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Pretreatment with montelukast blocks NSAID-induced urticaria and angioedema

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To the editor:

Urticaria and angioedema are frequent reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). They are observed more often in atopic individuals,¹ though rarely during childhood.² Although the mechanisms of such reactions are not completely understood, the prevalent theory indicates that cyclooxygenase 1 inhibition is the most likely pathway.³ In support of this concept, we have demonstrated that selective COX-2 inhibitors are better tolerated than nonselective NSAIDs in NSAID-sensitive patients.⁴

Weak COX-1 inhibitors as well as COX-2 inhibitors have been recommended in intolerant subjects for the treatment of inflammatory and painful conditions. It must be noted, however, that when increased doses are given to NSAID-sensitive patients, reactions to these alternative drugs can occur. Desensitization, as used successfully for aspirin-induced asthma, has also been tried in urticaria/angioedema with negative results.⁵

Montelukast, a Cys-LT1 receptor antagonist, has been shown to attenuate aspirin-induced

respiratory reactions⁶ and has been empirically used in patients with diverse forms of urticaria.^{7 8} Because leukotrienes are major mediators of NSAID-triggered adverse reactions, we have investigated the prophylactic effect of montelukast on NSAID-induced urticaria and angioedema in a group of intolerant patients.

Healthy individuals with histories of recurrent episodes of urticaria and/or angioedema occurring after the administration of at least 2 different COX inhibitors were studied. After signing informed-consent forms, these subjects were submitted to oral ibuprofen challenges. The protocol was approved by the Ethics Committee, Medical Faculty, Central University of Venezuela. Patients with chronic idiopathic urticaria and those with Samter's triad were excluded.

Single-blinded oral challenges with placebo and ibuprofen 400 mg were carried out as previously described.¹ Results were assessed in terms of the percentage of body surface area involved either by urticaria or angioedema, as follows: head and neck, 30%; chest, 20%; abdomen, 20%; upper limbs, 15%; lower limbs, 15%.

Two weeks later, ibuprofen challenge was repeated after pretreatment with montelukast 20 mg, which was given 4 hours before the test. Antihistamines were discontinued 72 hours before the challenge, and corticosteroids were withheld for 2 weeks.

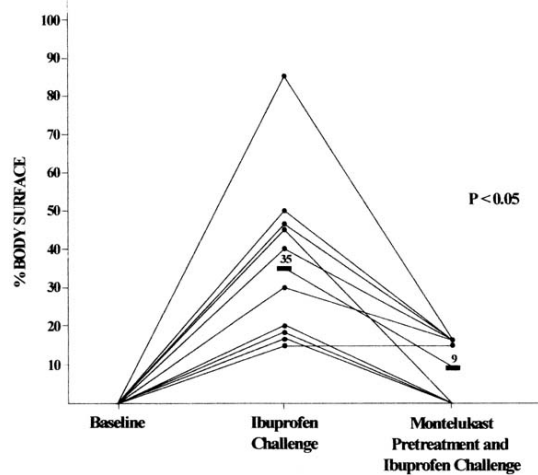
Statistical analysis was done through use of the nonparametric Wilcoxon test for paired samples with a significance level of $P < .05$.

Seventeen patients were included; 12 were female and 5 male. Of these, 12 patients had positive ibuprofen test results and 10 (7 female and 3 males; mean age, 34 ± 11.3 years; age range, 17-50 years) underwent montelukast pretreatment before the second ibuprofen challenge. Two patients withdrew their consent for the second test.

During the first ibuprofen challenge, 12 patients had positive results: 4 showed facial angioedema, 3 facial angioedema and urticaria, 1 urticaria alone, and 4 angioedema plus respiratory symptoms.

Montelukast pretreatment induced complete blockade of the reaction in 3 patients, partial blockade in 6 patients, and no change in 1 patient, as shown in Fig 1.

Fig. 1. Pretreatment with montelukast blocks ibuprofen-induced urticaria and angioedema.



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Bernstein et al⁹ reported in 1991 the inhibition of wheal and erythema induced by skin injection of LTD₄ with the administration of the leukotriene receptor antagonist ICI 204,219. In the present study, we have demonstrated that montelukast pretreatment is able to block the production of cutaneous reactions induced by ibuprofen in NSAID–cross-reactor patients. To our knowledge, this is the first study to show that leukotriene receptor antagonists can be useful for the prevention of urticaria/angioedema triggered by NSAIDs.

Present results would also support the view that cysteinyl leukotrienes are involved in the pathogenesis of NSAID-induced cutaneous reactions, as has been proposed in aspirin-induced respiratory disease.¹⁰ Given that leukotriene antagonists interfere with NSAID-induced urticaria and angioedema, studies should be designed for defining its prophylactic or therapeutic potential in other skin conditions in which cysteinyl leukotrienes appear to be involved. The role of leukotrienes, the mechanisms involved in their overproduction, and the expression of symptoms only in some individuals exposed to NSAIDs remain to be clarified.

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Allen P. Kaplan, Malcolm W. Greaves

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Journal of Allergy and Clinical Immunology, The

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Advances in allergic skin diseases

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March 2003, part 2 • Volume 111 • Number 3

Donald Y.M. Leung, MD, PhD^a, Mark Boguniewicz, MD^b

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