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Cutaneous hypersensitivity to multiple NSAIDs: never take tolerance to selective COX-2 inhibitors (COXIBs) for granted!

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Nonsteroidal anti-inflammatory drugs are one of the most frequent causes of immediate drug-induced skin hypersensitivity reactions worldwide (1). While a proportion of patients show reactivity to single, specific drugs, many others are intolerant to multiple NSAIDs; about one half of multiple reactors suffer from chronic spontaneous urticaria, while in the remaining no underlying factor can be detected although these patients are often characterized by autoreactivity (2). Based on a number of studies carried out during the last 20 years it is generally believed that inhibition of cycloxygenase 1 (COX-1) enzyme by the offending drugs plays a relevant pathogenic role in multiple NSAID reactors (3-5). These subjects are in many cases able to tolerate NSAIDs and other drugs exerting little or no inhibition on COX-1, such as paracetamol, tramadol, nimesulide, benzidamine, meloxicam or selective COX-2 inhibitors (coxibs). Table 1 summarizes the results of one decade of challenge tests with different coxibs performed by several researchers in patients with two or more episodes of urticaria induced by different NSAIDs (6-37). Aggregated results don't differ significantly between the various coxib molecules.

Etoricoxib is presently the only surviving coxib on the market (the others have been retired due to cardiovascular adverse effects). Along with rofecoxib it is the most COX-2-selective drug of this family produced so far, and has been tolerated by the large majority of subjects hypersensitive to other NSAIDs. Based on the results of previous studies it might be tempting to prescribe this drug to multiple NSAID-hypersensitive subjects without checking for its tolerance in a proper setting. Two cases tackling this idea are presented here.

Case 1. A 42 year-old woman suffering from frequent headaches presented reporting repeated episodes of periorbital angioedema during the last 6 months, always about 1 hour after taking a tablet of indomethacin. The woman tolerated frovatriptan alone well. One month before the visit another episode of ocular angioedema occurred about 1 hour after the ingestion of diclofenac 100 mg. The patient had never suffered from spontaneous urticaria before. A series of challenge tests with alternative drugs, given at incremental doses one hour apart up to a therapeutic dose, was carried out at this allergy department. She tolerated paracetamol (cumulative dose 1000 mg), and tramadol (50 mg) without any problem, but experienced urticaria about one hour after taking 45 mg of etoricoxib (corresponding to about ½ single dose). The patient refused re-challenge

Table 1 - Reactivity to different coxibs on oral challenges in patients with multiple NSAID hypersensitivity

Authors	Ref.	Year	Drug	No. intolerant/No. tested (%)
Enrique E, et al	6	2000	Rofecoxib	0/2 (0%)
Sánchez-Borges M, et al	7	2001	Rofecoxib	1/24 (4%)
Berges-Jimeno MP, et al	8	2001	Rofecoxib	0/33 (0%)
Asero R	9	2001	Rofecoxib	6/34 (18%)*
Pacor ML, et al	10	2002	Rofecoxib	0/12 (0%)*
Nettis E, et al	11	2002	Rofecoxib	1/139 (0.7%)
Quiralte J, et al	12	2002	Rofecoxib	0/12 (0%)
Leong PK, et al	13	2002	Rofecoxib	0/11 (0%)
Fernández-Meléndez S, et al	14	2002	Rofecoxib	0/44 (0%)
Valero A, et al	15	2002	Rofecoxib	1/58 (2%)
Perrone MR, et al	16	2003	Rofecoxib	1/118 (1%)
Zembowicz A, et al	17	2003	Rofecoxib	0/5 (0%)*
Kruse R, et al	18	2003	Rofecoxib	2/6 (33%)
Muñoz-Bellido FJ, et al	19	2003	Rofecoxib	1/55 (2%)
Matucci A, et al	20	2004	Rofecoxib	8/23 (29%)
Senna G, et al	21	2004	Rofecoxib	1/76 (1%)
Bavbek S, et al	22	2004	Rofecoxib	1/51 (2%)
Sánchez-Borges M, et al	23	2005	Rofecoxib	2/20 (10%)
Sánchez-Borges M, et al	7	2001	Celecoxib	5/20 (25%)
García-Rodríguez RM, et al	24	2002	Celecoxib	0/20 (0%)
Zembowicz A, et al	17	2003	Celecoxib	0/5 (0%)
Kruse R, et al	18	2003	Celecoxib	1/5 (20%)
Ahlbach S, et al	25	2003	Celecoxib	0/77 (0%)
Senna G, et al	21	2004	Celecoxib	2/76 (2%)
Viola M, et al	26	2005	Celecoxib	1/56 (2%)
Celik G, et al	27	2005	Celecoxib	0/54 (0%)
Sánchez-Borges M, et al	28	2005	Celecoxib	6/54 (11%)
Liccardi G, et al	29	2005	Celecoxib	0/9 (0%)
Nettis E, et al	30	2005	Etoricoxib	2/141 (1%)
Sánchez-Borges M, et al	28	2005	Etoricoxib	4/56 (7%)
Muratore L, et al	31	2007	Etoricoxib	3/37 (8%)
Viola M, et al	32	2007	Etoricoxib	0/15 (0%)
Asero R	33	2007	Etoricoxib	0/11 (0%)*
Pagani M, et al	34	2010	Etoricoxib	1/56 (2%)
Dona I, et al.	35	2011	Etoricoxib	15/97 (15%)
Sánchez-Borges M, et al	23	2005	Valdecoxib	1/20 (10%)
Viola M, et al	36	2006	Parecoxib	0/11 (0%)
Colanardi MC, et al	37	2008	Parecoxib	0/79 (0%)
Total Rofecoxib				**25/723 (3.4%)**
Total Celecoxib				**15/396 (3.8%)**
Total Etoricoxib				**25/413 (6.0%)**
Total Valdecoxib				**1/20 (10%)**
Total Parecoxib				**0/90 (0%)**

*most patients with chronic urticaria

with etoricoxib preceded by anti-histamine premedication.

Case 2. A 51 year-old woman experienced generalized urticaria after the intramuscular injection of ketoprofen during a hospital stay following a surgical treatment of the hip. Subsequently she tolerated paracetamol. The patient had never experienced adverse drug reactions before, nor suffered from chronic spontaneous urticaria. In our allergy department, a challenge test with aspirin was performed first in order to detect whether she was a single or a multiple NSAID reactor (38). About 1 hour after taking 100 mg of aspirin, generalized urticaria appeared that promptly responded to i.m. antihistamine treatment. In view of this response, oral challenges with tramadol and etoricoxib were carried out 2 weeks later. The woman tolerated 50 mg of tramadol, but reacted to 45 mg of etoricoxib (urticaria; latency 40 min); the reaction subsided after the administration of i.m. anti-histamine. Two weeks later the woman presented again >1 hour after taking an oral antihistamine (rupatadine 10 mg) and was able to tolerate 90 mg of etoricoxib as a single dose on oral re-challenge.

These two clinical cases prompt the following remarks. First, coxibs represent a viable alternative in most patients with NSAID-hypersensitivity but tolerability to these drugs varies widely among multiple-reactors, as a minority of patients reacts even to coxibs (0-33%) (6-37). What causes apparently identical patients to respond differently on oral challenge with alternative drugs remains unclear. Doña and co-workers (35) have detected a significantly higher propensity to react to etoricoxib among NSAID reactors who don't tolerate paracetamol as well. For these reasons, tolerance to alternative drugs should be always ascertained in a proper clinical setting before prescribing them to NSAID-hypersensitive patients. Second, managing subjects with NSAIDs hypersensitivity who react even to coxibs may be a problem, particularly if they suffer from chronic arthritis or other conditions that require anti-inflammatory or anti-febrile treatments. As reported in the second case and in a preliminary study (39), premedication with a second generation non-sedating antihistamine could be effective in preventing skin reactions induced by coxibs. These observations open new opportunities for such patients but further studies are needed to confirm the validity of this approach.

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