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Cetirizine premedication prevents acute urticaria induced by weak COX-1 inhibitors in multiple NSAID reactors

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Key words

Non-steroidal anti-inflammatory drugs, drug allergy, urticaria, cycloxygenase, oral challenges, antihistamines, cetirizine

Summary

Background: *In multiple NSAID reactors, intolerance to weak COX-1 inhibitors may pose relevant therapeutic problems when painful, febrile or rheumatic disorders co-exist.* ***Objective:*** *To assess whether pre-medication with a second generation antihistamine is able to prevent urticaria induced by "alternative" NSAIDs.* ***Methods:*** *87 with a history of urticaria following the administration of multiple, chemically unrelated NSAID underwent 250 oral tolerance tests with alternative drugs exerting little or no COX-1 inhibition (paracetamol, coxibs, nimesulide, tramadol). Twenty-eight challenges scored positive in 21 subjects: 8, 5, 9, and 6 reactions were induced by paracetamol, tramadol, coxibs, and nimesulide, respectively. Thirteen of 21 underwent a new oral challenge with the offending drug(s) 2-6 hours after taking cetitrizine 10 mg.* ***Results:*** *All the drugs were tolerated on re-challenge except paracetamol that was not tolerated in 2/4 cases.* ***Conclusion:*** *In most cases urticaria induced by alternative drugs exerting little or no COX 1-inhibition is slight, and can be adequately prevented by oral antihistamine pre-medication. These observations open new opportunities for patients with multiple NSAIDs intolerance that have to treat painful or febrile conditions or rheumatic disorders.*

Introduction

According to the most recent classification of NSAID-induced immediate adverse reactions of allergological interest (1, 2) both patients with and without underlying chronic urticaria may experience acute urticaria following the ingestion of multiple, chemically unrelated non-steroidal anti-inflammatory drugs. It is generally believed that cycloxygenase (COX) inhibition plays a relevant pathogenic role in these adverse reactions as they are mostly associated with non-selective, both COX-1 and COX-2 inhibiting drugs (1, 2). Although selective COX-2 inhibitors, such as nimesulide, paracetamol, floctafenine, meloxicam, or coxibs, have been shown to be well tolerated by the large majority of multiple NSAID reactors over the last 2 decades (3-10), a proportion of patients remains that react to such substances as well when they are challenged in the office (5, 11-13). Further, interestingly, some patients are unable to tolerate even drugs that don't exert any effect on COX, such as the opioid derivative, tramadol (14), suggesting that mechanisms other than cycloxygenase inhibition might be also involved in histamine release in some patients. These "hyper-reactors" pose a serious clinical problem, because they present ask-

ing for safe drugs to be taken in case of fever, pain or inflammatory conditions but are found to react also to those substances that are regarded as the only viable alternative drugs for multiple NSAID reactors.
The present study tried to address this problem from a practical point of view, investigating whether the premedication with a second-generation anti-histamine, namely cetirizine, at a licensed dose is able to prevent the urticaria reaction induced by the administration of therapeutic doses of weak COX-2 inhibitors.

Patients and methods

Patients

Subjects who presented at the outpatient allergy department of the Clinica San Carlo, from January, 2003 up to December, 2009 with a history of either acute urticaria induced by multiple, chemically unrelated NSAIDs, or of chronic urticaria exacerbated by at least one NSAID, and who accepted to undergo oral tolerance tests with alternative NSAIDs exerting little or no inhibition on COX-1 were considered for this study.

Oral tolerance tests

Challenged drugs included acetaminophen (paracetamol), nimesulide, one coxib (rofecoxib until its withdrawal from the market; subsequently etoricoxib), and/or the opioid derivative tramadol. Challenges were carried out as previously described (10-14). Briefly, each drug was challenged electively in an open fashion; progressively increasing doses of each drug under examination (1/4 and 3/4 of a therapeutic dose) were administered orally one hour apart. Patients were kept under observation at the clinic for at least 2 hours following the second dose. Total doses of each drug given were the following: 500 mg paracetamol, 100 mg nimesulide, 25 mg rofecoxib, 90 mg etoricoxib, and 50 mg tramadol. The challenge was stopped if urticaria appeared following the first administered dose. Only the occurrence of clear-cut urticaria following the ingestion the challenged drug was considered as a positive response; in patients with chronic urticaria only a clear-cut exacerbation of their disease was considered as a positive response. Patients with a history of chronic urticaria were challenged in a phase of slight activity of their disease with the patients off antihistamine therapy for al least 7 days without any sign of exacerbation of their underlying disease,

Subjects reacting to one or more of the challenged drugs were offered a second oral challenge with the positive substance while taking cetirizine 10 mg. Those who accepted to be re-challenged were recommended to take one tablet of cetirizine 10 mg, 2-6 hours before the start of the new procedure; on re-challenge, the entire dose of the drug under examination was given at the start of the test and the patient was kept under control for the following 3 hours. All re-challenges were carried out at least 2 weeks after the previous positive challenge.
All patients gave an informed written consent before the start of every challenge. Since the study was carried out within the routine clinical practice following patients' request for tolerated drugs no approval by ethical review board was required.

Statistics

Comparisons between the subgroups were carried out using the chi-square test with Yates' correction. Probability values < 5% were considered statistically significant.

Results

A total of 87 (M/F 24/63; age 17-76 years) patients were included. 52 had a history of chronic urticaria exacerbated by at least 1 NSAID, and 35 were otherwise normal subjects with a history of acute urticaria following the ingestion of at least 2 chemically unrelated NSAIDs. The two subsets did not show any difference in terms of sex and mean age. These 87 patients underwent a total of 250 oral tolerance tests: 81, 77, 73, and 19 with paracetamol, tramadol, coxib (either rofecoxib or etoricoxib), and nimesulide, respectively. A total of 28 challenges scored positive in 21 patients (M/F 2/19); 14/52 (27%) subjects with chronic urticaria and 7/35 (20%) multiple NSAID reactors without chronic urticaria. The prevalence of intolerance to alternative challenged medications did not differ between the two subgroups (p = NS). Female patients showed a higher propensity to react to alternative drugs on oral challenges, although the difference with male patients did not reach the statistical significance. The main results of oral tolerance tests with alternative weak COX-1 inhibitors are summarized in table 1. Tramadol showed the lowest prevalence of positive challenges 5/77 (6%), followed by paracetamol and coxibs (about 10%), while nimesulide was not tolerated by about one third of challenged subjects. In all cases the urticaria

Table 1 - Oral challenges, adverse reaction recorded, and effect of cetirizine pre-medication.

	Total challenges	Positive challenges	Tolerated with Cetirizine
Paracetamol	81	8 (10%)	2/4 (50%)
Tramadol	77	5 (6%)	5/5 (100%)
Coxib	73	9 (12%)	7/7 (100%)
Nimesulide	19	6 (32%)	1/1 (100%)
Total	250	28 (11%)	15/17 (88%)

reaction induced by the challenged drugs was reportedly slighter than that caused by non-selective COX inhibitors, and was easily controlled by injection chlorfenamine 10 mg.

Seventeen drugs that had not been tolerated on open oral challenges were re-challenged in 13 subjects (9 and 4 with and without a history of chronic urticaria, respectively) 2-6 hours after taking oral cetirizine 10 mg; challenged drugs included paracetamol, tramadol, coxibs, and nimesulide in 4, 5, 7, 1 cases, respectively. On re-challenge, the drugs were administered as a single full dose. All the drugs were tolerated on re-challenge with the exception of paracetamol that was not tolerated in 2/4 cases. Of the 2 paracetamol reactors 1 had a history with chronic urticaria and one was an otherwise normal subject. These urticaria reactions occurred about 60 min after the administration, were slight and resolved rapidly after the administration of intramuscular chlorfenamine 10 mg.

Discussion

The prevalence of urticaria reactions induced by the challenged drugs on oral tolerance tests was in line with that observed in previous studies (10-14), and roughly directly related with the COX-1 inhibiting activity of the single substances, with nimesulide causing urticaria in about one third of challenged subjects, and tramadol (an opioid derivative) inducing rarely skin reactions. Interestingly, no difference in the prevalence of intolerance to the alternative medications challenged was observed between patients with or without a history of chronic spontaneous urticaria.

This study addressed an important practical problem, that is what to do in patients with multiple NSAID reactors (either with or without underlying chronic urticaria) that don't tolerate drugs exerting little or no inhibition on COX-1 on tolerance tests and that are generally tolerated by the large majority of these subjects. Although this problem concerns a limited number of subjects it is, nonetheless, relevant because all patients with a history of NSAID-induced urticaria present at allergy clinics asking for safe drugs to be used when necessary. The findings of this study clearly show that in most cases urticaria induced by alternative drugs exerting little or no COX 1-inhibition is slight, and can be adequately prevented by oral antihistamine pre-medication. These observations open new opportunities for patients with multiple NSAIDs intolerance that have to treat painful or febrile conditions or have rheumatic disorders.

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