

EDITORIAL

Non-steroidal anti-inflammatory drugs-induced urticaria and angioedema: more research on mechanisms needed

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Non-steroidal anti-inflammatory drugs (NSAID) can precipitate adverse reactions on a cutaneous (urticaria, angioedema), respiratory (bronchospasm) and nasal (rhinorrhoea, nasal obstruction) level. Reactions to NSAID may occur as isolated phenomena in the skin or in the respiratory tract or may occur as mixed respiratory/cutaneous reactions in the same patient [1].

Cutaneous reactions can occur as chronic urticaria exacerbated by NSAID and as NSAID-induced urticaria in subjects without any underlying disease. Mixed reactions usually occur in asthma patients with chronic rhinosinusitis and nasal polyps [1].

The mechanisms responsible for NSAID-induced adverse cutaneous reactions are probably complex and varied. IgE-mediated reactions are involved in most cutaneous reactions precipitated by pirazolones in patients who tolerate other NSAID [1]. In most patients with NSAID-exacerbated chronic urticaria and NSAID-induced urticaria/angioedema, the adverse reaction is directly related to the inhibition of the enzyme cyclooxygenase 1 (Cox-1) [1].

It has been reported that NSAID-intolerant asthma patients excrete 2–10 times greater amounts of leukotrienes (LT)E₄ in urine than aspirin-tolerant asthmatics [2, 3]. Oral, bronchial and nasal aspirin challenges in NSAID-sensitive asthmatics cause further LTE₄ release in urine and bronchial or nasal secretions [2–4]. Similarly, patients with chronic urticaria and NSAID-induced urticaria/angioedema also have elevated release of LTE₄ in urine, which further increases after aspirin oral challenge [5]. Patients with NSAID-induced bronchospasm and those with NSAIDs-exacerbated chronic urticaria and NSAIDs-induced urticaria/angioedema tolerate selective Cox-2 inhibitors [6–13]. This finding supports the notion that the mechanisms responsible for NSAID-induced respiratory and for most cutaneous adverse reactions should be the same. Nevertheless, there is a small difference between asthmatics and patients with urticaria/angioedema: a 100% of asthma patients tolerate selective Cox-2 [6–11], but this percentage is slightly reduced in patients with NSAIDs-induced cutaneous reactions [10–13]. Some of the latter patients do not even tolerate the most selective Cox-2 inhibitors, such as celecoxib and rofecoxib, and those without little or no Cox-1 inhibitory effect such as paracetamol. The origin of this difference is unknown and may be because of a mechanism other than inhibition of Cox-1.

Although the mechanism involved in NSAID-induced asthma has not been completely elucidated, considerable progress has been made in the clarification of this intriguing syndrome in the last two decades [1]. We know now that these patients have differences in the regulation of the cyclooxygenase [14–18], 5-lipoxygenase [19] and 15-lipoxygenase

pathways [15, 20] of arachidonic acid metabolism with respect to NSAID-tolerant asthmatics and healthy subjects.

Alterations have been reported in the Cox pathway, resulting in an abnormally low production of prostaglandin E₂ (PGE₂) [14–16], probably related to the down-regulation of Cox-2 [17, 18]. Cox-2 is an inducible enzyme regulated by an early gene and it is generally accepted that its expression increases under conditions of inflammation, and the activation of the enzyme results in the increased production of prostanoids such as PGE₂. For unknown reasons, the expected up-regulation of Cox-2 and the increased production of PGE₂ do not occur in the airway cells of NSAID-intolerant asthmatics [17, 18]. It has been suggested that the lack of adaptation of Cox-2 to the airway inflammatory situation may be partially replaced by an increased expression of Cox-1 [18]. Because PGE₂ exerts regulatory functions on cysteinyl leukotrienes (cys-LTs) release, it may well be that the control of synthesis in inflammatory conditions is taken on by the Cox-1 in NSAID-intolerant asthmatics [18, 21]. This could explain why only drugs that inhibit Cox-1 precipitate asthma attacks, while selective Cox-2 inhibitors are well tolerated. Because Cox-2 is not activated in the inflamed airways of NSAID-intolerant asthmatics, it has no regulatory effect on cys-TLs release and therefore its inhibition has no effects on the release of these metabolites.

The increased production of cys-LTs in NSAID-intolerant asthmatics at baseline and the further increase after aspirin challenge are mostly because of the up-regulation of the leukotriene C₄ synthase (LT-C₄s) [19]. Cys-LTs are a family of fatty acid mediators that are synthesized during the process of the conjugation of LT A₄ to reduced glutathione. This process is mediated by leukotriene C₄ synthase (LT-C₄S) and leads to the intracellular formation of leukotriene C₄ (LTC₄). LTC₄ is exported out of the cells and it is processed extracellularly by a glutamyl transpeptidase and a dipeptidase, which yield LTD₄ and LTE₄, respectively [1, 22]. It has been reported that the number of cells expressing LT-C₄S in bronchial biopsies was five times higher in NSAIDs-intolerant asthmatics than in aspirin-tolerant asthma subjects and eighteen times higher than in normal subjects [19]. Most of the cells that expressed LT-C₄S were eosinophils, with smaller numbers being mast cells and macrophages. LT-C₄S-positive cell counts correlated significantly with basal levels of cys-LTs in bronchoalveolar fluid. The number of LT-C₄S positive cells was also significantly correlated to the provocation dose of lysine–aspirin to induce bronchoconstriction [19].

Given the similarities between cutaneous and respiratory reactions in NSAID-intolerant patients, it would be expected that the alterations in the expression of the enzymes of arachidonic acid metabolism detected in the airways in

NSAID-intolerant asthma would also be present on the skin of patients with NSAID-induced urticaria/angioedema. Many studies have examined the mechanisms involved in NSAID-induced asthma, but no similar studies have been carried out in patients with cutaneous reactions. As the skin is readily accessible for exploration and biopsy, in contrast to the complexity of lower airways examination and biopsy, it is surprising to see that nobody has been interested in the study of the regulation of Cox and LT-C4s enzyme on the skin of patients with NSAID-induced urticaria/angioedema.

The Asero study [23] shows that in a high percentage of patients with NSAID-induced urticaria/angioedema, the reaction results from the inhibition of Cox-1 and that this mechanism can be easily detected using the oral aspirin challenge. This study also confirms that some of these patients do not even tolerate the most selective Cox-2 inhibitors. It is unclear whether this phenomenon is because of a mechanism other than the inhibition of the Cox-1. A relatively easy way to answer this question is to measure the levels of LTE₄ excreted in the urine before and after the challenge with these drugs. If the levels increase, we can conclude that the mechanism is the same; if not, we should look for another explanation.

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