

Adverse Cutaneous Reactions to Selective Cyclooxygenase 2 Inhibitors: Experience of an Italian Drug-Surveillance Center

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Background: Selective cyclooxygenase (COX) 2 nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with a general lower incidence of side effects compared with nonselective NSAIDs. Postmarketing information has highlighted the need to reassess the risk evaluation for specific organs, including the skin.

Objective: A prospective databank to record all cases of adverse cutaneous reactions associated with the use of COX inhibitors was conducted at the Centre for Drug Surveillance of the Dermatology Department of Cagliari University.

Material and Methods: An intensive surveillance program from November 2000 to October 2004, adopting the World Health Organization Collaborating Centre for Drug Monitoring causality assessment criteria and algorithm.

Results: Seventeen cases, 4 male and 13 female, were studied. None had previously presented any drug intolerance or allergy. Clinical manifestations were mainly maculopapular exanthema followed by urticaria-angioedema. A severe case of leukocytoclastic vasculitis was also observed. Responsible drugs were celecoxib (13 cases; 76%), rofecoxib (3 cases; 18%), and etoricoxib (1 case; 6%). All cases recovered with drug withdrawal. Causality was probable for all eruptions, except for the fixed drug eruption, for which causality was certain.

Discussion: Although most cases were associated with celecoxib, the observation of severe eruptions owing to rofecoxib and etoricoxib in this prospective study is consistent with a class effect of COX inhibitors on the skin, which merits further studies to explain the fine underlying mechanisms.

Antécédents: Les anti-inflammatoires non stéroïdiens (AINS) sélectifs du groupe de cyclooxygénase (COX) 2 ont été associés à une plus faible incidence d'effets secondaires que les AINS non sélectifs. L'information après commercialisation a souligné le besoin de réévaluer le risque inhérent à des organes spécifiques, dont la peau.

Objectif: Une base de données prospective pour consigner tous les cas de réactions cutanées nocives à la suite de l'exposition aux Coxibs a été établie au Centre for drug-surveillance du Service de dermatologie de la Cagliari University.

Matériel et méthodes: Établissement d'un programme de surveillance intensive de novembre 2000 à octobre 2004, adoptant les critères et l'algorithme d'évaluation du Centre collaborateur de l'Organisation mondiale de la Santé pour la pharmacovigilance internationale.

Résultats: Dix-sept cas, 4 hommes et 13 femmes, ont été étudiés. Aucun des patients n'avait présenté auparavant une intolérance ou une allergie aux médicaments. Les manifestations cliniques étaient surtout des exanthèmes maculopapulaires suivis d'une urticaire géante. On a observé également un cas grave d'angéite leucocytoclastique. Les médicaments responsables étaient célécoxib (13 cas ; 76 %), rofécoxib (3 cas ; 18 %), et etoricoxib (1 cas ; 6 %). Tous les patients se sont remis après l'arrêt du médicament. La causalité était probable pour toutes les éruptions sauf pour les éruptions fixes d'origine médicamenteuse où la causalité n'était pas probable.

Discussion: Bien que la plupart des cas aient été liés au célécoxib, l'observation d'éruptions graves après la prise de rofécoxib et d'etoricoxib est compatible avec les effets de la classe des Coxibs sur la peau, ce qui justifie des études additionnelles pour expliquer les mécanismes sous-jacents.

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ADVERSE CUTANEOUS REACTIONS TO NON-
STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) are frequent¹ and usually explained by the inhibition of cyclooxygenase (COX), causing a collateral availability of the prostaglandin precursor arachidonic acid,



Figure 1. Celecoxib exanthema.

which activates the lipoxygenase pathway and final leukotriene release. COX inhibitors are a subclass of NSAIDs designed to selectively inhibit COX-2, which is the source of proinflammatory human prostaglandins E and I. Preservation of COX-1 is important in cytoprotection as it is the source of prostaglandins in gastric epithelium.² Experimental evidence suggests that selective COX-2 inhibition does not elicit increased leukotriene production and demonstrated a good safety profile in patients with previous pseudoallergic respiratory and cutaneous reactions to NSAIDs.^{3–6} However, postmarketing data collection is mandatory to assess the true safety and tolerability of a new drug, and a reassessment of the cardiovascular risk⁷ recently led to the withdrawal of some drugs and the revision of authorization for others. Severe cutaneous adverse reactions related to celecoxib exposure have been reported.^{8–10} The problem arises from a lack of a clear estimate of cutaneous risks with this new class of drugs.

As part of an intensive drug-surveillance program, a prospective study was conducted at the Dermatology Department of Cagliari University to record and analyze all cases of adverse cutaneous reactions associated with the use of selective COX-2 inhibitors.

Material and Methods

From November 2000 to October 2004, all cutaneous adverse reactions to drugs were recorded on magnetic support, including outpatients, patients admitted to the Dermatology Department, and patients hospitalized in other

departments of the city. All cases were analyzed. The diagnosis of drug-associated eruption was based on clinical features, circumstantial evidence, time relationships between taking the drug and onset of the rash, and exclusion of alternative diagnoses. Accurate allergic and pharmacologic anamnesis, as well as a history of previous reactions to drugs, was obtained from the patients and general practitioners. A skin biopsy was performed in doubtful cases. Final causality assessment followed the World Health Organization (WHO) Collaborating Centre for Drug Monitoring international criteria and algorithm.¹¹

Representative Case Reports

Case 1

A 64-year-old white woman was urgently admitted to the Dermatology Department for a rapidly evolving, very diffuse maculopapular exanthema with targetoid lesions (Figure 1). The patient was febrile (39°C) and reported severe itching. No mucosal lesions or lymphadenopathy was noted. The medication history revealed the introduction of a new anti-inflammatory drug, celecoxib (1 tablet daily), for the treatment of a chronic arthropathy, about 9 days before the eruption. The suspected drug was immediately withdrawn, and the patient was given full supportive therapy and oral antihistamines, with rapid amelioration and complete recovery in about a week.

Case 2

A 78-year-old white man was urgently admitted to the Dermatology Department for the sudden blossoming of erythematous-edematous lesions (Figure 2), confluent in giant, polycyclic configuration anywhere on the body, including the palms and soles. The medication history revealed the introduction of a new anti-inflammatory drug,



Figure 2. Rofecoxib urticaria.



Figure 3. Etoricoxib vasculitis.

rofecoxib (1 tablet daily), for the treatment of knee osteoarthritis, about 38 hours before the onset of urticaria. The suspected drug was stopped, and the patient was given oral antihistamines, with rapid amelioration and complete recovery in 4 days.

Case 3

A 79-year-old white man was admitted to hospital for a sudden purpuric rash affecting both the lower legs and feet and rapidly extending to the thighs (Figure 3), with sparse maculopapular lesions on the abdomen, trunk, and upper limbs. No general or prodromic symptoms were reported, except for a diffuse, severe itching that was unresponsive to antihistamine treatment 4 days before the eruption.

The patient was on etoricoxib therapy (1 tablet/day) for chronic spondyloarthritis for about 12 days. Blood testing for cryoglobulins, immunoglobulins, C3, C4, and antineutrophilic cytoplasmic antibody was normal. The histopathology of a skin biopsy was consistent with leukocytoclastic vasculitis. Etoricoxib was discontinued, and the cutaneous manifestations rapidly ameliorated and healed in about 2 weeks, without other specific treatment.

Case 4

A 60-year-old white man consulted the Dermatology Department outpatient service for recurrent, well-demarcated, erythematous-edematous, eroded plaques on the girdle region (Figure 4). The first lesion had started to appear 1 week after the introduction of celecoxib for the treatment

of lumbago and had progressively faded over several days, leaving a residual brown pigmentation. In 1 year, the patient suffered several episodes of lumbago, and on each readministration of the drug, the lesion recurred within 24 hours, whereas two additional small lesions appeared. The histopathology of a skin biopsy was consistent with fixed drug eruption. The drug was subsequently ceased, with resolution of the lesions 10 days later.

Results

In a 4-year period, as part of the activities of a dermatologic center of drug-surveillance, 380 adverse cutaneous reactions were reported: 99 cases (26%) were associated with NSAIDs. COX-2 inhibitors were third in frequency among NSAIDs, after acetylsalicylic acid and nimesulide. Adverse cutaneous reactions to COX inhibitors involved 17 patients, 13 women and 4 men, with a mean age of 65 years (Table 1). None of the patients reported a history of drug intolerance, especially to other NSAIDs and/or sulfonamides. Clinical manifestations were mainly maculopapular exanthems (10 cases), followed by urticaria-angioedema (5 cases), leukocytoclastic vasculitis (1 case), and fixed drug eruption (1 case). The severity of the adverse reactions was such to require immediate inpatient care, except for the fixed drug eruption. Exanthems evolved rapidly and were widespread, affecting 70 to 90% of the body surface, with targetoid and purpuric lesions. Severe pruritus, general malaise, and advanced age for the vast majority of the patients were other reasons for referral and strict monitoring. The mucosal epithelia were spared in all cases.

Laboratory investigations were within the normal range, except for a slight leukocytosis and eosinophilia (9–10%) in 11 cases. Hepatic and renal function were normal, as well as all of the electrocardiograms and chest radiographs. Serologic tests for cytomegalovirus and



Figure 4. Celecoxib fixed eruption.

Table 1. Responsible Drugs: Case Distribution according to Sex and Clinical Presentation

<i>Drug</i>	<i>N of Cases (%)</i>	<i>Sex</i>	<i>Clinical Presentation</i>
Celecoxib	13 (76)	M: 2; F: 11	Maculopapular exanthema (8 cases) Urticaria-angioedema (4 cases) Fixed drug eruption (1 case)
Rofecoxib	3 (18)	M: 1; F: 2	Maculopapular exanthema (2 cases) Urticaria-angioedema (1 case)
Etoricoxib	1 (6)	M	Leukocytoclastic vasculitis

Epstein-Barr virus and fungal and bacterial cultures were negative for prior infections. Cutaneous biopsy was performed for standard histopathology in doubtful severe eruptions to confirm the diagnosis of leukocytoclastic vasculitis in one case and the fixed drug eruption in another.

Responsible drugs were stopped, and the clinical manifestations improved soon after, with complete resolution within 5 to 10 days in all cases. Symptomatic treatment with oral antihistamines was given in the more severe cases. No relapse was observed during the 6-month follow-up.

The responsible drugs for these 17 cases retrieved from our databank were celecoxib (13 cases; 76%), rofecoxib (3 cases; 18%), and etoricoxib (1 case; 6%). Pharmacologic anamnesis was quite simple as eight patients were not taking any other drugs, five patients were under long-term antihypertensive treatment without previous problems, and four diabetic patients were under insulin medication only. Concomitant drugs were not discontinued, with no apparent influence on the eruption recovery. The time relationships between the introduction of the COX-2 inhibitor and onset of the rash were evocative: no more than 48 to 72 hours in urticaria cases and 7 to 14 days in exanthem and vasculitis cases. All cases, except for the fixed drug eruption, whose association was proven by rechallenge, were defined as probably related to the drug in the final causality assessment following the WHO program algorithm.¹¹

Discussion

Since the constitution of a specialized center devoted to drug surveillance in our dermatology department, a sustained interest has been paid to adverse cutaneous reac-

tions to NSAIDs, especially to selective COX-2 inhibitors in detail. Cutaneous reactions to COX-2 inhibitors are considered rare,¹² and celecoxib is considered safe in NSAID-sensitive patients.⁵ Our data are not statistically valuable in the absence of parameters such as the number of prescriptions and the true use of these drugs in the Sardinian population during the specified time period. Nevertheless, the frequency of COX-2 inhibitor reactions in our case reports, compared with the overall number of adverse cutaneous reports (17 cases over 380 reactions = 4%) and the number of reactions to NSAIDs (17 cases over 99 reactions = 17%), is remarkable and highlights the importance of a strict surveillance of this new generation of NSAIDs.

The extent of eruptions and advanced age of patients led to hospitalization in most cases (94%). Reactions owing to celecoxib seem to be more frequent than those to other COX inhibitors.^{8–10} Celecoxib is a sulfamide derivative, in which the absence of the aromatic amine group reduces the risk of cross-reactions to antibacterial sulfamides. Several trials have documented the safety of celecoxib in patients with a well-documented sensitivity to sulfamethoxazole-trimethoprim and other aromatic sulfamides.^{3–6} Nevertheless, its chemical structure is closer to furosemide and hydrochlorothiazide, other sulfamide derivatives having been reported as responsible for severe adverse cutaneous reactions.¹³ With regard to skin involvement, celecoxib was recently implicated in some severe macular eruptions, urticaria-angioedema, erythema multiforme, and fatal allergic vasculitis.^{8–10} Although most cases were associated with celecoxib, the observation of rofecoxib and etoricoxib eruptions in this prospective study is consistent with a class effect of COX inhibitors on the skin, which is worth further study to explain the fine underlying mechanisms. In fact, the chemical structure of rofecoxib is completely different from that of celecoxib and suggests that we should reconsider the real importance of the sulfamide origin in the induction of skin reactions. A class effect has been suggested to explain cardiovascular adverse events in long-term administration of COX inhibitors^{2,14}: COX-2 inhibitors may decrease vascular prostacyclin production and tip the balance in favor of prothrombotic eicosanoids (thromboxane A₂). Rofecoxib is more selective in its action on COX-2 and induces thromboembolic adverse effects more frequently than celecoxib and other conventional NSAIDs, confirming that cardiovascular side effects are directly related to the therapeutic activity on proinflammatory enzymes and thus inducible by other selective COX-2 inhibitors. If massive prescription is a critical point in the manifestation of rare and severe skin involvement, an increase in adverse reports

related to other COX-2 inhibitors is predictable. The second-generation COX-2 inhibitor etoricoxib, which was recently approved by the European Agency for the Evaluation of Medicinal Products (EMA), was responsible for one of the most severe reactions observed in our series: leukocytoclastic vasculitis. Faithful reporting of any cutaneous side effects seen with the administration of COX inhibitors is the major measure to assess the true size of the problem but also to draw the attention of regulatory agencies to the need for specific trials comparing the cutaneous safety of COX inhibitors with that of other NSAIDs, whose use is consolidated on the basis of many years of extensive use in the general population, such as naproxen. Comparison trials have been performed for cardiovascular and gastrointestinal risks, and skin involvement should have the same consideration as other organs in the risk-benefit assessment required for a new drug approval.

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