Acquired cold urticaria (ACU) is a physical urticaria triggered by exposure of the skin to cold. ACU tends to have a chronic course, with a mean duration of 4–5 years, and is idiopathic in the majority of cases (1). In the management of physical urticarias, the avoidance of culprit stimuli is recommended, although prevention is often difficult or impracticable, so that symptomatic treatment is required. Second-generation H1-antihistamines, which exert additional antiinflammatory effects, are the mainstay of treatment in urticaria (2).

Randomized clinical trials recently documented the efficacy and tolerability of rupatadine (Pafinur®; Rottapharm SpA, Monza, Milan, Italy), an N-alkyl pyridine derivative with both peripheral H1- and platelet-activator factor (PAF)-receptor antagonist properties, in patients with chronic idiopathic urticaria (CIU) (3, 4). The effects of rupatadine on ACU symptoms have not been investigated so far.

We evaluated the efficacy of two different daily dosages (10 and 20 mg) of rupatadine in three nonatopic patients with idiopathic and refractory ACU whose clinical and general characteristics are shown in Table 1. The idiopathic nature of ACU was assessed after exclusion of conditions known to be associated with the disease (1). After discontinuation of any active treatment for at least 7 days, patients received rupatadine 10 mg/day for 2 weeks and then 20 mg/day for other 2 weeks, with a 7-day treatment-free interval between the two therapeutic phases. Patients underwent the ice-cube test at the time of enrolment and at the end of each treatment period. This test was performed applying an ice-cube (with an area of 6.25 cm²) protected by a plastic bag on the forearm skin for 5 min. A positive reaction was defined by the presence of erythema and oedema in the contact area 10 min after ice-cube removal (5). At this time the wheal area was measured. After each treatment regimen, patients were asked to assess the change of symptoms severity from baseline using a visual analogue scale (VAS) ranged from 0 (= no change or worsening of symptoms) to 10 (= complete relief). Details of clinical response and patients’ features are summarized in Table 1. In two patients (n. 1 and n. 2 in the table) a marked improvement of symptoms, with a reduction of skin reactivity to the ice-cube application, was observed after rupatadine treatment, without significant differences between the two doses. In the third patient rupatadine at both dosages did not cause any relevant variation in the ice-cube test response as compared to baseline, although the patient’s self-

Table 1. Demographic and clinical features and outcome of rupatadine treatment in three patients with ACU

| n | Sex | Age (years) | Duration (months) | Triggers/Remarks | Previous treatments proved ineffective | Baseline Ice-cube test area (cm²) | VAS | Ice-cube test area (cm²) | VAS | Ice-cube test area (cm²) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 29 | 36 | Cold air, water and objects | Levocetrizine, fexofenadine and cyproheptadine (also at doses twofold higher than standard dosage) | 86.24 | 7 | 32.86 | 9 | 29.12 |
| 2 | F | 43 | 48 | Cold air (wind), objects, water, even raindrops. Generalized wheals during immersion in seawater | Levocetrizine; desloratadine alone or combined with montelukast (10 mg/day); ebastine alone or combined with ranitidine (150 mg/day) | 72.25 | 8 | 26.88 | 8 | 25.65 |
| 3 | F | 32 | 36 | Cold objects and water. Angioedema of the tongue eating an ice-cream | Cetirizine, levocetrizine and fexofenadine | 63.36 | 6 | 58.32 | 6 | 56.07 |

ACU, acquired cold urticaria; F, female; VAS, visual analog scale of relief after treatment with rupatadine from 0 (= no change/worsening of symptoms) to 10 (= complete relief of symptoms).
evaluation suggested an improvement of ACU symptoms over the course of rupatadine intake. Treatment was well tolerated and no adverse events, including somnolence, occurred.

Pathogenesis of ACU is still unknown. Histamine release after cold challenge in ACU patients has been widely demonstrated, but other proinflammatory mediators, such as PAF, were found to be released (6). The clear efficacy of rupatadine in two of our patients with ACU poorly responsive to other H1-antihistamines might be due not only to the antihistamine activity of the drug, but also to its inhibitory action on PAF. In addition, we were unable to detect differences in clinical response between two different dosages of rupatadine. These findings appear to be in agreement with the results of the phase III trial of rupatadine in CIU patients which failed to disclose any significant differences in efficacy between 10 and 20 mg/day (3), although the phase II study showed a greater effect of the daily dose of 20 mg on pruritus severity as compared to the 10-mg dose (4).

In conclusion, rupatadine seems an effective and safe antihistamine drug for the treatment of ACU, although controlled studies in larger patient samples are needed.

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**Immediate allergic reaction to atropine in ophthalmic solution confirmed by basophil activation test**

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**Key words:** allergy to mydriatics; atropine; basophil activation test.

We present the case of a 9-year-old girl, remitted to our department by the department of General Surgery after being diagnosed of incarcerated umbilical hernia that required surgery treatment.

The patient relates background of corneal opacities with loss of the right eye under periodic ophthalmic examination. This is the reason why, at the age of 7 months, she underwent pupil dilation with atropine; immediately after administration of a unique drop, she presented erythema and generalised oedema. She had undergone previous ophthalmic examinations, but the parents did not remember whether pupil dilation with atropine had been performed. No other known background of allergic processes.

After that incident, atropine was not used in other pupil dilations and the patient did not present any similar reaction.

Skin test with inhalant allergens and specific IgE determination to latex (0.01 kU/l) were negative. Skin tests with atropine, prick (1 mg/ml) was negative and intradermal test was positive with atropine 0.1 mg/ml (papule of 10 × 8 mm; histamine 11 mm x 8 mm). Ten controls were performed with atropine, all of them with negative result. The basophil activation test (BAT) was positive with atropine [basal activation: 0.60%; anti IgE: 4.50%; atropine 1.25 μg/ml (first dilution): 1.10%, and atropine 0.3 μg/ml (second dilution): 10.70%]. Three controls were performed with negative results.

The patient was diagnosed of allergy to atropine and was advised to avoid the administration of belladonna alkaloids (atropine, butylscopolamine, etc.). Subsequently, she underwent without problems surgery of umbilical hernia under general anaesthesia where neither atropine nor any other anticholinergic drug was used.

Atropine has been described to produce allergic and non-allergic reactions. Among the allergic ones anaphylactic reactions have been described (1). Allergic reactions to mydriatic eye drops are rare, with a prevalence of 6% and can be induced by the active pharmacological agent, by the preservatives or by other additives. The most frequently involved mydriatic is the phenylephrine (50–90% of the cases). In most cases they are induced by a type IV hypersensitivity being the type I mechanism rare, like in our case. We did not find in the literature any cases of immediate allergy to atropine after its administration in drops as a mydriatic although some cases of intraoperative anaphylaxis after intravenous administration of atropine have been described (2, 3).

**Atropine used as a mydriatic drug can induce type I hypersensitivity reactions. The basophil activation test is a useful tool to confirm these cases.**