
Effect of leukotriene modifier drugs on the safety of oral aspirin challenges

Andrew White, MD*; Elizabeth Ludington, PhD; Purvi Mehra, MD†; Donald D. Stevenson, MD†; and Ronald A. Simon, MD†

Background: Aspirin-exacerbated respiratory disease can be diagnosed with oral aspirin challenges and treated with aspirin desensitization.

Objective: To evaluate whether controller medications, particularly leukotriene modifier drugs, taken during oral aspirin challenges can reduce the risk of severe asthmatic responses.

Methods: The medical records of 676 patients who had undergone oral aspirin challenges, followed by aspirin desensitization, were reviewed. Asthmatic responses were stratified based on severity of bronchospastic response or lack of response. The effect of pretreatment with controller medications on the outcome of oral aspirin challenges was measured.

Results: Leukotriene modifier drugs had the most significant effect in protecting the lower airways from severe reactions ($P=.004$). The protective effect of leukotriene modifier drugs was observed in patients already taking systemic corticosteroids, where the addition of leukotriene modifier drugs significantly shifted the response toward a milder asthmatic response ($P<.001$).

Conclusion: Protection from significant aspirin-induced bronchospasm during oral aspirin challenge can be accomplished with leukotriene modifier drugs. The use of a combination of inhaled corticosteroids, long-acting β -agonists, systemic corticosteroids, and leukotriene modifier drugs stabilized underlying airways in preparation for a reasonably safe and accurate oral aspirin challenge. However, only pretreatment with leukotriene modifier drugs enhanced the safety of oral aspirin challenge in patients with aspirin-exacerbated respiratory disease by significantly decreasing the degree of asthmatic responses. Therefore, outpatient oral aspirin challenges in most well-selected patients appear to be a reasonable decision.

Ann Allergy Asthma Immunol. 2006;97:688–693.

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is often underrecognized but in a recent meta-analysis was shown to be present in 9% to 21% of asthmatic patients.¹ It is associated with nasal polyposis and chronic hyperplastic eosinophilic sinusitis, which have an attendant morbidity and a detrimental effect on quality of life.² Numerous studies now confirm that AERD can paradoxically be treated by aspirin desensitization and daily aspirin therapy.^{3,4} Although aspirin desensitization is effective in providing a safe method of administering aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) to those who require them (ie, those with ischemic heart disease or arthritis), it is the therapeutic effect that aspirin treatment has on AERD that presents the most compelling reason for daily aspirin treatment.

AERD pathophysiology has been well described.^{5,6} The central protective prostanoid in AERD is prostaglandin E₂ (PGE₂), which under normal circumstances inhibits 5-lipoxygenase and 5-lipoxygenase-activating protein. In AERD, diminished biosynthesis of PGE₂ has been measured at baseline.⁷ Thus, the administration of aspirin and NSAIDs further

prevents synthesis of PGE₂ with a loss of inhibition of 5-lipoxygenase and 5-lipoxygenase-activating protein, thus allowing uninhibited production of leukotrienes. The aspirin-induced lower respiratory tract reactions in AERD patients are almost certainly induced by leukotrienes via cysteinyl leukotriene receptor 1 (cysLT₁).⁸ Theoretically, leukotriene receptor antagonist should block smooth muscle constriction in lower airways and prevent lower airway reactions.

In patients with AERD, full therapeutic doses of aspirin or other NSAIDs can cause life-threatening asthma.^{9,10} Fortunately, aspirin- and NSAID-induced reactions exhibit a dose-dependent response, with small doses inducing smaller respiratory reactions. However, even 30 to 60 mg of aspirin may lead to large bronchospastic responses.¹¹

Two recent studies showed that of all controller medications used in AERD, pretreatment with leukotriene modifier drugs (LDs) had a significant effect in preventing asthmatic reactions in approximately half of the patients undergoing aspirin oral challenges.^{12,13} In this half of the AERD patients, LDs appeared to shift the response away from the lower airways so that reactions still occurred but were limited to the upper airway. However, for the other half of patients, asthma occurred during oral aspirin challenge. The degree of this asthmatic reaction has not been investigated. The safety of aspirin-induced reactions depends largely on how much asthma occurs in approximately half the patients where asthma is not completely blocked by LDs. This study evaluated precisely this important question and therefore by im-

* Department of Allergy and Immunology, Naval Medical Center San Diego, San Diego, California.

† Department of Allergy, Asthma, and Immunology, Scripps Clinic, San Diego, California.

Received for publication January 24, 2006.

Accepted for publication in revised form July 30, 2006.

plication the safety of oral aspirin challenges in patients pretreated with LDs compared with other controller regimens. This was accomplished by looking at degree of asthmatic responses as a marker of safety.

METHODS

Patients

Patients with suspected AERD were admitted to the General Clinical Research Center (GCRC) at Scripps Clinic in San Diego, CA. These patients all gave informed consent to receive oral aspirin challenges followed by aspirin desensitization and collection of these data. All information was treated according to the National Institutes of Health guidelines for GCRC facilities regarding confidentiality. Medical records of 689 patients with suspected AERD who were admitted to the GCRC were available. Our study population of 676 patients represented all patients who completed oral aspirin challenges between 1981 and 2004. Thirteen patients were excluded because of an inability to initiate oral aspirin challenges because of unstable asthma or another unstable medical condition. The patient population was 44% male and 56% female, with an age range of 17 to 79 years and an average age of 46 years.

To be considered for the aspirin desensitization protocol, patients must have had a history of asthma, nasal polyposis, and chronic sinusitis with at least one historical respiratory reaction to full therapeutic doses of aspirin or another NSAID. Severe bronchospasm, which in some cases was life threatening, was often precipitated during these past reactions after ingesting full therapeutic doses of aspirin (650 mg or greater) or other NSAIDs (equivalent doses). Rarely, patients had a history of naso-ocular symptoms with a milder asthmatic reaction. Urticaria, during historical exposure to aspirin or NSAIDs, in conjunction with airway symptoms was not considered an exclusion criterion. Almost every patient in this study was receiving topical nasal corticosteroids, and for the purpose of this study, their use was not considered in the analysis.

Controller Medications Taken During Challenges

Patients were referred to this study and on arrival at the GCRC were already taking controller medications for asthma, as prescribed by their referring physicians. The only medications whose use was discontinued at the time of admission were antihistamines and short-acting β -agonists.

Seventy-one patients were taking theophylline, 123 were taking long-acting bronchodilators (long-acting β_2 -agonist), 274 were taking systemic corticosteroids, 513 were taking inhaled corticosteroids, 260 were taking LDs, and 72 patients were taking no controller medications. Most patients were receiving a combination of these controller medications. Of the 260 patients receiving LDs, 201 were taking montelukast, 10 mg each day; 39 were taking zafirlukast, 20 mg twice daily; 14 were taking zileuton, 650 mg 4 times a day; and 6 were taking a combination of zileuton plus either zafirlukast or montelukast. All LDs had been prescribed by the referring

physician. No LDs were prescribed by the investigators at the time of consultation. Forty-two patients were taking the combination of inhaled corticosteroids, systemic corticosteroids, long-acting β_2 -agonists, and LDs. Medicines used before but not during the oral challenges with aspirin were not included in the analysis (ie, bursts of systemic corticosteroids).

Study Design

All 676 patients admitted to the GCRC underwent oral aspirin challenges in a similar manner. Patients were admitted between 2 and 3 days before aspirin challenge. Placebo challenges were performed during the early part of the hospital stay, and in some cases investigative challenges with other agents, such as tartrazine, monosodium glutamate, sulfites, or selective cyclooxygenase 2 inhibitors, all of which behaved like placebo challenges, were performed.¹⁴ Patients underwent spirometry every hour during challenges. The best of 3 efforts for forced expiratory volume in 1 second (FEV₁) was recorded. Patients were required to have a baseline FEV₁ of more than 60% (with absolute FEV₁ >1.5 L) and intraday variability of less than 10% during placebo challenges.

Patients with a low baseline FEV₁ may have been given systemic corticosteroids and if their baseline had improved to an FEV₁ greater than 60% would continue with the aspirin challenge protocol. Patients were excluded and discharged from the GCRC if an adequate baseline could not be recorded or if there was significant variability (>10% decline in FEV₁) between measurements on the placebo day. None of these excluded patients are included in the analysis for this study.

Oral aspirin challenges were performed using our standard protocol,¹⁴ beginning with 30 mg of aspirin and advancing doses (45 or 60 mg, 60 or 100 mg, 100 or 150 mg, 150 or 325 mg, and 650 mg) every 3 hours during 9-hour days during the following days of their admission. Patients were evaluated hourly or earlier as symptoms prompted. Aspirin challenges induce a spectrum of reactions. These included *classic reactions* with a decline in the FEV₁ of 15% or more combined with a naso-ocular reaction (nasal congestion, rhinorrhea, sneezing, conjunctival itching and/or injection, periorbital edema, and paranasal headache), *pure lower respiratory tract reactions* (wheezing and chest tightness combined with a 20% or greater decline in FEV₁), *naso-ocular reactions only*, or *negative responses*. Less than 20% of patients also had systemic symptoms, such as flush, abdominal cramping pain, hives, or hypotension (in 3 patients). If an aspirin-induced reaction occurred, the patient was treated symptomatically. Typical respiratory reactions lasted between 2 and 4 hours, although reactions occasionally lasted as long as 12 hours. Aspirin doses were then advanced until 650 mg of aspirin was given without adverse effects.

The percent change in FEV₁ from baseline during aspirin challenge was the primary end point of this study. The first analysis looked at all patients, including those patients with naso-ocular reactions. The FEV₁ changes were stratified into 1 of 4 groups: FEV₁ decrease of more than 20%, FEV₁ decrease of 10% to 20%, FEV₁ decrease of less than 10%, or

a completely negative challenge. Patients with completely negative aspirin challenges were not given a diagnosis of AERD but were included for completeness. The purpose of this analysis was to identify those patients with a positive challenge and characterize the degree of their bronchospastic component.

Although at the Scripps Clinic a 15% decline in FEV₁ is the definition of lower airways reaction, there is a spectrum of lower airways reactions. As such, a 13% decrease in FEV₁ would not be considered definitive evidence of bronchospasm, but the patient may meet the criteria for a positive challenge based on a naso-ocular reaction. This is contrasted to the group of patients with a completely negative challenge who had neither naso-ocular reactions nor significant declines in their FEV₁ values of less than 10%. Thus, a second analysis looked *only* at patients who had a defined asthmatic response ($\geq 15\%$ decrease in FEV₁). In these patients, lower airways reactions were stratified into 4 groups based on the magnitude of the FEV₁ change: 15% to 19%, 20% to 29%, 30% to 39%, and 40% or greater. Patients taking LDs in combination with any other controller therapy were compared with all other patients not receiving an LD.

Statistical Analysis

The Pearson χ^2 test was used to evaluate differences in FEV₁ responses among groups defined by medication use; the Fisher exact test was used for this evaluation in instances where the expected cell count was less than 5. A significant result from these tests indicated that overall the distribution of FEV₁ responses is not the same among the groups being compared. A 2-sample *t* test was used to compare the average decline in FEV₁ between patients taking a combination of LDs and systemic corticosteroids and those taking systemic corticosteroids alone. The level of statistical significance was set at $P < .05$. Sample sizes to determine the effects of theophylline, cromolyn sodium, or nedocromil were too small to analyze.

RESULTS

The effects of LDs are seen in Figure 1, which shows that fewer patients taking LDs had a more than 20% decline in FEV₁ compared with those 417 patients not taking an LD (17.7% vs 38.6%; $P < .001$). There were more patients having FEV₁ declines of less than 10% or 10% to 20% in patients receiving LD pretreatment compared with those patients not receiving LDs. Figure 2 evaluated all patients based on their need for systemic corticosteroids, who were therefore likely to have severe asthma. They were also evaluated based on whether they had been receiving treatment with LDs or not. χ^2 analysis demonstrated a significant difference in the pattern of responses, with the predominant difference being fewer severe ($>20\%$ declines in FEV₁) asthmatic responses in those 95 patients who were receiving an LD in conjunction with systemic corticosteroids ($P < .001$).

The effect of LDs was present regardless of the presence of systemic corticosteroids. This can be seen in Figure 2, which

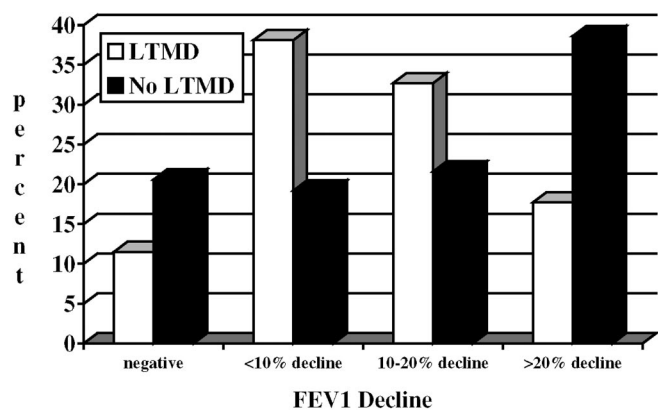


Figure 1. Comparison of forced expiratory volume in 1 second (FEV₁) change in all patients taking leukotriene modifier drugs (LTMDs) (n = 260) with all patients not taking LTMDs (n = 417) ($\chi^2 P < .001$).

shows that in patients taking systemic corticosteroids, the addition of LDs produced a significant shift toward milder asthmatic reactions. The use of systemic corticosteroids in both groups considerably diminished any selection bias. Those patients taking LDs alone were also compared with patients only taking systemic corticosteroids with no significant difference in the pattern of responses. This analysis could have isolated the individual effect of LDs or systemic corticosteroids, but the sample size was too small to detect a significant difference.

When evaluating LD treatment alone (n = 23) compared with control patients who were not receiving any controller therapy (n = 72) during aspirin challenge, no statistical difference was found, although there was a trend toward milder asthmatic reactions in the LD-treated patients. Patients receiving systemic corticosteroids alone (n = 27) had a statistically significant increase in the rate of severe asthmatic reactions ($>20\%$ decline in FEV₁; $P = .05$) compared with control patients receiving no controller therapy. Patients re-

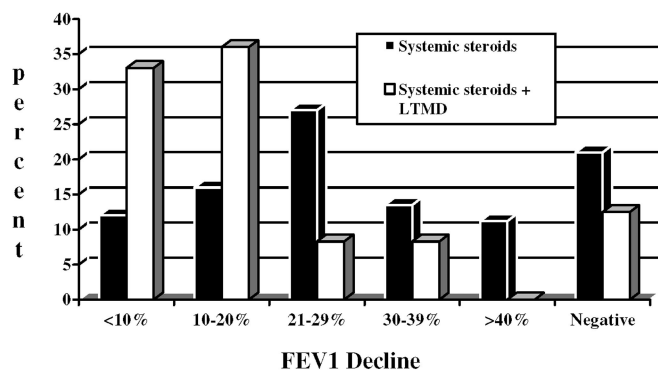


Figure 2. Comparison of forced expiratory volume in 1 second (FEV₁) change in all patients taking systemic corticosteroids without the use of leukotriene modifier drugs (LTMDs) (n = 178) compared with patients taking systemic corticosteroids and LTMDs (n = 95) ($\chi^2_5 P < .001$).

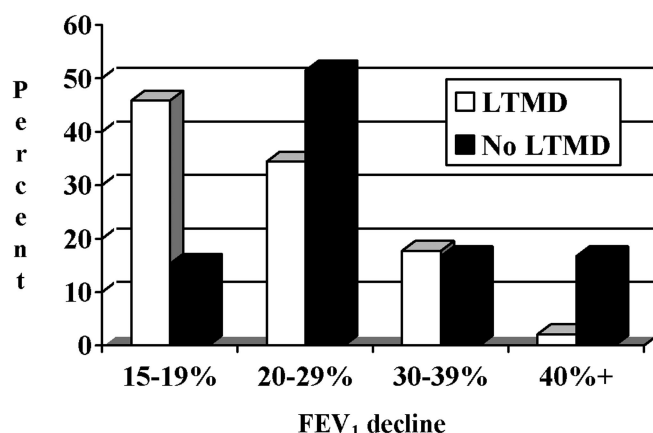


Figure 3. Differences in magnitude of decline in forced expiratory volume in 1 second (FEV₁) in all patients having asthmatic reactions while taking leukotriene modifier drugs (LTMDs) (n = 96) compared with 216 other patients (n = 216) (χ^2_3 $P < .001$).

ceiving long-acting β_2 -agonist, inhaled corticosteroids, LDs, and systemic corticosteroids (n = 42) had less severe reactions than control patients ($P = .05$).

The absolute decrease in FEV₁ for those patients who had an asthmatic reaction was considered for several groups. The average decline in FEV₁ was greater in those taking systemic corticosteroids alone (30%) compared with those taking a combination of LDs and systemic corticosteroids (23%) ($P < .001$). Using a decline in FEV₁ of 40% or more as a cutoff, all patients taking controllers, including systemic corticosteroids and LDs, were compared with those taking controller medications, including systemic corticosteroids and no LDs. No patients (0/36) in the systemic corticosteroid with LDs group had a decline of 40% or more in FEV₁ compared with 16 (19%) of 83 in the systemic corticosteroid but no LD group ($P = .003$). Figure 3 shows the results of stratifying patients based on FEV₁ decline. This analysis looked at all patients who had an asthmatic response (FEV₁ decline $>15\%$). Patients taking an LD alone or in combination with any other controller therapy had a significant shift toward a milder

reaction ($P < .001$). Only 2 of 96 patients had an FEV₁ decline of 40% or more in the LD group.

The results of aspirin challenge in 6 patients receiving both zileuton and a leukotriene receptor antagonist were analyzed independently. The individual responses can be seen in Table 1. Only 1 of 6 had an asthmatic reaction. The limited sample size precluded any statistical analysis.

DISCUSSION

Aspirin desensitization and ongoing therapy have become important options in patients with AERD who need unacceptably high doses of systemic corticosteroids, have aggressive sinus polyp disease, or have a medical indication for aspirin or an NSAID. Many patients with AERD fit into these categories, but physicians who are familiar with aspirin desensitization protocols are generally located only in large, hospital-based settings, which may be geographically inaccessible to AERD patients. Some physicians have become interested in performing aspirin desensitization in outpatient settings.

Our data demonstrated that the most significant addition to a patient's regimen before aspirin challenge was an LD. Such pretreatment shifts the response away from the lower airways and minimizes bronchial reactions when they occur. In our study, nearly all patients taking LDs were taking montelukast, 10 mg/d. It is uncertain whether higher doses of montelukast would provide even further protection of the lower airways, since such a study has not been performed. A smaller number of patients were taking zafirlukast and zileuton.

A limitation of our analysis is the selection bias that exists when retrospectively comparing those patients who have been prescribed one drug vs another. Referring physicians who prescribed an LD likely continued to use these drugs when a response was observed in their patients. Likewise, patients who did not notice a benefit from LDs may have discontinued use of their LD. This would preselect a group of patients already responsive to the blocking effects of LDs. Also, patients taking systemic corticosteroids during aspirin challenge likely represent those patients with the least stable bronchial airways. In patients not receiving controller medications, a milder disease can be reasonably assumed. The

Table 1. Individual Challenge Results in Patients Taking Both a Leukotriene Receptor Antagonist and a 5-Lipoxygenase Inhibitor

No. of patients	LDs	Other controllers	Naso-ocular reaction	Naso-ocular dose	Decrease in FEV ₁ , %	FEV ₁ dose
41	Zileuton and zafirlukast	Inhaled and systemic corticosteroids	Yes	60 mg of aspirin	None	0
47	Zileuton and zafirlukast	Inhaled corticosteroids	Yes	60 mg of aspirin	None	0
210	Zileuton and montelukast	Inhaled and systemic corticosteroids, theophylline	Yes	100 mg of aspirin	29	100 mg of aspirin
228	Zileuton and montelukast	Theophylline, inhaled corticosteroids	None	None	None	None
272	Zileuton and montelukast	Inhaled and systemic corticosteroids, long-acting β -agonist	Yes	60 mg	3	None
274	Zileuton and montelukast	Inhaled and systemic corticosteroids, long-acting β -agonist	No	None	None	None

Abbreviations: LD, leukotriene modifier drug; FEV₁, forced expiratory volume in 1 second.

selection bias represented herein could not be avoided and must be considered in the interpretation of our results. However, these patterns of asthma and their treatment regimens represent real-life presentations of patients expecting aspirin challenge and desensitization and therefore have both scientific and practical implications.

Previously, we have studied the effects of montelukast on 10 patients with AERD. During baseline aspirin challenges without montelukast, 8 of 10 had asthmatic responses ($\geq 15\%$ decline in FEV₁) to aspirin challenge in addition to naso-ocular symptoms.

Montelukast pretreatment prevented asthmatic responses in 4 of the patients and blocked both the naso-ocular and asthmatic responses in 1 individual.¹⁵ One of the 4 patients who had a decline in FEV₁ despite pretreatment with montelukast had a shift in the threshold dose of aspirin from 60 to 325 mg.

Montelukast pretreatment has been shown to significantly protect against aspirin-induced nasal obstruction as measured by acoustic rhinomanometry.¹⁶ Our study showed that although LDs shift the response away from the lower airways, blocking the nasal airways reaction did not occur.¹² This would suggest that complete blocking of the lower airways occurs and that modification, but not blockade, occurs in the upper airway. LDs, which in our study were predominantly the leukotriene receptor antagonists (241/261, 91%), appeared to have a stronger blocking effect in the lower airways compared with the upper airways. This could be because CysLT₁ is present in the lower airway, whereas CysLT₁ and CysLT₂ are both present in the upper airway.¹⁷ Furthermore, during oral aspirin challenges with resulting naso-ocular reactions, both histamine and PGE₂ were also measured in the nasal secretions of the upper airway and are likely to also participate in the upper airway reactions.^{18,19}

The combined effects of zileuton and a leukotriene receptor antagonist on outcomes in aspirin challenge are theoretically important but have not been systematically studied. By partially blocking 5-lipoxygenase and the formation of downstream mediators and blocking the action of CysLT₁ on bronchial smooth muscle, dual therapy with zileuton and a leukotriene receptor antagonist may augment the effect of either agent used alone. In this study of 6 patients taking both agents, only 1 (17%) had an asthmatic response.

Although controller medications significantly increased the safety of conducting aspirin challenges and desensitization, asthmatic reactions still occurred. Of the 676 patients who underwent desensitization, 42 were taking the combination of inhaled and systemic corticosteroids, long-acting β -agonists, and LDs. Nine (17%) of these patients had a more than 20% decrease in FEV₁ during aspirin challenge, despite taking these medications. This statistic must be interpreted in light of our data, which showed that no (0/37) patients taking systemic corticosteroids who were treated with LDs had a decline in FEV₁ of 40% or more. Furthermore, only 2 of 96 of all asthmatic reactions in patients receiving an LD during aspirin challenge had a severe asthmatic response (FEV₁ $\geq 40\%$). Both of these patients received routine treatment

with β -agonists and one with intramuscular epinephrine. Neither required transfer to our intensive care unit.

As the recognition of AERD and the need for aspirin desensitization rises so will the need for physicians to perform aspirin desensitization, many of whom practice primarily in an outpatient setting. Our data demonstrate that LDs will block approximately half of asthmatic reactions completely^{12,15} and, as shown in this study, attenuate the other half of asthmatic reactions. Clinical judgment is necessary when considering the setting in which to perform aspirin challenges, and patients with unstable pulmonary function should probably be referred to centers with experience in aspirin desensitization and access to intensive treatment. However, for most patients, our data showed that LD pretreatment predicts either no change or a much milder decrease in FEV₁ so that outpatient aspirin challenge and desensitization have become safe and viable options.

REFERENCES

1. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ*. 2004;328:434.
2. Fahrenholz JM. Natural history and clinical features of AERD. *Clin Rev Allergy Immunol*. 2003;24:113–124.
3. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2003;111:180–186.
4. Stevenson DD. Aspirin desensitization in patients with AERD. *Clin Rev Allergy Immunol*. 2003;24:159–168.
5. Szczeklik A, Sanak M, Nizankowska-Mogilnicka E, Kielbasa B. Aspirin intolerance and the cyclooxygenase-leukotriene pathways. *Curr Opin Pulm Med*. 2003;10:51–56.
6. Sanak M, Szczeklik A. Genetics of aspirin induced asthma. *Thorax*. 2000;55:S45–S47.
7. Kowalski ML, Pawliczak R, Wozniak J, et al. Differential metabolism of arachidonic acid in nasal polyp epithelial cells cultured from aspirin-sensitive and aspirin-tolerant patients. *Am J Respir Crit Care Med*. 2000;161:391–398.
8. Dafferen PJ, Mulenberg D, Hugli TE, Stevenson DD. Association of urinary leukotriene E₄ excretion during aspirin challenges with severity of respiratory responses. *J Allergy Clin Immunol*. 1999;104:559–564.
9. Picado C, Castillo JA, Montserrat JM, Agusti-Vidal A. Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. *Eur Respir J*. 1989;2: 127–129.
10. Ghannam RD, Schreier L, Vanselow NA. Fatal bronchial asthma: an analysis of terminal treatment in twenty cases. *Ann Allergy*. 1968;26:194–205.
11. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol*. 2003;111:913–921.
12. White AA, Stevenson DD, Simon RA. The blocking effect of essential controller medications during aspirin challenges in patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2005;95:330–335.
13. Berges-Gimeno MP, Simon RA, Stevenson DD. The effect of leukotriene modifier drugs on aspirin-induced asthma and rhi-

-
- nitis reactions. *Clin Exp Allergy*. 2002;32:1491–1496.
14. Stevenson DD, Simon RA, Zuraw BL. Sensitivity to aspirin and nonsteroidal anti-inflammatory drugs. In: Adkinson NF, Yuninger JW, Busse WW et al, eds. *Middleton's Allergy: Principles and Practice*. 6th ed. Philadelphia, PA: Mosby; 2003: 1695–1710.
15. Stevenson DD, Simon RA, Mathison DA, Christiansen SC. Montelukast is only partially effective in inhibiting aspirin responses in aspirin-sensitive asthmatics. *Ann Allergy Asthma Immunol*. 2000;85:477–482.
16. Micheletto C, Tognella S, Visconti M, et al. Montelukast 10mg improves nasal function and nasal response to aspirin in ASA-sensitive asthmatics: a controlled study vs placebo. *Allergy*. 2004;59:289–294.
17. Heise CE, O'Dowd BF, Figueroa DJ, et al. Characterization of the human cysteinyl leukotriene 2 receptor. *J Biol Chem*. 2000; 275:30531–30536.
18. Ferreri NR, Howland WC, Stevenson DD, Spiegelberg HL. Release of leukotrienes, prostaglandins and histamine into the nasal secretions of aspirin-sensitive asthmatics during reactions to aspirin. *Am Rev Respir Dis*. 1988;137:847–854.
19. Fischer AR, Rosenberg MA, Lilly CM, et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. *J Allergy Clin Immunol*. 1994;94: 1046–1056.
- Requests for reprints should be addressed to:*
Andrew White, MD
Department of Allergy and Immunology
Naval Medical Center San Diego
2650 Stockton Rd
Building 624
San Diego, CA 92106
E-mail: drew_white@hotmail.com
-