Prevalence of drugs as triggers of exacerbations in chronic urticaria

Short tittle: Drugs as triggers of chronic urticaria

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ABSTRACT

Background: Many patients with chronic spontaneous urticaria (CSU) identify different drugs as triggers of their symptoms and often make restrictions without enough information.

Objective: To estimate the clinical impact of the drugs most frequently reported as suspects of CSU exacerbations by patients.

Methodology: All subjects were questioned about their clinical history of urticaria and drug reactions. Drug challenge tests were performed on each patient with the suspicious drugs. A group of healthy subjects were included as control to evaluate the prevalence of self-reported drug reactions.

Results: 245 patients with CSU and 127 healthy subjects were included. 92 (37.5%) patients and 30 (23,6%) subjects in the control group reported at least one adverse drug reaction. Non-steroidal anti-inflammatory drugs (NSAIDs) (27.7%) and Beta-lactams (9.4%) were the most common drugs reported by CSU group and the control group, respectively. Positive results of challenge tests were lower than self-reports in CSU (13%) and the control group (0.7%).

Conclusion: Self-report is usually not enough to determine a drug reaction. Drug reactions to NSAIDs and beta-lactams are higher among patients with CSU than in subjects without urticaria. Drug challenge tests should be offered early during medical evaluation to avoid unnecessary restrictions.

KEY WORDS: Urticaria; Angioedema; Drugs; Aspirin; NSAIDs.

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INTRODUCTION

Urticaria is a common cutaneous disease. The chronic form affects around 1% of general population and has a significant impact on the quality of life. Chronic Spontaneous Urticaria (CSU) can appear at any time, and for this reason patients frequently associate foods, drugs and different activities as possible causes of exacerbations [1,2]. Usually, patients avoid suspicious medication and this conduct has implications for their clinical management. In acute urticaria, drugs can play a causal role in some patients, but in chronic forms the role of medications is not so clear [3].

Some studies have evaluated how often the triggers considered by the patient are actually associated with their symptoms. In a previous study, we observed that the prevalence of inducible urticaria by self-report was 75%, but the prevalence from positive challenge tests was only 36%, indicating that a high number of patients makes unnecessary restrictions [4]. According to self-reports, non-steroidal anti-inflammatory drugs (NSAIDs) are the drugs with the greatest association with exacerbations in CSU, being related in 20% to 50% of patients. In the 2018 GA^{2}LEN/WAO/EAACI guidelines, recommend avoidance of suspected triggers, including drugs such as NSAIDs. Then, if the patient is taking drugs that might exacerbate CSU those should be omitted. However, unless an objective evaluation is carried out, the restrictions may be unnecessary but may cause a deterioration in the quality of life of the patients [5,6]. However, to demonstrate “a clear relationship”, challenge tests are required and most studies evaluating the prevalence of drugs as a cause or trigger of chronic urticaria do not include this diagnostic test. There are few studies evaluating with objective diagnostic tests the clinical impact of drugs as triggers of urticaria in CSU patients: Sanchez M et al., [7] using oral challenges with Acetyl-salicylic Acid (ASA), observed that 12% of patients with chronic urticaria had NSAIDs-exacerbated cutaneous

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disease (NECD). The comparison between self-report and challenge test results suggest that self-report evaluation is not adequate to study drugs as triggers of CSU. In addition, the prevalence of NSAIDs as triggers of CSU has been evaluated in some studies, but there is less information about the role of other drugs.

In this study, we explore the prevalence of different drugs as triggers of urticaria in patients with CSU, taking into account the self-report and the challenge test. We also compared this frequency with the one found in a control group of subjects without CSU.

METHODOLOGY

Study population.

Based on a previously described cohort (URTICA project, ClinicalTrials.gov Identifier: NCT01940393), we conducted a multi-center, prospective study. The recruitment of patients was open, and participated patients from 6 different clinical centers. We collected data from patients older than 12 years diagnosed with CSU, which was defined as the recurrence of hives, with or without angioedema, in more than 3 days per week and persisting for at least 6 weeks. The exclusion criteria included the following: systemic disease that could explain the hives; use of systemic corticosteroids during the 3 weeks before recruitment; immunodeficiency, dermatitis, and/or any other disease that could alter the results of the skin test.

A control group of healthy people from the university of Antioquia (Medellin – Colombia) older than 12 years without history of chronic urticaria in the life were invited to compare the results of questionnaires and challenge tests. In the control group the subjects answered a questionnaire about drug reactions and challenge tests were performed in those patients

who reported an adverse reaction other than a clear history of anaphylaxis or a severe drug reaction (DRESS, NET, etc.)

Study design.

The aim of the study was to describe epidemiological data, on the possible triggering factors of urticaria exacerbations among patients with CSU. First, both groups were questioned about adverse drug reactions (ADR). As a second step, drugs suspected by patients or control subjects of being triggers of urticaria exacerbations were directly tested by challenge tests. After one year we asked patients with a self-report of a drug reaction and a negative challenge test if they had used the medication.

Evaluation of drug reactions with challenge tests.

Oral challenge test was blind and placebo controlled. Challenge tests with drugs suspected by the patients (one or more per patient) were performed using the same protocol: The equivalent to one daily dose of the drug was administered in two doses (10% and 90% respectively) separated by 1 hour. In patients with suspected severe reactions (e.g., anaphylaxis or respiratory distress), the administration of the daily dose was divided into 4 steps (10%, 20%, 30% and 40% respectively) separated by an hour. After the final dose was administered, the observation period at the clinic was 2 hours and patients were also instructed to notify in case of delayed reactions outside the clinic. The same protocol was performed for all challenge tests unless the protocols published in medical literature suggested any major changes for a specific drug.

Patients with a clear anaphylactic reaction in less than one hour after consuming the suspected drugs 12 months before recruitment, were considered positive and the challenge test was avoided. Anaphylactic reactions without a clear clinical history or any other type of reaction were confirmed by challenge test.

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The result of the challenge was considered positive only in the presence of objective symptoms on the skin or other system. If the patient after the first administration of the medication had an unclear reaction the treating physician could divide the following dose into a maximum of 4 doses with an interval of one hour between administrations.

Statistical analyses.

Statistical analyses were performed using the IBM SPSS Statistics for Windows program, Version 21.0 (IBM Corp, Armonk, New York). The mean and SDs were reported for the descriptive variables. The differences between proportions were analyzed using the Pearson´s chi-squared test. Given the sample size of previous studies that evaluated the presence of drug reactions in patients with CSU, we considered that a sample of at least 150 patients would be adequate to guarantee a power of 90% and an alpha error of 0.05 for the measurement of primary outcome. A "*p*" value of less than 0.05 was considered statistically significant.

RESULTS

General characteristics

A total of 245 patients with CSU (CSU group) and 127 healthy subjects (Control group) participated in this study (Table I). Atopy and asthma were significantly more frequent in patients with CSU than in the control group (*p* 0.05). In both groups, more than 20% of the people reported adverse skin reactions at some point in their life with one drug (37.5% vs. 23.6% respectively *p* 0.04) being higher in the CSU group. The average time between the adverse drug reaction and the performance of the challenge test was lower in the CSU group (9 months vs 14 months), but it was not statistically significant (*p* 0.07). No other differences in general characteristics were observed between the CSU group and the control

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group. During the recruitment phase, patients UAS was 3±1; 68% of them over 2 points indicating that urticaria was active.

Adverse drug reactions according self-report.

According to self-report (92 patients in CSU and 30 in control group), the most common drugs reported were (Figure 1): NSAIDs (68 (73.9%) of 92 patients), vs 10 (33.3% of 30 patients) respectively), Betalactamics (28 (30.4%) vs 12 (40%)), and "Natural Medicines" (8 (8.6%) vs 0) which included herbal over-the-counter products. Among NSAIDs, ASA (n=24), ibuprofen (n=24) and meloxicam (n= 20) were the most frequently reported, and from Beta-lactams was amoxicillin. Of the CSU group, 64% of patients with ADR to NSAIDs reported at least 2 different pharmacological agents.

"Other drugs" were more frequently reported in patients with CSU. 18 patients had self-reported adverse reactions with two drugs from unrelated groups, 3 of them with three pharmacological agents, and 2 with more than three. All subjects with a self-report of DAR restricted the suspicious drug and 45% made additional restrictions of non-related drugs to the clinical history of reactions. The main reasons for these restrictions were "doctor´s order" (33%) and "fear" (28%).

Two patients had a clear history of urticaria 6 months prior to the study enrollment and they were considered positive without an oral challenge test. In the rest of patients with suspected adverse drug reaction, the challenge test was performed.

Challenge tests and their association with self-report.

Of the total number of subjects in each group (245/127), 32 patients (13%) had a positive challenge test in the CSU group vs. one in the control group (0.7%) (Figure 2a). The cutaneous reactions were the most frequent (n 27) followed by the respiratory ones (n 7).

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Two patients had lower respiratory and skin symptoms and required treatment with adrenaline.

The CSU group had a better agreement between the self-report and the positive challenge tests results than the control subjects (Figure 2b).

Among patients with history of ADR with NSAIDs (CSU n 68 vs 10 in the control group), 28 CSU patients (41.1%) had a positive challenge test vs 0 in the control group.

One subject from the control group (10% 1/10) presented a positive challenge test with amoxicillin, and 6 patients from the CSU group (42.8% 12/28). There were no positive challenge test results for "natural medicines" in none of the groups.

When evaluating which factors could influence the results, we observed that unlike the control group, in the CSU group there was a higher frequency of atopy among the subjects with positive challenge tests (OR 3.14 CI 1.18 – 4.29 *p* 0.03). Other factors as age, gender and age of onset of the disease were not statistically significant.

Follow-up

30 patients had an indication to consume the medication; 22 of them consumed it without problems, one patient reported an intestinal reaction and another cutaneous one of erythema, but both continued using the medication for the indicated time. Six patients did not consume it because despite the negative result of the test they were afraid to consume it.

DISCUSSION

In CSU it is common for patients to associate the onset of symptoms with different activities they were performing [4], or medications [1] or foods [8] that they were consuming near the time of the reaction. Usually, patients avoid the suspicious medications and this has implications in their clinical management. Frequent use of drugs like NSAIDs

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has been paralleled by increasing occurrence of adverse reactions, which vary from mild local skin rashes or gastric irritation to severe, generalized symptoms and even life-threatening anaphylaxis [9]. Although NSAIDs have been recognized as a frequent cause of exacerbation among patients with chronic or acute urticaria [7,10], the actual incidence by objective tests such as the challenge test, its little known. In addition, the effect of other medications as triggers in patients with CSU is practically unknown [11].

Similarly, to what we previously reported about inducible urticaria [4], in this study we found a high frequency of self-reported ADR among CSU patients, but also in control subjects. When performing the challenge tests, we found that one out of every 3 patients with self-reported ADR has a positive challenge test result, while among the control group less than one in 10 subjects do. The low concordance between the self-report and the provocation test in both groups suggests that it is necessary to confirm the self-report through controlled tests to avoid unnecessary restrictions.

Despite the low association between the self-report and the challenge test, patients with urticaria had a much higher frequency of reactions than the control group, not only for NSAIDs, but also for beta-lactams. Sanchez M et al. [12], observed an association between ADR (by self-report) and higher levels of total IgE and sIgE for mites. Although many studies suggest that skin reactions to NSAIDs have different pathophysiological mechanisms from those responsible for common allergic (atopic) diseases [7,13,14], similar to Sánchez M, et al., the high prevalence of atopy and asthma observed in our patients with CSU is puzzling. It´s noteworthy that, similar to these results, Kim et al., observed that patients with aspirin-exacerbated acute and chronic urticaria showed a higher prevalence of atopy and total serum IgE [15]. The reasons for this association (atopy // urticaria // ADR) are not currently known but suggest that in some patients the development of atopy shares

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mechanisms with the development of hypersensitivity to medications. A common route for these two processes to develop could be the synthesis of leukotrienes. Several lines of evidence have suggested an interaction between IgE immune responses and the leukotriene pathway, for example, the proximity between the genes encoding IgE and leukotrienes [16] and the association of leukotrienes with hypersensitivity reactions that can affect the lung, such as NERD (NSAIDs-exacerbated respiratory disease) [17]. However, the role of leukotrienes in urticaria is controversial and this hypothesis wouldn´t clearly explain the association we found between atopy and reactions to other medications other than NSAIDs, such as beta-lactams.

An additional question that may arise from the association between atopy // urticaria // ADR, is whether those subjects with atopy, or those with a history of ADR, may have an increased risk of developing CSU. At the time, we do not know the answer to this question; according to the results of Doña I, et al. [18], who did a 12-year follow-up of 190 patients with NSAID-induced urticaria / angioedema, there is not an increased risk of developing CSU compared to the control group, but other studies found different results [19,20].

The consumption of products without medical prescription for the management of diseases is quite common in our population. Although there is evidence that many of these products can produce a non-specific degranulation of the mast cell and the development of acute urticaria [21], the subjects in our study who consumed these "drugs" from both groups tolerated the challenge test.

Our study has certain weaknesses. Because the challenge tests were only performed in the population with self-reported ADR, it is possible that the number of adverse reactions is underestimated since some subjects had not consumed the reported medications and others had consumed it more than a year ago, it cannot be ruled out that currently they have an

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ADR, especially in the CSU group. However, from the clinical point of view, subjects who do not have a history of ADR have no contraindications to use any medication, including patients with CSU. Therefore, it´s not necessary to perform challenge test on them. Although challenge test is the gold test to determine the association between an exposure and the development of immediate symptoms, conducting a challenge test does not ensure 100% tolerance to new exposures; an increase in the dose delivered could lead to a reaction not detected during the test. However, it is the most objective method to evaluate the reaction with a medication, Additionally, of the 24 patients who consumed the medication on an outpatient basis, 22 tolerated it without problems and the 2 who reported mild reactions finished the medication period.

Although our results suggest a high frequency of reactions to NSAIDs (33%) among the population with urticaria, other studies suggest a lower frequency (12%) [12], so it is necessary to perform multi-center studies to consider other factors that may be influencing these differences.

Among the strengths of our study is the use of a control group to evaluate the frequency of self-report, as well as the performance of challenge tests with the suspicious medication for each subject. When trying to compare our results with other studies of similar design in the CSU population, we found that most of them focused on patients with acute urticaria; they made the diagnosis based on the self-report and in almost all cases they evaluated the role of the NSAIDs but no other medications such as beta-lactams.

In conclusion, the self-report is usually not enough to determine an ADR and challenge tests must be offered early during the medical evaluation to avoid unnecessary restrictions. The pharmacological reactions to NSAIDs and beta- lactams among patients with CSU are higher than in subjects without urticaria.

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TABLES AND FIGURES

Table 1. General characteristics.

Characteristics	CSU group (n 245)	Control group (n 127)	*P*
Age (y)	28 (14-50)	27 (15-55)	> 0.05
Sex: female, n (%)	150 (61)	79 (62)	> 0.05
History of drug skin reaction (%)	92 (37)	30 (23)	0.04
Time since drug reaction (Months)	9 (3 – 24)	14 (6 – 36)	> 0.05
Atopy, n (%)	105 (42)	37 (29)	0.04
Asthma, n (%)	36 (14)	5 (3)	0.05
Rhinitis n (%)	105 (42)	50 (39)	> 0.05
Age of onset CSU (y)	25 (4-49)	NA	NA
DLQI score, mean + SD	15 $\pm$ 3	NA	NA
UAS, mean + SD	3 $\pm$ 1	NA	NA

Table 1. Characteristics of the study population.

Figure 1. Self-report of Adverse Drug Reactions.

Figure 1: Medications most frequently reported by patients with CSU and the control group.

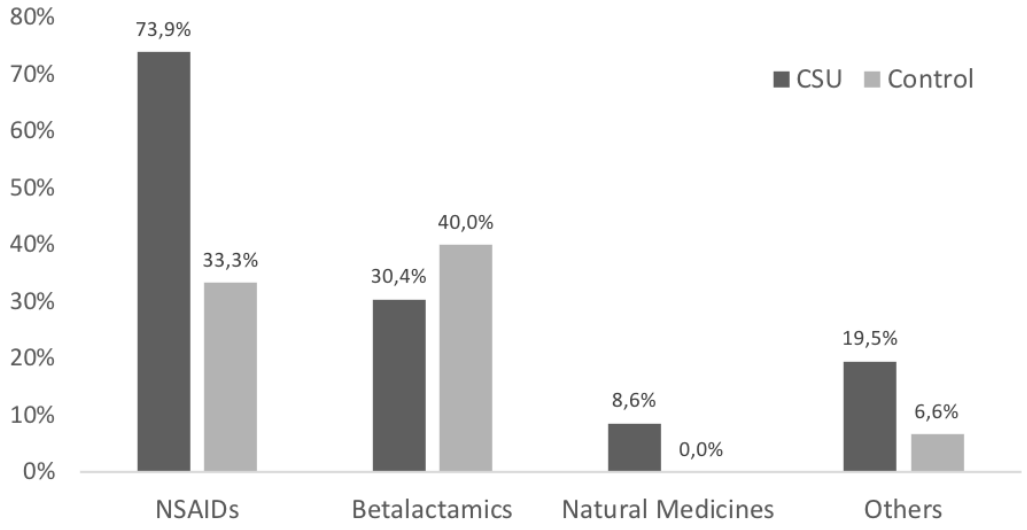

Figure 2. Comparison of Self-report and Challenge test results among CSU and control group.

Figure 2: In figure 2a the frequency was calculated according the total number of subjects in each group (247/127). Figure 2b, presents self-report subjects from each group (92/30) and negative (black) or positive (Gray) challenge tests. SR: Self-report. CT: Challenge Test.