

Clinical Communications

Multiple nonsteroidal anti-inflammatory drug hypersensitivity without hypersensitivity to aspirin

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Clinical Implications

- Subjects developing anaphylaxis or urticaria/angioedema after chemically unrelated nonsteroidal anti-inflammatory drug intake should not be classified as cross-hypersensitive unless they do not tolerate acetyl salicylic acid. Such cases should avoid the culprit drugs; however, they may still benefit from other nonsteroidal anti-inflammatory drugs, including acetyl salicylic acid.

TO THE EDITOR:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs most frequently involved in hypersensitivity drug reactions (HDRs).¹ They are prescribed worldwide and often available over the counter. HDRs to NSAIDs can be classified into 2 major groups: cross-hypersensitive and selective responders. In the first category, histamine and other vasoactive inflammatory mediators are released through the activation of biochemical pathways related to prostaglandin and leukotriene metabolites, whereas the second category is produced by specific immunological mechanisms.² A recent classification has been proposed comprising 5 major entities induced by NSAID hypersensitivity: NSAIDs-exacerbated respiratory disease, NSAIDs-exacerbated cutaneous disease, NSAIDs-induced urticaria/angioedema in otherwise healthy individuals, single-NSAID-induced urticaria/angioedema or anaphylaxis, and single-NSAID-induced delayed hypersensitivity reactions.³

NSAIDs-induced urticaria/angioedema in otherwise healthy individuals represents the most common group, with some cases also experiencing anaphylaxis.⁴ Subjects responding to several NSAIDs including acetyl salicylic acid (ASA) are considered cross-hypersensitive, whereas those responding to only 1 NSAID with good tolerance to other chemically unrelated NSAIDs are considered selective responders.⁵ However, in some cases, patients who develop immediate reactions to several NSAIDs are classified as cross-hypersensitive without assessing ASA tolerance.⁶

Here, we describe a patient who had several reactions with 3 chemically unrelated NSAIDs who was initially considered cross-hypersensitive without including ASA challenge in the allergological workup. After verifying ASA tolerance, the patient was considered to react selectively to 3 NSAIDs.

A 70-year-old woman with coronary disease who had previously undergone a cholecystectomy and who had been taking atorvastatin, ranitidine, and lorazepam regularly for over 5 years was referred to the

allergy department with symptoms of drug hypersensitivity. She reported having no history of allergic disease. According to the patient, in 1996 she developed 2 episodes of urticaria in her legs and abdomen, alongside facial angioedema, less than 1 hour after taking paracetamol. In 1999, she developed generalized urticaria 90 minutes after dipyrone intake. At that time she was evaluated by an allergologist, to whom she reported having had a similar episode 2 years earlier. Intradermal test results with dipyrone (2 mg/mL) and paracetamol (0.1 mg/mL) were positive. A week later, she was challenged with ASA, showing tolerance at full therapeutic doses (500 mg). In 2012, she suffered from an episode of facial angioedema and pruritus in the tongue after celecoxib intake. She reported previous tolerance to this drug on many occasions (Table I).

When the patient was reevaluated in September 2014, intradermal test result to paracetamol was negative (0.1 mg/mL), and intradermal test and basophil activation test results to dipyrone were positive (Table I).

Drug challenges were performed following previous protocols with some modifications.⁴ The patient was challenged with escalating doses of paracetamol, and 60 minutes after achieving a cumulative dose of 300 mg (50, 100, and 150 mg at 90-minute time interval) she developed generalized pruritus and wheals in the chest, neck, and shoulder. The symptoms were controlled with a single dose of corticosteroids (prednisone 40 mg) and antihistamines (dexchlorpheniramine 5 mg). Two weeks later, she presented pruritus in the tongue and ears, nasal itching and obstruction, and wheals in the neck after provocation with a cumulative dose of 100 mg of celecoxib, with no changes in FEV₁ values. After another interval of 2 weeks, tolerance to etoricoxib was observed at full therapeutic dose. Two weeks later, the patient tolerated ASA and ibuprofen during controlled challenge until therapeutic doses. In addition, around 2 months later, the patient received 2 independent 2-day treatment courses with these drugs, separated by a 2-week time interval.

This case illustrates that subjects may develop an immediate response to a number of NSAIDs, including some cyclooxygenase-1 (COX-1) and/or selective COX-2 inhibitors but tolerate strong COX-1 inhibitors. According to current guidelines, such individuals must be considered single responders to multiple drugs, even if they respond to several NSAIDs from different chemical groups.

The allergological workup carried out 15 years ago showed that this patient had suffered several episodes to dipyrone and paracetamol but could tolerate ASA, suggesting that this case could fit into the single-NSAID-induced urticaria/angioedema or anaphylaxis group. However, because the patient was exposed on several occasions to another NSAID, celecoxib, she probably become sensitized to this drug as well. In addition to good tolerance to ASA, we confirmed that this patient was a selective responder by also administering the full therapeutic dose of ibuprofen (also considered a strong COX-1 inhibitor) and observing tolerance. Because all the reactions occurred less than 1 hour after drug intake, we consider them to be immediate selective responses to these drugs, as reviewed by Canto et al.⁵ We believe that the term “multiple selective responders to NSAIDs” should be used to differentiate patients with these characteristics from cross-hypersensitive patients.

TABLE I. Summary of the reactions registered in the clinical history and of the allergological workup

Clinical history						
Year	Drug involved	Reaction	Drug in IDT	IDT result	Drug in DPT	DPT result (cumulative dose)
1996	Paracetamol	Urt/AE	—	—	—	—
1999	Dipyrone	Urt	Dipyrone	Positive (2 mg/mL)	—	—
			Paracetamol	Positive (0.1 mg/mL)	ASA	Negative (500 mg)
2012	Celecoxib	AE	—	—	—	—
Patient reevaluation						
Date	Drug involved	Reaction	Drug in IDT	IDT result	Drug in DPT	DPT result (cumulative dose)
2014			Paracetamol	Negative (0.1 mg/mL)	Paracetamol	Positive (300 mg)
			Dipyrone	Positive (2 mg/mL)*	Celecoxib	Positive (100 mg)
					ASA	Negative (500 mg)
					Ibuprofen	Negative (600 mg)

DPT, Drug provocation test (challenge); IDT, intradermal test; Urt/AE, urticaria/angioedema.

*The basophil activation test result was positive.

Concerning selective COX-2 inhibitors, our case also developed an immediate selective response to celecoxib but tolerated etoricoxib (another COX-2 inhibitor), as has been reported.⁷ Although both drugs consist of sulfone-containing tricyclic compounds, etoricoxib has a bipyridine nucleus with a chloride substituent whereas celecoxib contains a pyrazole nucleus substituted with a trifluoromethyl group. These differences may contribute to the generation of distinctive epitopes.

In the initial allergic response to paracetamol, skin testing was positive but became negative over time, as occurs in betalactam allergy.⁸ However, although skin and/or intradermal test results became negative, some subjects may still remain allergic as was observed in our patient. Concerning dipyrone response, our case had positive results to skin test and basophil activation test, which supports an IgE-mediated mechanism.

To our knowledge, this is the first case reporting an immediate allergic reaction to 3 chemically unrelated NSAIDs. This case shows the importance of testing for ASA tolerance when confronted by a patient who responds to several chemically unrelated NSAIDs. These patients should not be classified as cross-hypersensitive unless ASA challenge has been performed.

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