

Commentary

COX-2: where are we in 2003?

Specific cyclooxygenase-2 inhibitors and aspirin-exacerbated respiratory disease

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Abstract

The use of analgesic anti-inflammatory agents in patients with asthma is clinically challenging because of the prevalence (10–20%) of aspirin hypersensitivity. Aspirin-exacerbated respiratory disease (AERD), or aspirin-induced asthma, is characterized by asthma and rhinitis triggered by the ingestion of aspirin and non-steroidal anti-inflammatory drugs. AERD is associated with upper and lower respiratory-tract mucosal inflammation, progressive sinusitis, nasal polyposis, and asthma regardless of whether patients avoid triggering drugs. The mechanism underlying the propensity of aspirin and non-steroidal anti-inflammatory drugs to cause this reaction is thought to involve inhibition of the synthesis of protective prostaglandins (PGs), resulting in an increase in the synthesis of cysteinyl leukotrienes by eosinophils and mast cells. Clinical data suggest that protective PGs are derived from cyclooxygenase (COX)-1 because studies have now confirmed that drugs specifically inhibiting COX-2 are not cross-reactive with aspirin in patients with AERD.

Keywords: aspirin, asthma, cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs

Introduction

Up to 10–20% of the general asthmatic population have hypersensitivity to aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) leading to severe exacerbation of asthma and naso-ocular reactions [1,2]. Formerly termed aspirin-sensitive asthma, these patients are now characterized as having aspirin-exacerbated respiratory disease (AERD) because they have chronic upper and lower respiratory-tract mucosal inflammation, sinusitis, nasal polyposis, and asthma independent of their hypersensitivity reactions [3]. Because essentially all traditional NSAIDs also trigger the hypersensitivity reaction, treatment of pain and inflammation has been challenging. With the introduction of drugs that specifically inhibit cyclooxygenase (COX)-2, the question of whether these agents cross-react with aspirin to cause exacerbation of asthma and rhinitis becomes clinically relevant.

Eicosanoids are important mediators of bronchial reactivity and inflammation in asthma. In the asthmatic airway, arachidonic acid is metabolized to prostaglandins (PGs) and leukotrienes. PGE₂ functions as a bronchodilator and can also inhibit granulocyte functions [4]. PGs are produced through an enzymatic pathway that includes the COX enzymes. Both the COX-1 and COX-2 isoforms are expressed in the respiratory epithelium (basal and ciliated cells) in normal subjects and in patients with chronic stable asthma and chronic bronchitis [5]. Epithelial COX-1 expression is not different in asthmatics with or without aspirin sensitivity and in normal subjects, whereas COX-2 expression is increased in asthmatics compared with normals but is not different in aspirin-sensitive asthmatics compared with aspirin-tolerant asthmatics [4,6]. However, COX-2-expressing inflammatory cells are increased in the submucosa of aspirin-sensitive asthmatics.

AERD = aspirin-exacerbated respiratory disease; COX = cyclooxygenase; cys-LT = cysteinyl leukotriene; LT = leukotriene; NSAIDs = non-steroidal anti-inflammatory drugs; PG = prostaglandin.

ics [6]. Furthermore, COX-2 expression is increased in airway epithelium in non-corticosteroid-treated asthmatics compared with steroid-treated asthmatics and non-asthmatic controls [7].

Although COX expression does not consistently distinguish aspirin-sensitive from aspirin-tolerant asthmatics, a marked increase in expression of leukotriene C₄ (LTC₄) synthase in aspirin-sensitive asthmatics has been demonstrated [4]. The cysteinyl leukotrienes (cys-LTs) are potent bronchoconstrictors synthesized by the 5-lipoxygenase and the LTC₄ synthase enzyme pathways of hematopoietic cells [4]. In asthmatics with aspirin sensitivity there is a large increase in cys-LT production after exposure aspirin, and LT synthesis inhibitors and selective cys-LT receptor antagonists markedly attenuate aspirin-induced respiratory reactions [4]. This leads to the hypothesis that the aspirin- and NSAID-mediated inhibition of PGE₂ production releases a 'brake' on cys-LT synthesis by eosinophils and mast cells, leading to marked overproduction that mediates symptom exacerbation [4].

COX-2 inhibitors in asthma

The hypothesis that PGE₂ production in the setting of AERD is derived from a COX-1-dependent pathway is based chiefly on the clinical observation that selective inhibitors of COX-2 have not been reported to cross-react with aspirin in these patients. Initially, it was reported that relatively selective COX-2 inhibitors such as nimesulide and meloxicam had a reduced propensity to cross-react with aspirin in patients with AERD, particularly at low doses [3]. Several studies have now been reported to determine rigorously whether the specific COX-2 inhibitors rofecoxib and celecoxib trigger asthma exacerbation or naso-ocular symptoms in patients with AERD (Table 1) [3,8–10].

The most recent of these studies was reported by Woessner *et al.* [3]. Sixty asthmatic patients with a history of AERD completed a double-blind placebo-controlled challenge with 100 and 200 mg of celecoxib over 2 days, followed by an aspirin challenge to confirm the clinical history. All subjects exhibited adverse responses to aspirin, but no subject developed either a significant change in FEV₁ (forced expiratory volume in 1 s) or in the naso-ocular symptom score. The confidence interval for the probability of celecoxib inducing cross-reactions with aspirin in AERD patients was calculated to be between 0% and 5%. All subjects had a very clear history of AERD and demonstrated symptoms in response to aspirin on the day after absence of response to celecoxib, demonstrating a lack of desensitization. All subjects were allowed to remain on corticosteroids (nasal, inhaled, and systemic) and leukotriene modifiers, eliminating the confounder of withdrawing symptom-controlling medications.

Table 1

Specific COX-2 inhibitors in patients with aspirin-exacerbated respiratory disorders (aspirin-induced asthma)

| Study | COX-2 inhibitor | Number of patients | Adverse reaction* | Aspirin response |
|------------------------------|-----------------|--------------------|-------------------|------------------|
| Woessner <i>et al.</i> [3] | Celecoxib | 60 | No | Yes |
| Dahlen <i>et al.</i> [9] | Celecoxib | 27 | No | Not tested |
| Szczeklik <i>et al.</i> [8] | Rofecoxib | 12 | No | Yes |
| Stevenson <i>et al.</i> [10] | Rofecoxib | 60 | No | Yes |

* Decrease in FEV₁ (forced expiratory volume in 1 s) and/or induced naso-ocular symptoms.

Conclusions

Studies from several different laboratories have now concluded that the specific COX-2 inhibitors rofecoxib and celecoxib do not cross-react with aspirin and NSAIDs to cause exacerbation of asthma or naso-ocular symptoms in patients with AERD. These studies suggest that inhibition of COX-1 is required to trigger the increased cys-LT production associated with asthma exacerbation. However, the mechanism by which COX-1, but not COX-2, inhibition might cause this response remains unclear. Although these studies were performed as challenge tests rather than as long-term placebo-controlled trials, they are convincing. The fact that specific COX-2 inhibitors seem safe in AERD does not imply that other hypersensitivity reactions do not occur.

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