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Aspirin-induced urticaria and angioedema, but not bronchoconstriction, associated with cysteinyl leukotriene overproduction in 2 patients with asthma

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To the Editor:

There are 2 types of aspirin intolerance: the asthma-sinusitis type and the urticaria-angioedema type. There are significant differences in clinical characteristics between these 2 types, and the combination of the 2 types is very rare. Nonsteroidal anti-inflammatory drug (NSAID)-induced urticaria and angioedema are common in adult atopic individuals with chronic urticaria.¹ In contrast, NSAID-induced asthma and sinusitis (ie, aspirin-intolerant asthma [AIA]) are observed more often in asthmatic patients with chronic rhinosinusitis and nasal polyposis.

Recent reports have demonstrated the clinical effectiveness of a leukotriene receptor antagonist in NSAID-sensitive patients.^{2 3} In addition, Christie et al⁴ were first to demonstrate that urinary leukotriene E₄ (LTE₄) concentrations in patients with AIA are significantly increased and increased further after aspirin challenge. These findings provide the objective evidence that cysteinyl leukotrienes might play an important role in the pathophysiology of aspirin intolerance. However, there have been few studies on urinary

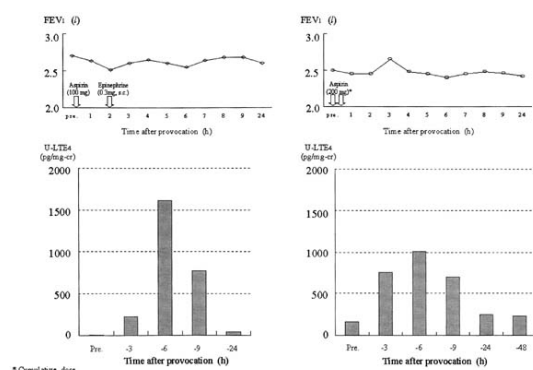
LTE₄ concentrations in patients with NSAID-induced urticaria and angioedema.

We encountered 2 asthmatic patients (40 and 59 years old, both men) with severe urticaria and angioedema but without respiratory or nasal symptoms induced by aspirin and other NSAIDs. Their clinical characteristics were adult-onset severe asthma and recurrent nasal polyposis with anosmia, which are similar to those of AIA. The asthma in patient 1 was classified as a nonatopic type because he had a low level of serum IgE (125 IU/mL) and had no positive reaction to skin tests for 15 major allergens, including house dust, mites, grass, cat, and fungi. Patient 2 had atopic asthma with a slightly high level of serum IgE (482 IU/mL). Patient 2 was sensitive to only cat dander. The provocative concentration of acetylcholine causing a 20% fall in FEV₁ evoked a moderate-to-severe bronchial hyperresponsiveness in these 2 patients (459 µg/mL and 1810 µg/mL, respectively). Both of these patients were taking inhaled fluticasone at a dose of 400 to 800 µg/d. They were not taking medications containing either H1 receptor antagonists or leukotriene receptor antagonists. Although they had no history of chronic urticaria, urticaria and angioedema episodes occurred about 60 minutes after the ingestion of at least 3 different NSAIDs. Because the predominant symptom of aspirin intolerance in asthmatic patients is bronchoconstriction,¹ the 2 patients described here are very rare.

After their informed consent was obtained, we performed an intravenous aspirin challenge test in a single-blind manner, as previously described. After the provocation, urine samples collected during the periods of 0 to 3, 3 to 6, 6 to 9, and 9 to 24 hours were assayed for LTE₄. The concentration of urinary LTE₄ was measured as previously described.⁵

During the aspirin challenge test (cumulative lysine-aspirin doses in the 2 patients were equivalent to 100 and 200 mg of aspirin), both patients showed facial and pharyngeal angioedema and urticaria, without respiratory or nasal symptoms. Moreover, subcutaneous administration of epinephrine was required to treat the severe pharyngeal angioedema in patient 1. FEV₁ was recorded every 30 minutes after provocation, and the FEV₁ values of the patients did not change by more than 10% from the prechallenge baseline value (Fig 1, A).

Fig. 1 Aspirin challenge results in a marked increase in urinary LTE₄ (*U-LTE₄*) concentration but does not affect pulmonary function in 2 patients. *The dose of aspirin is expressed as a cumulative dose.



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The baseline concentrations of urinary LTE₄ in these 2 patients were 14 and 162 pg/mg creatinine, respectively. We have observed a marked increase in the concentration of urinary LTE₄ after the aspirin challenge similar to that seen in patients with AIA. The maximum concentrations were noted during the collection period of 3 to 6 hours (1596 pg/mg creatinine, a 114-fold increase from the baseline value, and 1004 pg/mg creatinine, a 6.2-fold increase from the baseline value, respectively; Fig 1, B).⁶

Provocation with the same dose of aspirin (100 mg) was repeated in patient 1 after pretreatment with 20 mg of montelukast 4 hours before the test to reconfirm the involvement of cysteinyl leukotrienes in the pathogenesis of NSAID-induced urticaria and angioedema. The pretreatment with montelukast partially blocked the induction of urticaria and angioedema. He did not require treatment with subcutaneous administration of epinephrine. However, administration of the same dose of aspirin resulted in a similar increase in the urinary LTE₄ concentration at the peak of the 0- to 3-hour collection period (1210 pg/mg creatinine), and the pretreatment with montelukast did not affect the increase in urinary LTE₄ concentration, which was consistent with the results of Rasmussen et al.⁶

To our knowledge, this is the first report showing the relationship between the exacerbation of urticaria and angioedema in asthmatic patients and the overproduction of cysteinyl leukotrienes in vivo. In addition, we demonstrated that montelukast is useful in preventing urticaria and angioedema induced by NSAIDs. Results of our reconfirmatory test agree with those of a previous study by Perez et al.⁷ Taken together, it is clear that cysteinyl leukotrienes are involved in the pathogenesis of NSAID-induced urticaria and angioedema, as has been proposed in AIA.

Finally, we have also revealed, for the first time, that overproduction of cysteinyl leukotrienes in vivo does not necessarily induce bronchoconstriction, even in asthmatic patients who show a moderate-to-severe bronchial hyperresponsiveness. We aim to clarify the difference in sensitivity to cysteinyl leukotrienes between the skin and bronchus and to determine the main organ that produces cysteinyl leukotrienes in patients with aspirin intolerance.

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ABSTRACT

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