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Cross-reactivity and tolerability of celecoxib in adult patients with NSAID hypersensitivity

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TO THE EDITOR:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for anti-inflammatory and analgesic indications, but their therapeutic use is limited by reported adverse drug reactions (ADRs), which include both known side effects such as gastrointestinal upset and bleeding, and hypersensitivity reactions. NSAID ADRs are the second most commonly reported class of drug allergies, surpassed only by antibiotic allergies.¹

However, it is estimated that fewer than 20% of adult outpatients with NSAID ADRs reported in the electronic health record have reactions consistent with hypersensitivity.² Furthermore, the majority of true NSAID hypersensitivity reactions are mediated by pharmacologic inhibition of the constitutively expressed COX-1 enzyme, rather than an immunologic (eg, IgE or T-cell-mediated) mechanism.³ Although cross-reactivity to nonselective NSAIDs is common in these patients, it follows logically that selective COX-2 inhibitors should be well tolerated. No standardized *in vitro* tests exist for evaluation of NSAID hypersensitivity and diagnosis is primarily based on clinical history and drug provocation testing. However, we suspected that allergy over-reporting and lack of reaction clarification may lead to unnecessary avoidance of aspirin and NSAIDs, and increased use of alternative anti-inflammatory and analgesic medications.

To better understand the safety of selective COX-2 inhibitor use in patients with NSAID hypersensitivity, we conducted an updated systematic electronic search of MEDLINE databases using a prespecified search strategy to identify all blinded, placebo-controlled studies published before November 2018. The following search terms were included: celecoxib or rofecoxib or etoricoxib or valdecoxib or parecoxib AND hypersensitivity or intolerance. No language restriction was predefined, and retrospective articles and case reports were excluded. Manual searches from reference lists of included trials were completed to identify additional relevant studies (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

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We identified a total of 62 articles describing patients with any type of NSAID hypersensitivity who underwent a total of 3218 single- or double-blind placebo-controlled drug challenges with selective COX-2 inhibitors. Celecoxib and rofecoxib were the 2 most commonly studied COX-2 inhibitors. Of the oral challenges performed, there were 106 total reactions reported, for a reaction rate of 3.29% (see Table E1 in this article's Online Repository at www.jaciinpractice.org). The majority of challenge-induced reactions consisted of urticaria and/or angioedema and pruritis, though bronchospasm, headache, cough, and 1 episode of laryngeal edema were also reported. Importantly, no studies described any severe reactions requiring either emergency medical care or epinephrine use.

NSAID hypersensitivity is classified into 5 distinct pheno-types: (1) NSAID-exacerbated respiratory disease, also called aspirin-exacerbated respiratory disease (AERD) or aspirin-induced asthma (AIA), (2) NSAID-exacerbated urticaria/ angioedema in patients with chronic idiopathic urticaria (CIU), (3) NSAID-exacerbated urticaria/angioedema in patients without underlying CIU, (4) urticaria/angioedema or anaphylaxis induced by a single NSAID, or (5) delayed hypersensitivity reactions.³ The tolerability of COX-2 inhibitors in patients with stable mild-moderate asthma with AERD has previously been reported to be safe, and oral challenges with specific COX-2 inhibitors are often not required or recommended in this population.⁴ However, the cross-reactivity of COX-2 inhibitors in the larger population of patients with AERD, AIA, or isolated respiratory reactions to NSAIDs remains unknown. In our systematic analysis, we separately analyzed the results of single- or double-blind COX-2 inhibitor challenges in patients with a history of respiratory reactions to NSAIDs, and found that of 753 total drug-provocation challenges, only 1 patient was reported to have a reaction (reaction rate 0.13%) (Table I). This patient had a history of AIA confirmed by aspirin challenge, and experienced transient urticaria with a 5 mg challenge dose of rofecoxib but subsequently tolerated higher doses without any symptoms.⁵ In addition, the authors reported that aspirin challenge in their AIA subjects led to a significant increase in urinary leukotriene E₄ (LTE₄) excretion within 6 hours, but the rofecoxib and placebo challenges did not result in any changes in the urinary LTE₄ level.

Rare case reports in the literature have described symptomatic reactions induced by celecoxib in patients with a history of respiratory symptoms on NSAID exposure. In 2 open drug provocation challenges, celecoxib induced flushing, dyspnea, urticaria, and forced expiratory volume in 1 second (FEV₁) decrease by 21% in a 30-year-old patient with poorly controlled corticosteroid-dependent asthma and AERD,⁶ and dyspnea with a 64% decrease in FEV₁ requiring reversal with epinephrine administration in a 25-year-old patient with brittle asthma and AIA.⁷ A third patient with poorly controlled asthma and AERD underwent single-blind celecoxib challenge and developed bronchospasm with an FEV₁ drop of approximately 40% at a 15 mg dose.⁸ A fourth patient with poorly controlled asthma developed nasal symptoms, urticaria, and dyspnea with a decrease in FEV₁ from 2.84 to 0.81 L on 50 mg celecoxib challenge; however, with improved asthma control, repeat celecoxib challenge to a target dose of 200 mg 2 months later was entirely negative.⁹ Taken together, these isolated reports suggest that although COX-2 inhibitors appear to be an extremely safe and viable option in patients with NSAID hypersensitivity, it may be prudent to consider delaying first administration of this drug in individuals with severe or poorly controlled asthma.

This study provides an updated and comprehensive review of placebo-controlled drug challenges with COX-2 inhibitors in patients with NSAID hypersensitivity in general, and isolated respiratory reactions in particular. On the basis of our findings, we developed a novel evidence-based clinical guideline tool for nonallergy providers that uses the allergy history to risk stratify patients with reported NSAID ADRs and identifies candidates for COX-2 inhibitor use or formal allergy evaluation (Figure 1). We propose that celecoxib, the only selective COX-2 inhibitor available in the United States, may be used without any further testing in patients with low-risk isolated respiratory reaction histories to NSAIDs. Although COX-2 inhibitors are also well tolerated by the vast majority of patients with a history of urticaria and/or angioedema or anaphylaxis, given the small risk of cross-reactivity we recommend either administration under supervision or allergy evaluation and formal drug challenge with a 2-step oral challenge (one-tenth to one-quarter dose [as available] followed by a full dose, with a 1-hour observation period following each), if indicated. Of note, meloxicam is a preferential COX-2 inhibitor at low doses, but also has effects on COX-1 at higher doses. We found that cross-reactivity in patients with NSAID hypersensitivity is higher with meloxicam than with the coxibs, with a reaction rate of 4.72% among 847 single-blind placebo-controlled drug challenges (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). As such, allergy evaluation is recommended before meloxicam use in this population.

In summary, the current literature indicates that selective COX-2 inhibitors are well tolerated in patients with NSAID hypersensitivity, and particularly those with a history of AERD, AIA, or isolated respiratory reactions to NSAIDs. We recommend that for patients with well-controlled asthma and history of respiratory reactions to NSAIDs, celecoxib may be used without supervised challenge. These recommendations are currently standard practice at Brigham and Women's Hospital AERD Center, a national referral center caring for >900 patients with AERD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Implications

- The therapeutic use of nonsteroidal anti-inflammatory drugs (NSAIDs) is often limited by reports of adverse drug reactions. Selective COX-2 inhibitors are well tolerated in patients with histories of isolated respiratory reactions to NSAIDs, and utilization of celecoxib without drug provocation testing should be considered.

Aspirin/NSAID Hypersensitivity Pathway

FIGURE 1.

Proposed clinical pathway for the management of patients with reported NSAID adverse drug reactions by nonallergy providers. DRESS, drug reaction with eosinophilia and systemic symptoms; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug.

Reactivity to selective COX-2 inhibitors with single-blind or double-blind placebo-controlled oral challenges in patients with NSAID-induced respiratory reactions

TABLE I.

	No. of reactions	No. of DPT	Percentage of reactions
Celecoxib (n = 14)	0	297	0
Rofecoxib (n = 15)	1 *	356	0.28
Etoricoxib (n = 2)	0	88	0
Parecoxib (n = 2)	0	12	0
Valdecoxib (n = 0)	N/A	N/A	N/A
COX-2 inhibitors combined	1	753	0.13

DPT, Drug provocation test; *n*, number of studies; *NSAID*, nonsteroidal anti-inflammatory drug.

*. Transient urticaria with 5 mg, but tolerated higher doses without symptoms.