Prediction of the Efficacy of Antihistamines in Chronic Spontaneous Urticaria Based on Initial Suppression of the Histamine-Induced Wheal

Sánchez J1,2,3, Zakzuk J1,2, Cardona R3

1Foundation for the Development of Medical and Biological Sciences (FUNDEMEB), Cartagena, Colombia
2Institute for Immunological Research, Universidad de Cartagena, Cartagena, Colombia
3Group of Clinical and Experimental Allergy, IPS Universitaria Universidad de Antioquia, Medellín, Colombia

Abstract

Background: Antihistamines are the first line of treatment for chronic spontaneous urticaria. However, there is no effective method to predict whether an antihistamine will have a beneficial clinical effect or not.

Objective: To assess whether the change in histamine-induced wheal and flare measurements 24 hours after administration of antihistamine can predict the efficacy of treatment.

Methods: We performed a multicenter, triple-blind, randomized study. Patients received a daily oral dose of cetirizine, fexofenadine, bilastine, desloratadine, or ebastine over 8 weeks. After 4 weeks, a higher dose of antihistamine was administered to patients who did not experience a clinical response. A histamine skin prick test was carried out at baseline and 24 hours after the first dose of antihistamine. Disease severity (Urticaria Activity Score [UAS]), response to the histamine skin prick test, and impact on the patient’s quality of life (Dermatology Life Quality Index [DLQI]) were determined every 2 weeks.

Results: The study population comprised 150 patients (30 per group) and 30 controls. Twenty-four hours after administration of antihistamine, inhibition of the histamine wheal by >75% was significantly associated with better UAS and DLQI scores. The safety and efficacy of the 5 antihistamines were similar. After updosing, rates of disease control (DLQI score <5) increased from 58.7% to 76.7%.

Conclusions: Measurement of the histamine-induced wheal can predict which patients will have a strong clinical response to antihistamines but has limited utility for identifying nonresponders. The clinical significance of these data could be relevant in the search for new urticaria treatment regimens.


Resumen

Antecedentes: Los antihistamínicos son la primera línea de tratamiento en la urticaria crónica espontánea (UCS) pero actualmente no hay un método eficaz para predecir si un antihistamínico tendrá un efecto clínico beneficioso o no.

Objetivo: Evaluar si la prueba cutánea con histamina puede predecir la efectividad del tratamiento con antihistamínicos.

Métodos: Se realizó un estudio multicéntrico, triple ciego, aleatorizado. Los pacientes recibieron una dosis oral diaria de cetirizina, fexofenadina, bilastina, desloratadina o ebastina durante 8 semanas. Después de 4 semanas, en los pacientes sin respuesta clínica, se administró una dosis más alta de antihistamínico. Al inicio del estudio, después de 24 horas y cada dos semanas tras la primera administración de los antihistamínicos, se llevó a cabo una prueba intraepidérmica con histamina. La severidad de la enfermedad (escala UAS) y el impacto en la calidad de vida de los pacientes (escala DLQI) fueron evaluados cada dos semanas.

Resultados: 150 pacientes (n = 30, en cada grupo) y 30 sujetos control participaron en este estudio. Después de 24 horas de la administración de antihistamínicos, una inhibición de histamina mayor al 75% del basal, se asoció significativamente con mejores resultados en el UAS y el DLQI. La seguridad y eficacia de los cinco antihistamínicos fueron similares. Después de aumentar la dosis, las tasas de control de la enfermedad (puntuación DLQI <5) paso de 58,7% a 76,7%.

(ClinicalTrials.gov identifier: NCT01940393)
Introduction

International guidelines agree that antihistamines are the cornerstone for treatment of symptoms in chronic spontaneous urticaria (CSU) [1,2]. Some clinical guidelines recommend the use of second-generation antihistamines over first-generation antihistamines owing to their excellent safety profile and clinical efficacy [3]. However, in many cases, disease cannot be controlled at conventional doses [4]. While increasing the dose of antihistamines seems to improve control, differences in pharmacokinetics and pharmacodynamics between agents may lead to different responses between patients [5-8]. According to clinical guidelines, it takes at least 1-4 weeks to evaluate the therapeutic efficacy or failure of an antihistamine [3,9]. In patients for whom therapy is unsuccessful, this trial period generates additional economic and time costs, and unresponsive patients must undergo a new test in which the dose of the same antihistamine is increased or a new antihistamine is introduced.

An in vitro test to measure receptor affinity could help to evaluate the potency of an antihistamine, although such tests are not always available. In head-to-head comparisons of 2 or more antihistamines, measurement of the wheal and flare reaction induced by a histamine prick or intradermal test is a good indicator of the potency; however, it is less clear whether suppression of the reaction can predict clinical impact, especially with higher doses [10]. The aim of this study was to evaluate whether measurement of the histamine-induced wheal and flare reaction can be used in clinical practice to predict the response of CSU to antihistamines at conventional or higher doses. The clinical utility of urticaria guidelines was evaluated as a secondary endpoint.

Material and Methods

Patients

The study population comprised 213 patients aged 12 to 50 years with a clinical diagnosis of chronic urticaria, which was defined as recurrent wheals with/without angioedema for at least 3 days per week and lasting for ≥6 weeks (Figure 1). A questionnaire to determine physical or other suspected triggers was completed, and a provocation test was applied to evaluate whether wheals were elicited by cholinergic or physical stimuli (water, heat, pressure, friction, or contact with cold) [11,12]. Sensitization to allergens was evaluated at baseline using a panel of extracts including aeroallergens and foods [13] (Inmunotek, Madrid, Spain).

Patients with a positive provocation test result or with a Dermatology Life Quality Index (DLQI) score <7 points were excluded. Other exclusion criteria were immunodeficiencies, atopic dermatitis, or any other condition that could alter the results of the skin test. We also excluded immunocompromised patients with recurrent infections requiring frequent antibiotics and other systemic medications, since these medications can trigger urticaria. The demographic characteristics of the study sample are summarized in Table 1.

Study Design

We performed a prospective, randomized, triple-blind trial (URTICA cohort; Urticaria Research of Tropical Impact and Control Assessment. ClinicalTrials.gov identifier: NCT01940393) in 6 health care centers in 2 cities in Colombia. The primary objective was to assess whether the change in histamine prick test results could predict the clinical response of patients with CSU 24 hours after administration of antihistamines.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and pursuant to Good Clinical Practice guidelines. Written informed consent was obtained from all participants and/or their parents (for patients aged <18 years). The Ethics Committee of Universidad de Antioquia, Medellín, Colombia approved this protocol (Code: BE-IIM). We did not include a placebo group, since it would have provided little information on the primary outcome of the study and there is consistent evidence supporting the effectiveness of antihistamines as first-line treatment in patients with urticaria [3]. The control group comprised 30 individuals without urticaria who did not receive antihistamines during follow-up and were evaluated to determine whether histamine-induced wheal and flare measurements changed over time.

Participants were randomized (1:1:1:1:1) to receive 1 of the 5 antihistamines using Microsoft Excel 2010 (Microsoft Corporation). For 2 months, participants received a daily oral dose of cetirizine (10 mg), fexofenadine (180 mg), bilastine (20 mg), desloratadine (5 mg), or ebastine (20 mg) between 7 AM and 8 AM. All antihistamines were supplied in identical capsules by a third party in a blinded manner and stored and distributed by the Pharmacy Department of Universidad de Antioquia. A group of pharmacologists, who did not have contact with patients or physicians, masked the capsules, and another group administered them to the patients every 2 weeks during the follow-up stage. Neither the patients nor the medical staff involved in the study knew which antihistamine they were receiving.

A skin prick test (SPT) was performed at baseline and 24 hours after the first administration, and the wheal and flare reaction was measured (diameter and area). An allergist evaluated the clinical
course of the disease every 2 weeks until the end of the follow-up. Histamine SPTs were also performed at each visit.

During follow-up, the antihistamine dose was modified according to its clinical effectiveness and adverse reactions. After 4 weeks, patients whose disease was clinically controlled (DLQI<5) but who experienced a strong sedative effect were switched to 48-hour dosing for the rest of the study. In contrast, the antihistamine dose was increased (2- or 4-fold) in patients whose dose did not achieve clinical control by administering the antihistamine twice (1 or 2 tablets according to the individual patient in the morning [7 am to 8 am] and in the evening [7 pm to 8 pm]). If the participant reported no sedative adverse effects with the conventional dose, the dose was quadrupled; if a moderate sedative effect was reported, the dose was doubled. After 2 weeks, the dose was reduced to a double dose until the end of the study in patients who achieved clinical control with a quadrupled dose but experienced a strong sedative effect.

Table 1. Characteristics and Symptom Scores of the Study Population at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Cetirizine</th>
<th>Bilastine</th>
<th>Desloratadine</th>
<th>Fexofenadine</th>
<th>Ebastine</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y(^a)</td>
<td>30 (14-50)</td>
<td>28 (14-46)</td>
<td>27 (14-48)</td>
<td>29 (15-48)</td>
<td>27 (14-50)</td>
<td>26 (18-44)</td>
</tr>
<tr>
<td>Onset of urticaria(^a)</td>
<td>28 (13-49)</td>
<td>26 (7-45)</td>
<td>24 (12-47)</td>
<td>27 (13-47)</td>
<td>26 (13-49)</td>
<td>NA</td>
</tr>
<tr>
<td>Female gender, No. (%)</td>
<td>15 (50.0)</td>
<td>19 (63.3)</td>
<td>18 (60.0)</td>
<td>21 (70.0)</td>
<td>21 (70.0)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Atopy, No. (%)</td>
<td>13 (43.3)</td>
<td>18 (60.0)</td>
<td>15 (50.0)</td>
<td>8 (26.7)</td>
<td>12 (40.0)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Asthma, No. (%)</td>
<td>3 (10.0)</td>
<td>6 (20.0)</td>
<td>6 (20.0)</td>
<td>3 (10.0)</td>
<td>3 (10.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rhinitis, No. (%)</td>
<td>13 (43.3)</td>
<td>15 (50.0)</td>
<td>16 (53.3)</td>
<td>10 (33.3)</td>
<td>9 (30.0)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>DLQI(^b)</td>
<td>15 (9-24)</td>
<td>16 (9-27)</td>
<td>15 (9-26)</td>
<td>15 (9-27)</td>
<td>15 (9-23)</td>
<td>NA</td>
</tr>
<tr>
<td>UAS(^a)</td>
<td>3.57 (1-6)</td>
<td>3.73 (1-6)</td>
<td>3.63 (1-6)</td>
<td>3.23 (0-5)</td>
<td>3.47 (0-6)</td>
<td>NA</td>
</tr>
<tr>
<td>Wheal diameter, mm</td>
<td>21 (8-63)</td>
<td>20 (8-45)</td>
<td>21 (11-45)</td>
<td>21 (8-56)</td>
<td>22 (10-51)</td>
<td>20 (8-65)</td>
</tr>
</tbody>
</table>

Abbreviations: DLQI, Dermatology Life Quality Index; NA, not applicable; UAS, Urticaria Activity Score.
\(^a\)Mean (range).
The DLQI was selected as the quality of life questionnaire for this study, since it had already been validated in Colombia [14]. We used the Urticaria Activity Score (UAS) [3] to measure disease severity and monitor treatment results in daily practice.

Evaluation of Tolerance

Safety and tolerability were assessed according to the adverse events reported by participants during each postrandomization visit. In addition, laboratory examinations (complete blood count, aspartate aminotransferase, alanine aminotransferase, creatinine, and blood urea nitrogen) and an electrocardiogram were performed before antihistamine therapy was started and every month thereafter. Sedation was evaluated using 3 questions: Do you feel sleepier or drowsier than usual?, Do you think sleepiness or drowsiness interferes with your daily activities?, and Do you feel that your sleep is not restful? The replies were scored as follows: none (0), little (1), moderate (2), or much (3). The sedative effect was considered strong when patients had 3 points in 1 of the 3 questions or 6 to 9 points in total.

Adherence

Adherence to treatment was defined as the percentage of the total scheduled number of tablets taken between the randomization visit and the end-of-treatment visit.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics, version 20.0 (IBM Corp). Demographic continuous variables were described using mean (SD). Differences between proportions were analyzed using the Pearson chi-square test. Correlation was reported as the Pearson R coefficient and its respective P value. A paired t test was used for comparison of continuous variables with only 2 values for each participant (before and 24 hours after treatment); otherwise, a repeated-measures ANOVA was used when all time points were analyzed. Linear mixed models were also used to evaluate whether the type of medication received (treated as fixed factors) affected serial assessments of DLQI scores [15,16].

Univariate and multivariate binary logistic regression were used to analyze the relationships between exposures and outcomes. The main outcome was disease control, categorized as controlled (DLQI≤5), moderate (DLQI 6–9), or uncontrolled (DLQI≥10). Predictive exposures included change in histamine wheal diameter after 24 hours (HWDC, %), gender, age, and age at onset of symptoms. These variables were included in the multivariate models as covariates. The crude odds ratio (OR), adjusted odds ratio (aOR), 95% confidence interval (95%CI [OR]), and P values were calculated.

Sample Size

Taking into consideration sample sizes for antihistamine wheal response with prick tests reported elsewhere [8] and based on an analysis to detect a difference in the pharmacologic relevance of wheal area between active groups with a power of 90% and α error of 0.05, a sample size of 20 patients per group was selected. Given the possibility of dropouts during follow-up, 10 additional patients per group were included (30 patients per group).

Results

Patient Characteristics

Of the 213 patients with chronic urticaria who agreed to participate in the study, 63 were excluded (Figure 1). A total of 150 participants met the inclusion criteria and were randomized to receive 1 of the 5 antihistamines (30 per group) (Figure 1). No significant differences were observed between groups with respect to gender, age, or age at onset of symptoms (Table 1).

A total of 87 patients (58.0%) experienced at least 1 postbaseline drug-related adverse event. Sedation was reported by 77 patients (51.3%; 43 [28.6%] with a conventional dose and 34 [22.6%] with a higher dose). Severe sedation events were more frequent in the group of patients who received cetirizine (7 out of 28 [25%] at 8 weeks) and less common in those treated with fexofenadine (1 out of 30 [3.3%]). Two patients from the cetirizine group left the trial because of sedation. There were no alterations in vital signs, the results of the physical examination, electrocardiogram, or clinical laboratory data. Most adverse events were mild, and in 16 patients they disappeared during follow up (sedation, 7; headache, 8; constipation, 1).

DLQI Score and Wheal Diameter Were More Sensitive Than UAS and Flare Area for Evaluation of Clinical Changes During Follow-up

In most patients (>95%), the flare disappeared completely in the SPT after starting antihistamines; therefore, it was not useful for assessing clinical response. The largest diameter of the wheal and total area were highly correlated (baseline, R=0.91; after 24 hours, R=0.96; P<.01 for both comparisons), but only wheal diameter results are shown, since this measure is easy to apply in clinical practice.

Since the UAS was lower than 3 points in most patients (95.0%) at the visits and DLQI score was more sensitive to rate changes during follow-up, these were selected as the measures of clinical control for analysis. There was no correlation between the baseline dimensions of wheal and flare and disease severity.

Histamine Wheal Diameter Remains Stable in the Control Group

HWDC was significantly lower in patients after 24 hours of antihistamine consumption (P<.0001), but there were no significant differences regarding the type of antihistamine used (P=.90). No significant HDWC was found in the control group without antihistamines at 24 hours after the first measurement (paired t test, mean difference, 0.60 [2.28] cm, P=.16) or during follow-up (repeated-measures ANOVA, P=.39) (Figure 2).

Change in Histamine Wheal Diameter 24 Hours After Intake of Histamine Was Inversely Correlated With DLQI Score

The percentage HWDC was significantly and negatively correlated with the DLQI score (R=−.32, P<.0001). When HDWC values were categorized into 4 groups (<25%, 25-50%, 51-75%, and >75%), a trend toward better control of disease was observed with increases in HWDC (Figure 3). Disease was
controlled with antihistamine medication in almost all patients with HWDC >75% (93.9%) (DLQI score <5), and no differences were found between the antihistamines. Furthermore, logistic regression analysis showed that HWDC >75% was significantly associated with disease control, independently of age, gender, and age at onset of symptoms (Table 2).

**Additional Control of DLQI Was Observed During Follow-up With Updosing**

At baseline, disease was uncontrolled in all patients (Figure 4). After 2 weeks, 55 patients (36.7%) were well controlled and 79 moderately controlled (52%). Patients with good disease control but strong sedation were switched to alternate-day dosing for the rest of the study. As symptoms were controlled and sedation was less frequent, patients were not removed from the statistical analyses.

After 4 weeks with antihistamines at conventional doses, 58.7% of patients (n=88) were controlled and 30.7% (n=46) were partially controlled. Clinical response in patients with DLQI >5 improved when the antihistamine dose was increased. After this adjustment, measurements at week 8 of follow-up revealed that 76.7% of patients were controlled (n=115), 15.3% partially controlled (n=23), and 6.7% uncontrolled (n=10).

No significant differences in DLQI or UAS scores were recorded in the antihistamine groups (data not shown). At the end of follow-up, none of the patients from the cetirizine group had poor control, although the difference with the other groups was not statistically significant. However, linear mixed model analysis revealed a trend toward lower DLQI scores throughout follow-up in patients receiving cetirizine (estimate: −1.44, 95% CI, −2.92 to 0.04; P=0.056).

**Table 2.** Logistic Regression Analysis: Relationship Between Change in Histamine Wheal Size (HDWC% >75) and Disease Control

<table>
<thead>
<tr>
<th>Follow-up, wk</th>
<th>Unadjusted OR (95% CI)*</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4.48 (2.06-9.76)</td>
<td>&lt;.001</td>
<td>4.61 (2.07-10.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>4</td>
<td>9.13 (3.04-27.44)</td>
<td>&lt;.001</td>
<td>9.05 (2.99-27.33)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>6</td>
<td>4.73 (1.36-16.47)</td>
<td>.01</td>
<td>4.92 (1.40-17.27)</td>
<td>.013</td>
</tr>
<tr>
<td>8</td>
<td>6.78 (1.54-29.91)</td>
<td>.01</td>
<td>6.86 (1.55-30.35)</td>
<td>.011</td>
</tr>
</tbody>
</table>

*Adjusted for city of residence, age, gender, and onset of disease.
Discussion

Since histamine plays a major role in the pathophysiology of urticaria [17], use of the histamine-induced wheal and flare reaction to evaluate the pharmacodynamics and activity of histamine receptor antagonists is widely accepted [10,18]. However, there is no agreement on the usefulness of SPT as a surrogate measure of clinical efficacy. Devillier et al [19] searched the literature from 1980 to 2006 and concluded that histamine SPT or intradermal testing should not be used to compare the clinical efficacy of antihistamines in allergic rhinitis or chronic urticaria. On the other hand, in a more recent study published in 2012, Church and Maurer [10] concluded that the wheal and flare response appears to be the best tool for evaluation of the effectiveness of antihistamines in clinical practice. These reviews are limited by the fact that their evaluation of whether histamine skin tests can predict clinical response is hampered by the diversity of the protocols used, most of which evaluated the potency of histamines only in healthy volunteers. In addition, few compared the effects of a high dose of antihistamines.

The primary objective of our study was to assess whether the reduction in the dimensions of the wheal or flare could be useful for predicting clinical response. We observed that using histamine SPT as a prognostic evaluator has certain limitations. With an HWDC >75%, histamine SPT identified 94% of patients with a clinical response to antihistamines; however, with an HWDC <25%, disease was controlled in only 50% of patients. Nevertheless, patients with well-controlled disease and HWDC <25% are less likely to respond with conventional doses, and most (62%) required an increased dose. Therefore, the histamine SPT could predict patients who will present a marked clinical response to antihistamines but has limited utility for identifying nonresponders.

Devillier et al [19] concluded that measuring suppression of the wheal and flare reaction by antihistamines does not correlate with clinical efficacy based on multiple intervening factors, including—but not limited to—dose, metabolism, and effects of other mediators on the course of chronic urticaria. Kalogeromitros et al [20] observed that environmental and metabolic factors such as menstrual cycle could affect test reactivity [20]. Consistent with findings reported elsewhere [21], a pilot study performed by our group showed that measurement of wheal size is reproducible, with a low coefficient of variation at histamine concentrations of 10 mg/mL and 100 mg/mL during follow-up in a control group (data not shown). In contrast, the flare reaction disappeared in most patients; therefore, it may be necessary to assess the flare reaction using more specialized methods of measurement such as thermography or laser Doppler flowmetry. In this study, DLQI was more informative than the UAS in clinical monitoring, perhaps because UAS7, which covers a longer period of time, was not applied [22].

The significant changes in symptom relief and decreased impairment of activity associated with the 5 antihistamine groups included in this trial are consistent with previous findings [6]. Using conventional doses, we observed that 4 weeks was better than 2 weeks for evaluation of the clinical effect (additional 22% of patients with DLQI<5) and that an additional number of patients (18%) achieved good control (DLQI<5) when the daily dose of the antihistamine was increased. A longer-term evaluation did not show a significant increase in the number of patients for whom antihistamines had a beneficial effect.

We found that urticaria was controlled (DLQI<5) with antihistamines in most patients, a finding that contrasts with those of previous studies [23,24]. This variation could be the result of differences in the methods used to evaluate control: counting the number of wheals and rating pruritus are not suitable approaches to comprehending the full impact of chronic spontaneous urticaria [23]. A better approach is to measure impairment of quality of life using the DLQI, as we did in our study. Another important difference between studies is the type of population. Since we did not include patients with inducible urticaria, our results cannot be generalized to patients with inducible urticaria or angioedema syndromes [24]. The impact of the geographical and cultural characteristics of each population may have played a role, but these factors have been poorly explored for urticaria.

Some forms of urticaria may be caused by non–histamine-mediated mechanisms [25,26], thus explaining why not all patients respond well to antihistamines. Although this study was not designed to compare antihistamines, we did observe a tendency toward a better clinical response with cetirizine. Nevertheless, it was the only antihistamine for which 2
patients dropped out owing to sedation. Sedation was less common with fexofenadine than with the other antihistamines, although in most cases, sedation was not a critical problem, even at high doses, for bilastine, desloratadine, or ebastine. In 11 patients who experienced sedation but maintained control of symptoms at conventional doses, doses were administered on alternate days, a regimen that is neither encouraged nor discouraged in current guidelines. Of note, subjective patient reports of lack of sedation do not guarantee that a particular drug has not crossed the blood–brain barrier, and objective psychometric assessments are essential to determine the extent of impairment [8].

In conclusion, evaluation of the diameter of a wheal induced by the histamine SPT could be a useful tool for predicting which patients will respond well to antihistamines, although this approach is of limited use for identifying nonresponders. The clinical significance of these data could be relevant when developing novel regimens for treatment of urticaria. Increasing the dose of antihistamines could be useful in patients whose symptoms remain uncontrolled after 1 month with conventional doses of cetirizine, fexofenadine, bilastine, ebastine, or desloratadine.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


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Jorge Sánchez
Kra 42 #7A Sur 92 Apto 1710 Bloq 3
Cartagena, Colombia
E-mail: jotamsc@yahoo.com