

Cross-reactivity of cyclooxygenase 2 inhibitors in patients with a history of cutaneous reactions to cyclooxygenase 1 inhibitors

It has been established that patients with aspirin-exacerbated respiratory disease (AERD) do not have cross-reactions between aspirin and the highly selective cyclooxygenase 2 (COX-2) inhibitors rofecoxib and celecoxib.¹⁻³ However, the situation with patients who have a history of cutaneous reactions to COX-1 inhibitors is not as clear. This is in part because all AERD patients have an underlying inflammatory respiratory disease and experience respiratory reactions to aspirin and any drug that inhibits COX-1. By contrast, there are a number of different cutaneous reactions to COX-1 inhibitors, and these reactions occur in individuals who otherwise appear to be healthy or in patients with an underlying cutaneous disease.⁴

CUTANEOUS REACTIONS TO COX-1 INHIBITORS IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA

Beginning with the most clearly defined subset of patients, those who have chronic idiopathic urticaria or angioedema (CIUA), studies at Scripps Clinic, La Jolla, CA, showed that up to 80% of CIUA patients react to COX-1 inhibitors when they are experiencing active urticaria.⁵ However, when urticaria is in relative remission, most aspirin and nonsteroidal anti-inflammatory drug (NSAID) challenge studies found cutaneous reaction rates of approximately 30% to 50% of such study groups.⁶⁻⁸ It has now been definitively shown that cross-reactions to NSAIDs, in patients with CIUA, involve inhibition of COX-1 and synthesis of new leukotrienes. Zembowicz et al⁹ studied 36 patients with CIUA. All underwent single-blind oral aspirin challenges, and 18 (50%) of 36 experienced flare-ups of their urticaria. These 18 patients then underwent double-blind crossover challenges with rofecoxib, 12.5 and 25 mg, and celecoxib, 100 and 200 mg. There were no reactions to either COX-2 inhibitor. By contrast, double-blind oral challenges with naproxen yielded positive urticarial reactions in 5 of 7 patients. Concomitantly, urine leukotriene E₄ levels increased during aspirin and naproxen reactions but did not change during challenges with the 2 COX-2 inhibitors. This finding that the cutaneous aspirin disease CIUA behaves precisely as does its respiratory equivalent when exposed to aspirin and the older NSAIDs has been confirmed in a more recent study.¹⁰ Therefore, like AERD, there is no reason to expect COX-2 inhibitors (which cannot

enter the narrow COX-1 channel) to cross-react in patients with CIUA, since only inhibition of COX-1 starts the reaction.

REACTIONS TO COX-1 INHIBITORS IN HEALTHY PATIENTS

In contrast to patients with CIUA, otherwise healthy individuals can experience a variety of cutaneous reactions after challenges with aspirin and NSAIDs. These reactions run the gamut from urticaria and angioedema to erythema multiforme, Stevens-Johnson syndrome, serum sickness, exfoliative dermatitis, erythema nodosum, and maculopapular reactions.⁴ Furthermore, healthy individuals can experience urticarial reactions to one NSAID alone (probably IgE mediated) or too many NSAIDs (COX-1 inhibition). Most individuals develop urticaria and/or angioedema when they ingest a single COX-1 inhibitor (most commonly ibuprofen in the experience of the authors). These individuals can tolerate any other COX-1 inhibitor, including aspirin, without cutaneous reactions. There are some patients who appear to be healthy but who develop urticaria and/or angioedema when they ingest aspirin and any other COX-1 inhibitor. This tendency may be a harbinger of future CIUA.¹¹

CUTANEOUS CROSS-REACTIVITY TO COX-2 INHIBITORS IN PATIENTS WITH COX-1 REACTIONS

To make correct conclusions about COX-2 inhibitor cross-reactivity, it is important to know which group of patients are undergoing challenges and what type of reactions occurred in the past after challenges with COX-1 inhibitors. This issue of the *Annals* and a previous issue include 3 studies that involve patients with prior cutaneous reactions to COX-1 inhibitors who underwent challenges with COX-2 inhibitors.¹²⁻¹⁴ These studies help to advance our knowledge about this complex problem.

In the article by Quirarte et al, published in the October 2004 issue of the *Annals*, all 33 study patients clearly had single COX-1 inhibitor-induced urticarial reactions; therefore, not surprisingly, none reacted to the 2 COX-2 inhibitors (rofecoxib and celecoxib). None of their patients had ever been exposed to the 2 COX-2 inhibitors previously and therefore could not have been sensitized *de novo* before this

challenge study. Single NSAID-induced reactions are probably IgE mediated and require prior sensitization.^{15,16}

This brings us to the 2 studies published in this issue of the *Annals*. The study by Nettis et al¹³ is comprehensive, involves a large study population, and includes follow-up of patients after they underwent challenges to rofecoxib that produced negative results. The waters are a bit muddy, because the patients in this study were chosen on the basis of their history of a prior cutaneous reaction to 1 or more COX-1 inhibitors. The COX-1 inhibitor challenges were not performed. Therefore, prior cutaneous reactions, which were attributed to the listed COX-1 inhibitors by the authors, may have been caused by something else or may have been a different cutaneous reaction from the one reported. We have no way of definitively knowing how many of their 182 patients fit into which category. On the other hand, most patients remember details of their prior historical reactions, and it would be overly cynical to believe that all of the patients who reported reactions had been misclassified or reactions never occurred. Although the authors may have inadvertently misapplied some reactions, careful reading of the "Methods" section shows that 12 (6.6%) of the 182 patients probably had CIUA, with the remaining 170 patients (93.4%) having no underlying disease. With respect to the various types of prior COX-1 inhibitor-associated reactions reported by these patients, 9 sounded like exanthems and 2 like Stevens-Johnson syndrome. This leaves 169 (92.8%) of the study population who reported what was believed to be urticaria, angioedema, or both as their prior cutaneous reactions to COX-1 inhibitors. Of this group of 169, 104 (62%) reported urticaria or angioedema after 1 NSAID only (single-drug reactors or probably IgE mediated), and 65 (38%) reported urticaria or angioedema after reacting to 2 or more NSAIDs (probable COX-1 inhibition reactions). None of the 182 patients reported having taken rofecoxib previously. Regardless of correct or incorrect category of prior reactions, none of the 182 patients reacted to rofecoxib, 25 mg, during single-blind, placebo-controlled challenges. In addition, when these patients responded to questionnaires and follow-up visits during the next 3 years, 131 (72%) used rofecoxib for treatment of various musculoskeletal conditions, whereas 51 (28%) were never exposed to rofecoxib again. Of the 131 patients reexposed to rofecoxib, only 7 (5.3%) experienced cutaneous reactions in association with taking rofecoxib. Six of the 7 reported urticarial reactions and 1 reported an exanthem. In other words, sensitization to rofecoxib occurred during reexposure, and next-dose rofecoxib-induced urticaria then ensued. This finding is expected when patients are exposed to COX-2 inhibitors that readily bind to carrier proteins and have been reported to cause urticaria and anaphylaxis after multiple exposures to the drugs.¹⁷⁻¹⁹ When conducting challenge studies with any NSAIDs, including the COX-2 inhibitors, prior exposure to the drug means that if a current reaction occurs during challenge studies it might be an IgE-mediated reaction to that specific drug due to prior sensitization and not a cross-reaction.

In this issue of the *Annals*, a study is reported by Sanchez-Borges et al¹⁴ and is a continuation of their prior investigations. In their prior study,²⁰ they reported that 5 (25%) of 20 patients, previously shown to have urticaria or angioedema reactions after 2 or more older NSAIDs, also cross-reacted with celecoxib. Interestingly, in another set of challenges in that same report, 5 (50%) of 10 patients previously reacting to a single NSAID also developed urticaria after challenges with celecoxib. As noted herein, single NSAID-induced reactions are most likely IgE mediated. It is therefore perplexing to contemplate why these 5 patients should be cross-reactive to celecoxib, since these same patients were not cross-reactive to other COX-1 inhibitors or to rofecoxib and meloxicam. The article did not state whether the celecoxib challenges in this first report by Sanchez-Borges et al²⁰ were the patients' first exposure to celecoxib. The only other challenge study with celecoxib in patients with urticarial reactions involved 20 patients with a history of reacting to at least 2 COX-1 inhibitors.²¹ None of the 20 patients reacted to 100 or 200 mg of celecoxib even when a second challenge with celecoxib was performed 1 week later (to rule out rapid sensitization).

With respect to rofecoxib and urticarial reactions, there are 5 published studies, involving a total of 183 patients.^{20,22-26} Only 2 (0.7%) of these 183 patients were reported to have reacted to rofecoxib (1 in each of 2 of these 5 studies). Furthermore, in one of the studies, it is not stated whether the study patients were single- or multiple-COX-1 inhibitor reactors, and neither report stated whether or not the rofecoxib challenges were the patients' first rofecoxib exposure. Neither of the 2 studies included a subsequent double-blind, placebo-controlled challenge with rofecoxib to validate the results of the first challenge. Even if confirmatory rechallenges had demonstrated reactions to rofecoxib, with a maximum cross-reactivity rate of 0.7%, the relative safety of rofecoxib in patients with prior COX-1 inhibitor cutaneous reactions was well established even before publications of these studies in the *Annals*. One additional report described 2 of 12 patients with positive challenges to rofecoxib, but these patients were not challenged to any COX-1 inhibitors to confirm their history of COX-1 inhibitor sensitivity, and prior exposure to rofecoxib was not stated and cannot be excluded.²⁷

In the article by Sanchez-Borges et al¹⁴ in this issue of the *Annals*, 26 patients with a history of COX-1 inhibitor-induced urticaria or angioedema were given 50 mg of rofecoxib and 40 mg of valdecoxib in single-blind, placebo-controlled challenges. Of the 26 patients, 2 (7.1%) were reported to react to rofecoxib and 1 (3.5%) to valdecoxib. However, although the "Methods" section indicates patients with AERD were excluded, how this was accomplished is not stated. This is important because 2 of the 3 reacting patients were reported to have blended (respiratory and cutaneous) reactions during prior challenges with COX-1 inhibitors. Patients with AERD should not be included in an urticarial study. It has already been demonstrated that there is no cross-reactivity to COX-2 inhibitors in patients with AERD.¹ One must also wonder

why, if no patients with chronic idiopathic urticaria were included, the criteria for a positive challenge of a “20% increase in urticaria” makes any sense. If there was no urticaria at baseline, how could there be an increase? The “Results” section describes 1 rofecoxib reaction in a nonatopic patient with a history of rhinitis and asthma and a history of blended reactions to COX-1 inhibitors (sound like AERD patients?) who developed laryngeal edema, cough, and dyspnea after challenges with rofecoxib (not even blended reactions). Exactly how to interpret these data is difficult to determine, but what an atopic patient with “mixed reactions to aspirin” means is neither defined nor easily comprehensible. One would also like to know whether (or not) this patient reacted to other COX-1 inhibitors. In addition, dyspnea (a subjective response) and periorbital edema (a potentially subtle sign) were considered positive challenges. Most difficult to comprehend is that neither of the 2 patients who were reported to react to rofecoxib reacted to valdecoxib. What could be the mechanism of such reactions, especially if, as stated, the challenge was their first exposure to rofecoxib? Similarly, the patient who is reported to have reacted to valdecoxib had a history of allergic rhinitis and asthma and reactions to multiple COX-1 inhibitors (although the reactions are not described). She developed urticaria following challenge with valdecoxib but not rofecoxib. Finally, double-blind, placebo-controlled confirmatory challenges were not repeated for any of these 3 patients. This leaves us wondering what actually occurred. Why would a cross-reaction that involved inhibition of COX-1 or COX-2 occur with one COX-2 inhibitor but not another? Why would it occur with any of the highly selective COX-2 inhibitors? Why were the other 2 studies in this issue of the *Annals* unable to detect any cutaneous reactions to rofecoxib or celecoxib (33 patients in the study by Quirarte et al and 182 patients in the study by Nettis et al, totaling 215 patients)?

CONCLUSIONS AND RECOMMENDATIONS

After looking at all the published studies to date, we conclude that patients with a history of COX-1 inhibitor cutaneous reactions can probably tolerate any COX-2 inhibitor on first exposure to the drug. Practically speaking, we would suggest having the patient take the first dose of their COX-2 inhibitor in their physician’s office and be observed for 2 hours. Since the oral challenge will not result in anaphylaxis or internal angioedema, this can be done without any premedication or intravenous access. Should a cutaneous reaction occur after ingesting a first dose of a COX-2 inhibitor (an event never observed by us), the urticaria and/or peripheral angioedema can be treated with oral antihistamines (and perhaps intramuscular epinephrine). For future publications, we encourage our colleagues, who are reporting “cross-reactions” between COX-1 and COX-2 inhibitors, to confirm such challenge results with a second double-blind, placebo-controlled challenge with the suspect COX-2 inhibitor.

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