

Antihistamines in urticaria

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Summary

Urticaria is one of the most common and, in its chronic course, excruciating dermato-allergic diseases. Apart from the dermatological diagnosis, the identification and evaluation of causal triggering factors is of utmost importance. Here a 'three-step guideline' (according to Ring and Przybilla) has gained acceptance, ranging from a general basic examination via an intensive investigation until oral provocation tests for food allergy and oral provocation tests for idiosyncrasy (OPTI) against food additives.

Apart from true IgE-mediated allergies, pseudo-allergic reactions against food additives as well as food contents represent a major problem in chronic urticaria. Recently gastric mucosal colonization with *Helicobacter pylori* as the trigger of chronic urticaria has received attention. New pathophysiological concepts describe autoantibodies that are directed either against IgE or against the high-affinity IgE-receptor on the surface of mast cells and basophil leucocytes. In the intradermal test with autologous serum positive wheal and flare reactions can be observed (Greaves' test).

In many patients with chronic urticaria considerable psychosomatic involvement is also observed.

Histamine is one of the major mediators of most forms of urticaria although in some cases, especially physical urticaria, other mediators seem to play a role. Therefore antihistamines, and mainly H₁ antihistamines, are the mainstay of antiurticaria therapy.

Some studies have shown a benefit of combined H₁- and H₂-antagonist treatment in special forms of urticaria namely urticaria factitia. Similarly pretreatment with combined H₁ and H₂ antagonists has been proven to reduce effectively the frequency of pseudo-allergic reaction to some histamine-releasing drugs used in radiology or surgery.

More than 50 years after the first introduction of an antihistamine into allergy therapy, antihistamines still represent modern and exciting agents contributing to the continuous improvement of antiallergic therapy.

Antihistamine therapy can be performed with either the classical or second generation antihistamines. Classical antihistamines are connected with considerable side-effects especially sedation and anticholinergic effects. New non-sedating antihistamines have been developed that do not cross the blood–brain barrier.

The efficacy of mizolastine, a new non-sedating H₁ antagonist, has been evaluated in several placebo-controlled and comparative clinical trials. Overall, mizolastine 10 mg/day was found to be significantly more effective than placebo and as effective as other second generation antihistamine drugs in the management of patients with chronic urticaria, with a rapid and sustained action.

Keywords: urticaria, antihistamines, mizolastine

Introduction

Urticaria is one of the most common and, in its chronic course, excruciating dermato-allergic conditions [1,2,3].

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In spite of great progress in experimental dermatology and allergology, this condition — or group of conditions — represents a major problem for both physicians and their patients. As reported in a large number of surveys, its prevalence varies with age, sex and the presence of other allergic or autoimmune conditions. In the general population, data regarding the prevalence of urticaria of

all types range between 0.05% and 35%. It is more frequent in children and adolescents, ranging from 2.0% to 6.7%. It has been reported to occur in 0.8–4.4% of patients coming to dermatology clinics. In atopic patients — those with other allergic conditions — it occurs with a higher frequency, ranging from 3% to 35% in adults and from 4.3% to 16% in children. In terms of its cumulative prevalence, urticaria, mostly in its acute form, occurs in between 15% and 25% of the population.

Urticaria can be regarded as a disease caused by a variety of mechanisms. The urticarial lesions most commonly present as a white, smooth, itchy erythematous circumscribed skin elevation, which disappears under pressure and are referred to as wheals. These wheals are surrounded by erythema. The lesions are usually fleeting, lasting from a few minutes to several hours, sometimes days, and they vary in size from a millimetre to several centimetres or longer in diameter. Two characteristics are almost constant: variability in time and location, and pruritus with a rubbing scratch response not eroding the skin surface. Angioedema, often regarded as a brother of urticaria, develops in the deeper dermis and subcutaneous tissues. Half of the patients affected with acute urticaria also experience angioedema. Urticaria, usually generalized, often is the first symptom or stage of the anaphylactic syndrome [1].

Chronic urticaria (CU) and angioedema typically occur daily, with lesions lasting up to 12 h. Often no apparent causal relationship to an inciting agent, stimulus, illness or circumstance can be established. CU is generally worse at night and in the early morning hours, following a diurnal rhythm. Forty percent of patients with CU experience only urticaria, 49% have both urticaria and angioedema and 11% have angioedema only [1].

The pathophysiology of urticaria is not yet completely known [1–5]. The urticarial lesion is due to the release of potent vasoactive mediators predominantly from mast cells and/or basophils. These mediators, especially histamine, induce vasodilatation, increased permeability of capillaries and small veins and itch. This results in erythema (due to the vasodilatation), wheal formation (due to the local oedema resulting from capillary leakage) and itching and pain (due to sensory nerve stimulation) via H_1 receptors. H_2 receptors might also be involved in cutaneous flush reactions. In addition to histamine, the other mediators that may be involved include arachidonic acid metabolites, leukotrienes, prostaglandins, serotonin, acetylcholine, platelet activating factor, heparin, kinin, and neuromediators released from cutaneous nerve endings. IgE-mediated immediate hypersensitivity is the basic immunological mechanism. However, non-immunological mechanisms can also elicit urticarial skin lesions via pseudo-allergic mechanisms [1,2].

Classification of urticaria

There are several ways of classifying urticaria. The first is a morphological classification. In this scheme, the lesions are described as small or large, localized or generalized, etc. This is, however, not a very satisfactory classification system. Urticaria may also be classified according to the route of contact with the inciting substance (Table 1a).

A commonly employed classification scheme is based on the kinetics of the lesions. Urticaria that occurs over a period of less than 6 weeks is called acute urticaria; when it recurs for more than 6 weeks — in some patients it may recur over many years — it is called chronic urticaria. Some cases, more difficult to classify according to this scheme, may be referred to as acute intermittent urticaria, others are called chronic relapsing urticaria.

An aetiopathophysiological classification (Table 1b), based on causative mechanism(s), is more informative than the preceding schemes:

- 1 Urticaria is a common symptom in patients with chronic allergic diseases, occurring in 20–30% of them at some time during the course of their illness.
- 2 Irritative-toxic urticarial lesions occurring after contact, for example, with nettles — the so-called ‘nettle rash’ — have been recognized for centuries and given the name of the disease (*urtica dioica* = nettle).
- 3 Patients with pseudo-allergic urticaria give a history of reacting to a certain substance — most often a drug or a food additive — without evidence for specific IgE antibodies, in either skin or serological tests. The only way to make the diagnosis in these patients is by an

Table 1 Classification of urticaria

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|----|--|
| a) | According to the route of contact with the allergen |
| | <ul style="list-style-type: none"> ● Oral – drugs, foods and food additives ● Parenteral – drugs, insect venoms, vaccines ● Percutaneous – drugs, cosmetic fragrances, latex ● Inhalation – aeroallergens ● Vaginal/rectal – drugs, seminal fluids, latex ● Endogenous – microbial toxins/proteins, implants, hormones, autoantigens |
| b) | According to the aetiopathophysiology |
| | <ul style="list-style-type: none"> ● Allergic ● Irritative-toxic ● Pseudo-allergic ● Physical ● Focus reaction ● Enzyme defects ● Autoimmune disease ● Psycho-social conflict situation ● Mastocytosis ● (Idiopathic) |

oral challenge test, preferably double-blinded and placebo-controlled.

- 4 The causes of the physical urticarias include cold, heat, exercise, pressure, vibration, water and electromagnetic radiation (UV and visible light).
- 5 Focus reactions are the consequence of a localized chronic infection which is often not recognized by the patient. One can be suspicious of the diagnosis when the patient's urticaria clears up after successful treatment of a chronic infection, such as chronic sinusitis, gastritis or cholecystitis.
- 6 Patients with hereditary angioedema have a defect in the C1-inactivator enzyme, now known to be located on chromosome 11p11. These patients can be recognized by finding a decreased serum level of the complement component C4.
- 7 Wheals persisting over a longer period of time are often the first sign of an autoimmune disease, such as systemic lupus erythematosus. A skin biopsy in these cases shows deposits of immune complexes, and the underlying pathology is known as urticarial vasculitis.
- 8 Psychological conflict situations are amplifying the manifestation of urticaria. Many patients with chronic urticaria are troubled by psychosomatic interactions, and their problems should be explored in depth.
- 9 The lesions of mastocytosis may be hidden, not always being as visible as those of urticaria pigmentosa, so this condition may easily be overlooked.

Finally, there is idiopathic urticaria. 'Idiopathic' is put in parentheses because it is a term that, while frequently used, is misleading in many cases. With regards to urticaria, it is a term for those of us who are lazy. In fact, there are probably few truly 'idiopathic' cases of urticaria. To arrive at this diagnosis, thorough investigation is sometimes necessary. At the same time, one must not neglect to treat the patient's symptoms.

Diagnostic approach to patients with urticaria

A three-step approach to the diagnosis of urticaria is used in the Dermatology/Allergy Clinic at the Munich Technical University:

- step 1 – basic investigations;
- step 2 – intensive investigations;
- step 3 – provocation and other tests.

In the basic step, one takes a careful allergy-relevant history, examines the patient and does simple physical tests. Laboratory investigation is limited to a complete blood count, an ESR and a total serum IgE level. A limited number of allergen skin tests are done to screen for atopy. The patient should be treated symptomatically for up to 4 weeks, and any causative factors that are found should be dealt with when possible. In many cases,

the urticaria will have disappeared within a month, meaning that it is not necessary to do further investigations.

If the condition persists, however, then more intensive investigation is indicated. This will include a detailed dietary history, examinations for foci of infection or malignancy, some additional laboratory tests (serum, urine, anti-nuclear antibodies), and tests for food and drug allergies.

Depending on the results of the preceding steps, some of the following additional investigations may be undertaken: more detailed history; additional allergy tests; elimination diet; food challenge and provocation diet; oral provocation test for idiosyncrasy (OPTI) with food additives; skin biopsy; serum complement level; thyroid hormone level, etc.

This diagnostic approach was followed in 190 CU patients. The laboratory findings in these patients, including 120 females and 70 males aged 4–84 years (median 41 years for the women and 38 years for the men) with the duration of their disease ranging from 5 weeks to 30 years (median 2.8 years for the women and 3.8 years for the men), who were investigated according to the above scheme, were as follows: elevated ESR, 15%; leukocytosis, 1%; proteinuria, 1%; parasites in the stool, 1%; candida in the stools, 49%; elevated serum IgE, 40%; positive serum AST assay, 1%; positive serum ANA assay, 3%.

The aetiopathophysiological diagnosis was arrived at in three-quarters of these 190 patients: infection in the ear, nose and/or throat (sinusitis, tonsillitis or otitis) was found in 20% of these patients, in the dental region (apical otitis or granuloma) in 3%, in the gastrointestinal (gastritis or cholecystitis) in 23%, and the urogenital tracts (adnexitis, prostatitis or pyelonephritis) in 11%. Recently, it has been recognized that gastric infection with *Helicobacter pylori* may be associated with CU. Based on a positive breath test, this bacterium was associated with CU in more than 20 patients. The urticaria cleared after eradication of this infection in approximately one third of these patients. However, the role of *H. pylori* in CU requires further investigation. A positive diagnosis of pseudo-allergy in double-blind, placebo-controlled challenge tests with food additives and colourants was found in one third of our patients. The association of *Candida albicans* colonization in the stool is a very controversial issue.

Among the 190 patients, the most severe cases were, unsurprisingly, the 23% in whom no underlying pathology could be found. Perhaps some of them had autoantibodies against the Fcε RI receptor, as proposed by M. Greaves [5], who showed that urticaria can be provoked in patients with these antibodies by intradermal injection of autologous serum, a procedure we call the 'Greaves test'.

In a long-term observation of these 190 patients over at least 2 years, 70–75% of them were cleared. This included some who had had this condition for more than 30 years. In many cases, this result came together with a change in lifestyle: divorce, marriage, change of occupation, moving to a different city, etc. This observation emphasizes the importance of the psycho-social component in the pathophysiology of CU.

Pharmacotherapy of urticaria

H₁-receptor antagonists (antihistamines) have been used in the treatment of allergic diseases and urticaria for more than 50 years [1]. It is now well established that antihistamines are the treatment of choice — and in many cases all that is required — in the treatment of acute urticaria [6–8]. The treatment of urticaria is palliative rather than curative, and long-term treatment is the rule for the patient affected by CU, a disorder which may last for months or years with relapsing exacerbations.

Furthermore, it is clear that the newer, non-sedating second-generation H₁ antihistamines are as effective and safer compared to the first generation antihistamines. The older and newer antihistamines are essentially differentiated by their adverse event profiles, e.g. sedation and anticholinergic effects, which characterized the first-generation antihistamines.

It is now thought that H₂-histamine receptors may also be involved in producing the increased vascular permeability that results from histamine release in the tissues. For that reason, a combination of H₁ and H₂ antagonists has been tested in the prophylaxis and treatment of some allergic and pseudo-allergic reactions. For example, a beneficial effect of a combination of these two types of drugs has been observed in the prophylaxis of anaphylactoid reactions evoked by urea-linked gelatin solutions or by radiographic contrast media [9]. Other studies have shown a beneficial effect of this combination in patients with CU.

Drugs other than antihistamines have also been used in some patients with urticaria. While they are widely used in the treatment of other allergic diseases, glucocorticoids are not generally recommended for the treatment of urticaria. There is no rational reason to use topical corticosteroids to treat the urticarial lesions. Systemic glucocorticosteroids may be useful in patients who have been found to have anti-IgE autoantibodies. Mast-cell blockers are sometimes used, especially when a food allergy or pseudo-allergy is diagnosed. Other classes of drugs that are sometimes used include β_2 -agonists and intravenous infusions of γ -globulin, as well as interferon- γ and cyclosporin (both reserved for very

severe cases). Psychotherapy is used as an adjunct to psycho-social therapy when deemed necessary.

Mizolastine in the treatment of urticaria

Evidence of efficacy and safety

Two important clinical trials have demonstrated the effectiveness and safety of mizolastine in the treatment of CU. The first report on the effectiveness of mizolastine in the treatment of chronic urticaria was published by Brostoff *et al.* [10]. This group conducted a two-centre, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy and safety of mizolastine in English patients with chronic (idiopathic) urticaria. Fifty-six out-patients, mean age of 38 ± 15 years, 55% females, with a documented history of CU of at least 6-weeks duration, associated or not with angioedema, and symptoms of urticaria at least twice a week in the absence of treatment, were included.

The investigator assessed the patients for the presence of the main symptoms and signs of CU (itch, wheals and erythema), using a four-point scale for itch (0 = not present at all, 1 = mild: present but not inconvenient, 2 = moderate: inconvenient but not interfering with normal daily activities or disturbing sleep, 3 = severe: continuously present and interfering with sleep, normal activities or both), and for wheals and erythema (0 = not present, 1 = isolated patches, 2 = numerous patches, 3 = florid rash).

Each morning, the patient completed a diary to record the number of urticarial episodes in the previous 24 h, the intensity of the itching on a 10-cm visual analogue scale (VAS), the number of wheals, and the intensity of the angioedema (0 = absent, 1 = light, 2 = moderate with some disfigurement and/or sensation of tension, 3 = severe, disfiguring with considerable sensation of tension). Patients also assessed the global severity of their symptoms over the previous 3 days on days 0, 7 and 28 on a 10-cm VAS.

At the first assessment, a complete medical history was obtained, as well as a detailed allergy history. Patients received single-blind placebo medication for a variable period of 4–10 days. The patients were seen again on days 7 and 28 and assessed in the same way as initially. Treatment consisted of one tablet (10 mg mizolastine: $n = 28$ or placebo: $n = 28$) daily, taken in the evening for 28 days. Symptoms were scored every day by the patient and recorded on a diary card according to the above four-point scale.

The principal criteria were as follows: total urticaria symptom score, defined as the sum of the scores for itch, wheal and erythema, calculated by visit and by patient

according to the body region (lower limbs, upper limbs, face and trunk); global discomfort as recorded on the VAS. The number of responder patients who had at least a 50% decrease in the VAS score on the final visit was determined.

There were no significant differences between the two groups in demography and baseline disease characteristics. On average, the patients had had symptoms of urticaria for more than 3 years, with a mean weekly number of episodes of 4.7 and a mean duration of 8.3 h per episode. More than half the patients in each group reported angioedema, and 93% reported having previously been treated for this condition, predominantly with antihistamines.

Five patients in the mizolastine group and 17 in the placebo group discontinued prematurely the treatment, mainly in the first week of the study, due to lack of efficacy.

Mizolastine (M: 10 mg daily) was clinically superior to placebo (P) in alleviating the symptoms of urticaria as shown in Fig. 1 and Table 2. Efficacy was demonstrated from the first assessment (day 7) and was maintained to the end of the study. The decrease in the total urticarial symptom score and the global discomfort (data not shown) were significantly greater in the mizolastine group compared to the placebo group at day 7 and also

at the end of the study. Three-quarters of the patients treated with mizolastine were considered responder patients compared to only one-quarter in the placebo group. Improvement in overall itching occurred in significantly more mizolastine-treated patients (M) compared to those who received placebo treatment (P), at both day 7 (M = 71% vs. P = 25%, $P = 0.0001$) and on the final day of treatment (M = 68% vs. P = 18%, $P = 0.0003$). The results of this clinical study demonstrate that 10 mg daily of mizolastine is effective and safe in the treatment of CU.

Ring and colleagues also conducted a study of the efficacy and safety of mizolastine 10 mg daily compared to a placebo in patients with CU [11], which was a double-blind, placebo-controlled, multicentre study, carried out in 10 dermatology-allergy centres in Germany. Seventy-eight patients (mean age 40 ± 13 years, 60% female) suffering from chronic urticaria and with at least two episodes of urticaria during the 7-day run-in period were entered in our study. After this run-in period, the patients were evaluated on day 0 (baseline data) by the investigator and those included were allocated randomly to one of the two treatment groups. They were evaluated again after 14 and 28 days. The criteria for evaluation of the efficacy and safety of mizolastine were similar to those used in the study by Brostoff *et al.* [10]

Analysis of the data demonstrated that mizolastine-treated patients improved significantly compared to patients receiving placebo. As shown in Table 3, at day 0 the number of urticarial episodes per week during the week before the visit was comparable in the two patient groups. At day 14 and at the end of the study, there was an increase in the number of episodes per week in the placebo group and a decrease in the mizolastine group, the differences being statistically significant. There was also a statistically significant decrease in the mean daily number of urticarial episodes as recorded in the patients' diaries (Table 4). In addition, the mean total urticarial symptom scores, based on the severity of pruritus and the number and size of the urticarial wheals, were comparable at baseline (5.1 ± 2.5 for the mizolastine group vs. 5.1 ± 1.8 for the placebo group), whereas at

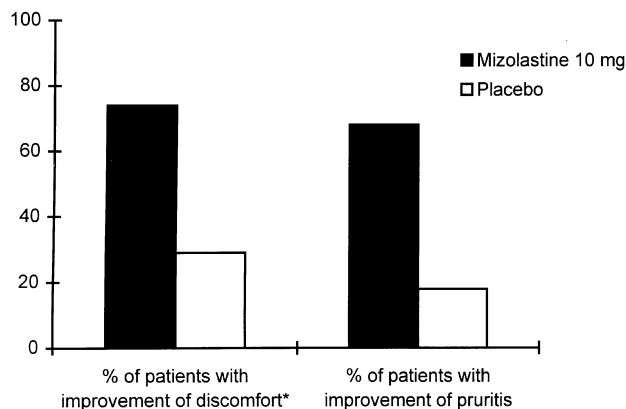


Fig. 1. Improvement in global discomfort and pruritus: percentage of responder patients. *Patient with VAS change score $> 50\%$ baseline; adapted from Brostoff *et al.* 1996.

Table 2 Improvement in total urticarial symptom score after 7 and 28 days of treatment with mizolastine 10 mg daily in comparison with placebo

	Mizolastine	Placebo	<i>P</i> *
Total urticaria symptom score			
Baseline	3.5 ± 1.7 (28)	3.2 ± 2.4 (28)	NS
Day 7	1.0 ± 1.7 (26)	2.4 ± 1.4 (28)	0.0004
Day 28	1.4 ± 1.8 (27)	2.8 ± 1.8 (28)	0.008
Day 7 – baseline	-2.5 ± 2.3 (26)	-0.8 ± 2.0 (28)	0.003
Day 28 – baseline	-2.1 ± 2.1 (27)	-0.4 ± 2.0 (28)	0.002

*Intergroup comparison; Adapted from Brostoff *et al.* 1996.

Table 3 Number of urticarial episodes during the week preceding the clinic visit in patients with CU treated for 28 days with mizolastine 10 mg daily vs. placebo, mean $\pm$ SD (number of patients)

	Mizolastine	Placebo	P*
At baseline	9.5 $\pm$ 7.7 (39)	8.9 $\pm$ 8.0 (38)	NS
Day 14	7.1 $\pm$ 7.2 (39)	10.4 $\pm$ 7.7 (39)	0.023
Day 28†	6.7 $\pm$ 6.1 (39)	9.2 $\pm$ 5.5 (39)	0.020

*intergroup comparison; †last available assessment; adapted from Ring *et al.* 1996

Table 4 Daily mean number of urticarial episodes, derived from the patient's diary in patients with CU treated for 28 days with mizolastine 10 mg daily vs. placebo, mean $\pm$ SD (number of patients)

	Mizolastine	Placebo	P *
Baseline	1.8 $\pm$ 1.2 (37)	1.3 $\pm$ 0.5 (33)	NS
Baseline $\rightarrow$ day 14	1.0 $\pm$ 0.8 (37)	1.4 $\pm$ 0.8 (33)	0.043
Day 15 $\rightarrow$ day end†	1.0 $\pm$ 0.9 (37)	1.4 $\pm$ 1.0 (33)	0.017
Baseline $\rightarrow$ day end†	1.0 $\pm$ 0.9 (30)	1.4 $\pm$ 0.7 (30)	0.043

*intergroup comparison; †last available assessment; adapted from Ring *et al.* 1996

the end of the study the mean score registered by the mizolastine group had decreased significantly (to 3.5 ± 2.6) while that of the placebo group had not (4.4 ± 1.5 ; P for the difference = 0.039).

The finding that treatment of CU patients with mizolastine 10 mg daily led to a significant decrease in the number of urticarial episodes per day and per week as well as a significant reduction in daily symptom scores, and also that there were no significant differences in side-effects between mizolastine and placebo, complements the results reported by Brostoff *et al.* [10]

Onset of action

In a clinical trial comparing 10 mg mizolastine and 10 mg loratadine vs. placebo daily, recently reported by Dubertret *et al.* [10], both drugs were associated with relief of symptoms compared to placebo throughout the treatment period. Most important, there was a sharp decrease in total urticarial symptom score over the first day with both active treatments, indicating that they had a rapid onset of action and gave prompt relief of symptoms.

Evidence of the duration of action of mizolastine

Lorette *et al.* [13] have recently reported the results of a study of the efficacy and safety of long-term treatment

with mizolastine in patients with CU. Two hundred and eleven patients (39.5 ± 13.0 years of age, 67% female) suffering from CU (21% with physical urticaria) were included in this open study. Patients received mizolastine 10 mg daily during the first month of treatment and could receive 15 mg daily if 10 mg was not sufficiently effective. Forty-one per cent of the patients dropped out of the trial before the twelfth month. From the first assessment after 2 weeks of treatment, significant improvement of global symptom discomfort (from the patients' VAS) was observed. The number of urticarial episodes was reduced from 5.4 ± 2.4 on day 0 to 1.1 ± 1.9 at the twelfth month. A significant reduction in itching was noted throughout the study: only 12% experienced moderate-to-severe itching at the twelfth month compared to 60% at day 0. The therapeutic effect was maintained throughout the study. No serious adverse events related to mizolastine intake occurred during the entire study period. Eleven per cent of the patients reported drowsiness at some time during the study. The authors concluded that the daily administration of 10 mg or, in some patients, 15 mg of mizolastine for up to a year safely and effectively relieves the symptoms in patients suffering from CU.

Evidence of the effectiveness of mizolastine in other urticarias

Acquired cold-induced urticaria (ACIU) is a relatively rare form of physical urticaria. The ice-cube test is used in the diagnostic workup of most patients with ACIU. The cold stimulation time test (CSTT), defined as the minimum time of cold contact stimulation required to induce an immediate coalescent wheal (CW) is also used in the diagnosis of this condition. Dubertret *et al.* [14] recently studied 28 patients (35 ± 17 years of age) suffering from ACIU for 6 ± 8 years in a double-blind, cross-over, placebo-controlled trial to evaluate the effect of mizolastine on the wheal response and the CSTT after an ice-cube test. Patients received mizolastine 10 mg or placebo daily in the first study period for 7 days and *vice versa* in the second period. On days 0, 7, 21 and 28, an ice cube was applied to the patient's forearm for up to 15 min, until a CW was induced. The diameter of the wheal was measured at 5, 10 and 20 min after removing the ice cube to allow for maximal wheal formation. When a positive ice-cube test was elicited, it was repeated at 3-, 6- and 10-min intervals to establish the CSTT. Pruritus was evaluated on a visual analogue scale (VAS). The results showed that the cold-induced wheal reaction was delayed (CSTT > 15 min) in 36% of the mizolastine-treated patients compared to only 14% of the placebo-treated patients ($P < 0.05$); that cold induced pruritus (mizolas-

tine vs. placebo, $P < 0.005$) and the CW at 3 and 10 min (mizolastine vs. placebo, $P < 0.01$ and $P < 0.009$, respectively) were decreased; and there was at least a 50% reduction in the total wheal response in 67% of the mizolastine-treated patients compared to 30% of the placebo-treated patients ($P < 0.001$). Safety of mizolastine was satisfactory. The authors concluded that mizolastine can be a safe and effective treatment for ACIU.

Conclusion

Urticaria is a common clinical disorder involving the skin and mucous membranes, with multiple aetiologies — undiscovered in many cases — and a complex pathophysiological mechanism in which histamine plays a major role. The newer second-generation H_1 antagonists, which now includes mizolastine, provide safe and effective symptomatic treatment for most urticaria patients.

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