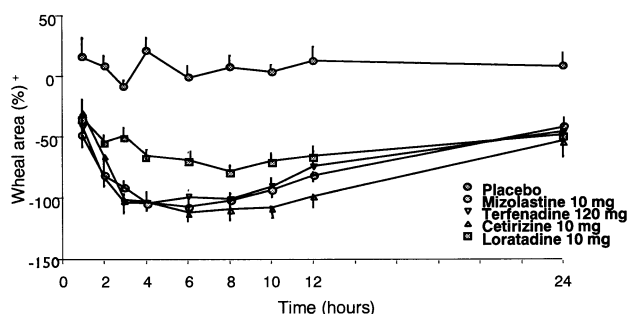


Figure 1. Inhibition of histamine-induced wheals with mizolastine and other antihistamines in a double-blind, placebo-controlled study in healthy volunteers. Reproduced with permission (10).

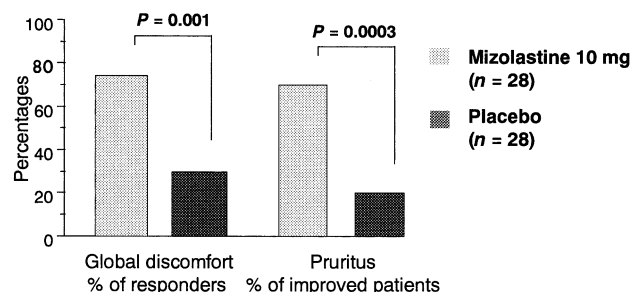


Figure 2. Improvement in urticarial symptoms with mizolastine vs placebo in a double-blind, placebo-controlled, parallel-group study of 28 days' duration. Responders were patients with visual analogue score of at least 50% less than baseline (11).

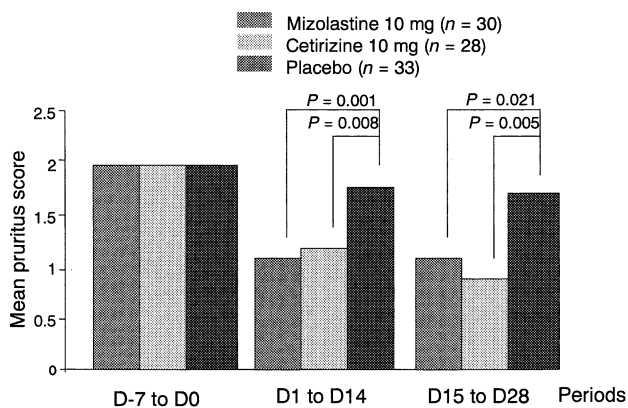


Figure 3. Reduction of pruritus intensity with mizolastine 10 mg vs cetirizine 10 mg and placebo in double-blind, placebo-controlled, parallel-group study of 28 days' duration (12).

Efficacy of mizolastine

In a five-way, double-blind, placebo-controlled, cross-over study, the antihistamine effects of single doses of mizolastine 10 mg were compared to single doses of terfenadine 120 mg, loratadine 10 mg, and cetirizine 10 mg on wheal and flare responses to histamine in 16 healthy volunteers (10). Mizolastine's effects were evident at 1–2 h, reached a maximum at 4–6 h, and were maintained at significant levels for 24 h (Fig. 1).

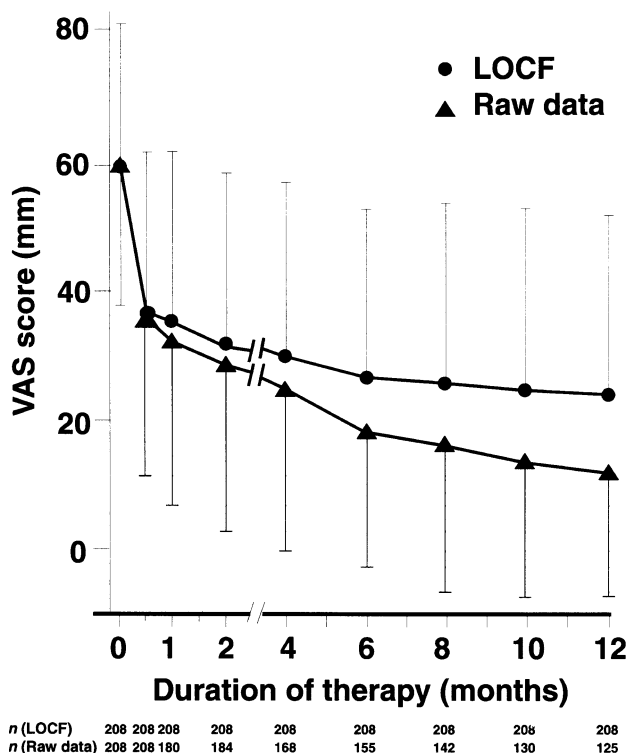


Figure 4. Efficacy of mizolastine 10 mg once daily during long-term treatment of chronic urticaria in a single-blind study involving 208 patients. Patients assessed their discomfort over previous 7 days by visual analogue scale. Values given are means $\pm$ SD of data obtained at indicated time point (raw data) or of data using last observation carried forward (LOCF) in case of missing data point. n = number of observations at each time point. Reproduced with permission (14).

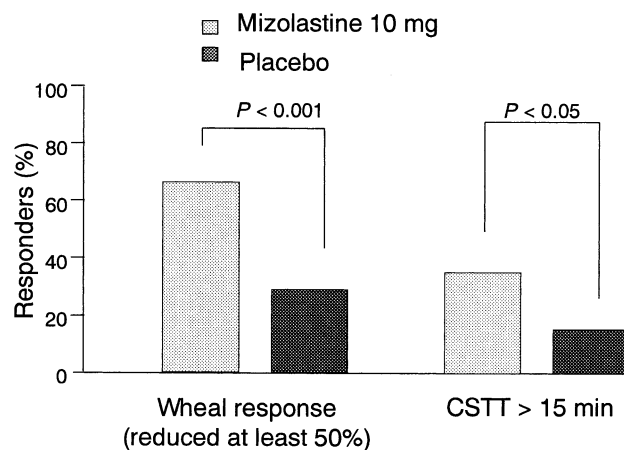


Figure 5. Efficacy of mizolastine 10 mg once daily in treatment of cold-induced urticaria compared with placebo in a double-blind, placebo-controlled study of 27 patients (17). CSTT: cold stimulation time test.

Mizolastine was significantly more effective than loratadine on the wheal ($P < 0.01$) and flare ($P < 0.05$) inhibition from 3 to 6 and 8 h, respectively. Compared with terfenadine, mizolastine was as active on both parameters; compared with cetirizine, mizolastine was as active on wheal inhibition, but less active ($P < 0.01$) on flare inhibition at 2 and 12 h after dosing. Regarding clinical safety, a similar number of subjects reported somnolence with mizolastine treatment (4) than with cetirizine (4) and terfenadine (3), compared with one subject in each of the loratadine- and placebo-treated groups. It is assumed, therefore, that mizolastine can be given conveniently once a day at a dose of 10 mg to control histamine-induced cutaneous symptoms.

A double-blind, placebo-controlled, parallel-group study lasting 4 weeks has shown that mizolastine 10 mg once daily ($n = 28$) significantly reduced global discomfort and individual symptoms, particularly pruritus, compared to placebo ($n = 28$) (11). Mizolastine produced a significantly greater decrease in the main symptoms of urticaria (itch, wheals, and erythema) than placebo ($P = 0.002$). Furthermore, the patient-rated global discomfort from symptoms, measured by a visual analogue scale (VAS), was significantly improved with mizolastine compared to placebo ($P = 0.003$). Lastly, the number of responder patients who had at least a 50% decrease in VAS score was greater in the mizolastine-treated (74.1%) than in the placebo-treated group (28.6%) ($P = 0.001$) (Fig. 2). No serious adverse events were reported; mild or moderate side-effects were reported by four patients in the placebo group (14%) and by six patients in the mizolastine group (22%), all of which spontaneously resolved by the end of the study.

Similar results were obtained in a double-blind, placebo-controlled, parallel-group, multicentre study of patients with chronic idiopathic urticaria, who also

showed overall improvement with mizolastine 10 mg once daily over a 4-week period compared to placebo (mizolastine group, $n=39$; placebo group, $n=39$) (2). In this study, the reduction in weekly episodes of urticaria was evaluated at days 14 and 28, and at both time points the number of urticaria episodes suffered during the previous week was reduced with mizolastine treatment compared with placebo ($P=0.023$ and $P=0.02$, respectively). This study also showed that mizolastine treatment compared to placebo resulted in a statistically significant decrease in the mean daily number of urticarial episodes as recorded in the patients' diaries, on the first re-evaluation day (day 14) and throughout the study period (day 28).

Mizolastine vs other antihistamines

Mizolastine has also been compared with other antihistamines, such as cetirizine and loratadine. In one double-blind, placebo-controlled, parallel-group study of patients with chronic urticaria, mizolastine 10 mg once daily ($n=30$) was compared with cetirizine 10 mg once daily ($n=28$) and placebo ($n=33$). The three groups of patients had comparable values at baseline (12). After a single-blind placebo run-in period, patients were allocated to one of the three treatment groups and evaluated after 14 and 28 days. Both mizolastine and cetirizine significantly improved urticarial symptoms according to VAS score ($P=0.045$ and $P=0.008$, respectively) after 14 days. The reduction in urticarial episodes from baseline also decreased more in the mizolastine- and cetirizine-treated patients than in those receiving placebo (11.1 ± 43.4 , 11.0 ± 26.8 , and 2.4 ± 13.9 , respectively). Throughout the study, the severity of pruritus was also significantly lower in the mizolastine and cetirizine groups than in those patients treated with placebo (Fig. 3).

A study ($n=247$) comparing 10 mg daily doses of mizolastine and loratadine in chronic urticaria showed that pruritus was significantly reduced by both mizolastine and loratadine at days 14 ($P=0.0001$ and $P=0.0006$, respectively) and 28 ($P=0.0065$ and $P=0.0265$, respectively) (13). The three parallel study groups (placebo, mizolastine, and loratadine) were comparable at baseline. Patients who received either mizolastine or loratadine treatment had a significant reduction in overall symptoms, which was evident from day 1; mizolastine significantly reduced total urticarial score at days 14 and 28 ($P=0.0022$ and $P=0.0096$, respectively) compared with placebo, and similar results were obtained with loratadine ($P=0.0038$ and $P=0.0064$, respectively). Overall, the number of patients who experienced at least one adverse event was comparable in the three treatment groups (39% in the mizolastine group, 34% in the loratadine group, and 27% in the placebo group). No serious laboratory

abnormalities were associated with either mizolastine or loratadine treatment, and no clinically relevant effects on heart rate, PR intervals, QRS duration, or QT or QT_c intervals were noted.

Long-term effects of mizolastine

An open study of 1-year duration studied the long-term effects of mizolastine 10 or 15 mg once daily in the treatment of chronic urticaria (14). It should be noted, however, that the recommended dose of mizolastine is 10 mg once daily. The study recruited 211 patients presenting with chronic urticaria, who assessed their discomfort over a run-in period of 7 days as follows: *severity of itching*: 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 largest wheals*: 0 = 0, 1 $\leq$ 1.5 cm, 2 > 1.5 cm, and $\leq$ 2.5 cm, 3 > 2.5 cm; *number of wheals*: 0 = 0, 1 $\leq$ 10, 2 > 10, and 3 = body covered in wheals. Patients also evaluated overall discomfort on a 100-mm VAS (0 = no discomfort; 100 = extreme discomfort) for the 7 days preceding each visit on days 0, 14, and 30, and monthly thereafter. From the first assessment after 14 days of treatment, there was a marked decrease in the number of patients reporting moderate or severe pruritus. Patient evaluation of overall discomfort (using the VAS) improved considerably after only 2 weeks of mizolastine treatment, and this improvement was sustained, with a tendency toward further improvement throughout the trial (Fig. 4). In the final assessment by the study investigator, 70% of patients were considered to have benefited from treatment, 28% to a moderate extent and 42% markedly. The number of urticarial episodes per week was reduced from 5.4 at baseline to 2.4 after 2 months' treatment, and remained at less than half the baseline value for the rest of the study. These results demonstrate that subsensitivity or tolerance to the therapeutic effects of mizolastine in urticaria is not observed upon prolonged administration. There were no drug-related serious adverse events, and cardiac repolarization assessed according to the QT_c intervals was not modified during prolonged administration.

This result is in agreement with previous work by Bousquet et al., who showed that mizolastine 10 mg once daily ($n=29$) for 56 days did not induce subsensitivity in atopic patients sensitive to grass pollen or house-dust mites (15). Skin prick tests were performed with five increasing concentrations of standardized allergen extracts at days 0, 7, 28, 42, and 56. Compared with baseline, inhibition of the wheal response was maintained at -76% with mizolastine treatment and about $+20\%$ with placebo ($n=31$) throughout the study. In addition, the inhibition of

the flare response was about -85% with mizolastine, in contrast to $+5\%$ with placebo, for the duration of the study. The safety profile of mizolastine was satisfactory during the study, although the incidence of adverse reactions was higher in the mizolastine than the placebo group (17/29 compared with 10/31 patients reported at least one event).

Similar results have also been obtained on histamine-induced wheal and flare in patients with chronic idiopathic urticaria in a comparative study of mizolastine and loratadine (16). In this study, prick skin tests were performed with four histamine concentrations (1.25, 2.5, 5, and 10 mg/ml), and patients received either mizolastine 10 mg once daily ($n=26$) or loratadine 10 mg once daily ($n=35$) for 28 days. Both drugs reduced histamine-induced wheal and flare at 14 and 28 days. However, this effect was more pronounced with mizolastine than loratadine, and the difference was statistically significant on day 14 with 2.5 mg/ml of histamine ($P=0.009$) and on day 28 with 10 mg/ml of histamine ($P=0.045$). Both drugs were well tolerated and no serious events were reported in this study.

Cold-induced urticaria

Cold-induced urticaria is a rare form of physical urticaria. The ice-cube test is used in diagnosis, and the cold stimulation time test (CSTT) is defined as the minimum time of cold contact stimulation required to induce an immediate coalescent wheal. A French group has studied cold urticaria in a double-blind, placebo-controlled, crossover study (17). Wheal responses on a scale of 0 to 5 were measured in 28 patients after an ice-cube test before and after the treatment period. Patients

were evaluated at days 0, 7, 14, and 28 when an ice cube was applied to the forearm for up to 15 min or until a wheal response was initiated. The severity of pruritus was measured on a visual analogue scale from 0 to 10 cm. In terms of the wheal response, at least a 50% reduction in total wheal response (sum of the diameter at 3, 6, and 10 min) was seen in 67% of patients who responded to mizolastine, compared with 30% with placebo ($P<0.001$) (Fig. 5). The cold-induced wheal reaction was delayed beyond 15 min in 36% of mizolastine-treated patients compared with 14% of patients with placebo ($P<0.05$) (Fig. 5). Furthermore, mizolastine significantly reduced pruritus ($P<0.005$) and the wheal diameter at 3 and 10 min compared with placebo ($P<0.01$ and $P<0.009$, respectively).

Conclusions

In conclusion, urticaria is a common disorder of multiple, complex, and often unrecognized aetiopathogenic mechanisms. In many aspects, urticaria causes as much disability as coronary artery disease. In addition to histamine, various other mediators are released, some of which may act synergistically or additively to induce wheals and perpetuate the allergic inflammation. Therefore, when treating urticaria, agents with a strong, rapid, and potent antagonistic H_1 action, which ideally also possess other antiallergic properties, are preferred. Mizolastine provides rapid, prolonged, and very effective control of urticarial symptoms. With its dual antihistamine and antiallergic properties, it appears to be effective in the more inflammatory forms of the disorders and possibly also in some forms of physical urticaria.

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