

Leukotriene receptor antagonists may prevent NSAID-induced exacerbations in patients with chronic urticaria

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Background: About 30% of patients with chronic urticaria experience flares of hives and/or angioedema after ingesting either aspirin or nonsteroidal anti-inflammatory drugs. In such patients, cross-reactivity to all NSAIDs seems to occur suggesting a mechanism dependent on cyclooxygenase inhibition.

Objective: To evaluate the preventive effect of leukotriene receptor antagonists on urticaria exacerbations induced by NSAIDs in a patient with chronic urticaria.

Methods: A 59-year-old woman with a 2-year history of recurrent urticaria exacerbated by different NSAIDs including aspirin 500 mg (2 episodes), piroxicam 20 mg, and nimesulide 100 mg (1 episode each) was studied. Acetaminophen 375 mg and floclofenine 50 mg induced a marked flare of urticaria/angioedema in a single-blind, placebo-controlled challenge.

Results: The patient was totally urticaria free during a 3-week course of montelukast 10 mg once a day. After montelukast withdrawal, a gradual relapse of urticaria/angioedema occurred along with a further acute urticaria/angioedema episode after a single piroxicam, 20-mg tablet. Zafirlukast 20 mg twice daily was started. After some days the patient was urticaria-free again, and after 3 weeks she tolerated a 6-day course of injective piroxicam (20 mg once a day) without any problem. To date the patient is still urticaria-free.

Conclusion: Leukotriene receptor antagonists may prevent the severe urticaria/angioedema exacerbations which follow the use of NSAIDs in some patients with chronic urticaria.

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INTRODUCTION

About 30% of patients with chronic urticaria experience flares of hives and/or angioedema after ingesting either aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).¹ In such patients, cross-reactivity to all NSAIDs seems to occur; moreover, their sensitivity is particularly high when urticaria is active, and disappears when the underlying disease is in remission.¹ The pathogenic mechanisms of such reactions are still

poorly defined; nonetheless, cross-reactivity between chemically different NSAIDs suggests a mechanism dependent on cyclooxygenase inhibition. This hypothesis is supported by some recent reports of the effectiveness of leukotriene antagonists in some patients with chronic urticaria^{2–5}; moreover, another study of aspirin-sensitive asthmatics found that the lipoxygenase-inhibitor zileuton prevented the development of dermal symptoms after ASA ingestion.⁶ The present case report adds further evidence that, at least in some patients, cyclooxygenase blockade plays a role in the pathogenesis of both spontaneous urticaria and NSAIDs-induced exacerbations.

CASE REPORT

In January 1999, a 59-years-old woman was referred to this allergy center because of a history of recurrent urticaria and angioedema. She experienced the first urticaria episode about 2 years before, during antibacterial treatment (Rokitamycin 400 mg twice daily). Further urticaria/angioedema episodes occurred during the following year about 60 minutes after the ingestion of aspirin 500 mg (2 episodes), piroxicam 20 mg, and nimesulide 100 mg (1 episode each). These episodes lasted 4 to 8 hours and were controlled by antihistamine injections given by the family doctor. During the last 6 months spontaneous worsening recurrent urticaria appeared. The patient controlled her symptoms by cetirizine 10 mg daily when needed, and eventually she had to take cetirizine daily. The patient chronically suffered from severe back pain, and asked for some safe analgesic drug.

All screening laboratory investigations (blood cell count, ESR, chemistry panel, ANA, thyroid antibodies, as well as thyroid function) were normal, and the patient did not respond to an additive-free diet regimen which was followed for 3 weeks. The intradermal injection of 0.05 mL of fresh autologous serum induced an unequivocal local wheal and flare response (by contrast, the intradermal injection of saline did not elicit any skin reaction). Auto-reactive chronic urticaria was diagnosed.⁷

In order to confirm or exclude possible macrolide intolerance as well as to detect at least one tolerated NSAID

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the patient underwent peroral challenges with rokitamycin, acetaminophen (a drug that the patient had taken several times without any consequence before the onset of urticaria), and floctafenine. The latter two substances were chosen as possible alternative drugs on the basis of previous reports showing their good tolerability in patients with a history of pseudo-allergic reactions to aspirin and other NSAID.^{8,9} Placebo-controlled peroral challenges were carried out in a single blind fashion. The following doses were scheduled: rokitamycin 100 mg, 300 mg; acetaminophen 125 mg, 375 mg; and floctafenine 50 mg, 150 mg.

Two placebo capsules were given at the beginning of each session (day 1), whereas active drugs were challenged on day 2. Doses were given 1 hour apart and the patient was controlled for 2 hours after the last provocative dose. Drugs under investigation were challenged at least 1 week apart. Cetirizine was stopped at least 3 days before each challenge. The patient gave an informed written informed consent before each challenge session. Since the patient showed some hives at the beginning of each challenge session, only the appearance of unequivocal worsening of urticaria (defined as pruritic and erythematous areas raised over normal skin) and/or the appearance of angioedema (defined as swelling of skin and/or external mucosa) were considered as a positive response.

No reactivity against placebo was noted. Rokitamycin was well tolerated, whereas a marked flare of generalized urticaria/angioedema occurred about 2 hours after the ingestion of 375 mg of acetaminophen, and about 45 minutes after the ingestion of 50 mg of floctafenine.

Montelukast 10 mg once a day was started. During the 3-week treatment period the patient was well and never took antihistamines. About 1 week after montelukast withdrawal, a gradual relapse of urticaria/angioedema occurred, and the patient had to resume cetirizine 10 mg daily to control her

symptoms. During this period the woman experienced a further acute urticaria/angioedema episode about 45 minutes after the ingestion of a single piroxicam 20-mg tablet (self-administered because of severe back pain). Notably, the woman was taking cetirizine when this episode took place. After 2 months with recurrent urticaria, the patient asked to resume anti-leukotriene treatment. Zafirlukast 20 mg twice daily was prescribed. After some days the patient was urticaria-free again and could withdraw cetirizine, and after 3 weeks she tolerated a 6-day course of injective piroxicam (20 mg once a day) without any problem. To date the patient is still urticaria-free and does not need antihistamine treatment.

DISCUSSION

The possibility that cyclooxygenase blockade plays a pivotal role in the pathogenesis of aspirin-induced asthma has been known for many years,¹ and was recently confirmed by the observation that leukotriene antagonists may prevent asthma following aspirin challenge.¹ The multiple NSAIDs sensitivity which characterizes a subset of patients with chronic urticaria raised the possibility that a similar pathogenic mechanism might play a role in these patients as well. This hypothesis was recently supported by the first studies reporting a favorable effect of leukotriene antagonists in patients with chronic urticaria,²⁻⁴ particularly in those with NSAIDs intolerance.⁵ The present study confirms these observations and further extends them showing that leukotriene receptor antagonists may prevent the severe urticaria/angioedema exacerbations which follow the use of NSAIDs. The patient described here tolerated a 6-day full dose injection course with a drug that had previously caused two flares after oral administration. The possibility that tolerance occurred by chance is very unlikely. It is well known that urticaria patients are particularly prone to NSAIDs reactiv-

ity during the active phases of their disease.¹ In this patient zafirlukast (as well as montelukast) induced a marked remission of the disease.

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