

## Oral aspirin challenges in patients with a history of intolerance to single non-steroidal anti-inflammatory drugs

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### Summary

**Background** In the clinical practice patients with a history of acute urticaria induced by a single non-steroidal anti-inflammatory drug (NSAID) and seeking for safe alternative drugs generally undergo tolerance tests with alternative NSAIDs that have little or no cyclooxygenase-1 (COX-1) enzyme inhibitory activity. This practice does not allow for the detection of single NSAID reactors and may lead to unnecessary avoidance of many potentially useful NSAIDs.

**Objective** Evaluate aspirin challenge as a means to distinguish single from multiple NSAID intolerance in patients with a clinical history of acute urticaria induced by a single NSAID.

**Methods** One hundred and seventeen otherwise normal subjects with a history of acute urticaria following the ingestion of a single NSAID (pyrazolones ( $n = 58$ ), nimesulide ( $n = 17$ ), propionic acid derivatives ( $n = 13$ ), aryl acetic acid derivatives ( $n = 14$ ), acetaminophen ( $n = 9$ ), piroxicam ( $n = 5$ ), and indometacin ( $n = 1$ )) underwent single-blind placebo-controlled oral challenges with aspirin. Aspirin-intolerant subjects underwent further tolerance tests drugs exerting little or no inhibitory activity on COX-1 enzyme (including paracetamol, nimesulide, rofecoxib, tramadol, and floctafenine).

**Results** Aspirin induced urticaria in 28/117 (24%) patients. Five out of 28 (18%) aspirin reactors did not tolerate alternative NSAID on subsequent oral challenges.

**Conclusion** In subjects with a history of urticaria induced by a single NSAID (other than aspirin) the diagnostic workup should start with an aspirin challenge in order to detect single/multiple NSAID reactors.

**Keywords** aspirin, drug allergy, non-steroidal anti-inflammatory drugs, oral challenge tests, urticaria  
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### Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), the most commonly prescribed drug class worldwide, are a rather frequent cause of immediate pseudo-allergic reactions. The multiplicity of NSAID-induced reactions along with the variety of terms employed to describe either respiratory or cutaneous drug-induced symptoms has generated much confusion in the past. Recently, Stevenson et al. [1] revised this issue and proposed a new classification system for allergic and pseudo-allergic reactions to NSAIDs. This classification distinguishes patients with underlying asthma or chronic urticaria exacerbated by several NSAIDs, otherwise normal subjects with urticaria induced by single or multiple NSAIDs, patients with single drug-induced anaphylaxis, and patients with mixed respiratory/cutaneous reactions induced by a single drug [1, 2]. It is now generally accepted that inhibition of cyclooxygenase-1 (COX-1) enzyme is the most likely pathogenic mechanism involved in reactions to multiple,

chemically unrelated substances, whereas reactions to single drugs are possibly IgE mediated [1, 2].

In the clinical practice, the main task of the allergologist is to classify correctly the patient with NSAID-induced urticaria using both clinical history and oral challenges. In most previous studies, tolerance tests with relative non-COX-1 inhibitors (including nimesulide, floctafenine, coxibs, paracetamol, and tramadol) have been carried out in NSAID-intolerant patients irrespective of clinical history [3–11]. While such practice may be appropriate in patients likely to react to several chemically unrelated COX-1 inhibitors (e.g. patients with chronic urticaria or aspirin-exacerbated respiratory disease) it is inadequate in subjects presenting with a history of intolerance to a single NSAID as it does not allow for diagnosis of single vs. multiple NSAID reactivity and may lead to unnecessary avoidance of potentially useful NSAIDs. Thus, patients with a history of single drug intolerance should theoretically be challenges first with strong COX-1 inhibitors other than the offending substance. However, so far this has been done only in limited series of patients with a history of drug-induced anaphylaxis [12–15], and occasionally in patients with a history single drug-induced urticaria [16–18]. The present study assessed aspirin tolerance in a large group

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of patients with a history of acute urticaria induced by a single NSAID.

## Patients and methods

### Patients

One hundred and seventeen subjects (male to female ratio 36/81; mean age 42 years, range 10–81 years) with an unequivocal history of recent (1–6 months before) acute urticaria/angioedema induced by a single NSAID other than aspirin seen at the allergy centres of Bollate hospital and Clinica San Carlo during the last 3 years were studied. In 21 cases the offending drug had caused urticaria episodes on more than one occasion. No patient reported urticaria episodes other than those induced by the offending drug. Pyrazolone drugs (including noramidopyrine, propiphenazone, feprazone, and aminophenazone) were the most frequently reported offending drugs ( $n = 58$ ), followed by nimesulide ( $n = 17$ ), aryl acetic acid derivatives (including diclofenac and ketorolac;  $n = 14$ ), propionic acid derivatives ( $n = 13$ ), acetaminophen ( $n = 9$ ), piroxicam ( $n = 5$ ), and indometacin ( $n = 1$ ). All the patients were asking for safe alternative drugs, and no subject had taken NSAID of any sort after the urticaria episode.

### Oral challenges

Due to the risk of severe adverse reactions patients were not re-challenged with the offending drug [19]. After an informed written consent was obtained, patients underwent single-blind placebo-controlled challenges with aspirin [20]. Placebo or aspirin (in identical opaque capsules) were given in a randomized sequence at least 1 week apart. In each session two doses of either placebo or active drug (first provocative dose: 125 mg; second provocative dose: 375 mg) were given 1 h apart. Patients were observed for 2 h after the last dose. Only the appearance of unequivocal urticaria with or without angioedema was considered as a positive reaction; urticaria was controlled by intravenous chlorfenamine 10 mg and the patient was observed for 1 further hour.

Patients who tolerated aspirin were considered true single-NSAID reactors. Aspirin-intolerant subjects were considered multiple-NSAID reactors and underwent further single-blind placebo-controlled tolerance tests with drugs exerting little or no inhibitory activity on COX-1, including acetaminophen, rofecoxib, nimesulide, tramadol, and/or flectafenine. These further tests were carried out at least 2 weeks after the positive challenge. Doses challenged are shown in Table 1.

## Results

Challenge tests results are summarized in Table 2. No reaction to placebo was observed. Eighty-nine out of 117 (76%) patients tolerated aspirin whereas 28 (24%) experienced urticaria that was easily controlled by chlorfenamine. In most cases (21/28 (75%)) aspirin reactivity occurred after the first dose of 125 mg. No patient experienced respiratory symptoms, gastrointestinal symptoms, or hypotension. The

**Table 1.** Provocative doses employed for oral challenges with different NSAIDs

| Drug          | First provocative dose (mg) | Second provocative dose (mg) |
|---------------|-----------------------------|------------------------------|
| Aspirin       | 125                         | 375                          |
| Acetaminophen | 125                         | 375                          |
| Rofecoxib     | 6                           | 19                           |
| Nimesulide    | 25                          | 75                           |
| Flectafenine  | 50                          | 150                          |
| Tramadol      | 25                          | 25                           |

NSAIDs, non-steroidal anti-inflammatory drugs.

**Table 2.** Challenge tests results

| Offending drug       | No. | Aspirin      |                  | Weak COX-1 inhibitors |
|----------------------|-----|--------------|------------------|-----------------------|
|                      |     | Tolerant (%) | Not tolerant (%) | Not tolerant (%)      |
| Pyrazolones          | 58  | 45 (78)      | 13 (22)          | 2/13 (15)             |
| Diclofenac/ketorolac | 14  | 10 (71)      | 4 (29)           | 1/4 (25)              |
| Piroxicam            | 5   | 3 (60)       | 2 (40)           | 1/2 (50)              |
| PAD                  | 13  | 8 (62)       | 5 (38)           | 1/5 (20)              |
| Nimesulide           | 17  | 13 (76)      | 4 (24)           | 0/4 (0)               |
| Acetaminophen        | 9   | 9 (100)      | 0 (0)            |                       |
| Indomethacin         | 1   | 1 (100)      | 0 (0)            |                       |

PAD, propionic acid derivatives; COX-1, cyclooxygenase-1.

28 aspirin reactors had a history of urticaria induced by pyrazolones ( $n = 13$ ), diclofenac/ketorolac ( $n = 4$ ), piroxicam ( $n = 2$ ), propionic acid derivatives ( $n = 5$ ), and nimesulide ( $n = 4$ ).

The 28 aspirin reactors underwent a total of 65 further tolerance tests with alternative drugs: 28, 16, 10, 8, and 3 with acetaminophen, rofecoxib, nimesulide, tramadol, and flectafenine, respectively. None of the patients recalled the ingestion of the challenged drugs before. Five out of 28 (18%) patients experienced a total of seven urticaria episodes following the oral administration of acetaminophen, nimesulide, and rofecoxib in four, two, and one cases, respectively. At least one safe alternative NSAID was eventually found in all cases. The four subjects with a history of nimesulide-induced urticaria who did not tolerate aspirin on oral challenge underwent a total of eight further challenges (two each) with alternative substances. No reactivity was observed to paracetamol ( $n = 4$ ), rofecoxib ( $n = 2$ ), tramadol ( $n = 1$ ), and flectafenine ( $n = 1$ ).

Four out of 28 (14%) aspirin reactors presented at the allergy centre 2–3 years after the oral challenges reporting the appearance of recurrent urticaria. On oral challenges all four had tolerated acetaminophen, 3/3 had tolerated rofecoxib, and 2/2 had tolerated tramadol.

## Discussion

Overall, about  $\frac{3}{4}$  (76%) of the study subjects tolerated aspirin on oral challenge suggesting that they were single NSAID reactors that could safely take all NSAID other than the offending one. This finding confirms previous observations

that patients with a history of urticaria induced only by pyrazolones, nimesulide, aryl acetic acid derivatives, or acetaminophen are frequently single drug reactors [12–15, 17, 18, 21]. To date, specific drug recognition based upon an IgE-mediated mechanism has been shown only in patients intolerant to pyrazolones [22]. In contrast, the findings in the four patients with a history of nimesulide-induced urticaria who did not tolerate aspirin on oral challenge clearly suggest a pathogenic mechanism based upon COX-1 inhibition as they were all able to tolerate drugs exerting little or no inhibition on COX-1 such as paracetamol, rofecoxib, tramadol, and flectafenine on a subsequent challenge.

Interestingly, four patients developed chronic urticaria 2–3 years after their aspirin intolerance was detected; this confirms that aspirin intolerance may precede by years the onset of chronic urticaria, a condition that is often characterized by multiple NSAID reactivity [23].

In keeping with previous studies [24–26], a minority (18%) of aspirin reactors did not tolerate at least one alternative NSAID. Had tolerance tests been carried out uniquely with alternative NSAID, only 5/33 (15%) multiple NSAID reactors would have been eventually correctly classified as such. Pathogenic mechanism underlying intolerance to alternative NSAIDs in some multiple NSAID reactors are unclear. It is likely that they differ from COX inhibition; in fact, while nimesulide still retains some inhibitory activity on COX-1, the dose of acetaminophen given during oral challenges is probably too low to induce any COX-1 inhibition, and rofecoxib has been known as a selective COX-2 inhibitor. The rapid onset of urticaria after the administration of these drugs in intolerant patients seems to suggest direct drug-induced histamine release. In effect, both patients with multiple NSAID intolerance [27] and with multiple drug allergy syndrome [28] are frequently characterized by circulating histamine-releasing factors that might play a relevant role in drug-induced urticaria reactions. All patients included in this study were otherwise healthy and skin reactions were directly observed at the allergy clinic; thus, it seems unlikely that the use of single-blind rather than double-blind oral challenges may have somehow biased the results.

Altogether, the present study suggests that in subjects with a history of urticaria induced by a single NSAID (other than aspirin) the diagnostic workup should start with aspirin challenges in order to distinguish single/multiple NSAID reactivity [1, 2]. Aspirin challenges seem quite safe in these patients; the fact that aspirin is chemically distinct from the offending drugs minimizes the risk of severe, IgE-mediated reactions.

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