

TOLERABILITY OF THREE SELECTIVE CYCLO-OXYGENASE-2 INHIBITORS, MELOXICAM, CELECOXIB AND ROFECOXIB IN NSAID-SENSITIVE PATIENTS

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SUMMARY :

Background: Patients with aspirin-sensitive respiratory and cutaneous diseases experience cross reactions to all nonsteroidal anti-inflammatory drugs (NSAIDs) which inhibit cyclo-oxygenase (COX) enzymes. As are now available drugs which selectively inhibit COX-2, questions are raised whether cross-reactivity occurs between aspirin and these COX 2 inhibitors.

Objective: The aim of this study was to evaluate the tolerability of three COX-2 inhibitors (meloxicam, celecoxib and rofecoxib) in subjects with previous pseudoallergic respiratory and cutaneous reactions to NSAIDs.

Methods: 76 subjects with documented previous cutaneous and respiratory pseudoallergic reactions to aspirin and/or other NSAIDs underwent a single blind challenge with celecoxib, meloxicam and rofecoxib.

Results: All subjects with previous respiratory reactions tolerated all drugs. Three subjects with multiple-drug induced urticaria complained of a generalized reaction after challenge (Two due to celecoxib and one due to meloxicam). Among the group of patients with NSAIDs-induced urticaria five complained of a relapse of the disease due to rofecoxib (one subjects), celecoxib (two subjects) and meloxicam (two subjects).

Conclusions: According to these results the cross-reactivity between aspirin and these COX-2 inhibitors does not occur in subjects with previous respiratory pseudoallergic reactions. A good safety profile was also demonstrated in patients with cutaneous reactions, being few reactions observed. However for this reason a controlled oral challenge with these drugs is useful for the proper management of patients sensitive to classic NSAIDs.

Key-words: Meloxicam - Rofecoxib - Celecoxib - Selective COX 2 inhibitors - Aspirin hypersensitivity.

INTRODUCTION

Cutaneous and respiratory adverse reactions triggered by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the enzyme cyclooxygenase (COX) constitute one of the most common drug related pseudoallergic reactions observed in both general practice and allergy setting. These reactions are generally rare in general population (1) but are more common in patients with asthma (2) and chronic urticaria (3). Moreover a history of urticaria after taking aspirin or other NSAIDs may be reported by otherwise normal subjects as well (4). During the last decade the recognition of two different prostaglandin synthetase iso-enzymes designated COX-1 and COX-2. COX-1 offered new insights in the pathogenesis and management of these pseudoallergic reactions (5). In fact in subjects with aspirin intolerance reactions can occur after the ingestion of ASA and of any of the NSAIDs that inhibit the COX-1 enzy-

me (6), whilst drugs such as paracetamol or nimesulide which poorly inhibit COX-1 are generally well tolerated in the same subjects (7) and can be responsible of reactions only at high dosages (8). Aim of this study is to determine the clinical tolerance of the recently available COX-2 inhibitors, meloxicam, rofecoxib and celecoxib in ASA intolerance.

MATERIALS AND METHODS

Study design

Out-patients with well-documented pseudoallergic reactions to ASA and NSAIDs were carefully selected based on definite criteria (see below). All patients underwent blindly an oral incremental challenge with three recently available COX-2 selective inhibitors such as meloxicam, rofecoxib and celecoxib under controlled conditions.

Patients

We selected 76 subjects, divided in three groups according to the recent classification of allergic and pseu-

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doallergic reactions to ASA and NSAIDs (9) (table 1). All patients had a documented history of ASA/NSAIDs. and had previous pseudoallergic reactions to at least two chemically unrelated NSAIDs. As shown in table 2 aspirin, ibuprofen and metamizole were most frequently responsible for pseudoallergic reactions.

Group	N° of patients	MeanAge (range)	Males/females
Group A	24	51.1 (34-79)	8/16
Group B	34	45.9 (16-75)	11/23
Groupe C	18	54.7 (32-72)	6/12

Table 1: Demographic data of patients. According to the recent classifications of sensitivity to NSAIDs (see reference 9) patients were divided in three groups: Group A: NSAID-induced rhinitis and asthma. Group B: Multiple drug-induced urticaria/angioedema. Group C: NSAIDs-induced urticaria/angioedema.

Drug	Cases
ASA	43
Metamizole	21
Ibuprofen	21
Propiphenazone	15
Diclofenac	14
Naproxen	11
Paracetamol	10
Ketoprofen	5
Nimesulide	4
Ketorolac	2

Table 2: Drugs responsible of pseudoallergic reactions.

The patients were selected according to the following criteria:

- history of at least two previous pseudoallergic reactions to NSAIDs one of them occurred during the past 12 months ;
- a documented relationship between the intake of the drug and the onset of symptoms (no more than 12 hours) ;
- a single NSAID drug was taken before each episode ;
- informed consent to undergo the challenge.

The time interval between challenges was at least 15 days and anti-histamines were omitted for 96 hours whereas steroids were stopped for at least 1 month.

Patients with significant active medical conditions (pulmonary, gastro-intestinal, cardiovascular, psy-

chiatric, hepatic, neurologic, renal or haematologic) and pregnant women were excluded from the study.

Oral provocation tests

The challenge test was performed in single-blind fashion, in three steps according to the schedule shown in table 3. In first day only placebo (talco) was administered whilst in other two days starting doses were a half of the final dose and they were given 2 hours apart. After every day session patients were evaluated for two hours.

Conditions required for starting the challenge with the active drug were (10):

- absence of cutaneous or respiratory symptoms or no exacerbation of urticaria in subjects with CIU ;
- FEV1 > 80% of the predicted value ;
- no reaction following placebo administration.

Drug	Day 1	Day2	Day 3
Meloxicam	Placebo	7.5 mg	15 mg
Rofecoxib	Placebo	12.5 mg	25 mg
Celecoxib	Placebo	100 mg	200 mg

Table 3: Schedule of challenge tests.

The challenges were performed in day-hospital regimen. Equipment and trained personnel for emergency resuscitation were available during the whole procedure. Respiratory function (FEV1), blood pressure and pulse rate were recorded before and 30 minutes after placebo or active drug administration. All patients were seen again 24 hours after the end of challenge in order to exclude a delayed reaction.

The response to challenge was considered positive in asymptomatic subjects (group A and B) whether one or more of the following symptoms appeared : erythema, urticaria/angioedema, rhinorrhea, nasal obstruction, sneezing, dyspnea or cough associated with a fall of FEV1 > 20% of the baseline, hypotension.

For the evaluation of the challenge test in subjects with urticaria the "rule of nines" was used and a test was considered positive if there was an increase of urticarial lesions of > 30% of the body surface (11)

RESULTS

The results of challenges are summarized in table 4. All patients with aspirin-induced asthma (Group A)

Group	Rofecoxib		Celecoxib		Meloxicam		Tot. Reactors
	Reactors	Tolerants	Reactors	Tolerants	Reactors	Tolerants	
Group A	0	24	0	24	0	24	0
Group B	0	34	2	32	1	38	3 (3.03%)
Group C	1	17	2	16	2	16	5 (10.2%)
Tot.	1 (1.3%)	75	4 (6.56%)	72	3 (4.1%)	73	8 (3.5%)

Table 4: Results of challenge tests.

tolerated the three drugs. Two patients with multiple drug-induced urticaria/angioedema (Group B) complained of urticaria after meloxicam challenge both at the dosage of 15 mg. Celecoxib provoked also urticaria in one of them at the dosage of 50 mg. Among the patients belonging to Group C one subject reacted to rofecoxib (12.5 mg), whilst two patients reacted both to meloxicam (7.5 mg) and celecoxib (50 mg and 100 mg respectively). No reactions to placebo were observed. No delayed reactions were reported.

DISCUSSION

Education of the patients with ASA-induced disease is very important. Avoidance of ASA and all cross-reacting NSAIDs prevents respiratory and urticarial cross-reacting events in previously sensitized patients. However the management of patients with pseudoallergic reactions to NSAIDs is a complex problem in clinical practice. Many physicians believe that patients who have complained of intolerance to one or more NSAIDs simply have to be forbidden to take all members of this class. This approach is rarely considered satisfactory by the patients, which usually require to be told what drugs they can use in the case of need. The recent observations about the role of COX1 and its inhibition in the pathogenesis of aspirin-induced asthma and pseudoallergic reactions have suggested that the use of selective COX2 inhibitors would be an optimal choice.

According to previous studies we report a good tolerability of these three molecules in aspirin-induced asthma, confirming the lack of cross-reactivity between these COX 2 inhibitors and aspirin in aspirin sensitive patients with asthma (12-19).

There are less informations available in the literature about the safety of new anti-inflammatory drugs with selective COX2 inhibitory properties in NSAIDs-intolerant patients with cutaneous reactions. According to previous studies (11,20) we report a low frequency of

reactions (table 4), supporting the hypothesis that COX1-inhibition represents the main mechanism involved in the pathogenesis of adverse cutaneous reactions to NSAIDs. Interestingly, as previously reported (11) also in our study the degree of cross-reactivity for COX-2 inhibitors seems to be related to the degree of COX1 inhibition in vitro (21,22), being rofecoxib the most tolerated drug. In contrast with these findings Asero in a study performed on multiple NSAID-intolerance reported two rofecoxib-intolerant subjects who tolerated nimesulide and moreover an high frequency of intolerance to paracetamol, a drug which has no effect on COX1. The Author suggest that in these patients drugs nonspecifically trigger histamine release from mast-cells and basophils and that such an effect do not depend on chemical structure or pharmacologic activity (20).

Despite these favourable results it is premature to recommend an indiscriminate use of COX2 inhibitors in NSAID-intolerant subjects. First it is established, according to also our results, that subjects with chronic urticaria or with isolated skin reactions represent a clinically distinct entity (23) in which the tolerability of COX2 inhibitors is less clearly demonstrated. Second a selective anaphylactic reaction to celecoxib has been reported in a subject with an history of a previous anaphylactic reaction to a COX1 inhibitor drug (24). Third although the safety of COX 2 in acute studies has been clearly established, large studies are needed before subjects with aspirin induced asthma can be advised to routinely take this new class of drugs. Moreover the tolerability of these drugs was evaluated in patients well controlled, but their safety has to be confirmed in daily practice, when the patient might be unstable.

Finally due to ethical reasons (25) we could not confirm the NSAIDs-intolerance by means a specific challenge, therefore it is possible that false positive cases were included in our population. However it has to be considered that a good reliability of clinical histories in NSAIDs-intolerant patients (26,27) has been

demonstrated. Moreover we tried to limit the possible confounding factors by selecting subjects taking only one NSAID at the time of the reaction, in order to exclude any interference of other drugs.

References

1. Hedman J., Kaprio J., Poussa T., Nieminen M.-M. - Prevalence of asthma, aspirin intolerance and chronic obstructive pulmonary diseases in a population-based study. *Int J Epidemiol* 1999;28:717-722.
2. Vally H., Taylor M.-L., Thompson P.-J. - The prevalence of aspirin-intolerant asthma in Australian asthmatic patients. *Thorax* 2002;57:569-74.
3. Mathison D.-A., Lumry W.-R., Stevenson D.-D. et al. - Aspirin in chronic urticaria and/or angioedema: studies of sensitivity and desensitization. *J Allergy Clin Immunol* 1982;69:135.
4. Asero R. - Multiple sensitivity to NSAID. *Allergy* 2000;55:893-4.
5. Szczeklik A., Stevenson D.-D. - Aspirin-induced asthma: advances in pathogenesis, diagnosis and management. *J Allergy Clin Immunol* 2003;111:913-20.
6. Szczeklik A., Sanak M. - The role of COX 1 and COX 2 in asthma pathogenesis and its significance in the use of selective inhibitors. *Clin Exp Allergy* 2002;32:339-42.
7. Quarantino D., Romano A., Papa G., Di Fonso M. et al. - Long-term tolerability of acetaminophen and nimesulide in non steroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 1997;79:47-50.
8. Settipane R.-A., Schrank P.-J., Simon R.-A., Mathison D.-A., Christiansen S.-C., Stevenson D.-D. - Prevalence of cross-reactivity with acetaminophen in aspirin-sensitive asthmatic patients. *J Allergy Clin Immunol* 1995;96:480-7.
9. Stevenson D.-D., Sanchez-Borges M., Szczeklik A. - Classification of allergic and pseudo-allergic reactions to drugs that inhibit cyclo-oxygenase enzymes. *Ann Allergy Asthma Immunol* 2001;87:177-80.
10. Aberer W., Bircher A., Romano A. et al. - Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Position paper 2003;58:854-63.
11. Sanchez-Borges M., Capriles-Hulett A., Caballero-Fonseca F., Perez C.-R. - Tolerability to new COX2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001;87:201-4.
12. Kosnik M., Music E., Matjaz F., Suskovic R. - Relative safety of meloxicam in NSAID-intolerant patients. *Allergy* 1998;53:1231-2.
13. Szczeklik A., Nizankowska E., Bochenek K., Nagraba K., Meiza F., Swierczynska M. - Safety of a specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy* 2000;31:219-25.
14. Quarantino D., Romano A., Di Fonso M. et al. - Tolerability of meloxicam in patients with histories of adverse reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2000;84:613-7.
15. Stevenson D.-D., Simon R.-A. - Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* 2001;108:47-51.
16. Valero A., Baltasar M., Enrique E., Pau L. et al. - NSAID-sensitive patients tolerate rofecoxib. *Allergy* 2002;57:1214-5.
17. Woessner K.-M., Simon R.-A., Stevenson D.-D. - The safety of celecoxib in patients with aspirin-sensitive asthma. *Arthritis & Rheumatism* 2002;46:2201-6.
18. Martin-Garcia C., Hinojosa M., Berges P., Camacho E., Garcia-Rodriguez R., Alfaya T., Iscar A. - Safety of a cyclooxygenase-2 inhibitor in patients with aspirin-sensitive asthma. *Chest* 2002;121:1812-7.
19. Gyllfors P., Bochenek G., Overholt J., Drupka D. et al. - Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgetic drug celecoxib. *J Allergy Clin Immunol* 2003;111:1116-21.
20. Asero R. - Tolerability of rofecoxib. *Allergy* 2001;56:916-7.
21. Vane J. - Aspirin and other anti-inflammatory drugs. *Thorax* 2000;55(Suppl 2):S3-9.
22. Warner T.-D., Giuliano F., Voinovic I. et al. - Non steroidal drug selectivities for cyclooxygenase 1 rather than cyclooxygenase 2 are associated with human gastrointestinal toxicity: a full *in vitro* analysis. *Proc Natl Acad Sci USA* 1999;96:7563-8.
23. Stevenson D.-D., Simon R.-A. - Sensitivity to aspirin and non steroidal anti-inflammatory drugs. In: Middleton E., Reed C.-E., Ellis F.-F., Adkinson N.-F., Yunginger J.-W., Busse W.-W. *Allergy Principles and practice*. 4th ed. Mosby 1993;1747-65.
24. Schellenberg R.-R., Isserow S.-H. - Anaphylactoid reaction to a cyclo-oxygenase 2 inhibitor in a patient who had a reaction to a cyclooxygenase 1 inhibitor. *N Eng J Med* 2001;345:1856.
25. SIAIC Memorandum on drugs allergy/intolerance diagnosis. *Ital J Allergy Clin Immunol* 1998;8:568-95.
26. Delaney J.-C. - The diagnosis of aspirin idiosyncrasy by analgesic challenge. *Clin Allergy* 1976;6:177-81.
27. Falliers C.-J. - Acetaminophen and aspirin challenges in subgroups of asthmatics. *J Asthma* 1983;20:39-40.



UCB PHARMA

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Its objective was to compare the efficacy of XYZALL® to that of desloratadine on symptoms of SAR, in terms of time to onset of action and duration of action, intensity and the maintenance of efficacy.

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