

Critical temperature threshold measurement for cold urticaria: a randomized controlled trial of H₁-antihistamine dose escalation

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Summary

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Conflicts of interest

M. Magerl is, or was recently, a speaker for Almirall, Essex Pharma and Jerini/Shire. P.S. is, or was recently, involved in clinical trials supported by Essex Pharma (now MSD) and has been compensated for educational lectures by Essex Pharma (now MSD), Novartis and Shire. M.K.C. has received honoraria for lectures or consulting from UCB Pharma, Glaxo Smith Kline, Aventis, FAES Pharma and Schering Plough. M. Maurer is, or was recently, a speaker and/or advisor for Almirall Hermal, Bayer Schering Pharma, Biofrontera, Essex Pharma, Genentech, JADO Technologies, Jerini, Merckle Recordati, Novartis, Sanofi Aventis, Schering-Plough, Leo, MSD, Merck, Shire, Symbiopharm, UCB and Uriach. D.P. and P.M. declare no conflicts of interest. None of the authors has patents or commercial interests in products in development or marketed products to declare.

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Cold urticaria is a rare but severe and potentially lethal condition. It is characterized by itchy weal and flare responses in areas of the skin exposed to the cold. However, life-threatening angio-oedema and anaphylaxis may occur after ingestion of cold foods and systemic exposure to cold, respectively. It is essential, therefore, to be able to predict the potential risk that

Background Cold urticaria is a rare but severe and potentially lethal condition. It is primarily treated symptomatically with H₁-antihistamines. However, patients have a variable response to these drugs and, to date, it has not been possible to predict readily the response to therapy of individual patients.

Objectives To assess the severity of the cold urticaria in naive patients and the response to therapy of patients treated with increasing doses of an H₁-antihistamine by measurement of critical temperature thresholds (CTT) for producing weals on the forearm.

Methods This was a two-centre, hospital-based, double-blind, randomized, parallel-group study of patients with a confirmed diagnosis of cold urticaria of at least 6 months' duration. Patient groups received either a constant dose of desloratadine 5 mg daily for 6 weeks (n = 13), or escalating doses of desloratadine: 5 mg daily for the first 2 weeks, 10 mg daily for the second 2 weeks and 20 mg daily for the final 2 weeks (n = 15). Only one adverse event that appeared to be drug related was reported: mild fatigue after treatment with desloratadine 10 mg that lasted for about 3 weeks and resolved at the end of the study.

Results The desloratadine 5 mg daily dose produced a submaximal reduction of mean CTT which remained relatively constant over 6 weeks. Dose escalation increased efficacy, the reduction in mean CTT at four-times the standard daily dose being significantly greater (P = 0.03) than with the standard dose. Individually, no patient became symptom free (CTT < 4 °C) on 5 mg, while two became symptom free on 10 mg and a further three on 20 mg desloratadine daily.

Conclusions Measurement of CTT allows for individualized risk management and therapy in patients with cold urticaria.

each individual patient faces and how this may be ameliorated by therapy.

It has recently become possible to measure critical temperature thresholds (CTT) for production of weal responses on discrete areas of the skin using a Peltier effect-based electronic device (Temp Test[®]; Emosystems, Berlin, Germany).^{1,2} Using

this device, CTT and changes in CCT are correlated with disease severity and with changes in disease activity, respectively, in patients with cold urticaria.³ Furthermore, it has been shown that rupatadine 20 mg daily for 7 days caused a median 8 °C decrease in CTT,⁴ and desloratadine 20 mg was more effective than desloratadine 5 mg for 7 days in reducing CTT.⁵

This double-blind, parallel-group study extends the previous observations by using the measurement of CTT to predict the potential risk of cold urticaria in untreated patients and the response to therapy following treatment with either a standard or increasing doses of an H₁-antihistamine as recommended in the European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization urticaria guidelines.⁶

Methods

This was a double-blind, randomized, parallel-group study in which patients with a confirmed diagnosis of cold urticaria of at least 6 months' duration were recruited from the Departments of Dermatology Charité-Universitätsmedizin, Berlin and Johannes Gutenberg-Universität, Mainz. The study was approved by the ethics committee of the State of Berlin (EudraCT number: 2008-005746-22) and was conducted according to the Declaration of Helsinki and the 'Good Clinical Practice, Standard Operating Procedures of the Allergy Centre Charité and the Coordination Centre for Clinical Studies of the Charité-Universitätsmedizin Berlin'. The clinicaltrials.gov identifier number is NCT01444196. Recruitment began in August 2009 and the study was completed in May 2010. All participants gave signed informed consent at the beginning of the study.

Protocol

Patients were assigned to one of two groups, designated group A and group B. Group A received a constant dose of desloratadine 5 mg daily for 6 weeks. Group B received escalating doses of desloratadine: 5 mg daily for the first 2 weeks,

10 mg daily for the second 2 weeks and 20 mg daily for the final 2 weeks (Fig. 1). CTTs, defined as the highest temperature which produces a positive weal response,⁵ were determined before and at 2-week intervals after the commencement of drug therapy. If, at the end of any 2-week period, any patients were symptom free, i.e. they had a CTT of < 4 °C, they were withdrawn from the study.

CTT were determined using a Temp Test[®] 3.0 (Emosystems), a Peltier effect-based electronic device designed specifically for diagnosing and monitoring symptoms of cold contact urticaria.² The temperature head of this device, which was placed directly on the volar surface of the forearm, consists of 12 elements, each 10 mm in diameter, arranged in two parallel rows. The device was set to deliver temperatures of 26, 24, 22, 20, 18, 16, 14, 12, 10, 8, 6 and 4 °C (each ± 0.1 °C) to the skin for a constant period of 5 min. Photographs of a patient's response to cold challenge with this device are shown in Figure 2.

Assignment

Thirty patients (age range 21–66 years) were randomized into two groups of 15, this size being estimated using a power of 80% (t-test) with a two-sided significance level of 5% and a medium effect of 1.2 SD. Patients were randomized by receipt of sequentially numbered packages of capsules as described below. None of the participants had used topical corticosteroids or taken H₁- or H₂-antihistamines or leukotriene antagonists for 1 week or systemic corticosteroids for 4 weeks before the start of the study.

Masking

Production, randomization and blinding of study medication – identical capsules containing desloratadine 5, 10 or 20 mg – were performed by the pharmacy of the Charité-Universitätsmedizin Berlin, after approval by the BfArM (Federal Institute for Drugs and Medical Devices) and a positive evaluation by the competent ethics committee. The pharmacy has a manufacturing authorization according to Section 13 AMG (German

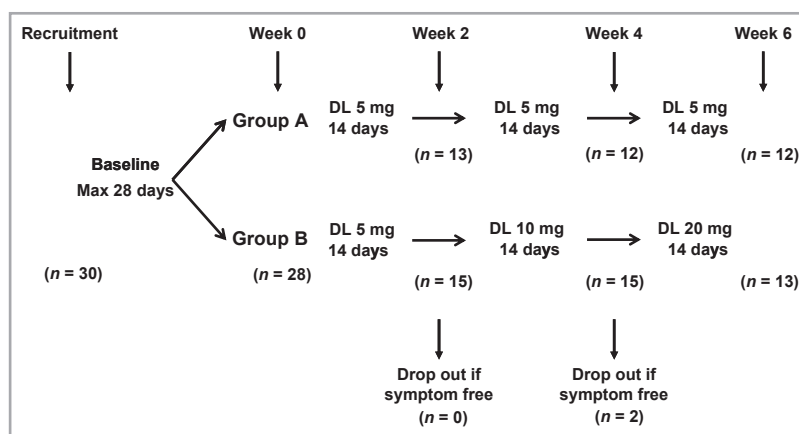


Fig 1. Diagrammatic representation of the protocol and flow of participants. DL, desloratadine.

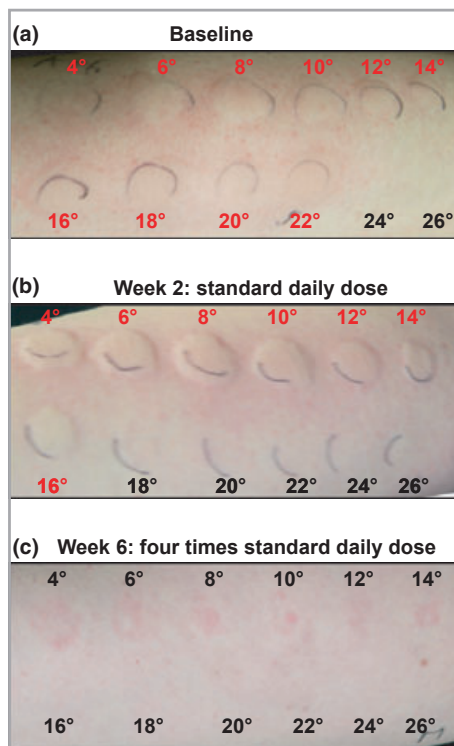


Fig 2. Photographs of a patient from group B showing: (a) a baseline critical temperature threshold (CTT) of 22 °C; (b) a CTT of 16 °C while receiving a standard daily antihistamine dose; and (c) a CTT of < 4 °C while receiving four-times the standard daily antihistamine dose. Temperatures in red indicate the presence of weals and those in black the absence of weals.

Drug Act) for clinical specimens. The packages received by the investigators were numbered sequentially.

Participant flow

Twenty-seven patients completed the study and were included in the analysis, 12 in group A and 15 in group B. Two patients were excluded at the randomization visit because of lack of symptoms and one failed to complete the study for personal reasons.

Follow-up

As this was a study involving a licensed and widely used H₁-antihistamine, no formal follow-up was undertaken. However, there were no reported adverse responses after the end of the study.

Analysis

As the data were normally distributed, the significance of differences in CTTs at different times within groups was calculated using Student's *t*-test for paired data. Differences between groups were calculated using Student's *t*-test for

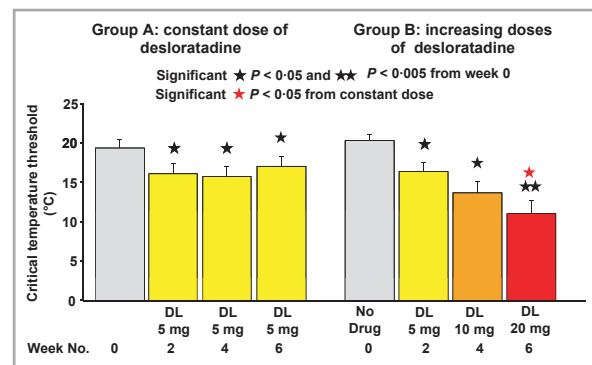


Fig 3. The mean (+SEM) critical temperature threshold values throughout the study. Group A contained 12 patients throughout and Group B contained 15 patients for the first 4 weeks and 13 patients at week 6. DL, desloratadine.

unpaired data. The differences between the numbers of patients obtaining complete remission of symptoms at different times within groups were tested using Fisher's exact test.

Results

There was no significant difference between the baseline CTT of two groups, the mean ($\pm$ SEM) values being 19.3 ± 1.2 and 20.3 ± 0.8 °C for groups A and B, respectively (Figs 3 and 4). A standard daily dose of desloratadine (group A) produced a statistically significant reduction of CTT values, which remained relatively constant over the 6-week period. In contrast, dose escalation (group B) resulted in increased effects, with the reduction in mean CTT at four-times the standard daily dose being significantly greater than with the standard dose. The reduction in CTT with desloratadine 20 mg was significantly greater than with desloratadine 5 or 10 mg ($P = 0.003$ and $P = 0.037$, respectively). Furthermore, the reduction in CTT with desloratadine 20 mg was significantly greater ($P = 0.008$) than with desloratadine 5 mg at 6 weeks in group A.

Of the 12 patients in group A (Fig. 4), only one showed a strong effect (a reduction in CTT of > 6 °C), five showed a weak effect (a reduction in CTT of 4–6 °C), and in the remaining six the effect was negligible (a reduction in CTT of 2 °C or less). None showed complete remission of symptoms (no weal at 4 °C). Of the 15 patients in group B, two showed complete remission of symptoms on desloratadine 10 mg at 4 weeks and were withdrawn from further participation in the study. Of the remaining 13 progressing to 20 mg daily, three showed complete remission of symptoms, five showed a strong effect, one showed a weak effect (a reduction in CTT of 4–6 °C), and in the remaining four the effect was negligible. The number of patients with complete remission of symptoms was significantly ($P = 0.008$) greater in the dose escalation group compared with the constant dose group. There was no correlation between the starting CTT of untreated patients and the CTT after the final week of therapy

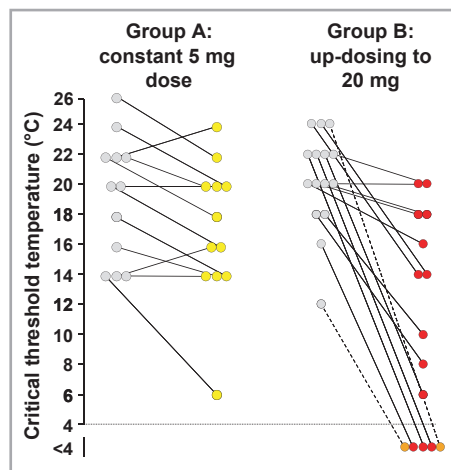


Fig 4. Individual critical temperature thresholds (CTT) with desloratadine therapy in cold urticaria. Group A: patients received a constant 5 mg dose of desloratadine (grey circles, CTT at baseline; yellow circles, CTT at 6 weeks). Group B: patients received an escalating dose of desloratadine (grey circles, CTT at baseline; orange circles with broken line, CTT of patients who became symptom free on 10 mg daily at 4 weeks; red circles, CTT of the remaining patients at 6 weeks on 20 mg daily).

in either group (group A: $r = 0.11$, $P = 0.733$; group B: $r = 0.22$, $P = 0.437$).

Eight adverse events were reported in group A and 19 in group B. This difference was not statistically significant ($P = 0.22$, chi-square test for trend). Only one adverse event appeared to be drug related – mild fatigue after treatment with desloratadine 10 mg that lasted for about 3 weeks and resolved at the end of the study.

Discussion

Patients with cold urticaria exhibit a wide variability in terms of their risk when untreated. Treatment of one group with a standard licensed 5 mg dose of desloratadine, although giving a statistically significant reduction in CTT, was poorly effective in clinical terms. Efficacy did not increase after the first 2 weeks by which time steady state levels would have been reached.⁷ In the other group, nine of the 10 patients who showed significant improvement responded dose-dependently with increasing H₁-antihistamine doses. In addition, some patients (~30%) experienced complete protection when treated with desloratadine 10 or 20 mg daily while other patients (~20%) did not show a significant reduction of CTT even with high-dose H₁-antihistamine treatment.

The strength of this study is the use of CTT determination to assess quantitatively the severity of cold urticaria and the response to therapy in individual patients. Clearly, this is a major advance from the 'ice cube' test which has been in routine use for some 35 years.⁸ Further, the dose escalation used in this study to determine the responsiveness of individuals to H₁-antihistamine therapy advances the three proof-of-concept studies measuring CTT.^{3,5} The weakness of the study is that

no correlations with the clinical severity of the condition were made in these individuals. However, a previous study in which the severity and activity of cold urticaria were assessed using Likert scales significantly correlated with CTT.³

From the practical viewpoint, the measurement of CTT allows for individualized management and advice to patients with cold urticaria so allowing for a better and personalized management of disease. Clearly, the CTT determined by the Peltier method reflect the skin temperature rather than air temperature. Thus, positive advice may be given about physical stimuli that touch the skin directly, e.g. the minimum tolerable water temperature in a swimming pool or shower, for drinks or for washing vegetables under the tap. However, although less easy to explain, patients must also be aware that low air temperatures may also be problematical, e.g. wind chill temperature has an impact and can cool down the skin to very low temperatures.

From a therapeutic viewpoint, the measurement of CTT allows for the identification of the lowest effective dose of H₁-antihistamine for individual patients and the rapid identification of patients who are not responsive to H₁-antihistamine therapy.

In conclusion, this study shows that the measurement of CTT allows practising clinicians to individualize therapy and advice to patients with cold urticaria so allowing for a better and personalized management of this potentially lethal disease.

What's already known about this topic?

- Cold urticaria is a rare but severe and potentially lethal condition.
- It is primarily treated symptomatically with H₁-antihistamines. However, patients have a variable response to these drugs and to date it has not been possible to predict readily the response to therapy of individual patients.

What does this study add?

- Determination of critical temperature thresholds (CTT) for producing weals on the forearm can determine the severity and response of cold urticaria to H₁-antihistamine therapy.
- Dose escalation of desloratadine at 2-weekly intervals from 5 to 20 mg daily produced significantly greater efficacy than a constant daily 5 mg dose for 6 weeks.
- Measurement of CTT allows for individualized risk management and therapy in patients with cold urticaria.

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