Original Article

Safety of Celecoxib in patients with adverse skin reactions to acetaminophen (paracetamol) and other non-steroidal anti-inflammatory drugs

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Summary. *Background:* Acetaminophen (paracetamol-P) is a widely used analgesic-antipyretic drug with no anti-inflammatory effects and its rate of adverse hypersensitivity reactions is very low. On the contrary non-steroidal anti-inflammatory drugs (NSAIDs) are commonly involved in side effects. 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 to classic NSAIDs.
Methods: We studied 29 patients with hypersensitivity to P and classic NSAIDs. The diagnosis of P-induced skin reactions was based on *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 was given. After 2-3 days, a single dose of 200 mg was administered. All patients were observed for 6 hours after each challenge, and they were controlled again after 24 hours to exclude delayed reactions. The challenge was considered positive if one or more of the following appeared: erythema, rash or urticaria-angioedema.
Results: No reaction was observed with placebo and twenty eight patients (96.5 %) tolerated CE. Only one patient developed a moderate angioedema of the lips.
Conclusion: Only one hypersensitivity reaction to CE was documented among 29 P-intolerant patients. Thus, we conclude that CE is a reasonably safe alternative which can be used in subjects who do not tolerate P.

Key words: Celecoxib, drug allergy, cutaneous adverse reactions, NSAIDs, paracetamol.

Introduction

Acetaminophen (paracetamol-P) is a widely used analgesic-antipyretic drug with no anti-inflammatory effects.

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 NSAID-induced inhibition of the isoform 1 of the cyclo-oxigenase (COX-1) enzyme 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 P after a specific challenge [4]. Settipane et al [5] recommend that high

doses of acetaminophen (1000 mg or greater) should be avoided in aspirin-sensitive asthmatic patients.

Considering the enormous consumption of P worldwide, the rate of adverse hypersensitivity reactions is very low, but urticaria-angioedema, maculopapular eruption, bronchial obstruction as isolated manifestations, as well as generalized reactions (anaphylaxis, vasculitis, rabdomyolysis etc) have been described [6-8].

In patients suffering from pseudoallergic reactions induced by the intake of P and NSAIDs the identification of a safe alternative drug represents a compelling need.

Celecoxib (CE), a novel high affinity COX-2 inhibitor, has an efficacy and safe profile similar to the classic NSAIDs with a very low rate of adverse events [9,10].

Very few studies have so far investigated the tolerability and safety profile of CE in patients with NSAIDs hypersensitivity [11-13].

The 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 other 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 some common NSAIDs. The second inclusion criterion and exclusion criteria are listed in Table 1.

All the adverse drug reactions needed to be documented in detail in the 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 the Italian Society of Allergology and Clinical Immunology [14]. This is the reason why the challenge tests do not require the authorization of an ethical committee.

The diagnosis of P-induced skin reactions was confirmed by us after an oral challenge. All patients of this study have been challenged previously with P 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 [15].

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 ensured 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,

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

Inclusion criteria
- A history of adverse cutaneous reactions induced by administration of P and NSAIDs.
- Availability to give a written consent.

Exclusion criteria
- Recent (within the interval of two months) reported episode/s of P-and 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 ß blockers) for at least two days before the challenge.
- Presence (or also a history of recent presence) of cutaneous symptoms such as urticaria-angioedema and/or itching induced by any cause at the time of the challenge.
- A history of respiratory symptoms (associated or not with cutaneous symptoms) after administration of P and NSAIDs.
- Pregnancy or lactation.
- Lactose intolerance.
- Contraindication to eventual use of epinephrine.
- Subjects with psychosomatic disorders.

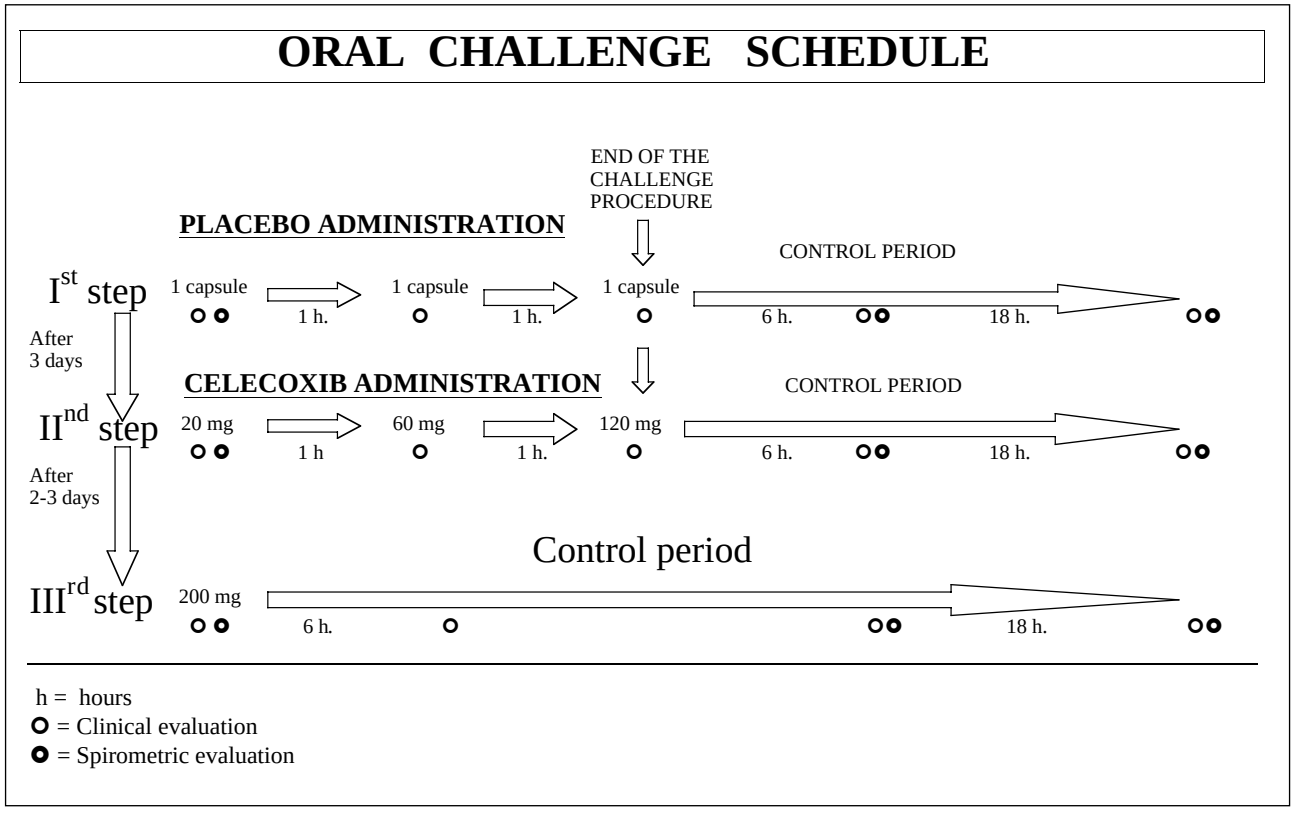

Figure 1. Schedule of oral challenge.

120 mg and 200 mg. The latter represents the therapeutic dose contained in the commercial product. On the first day, three placebo capsules were given at 1-hour intervals. 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 appeared: erythema, rash or urticaria-angioedema. The challenge procedure is summarized in Figure 1.

Results

Twenty-nine patients (9 male and 20 female; aged 15-68; mean age 34) were included in the study, according to criteria listed in Table 1.

Among these 29 patients, 16 (55.1%) had a family history of allergy and 7 (24.1%) had a clinical history of respiratory or food allergy. In those patients, SPTs with inhalant and food allergens confirmed their allergic sensitization. Furthermore 8 patients (27.5%) reported cutaneous symptoms after the intake of other drugs: 7 with antimicrobials (7 ßlactams, 2 macrolides, 1 aminoglycoside), 1 with acyclovir.

All patients had a clinical history of adverse reaction to acetaminophen associated with one or more NSAIDs (Table 2).

None of the patients reacted to placebo. Twenty – eight patients (96.5%) 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 administration of the single cumulative dose of CE (200 mg). This adverse event resolved in less than 2 hours after administration of oral cetirizine (10 mg) and

Table 2. Drugs causing adverse skin reactions.

Drugs	**nº patients**	**%**
Paracetamol + nimesulide	9	31.1
Paracetamol + ASA	7	24.1
Paracetamol + ASA + Others*	2	6.9
Paracetamol + others*	11	37.9
Total	29	100

* NSAIDs: morniflumate, diclofenac, ketorolac, oxicams, metamizol.

intravenous methyl prednisolone (40 mg). No change in blood pressure, pulmonary function or oxygen saturation was recorded.

Anamnestic data of this patient were positive for family (mother with allergic rhinitis) and personal history of IgE-mediated pollen allergy, since she suffered also from allergic rhinitis induced by sensitization to grass pollen allergens. Some years ago she experienced, in two different occasions, urticaria-angioedema 1-2 hours after the intake of P and nimesulide.

Discussion

Although some reports of anaphylactic/ anaphylactoid reactions induced by CE have been reported [16-18], there is general agreement that "coxibs" are overall safe and well tolerated in patients suffering from ASA – induced asthma [19,20] and chronic idiopatic urticaria (CIU) with sensitivity to NSAIDs [21]. These subjects were submitted to an aspirin challenge test followed by a randomized, prospective, double blind, placebo-controlled crossover trial using cyclooxygenase 2 inhibitors (celecoxib and rofecoxib), seven patients received naproxen sodium as a positive control. The outcome measures were skin examination, skin biopsy with whole cell count, urinary levels of leukotriene E4 (LTE4) and serum levels of tryptase. The results of this study showed that cyclooxygenase inhibitors do not induce urticaria in patients with CIU sensitive to NSAIDs.

Indeed, at present there are more data concerning rofecoxib [22-25] than CE [12].

However, to our knowledge there are no studies which have evaluated the tolerability of CE as an alternative drug in patients suffering from P-hypersensitivity. Due to its favourable profile of tolerability and efficacy the use of this drug is very common worldwide. The number of patients referring for P intolerance remains low, when compared to that of ASA and other NSAIDs hypersensitivity. A further demonstration of the low rate of P hypersensitivity has been recently published by Kvedariene et al [26] by using oral provocation tests. These authors showed that only 15 patients (15.5%) among 84 subjects with a suspected P hypersensitivity are truly allergic to this drug. Probably, patients suffering from P hypersensitivity should be considered as a highly reacting population. The finding of only one positive response (3.4%) to oral challenge with CE in a group of highly reacting patients suggests that this agent has a favourable safety profile.

Recently, some studies have indicated possible adverse effects of coxibs on the cardiovascular system, especially in patients with osteoarthritis requiring a prolonged use of these drugs [27-29]. However, it is important to outline that a prolonged use of all NSAIDs is not recommended in patients suffering from NSAID hypersensitivity because of the higher risk of inducing cutaneous / respiratory reactions after the intake of previously well-tolerated anti-inflammatory agents.

Indeed, this and similar studies evaluating the tolerability of a given alternative drug have some intrinsic limits, the most important of which is the use of a single cumulative dose. The effects of higher doses or the prolonged use of a commercial product cannot be evaluated under the present experimental conditions.

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