H₁-antihistamine inhibition of histamine and codeine-induced wheals does not predict response in chronic cold urticaria

Marina Gorczyza¹, Laia Curto-Barredo², MD, Karoline Krause¹, MD, Martin K. Church¹, MD, Tomasz Hawro¹, MD, Martin Metz¹, MD, Ana Giménez-Arnau², MD, Marcus Maurer¹, MD

¹Department of Dermatology and Allergy, Allergie-Centrum Charité, Charité - Universitätsmedizin Berlin, Germany

²Department of Dermatology, Hospital del Mar, Institut Hospital del Mar d'Investigacions Mèdiques(IMIM), Universitat Autònoma de Barcelona

Corresponding author

Marcus Maurer, MD,

Professor of Dermatology and Allergy

Director of Research, Allergie – Centrum Charité/ECARF

Dept. for Dermatology and Allergy

Charité – Universitätsmedizin Berlin

Charitéplatz 1, 10117 Berlin, Germany

Tel: +49 30 450 518 043

Fax: +49 30 450 518 972

Email:marcus.maurer@charite.de

Email addresses of the authors: marina.gorczyza@charite.de,
lculto@parcdesalutmar.cat, karoline.krause@charite.de, M.K.Church@soton.ac.uk,
tomasz.hawro@charite.de, martin.metz@charite.de, 22505aga@comb.cat,
marcus.maurer@charite.de

Funding: The study was funded by an unrestricted grant from J. Uriach & Co., SA, Barcelona, Spain.

Word count: 955

Clinical implications: The effects of an H₁-antihistamine on skin responses to injected histamine do not reflect responses of clinical symptoms in patients with chronic cold urticaria. According to our findings, H₁-antihistamine dosing should be based on clinical effects and/or effects on cold provocation testing.

TO THE EDITOR:

Chronic cold urticaria (ColdU) is a rare but debilitating disease characterized by the development of wheal and flare type skin reactions, angioedema, or both after skin exposure to cold. Extensive cold contact (e.g. swimming in cold water) may lead to systemic reactions including generalized urticaria and anaphylactic shock (1). Because of this, ColdU patients require prophylactic treatment to prevent cold-induced symptoms.

The symptoms of chronic cold urticaria are caused by the activation and subsequent degranulation of skin mast cells and their release of proinflammatory substances, with histamine purported to be the main driver of wheal development (2). Histamine induces vasodilation, increases vascular permeability, and leads to the appearance of wheals and angioedema (3). As a consequence, second generation H₁-antihistamines are recommended as the first line therapy for ColdU by the current EAACI/GA²LEN/EDF/WAO guideline on urticaria and the EAACI/GA²LEN/EDF/UNEV recommendations on chronic inducible urticaria (4, 5).

In clinical practice, some ColdU patients require higher than standard doses of H₁-antihistamines for them to work, and in up to a third of cold urticaria patients even higher doses of H₁-antihistamines do not result in complete symptom prevention (6, 7). At present, finding the correct dose of the right antihistamine for each patient is a matter of “trial and error” as neither disease severity or duration nor other markers predict treatment responses. Predictors of response to treatment would be helpful for the management of ColdU patients.

The effects of H₁-antihistamines on wheals induced by histamine or the mast cell degranulator codeine have been claimed to correlate with the clinical responses to antihistamines in patients with mast cell-driven diseases including urticaria (8, 9). To ascertain whether this is also true for ColdU, we performed a placebo-controlled crossover study with 20 mg rupatadine daily for one week. First, we observed the inhibition of the response to intradermal injections of histamine and codeine. Then, we assessed the inhibition of a cold urticaria provocation test by measuring the change in critical temperature thresholds (6).

The study was a two-centre, randomized, double-blind, placebo-controlled, crossover study, in which patients with a confirmed diagnosis of ColdU of at least 6 months' duration were recruited from the Departments of Dermatology Charité - Universitätsmedizin, Berlin and Hospital del Mar IMIM UAB, Barcelona. The study was approved by the ethics committee and authorities of the State of Berlin and Barcelona (EudraCTnumber: 2011-004094-93) and was conducted according to the Declaration of Helsinki and applicable local and European laws and regulations. The clinicaltrials.gov number is NCT01605487. Details of the study design and primary readout have been recently reported (7).

In this crossover study, 23 patients with ColdU (17 female, mean age 45 years, range 19-68 years) were allocated randomly to receive rupatadine 20 mg or placebo daily for one week each, with a 2 week washout period between treatments. Patients were injected intradermally with 0,05 ml each of histamine (Histamine dihydrochloride 0.01%, ALK Scherax, Germany), codeine (Codeine phosphate 0.09%, Charité – Universitätsmedizin Berlin pharmacy, Germany) and saline (0.9%, B Braun, Germany) as negative control at the end of both treatment periods. Wheal and flare diameters were measured with a transparent ruler 15 minutes thereafter, and the largest diameters were recorded. This was followed by cold provocation testing with TempTest® 3.0 (EMO Systems GmbH, Berlin, Germany). This is a Peltier element-based electronic device, which allows simultaneous testing of temperatures from 4 to 42°C in a reproducible and standardized way for diagnosis of ColdU and assessment of critical temperature thresholds (CTTs), i.e. the highest temperature that induces a wheal response. The CTT was determined for each patient before and after treatment. In patients who did not develop a wheal at the lowest temperature tested (4°C), the CTT was recorded as <4°C.

Four patients were excluded from the final analysis because of incomplete data. In the remaining 19 patients, rupatadine 20 mg daily for one week resulted in smaller histamine- and codeine-induced wheals and reduction of CTT compared with placebo. The diameters (mean $\pm$ SEM) of histamine-induced wheals were 29% smaller, reduced from 17.8 ± 1.1 to 12.8 ± 1.1 mm ($P < 0.001$). Codeine-induced wheals were 30% smaller, reduced from 18.0 ± 1.3 to 12.5 ± 0.7 mm ($P < 0.001$). In the cold provocation test, the mean CTT was reduced by 46% from $17.1 \pm 1.4^\circ\text{C}$ to $9.6 \pm 1.8^\circ\text{C}$ ($P < 0.001$).

Rupatadine reduced all responses, but did the inhibition of histamine- or codeine-induced wheals predict CTT reductions in individual patients? Figure 1 shows clearly that they did not. The correlation coefficients for the percentage inhibition of histamine- and codeine-induced wheals were $r = -0.0915$ and $r = 0.0374$, both not statistically significant.

The clear message from this brief report is that the responsiveness of histamine- and codeine-induced wheals cannot be used to predict the responsiveness of cold urticaria to H₁-antihistamine therapy. As this was not a mechanistic study, the reasons for this lack of correlation may only be speculative. However, it is clear from Figure 1 that there was a wide spectrum of responsiveness of individuals to the H₁-antihistamine even when wheals were provoked with a constant dose of histamine. In ColdU this variability would have been compounded by different levels of histamine (6). As histamine diffuses negligibly in the skin (10), very high local concentrations may occur in some patients, thus reducing the possible effectiveness of rupatadine. In addition, other mediators besides histamine may also play a role in cutaneous reactions in ColdU. Further mechanistic studies are necessary to investigate the exact role of different proinflammatory factors in the pathomechanism of ColdU and to identify markers that allow for treatment outcome prediction.

In conclusion, the responsiveness of histamine- or codeine-induced dermal wheals to inhibition by an H₁-antihistamine is not predictive of its effect in chronic cold urticaria.

References:

1. Wanderer AA, Grandel KE, Wasserman SI, Farr RS. Clinical characteristics of cold-induced systemic reactions in acquired cold urticaria syndromes: recommendations for prevention of this complication and a proposal for a diagnostic classification of cold urticaria. *J Allergy Clin Immunol* 1986;78(3 Pt 1):417-423.
2. Kaplan AP, Garofalo J, Sigler R, Hauber T. Idiopathic cold urticaria: in vitro demonstration of histamine release upon challenge of skin biopsies. *N Engl J Med* 1981;305(18):1074-1077.
3. Kaplan AP, Horakova Z, Katz SI. Assessment of tissue fluid histamine levels in patients with urticaria. *J Allergy Clin Immunol* 1978;61(6):350-354.
4. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;69(7):868-887.
5. Magerl M, Altrichter S, Borzova E, Gimenez-Arnau A, Grattan CE, Lawlor F, et al. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. *Allergy* 2016;71(6):780-802.
6. Krause K, Spohr A, Zuberbier T, Church MK, Maurer M. Up-dosing with bilastine results in improved effectiveness in cold contact urticaria. *Allergy* 2013;68(7):921-928.
7. Abajian M, Curto-Barredo L, Krause K, Santamaria E, Izquierdo I, Church MK, et al. Rupatadine 20 mg and 40 mg are Effective in Reducing the Symptoms of Chronic Cold Urticaria. *ActaDermVenereol* 2016;96(1):56-59.

8. Staevska M, Popov TA, Kralimarkova T, Lazarova C, Kraeva S, Popova D, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol* 2010;125(3):676-682.
9. Church MK, Maurer M. H(1)-antihistamines and urticaria: how can we predict the best drug for our patient? *Clin Exp Allergy* 2012;42(10):1423-1429..
10. Petersen LJ, Church MK, Skov PS. Histamine is released in the wheal but not the flare following challenge of human skin in vivo: a microdialysis study. *Clin Exp Allergy* 1997;27(3):284

Statement of conflicts of interest: None of the authors have any conflict of interest in relation to this article.

Author contributions

Marina Gorczyza, Karoline Krause, Martin Church, Martin Metz, Marcus Maurer and Ana Giménez-Arnau were responsible for experimental design and preparation of the manuscript. Marina Gorczyza and Laia Curto Barredo were responsible for patient recruitment and practical aspects. Marina Gorczyza, Martin Church and Tomasz Hawro provided statistical analyses of the data and graphics.

Acknowledgements: We thank Iñaki Izquierdo and his team of the Department of Clinical Development, J. Uriach & Co., SA, Barcelona, Spain for their generous support of this project.

Figure Legend

Figure 1. Pearson correlations of the percentage inhibition of critical temperature thresholds (CTT) by treatment with 20 mg rupatadine daily for 7 days with the diameter of wheals induced by intradermal histamine (A) and codeine (B). The r values of -0.0915 and 0.0374 are not statistically significant.