

EDITORIAL

COX-1 sparing drugs in aspirin-sensitive asthma

Non-steroidal anti-inflammatory drugs (NSAIDs) are currently among the most widely prescribed drugs worldwide [1]. NSAIDs play a major role in the management of inflammation and pain [1,2]. Adverse effects of NSAIDs are serious, mainly related to gastrointestinal bleeding and renal damage [1,2]. Aspirin and other NSAIDs are usually well tolerated by most asthma patients, but they cause bronchoconstriction in about 10% and relieve asthma in less than 1% of patients [3]. This variability in the response reveals the complexities of the regulation of arachidonic acid metabolism in asthma.

Most aspirin-sensitive asthma patients present a typical clinical syndrome, i.e. 'asthma triad' involving aspirin sensitivity, bronchial asthma and chronic rhinosinusitis with nasal polyposis. The basic mechanism underlying aspirin sensitivity is not immunological, and seems to involve inhibition of cyclo-oxygenase (COX) with subsequent release of leukotrienes and possibly other mediators as well [3].

COX appears to be the key enzyme in the explanation of aspirin-sensitive asthma. There are two isoforms of COX, namely COX-1 and COX-2. The metabolites derived from COX-1 are involved in cellular housekeeping functions, while the inducible isoform COX-2, is induced by pro-inflammatory stimuli and growth factors in a number of mammalian cells, including epithelial cells, fibroblasts, eosinophils, monocytes and macrophages [2].

The ability of NSAIDs to inhibit COX-2 may explain their therapeutic potential as anti-inflammatory drugs, whereas inhibition of COX-1 may account for their unwanted side-effects, such as gastric damage and aspirin-induced asthma [2]. Therefore, NSAIDs that inhibit COX-2 but not COX-1 can be a very useful alternative in the treatment of inflammatory and painful processes in aspirin-sensitive asthmatics.

Two theories have been proposed to explain aspirin-sensitive asthma, the cyclo-oxygenase theory [4] and the leukotriene C₄ synthase (LTC₄s) overexpression theory [5]. The COX theory suggests that an abnormality in the COX pathway might explain the selective and high sensitivity of some asthma patients to the inhibitory action of NSAIDs. The following observations support the COX theory:

- NSAIDs with anticyclooxygenase activity invariably precipitate bronchoconstriction in aspirin-sensitive patients [4].
- There is a positive correlation between the potency of

NSAID to inhibit COX *in vitro* and their potency to induce bronchospasm in the sensitive patient [6].

- NSAIDs without effect on COX activity do not precipitate asthma attacks [4].
- Prostaglandin E₂ (PGE₂) administered by inhalation inhibits aspirin-induced bronchoconstriction [7].

Some *in vitro* observations suggest that the COX pathway of aspirin-sensitive asthma is more sensitive to the effect of NSAIDs than that of aspirin-tolerant patients [8]. This increased sensitivity has been attributed to an abnormal downregulation of COX-2 [9] resulting in a lower production of endogenous PGE₂ [10] which may render these asthma patients more susceptible to the inhibitory effects of NSAIDs on COX-1 [9]. However, a number of observations appear to militate against the COX theory:

- The abnormalities in the COX pathway have been found in nasal polyps [8–10] but not in the lower airway where immunostaining for COX-2 shows no differences in bronchial biopsies of aspirin-sensitive patients as compared with aspirin-intolerant asthmatic [5,11].

- Baseline bronchoalveolar [12] and nasal lavage [13] levels of PGE₂ and other prostanoids are not different in aspirin-sensitive asthmatics and aspirin-tolerant patients.

- Both nasal instillation and bronchial inhalation of lysine-aspirin reduce the nasal and BAL fluid PGE₂ levels, respectively, in aspirin-sensitive patients to the same extent as in aspirin-sensitive patients [12,13].

These findings do not support the existence of either a decreased production of PGE₂ or an increased susceptibility of COX pathway to NSAIDs in aspirin-sensitive patients.

It is difficult to reconcile these differences since compelling evidence suggests that the diseases which affect the upper airway (rhinosinusitis and nasal polyps) and lower airway (asthma) in aspirin-sensitive asthmatics share common pathogenic mechanisms [14].

The LTC₄s theory proposes that aspirin-induced asthma is merely the consequence of an increased bronchial expression of LTC₄ synthase [5]. Evidence in favour of the LTC₄s theory can be summarized as follows:

- Inhibition of the COX pathway by NSAIDs leads to an increased release of cysteinyl leukotrienes (Cyst-LTs) in aspirin-sensitive asthmatics but not in aspirin-tolerant patients or healthy subjects [12,13].
- Leukotriene-modifying drugs are effective in blocking the bronchospasm provoked by NSAIDs in aspirin-sensitive patients [15].

- Expression of LTC₄s in bronchial biopsies is five-fold higher in aspirin-sensitive patients than in asthmatics who tolerate aspirin, and nineteen-fold higher than in bronchial biopsies from healthy subjects [5].

According to this theory, the enhanced LTC₄s expression in aspirin-sensitive asthmatics may explain the increased release of Cyst-LTs in these patients, without the presence of a higher susceptibility of COX to NSAIDs. NSAIDs may reduce PGE₂ synthesis to the same extent in all subjects, but more LTC₄-generating cells are liberated from PGE₂ suppression in the airways of aspirin-sensitive patients than in the airways of aspirin-tolerant or healthy subjects, leading to an excessive Cyst-LT release which results in bronchoconstriction only in aspirin-sensitive patients [5].

The LTC₄s theory may account for the overproduction of Cyst-LT in aspirin-sensitive asthma but can hardly explain the peculiar and selective sensitivity to NSAIDs of a limited number of asthma patients. In fact, aspirin-sensitive patients who have a high density of LTC₄s produce large amounts of Cyst-LT, which rise significantly (five-fold) after aspirin challenge, whereas the aspirin-tolerant patients with one-fifth the density of LTC₄s generate minimal quantities of Cyst-LT, which do not change after aspirin challenge [5]. According to LTC₄s theory, an increase of at least two-fold in the production of Cyst-LT would be expected in aspirin-tolerant asthmatics, but this was not observed.

The LTC₄s theory tries to explain aspirin sensitivity in asthma on the basis of the presence of progressive differences in the expression of this enzyme. As long as the expression of the enzyme increases, more susceptibility to NSAIDs should be detected, but this seems to be the case only in the subgroup of aspirin-sensitive patients. According to the LTC₄s overexpression theory, a five-fold increase in the mean precipitating aspirin dose should also precipitate bronchospasm in aspirin-tolerant patients with five-fold less LTC₄s bronchial expression than aspirin-sensitive asthmatics. However, the percentage of aspirin sensitive patients among the whole asthma population does not progressively go up by increasing the provoking dose of aspirin. In fact, most, if not all, aspirin-sensitive asthmatics develop bronchoconstriction with doses of 500 mg or lower of aspirin. The use of higher doses does not increase the number of sensitive patients detected by aspirin challenge.

Aspirin-sensitive asthma appears to be a 'yes' or 'no' phenomenon: asthma patients can be divided into two groups, those who are sensitive to NSAIDs and those who are not. Aspirin sensitivity is probably determined by an abnormality in the COX pathway, whereas the level of expression of LTC₄ synthase appears to regulate the intensity of the bronchospasm induced by NSAIDs only in aspirin-sensitive patients.

Intolerance to NSAIDs is a crucial therapeutic problem

because these drugs are frequently used in medical treatment. Cases of severe bronchospasm and/or anaphylactic reactions are relatively frequent. Fatal and near-fatal episodes of bronchoconstriction after ingestion of NSAIDs have been reported [16]. Choosing an alternative anti-inflammatory agent for a patient who had suffered adverse reactions to NSAIDs is a frequent problem in clinical practice. The most common approach is to prescribe a drug which has had its tolerability verified by oral provocation test. A number of drugs are usually recommended to treat aspirin-sensitive patients, including paracetamol, nimesulide and meloxicam. However, adverse reactions to these drugs have also been reported; these reactions are usually detected when patients are challenged or treated with high doses.

Cross-sensitivity between paracetamol and aspirin has been reported with frequencies ranging from 0–34% [17–20]. Nimesulide is the most widely studied drug as regards tolerance in NSAIDs-sensitive patients: various authors have reported tolerance percentages ranging from 91% to 100% of patients [20–23]. Several studies have also assessed meloxicam in NSAIDs-sensitive patients, showing tolerance ranging from 80 to 99% of patients [24,25]. Meloxicam and nimesulide are about 10 times more active on COX-2 than on COX-1 in the human whole blood assay [2].

Two new very selective inhibitors of COX-2, rofecoxib and celecoxib, have been recently launched in many countries [1,2]. Rofecoxib seems to be the most selective COX-2 inhibitor available at the moment [2]. If inhibition of COX-1 is the main cause of aspirin-induced bronchoconstriction, an almost general tolerance to this compound should be expected in aspirin-sensitive patients. Szczeklik et al. [26] investigated the tolerability of rofecoxib in a group of 12 aspirin-sensitive asthmatics, using a double-blind, placebo-controlled oral challenge procedure. No patient on rofecoxib developed either respiratory, cutaneous or systemic symptoms, or a significant fall in FEV₁. Moreover, mean urinary LTE₄ levels remained unchanged. These results suggest that rofecoxib can be added to the list of NSAIDs that can be safely taken by aspirin-sensitive asthmatics. Nevertheless, more patients, taking larger doses of rofecoxib, and for longer periods of time, are needed to establish with certainty the degree and duration of tolerance of rofecoxib in aspirin-sensitive patients.

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