

Selective celecoxib-associated anaphylactoid reaction

To the Editor:

Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin (ASA) are well-known causes of a variety of adverse reactions, including anaphylactic or anaphylactoid reactions in sensitized patients. NSAIDs act by inhibiting the activities of the enzymes cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). In recent years, several pharmaceutical companies have developed and marketed selective COX-2 inhibitors to abrogate the adverse side effects of COX-1 activity. Celecoxib (Celebrex, Pfizer/Searle, Caguas, Puerto Rico) is one such selective COX-2 inhibitor. Of interest, celecoxib also contains a sulfonamide grouping, which raises concerns about possible cross-sensitivity between celecoxib and sulfonamides in patients with allergy to the latter types of agents. However, there is no evidence that celecoxib is any more allergenic than non-sulfonamide-containing NSAIDs.¹ To date, there have been 3 reports of adverse reactions, suggestive of anaphylactic shock, associated with the use of celecoxib.²⁻⁴ However, it remains unclear whether these reactions were attributable to the drug's COX-2 inhibitory activity (biochemical and thus anaphylactoid in nature) or to its molecular structure per se (IgE-mediated and therefore anaphylactic). Because of this, physicians suggest that patients with celecoxib sensitivity avoid ASA, NSAIDs, and other selective COX-2 inhibitors. According to the package insert, "patients suspected of having sulfonamide allergy should be excluded from celecoxib therapy."

Here we report a case of celecoxib-specific anaphylactic or anaphylactoid reaction with no evidence of sensitivity either to other COX-2 inhibitors or to sulfonamide.

A 49-year-old man experienced adverse reactions after taking celecoxib for joint pain on 3 separate occasions. The reactions became progressively more severe and always developed within 30 to 60 minutes of his taking the drug. On the first occasion, the manifestation was limited to generalized pruritus, no rash of any type being noted. The problem resolved relatively quickly without treatment. A nonspecific pruritus cannot be excluded, but the symptoms occurred within minutes of the taking of the celecoxib.

The second time that the drug was taken there was a gradual development of angioedema involving the hands, eyes, and lips. There was no respiratory distress. The patient presented himself to a hospital emergency department, where he was treated with antihistamines and "observed." It appears that the association between the drug ingestion and the angioedema was not made.

On the third occasion that the celecoxib was taken, the reaction was far more severe and clearly anaphylactic/anaphylactoid in nature. Within a few minutes of taking the drug, the patient developed facial angioedema, diffuse pruritus, respiratory distress, and loss of consciousness.

When seen at the emergency department of a community hospital he had a systolic blood pressure of 60 mm Hg and his radial pulse was undetectable. He was treated with a combination of subcutaneous epinephrine, intramuscular Benadryl (Pfizer Canada, Toronto, Ontario, Canada), intravenous corticosteroids, and inhaled salbutamol, and he was then admitted to the hospital's intensive care unit. A careful history was taken to rule out other possible causes of the anaphylactic/anaphylactoid reaction; it was non-contributory. The patient gave no previous history of drug allergy. He had previously taken Naprosyn (Hoffmann-La Roche, Mississauga, Ontario, Canada) without difficulty, and he had been given celecoxib to avoid the side effects of COX-1 inhibitory activity. He had never taken any sulfonamide-containing medication. When he was first seen in our clinic, 4 months after the third adverse reaction, he was still using Naprosyn as needed for joint pain.

Because of the severity of the reactions that he had experienced, the patient was not challenged with celecoxib, to which he was clearly sensitive. We did not perform skin testing or immunoassay for IgE antibodies to celecoxib because there are no standardized assays or skin test reagents available for this agent. After appropriate consent was obtained from the patient, he was challenged with a number of drugs to determine whether he had any related drug sensitivities. These challenges were performed under close medical supervision. Vital signs and pulmonary function tests were obtained before, during, and for some hours after each drug challenge.

The first challenge was done with another COX-2 inhibitor, rofecoxib (Vioxx, Merck Frosst Canada, Montreal, Quebec, Canada). He was given gradually increasing doses of the medication—from 0.1 to 12.5 mg—by mouth. No adverse reaction of any type was seen or experienced. Over a period of the next few weeks, he took rofecoxib, on an irregular basis and did not experience any adverse effects. To determine whether the celecoxib hypersensitivity might have been related to the sulfonamide group on the molecule, we used Septra (GlaxoSmithKline, Mississauga, Ontario, Canada) as the drug for challenge. (Sulfonamide alone would have been the drug of choice for this purpose, but it is no longer commercially available in Canada.)

To avoid confusion between the trimetoprim and sulfonamide portions of the Septra, the patient was first challenged with trimetoprim through use of the following regimen: 20 mg, 50 mg, and finally 100 mg of the preparation taken orally, at intervals of 20 to 30 minutes. He showed no adverse reaction to trimetoprim. The following day, he underwent the Septra challenge. The following regimen was used: 0.2 mg, 2 mg, 20 mg, 200 mg, and 400 mg taken orally, at intervals of 20 to 30 minutes. Again, the patient experienced no difficulty of any sort. To rule out any possibility of desensitization with the regimen that was used, the patient was given a full dose of Septra, again under medical supervision, 3 months

after the initial challenge; he again showed no evidence of an adverse drug reaction.

To our knowledge, this is the first report of a celecoxib-specific anaphylactic or anaphylactoid reaction, given that the patient could safely take another NSAID, Naprosyn, another COX-2 inhibitor, Vioxx, and a sulfonamide-containing drug.

Two important observations devolve from this case study. First, the anaphylactic/anaphylactoid reaction to celecoxib is not necessarily due to the COX-2 inhibitory activity of the drug, and other medications of the same class can be well tolerated. This is consistent with the observations of Stevenson⁵ that anaphylactoid reactions to NSAIDs are usually selective for a single agent. In like fashion, cross-reactivity between NSAIDs and cyclooxygenase inhibitor is rare. Again, our patient tolerates Naprosyn, suggesting that a selective mechanism is involved with celecoxib sparing COX-1 inhibitors. On the other hand, the exact mechanism of COX-2 hypersensitivity is still unclear, inasmuch as a case of cross-reactivity between COX-1 and COX-2 inhibitors has been reported.⁶ Second, the hypersensitivity was not related to sulfonamide allergy, inasmuch as the patient tolerated a full dose of Septra.

This case report also demonstrates that celecoxib, like other sulfonamide group-containing agents (eg, many of the diuretics), has a low propensity for cross-allergenicity with sulfonamide antimicrobials.^{7,8} In general, these observations are important in the management of patients who have had allergic reactions to celecoxib in that systematic avoidance of all COX-2 inhibitors and sulfonamide-related medications might well not be necessary. Hence, the decision on how to proceed with therapy after a patient has had an adverse reaction to celecoxib must be taken on a case-by-case basis after appropriate challenges have been performed.

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Atopy and allergic respiratory diseases in multitransfused patients: A new insight into the increase in the prevalence of atopy

To the Editor:

In 173 patients affected by major β -thalassemia (BT) and a control group of 253 blood donors, we performed skin prick tests (SPTs) with glycerinate extracts (1/20 w/v; Bayropharm, Milan, Italy) of the most common inhalant substances (*Dermatophagoides pteronyssinus*, cat and dog allergens, *Alternaria alternata*, grass pollen, *Parietaria officinalis*, and olive) according to the recommendations of the European Academy of Allergology and Clinical Immunology.¹ The presence of asthma and/or rhinitis was investigated through use of a standardized questionnaire (ISAAC).²

The data were analyzed on an IBM-compatible personal computer with the statistical package program SPSS for Windows; we used the χ^2 test or multiple logistic regression as indicated. A *P* value of less than .05 was considered significant.

The 173 patients affected by BT had a mean ($\pm$ SD) age of 28 ($\pm$ 6) years (range, 8-42 years). Eighty-six (49.7%) of the patients were male; the other 87 (50.3%) were female. The patients had had their first transfusions at a mean ($\pm$ SD) age of 18.7 ($\pm$ 4.2) months, and they had been transfused regularly for a mean ($\pm$ SD) period of 27 ($\pm$ 6.5) years. Sixty percent of the patients underwent splenectomy; 90% were hepatitis C virus-positive. The control population had a mean ($\pm$ SD) age of 30 ($\pm$ 4) years (range 20-46 years); 129 were male and 124 were female. The prevalence of atopy (at least 1 positive SPT result for major inhalant allergens) was significantly lower in patients with BT than in the control population (28% [49/173 vs 45.28% [114/253]; *P* < .00001). Even when corrected for sex and age in a multiple logistic regression, subjects with BT were still protected for the development of atopy (*P* = .0045). Also significantly lower in the patients with BT than in the control group were the prevalence of asthma (3% vs 13%; *P* < .00001) and the prevalence of rhinitis (18% vs 31%; *P* < .0001). Patients who underwent splenectomy were not significantly different from patients who did not with respect to frequency of atopy (24.2% vs 34.2%; *P* = .15), rhinitis (14.2% vs 24.2%; *P* = .071), or asthma (1.9% vs 4.2%; *P* = .36).

A few years ago our group studied the prevalence of atopy among patients with BT compared with a control population of the same age. At that time, the subjects with BT had a mean age of 11.8 years and the prevalence of positive SPT results was 10%, which compared with 21% for the control population.³ In the present study, the mean age of the patients with BT was 28 years and the