

SAFETY OF CELECOXIB IN PATIENTS WITH ADVERSE SKIN REACTIONS TO ACETAMINOPHEN (PARACETAMOL) AND NIMESULIDE ASSOCIATED OR NOT TO COMMON NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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SUMMARY:

■ **Background:** Acetaminophen (paracetamol- P) and Nimesulide (N) are widely used analgesic-antipyretic/anti-inflammatory drugs. The rate of adverse hypersensitivity reactions to these agents is generally low. On the contrary non-steroidal anti-inflammatory drugs (NSAIDs) are commonly involved in such reactions. Celecoxib (CE) is a novel drug, with high selectivity and affinity for COX-2 enzyme.

■ **Objective:** We evaluated the tolerability of CE in a group of patients with documented history of adverse cutaneous reactions to P and N associated or not to classic NSAIDs.

■ **Methods:** We studied 9 patients with hypersensitivity to P and N with or without associated reactions to classic NSAIDs. The diagnosis of P and N-induced skin reactions was based in vivo challenge. The placebo was blindly administered at the beginning of each challenge. After three days, a cumulative dosage of 200 mg of CE in refracted doses were given. After 2-3 days, a single dose of 200 mg was administered. All patients were observed for 6 hours after each challenge, and controlled again after 24 hours to exclude delayed reactions. The challenge was considered positive if one or more of the following appeared: erythema, rush or urticaria-angioedema.

■ **Results:** No reaction was observed with placebo and eight patients (88,8 %) tolerated CE. Only one patient developed a moderate angioedema of the lips.

■ **Conclusion:** Only one hypersensitivity reaction to CE was documented among 9 P and N- highly NSAIDs intolerant patients. Thus, we conclude that CE is a reasonably safe alternative to be used in subjects who do not tolerate P and N.

Key-words: Celecoxib - Drug allergy - Cutaneous adverse reactions - Nimesulide, NSAIDs - Paracetamol.

Acetaminophen (paracetamol-P) and nimesulide are widely used analgesic-antipyretic / anti-inflammatory drugs.

The pathogenetic mechanisms underlying hypersensitivity reactions to aspirin and other common non-steroidal anti-inflammatory drugs (NSAIDs) are not fully understood. However it is widely recognized that the inhibition of the isoform 1 of the cyclo-oxygenase (COX-1) enzyme induced by NSAIDs is frequently responsible for pseudoallergic reactions other than gastric damage (1-3). On the contrary acetaminophen is a weak inhibitor of prostaglandin synthesis, as a consequence, less than 5% of aspirin sensitive subjects react to paracetamol after a specific challenge (4). N is a prevalent COX-2 inhibitor and, in fact, it is usually well tolerated by patients suffering from NSAIDs hypersensitivity (5, 6).

Considering the enormous consumption of P worldwide the rate of adverse hypersensitivity reactions is very low. However, urticaria-angioedema, maculopapular eruption, bronchial obstruction as isolated manifestations, as well as generalized reactions (anaphylaxis, vasculitis, rhabdomyolysis etc.) have also been described (7-9).

In these highly sensitive patients suffering from pseudoallergic manifestations induced by the intake of P and N with or without NSAIDs the identification of a safe alternative drug represents, therefore, a compelling need.

Celecoxib (CE), a novel high affinity COX-2 inhibitor, has an efficacy profile similar to the classic NSAIDs with a very low rate of adverse events (10, 11).

Very few studies have so far investigated the tolerability and safety profile of CE in patients with NSAIDs hypersensitivity (12-14).

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Aim of this study was to assess the safety of CE in a group of patients with a history of adverse cutaneous reactions to P and N alone or associated with common NSAIDs.

MATERIAL AND METHODS

Patients and diagnosis

Subjects were enrolled among outpatients referred to our clinic for adverse drug reactions. The main inclusion criterion was a clinical history of skin reactions (generalized itching, erythema and/or urticaria-angioedema) following the intake of acetaminophen and N with or without some common NSAIDs. The second inclusion criterion and exclusion criteria are listed in table 1.

■ Inclusion criteria ;

- an history of adverse cutaneous reactions induced by administration of P and N with or without NSAIDs ;
- availability to give a written consent.

■ Exclusion criteria:

- Recent (within the interval of two months) reported episode / s of P and N with or without NSAIDs induced cutaneous adverse reactions.
- Contraindication to discontinue the use of anti-H1 receptor antagonists in the week prior to the oral challenge.
- Contraindication to discontinue the use of any type of drugs (including- β -blockers) for at least two days before the challenge.
- Presence (or also an history of recent presence) of cutaneous symptoms such as urticaria-angioedema and/or itching induced by any cause at the time of the challenge.
- An history of respiratory symptoms (associated or not with cutaneous symptoms) after the administration of P and N with or without NSAIDs.
- Pregnancy or lactation
- Lactose intolerance
- Contraindication to eventual use of epinephrine
- Subjects with psychosomatic disorders.

Table 1: Inclusion and exclusion criteria for oral challenge with CE.

All the adverse drug reactions had to be documented in detail by clinical history or, preferably, by medical documentation (i.e. GP's report or documentation from emergency care unit).

All patients signed an informed consent before the challenge test. However the challenge with safe alternative drugs is routinely carried out in our laboratory under day hospital recovery and under the Guidelines of Italian Society of Allergology and Clinical Immunology (15). This is the reason why the challenge tests do not require the authorization of an ethical committee.

The diagnosis of P and N -induced skin reactions was confirmed by us after an oral challenge. All patients of this study have been challenged previously with P and N to identify a safe alternative drug to NSAIDs.

After the first interview, all patients underwent physical examination. When indicated, spirometry and skin-prick tests (SPTs) with standardized allergenic extracts for common inhalant and food allergens (ALK Abello Group, Milan Italy) were also carried out. SPTs were performed and interpreted according to a standardized method (16).

Celecoxib challenge

To evaluate the tolerability of CE as alternative drug, all patients underwent a single-blind placebo-controlled oral challenge. During the whole challenge procedures a continuous medical supervision was warranted and emergency care equipment was available. CE and placebo (lactose) were administered in identical capsules prepared by the hospital's Pharmacy. Four doses/capsule of CE were used during the challenge: 20 mg, 60 mg, 120 mg and 200 mg. This latter, represents the therapeutic dose contained in the commercial product. On the first day, three placebo capsules were given at 1-hour interval. During the second session, after 3- 4 days, the patients received 20, 60 and 120 mg CE hourly. In the third step, again 3 - 4 days later, a single therapeutic dose of 200 mg CE was given. The patients were evaluated clinically (pulse rate, arterial pressure, pulse-oxymetry, respiratory rate) at scheduled intervals during the challenge. A standard spirometry was also performed before beginning each challenge session and after 6 and 24 hours (in order to exclude delayed reactions). The challenge was considered positive if one or more of the following objectivable symptoms appeared: erythema, rush or urticaria-angioedema. The challenge procedure is summarized in figure 1.

RESULTS

Nine patients (4 male and 5 female; aged 16-68; mean age 41) were included, according to criteria listed in table 1.

Out of the 9 patients, 4 (44,4%) had a family history of allergy, 3 (33,4%) had an history of urticaria-angioedema and 4 (44,4%) had a clinical history of respiratory or food allergy : In these patients, SPTs with inhalant and food allergens confirmed their allergic sensitization. Furthermore 4 patients (44,4%) reported cutaneous symptoms after the intake of antimicrobials (3 β -lactams, 1 macrolide). All patients had a clinical history of adverse reaction to acetaminophen and N associated or not with one or more NSAIDs (table 2).

None of the patients reacted to placebo. Eight patients (88,8%) tolerated the therapeutic dose of CE (200 mg) without any reaction. Only one patient (a 35 year-old woman) developed a moderate angioedema of the lips about 40 minutes after the administration of the single cumulative dose of CE (200 mg). This adverse event resolved in less than 2 hours after the administration of oral cetirizine (10 mg) and intravenous methyl prednisolone (40 mg). No change in blood pressure, pulmonary function or oxygen saturation was recorded.

DISCUSSION

Although some reports of anaphylactic/anaphylactoid reactions induced by CE have been reported (17-19), it is generally recognized that "coxibs" are overall safe

and well tolerated especially in patients suffering from ASA - induced asthma (20,21). Indeed, at present there are more data concerning rofecoxib (22-25) than CE (11).

To our knowledge no study has so far evaluated the tolerability of CE as an alternative drug in patients suffering from associated P and N -hypersensitivity.

The use of these drugs is very common, due to their favourable profile of tolerability and efficacy. In fact the absolute number of patients referring for P and/or N intolerance remains low, when compared to that of ASA and other NSAIDs hypersensitivity. Probably, patients suffering from associated P and N hypersensitivity should be considered a highly reactive population. The finding of only one positive response (11,1%) to oral challenge with CE in this group of highly reactive patients suggests that this agent has a favourable safety profile.

An important limit of this type of study is the use of a single cumulative dose. For this reason the effects of higher doses or the prolonged use of this agent on development of hypersensitivity remain to be evaluated.

References

1. Mitchell J.-A., Warner T.-D. - Cyclo-oxygenase. Pharmacology, physiology, biochemistry and relevance to NSAID therapy. *Br J Pharmacol* 1999;128:1121-32.
2. 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.
3. Vane J. - Aspirin and other anti-inflammatory drugs. *Thorax* 2000;55(Suppl 2): S3-S9.
4. Szczeklik A. - Analgesics, allergy and asthma. *Drugs* 1986;32:148-63.
5. Andri L., Senna G.-E., Bettoli C. *et al.* - Tolerability of nimesulide in aspirin-sensitive patients. *Ann Allergy* 1994;72:29-32.
6. Quarantino D., Romano A., Papa G. *et al.* - Long-term tolerability of nimesulide and acetaminophen in non-steroidal anti-inflammatory drug-intolerant patients. *Ann allergy Asthma Immunol* 1997;79:47-50.
7. Ayonrinde O.-T., Saker B.-M. - Anaphylactoid reactions to paracetamol. *Postgrad Med J* 2000;76:501-02.
8. Ibanez M.-D., Alonso E., Munoz M.-C., Martinez E., Laso M.-T. - Delayed hypersensitivity reaction to paracetamol (acetaminophen). *Allergy* 1996;51:121-23.
9. Moneret-Vautrin D.-A., Morisset M., Humbert J.-C., Beaudonin E., Tupin N., Plantier L. - Acetaminophen-induced rhabdomyolysis. *Allergy* 1999;54:1115-16.
10. Fitzgerald G.-A., Patrono C. - The coxibs, selective inhibitors of cyclo-oxygenase-2. *N Engl J Med* 2001;345:433-42.
11. Clemett D., Goa K.-L. - Celecoxib : a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* 2000;59:957-80.
12. Patterson R., Bello A.-E., Lefkowitz J. - Immunologic tolerability profile of celecoxib. *Clin Ther* 1999;21:2065-79.
13. Garcia-Rodriguez R.-M., Hinojose M., Camacho-Garrido E., Berges-Gimeno P., Martin Garcia C. - Celecoxib is safe in NSAID intolerance. *Allergy* 2002;57:1085-86.

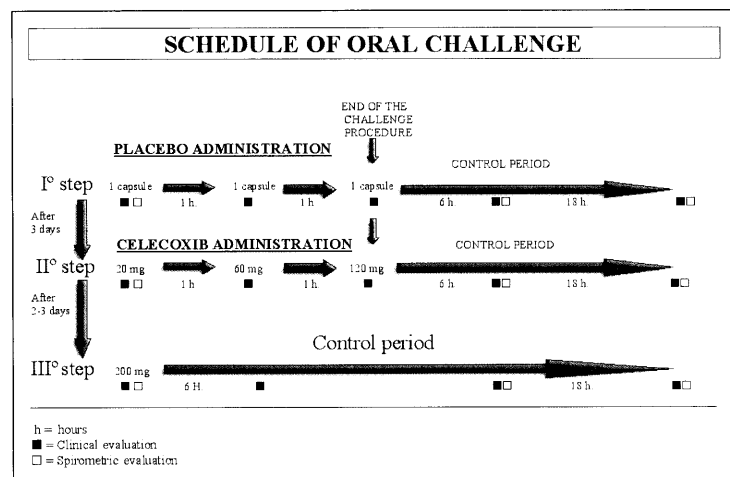


Figure 1:

DRUGS	n° PATIENTS	%
Paracetamol + nimesulide	3	33,4
Paracetamol + nimesulide +ASA	4	44,4
Paracetamol + nimesulide + ASA + Others*	1	11,1
Paracetamol + others*	1	11,1
TOTAL	9	100

Table 2: Drugs causing adverse skin reactions.

* NSAIDs : morniflumate, diclofenac, ketorolac, metamizol.

14. Dahlen B., Szczeklik A., Murray J.-J. - Celecoxib in patients with asthma and aspirin intolerance. *N Engl J Med* 2001;344:142.
15. Ortolani C., D'Amato G., Giannetti A., Marone G., Moscato G., Meneghini A. - Memorandum SIAIC nella diagnosi di allergia/ intolleranza ai farmaci. *Giorn I t Allergol Clin Immunol* 1998;8:568-95.
16. Dreborg S., Frew A. - Position Paper. Allergen standardization and skin tests. *Allergy* 1993;48(Suppl 14):49-83.
17. Hubky R., Vermeulen C., Bachmeyer C., Charoud A., Mofredi A. - Anaphylactic shock induced by celecoxib. *Ann Int Med* 2001;152:355.
18. Levy M.-B., Fink J.-N. - Anaphylaxis to celecoxib. *Ann Allergy asthma Immunol* 2001;87:72-73.
19. Gagnon R., Julien M., Gold P. - Selective celecoxib-associated anaphylactoid reaction. *J Allergy Clin Immunol* 2003;111:1404-05.
20. Szczeklik A., Nizankowska E., Bochenek G., Nargaba K., Mejza F., Swierczynska M. - Safety of a specific COX-2 inhi-

- bitor in aspirin-induced asthma. *Clin Exp Allergy* 2001;31:219-25.
21. Martin Garcia C., Hinojosa M., Berges P. *et al.* - Safety of a cyclo-oxygenase-2 inhibitor in patients with aspirin-sensitive asthma. *Chest* 2002;121:1812-17.
22. Pacor M.-L., Di Lorenzo G., Biasi D., Barbagallo M., Corrocher R. - Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and/or non-steroidal anti-inflammatory drugs. *Clin Exp Allergy* 2002;32:397-400.
23. Asero R. - Tolerability of rofecoxib. *Allergy* 2001;56:916-17.
24. Nettis E., Di Paola R., Ferranini A., Tursi A. - Tolerability of rofecoxib in patients with cutaneous adverse reactions to non-steroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2002;88:331-34.
25. Perrone M.-R., Artesani M.-C., Viola M., Gaeta F., Caringi M., Quarantino D., Romano A. - Tolerability of rofecoxib in patients with adverse reactions to non-steroidal anti-inflammatory drugs: a study of 216 patients and literature review. *Int Arch Allergy Immunol* 2003;132:82-86.



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