

Tolerability of rofecoxib

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Key words: drug allergy; nonsteroidal anti-inflammatory drugs; urticaria; rofecoxib; COX-2 inhibitors.

• ABOUT 30% of patients with chronic urticaria experience flares of hives after ingesting either aspirin or other NSAID (1), and a history of urticaria after taking several, chemically unrelated NSAID may be reported by otherwise normal subjects as well (2, 3). The mechanisms responsible for such reactions are unknown, but the observation that many of these patients tolerate weak cyclooxygenase-1 (COX-1) inhibitors, such as paracetamol and nimesulide (4–6), has led researchers to hypothesize the involvement of either COX-1 inhibition or increased

A possible alternative in multiple NSAID urticaria.

sensitivity to leukotrienes (LT). Recently, two selective inhibitors of the inducible cyclooxygenase isoenzyme COX-2, rofecoxib and celecoxib, have been marketed. These compounds represent an interesting opportunity to investigate the role of COX isoenzymes in NSAID-induced skin reactions. Two cases of tolerance to rofecoxib in subjects with multiple NSAID hypersensitivity were recently reported (7). This study assessed the tolerability of rofecoxib in a larger group of patients.

Thirty-four adults (M/F 5/29; age 23–76 years) with a history of urticaria and/or angioedema after the ingestion of at least two chemically unrelated NSAID were studied. Twenty-two had chronic urticaria, whereas 12 were otherwise normal subjects. All underwent single-blind, placebo-controlled oral tolerance tests with rofecoxib (12.5 and 25 mg given 1 h

apart); moreover, in the absence of a history of specific intolerance, the patients were offered oral challenges with paracetamol and/or nimesulide as well (2). Patients were controlled for 2 h after the last provocative dose. Only the appearance of unequivocal urticaria and/or angioedema (or of unequivocal worsening of hives in patients with chronic urticaria) was considered a positive reaction. No patient had taken antihistamines for at least 1 week before the oral challenges. Placebo did not induce any adverse reaction. Rofecoxib was not tolerated by 6/34 (18%) patients, with no difference between patients with (4/22 [18%]) or without (2/12 [17%]) chronic urticaria. Reactions appeared 30–60 min after the first ($n=3$) or second ($n=3$) provocative dose. Rofecoxib was tolerated by 14/17 (82%) of nimesulide-intolerant and by 8/11 (73%) of paracetamol-intolerant patients, respectively. In five cases, rofecoxib was the only NSAID tolerated.

Patients with multiple NSAID intolerance are clearly prone to react to other NSAID. As a consequence, in this study, the proportion of patients who did not tolerate paracetamol (11/34 [32%]) and/or nimesulide (17/34 [50%]) was higher than in previous works (2–6, 8). Even in such a selected, “at risk” population, rofecoxib was tolerated by 82% of patients. The mechanisms underlying intolerance to chemically unrelated NSAID are unclear. One theory is that these patients show an exaggerated sensitivity to the effects of LT. On a molecular basis, LT are 100 times more active than histamine in inducing wheal and flare reactions (9). Blockade of both COX-1 and COX-2 isoenzymes by nonselective NSAID results in an increased production of LT by the lipoyxygenase pathway (10), whereas selective COX-2 inhibitors do not induce an increased

release of either LTB₄ or cysteinyl-LTs (11, 12). However, in this study, over 80% of patients who did not tolerate nimesulide, another selective COX-2 inhibitor, tolerated rofecoxib, and two rofecoxib-intolerant patients tolerated nimesulide. If the LT theory holds true, rofecoxib and nimesulide would have been expected to exert similar effects in this population. Moreover, 11 (32%) patients did not tolerate paracetamol, a drug that has no effect on COX. These observations suggest that in these patients, drugs nonspecifically trigger histamine release from mast cells and basophils, and that such an effect does not depend on chemical structure or pharmacologic activity. COX-2 inhibitors should be included among alternative drugs to be challenged in patients with a history of multiple NSAID intolerance, particularly in patients reactive to paracetamol and/or nimesulide. As 20% of these patients are potential rofecoxib reactors, its tolerability should be always assessed in a proper clinical setting.

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CD23 during SIT

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● CD23, a differentiation marker of B cells, is continuously cleaved by autoprolysis into soluble fragments called sCD23 that have been found in patients with allergic and inflammatory diseases (1–3).

The subjects of this study included 20 nonatopic healthy controls and 177 atopic patients (89 male and 88 female). Sixty-nine patients (39%) were monosensitized, and 108 (61%) were polysensitized to inhalant allergens; 18 of them had bronchial asthma, 94 rhinoconjunctivitis, and 65 both asthma and rhinoconjunctivitis. All patients were taking oral or subcutaneous specific immunotherapy (SIT) for pneumoallergens. Peripheral blood samples

for determination of sCD23 levels were obtained from the 20 controls and all patients receiving SIT just before administration of the allergen extract. Serum sCD23 concentrations were measured by an immunoenzymatic technique (EASIA, Medgenix) according to the manufacturer's instructions, and the results were expressed in U/ml. The median values of serum sCD23 levels and the respective 25th and 75th percentile values of 3/5 subgroups of patients are reported in Table 1, together with the results of the statistical analysis, performed with nonparametric tests (Mann–Whitney *U*-test, Kruskal–Wallis ANOVA by ranks). In addition, a multiple regression analysis was performed to evaluate the effects of the dose and duration of SIT on sCD23 serum levels.

Median serum sCD23 levels were higher in the 177 atopic patients with respiratory diseases than in the 20 controls ($P<0.001$). sCD23 levels were significantly higher ($P=0.03$) in the patients with asthma than in the other two diagnostic groups; they were also

Table 1. sCD23 serum levels in three of five subgroups of patients

sCD23									<i>P</i>
U/ml (1 U = 1.25 mg/ml)									
Diagnosis									0.03*
Asthma (18)			Rhinoconjunctivitis (94)			Asthma plus rhinoconjunctivitis (65)			
25th	50th	75th	25th	50th	75th	25th	50th	75th	
1.2	1.7	1.95	0.5	1.2	1.64	0.5	1.2	1.76	
Mono- and polysensitized									
Mda					Polysensitized (108)				0.06^
Monosensitized (69)									
Median level					Median level				
1.2					1.4				
Duration of SIT									
SIT >3≤36 months (144)					SIT >36 months (33)				0.04^
25th	Mean value		75th	25th	Mean value		75th		
0.5	2.31		1.7	1.0	1.59		1.9		

* Kruskal–Wallis ANOVA by ranks.

^ Mann–Whitney *U*-test.