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Histamine intolerance: lack of reproducibility of single symptoms by oral provocation with histamine: A randomised, double-blind, placebo-controlled cross-over study

Peter Komericki[1], Georg Klein[2], Norbert Reider[3], Thomas Hawranek[4], Tanja Strimitzer[5], Roland Lang[4], Bettina Kranzelbinder[1], Werner Aberer[1]

[1]Department of Environmental Dermatology and Venereology, Medical University of Graz, Graz, Austria
[2]Department of Dermatology, Elisabethinen Hospital, Linz, Austria
[3]Clinical Department of Dermatology and Venereology, Medical University of Innsbruck, Innsbruck, Austria
[4]Department of Dermatology, Private Medical University "Paracelsus", Salzburg, Austria
[5]Austrian Agency for Health and Food Safety, Data Collection, Statistics and Risk Assessment, Austria

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Histaminintoleranz: Fehlende Reproduzierbarkeit der einzelnen Symptome durch orale Provokation mit Histamin: Eine randomisierte, doppelblinde, Placebo-kontrollierte cross-over Studie

Zusammenfassung. *Hintergrund:* Der Terminus Histamin-Intoleranz steht für eine ganze Reihe von Symptomen an unterschiedlichen Effektororganen, die nach dem Genuss Histamin-reicher Nahrung auftreten. Das Studienziel war, Histamin-assoziierte Beschwerden durch die Provokation mit einer standardisierten Menge an Histamin zu objektivieren und zu quantifizieren und zu prüfen, ob oral verabreichte Diaminoxidase (DAO) das Beschwerdeausmaß beeinflusst.

Patienten und Methoden: Vier Institutionen in Österreich nahmen teil. Es wurden Patienten rekrutiert, die den Verdacht auf Histamin-Intoleranz äußerten. Zunächst erfolgte eine offene orale Provokation mit 75 mg Histamin in Tee. Alle Probanden, die dabei Beschwerden entwickelten, wurden in den verblindeten Teil der Studie eingeschlossen und erhielten in drei weiteren verblindeten, einem cross-over Design folgenden Provokationsschritten Kombinationen aus Histamin-freiem und Histamin-hältigem Tee mit Diaminoxidase- und Placebo-Kapseln. Es wurden Haupt- und Nebensymptome (stärkste und weniger starke Beschwerden an den einzelnen Effektororganen auf einer 10-Punkte-Skala) definiert, die Reproduzierbarkeit dieser Beschwerden in Bezug auf die jeweiligen Effektororgane geprüft, die Beschwerden weiters in ihrer Gesamtheit (Summe der Beschwerdepunkte aller Effektororgane) erfasst und Veränderungen nach Supplementation von DAO beurteilt.

Ergebnisse: 39 von 56 Patienten reagierten in der offenen Provokation und wurden in den verblindeten Studienabschnitt eingeschlossen. Haupt- und Nebensymptome waren dabei nicht zu reproduzieren, die Probanden reagierten quasi zufällig. Allerdings brachte die Einnahme von DAO eine statistisch signifikante Reduktion von Beschwerden (definiert durch den Rückgang der aufsummierten Gesamtpunkte) im Vergleich zur Placebo-Gruppe.

Schlussfolgerung: Die Ergebnisse erscheinen kontrovers. Möglicherweise reagieren Histamin-intolerante Personen zu unterschiedlichen Zeiten mit unterschiedlichen Symptomen. Die Reproduzierbarkeit definierter Symptome allein würde dann nicht genügen, um eine Histamin-Intoleranz zu bestätigen. Am Kollektiv zeigte sich weiters, dass die Einnahme von DAO-Kapseln im Vergleich mit Placebo-Kapseln zu einer statistisch signifikanten Abschwächung von Beschwerden nach Histamin-Provokation führte.

Summary. *Objectives:* The term histamine intolerance stands for a range of symptoms involving various effector organs after the consumption of histamine-rich food. Our intention was to objectify and quantify histamine-associated symptoms and to analyse whether oral administration of the histamine-degrading enzyme diamine oxidase (DAO) caused a reduction of symptoms.

Patients and methods: Four Austrian centres participated. Patients suspected to be histamine intolerant were

Correspondence: PD Dr. Peter Komericki, Department of Environmental Dermatology and Venereology, Medical University of Graz, Auenbruggerplatz 8, 8036 Graz, Austria,
E-mail: peter.komericki@medunigraz.at

recruited. The first step consisted in the open oral provocation of these patients with 75 mg of liquid histamine. Patients who developed symptoms were tested in a randomised double blind crossover provocation protocol using histamine-containing and histamine-free tea in combination with DAO capsules or placebo. Main and secondary symptoms (strongest and weaker symptoms based on a ten-point scale) were defined, the grand total of all symptoms of the individual provocation steps was determined and changes in symptoms after administration of DAO were measured.

Results: Thirty nine patients reacted to the open histamine provocation and were enrolled in the blinded part. Here, both the main and secondary symptoms were not reproducible. Subjects reacted sometimes unexpectedly and randomly. Regarding the total symptom scores, the differences between the three treatment groups were statistically significant. The intake of DAO demonstrated a statistically significant reduction of histamine-associated symptoms compared to placebo ($P = 0.014$).

Conclusions: Oral provocation with 75 mg of liquid histamine failed to reproduce histamine-associated single symptoms in many patients. One may suggest that histamine-intolerant subjects reacted with different organs on different occasions. As a consequence, reproducibility of single symptoms alone may not be appropriate to diagnose histamine-intolerance whereas a global symptom score could be more appropriate. The fact, that the intake of DAO capsules compared to placebo led to a statistically significant reduction of total symptom scores, may indirectly point in the same direction.

Key words: Biogenic amines, DAO, diamine oxidase, histamine intolerance, oral provocation.

Introduction

Histamine, an alkaline biogenic amine with a molecular weight of 111 daltons, represents a highly reactive messenger substance (IUPAC – International Union of Pure and Applied Chemistry – name 1H-imidazole-4-ethylamine). This decarboxylation product of histidine is detectable in all body tissues, especially in mast cells and basophil granulocytes [1]. Histamine is stored in cytoplasmic granules and can be released quickly by degranulation. However, histamine is not only produced by the body but also constantly ingested with food to different degrees [2]. Hundreds of goods produced with bacteria regularly contain histamine. They include for example wine, cheese and Sauerkraut. In addition, histamine develops during the storage process of protein-containing food (canned fish and sausage, etc.) [3]. It is the responsible agent in fish poisoning [4]. Some patients describe food intolerance that occurs with subtoxic histamine doses. The term "histamine intolerance" was introduced as common denominator for symptoms such as abdominal pain, flatulence, diarrhoea, headache, pruritus, blepharedemas, urticaria, rhinorrhoea, dysmenorrhoea, respiratory obstruction, tachycardia, extrasystoles and hypotension occurring after the consumption of histamine-rich foods [5].

Histamine is degraded by two enzymes. Histamine-N-methyltransferase (HNMT, EC 2.1.8) is an enzyme predominantly located intracellular in blood cells and the liver [6]. Diamine oxidase (DAO, EC 1.4.3.6) is mainly produced by enterocytes and is used for the degradation of extracellular histamine [7]. Thus histamine ingested with food is largely degraded in the intestines [8]. When passing through the intestinal mucosa, additional histamine is degraded by the DAO located there. 6-hydroxydopa [9] and pyridoxal phosphate (vitamin B_6) [10] serve as co-factors of DAO.

Histamine intolerance is attributed to an imbalance of histamine and DAO [11]. The DAO activity can be reduced by other biogenic amines, alcohol and its decomposition product acetaldehyde as well as various drugs [12].

Nevertheless, the symptoms of histamine intolerance are not clearly defined and not always identifiable. The purpose of the present study was to examine whether the oral provocation with a standardised histamine quantity in a selected patient sample yields reproducible subjective symptoms and whether the ingestion of commercially sold oral diamine oxidase (PelLind®) reduces or suppresses the symptoms.

Patients and methods

Four Austrian allergological outpatient units of dermatological departments participated in a multicentre, double-blind, placebo-controlled crossover study: Graz, Innsbruck, Linz and Salzburg. The study was conducted in accordance with the principles of Good Clinical Practice (GCP) corresponding to the ICH guidelines (International Conference on Harmonisation of drugs and medical devices). A positive vote was obtained from an inde-

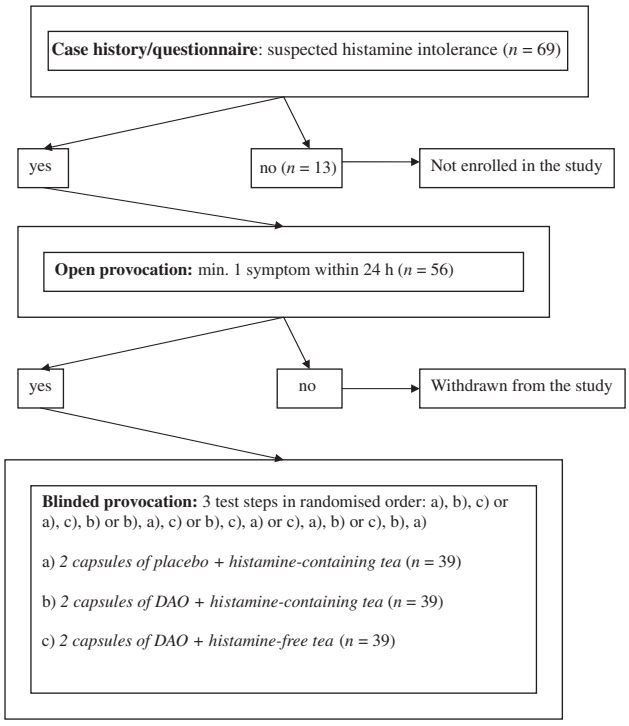

Fig. 1. Schematic illustration of study sequence including the number of participants of each step (n = number)

pendent ethics committee (protocol number 274/06). Before enrolment, every patient signed a declaration of consent after being provided with thorough verbal and written information.

Figure 1 contains a schematic illustration of the study sequence. In the first step patients who had repeatedly observed intolerance reactions after consuming histamine-rich food were selected. The enrolment age was between 18 and 75 years. Exclusion criteria were pregnancy, coronary heart disease, instable hypertension, bronchial asthma and regular H1 blocker intake. The patient history was recorded by means of a standardised questionnaire. Those patients who had regularly developed symptoms consistent with histamine intolerance (HIT) after the intake of food were invited to participate in the study.

The study sequence was divided into two phases: the first phase consisted of an open provocation with 75 mg of pure histamine in 100 mL of peppermint tea, to identify histamine-sensitive persons, and to objectify and to quantify the symptoms reported by the patients. In addition, this step was used to define the main symptom, i.e. the one of four symptoms patients marked as the strongest on a 10-point scale. Ten points were awarded for the maximum degree of symptoms. Less pronounced symptoms were classified as secondary symptoms. This 10 point symptom scale was used for the four symptoms I) headache, II) symptoms involving the skin (pruritus, erythema, and urticaria), III) symptoms involving the mucous membranes (itching, erythema/enanthema, and rhinorrhoea), and IV) gastrointestinal symptoms (nausea, vomiting, abdominal pain, flatulence, and diarrhoea). The symptoms were evaluated 90 min and 24 h after the oral provocation. Patients who did not develop any symptoms after the open provocation were excluded.

Patients who reached at least one symptom were subjected to a double-blind and randomised crossover provocation test. They were randomised according to a scheme defined before the study. Three provocation steps followed, consisting of a) *2 capsules of placebo + histamine-containing tea*, b) *2 capsules of DAO + histamine-containing tea* and c) *2 capsules of DAO + histamine-free tea* assigned in random order. The DAO capsule manufacturer supplied one package each for every subject. Configurations a), b), and c) were randomly assigned to the colours green, blue and orange and the prepared packages provided to the test centres.

DAO (PelLind®) capsules are a gastric acid resistant nutrition supplement for patients with histamine intolerance. One capsule contains 0.25 mg of protein extract with natural DAO, which was extracted from pigs' kidneys, and holds an activity of 10,000 HDU (histamine degrading units) and an amount of 11 mg of vitamin C, and mainly microcrystalline cellulose and gelatine. In placebo capsules, the protein extract with DAO was replaced by microcrystalline cellulose. The provocations were administered after a 24-hour histamine-free diet at an interval of at least 48 hours and at most 10 days. The symptoms I) headache, II) symptoms involving the skin, III) symptoms involving the mucous membranes and IV) gastrointestinal symptoms were evaluated after 90 minutes and 24 h and were used to define the possible main symptom as well as secondary symptoms as it was done after the open provocation. The evaluation after 90 min was performed by the subject with the support of a test physician; the evaluation after 24 h by the subject alone. The evaluations after 90 min and 24 h were recorded separately for every symptom and later summarised to a single score for statistical calculation.

The primary objective was defined as the reduction of the main symptom score based on the 10-point-scale. An improvement by 40% or more was considered a good outcome and an improvement by 30–39% a satisfactory result. Other deviations of the score were referred to as not satisfactory. The secondary objective was defined as the reduction of the symptom score of the most severe secondary symptom (points awarded analogous to the main symptom score) and the tertiary objective was defined as reduction of the total score of all indicated symptoms.

The reproducibility of symptoms observed with open provocation was referred to as exploratory criterion. The symptom score of the blinded provocation *2 capsules of placebo + histamine-containing tea* was used as comparison. A score deviation by plus/minus two points on the 10-point scale was deemed good reproducibility.

Statistical methods

Ten points were awarded for the maximum degree of symptoms per target region (symptoms I–IV) and time (90 min and 24 h), and 2 points for the minimum degree of symptoms. One point was awarded for no symptoms.

The overall symptom score was calculated by adding the symptom points of 4 target organs at 2 points of time.

Consequently, the highest possible total score per person for each of the three test conditions and the open provocation was 80 points. Based on this scale, persons with a total score of 8 points are deemed "symptom-free".

In the descriptive part, the specific values (case number, median, minimum and maximum) were calculated for each of the three test conditions (Table 1). In addition, the distribution was visualised with box plots (Fig. 2).

The recovery of symptoms was statistically tested with the calculation of a rank correlation (Spearman Rho) between the individual localisations of the open provocation and the ones of the condition *placebo + histamine-containing tea*.

Non-parametric methods are used for the inference statistical evaluation.

The regular distribution analysis was performed according to Kolmogorov–Smirnov and to Shapiro-Wilk. The rank test according to Friedman was used for the evaluation of the entire model. Multiple paired comparisons were performed according to Wilcoxon.

Results

In total 56 subjects underwent the open provocation. 39 (35 females (average age 47 years), 4 males (average age 39 years)) out of 56 (69.6%) displayed at least one symptom

Table 1. Specific values of total scores for the 3 test conditions

	n	Median	25th percentile	75th percentile	Minimum	Maximum
DAO + histamine-containing tea	39	10	9	17	8	35
DAO + histamine-free tea	39	10	8	14	8	40
Placebo + histamine-containing tea	39	15	9	24	8	40

n: number of patients in the blinded part.

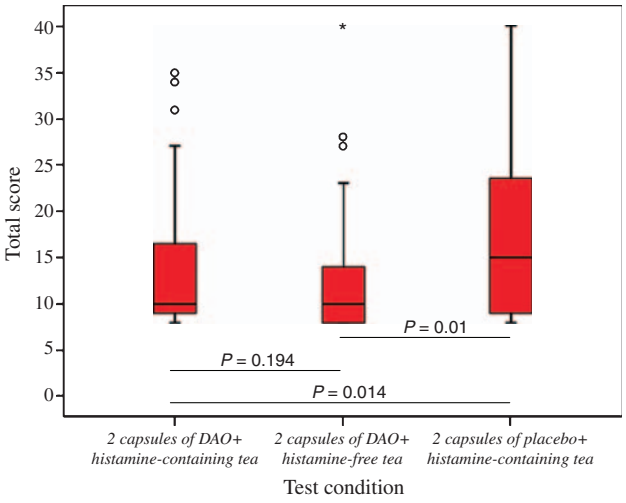

Fig. 2. Box plots for the 3 test conditions. The boxes represent the 1st and 3rd quartile and the median. Outliers and extreme outliers are marked by rings or stars, respectively. The difference is statistically significant (according to Friedman). *P*-values resulted from paired comparison of the 3 test conditions according to Wilcoxon (significance test)

and were enrolled in the blinded part of the study (subject distribution: Graz 13, Innsbruck 14, Linz 5 and Salzburg 7).

25 of these 39 (64.1%) subjects developed at least one symptom after a blinded provocation with *DAO + histamine-free tea*.

Nine of 39 (23.1%) did not have a reaction to the combined administration of *placebo + histamine-containing tea*. However, seven of this group (78%) responded with at least 1 symptom to the test configuration *DAO + histamine-free tea*. Number and percentage of subjects with at least 1 positive reaction among treatment groups are provided in Table 2.

Neither the main symptoms nor the secondary symptoms were reproducible. The main symptom was fully recoverable in 11 of 39 cases (28.2%), and partially recoverable in three cases (8 %). Partially recoverable referred to constellations in which two or more main symptoms (with identical numeric values on the 10-point scale) were found, but only a part of them was reproducible according to the defined criteria.

The findings were similar with respect to the secondary symptoms. They were completely reproducible in 15 of 39 cases (38.5%) and partially reproducible in one case (2.6%).

Moreover, we calculated a correlation for the two groups *open provocation* and *placebo + histamine-containing tea* for all symptoms independent of localisation. Although the most common response among the groups was 1 (i.e. no symptom) in both cases, we were only able to determine a correlation coefficient of 0.4, which means the lack of any correlation. Due to the random reactions and thus the lack of reproducibility, primary and secondary objectives could not be evaluated.

Table 2. Number (*n*) and percentage (%) of subjects with at least 1 positive reaction among blinded treatment groups

	n	*n* of positive reactions	% of positive reactions
DAO + histamine-containing tea	39	30	76.9
DAO + histamine-free tea	39	25	64.1
Placebo + histamine-containing tea	39	30	76.9

Table 3. The difference in the sum of symptoms (total score) in the 3 test conditions is statistically significant (according to Friedman)

N	39
Chi squared	6.592
d.f.	2
Asymptotic significance	0.037
Exact significance	0.036

Regarding the *total* symptom scores (tertiary objective, Table 1 and Fig. 2), the differences between the three treatment groups (*DAO + histamine-containing tea* versus *DAO + histamine-free tea* versus *placebo + histamine-containing tea*) were statistically significant ($P = 0.036$, Table 3). Paired comparisons of treatment groups according to Wilcoxon revealed the following (Fig. 2): *placebo + histamine-containing tea* showed a statistically significant difference compared to *DAO + histamine-free tea* towards stronger symptoms with the first test configuration ($P = 0.01$). The situation was similar with the paired comparison of *placebo + histamine-containing tea* and *DAO + histamine-containing tea*. There was a statistically significant reduction of symptoms with the configuration *DAO + histamine-containing tea* ($P = 0.014$). By contrast, the symptoms of the test configuration *DAO + histamine-free tea* were not different from the combination with *DAO + histamine-containing tea* ($P = 0.19$).

Discussion

A wide range of symptoms has been described after the intake of histamine-rich food, alcoholic beverages or histamine-releasing or DAO-blocking drugs. The symptoms are variable and heterogeneous. As a result, the diagnosis of histamine intolerance may be underdiagnosed [13].

Otherwise, identical symptoms may also occur within the scope of food allergies as well as in intolerance reactions against other biogenic amines such as tyramine [13], where the evidence for these is considered weak based on double-blind, placebo-controlled provocations (DBPCPs) [14]. Some biogenic amines are expected to be capable of triggering various symptoms by inhibiting DAO [15] or by directly liberating histamine from the mucosa [16]. However, the actual allocation of a certain symptom to a defined biogenic amine is impossible. In addition, many types of foods contain antioxidants, preservatives such as sulphites, colorants and carrier substances with the capability of triggering "pseudo allergic" reactions [17, 18]. All these factors, however, cannot explain the results of our study, as only pure peppermint tea with or without histamine was used.

Due to the heterogeneous symptoms and the in part controversial data records, additional DBPCPs using histamine are required. Due to the variable histamine content of natural food products they should be conducted in a standardised form [13].

For our study, we targeted patients with a positive history with respect to the intolerance of histamine-rich food. These preselected subjects were provoked with 75 mg of histamine, an internationally recommended regimen [13]. The development of subjective symptoms within 24 h was

defined as condition for the subsequent DBPCP with liquid histamine. Patients without symptoms were excluded. Subjects who developed subjective symptoms during this provocation underwent further double-blind testing.

The statistical evaluation of the data reveals a lack of symptom reproducibility. Neither the main nor the secondary symptoms could be reproduced reliably. Therefore, it was impossible to evaluate the changes of main and secondary symptoms defined as target criteria before the start of the study (primary and secondary objectives).

The calculation of correlations between the individual symptoms equally demonstrated a lack of any correlation. These findings are consistent with the observation that 64.1% of subjects reacted with at least one symptom to the histamine-free provocation solution. In turn, the positive provocation with a histamine-containing provocation solution and placebo capsules was no longer possible for 23%, even though all patients from this group clearly responded to at least one of the two other test configurations. The majority even responded after provocation with histamine-free tea.

Based on these observations it can be concluded that our test configuration was unable to achieve clear histamine-associated symptoms. The reason remains unclear. One may speculate that 75 mg of histamine are not enough to consistently provoke symptoms in histamine intolerant subjects or that some patients were not histamine intolerant despite their reactions after open provocation. To a certain extent, the described symptoms occurred randomly. Similar observations were made with a DBPC wine test in patients suffering from chronic urticaria as well as subjects with "wine intolerance". It was not possible to demonstrate a correlation between the wine intolerance and the histamine content of wine. Similarly to our study, 87% of these subjects equally reacted to placebo [19].

These results let us suppose that psychosomatic factors play an important role in the genesis of symptoms in a considerable proportion of patients with suspected histamine intolerance. The expectation of a reaction leads to increased self-observation and triggers subjective symptoms.

Focusing on the reproducibility of main and secondary symptoms was unsuitable to approve or exclude histamine intolerance. A similar observation was recently published after investigation of histamine sensitivity in healthy subjects [20]. Half of the study population had responded to a provocation with 75 mg liquid histamine. It was assumed that histamine intolerant patients possibly do not respond with the same effector organ, but that the histamine-sensitive biological system "human body" is affected as a whole and responds in various organ systems on different occasions. However, only very few subjects ($n = 10$) had been provoked.

The evaluation actually reveals a statistically significant difference between the total scores of the three test configurations (tertiary objective). It revealed that subjects provoked with histamine-containing tea experienced less symptoms with the simultaneous intake of two DAO-containing capsules instead of placebo capsules ($P = 0.014$). Not surprisingly, fewer symptoms were observed after provocation with a histamine-free solution compared to the histamine-containing solution ($P = 0.01$). Both calculations were statistically significant. The fact, that no difference was seen between histamine-free and histamine-containing tea after supplementation of DAO ($P = 0.19$), point in the same direction. Regarding those for all groups constant test parameters except the test configurations *placebo capsules, DAO-containing capsules, histamine-free tea, and histamine-containing tea*, these changes of test *configurations must have been the reason for the differences in total scores.*

A limitation of the current study is the lack of a negative control group provoked with *placebo capsules* and *histamine-free tea*. The negative control in this study (DAO+ histamine-free tea) is not a real negative control, as the DAO capsules could have improved underlying basal symptoms which could be present in some patients with histamine intolerance also under basal conditions and which could be worsened by intake of histamine-rich food, alcohol or drugs releasing histamine and/ or blocking DAO. Furthermore, we did not divide into objective and subjective parameters, so that strong clinical end points are lacking. However, the importance of the psychological aspect in the field of histamine intolerance has been demonstrated using these protocols.

Conclusions and perspective

A well-established test procedure, oral provocation with 75 mg of liquid histamine, failed to reproduce histamine-associated subjective symptoms in several of our pre-selected histamine-sensitive patients. They often reacted unexpectedly and randomly (e.g. symptoms after provocation with pure tea). A psychosomatic influence has to be suspected. Moreover one may suggest that histamine-intolerant subjects reacted with different organ systems on different occasions. As a consequence, reproducibility of single symptoms alone may not be appropriate to diagnose histamine-intolerance whereas a global symptom score could be more appropriate. The fact that the intake of DAO capsules compared to placebo led to a statistically significant reduction of total symptom scores may indirectly point in the same direction.

To clarify these points additional double-blind and placebo-controlled provocation studies are required, where the subjects should be exposed to different amounts of histamine. Additionally, these investigations should be done in a larger collective of healthy subjects compared to the study of Wöhrl et al. [20], where half of 10 subjects had reacted to 75 mg histamine. A recent publication suggests DBPCP with oral histamine and determination of plasma histamine concentration and of objective physical parameters such as heart rate, blood pressure, and erythema [21]. Patients will benefit from a clear, evidence-based diagnostic and therapeutic procedure [22].

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Conflict of interest
The authors declare that there is no conflict of interest.

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