
Use of ketoprofen oral challenges to detect cross-reactors among patients with a history of aspirin-induced urticaria

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Background: In patients with a history of urticaria induced by a single nonsteroidal anti-inflammatory drug (NSAID), advising elimination of all drugs that inhibit cyclooxygenase 1 (COX-1) can lead to unnecessary avoidance of useful NSAIDs.

Objective: To classify patients with a history of aspirin-induced urticaria as cross-reactors or single-drug reactors by oral challenges with another strong COX-1 inhibitor, namely, ketoprofen.

Methods: Forty otherwise healthy patients with a history of acute urticaria after the ingestion of aspirin underwent single-blind, placebo-controlled oral challenges with ketoprofen. In patients who did not tolerate ketoprofen, tolerance tests with drugs exerting either COX-1 inhibition at high doses (acetaminophen and nimesulide) or no COX-1 inhibition at therapeutic doses (rofecoxib and tramadol) were performed.

Results: In 24 patients (60%), ketoprofen induced urticaria that was controlled by an intravenous antihistamine; 18 (75%) of the 24 patients reacted after the first provocative dose. On subsequent challenges, 3 (38%) of 8 ketoprofen reactors did not tolerate nimesulide, whereas acetaminophen tramadol and rofecoxib were tolerated by 18 of 18, 14 of 14, and 16 of 16 ketoprofen reactors, respectively. Three ketoprofen reactors reported the onset of spontaneous recurrent urticaria 1 to 3 years after the challenge tests.

Conclusion: In patients with a history of urticaria induced by a single NSAID, oral challenges with alternative COX-1 inhibitors are helpful in detecting whether they are true single-NSAID reactors; weak COX-1 inhibitors should be challenged subsequently only in those who show multiple-NSAID intolerance.

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INTRODUCTION

Aspirin, the most popular drug in the world, is a common cause of immediate pseudoallergic cutaneous reactions. In their recent classification system, Stevenson et al¹ distinguished essentially 2 types of patients with nonsteroidal anti-inflammatory drug (NSAID)-induced urticaria and/or asthma: (1) multiple-NSAID reactors, including patients with underlying asthma or chronic urticaria exacerbated by several NSAIDs and otherwise healthy patients, and (2) single-NSAID reactors with a history of urticaria, anaphylaxis, or mixed respiratory and cutaneous reactions.^{1,2} The pathogenesis of multiple reactions is generally considered associated with inhibition of cyclooxygenase 1 (COX-1) enzyme, whereas single-drug reactions are possibly IgE mediated.^{1,2}

In most previous studies, patients with a history of either single- or multiple-NSAID intolerance were submitted to oral challenges with alternative drugs that exert little (eg, nimesulide, acetaminophen, coxibs, and/or floctafenine) or no (eg, tramadol) COX-1 inhibition.^{3–11} In genuine single-drug cutaneous reactors, this behavior may eventually lead to the avoidance of a number of effective and potentially useful NSAIDs in the absence of any evidence that these drugs

cannot be tolerated. In effect, in a recent study of patients with a history of urticaria induced by a single NSAID other than aspirin, the latter was tolerated by approximately 75% of patients undergoing oral challenge tests.¹² The present study aimed to evaluate the safety and effectiveness of such an approach in patients with a history of urticaria induced by aspirin.

METHODS

Study Participants

Forty patients (male-female ratio, 15:25; mean age, 43 years; age range, 18–72 years) with an unequivocal history of acute urticaria or angioedema induced by aspirin that occurred during the last 6 months seen at the allergy centers of Bollate hospital and Clinica San Carlo in Italy during the last 3 years were studied. In 11 cases, aspirin had caused urticaria on more than one occasion. No patient had chronic urticaria or reported urticaria episodes other than those induced by aspirin. All the study patients were asking for safe alternative drugs, and no patients had taken other NSAIDs after the last urticaria episode.

Oral Challenges

Study patients were not rechallenged with aspirin to minimize the risk of severe adverse reactions.¹³ No patient was taking antihistamines when oral challenges were performed.

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Patients underwent single-blind, placebo-controlled challenges with the alternative, strong COX-1 inhibitor ketoprofen.¹⁴ Placebo (talc, 100 mg) or ketoprofen (both in identical opaque capsules) were challenged in a randomized sequence at least 1 week apart. At each session, 2 doses of either placebo or ketoprofen (first provocative dose, 20 mg; second provocative dose, 60 mg; cumulative dose, 80 mg) were given 1 hour apart, and patients were kept under clinical control for 2 hours after the last dose. Only the appearance of unequivocal urticaria with or without angioedema was considered as a positive reaction; urticaria was controlled by intravenous chlorfenamine, 10 mg, and the patient was kept under control for 1 additional hour. All study participants gave informed written consent before the start of the procedure.

Patients who tolerated ketoprofen were classified as single cutaneous reactors to aspirin. Ketoprofen reactors were considered as multiple-NSAID reactors and were offered further single-blind, placebo-controlled tolerance tests with drugs that exert inhibitory effect on COX-1 only at high doses (nimesulide and acetaminophen) or no inhibitory activity on COX-1 at therapeutic doses (rofecoxib and tramadol). Tramadol is a weak synthetic opiate agonist that derives its antinociceptive effect from attachment to the μ -receptor and blockage of norepinephrine reuptake. Tolerance tests with such drugs were performed at least 2 weeks after the positive ketoprofen challenge result. Only one drug was tested on 1 single day, and drugs were challenged at least 1 week apart. Again, 2 doses of either placebo or active dose were given 1 hour apart: acetaminophen: first provocative dose, 125 mg; second provocative dose, 375 mg (cumulative dose, 500 mg); tramadol: first provocative dose, 25 mg; second provocative dose, 25 mg (cumulative dose, 50 mg); nimesulide: first provocative dose, 25 mg; second provocative dose, 75 mg (cumulative dose, 100 mg); and rofecoxib: provocative dose, 6 mg; provocative dose, 19 mg (cumulative dose, 25 mg). Patients were kept under clinical control for 2 hours after the last dose. Also in this case only the appearance of unequivocal urticaria with or without angioedema was considered a positive reaction.

RESULTS

Results of challenge tests with ketoprofen and alternative NSAIDs in patients with aspirin-induced urticaria are given in Table 1. No reaction to placebo was observed. Sixteen patients (40%) tolerated ketoprofen, whereas in 24 patients (60%) the drug induced urticaria that was easily controlled by intravenous antihistamine; 18 (75%) of the 24 patients reacted after the first provocative dose. No patient experienced either respiratory or gastrointestinal symptoms or hypotension. Twenty-two (92%) of 24 ketoprofen reactors agreed to undergo further tolerance tests with alternative drugs: 18, 14, 16, and 8 were challenged with acetaminophen, tramadol, rofecoxib, and nimesulide, respectively. Three (38%) of 8 patients reacted to nimesulide, whereas acetaminophen, tramadol, and rofecoxib were tolerated by all patients challenged. At least 1 safe alternative drug was eventually found

Table 1. Results of Challenge Tests With Ketoprofen and Alternative Nonsteroidal Anti-inflammatory Drugs in Patients With Aspirin-Induced Urticaria*

Drug	No. (%) of reactors	Top challenge dose, mg
Ketoprofen	24/40 (40)	60
Acetaminophen	0/18 (0)	375
Nimesulide	3/8 (38)	75
Rofecoxib	0/16 (0)	19
Tramadol	0/14 (0)	25

*Acetaminophen, nimesulide, rofecoxib, and tramadol were challenged in patients reactive to both aspirin and ketoprofen.

in all 22 patients. One to 3 years after oral ketoprofen challenges, 3 patients (12%) (all ketoprofen reactors) developed spontaneous recurrent urticaria unrelated to ingestion of either aspirin or ketoprofen.

DISCUSSION

In this study, most patients (60%) with a history of recent aspirin-induced urticaria did not tolerate the alternative COX-1-inhibiting NSAID ketoprofen on oral challenge. This finding is clearly in contrast with those of a recent study that showed that approximately 75% of patients with a history of acute urticaria induced by an NSAID other than aspirin are able to tolerate aspirin on oral challenge.¹² The populations in the 2 studies were virtually identical in age and sex, but the prevalence of intolerance to the alternative drug given was significantly higher in patients with a history of aspirin-induced urticaria (24/40 [60%] vs 28/117 [24%]; $P < .001$ by χ^2 test with Yates correction). Altogether, the present study seems to suggest that aspirin-induced urticaria is more frequently associated with a pathogenic mechanism based on COX-1 inhibition (and hence with cross-reactivity among chemically unrelated NSAIDs), whereas reactivity to single NSAIDs other than aspirin seems more frequently caused by specific drug recognition. This conclusion is indirectly supported both by a previous study that showed that (compared with pyrazolone-intolerant patients) patients with a history of aspirin-induced urticaria are at higher risk of acetaminophen and/or nimesulide intolerance¹⁵ and by the appearance of chronic urticaria after more than 1 year in 3 patients who did not tolerate both aspirin and ketoprofen; recent studies showed that aspirin-induced urticaria may precede by years the onset of chronic urticaria, a condition that is often characterized by multiple-NSAID reactivity.¹⁶

Among alternative NSAIDs, only nimesulide induced urticaria in 3 patients; this finding is in keeping with the fact that nimesulide inhibits COX-1 enzyme more than rofecoxib, paracetamol, and tramadol¹⁴ but also confirms previous findings that a proportion of patients with a history of aspirin-induced urticaria react to alternative NSAIDs.¹⁵

In conclusion, oral challenges with COX-1 inhibitors may be useful in discriminating single-aspirin cutaneous reactors from multiple-NSAID reactors. These diagnostic tests seem

safe; the chemical difference between aspirin and the challenged drug minimizes the risk of potentially severe IgE-mediated reactions. In patients with a history of aspirin-induced urticaria, tolerance to weak COX-1 inhibitors such as acetaminophen, coxibs, nimesulide, or tramadol should be evaluated only after intolerance to alternative COX-1 inhibitors has been unequivocally demonstrated.

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