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ORIGINAL PAPER

THE SAFETY PROFILE OF ETORICOXIB IN AUTOREACTIVE URTICARIA

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Abstract. Background: A subset of chronic idiopathic urticaria (CIU) has recently been classified as autoreactive urticaria on the basis of the presence of anti-IgE and/or anti-IgE receptor antibodies. Such antibodies can be detected by skin testing with autologous serum (ASST). The clinical forms of hypersensitivity to nonsteroidal antiinflammatory drugs (NSAIDs) are rhinitis, frequently associated with nasal polyps, aspirin-intolerant asthma or nonselective NSAIDs, urticaria / angioedema, anaphylaxis and, rarely, hypersensitivity pneumonitis. In subjects with hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) and autoreactive urticaria, tolerance to selective COX-2 inhibitors has not been evaluated in large series of well-phenotyped cases. **Methods:** We evaluated 238 patients referred to our clinic, during a 12-month period, for evaluation of chronic urticaria (more than six-week duration). Autologous serum test was performed in all these patients (ASST). From them, we selected subjects having history of hypersensitivity to NSAIDs, manifested as urticaria and/or angioedema. All patients with a history of hypersensitivity to NSAIDs underwent drug challenge test with etoricoxib. The cumulative dose was 60 milligrams. **Results:** One hundred thirty-three patients (55.88%) were evaluated having strong positive ASST. In this group we detected ninety-eight patients (73,68%) with a history of hypersensitivity to NSAIDs (urticaria and/or angioedema). In the group of patients with negative ASST, twenty patients had a history of hypersensitivity to NSAIDs. All patients with this history (one hundred eighteen) underwent drug challenge test for etoricoxib 60 mg total dose. Only two patients (1,69%) developed urticaria in approximately two hours after reaching the total dose. Both cases belonged to the group with positive ASST. **Conclusion:** The hypersensitivity to NSAIDs was more frequent in patients with positive ASST. Etoricoxib is a COX-2 selective inhibitor and appears to be well tolerated by patients with history of hypersensitivity to traditional NSAIDs (98,31%). These findings suggest that a common mechanism may be responsible for the pathogeneses of both autoreactivity and NSAID hypersensitivity in chronic urticaria. It might be further speculated that delayed, prolonged, and pronounced autoreactivity may be a possible predictor for multiple NSAID sensitivity. Patients with autoreactive urticaria should avoid all inhibitors of COX-1. These patients may use COX-2 inhibitors, after single-blinded oral challenge.
Key words: autoreactive urticaria, autologous serum skin test, nonsteroidal antiinflammatory drugs, etoricoxib

Introduction

Urticaria is defined in the last position paper EAACI/GA2LEN/EDF/WAO as a heterogeneous group of disorders with distinct characteristics, urticarial lesion, with edema and vasodilation in the superficial dermis, papule of varying sizes surrounded by a reflex erythema, sometimes associated with itching and burning, and is sometimes associated angioedema. Urticarial papule appears rapidly and resolves within 1-24 hours without residual lesions [1] referințele numerice între paranteze drepte .

A unified and simple scoring system, the urticaria activity score (UAS), was proposed in the last version of the guidelines. The use of UAS facilitates comparison of study results from different centres. The UAS (Table I) is based on the assessment of key urticaria symptoms (wheals and pruritus). An evaluation of disease activity by urticaria patients

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and their treating physicians is also suitable [1], a scoring system that has already been validated [2]. As urticaria symptoms frequently change in intensity, overall disease activity is best measured by advising patients to document 24-h self-evaluation scores for several days. The UAS, i.e. the sum score of 7 consecutive days, should be used in routine clinical practice to determine disease activity and response to treatment of chronic urticaria patients [1].

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate(20-50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Table I. Assessment of disease activity in urticaria patients

Sum of score: 0–6. T. Zuberbier et al, Position paper EAACI/GA2LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria Allergy 2009: 64: 1417–1426

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According to European guidelines, chronic autoreactive urticaria is a subgroup of chronic urticaria. The mechanism may be mediated by functional autoantibodies directed against the IgE receptor. Such antibodies can be detected by skin testing with autologous serum [3].

NSAIDs are the drugs most frequently implicated in hypersensitivity reactions by inhibiting the cyclooxygenase (COX) [4]. According to new data it seems that inhibition of COX 1 enzyme is the main mode of occurrence of hypersensitivity to NSAIDs.[5] Many studies have shown good tolerance of NSAIDs which are highly selective inhibitors of COX-2 [6].

The subject of our study was to verify the tolerance of etoricoxib in Romanian patients with urticaria and history of hypersensitivity to nonselective NSAIDs.

Material and Methods

We included in our study group 238 patients, referred to our clinic, during a 12-month period, for evaluation of chronic urticaria (more than six-week duration), we performed autologous serum skin test (ASST). Among these we selected subjects having history of hypersensitivity to NSAIDs, manifested as urticaria and/or angioedema.

ASST was performed according to EAACI/GA^{2}LEN (European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network) task force consensus report guidelines. Autologous serum was obtained by centrifugation (3000*rpm*,1348 *g*, 4 min, 22°C) from venous blood (cubital vein) in sterile Vacuette® serum tubes without clotting accelerator, allowed to clot for 30 min. A samples 50 μL A.S. and 0.9% saline (from sterile individual vials) separately were injected intradermal into volar forearm exposed upward, with the 29-gauge needle, at 15-degree angle at least 3-5 cm apart. H1 antihistamines were withdrawn at least two days and systemic corticosteroids for two months. The autologous serum skin test was considered strong positive if erythematous papule diameter was at least 5 mm higher than the control test at 30 min.

Screening for HIV-1 and -2, HBV and HCV serological markers was performed in all patients with written informed consent obtained.

Clinical monitoring of disease activity was performed by using urticaria activity score (UAS) of 0-6 points, depending of the daily number of wheals and the intensity of pruritus.

All patients in the study were subjected to drug provocation test (DPT) with a total dose of 60 mg etoricoxib. DPT was conducted, under medical supervision to highlight or exclude the diagnosis of drug hypersensitivity and in some cases to provide an alternative medication to the patient. DPTs were performed under medical surveillance with gradually increasing doses until the cumulative dose of sixty milligrams. Patients were monitored in terms of hypersensitivity reactions for 24 hours using UAS.

Results

We screened 238 adult subjects with chronic urticaria with a mean age of 43.19 ± 15.4 years (limits 18; 82 years), 70.16% females (figure 1).The mean duration of urticaria was 30.35 ± 24.11 months, treated with standard or high doses of H_1 antihistamines.

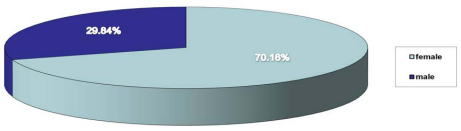

Figure 1. Sex ratio of patients with CU screened (n=238) during one year-period

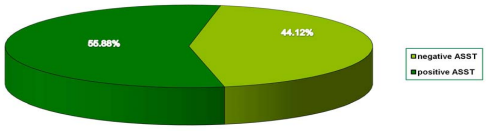

Figure 2. Percentage of patients with positive ASST (n=133 from total pacients=238)

Figure 3. Strong positive autologous serum skin test

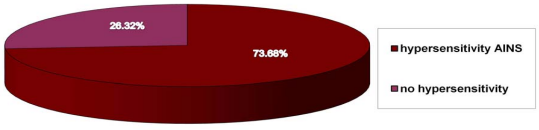

Figure 4. Percentage of patients with hystory of hypersensitivity to NSAIDs in the group with positive ASST (n=98 from total pacients=133)-73.68%

133 patients (55.88%) were evaluated having strong positive ASST (figures 2, 3), from which we detected ninety-eight patients (73.68%) with a history of hypersensitivity to NSAIDs (urticaria and/or angioedema) (figure 4). In the group of patients with negative ASST (105 patients), twenty patients (19.04%) had a history of hypersensitivity to NSAIDs (figure 5). All patients with this history (one hundred eighteen) underwent drug challenge test for etoricoxib 60 mg total dose (figure 6). Only two patients (1,69%) developed urticaria in

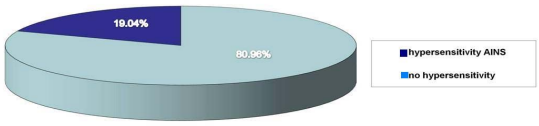

Figure 5. Percentage of patients with history of hypersensitivity to NSAIDs in the group with negative ASST (n=20 from total patients=105)

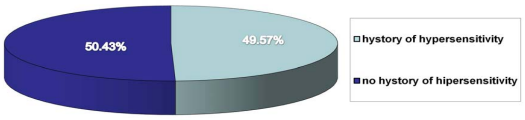

Figure 6. Percentage of patients with history of hypersensitivity to NSAIDs (n=118 from total patients=238)

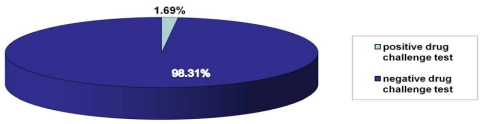

Figure 7. Percentage of patients with positive drug challenge test to etoricoxibum 60 mg (n=2 from total patients=118)

approximately two hours after reaching the total dose (figure 7). Both cases belonged to the group with positive ASST and their urticaria activity score was four (table I).

Tests were performed during the remission of the disease when patients were not taking antihistamines or other background medication. All patients in the study were informed about the risks of challenge drug test and signed the written consent of test performance).

Of all patients with chronic urticaria enrolled in our study, 49.57% had a history of hypersensitivity to NSAIDs. Percentage increases significantly in the group of patients with positive autologous serum test (73,68%).

Regarding the safety of etoricoxib in terms of allergy, our data are encouraging. Only two patients in one hundred eighteen patients with a history of hyper-reactivity to NSAIDs had urticaria during the drug provocation test.

In patients with positive autologous serum skin test, history of hypersensitivity to NSAIDs was

present in 73.68% **(98/133)** of patients, while those with negative ASST, the percentage of patients with this history was 19.04%**(20/105).**

The relative risk was 3,869 (73,68/19.04). In other words, the risk for developing hypersensitivity to NSAIDs in our study group was four times higher in patients with positive autologous serum test compared with those in whom the test was negative.

Rates of hypersensitivity to NSAIDs were:

- For those with positive ASST= 98/133
- For those with negative ASST= 20/105

The ratio of two rates was Odds Ratio: the ratio of 98/133 (0.7368) and 20/105 (0.19) = 3, 877 (table II).

and hypersensitivity to NSAIDs [12]. The rates of autoreactivity prevalence were 93.3% (28/30) and 17.5% (14/80) in patients with and without ASA/NSAID intolerance, respectively (P<.001). Thirteen of the 25 ASST-positive patients (52%) who had single or multiple NSAID intolerance showed early (before or at 30 min) and mild autoreactivity of short duration, whereas 15 of the remaining 17 ASST-positive patients (88.2%) who all had multiple NSAID intolerance showed delayed (later than 30 min) and prolonged autoreactivity (P<.05).

In our study, the hypersensitivity to NSAIDs was more frequent in patients with positive ASST. Moreover, in the case of two patients with positive oral challenge test to etoxicoxib the ASST was of

		Hypersensitivity to NSAIDs		
		Hs AINS"+"	**Hs AINS"-"**	**Total**
Autologugus serum skin test	**„+" ASST**	**98**	**35**	**133**
	„-„ ASST	**20**	**85**	**105**
	Total	**118**	**120**	**238**

Table II. Relative risk and Odds Ratio was statistically significant:

Discussions

The prevalence of hypersensitivity to NSAIDs varies in different studies between 0,5 percent to 1,9% of the general population, whereas NSAIDs are responsible for 21 to 25% of all adverse reactions to drugs [7]. One third of patients with chronic urticaria shows exacerbation of the eruption after administration of NSAIDs. Exacerbations of urticaria and/or angioedema induced by COX-1 inhibitors are observed more often with drugs of the heteroaryl group (naproxen, diclofenac, ibuprofen) [8]. Various genetic polymorphisms, including genes coding for HLA antigens, LTC4 synthase, 5 lipooxygenase, and the high affinity receptor for IgE have been observed in these patients [9].

In our study this hypersensitivity to NSAIDs in patients with chronic urticaria was 49.57%. The percentage increased significantly in patients with autoreactive urticaria. If the positivity of autologous serum skin tests coexisted, the hypersensitivity reactions to NSAIDs increased up to 73.68%. (percentages were obtained by analyzing the patient over a period of one year).

Significantly higher prevalence of chronic urticaria in women (70.16%) and percentage of positivity of the test to autologous serum in patients with chronic urticaria (55.88%) were consistent with results of similar studies [10,11].

Erbagci Z published in 2004 a study on the possible correlation between the positivity ASST high intensity and persistent over one hour.

These findings suggest that a common mechanism may be responsible for the pathogeneses of both autoreactivity and NSAID hypersensitivity in chronic urticaria. It might be further speculated that delayed, prolonged, and pronounced autoreactivity may be a possible predictor for multiple NSAID sensitivity.

Patients with CIU intolerant to ASA/NSAIDs should avoid all inhibitors of COX-1. These patients may use COX-2 inhibitors, after single-blinded oral challenge [13,14].

Etoricoxib is a COX-2 selective inhibitor and appears to be well tolerated by patients with history of hypersensitivity to traditional NSAIDs (98,31%). Patients still need a test of tolerance drug under close medical supervision.

Conclusions

Screening for the presence of autoreactivity may be an important possible predictor for hypersensitivity to NSAIDs.

COX-2 selective inhibitor appears to be well tolerated by patients with history of hypersensitivity to traditional NSAIDs [15].

Abbreviations

NSAIDs - nonsteroidal anti-inflammatory drugs; COX-cyclooxygenase; CIU- chronic idiopathic urticaria; ASST- autologous serum skin test;

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