

Short communication

Acquired cold urticaria symptoms can be safely prevented by ebastine

Background: Acquired cold urticaria (ACU) is a skin condition, in which exposure to cold results in wheals and itching and sometimes general systemic complications. It has a profound impact on patient quality of life. Second-generation antihistamines are recommended as the first-line treatment, but to date only a few have been scientifically tested for this condition.

Aim: To assess the safety and efficacy of ebastine in preventing ACU symptoms.

Methods: Twenty-two adult ACU patients participated in a double-blind crossover trial of 20 mg ebastine. The safety of ebastine was sensitively assessed with a psychometric battery testing cognitive performance and mood. After cold challenge, wheal and erythema were assessed by the investigator and the intensities of pruritus and burning were rated by the subject.

Results: Ebastine had no negative impact on any of the parameters of cognitive performance or mood. It dramatically reduced the number of patients who experienced wheals, pruritus, and burning after challenge.

Conclusion: Ebastine is safe and effective in preventing the symptoms of ACU.

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Key words: acquired cold urticaria; ebastine; histamine;
mast cells.

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Accepted for publication 24 June 2007

Urticaria is a common skin condition with a wide range of subtypes. It is characterized by the rapid appearance of wheals and sometimes angioedema (1–3). The wheals are associated with an itching or burning sensation, while the angioedema is sometimes painful rather than itchy. Most subtypes of urticaria have a profound impact on patient quality of life, necessitating effective treatment (2, 4, 5). The physical urticarias are chronic conditions triggered by their respective namesake physical factors (1, 2). Their pathogenesis remains mostly unclear, but it is known that mast cell degranulation releases histamine and other mediators, thus causing the wheal-and-flare reaction (2, 6, 7).

Acquired cold urticaria (ACU) is defined as an urticarial reaction upon exposure to cold. Lesions usually appear only on the cold-exposed skin but can be generalized. ACU patients exposed to cold are at risk of systemic symptoms and even life-threatening complications (6–8). Diagnosis is made on the basis of the history and cold challenge tests (6, 7, 9, 10). In the vast majority of patients, ACU is idiopathic, but in rare cases it may also result from infections, neoplasms, or autoimmune diseases, which should be treated directly (2). ACU affects mainly young adults and is twice as frequent in women (6, 7, 11). Untreated, it has a mean duration of 4–5 years (11). As in all physical urticarias, avoidance of the triggering factors is a basic part of managing the condition (5).

Second-generation antihistamines have been recommended by the most recent guidelines as first-line treatment for urticaria (5). These medications have been widely used in chronic urticaria, one of 14 urticaria conditions in which they have been shown to be safe and effective (5). So far though, there have been only four studies on second-generation antihistamines in ACU (5). Moreover, unresponsive patients are more than rare exceptions, and expert opinion holds that individuals respond differently to various antihistamines (5). Therefore, there is a need for more efficacy studies on multiple antihistamines.

The present trial investigates ebastine in ACU. Ebastine is a selective, long-acting, nonsedating, second-generation antihistamine. It has been reported to be safe and effective in the treatment of allergic rhinitis and chronic idiopathic urticaria (12). Here, we present our findings on its safety and efficacy for ACU.

Methods

Study design

This study was designed as a double-blind, crossover, placebo-controlled, investigator-initiated trial. It was approved by the Charité Ethics Committee and conducted according to the Declaration of Helsinki, applicable laws, and further guidelines. The

protocol randomly assigned the subjects to two groups. Group A received ebastine 20 mg 10 ± 2 h before visit 1 and placebo 10 ± 2 h before visit 2, whereas group B received them in the reverse order. Compliance was explicitly checked. The two visits were separated by a washout period of at least 7 days. At each visit, ACU symptoms were experimentally provoked with a 4°C cold pack for 5 min on two 10×20 cm areas of the forearms at time point 0 : 00. If needed, rescue antihistamines were administered after each visit.

Subjects

Subjects were recruited from our outpatient clinic. The inclusion criteria were: (1) age 18–70, (2) ACU for at least 6 weeks, (3) presence of wheal and itch symptoms, (4) history of beneficial effects of antihistamine treatment, and (5) ability to assess symptom scores and to perform psychometric tests. Patients were excluded for any criteria from a list of medical conditions or drug intakes that could interfere with the study or put them at extra risk. Prior to enrollment, patients were informed about the study and its risks, and written informed consent was obtained. The study enrolled 22 patients, 20 (91%) of whom were female. The median age was 43.5 years, with an interquartile range of 35–55.

Safety outcome measures

At each visit, open questions about adverse events were put to the patient and all information was recorded and coded.

Cognitive performance and mood were assessed at each visit before challenge testing using a psychometric battery that consisted of three standardized tests: (1) Differential Attention Test (DAKT), (2) Vienna Test System's Determination Test (DT), form S1 – short adaptive, and (3) Profile of Mood States (POMS), German short version (13). The DAKT measures perceptual speed and perceptual accuracy. The DT measures reaction capacity, confusion/impaired attention, and resignation. The German POMS measures four mood factors: depression, anger, vigor, and fatigue.

Clinical outcome measures

Symptom severity was evaluated +0 : 10 after challenge at each visit. The clinician recorded the development of urticaria wheals and erythemas at the skin challenge site. The subjects evaluated their pruritus and burning on a 4-point scale (none, mild, moderate, and severe).

Statistics

All statistical analysis was performed with SPSS 14.0.1 or DELTA-GRAPH 4.05. Primary parameters were assessed by paired tests between both phases in each group. Psychometric assessments were analyzed by independent *t*-tests. Clinical outcome was assessed by a two-sided chi-squared test (Fisher's exact test).

Results

Safety

No adverse events were registered in any of the subjects.

Cognitive performance remained virtually identical under both study conditions. Perceptual speed (Fig. 1A), perceptual accuracy (Fig. 1A), and reaction capacity (Fig. 1B) remained undiminished under ebastine compared to placebo. Likewise, ebastine did not raise the low levels of confusion/impaired attention or resignation (Fig. 1B).

Mood states also remained virtually the same under both study conditions (Fig. 1C). There was no noteworthy or statistically significant change in the scores on the scales for depression, anger, vigor, and fatigue.

Efficacy

Ebastine was significantly effective in preventing the signs and symptoms of urticaria from cold challenge (Fig. 2).

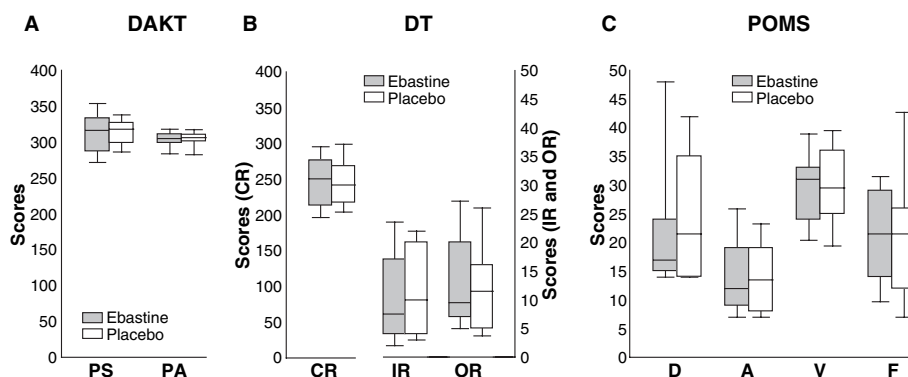


Figure 1. Psychometric assessment of the safety of ebastine as prophylaxis against cold urticaria. All panels present box-and-whisker plots, whereby the box's internal midline represents the median score, the box ends represent the interquartile range, and the whisker ends represent the 10th percentile. Ebastine is presented in gray, placebo in white. (A) Differential Attention Test (DAKT), presents the perceptual speed (PS) and perceptual accuracy (PA). (B) Determination Test (DT), presents the correct reactions (CR), the incorrect reactions (IR), and the omitted reactions (OR), which, respectively, represent reaction capacity, confusion/impaired attention, and resignation. (C) Profile of Mood States (POMS), presents four mood factors: depression (D), anger (A), vigor (V), and fatigue (F).

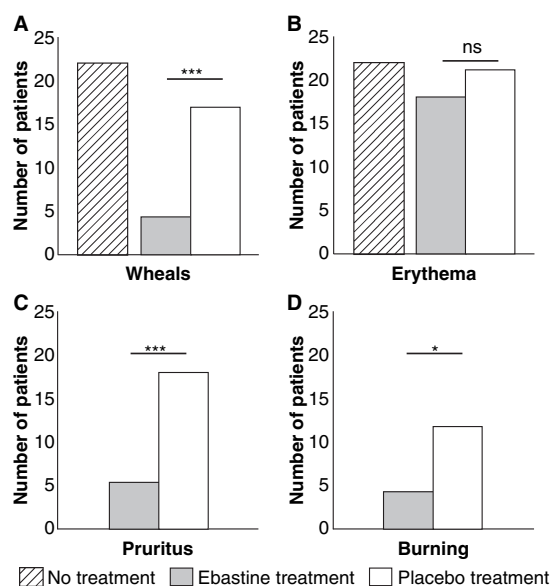


Figure 2. Clinical evaluation of the efficacy of ebastine as prophylaxis against cold urticaria. The presence of wheals (A) and of erythema (B) at the cold provocation site was assessed by the clinician and is presented as the number of patients with vs without these symptoms after cold challenge. The 'No Treatment' columns show that all 22 subjects experienced both wheals and erythema in response to cold challenge at the initial screening for the trial, as per the formal inclusion criteria of the study. Pruritus (C) and burning (D) were rated by the patients on a 4-point scale (none, mild, moderate, and severe), and patients rating these symptoms as moderate or severe are grouped together as having the symptom. * $P < 0.05$, *** $P < 0.001$, ns = not significant.

Of the 22 ACU patients subjected to cold challenge, only four experienced wheals after ebastine treatment, whereas 17 patients experienced wheals after placebo treatment (Fig. 2A, $P < 0.001$). Similarly, the number of patients who experienced moderate or severe pruritus dropped to 5 after ebastine treatment when compared to 18 after placebo treatment (Fig. 2C, $P < 0.001$), and the number of patients experiencing a moderate or severe burning sensation was reduced to 12 and 4 by placebo and ebastine treatment, respectively (Fig. 2D, $P < 0.05$). As expected, ebastine treatment did not alter erythema development, either because erythema is the physiologic skin response to cold challenge or because antihistamines do not normally alter erythema, because it is driven by neuropeptides (Fig. 2B).

Discussion

Second-generation antihistamines are the recommended first-line treatment for physical urticarias, but so far only

four have been shown to be effective for ACU (5). The sedative antihistamine cyproheptadine has also repeatedly shown efficacy for cold urticaria (14–16). Because the individual response to different antihistamines may vary and a portion of patients may not benefit from a given antihistamine, clinicians need a selection of proven antihistamines to individualize the treatment for each patient. This double-blind, crossover trial provides evidence that ebastine is suitable for preventing ACU symptoms.

Before even starting the trial, we already knew from past studies that ebastine is well tolerated, non-sedating, and safe (12). So, we designed our study to use sensitive, analytical psychometric tests, which could detect more subtle and more specific changes in the cognitive performance or mood state of the subjects. (Of course we nonetheless checked also for adverse events, and as expected, none was reported.) As can be seen by comparing the median and interquartile range for any of these parameters (Fig. 1), there was no appreciable difference between ebastine and placebo. This is consistent with the fact that second-generation antihistamines do not easily cross the blood–brain barrier. These findings indicate that ebastine would not significantly interfere with the patients' performance at school or work, nor alter their mood and social interactions.

Ebastine was effective in preventing the signs and symptoms of ACU after challenge. The vast majority of patients (17 of 22) no longer reacted with wheals. The number of patients who reported moderate and severe pruritus or burning was also dramatically reduced. In contrast, ebastine did not have a significant effect on erythema, which suggests that it does not interfere with the physiologic skin response to cold. Urticaria patients often require higher dosages of antihistamines, up to four times the standard (5). Here, we used 20 mg, which is the higher of the manufacturer's two standard dosages for the treatment of allergic rhinitis. This standard dose was already effective for the majority of subjects.

In conclusion, this double-blind crossover trial shows that ebastine is safe and effective for patients with ACU.

Acknowledgments

These studies were supported by GA²LEN and the urticaria network e.V. and, in part, by grants from Almirall and the European Centre of Allergy Research Foundation (ECARF). We thank Hesna Gözlükaya and Nikki Rooks for excellent technical assistance; Gerald Spletstößer for statistical analyses; Michael Hanna PhD (Medical Manuscript Service, New York) for providing medical writing services; and Jodie Urcioli for proof reading the manuscript.

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