
Failure of zafirlukast to prevent ibuprofen-induced anaphylaxis

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Background: Anaphylaxis to nonsteroidal anti-inflammatory drugs is thought to depend on cyclooxygenase inhibition coupled to upregulation of 5-lipoxygenase-dependent pathways. The introduction of leukotriene-receptor antagonists afforded the opportunity to test this hypothesis. These agents provide at least partial protection against aspirin-induced anaphylaxis during *controlled* challenges but we did not know whether the level of protection was high enough to block symptoms from ingestion of a full dose of aspirin.

Methods: We report a patient with moderately severe asthma who experienced an episode of anaphylaxis following ingestion of 400 mg of ibuprofen while under therapy with 20 mg of zafirlukast given twice a day.

Results: No further episodes of anaphylaxis have been noted following institution of complete avoidance to all nonsteroidal anti-inflammatory drugs.

Conclusions: Patients who are sensitive to cyclooxygenase inhibitors should practice complete avoidance of these drugs even while under therapy with leukotriene modifiers.

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INTRODUCTION

In the past few months both a leukotriene (LT)-receptor antagonist, zafirlukast, and a specific 5-lipoxygenase inhibitor, zileuton, have been approved for the treatment of asthma in the US. Of these two drugs, only zileuton has been shown to effectively block the pulmonary and systemic manifestations of an aspirin challenge in aspirin-sensitive subjects.¹ Similar challenge studies performed against several specific LT-receptor antagonists have shown only partial degrees of efficacy in preventing aspirin-induced asthma.^{2,3}

The incomplete protection afforded by LT-receptor antagonists during incremental dosing challenges raises the issue of whether aspirin-sensitive subjects being treated with these agents reduce their risk of anaphylaxis upon inadvertent ingestion of a full dose of a non-steroidal anti-inflammatory drug. As evidence that this is not the case, we report our experience with a 14-

year-old boy who suffered a serious episode of ibuprofen-induced anaphylaxis while under treatment with zafirlukast.

CASE REPORT

The patient is a 14-year-old boy with a life-long history of moderately severe asthma. His regular asthma therapy consisted of Flovent 220, 3 puffs bid, albuterol, cromolyn, and ipratropium by compressor-driven nebulizer bid and as needed, and zafirlukast 20 mg bid. On the day in question, he took 400 mg of ibuprofen for a headache at approximately 6:45 AM, followed by his morning dose of zafirlukast. He had had no previous history of NSAID intolerance. Within 30 minutes he began experiencing chest and throat tightness, shortness of breath, coughing, sneezing, runny nose, and generalized weakness. He self-administered 8 puffs of albuterol from a metered-dose inhaler over 30 minutes followed by a nebulizer treatment with albuterol solution obtaining only minimal relief.

He was seen an hour and 45 minutes after ingestion still suffering from significant respiratory distress. His oxy-

gen saturation was 89%, his blood pressure was 100/60, pulse 119, respirations 24 and labored. Forced expiratory volume in one second was 24% of predicted improving to 37% of predicted following treatment with inhaled albuterol. He then received subcutaneous epinephrine, intravenous methylprednisolone, and oral loratidine and diphenhydramine. A serum tryptase level was drawn which later was reported as 3.4 U/L (normal less than 0.5). Upon discharge from the clinic one hour later his FEV₁ had improved to 50% of predicted and he was asymptomatic. He was stable when seen in follow-up 1 week later but his FEV₁ remained at 50% of predicted.

DISCUSSION

We have known for many years that nonsteroidal anti-inflammatory drugs such as ibuprofen can induce acute anaphylactic reactions in susceptible populations.⁴ These drugs vary considerably in chemical structure but they all share the ability to inhibit cyclooxygenases. This latter activity coupled to increased generation of LT via the 5-lipoxygenase pathway was thought crucial to the clinical manifestations of aspirin-sensitivity. The discovery of specific LT-receptor antagonists and 5-lipoxygenase inhibitors allowed investigators to test this hypothesis. Israel et al⁵ were able to show that zileuton, at doses that inhibit about 80% of ex vivo LTB₄ production, can abolish the pulmonary, ocular, nasal, gastrointestinal, and dermal reactions following aspirin challenge with a previously determined threshold dose of about 90 mg. By contrast, LT-receptor antagonists show marked variability in protection during challenge studies with some subjects failing to be protected at all.

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It appears that zileuton, and to a lesser extent, zafirlukast, may offer some protection to aspirin-sensitive individuals by shifting the dose-response curve to aspirin; but, based on the experience reported here, these agents do not appear to reduce the risk of exposure to full doses of nonsteroidal anti-inflammatory drugs. Since challenging these patients with full rather than incremental doses of aspirin would be extremely risky, it is only through inadvertent exposures, such as occurred in our case, that we can begin to ascertain the clinical benefits and limitations of these agents in the management of aspirin-sensitive patients.

Furthermore, the presence of tryptase in the peripheral blood of our patient is supportive of the concept of mast cell involvement in aspirin-induced anaphylaxis.⁶ It is likely that other mediators, both stored as well as newly sensitized, and which are re-

leased independently of 5-lipoxygenase pathways account for some of the clinical manifestations of this syndrome.

Consequently, it seems prudent to continue to recommend avoidance of nonsteroidal anti-inflammatory drugs to aspirin-sensitive patients receiving therapy with leukotriene modifiers.

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