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Urticaria and angioedema induced by COX-2 inhibitors

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To the editor:

Pseudoallergic reactions caused by acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) often resemble immediate-type hypersensitivity reactions maintaining as urticaria, angioedema, rhinoconjunctivitis, asthma, or anaphylactoid reactions.^{1 2} Yoshida et al,³ Dahlén et al,⁴ and Szczeklik et al⁵ argue that the inhibition of COX-1 is the likely link between NSAID ingestion and ASA idiosyncrasy. They conclude that the 2 new highly selective inhibitors of COX-2, celecoxib and rofecoxib, are alternative NSAIDs for patients with ASA intolerance.

In contrast to these studies,^{3 5} we report the case of a 51-year-old ASA-sensitive Caucasian woman who developed generalized urticaria and angioedema 2 hours after her first oral intake of 12.5 mg rofecoxib for joint pain. Two months later, she presented at our department for allergy diagnosis.

Results of skin prick testing with celecoxib, rofecoxib, ASA, piroxicam, ibuprofen, and paracetamol were negative.

In a placebo-controlled, double-blinded investigation, ASA 500 mg induced generalized pruritus and urticaria 2 hours after an oral provocation test (OPT). Rofecoxib 12.5 mg (COX-2-selective) led to angioedema and generalized urticaria after 3^{1/2} hours; celecoxib 100 mg (COX-2-selective) triggered generalized urticaria and angioedema within 4 hours. Piroxicam 30 mg induced wheals, and paracetamol 250 mg led to rhinitis and urticaria 2 hours after OPT. The first provocation with ibuprofen 380 mg was tolerated, whereas 4 weeks later, ibuprofen 380 mg led to generalized urticaria. Multiple placebo controls (mannitol 500 mg) did not trigger any symptoms (Table I).

Table I. Symptoms after oral provocation with COX inhibitors

Day of OPT	Drug	Symptoms	Time to appearance of symptoms after exposition (h)
1	ASA 500 mg	Urticaria	2
5	Rofecoxib 12.5 mg	Angioedema and urticaria	3 ^{1/2}
8	Celecoxib 100 mg	Angioedema and urticaria	4
10	Paracetamol 250 mg	Urticaria and rhinitis	2
11	Ibuprofen 380 mg	No symptoms (first exposure)	—
12	Piroxicam 30 mg	Wheals at the lower extremity	2 ^{1/2}
4,9,14	Mannitol 500 mg	—	—
(4 weeks later)	Ibuprofen 380 mg	Urticaria (second exposure)	3

OPT, Oral provocation test.

Yoshida et al,³ Dahlén et al,⁴ and Szczeklik et al⁵ show that the selective inhibition of COX-2 is not involved in the mechanism of bronchial constriction in ASA-induced asthma. It is possible that the COX-2 inhibition-induced urticaria of our ASA-sensitive patient followed a pathomechanism that is different from that of the asthma of ASA-intolerant patients that is triggered by COX-1 inhibition. Interestingly, the wheals of our patient appeared 2 hours after exposure at the earliest.

It is tempting to speculate that specific COX-2 inhibitors might be especially harmful to a subgroup of ASA-sensitive patients. Although ASA-sensitive patients develop asthmatic reactions after COX-1 inhibition, COX-2 inhibition seems to play a role in the pathogenesis of our patient's urticaria.

The reported case shows that rofecoxib and celecoxib are able to elicit pseudoallergic reactions, which is contrary to other reports.^{3 5}

We conclude that a selective inhibition of COX-2 is no guarantee of the safety of NSAID use in ASA-sensitive patients.**1/8/121315**

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