

Prevention and Treatment of Reactions to NSAIDs

Ronald A. Simon

*Division of Allergy, Asthma, and Immunology, The Scripps Clinic and Research Institute,
10666 North Torrey Pines Road, La Jolla, CA 92037, E-mail: rsimon@scrippsclinic.com*

Abstract

Avoidance of ASA and other NSAIDs prevents the reactions and careful attention to clinical history along with patient education are important. However, blanket advice to avoid all NSAIDs is no longer reasonable. Except for AERD and chronic urticaria, cross-reactivity with other NSAIDs does not occur. A physician can definitively prove this by giving the patient another NSAID in their office and observing no reaction. Furthermore, for patients with AERD and chronic urticaria, they can be given the new selective COX-2 inhibitors (rofecoxib and celecoxib) without any cross-reactivity. All AERD patients can be desensitized to ASA and treated with ASA indefinitely. However, ASA desensitization in chronic urticaria is not possible.

Underlying mild and moderate AERD responds well to topical and systemic corticosteroids and leukotriene modifiers. However, the severe forms of the disease should be desensitized to ASA and treated with this drug on a long term basis. In the future, new drugs that prevent eosinophil activation and chemotaxis or enhance eosinophil apoptosis are likely to be useful. Specific blockers of the second cystLT receptor would also be useful. Ultimately as the genetics of these heterogeneous disorders are unraveled, gene substitution therapy may be the ultimate answer.

Index Entries:

Aspirin (ASA); non-steroidal antiinflammatory disease (NSAID); aspirin-exacerbated respiratory disease (AERD); cyclooxygenase-2 (COX-2); cysteinyl leukotriene receptor (cysLTR).

Table 1
Oral Challenges with ASA to Detect Probable IgE-Mediated Cutaneous and Systemic Reactions Which Previously Occurred After Ingestion of ASA or an Individual NSAID in Patients who Otherwise Appeared to be Normal

Historical Reaction Types	Responses	Initial Dose ASA (mg)	Advance Dose Schedule	Interval Between Challenges (min)	Range Reaction Dose (mg)
Acute urticaria to one NSAID	None	81 or 325	None	Observe for 4 h	
Acute urticaria ^a	Urticaria/angioedema	20	Doubling	30	30–60
Anaphylaxis ^b	Anaphylaxis	3	Doubling	30	20–30

^aPerformed in outpatient office with iv line in place

^bPerformed in ICU with iv line in place and cardiovascular monitoring

Avoidance of ASA and NSAIDs

Avoidance of ASA and all crossreacting NSAIDs prevents respiratory and urticarial crossreacting events in previously sensitized patients. Avoidance of the specific NSAID or ASA that induced the original reaction is important in preventing recurrence of acute urticarial reactions, anaphylaxis, aseptic meningitis, and hypersensitivity pneumonitis. Unless patients are known or suspected to have reactions to ASA and NSAIDs, have underlying nasal polyps, sinusitis, and asthma, or chronic urticaria, it is unreasonable to advise them to avoid all NSAIDs. For those patients who are crossreactive among the NSAIDs, patient education should include a discussion of adverse effects, crossreactivity between ASA and COX-1-inhibiting NSAIDs, and reaction potential of new drugs. Appropriate charting, flags on the front of the written or electronic medical records, and communication among health care professionals are also important. For prescribed NSAIDs, the information about NSAID sensitivity in the pharmacy computer is generally the last line of defense before a reaction to a newly prescribed NSAID.

Use of Oral Challenges to Determine Which NSAIDs to Avoid

In patients with single NSAID-induced urticaria, some blended reactions, anaphylaxis, hypersensitivity pneumonitis and aseptic meningitis, it is not necessary to avoid dissimilar NSAIDs, which cannot be immunologically recognized (1,2). Strategies for challenging patients with these conditions using NSAIDs, which have never been administered previously, have been developed and can be performed in the outpatient office (*see* Table 1).

Identification of Anaphylactic Sensitivity to ASA or NSAIDs

In vitro testing and immediate cutaneous testing have proven to be valuable in detecting specific NSAIDs that might induce anaphylaxis during the next exposure. Drug challenges for anaphylaxis carry a risk, since the end point may be a severe systemic reaction. For the most part, physicians rely upon a history of the prior anaphylactic reactions. Unfortunately, faulty patient memory with distortions of remembered events may lead to false conclusions about the role of NSAIDs in the prior reaction. However, one should suspect single-entity NSAID anaphylaxis if the reaction was to one NSAID, and especially if the patient has

tolerated another COX-1 inhibitor since their last reaction. Since single-NSAID-induced anaphylaxis is the expected sequence, as is often the case, and the patient has avoided all NSAIDs, the worst reaction that would occur with an oral challenge would be urticaria and (peripheral) angioedema. If one is prepared to treat this in the office, then with proper informed consent, one can proceed with a graded-dose challenge to any other NSAID of choice. For extra safety an intravenous (iv) line should be in place in case iv diphenhydramine (50 mg) or ranitidine (50 mg) is needed to control more severe reactions (*see* Table 1).

Oral challenges for anaphylactic reactions to drugs, suspected of inducing anaphylaxis, have been conducted and reported (3). However, indications for these challenges are limited (4). For all practical purposes, aspirin is the only NSAID that does not have a substitute NSAID that could inhibit platelets and prevent arterial thrombosis. Therefore, only aspirin falls into the category of being worth the risk of inducing anaphylaxis to determine whether or not the patient is still allergic to ASA (*see* Table 1). For suspected NSAID-induced anaphylactic reactions, challenging with a full therapeutic dose of a structurally different NSAID, and documenting no reaction to the second NSAID is the preferred strategy for providing a safe NSAID for therapy (2,5). For suspected ASA-induced anaphylaxis, in cases where ASA may be needed for anticoagulation, oral challenges can start with small doses (3 mg) of ASA and be conducted in an intensive care unit (ICU) with iv lines in place, cardiovascular monitoring and with the patient's informed consent (2,6). Table 1 contains details for such challenges. Most of the time, challenges to ASA are completely negative, because of a misinterpreted history or diminished sensitivity over time. However, if the challenge is positive, rapid desensitization with ASA can be attempted with a top dose of 81 mg/d being the desired end point (2).

Alternative Agents for Analgesia

Our studies have shown that patients with AERD patients can tolerate up to 650 mg of acetaminophen safely. However, 31% of AERD patients experienced reactions to 1,000 mg of acetaminophen, although these reactions were milder than reactions to aspirin (7). These patients can also tolerate non-acetylated forms of aspirin such as magnesium, sodium, and choline salicylate or up to 1500 mg of disalcid (8).

Avoidance of Non-COX-1 Inhibitors

Our studies have shown that patients with AERD do not crossreact with tartrazine (FD&C yellow #5), hydrocortisone, sulfites, or monosodium glutamate (MSG) (9–12).

Avoidance of COX-2 Inhibitors

Theoretically, highly specific COX-2 inhibitors should not crossreact in AERD patients. COX-2 is an inducible enzyme formed in inflammatory cells at sites of inflammation. Since COX-1 is synthesized by most mammalian cells and is present in virtually all our body's cells, which continue to produce PGE₂ in the presence of a selective COX-2 inhibitor, the decrease in PGE₂ caused by COX-2 inhibition should not be significant. Therefore COX-2 inhibitors should not be able to induce a reaction by the depletion of PGE₂. However, since patients with AERD were not given COX-2 inhibitors in pre-approval clinical trials, the FDA required that a warning be placed in the package insert of celecoxib and rofecoxib (the first two highly specific COX-2 inhibitors approved in the United States in 1999). The warning stated that practitioners should not prescribe these agents in aspirin-sensitive individuals. However, our studies in 60 consecutive AERD patients who were undergoing negative challenges with COX-2 inhibitors (rofecoxib and celecoxib) have shown with greater than 95% confidence that these agents can safely be given to patients with AERD (13,14).

Unfortunately, the situation is not as clear in patients with urticaria induced by more than one COX-1 inhibitor. One report has documented that 5/20 (25%) of such patients also had urticaria/angioedema during challenges with celecoxib, and 1/24 (4.1%) experienced an urticarial reaction during a challenge with rofecoxib (15). The report does not state whether the reaction to the COX-2 inhibitor was with the first dose of the COX-2 inhibitor. This is critical because single-entity, presumed IgE-mediated reactions to COX-2 inhibitors have been reported. Furthermore, three other recent reports that did not observe crossreactivity to the highly selective COX-2 inhibitor rofecoxib in subjects with a history of COX-1-inhibitor provoked cutaneous reactions. Pacor et al. (16) studied 104 subjects with a history of cutaneous reactions to COX-1 inhibitors. These patients underwent double-blind placebo-controlled challenge with rofecoxib, and none reacted. In another publication by Quiralte et al. (17), 15 subjects underwent placebo-controlled oral challenges with at least two COX-1 inhibitors with urticarial reactions to both NSAIDs. At a later time, they underwent single-blind placebo-controlled challenges with rofecoxib, and none reacted. In a third paper by Berges-Gimeno et al. (18), 33 patients with prior urticaria/angioedema reactions to at least two COX-1 inhibiting NSAIDs underwent single-blind challenges with rofecoxib, and none reacted. We have not observed cutaneous reactions to COX-2 inhibitors in our COX-1-sensitive chronic idiopathic urticaria patients, although this group has not been rigorously evaluated in a research study at the Scripps Clinic. A further discussion of this perplexing finding is found in the section of this series devoted to urticarial and angioedema reactions.

Patients With AERD: Treatment of Respiratory Reactions

Severity of reactions to ASA can usually be reduced by pretreatment with cysLT_1 -receptor antagonists (19). Therefore, with the simulta-

neous use of montelukast and zafirlukast, it is much easier to perform oral ASA challenges in AERD patients. Naso-ocular reactions continue to occur, but bronchospasm is blocked about 50% of the time, or usually—but not always—modified. After reactions to ASA occur, rapid intervention with the following treatment is recommended, depending upon the responses in various shock organs. For bronchospasm, inhaled beta agonists using a nebulizer, delivering up to five inhalations every 5–10 min, may be continued for a number of hours. For laryngospasm, epinephrine SQ and racemic epinephrine 0.25 mg/mL by nebulizer is usually helpful. For nasal congestion with paranasal headache, topical oxymetazoline is an effective rapidly acting decongestant and oral antihistamines are also useful. For systemic reactions, such as gastric cramping pain and cutaneous flushing, iv H_1 and H_2 blockers are helpful in stopping the reactions. Topical antihistamine and decongestant solutions can be instilled in the conjunctivae. If asthma progresses or persists while the patient is tiring, despite standard anti-asthmatic treatment, transport to an intensive care unit, where intubation and mechanical ventilation are available, should be activated.

Aspirin Desensitization in Respiratory Reactors

Desensitization is used here in its broadest sense, and refers to eliminating respiratory reactions to ASA by repeated and increasing exposure to oral ASA (20,21). In 1922, Widal (22) was the first physician to report desensitization to ASA. All AERD patients can be desensitized to ASA. The reader is referred to the section of this series on ASA desensitization.

Aspirin Desensitization in Urticarial Reactors

For patients with single-entity COX-1-inhibitor sensitivity (urticaria/angioedema or anaphylaxis) avoidance of the offending NSAID

and use of any other COX-1 or COX-2 inhibitor is the most practical approach. However, since these reactions are likely to be IgE-mediated, graded-dose oral challenge and desensitization (as can be done for penicillin hypersensitivity) is the alternative. Beginning with 3–10 mg of ASA and increasing the dose every 30 min is the proper course. An iv line should be in place and rapid infusion of diphenhydramine and ranitidine should be given if a reaction occurs (*see* Table 1). Clinical experience, rather than published studies, has addressed this approach.

A second situation involves patients with chronic idiopathic urticaria who have reacted to ASA and other NSAIDs (crossreacting urticaria patients). We have attempted ASA desensitization treatment in patients with chronic idiopathic urticaria and ASA sensitivity (23). Although we were universally successful at acutely desensitizing 25 patients to 650 mg aspirin sensitivity (ASA); whether we withheld further ASA or attempted regular ASA treatment; hives returned (with a vengeance) within 24 h. The resulting hives persisted without ASA doses for a number of days, and usually required a burst of prednisone to bring them under control. Any attempt to continue ASA, after the flare of hives reappeared, was associated with increasing urticaria rather than ASA desensitization. Therefore unlike patients with AERD, ASA-desensitization treatment is not an option for patients with chronic idiopathic urticaria. There are no published studies concerning (and we have not attempted) ASA-desensitization treatment for the group of patients who have COX-1-inhibitor-induced urticaria/angioedema without chronic idiopathic urticaria.

Treatment of Underlying Aspirin-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease (AERD) is an ongoing inflammation of both the upper and lower respiratory tract. Asthma activity increases with acute and chronic sinus

infections (24). Therefore, a major goal in controlling ASA disease, and its component of corticosteroid-dependent asthma, are strategies to reduce inflammation in the upper and lower airways. Prevention of nasal polyp formation, secondary sinusitis, and worsening asthma are important goals. High doses of topical corticosteroids, by both nasal insufflations and oral inhalation, reduce inflammation and retard nasal polyp formation in some patients (25). Unfortunately, inflammation in other AERD patients cannot be controlled by topical corticosteroids alone. Bursts of systemic corticosteroids are usually required during infectious episodes and to shrink nasal polyps, reestablishing temporary sinus drainage and decreasing infiltration of eosinophils. Some patients gradually convert to a dependency on monthly bursts of systemic corticosteroids and then continuous systemic corticosteroid therapy. Side effects from corticosteroids then become an important component of disease management. In our population of 300 AERD patients referred to the Scripps Clinic for aspirin desensitization, the following use of systemic corticosteroids were recorded: burst in 134 (45%), daily or alternate day in 95 (32%), and none in 71 (23%) patients (26).

Long courses of broad-spectrum antibiotics are usually required to treat purulent nasal secretions (27). However, the same problem with identifying causative microorganisms, which is found in other patients with chronic sinusitis, also dominates the discussions about patients with AERD. If medical treatment fails, patients should undergo sinus CAT scans and be referred to a competent surgeon for consideration of sinus drainage, polypectomies, and removing infected mucosa (Lanza, 1992 #135). In fact, sometimes it is impossible to avoid surgery because the mass of polyps in the nose is unresponsive to systemic corticosteroids and completely obstructing the nasal passages. Alternatively, systemic corticosteroids shrink nasal polyps, but side effects from these drugs preclude continuous use. Patients with AERD

do have remissions after careful sinus and polyp surgery (28). In a study of 22 patients with AERD, who underwent endoscopic sinus surgery, and were followed for 1 yr, improvement in pulmonary function tests, need for topical and systemic corticosteroids, and quality of life were all recorded (29). However, in general, AERD patients have been shown to have poorer outcomes with respect to long-term remissions after sinus surgery, when compared to ASA-tolerant patients (30,31). This may be caused by the sheer mass of polypoid tissue found in AERD patients. Kennedy reported that AERD patients have the same long-term post-surgical outcomes as ASA-tolerant patients, if they have the same degree of mucosal disease (31). However, aggressive reformation of new polypoid tissue, after sinus surgery, continues to be a problem in many AERD asthmatics. In patients referred to the Scripps Clinic, the average length of time between sinus/polyp operations was only 3 yr (32).

Both zileuton and montelukast have been evaluated in the treatment of AERD in double-blind, placebo-controlled treatment trials (33–35). For those physicians, who treat AERD with zileuton, partial control of the upper and lower airway is usually the outcome. In patients treated with montelukast, variable responses are characteristic, ranging from no obvious therapeutic benefit to complete control of the disease (34). Use of both a 5-LO inhibitor and a $cys\ LT_1$ -receptor antagonist simultaneously is beneficial in some patients. Since availability of leukotriene-modifier drugs (LTMDs) in the winter of 1998, of 192 AERD patients referred to the Scripps Clinic for ASA desensitization between 1998 and 2000, 108 (56%) were taking LTMDs at the time of admission (75 montelukast, 21 zafirlukast, and 12 zileuton). Since then, the use of LTMDs, particularly montelukast, has almost become routine in the management of patients with AERD. Between January 2001 and July 2002, 112 patients were referred to the Scripps Clinic for ASA desensitization.

Of these patients, 89/112 (80%) were taking leukotriene-modifier drugs (LTMDs): 70/89 (77%) were taking montelukast, 15/89 (17%) were taking zafirlukast, and 4/89 (4%) were taking zileuton. In three-quarters of the patients taking zileuton, this LTM was added to a controller program that already included montelukast, with the theory that blocking leukotriene production and receptors was better than either alone. Therefore, the percentage of AERD patients, who were taking an LTMD at the time of entry to our research programs, had increased from 56% 1998–2000 to 80% from 2000–2002.

ASA Desensitization Treatment for AERD

In 1980, Stevenson, Simon, and Mathison first reported the use of aspirin to treat patients with AERD (36). When one first considers this therapeutic approach, the initial perception is that it does not make any sense. Why would one give daily aspirin to an aspirin-sensitive asthmatic? However, the idea grew out of the observation of one patient who had just been desensitized to aspirin and noted clearing of her nasal passages and the return of smell. Because of this initial clinical observation, the first two patients were treated with daily ASA, 325 mg BID for 1 yr. During that time, both patients had fewer sinus infections, enjoyed smell, improved nasal congestion and either stopped alternate-day prednisone or decreased it by one-half (36). Stevenson et al. (37) then studied the efficacy of ASA-desensitization treatment in 25 ASA-sensitive asthmatics in a 7-mo, randomized, double-blind, placebo-controlled crossover trial. Patients experienced significant improvement in nasal symptom scores and decreased use of intranasal corticosteroids during the ASA treatment arm. This first study undertreated with ASA in the sense that doses of ASA averaged 325 mg BID. We now know that twice that dose is appropriate treatment in the majority of patients. Nevertheless, improvement in nasal symptoms and a

reduced need for topical nasal corticosteroids pointed the way toward the main effects of this treatment. Using larger doses of ASA (650 mg BID on average) over a number of years, several additional studies have shown a significant reduction in respiratory disease activity, need for further sinus surgery, reduction in hospitalizations and requirement for systemic corticosteroids (p values 0.004 – <0.0001) (32,38). Side effects from daily ASA therapy were usually limited to gastric irritation, but in 13% of treated patients ASA had to be discontinued because of this complication (32). In unpublished data from our most recent series of 172 AERD patients, who were followed from 1995 to 2000 after ASA desensitization and daily ASA treatment, the following results were observed: 24 (14%) discontinued ASA because of side effects (usually gastritis), and 31 (18%) failed to respond to questionnaires, discontinued ASA for reasons other than side effects, or discontinued ASA because they believed it was not an effective treatment for their respiratory disease. The remaining 117/172 (68%) responded to ASA treatment. In Italy, treatment of nasal polyposis with daily nasal application of ASA-lysine solution has been successful (39).

Selection of patients for ASA-desensitization therapy should include all AERD patients, except those whose disease is controlled with topical corticosteroids (25) and LTMDs (33–35). Since ASA-desensitization treatment is particularly effective in reducing upper-airway mucosal congestion and reducing nasal polyp formation, ideal candidates are patients with recurrent or chronic sinusitis and nasal polyps. However, by substantially reducing the number of sinusitis episodes, a concomitant reduction in flares of asthma and a need for systemic corticosteroids are also observed. Thus, although ASA-desensitization treatment appears to be predominantly directed at upper-airway inflammation, there are positive, indirect effects on the lower airways.

Future Treatment of AERD

In view of the heterogeneous inflammatory pathways that are active in this disease, it should not be surprising that AERD patients experience variable responses to current medical therapy. Except for the almost universal benefit of high-dose systemic corticosteroids, AERD patients do not always benefit from interventions with only a leukotrine modifier, antihistamines alone, topical and low-dose systemic corticosteroids alone, and aspirin desensitization as the only intervention. In fact, the optimal treatment regimen is to use of all of these interventions, except daily systemic corticosteroids. Therefore, it seems logical that incremental advances will occur over the ensuing decade, when additional inflammatory blockers will be invented and undergo appropriate clinical trials. Molecules that can prevent eosinophil activation and chemotaxis or enhance eosinophil apoptosis are likely to enhance our treatment options. Similarly, mast-cell stabilizers or specific blockers of mast-cell products may also be beneficial. With the discovery of a second cysLT receptor, which cannot be blocked by currently available cysLT₁ antagonists, efforts to develop a new generation of cyst LT₂-receptor antagonists also seems worthwhile. As specific genes that regulate synthesis of inflammatory enzymes are revealed, gene-substitution treatment is a longer-term project, which might substantially correct the basic disease states of AERD.

References

1. Stevenson, D. and Simon, R. A. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs, in *Allergy: Principles and Practice*, Middleton, Jr., E., Ellis, E. F., Yunginger, J. W., Reed, C. E., Adkinson, N. F., Jr., and Busse, W. W., eds., vol. 2, 5th ed., Mosby, St. Louis, 1998, pp. 1225–1234.
2. Stevenson, D. D. (2001), Anaphylactic and anaphylactoid reactions to aspirin and nonsteroidal antiinflammatory drugs. *Immunology and Allergy Clinics of North America* **21**, 745–768.
3. Czerniawska-Mysik, G. and Szczeklik, A. (1981), Idiosyncrasy to pyrazolone drugs. *Allergy* **36**, 381–384.

4. Stevenson, D. D. (1995), Aspirin and nonsteroidal antiinflammatory drugs. *Immunology and Allergy Clinics of North America* **15**, 529–549.
5. Quiralte, J., Blanco, C., Castillo, R., Ortega, N., and Carrillo, T. (1997), Anaphylactoid reactions due to nonsteroidal antiinflammatory drugs: clinical and crossreactivity studies. *Ann. Allergy Asthma Immunol.* **78**, 293–296.
6. Stevenson, D. (1998), Adverse reactions to nonsteroidal antiinflammatory drugs. *N. American Clinics Allergy and Immunology* **18**:4, 773–798.
7. Settignano, R. A. and Stevenson, D. D. (1989), Cross sensitivity with acetaminophen in aspirin sensitive asthmatics. *J. Allergy Clin. Immunol.* **84**, 26–33.
8. Stevenson, D. D., Hougham, A., Schrank, P., Goldlust, B., and Wilson, R. (1990), Disalcid cross-sensitivity in aspirin sensitive asthmatics. *J. Allergy Clin. Immunol.* **86**, 749–758.
9. Stevenson, D. D., Simon, R. A., Lumry, W. R., and Mathison, D. A. (1986), Adverse reactions to tartrazine. *J. Allergy Clin. Immunol.* **78**, 182–191.
10. Stevenson, D. D. and Simon, R. A. (1987), Sulfite induced asthma, in *Current Therapy in Internal Medicine*, Bayless T. M., Brain M. C., and Cherniack, R. M., eds., 14–20, 1987.
11. Feigenbaum, B. A., Stevenson, D. D., and Simon, R. A. (1995), Lack of cross-sensitivity to IV hydrocortisone in aspirin-sensitive subjects with asthma. *J. Allergy Clin. Immunol.* **96**, 545–548.
12. Woessner, K., Simon, R. A., and Stevenson, D. D. (1999), Monosodium glutamate sensitivity in asthma. *J. Allergy Clin. Immunol.* **104**, 305–310.
13. Stevenson, D. and Simon, R. A. (2001), Lack of crossreactivity between rofecoxib and aspirin in aspirin sensitive asthmatic patients. *J. Allergy Clin. Immunol.* **108**, 47–51.
14. Woessner, K., Simon, R. A., and Stevenson, D. D. (2002), The safety of celecoxib in aspirin exacerbated respiratory disease. *Arthritis Rheum.* **46**, 2201–2206.
15. Sanchez-Borges, M., Capriles-Hulett, A., Caballero-Fonseca, F., and Ramon-Perez, C. (2001), Tolerability to new Cox-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann. Allergy Asthma Immunol.* **87**, 201–204.
16. Pacor, M., Di Lorenzo, G., Biasi, D., Barbagallo, M., and Corrocher, R. (2002), Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and/or non-steroidal antiinflammatory drugs. *Clin. Exp. Allergy* **32**, 397–400.
17. Quiralte, J. Sd. S. P. and Florido, J. J. (2002), Safety of selective cyclooxygenase-2 inhibitor rofecoxib in patients with NSAID-induced cutaneous reactions. *Ann. Allergy Asthma Immunol.* **89**, 63–66.
18. Berges-Gimeno, M., Camacho-Garrido, E., Garcia-Rodriguez, R. M., Martin-Garcia, C., Alfaya, T., and Hinojosa, M. (2001), Rofecoxib: safe in NSAID intolerant patients. *Euro. J. Allergy Clin. Immunol.* **56**, 1017–1018.
19. Berges-Gimeno, M., Simon, R. A., and Stevenson, D. D. (2002), The effect of leukotriene modifier drugs on asa-induced asthma and rhinitis reactions. *Clin. Exp. Allergy*.
20. Zeiss, C. R. and Lockey, R. F. (1976), Refractory period to aspirin in a patient with aspirin-induced asthma. *J. Allergy Clin. Immunol.* **57**, 440–448.
21. Pleskow, W. W., Stevenson, D. D., Mathison, D. A., Simon, R. A., Schatz, M., and Zieger, R. S. (1982), Aspirin desensitization in aspirin sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. *J. Allergy Clin. Immunol.* **69**, 11–19.
22. Widal, M. F., Abrami, P., and Lermeyez, J. (1922), Anaphylaxie et idiosyncrasie. *Presse Med.* **30**, 189–192.
23. Mathison, D. A., Lumry, W. R., and Stevenson, D. D. (1982), Aspirin in chronic urticaria and/or angioedema: studies of sensitivity and desensitization. *J. Allergy Clin. Immunol.* **69**, 135.
24. Slavin, R. G. (1992), Asthma and sinusitis. *J. Allergy Clin. Immunol.* **90**, 534–537.
25. Mastalerz, L., Milewski, M., Duplaga, M., Nizankowska, E., and Szczeklik, A. (1997), Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. *Allergy* **52**, 895–900.
26. Berges-Gimeno, M., Simon, R. A., and Stevenson, D. D. (2002), The natural history and clinical characteristics of aspirin exacerbated respiratory disease. *Ann. Allergy Asthma Immunol.* **89**, 474–478.
27. Mathison, D. A. and Stevenson, D. D. Aspirin sensitivity in rhinosinusitis-asthma, in *Current Therapy in Allergy, Immunology and Rheumatology*, Lichtenstein, L. M. and Fauci, A. S., eds., vol. 1, 1st ed., Mosby, St. Louis, 1985, pp. 27–30.
28. McFadden, E. A., Woodson, B. T., Fink, J. N., and Toohill, R. J. (1997), Surgical treatment of aspirin triad sinusitis. *Am. J. Rhinol.* **11**, 263–270.
29. Nakamura, H., Kawasaki, M., Higuchi, Y., and Takahashi, S. (1999), Effects of sinus surgery on asthma in aspirin triad patients. *Acta Otolaryngol.* **119**, 592–598.
30. Schaitkin, B., May, M., Shapiro, A., Fucci, M., and Mester, S. J. (1993), Endoscopic sinus surgery: 4-year follow-up on the first 100 patients. *Laryngoscope* **103**, 1117–1120.
31. Kennedy, D. W. (1992), Prognostic factors, outcomes and staging in ethmoid sinus surgery. *Laryngoscope* **102**, 1–18.
32. Stevenson, D. D., Hankammer, M. A., Mathison, D. A., Christensen, S. C., and Simon, R. A. (1996), Long term ASA desensitization-treatment of aspirin sensitive asthmatic patients: clinical outcome studies. *J. Allergy Clin. Immunol.* **98**, 751–758.
33. Dahlen, B. N. E., Szczeklik, A., Zetterstrom, O., Bochenek, G., Kumlin, M., Mastalerz, L., et al. (1998), Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspi-

- rin-intolerant asthmatics. *Am. J. Respir. Crit. Care Med.* **157**, 1187–1194.
34. Dahlen, S., Malstrom, K., Nizankowska, E., Dahlen, B., Kuna, P., Kowalski, M., et al. (2002), Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist. A randomised, double blind, placebo controlled trial. *Am. J. Respir. Crit. Care Med.* **165**, 9–14.
35. Dahlen, B. (2000), Treatment of aspirin-intolerant asthma with antileukotrienes. *Am. J. Respir. Crit. Care Med.* **161**, S137–S141.
36. Stevenson, D. D., Simon, R. A., and Mathison, D. A. (1980), Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. *J. Allergy Clin. Immunol.* **66**, 82–88.
37. Stevenson, D. D., Pleskow, W. W., Simon, R. A., Mathison, D. A., Lumry, W. R., Schatz, M., et al. (1983), Treatment of aspirin sensitive asthma rhinosinusitis with aspirin. *J. Allergy Clin. Immunol.* **71**:(2), 272–280.
38. Sweet, J. A., Stevenson, D. D., Simon, R. A., and Mathison, D. A. (1990), Long term effects of aspirin desensitization treatment for aspirin sensitive rhinosinusitis asthma. *J. Allergy Clin. Immunol.* **86**, 59–65.
39. Patriarca, G., Bellioni, P., Nucera, E., Schiavino, D., Papa, G., Schinco, G., et al. (1991), Intranasal treatment with lysine acetylsalicylate in patients with nasal polyposis. *Ann. Allergy* **67**, 588–593.