CASE REPORT

NSAID-Sensitive Antihistamine-Induced Urticaria/Angioedema

S Cimbollek, M Ortega Camarero, R Avila, J Quiralte, M Prados

Allergy Department, Hospital Virgen del Rocio, Seville, Spain

Abstract

We present a case of urticaria caused by antihistamines in a patient with nonsteroidal anti-inflammatory drug (NSAID) sensitivity. A 35-year-old man experienced, on 2 separate occasions, immediate generalized urticaria during treatment with ibuprofen and naproxen, respectively. A single-blind, placebo-controlled oral challenge (SBPCOC) with piroxicam was carried out, and resulted in urticaria and angioedema 3 hours later. Two hours after initial clinical resolution, the patient developed multiple wheals on the trunk and upper limbs. He described similar delayed reactions after oral antihistamine administration on previous occasions. SBPCOCs with acetaminophen and etoricoxib were performed, with good tolerance. Skin prick and patch tests with loratadine and cetirizine were negative. After an SBPCOC with loratadine, the patient developed generalized urticaria 90 minutes after intake. Tolerance to fexofenadine 180 mg was confirmed. We describe the first case of a possible new subset of antihistamine urticaria, and suggest calling this NSAID-sensitive antihistamine-induced urticaria/angioedema.

Key words: Antihistamines. Urticaria. NSAID sensitivity.

Introduction

Antihistamines are common drugs used in allergic disease and urticaria. They are inverse agonists of histamine at H1 receptor sites and their purpose is to shift the equilibrium of this receptor towards the inactive state. A wide spectrum of adverse reactions have been attributed to antihistamines, but skin reactions are rare. We present a case of urticaria caused by antihistamines in a patient with nonsteroidal anti-inflammatory drug (NSAID) sensitivity.

Case Description

A 35-year-old man, with no history of asthma or atopic diseases, experienced immediate oral itching, facial angioedema, and generalized urticaria during treatment with ibuprofen on 1 occasion and with naproxen on another. Both episodes resolved with treatment. A single-blind, placebo-controlled oral challenge (SBPCOC) with piroxicam was carried out in a hospital setting. The patient developed urticaria and tongue angioedema after a cumulative 20-mg dose of piroxicam. Parenteral corticosteroids and oral cetirizine were administered, with rapid initial clinical resolution. Two hours later, however, the patient developed multiple wheals on the trunk and upper limbs. He reported a similar delayed reaction after oral antihistamine administration on previous occasions. Two weeks later, SBPCOCs with acetaminophen and etoricoxib were performed, with no adverse reactions occurring during the procedure (Table 1).

The patient underwent skin prick tests (10 mg/mL) and patch tests (5% in petrolatum) with loratadine and cetirizine, with
A patient had a type 2 NRC disorder characterized by multiple complex phenotypes (within what is known as the NSAID-exposure to NSAIDs; these disorders can be assigned to several functional classes, antihistamines. First, the antihistamines may shift the H1 histamine receptor from the inactive to the active state [2,5] and second, the direct activation may occur due to cross-reactivity, involving unclear mechanisms, between the different metabolites of the drugs [7]. The novel clinical observation of concomitant NSAID sensitivity in a patient with H1 antihistamine–induced urticaria might not just be a coincidence but rather the result of a common pathogenic mechanism. Several type 2 antihistamines show selective alterations in the enzyme activity of the arachidonic pathway, possibly contributing to their anti-inflammatory properties. In a COX-screening assay with ovine COX-1/COX-2 compared to a known investigational highly selective COX-2 inhibitor, it was observed that loratadine inhibited COX-1 activity at low concentrations, while fexofenadine preferentially inhibited COX-2 activity [8]. This may explain why our patient tolerated fexofenadine, even though he had a positive challenge test with loratadine, another piperidine-derivative antihistamine. In other words, the 2 antihistamines would have interacted differently with the cyclooxygenase pathway.

The mechanisms of type 2 NRC disorders are unknown, but an enzymatic activity inhibition of at least the COX-1 isoform, which may inhibit prostaglandin synthesis and thus dysregulate the 5-lipoxygenase pathway, with cyc-leukotriene hyperproduction in some susceptible patients has been proposed [1]. Therefore, all NSAIDs that inhibit the COX-1 isoform could precipitate the reaction. For this reason, we believe that multiple reactivity

Abbreviation: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.

# Table 1. Drugs and Doses Used for Single-Blind, Placebo-Controlled Oral Challenge

<table>
<thead>
<tr>
<th>NSAID Reactivity pattern</th>
<th>Clinical Form</th>
<th>Associated Underlying Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly selective COX-2 inhibitor NSAID</td>
<td>Etoricoxib</td>
<td>30, 60*</td>
</tr>
<tr>
<td>Weak, nondiscriminatory COX-1/COX-2 inhibitor</td>
<td>Paracetamol</td>
<td>100, 250, 500, 1000*</td>
</tr>
<tr>
<td>Potent, nondiscriminatory COX-1/COX-2 inhibitor</td>
<td>Piroxicam</td>
<td>10, 20*</td>
</tr>
<tr>
<td>Second generation antihistamines</td>
<td>Loratadine, Fexofenadine</td>
<td>5, 10*, 30, 90, 180*</td>
</tr>
</tbody>
</table>

Abbreviation: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.

*Administered in an opaque gelatine capsule at 60-minute intervals.

Table 2. Clinical Classification of NSAID Reaction Complex Phenotypes

<table>
<thead>
<tr>
<th>NSAID Reactivity pattern</th>
<th>Clinical Form</th>
<th>Associated Underlying Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1: Naso-ocular and/or asthmatic reaction</td>
<td>Rhinitis and/or bronchial asthma with or without nasosinusual polyposis</td>
<td></td>
</tr>
<tr>
<td>Type 2: urticaria and/or angioedema</td>
<td>Chronic urticaria/angioedema</td>
<td></td>
</tr>
<tr>
<td>Type 3: isolated periorbital angioedema</td>
<td>Atopic disease (rhinitis and/or bronchial asthma and NSAID-sensitivity mite ingestion reaction syndrome)</td>
<td></td>
</tr>
<tr>
<td>Type 4: systemic anaphylaxis and urticaria</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug.

In our case, urticaria exacerbation was also caused by different antihistamines, including cetirizine (a piperazine) during the treatment of the positive SBPCOC with piroxicam and loratadine (a piperidine derivative) throughout the controlled oral challenge. Tolerance of fexofenadine (a piperidine derivative) was confirmed.

Urticaria after the oral administration of second-generation functional class antihistamines is an infrequent but rather well-known adverse effect. Since 2006, at least 14 cases and 2 clinical patterns have been described [2-4]. The most common pattern is the paradoxical exacerbation of chronic urticaria by H1 antihistamines. It has been suggested that this feature often implies an autoimmune/autoreactive mechanism that could be present in the pathogenesis of chronic urticaria [5]. The second pattern is acute urticaria/angioedema after the intake of antihistamines (eg, to relieve allergic rhinitis). In this case, chronic urticaria has not been observed and the skin reaction has only occurred following the administration of antihistamines during a challenge [2].

Our patient cannot be included in the first group because he lacked a previous history of chronic urticaria. The concomitant presence of NSAID sensitivity also suggests that his reaction cannot simply be allocated to the second group. Rather, we believe that it may indicate the existence of a new group of patients with antihistamine urticaria in the context of an NRC. It is possible that NSAID-sensitivity antihistamine-induced urticaria has been underdiagnosed considering that NSAID sensitivity may be present in up to 30% of patients with chronic urticaria [6]. Multiple reactivity between structurally unrelated antihistamines occurs in all types of antihistamine-induced urticaria, meaning that antihistamine immunoglobulin E recognition is highly improbable. Two hypotheses have been proposed to explain the paradoxical acute urticarial exacerbation induced by H1 antihistamines. First, the antihistamines may shift the H1 histamine receptor from the inactive to the active state [2,5] and second, the direct activation may occur due to cross-reactivity, involving unclear mechanisms, between the different metabolites of the drugs [7]. The novel clinical observation of concomitant NSAID sensitivity in a patient with H1 antihistamine–induced urticaria might not just be a coincidence but rather the result of a common pathogenic mechanism. Several type 2 antihistamines show selective alterations in the enzyme activity of the arachidonic pathway, possibly contributing to their anti-inflammatory properties. In a COX-screening assay with ovine COX-1/COX-2 compared to a known investigational highly selective COX-2 inhibitor, it was observed that loratadine inhibited COX-1 activity at low concentrations, while fexofenadine preferentially inhibited COX-2 activity [8]. This may explain why our patient tolerated fexofenadine, even though he had a positive challenge test with loratadine, another piperidine-derivative antihistamine. In other words, the 2 antihistamines would have interacted differently with the cyclooxygenase pathway.

The mechanisms of type 2 NRC disorders are unknown, but an enzymatic activity inhibition of at least the COX-1 isoform, which may inhibit prostaglandin synthesis and thus dysregulate the 5-lipoxygenase pathway, with cyc-leukotriene hyperproduction in some susceptible patients has been proposed [1]. Therefore, all NSAIDs that inhibit the COX-1 isoform could precipitate the reaction. For this reason, we believe that multiple reactivity
between COX-1 inhibitor NSAIDs (2 propionic and 1 oxicam derivatives) occurred in our patient. In this sense, any functional non-NSAID COX-1 inhibitor (eg, loratadine) might also induce a clinical reaction in a highly sensitive patient with a type 2 NRC skin disorder, like our patient.

In summary, our patient, who had challenge-proven NSAID sensitivity experienced a clinical reaction following the use of functional COX-1 inhibitors (in this case, a nondiscriminatory NSAID) or, as it seems, antihistamines with COX-1 inhibitor capacity.

We have described the first case of a possible new subset of antihistamine urticaria, and suggest calling it NSAID-sensitive antihistamine-induced urticaria/angioedema. More large-scale challenges studies are needed to investigate the existence of this entity and to determine the prevalence of this clinical finding in type 2 NRC disorders.

References