CASE REPORT

NSAID-Sensitive Antihistamine-Induced Urticaria/Angioedema

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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.

Resumen

Presentamos un caso de urticaria por antihistamínico en un paciente con intolerancia a AINEs. Un paciente de 35 años de edad presentó en dos ocasiones separadas en el tiempo urticaria generalizada inmediata tras la toma de ibuprofeno y naproxeno respectivamente. Se realizó test de tolerancia con piroxicam, simple ciego controlado con placebo, con aparición a las 3 horas de urticaria/angioedema. Tras una resolución clínica inicial presentó a las dos horas habones múltiples en tronco y extremidades superiores. El paciente refiere reacción retardada similar tras la toma de antihistamínico oral en los episodios adversos previos. Se realizó test de tolerancia, simple ciego, controlado con placebo, con paracetamol y etoricoxib con buena tolerancia. Las pruebas cutáneas en prick y epicutáneas con loratadina y cetirizina fueron negativas. Tras el test de tolerancia, simple ciego, controlado con placebo con Loratadina el paciente comenzó a los 90 minutos con urticaria generalizada. Se confirmó tolerancia a 180 mg de fexofenadina.
Describimos el primer caso de un posible nuevo subtipo de urticaria por antihistamínicos que sugerimos se llame urticaria/angioedema inducido por intolerancia a AINE.

Palabras clave: Antihistamínicos. Urticaria. Intolerancia AINE.

Introduction

Antihistamines are common drugs used in allergic disease and urticaria. They are inverse agonists of histamine at H_1 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 3 hours 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

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

		Doses, mg
Highly selective COX-2 inhibitor NSAID	Etoricoxib	30, 60[a]
Weak, nondiscriminatory COX-1/COX-2 inhibitor	Paracetamol	100, 250, 500, 1000[a]
Potent, nondiscriminatory COX-1/COX-2 inhibitor	Piroxicam	10, 20[b]
Second generation antihistamines	Loratadine Fexofenadine	5, 10[a] 30, 90, 180[a]

Abbreviation: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.
[a]Administered in an opaque gelatine capsule at 60-minute intervals.
[b]Administered in an opaque gelatine capsule at 120-minute intervals.

negative results. After an SBPCOC with 10 mg of loratadine, the patient developed generalized pruritic wheals, which resolved with corticosteroids, 90 minutes after intake. Tolerance to fexofenadine 180 mg was confirmed with a similar oral challenge.

Discussion

Previous studies have revealed skin reaction disorders after exposure to NSAIDs; these disorders can be assigned to several complex phenotypes (within what is known as the NSAID-induced reaction complex, or NRC) depending on the type of reaction, the cross-reactivity pattern between different NSAIDs, and the existence of concomitant diseases (Table 2) [1]. Our patient had a type 2 NRC disorder characterized by multiple nondiscriminatory cyclooxygenase (COX)-1/COX-2 urticaria/angioedema.

Table 2. Clinical Classification of NSAID Reaction Complex Phenotypes

NSAID Reactivity pattern	Clinical Form	Associated Underlying Diseases
Cross-reactive syndromes	Type 1: Naso-ocular and/or asthmatic reaction	Rhinitis and/or bronchial asthma with or without nasosinusal polyposis
	Type 2: urticaria and/or angioedema	Chronic urticaria/ angioedema
	Type 3: isolated periorbital angioedema	Atopic disease (rhinitis and/or bronchial asthma and NSAID-sensitivity mite ingestion reaction syndrome)
Selective syndromes	Type 4: systemic anaphylaxis and urticaria	None

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 H_1 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 H_1 antihistamines. First, the antihistamines may shift the H_1 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 H_1 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-lipooxygenase pathway, with cys-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.

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