

Early effects of aspirin desensitization treatment in asthmatic patients with aspirin-exacerbated respiratory disease

M. Pilar Berges-Gimeno, MD*†; Ronald A. Simon, MD*‡; and Donald D. Stevenson, MD*‡

Background: Aspirin (ASA)-exacerbated respiratory disease (AERD) is characterized by aggressive inflammation of the respiratory tract and often requires topical and/or systemic corticosteroids to maintain partial control of this disease. Previous studies have revealed that ASA desensitization and subsequent treatment with ASA is associated with clinical improvement in AERD.

Objective: The aim of the present study was to determine the effect of daily ASA treatment for the first 4 weeks after ASA desensitization.

Methods: Thirty-eight patients underwent ASA oral challenge followed by ASA desensitization and daily ASA therapy. Changes in nasal and asthma symptoms, combined with changes in oral prednisone, were recorded daily during 4 weeks before and after desensitization. Severity of symptoms ranged from a scale of 1 to 5 (1 = asymptomatic and 5 = most severe symptoms). For statistical analyses the sum of nasal symptoms and asthma symptoms was calculated. Olfactory scores were also analyzed.

Results: Nasal and asthma symptom scores, as well as olfactory scores, improved significantly ($P < 0.0001$). For the 15 patients taking prednisone, their mean doses decreased from 10.7 to 5.9 mg daily ($P = 0.0003$).

Conclusions: Our study suggests that ASA desensitization treatment is effective during the first 4 weeks of daily treatment with ASA.

Ann Allergy Asthma Immunol 2003;90:338–341.

INTRODUCTION

Aspirin (ASA)-exacerbated respiratory disease (AERD) is a disease characterized by respiratory mucosal inflammation and bronchospasm.^{1,2} The pathogenesis of AERD is not mediated by allergic mechanisms but is instead a multifaceted inflammatory disease, in which alterations in arachidonate metabolism appear to play a prominent role.³

In 1922, Widall et al,⁴ described the association between ASA sensitivity and nasal polyposis, and his group was the first to conduct ASA desensitization. Subsequently, in 1976 Zeiss and Lockey⁵ and in 1977 Pasargiklian et al⁶ were able to desensitize AERD patients to indomethacin and ASA. However, it was not until 1980, that Stevenson et al⁷ reported two patients with AERD who became refractory to ASA after ASA-induced respiratory reactions. Both patients were then discharged from the hospital and treated with daily ASA while continuing their state of desensitization. Over the next year these patients experienced improvement in nasal symptoms, reduction in sinusitis episodes, and a reduced need for systemic corticosteroids. On the basis of that original observation, our hypothesis was that ASA desensitization treatment was

an effective treatment but probably involved changes in inflammation over at least 1 year of treatment.

Since then, several studies have reported that after ASA desensitization, if ASA is taken daily, patients frequently experience improvement in their chronic respiratory symptoms.^{8–10} In 1996, Stevenson et al¹⁰ reported that 65 patients with AERD, who were treated with an average of 1,300 mg of ASA daily, experienced significant improvement in their disease and reduction in use of systemic and nasal corticosteroids, when measured at 1 to 3 years and 3 to 6 years of followup. In this article,¹⁰ we pointed out that double-blind, placebo-controlled studies of the effects of ASA desensitization treatment could not be conducted because nasal decongestion occurred in most patients at the time of acute desensitization. Further, 48 to 72 hours after discontinuing ASA, nasal congestion returned, thus unblinding the study.

The purpose of this study was to determine whether or not ASA desensitization and treatment with daily ASA provides clinical therapeutic benefit during the first month of treatment. To accomplish this goal, we designed a study in known AERD patients, such that before and after symptom scores, as well as concomitant reduction in use of systemic corticosteroids, were the study variables.

METHODS

Patient Population

Thirty-eight adult patients volunteered to participate in this study and were admitted to the General Clinical Research Center (GCRC) of Scripps Clinic, between 1995 and 2001. All patients signed institutional consent forms approved by

* The Scripps Research Institute, La Jolla, California.

† Allergy, Hospital Ramon y Cajal, Madrid, Spain.

‡ Division of Allergy, Asthma and Immunology, Scripps Clinic, La Jolla, California.

Grant support: Skaggs Fellowship Grant from the Scripps Research Institute (Dr. Stevenson) and a GCRC Grant from the NIH (M01RR00833).

Received for publication July 9, 2002.

Accepted for publication in revised form October 5, 2002.

the Scripps Human Subjects Committee. Of the 38 patients, 20 (53%) were males and 18 (47%) were females with a mean age of 49 years (range 30 to 74 years). All subjects met the criteria for diagnosis of asthma and were undergoing treatment according to the National Institute of Health guidelines.¹¹ Each of the patients gave a convincing history of asthma attacks induced by nonsteroidal anti-inflammatory drugs in the past.

On average, patients had experienced 5.2 sinus infections per year and had undergone 3.4 sinus/polyp operations during the course of their disease. None of the patients had significantly obstructing polyps at the time of this evaluation, either because of recent surgery, current treatment, or phase of their underlying disease. Twenty-six patients were taking nasal topical corticosteroids, and 32 were using topical bronchial corticosteroids. Six were receiving daily cysteinyl leukotriene 1 (cysLT₁) receptor antagonists (one zafirlukast and five montelukast). Patients were instructed to continue the same doses of these controller medications during the 2 months of evaluation. Fifteen patients were taking prednisone during the month before ASA desensitization (10 patients with daily doses and 5 on every other day). Another 14 patients had used bursts of prednisone in the past years for sinusitis/asthma episodes but did not take any prednisone during the 2 months of this study. The 15 patients, who were taking daily or alternate day prednisone, were instructed to reduce their average dose of prednisone, if they could do so without increasing their symptom scores for rhinitis, asthma, and olfaction.

Study Protocol

Patients were admitted to GCRC 2 to 3 days before ASA challenges were started. Placebo challenges were conducted and lung function stability was established: placebos were given every 3 hours, for 9 hours, and forced expiratory volume in 1 second (FEV₁) values and nasal scores were obtained. Asthma was considered stable if FEV₁ values were >70% predicted at baseline and varied by less than 10% during placebo challenge. If airway stability was established, single-blind ASA challenges were started.

During standard oral ASA challenges,^{12,13} all 38 patients experienced respiratory reactions after a mean challenge doses of 58 mg ASA. The evidence for ASA-induced respiratory reactions was evaluated at least hourly and consisted of the following: naso-ocular reaction (rhinorrhea, nasal congestion, ocular injection, periorbital edema) in 38 patients and bronchial reactions, defined as a decline of 20% or more in FEV₁, 15 of 38 (39%) or declines in FEV₁ values between 15 and 20%, 4 of 38 (10%). When a respiratory reaction occurred after a challenge dose of ASA, challenges were suspended. After ASA-induced respiratory reactions were treated and had cleared, the same dose of ASA was repeated. Doses were then escalated over several days until 650 mg ASA was tolerated without any adverse signs or symptoms. At this point, all patients achieved ASA desensitization. Nasal decongestion of the turbinates was noted in all 38 patients at the time of acute ASA desensitization.

After ASA desensitization, all subjects were instructed to take 650 mg ASA twice daily and were discharged from the GCRC. All patients continued the same dose of ASA 650 mg, twice daily, during the study month. For the 15 patients taking systemic corticosteroids, doses were reduced according to clinical improvement in respiratory disease, with a goal of minimum effective dose. All other controller drugs were continued in the same dosages as were recorded during the month before ASA desensitization.

Pre- and Followup Study Design

Each of the 38 patients filled in a daily diary card during 4 weeks before admission to GCRC and 4 weeks after desensitization with ASA. Dairy cards included nasal symptoms (running nose, nasal congestion, postnasal discharge, sinus pain, sense of smell), asthma symptoms (chest tightness, wheezing, coughing, shortness of breath, chest congestion) and daily corticosteroid doses. All subjects recorded their nasal symptoms and asthma symptoms according to a scale of 1 to 5. The scores for the symptoms, excepting sense of smell, were rated as: 1 = no symptoms, 2 = minor symptoms, 3 = moderately severe, 4 = considerably severe, 5 = extremely severe. Symptom scores for sense of smell were: 1 = smell excellent (perfect and continuous sense of smell), 2 = smell good (complete sense of smell the majority of the time), 3 = sense of smell fair (partial sense of smell the majority of the time), 4 = poor (intermittent partial sense of smell), and 5 = no sense of smell at any time.

Patients also recorded their use of controller medications, including daily requirement for oral prednisone. To compare and analyze the results statistically, methylprednisolone, which was used by two patients, was converted to prednisone equivalent at a ratio of 4:5; in patients who were taking prednisone on alternate days, we calculated the daily dose equivalent, using half of the every-other day dose. All patients traveled from some distance to undergo ASA desensitization in our GCRC. They brought their daily symptom medication cards with them at the time of admission and 1 month later mailed their postdesensitization cards back to us. All data were obtained from the symptom and medication cards.

Statistical Analyses

Mean values for the baseline periods and for the 4 weeks of ASA desensitization treatment were calculated. For statistical analyses the sum of nasal and asthma symptoms was used for mean values and statistical calculations.

For parametric statistics, paired *t* test was used to analyze the changes in nasal scores, asthma scores, changes in olfaction, and prednisone doses for 4 weeks before and 4 weeks after ASA desensitization

The statistical software program used was 4.01 (Abacus Concept, Berkeley, CA) for IBM.

RESULTS

Table 1 summarizes our analysis of symptom scores, changes in olfaction, and doses of prednisone before and 4 weeks after ASA desensitization treatment.

Table 1. Analysis of Combined Symptom Scores and Doses of Prednisone, 4 Weeks before and after ASA Desensitization Treatment (n = 38)

	4 weeks before		4 weeks after		P values
	Mean	SEM	Mean	SEM	
Total nasal scores	11.3	0.6	8.9	0.5	<0.0001
Sense of smell	4.2	0.2	3.3	0.2	<0.0001
Total asthma scores	6.7	0.2	5.5	0.1	<0.0001
Prednisone mg/day*	10.7	1.3	5.9	1.0	0.0003

Values were determined with paired *t* test.

Smell scores ranged from perfect and continuous smell (1 score) to complete and continuous anosmia (5 score).

* For the 15 patients taking prednisone.

SEM, standard error of mean.

For the 38 patients, there was a highly significant ($P < 0.0001$) improvement in total nasal and asthma symptom scores. We independently analyzed olfactory scores. There was a highly significant improvement in olfactory scores from a baseline of 4.2 to 3.3 ($P < 0.0001$). In further analyzing the 38 patients, we found that 10 (26%) had complete anosmia at baseline and did not change at 1 month. Another 15 (39%) had complete anosmia at baseline and recovered some smell at 1 month of ASA desensitization treatment (8 patients from scores of 5 to 4, and 7 patients from scores of 5 to 3). Thirteen (34%) had partial to complete smell (4 to 1 scores) at baseline and either improved their smell in 5 patients or had the same smell for 8 patients (one patient with a score of 1 before and after and 7 patients with scores of 2 before and after treatment with ASA desensitization).

At the same time, there was a significant (10.7 to 5.9 mg/day, $P = 0.0003$) reduction in mean daily dose of prednisone for the 15 patients taking prednisone. Of these 15 patients, who were taking daily (10 patients) or every other day (5 patients) doses of oral prednisone, 5 patients continued taking the same dose. But 8 patients reduced their doses by 50% or more and 2 of 5 patients who had been taking every-other day doses of prednisone discontinued this treatment during the first month. None of the patients started to take continuous prednisone during the 4 weeks of ASA desensitization treatment, and none increased their doses or required bursts of systemic corticosteroids for asthma exacerbation. According to patient diaries, none of the patients changed their other controller medications (nasal and inhaled corticosteroids or cysLT₁ receptor antagonists) during the 2 months of study. There were no complications from taking ASA and none of the patients dropped out of the study.

DISCUSSION

Our current study demonstrated that ASA desensitization treatment is associated with early improvement in nasal and asthma symptoms, improvement in sense of smell, and early reduction of prednisone therapy. Because it is impossible to conduct a meaningful double-blind, placebo-controlled study of ASA desensitization treatment, for the reasons stated in the introduction, this study did not contain a placebo-treated control group. In other words, all 38 patients knew they were

taking ASA daily and had already noted significant decongestion of their nasal passages at the time of acute ASA desensitization in the GCRC. Their baseline symptom scores and medication uses had been turned in at the time of admission to the GCRC. Nevertheless, these patients may have overemphasized their improvement. However, because previous studies, using objective criteria for improvement^{8-10,14} and a control group that was not treated with ASA,^{8,9} have already demonstrated efficacy of ASA desensitization treatment, the main value of this current study was to determine how quickly patients improved. This has some practical importance in that earlier reduction in ASA doses, perhaps after 1 month, can now be studied with some sense of potential success. Decreasing doses of ASA has the potential of decreasing gastric side effects.

Systemic corticosteroids are highly effective in treating AERD, with routine return of smell during bursts of corticosteroids. Therefore, we felt it was important to attempt to decrease prednisone as much as possible during this first month to expose the therapeutic efficacy or lack of efficacy of ASA treatment. Fortunately, none of the 38 patients had to increase or take bursts of systemic corticosteroids during the 2 months of study. At the same time, there were no changes in treatment with the other controller medications. Therefore, any differences in symptoms were most likely attributable to intervention with ASA desensitization treatment or excessive reduction of prednisone doses.

In 1986, Kowalski et al¹⁴ reported the effect of ASA desensitization treatment in 16 patients, comparing clinical parameters for 4 weeks before to 4 weeks after ASA desensitization and treatment with ASA 600 mg daily. Two patients dropped out because of exacerbations of asthma and bursts of prednisone. Eight of 12 patients, who had perennial rhinitis, experienced significant improvement in nasal symptoms scores; 7 of 14 subjects noted a reduction in both the mean asthma score and in daily β -agonist use. The geometric mean of provocation concentration of histamine decreased (1.8 to 5.8 mg/mL) in the 13 patients undergoing histamine inhalation challenges. The authors concluded that daily ASA administration after desensitization was helpful in the management of "some ASA-sensitive asthmatic patients." Our results are in accordance with observations from this smaller study.

During acute desensitization, defined as 3 hours after the first ingestion of 650 mg of ASA without reaction, most AERD patients report significant decreases in nasal congestion, and some are able to begin to smell. Thus, immediately after achieving ASA desensitization, inspection of the nasal passages shows decongestion of the turbinates with considerable improvement in nasal airflow in most patients whose noses are not filled with polyps. In this study of 38 patients, we selected participants who did not have significantly obstructing polyps, which would have added a confounding variable in this short-term study.

Previous studies have demonstrated that several biochemical events occur directly after achieving ASA desensitization. Histamine and leukotriene C_4 disappeared in the nasal secretions.¹⁵ Plasma histamine and serum tryptase levels became unmeasurable,¹⁶ and peripheral blood monocytes synthesized significantly less thromboxane B_2 and leukotriene B_4 .¹⁷ Immediately after ASA desensitization, a 20-fold decrease in bronchial airway responsiveness to inhaled leukotriene E_4 was reported,¹⁸ but similar studies have not been reported in nasal airways. Interestingly, during acute desensitization, urinary leukotriene levels are the same as levels measured at baseline.¹⁹ Therefore, although rapid changes in some mediator profiles occur, leukotrienes are still being synthesized at the time of acute ASA desensitization. This implies that early effects of ASA desensitization are independent of production of leukotrienes. The effects of ASA might either be in interference with the ability of the $cysLT_1$ or $cysLT_2$ receptors to signal intracellular molecular events in target cells or directly interfering with other mediators or activated inflammatory cells through undiscovered mechanisms.

CONCLUSION

We have presented data that support the hypothesis that ASA desensitization is effective in reducing important markers of disease activity in AERD patients as early as the first month of treatment. The fact that this effect begins during the first month of ASA treatment, suggests that ASA interferes with a fundamental cellular molecular event, independent of the synthesis of leukotrienes. Precisely what that therapeutic effect might be is under investigation but continues to elude us.

ACKNOWLEDGMENTS

We thank the nurses in the GCRC for their expert care of our patients. In addition, special recognition goes to Mrs. Aliene Duvalian, RN, Aspirin Project Coordinator, for her considerable effort on behalf of this study. We also thank James A. Koziol, PhD, Biostatistician of The Scripps Research Institute, for his helpful advice in the selection of statistical analyses.

REFERENCES

1. Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. *Ann Allergy Asthma Immunol* 2001;87:177–180.
2. Stevenson D, Simon, RA. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs. In: Middleton E Jr, Ellis EF, Yunginger JW, et al, editors. *Allergy: Principles and Practice*. Vol 2. St.

- Louis, MO: Mosby, 1998:1225–1234.
3. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. *J Allergy Clin Immunol* 1999;104:5–13.
4. Widal MF, Abrami P, Lermeyez J. Anaphylaxie et idiosyncrasie. *Presse Med* 1922;30:189–192.
5. Zeiss CR, Lockey RF. Refractory period to aspirin in a patient with aspirin-induced asthma. *J Allergy Clin Immunol* 1976;57:440–448.
6. Pasargiklian M, Bianco S, Allegra L, et al. Aspects of bronchial reactivity to prostaglandins and aspirin in asthmatic patients. *Respiration* 1977;34:78–91.
7. Stevenson DD, Simon RA, Mathison DA. Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. *J Allergy Clin Immunol* 1980;66:82–88.
8. Stevenson DD, Pleskow WW, Simon RA, et al. Aspirin-sensitive rhinosinusitis asthma: a double blind, cross-over study of treatment with aspirin. *J Allergy Clin Immunol* 1984;73:500–507.
9. Sweet JM, Stevenson DD, Simon RA, Mathison DA. Long-term effects of aspirin desensitization-treatment for aspirin-sensitive rhinosinusitis-asthma. *J Allergy Clin Immunol* 1990;85:59–65.
10. Stevenson DD, Hankammer MA, Mathison DA, et al. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J Allergy Clin Immunol* 1996;98:751–758.
11. Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Institutes of Health, 1997; Publication no. 97–4051:1.
12. Stevenson DD. Oral challenges to detect aspirin and sulfite sensitivity in asthma. *N Engl J Allergy Proc* 1988;9:135–142.
13. Stevenson DD. Anaphylactic and anaphylactoid reactions to aspirin and nonsteroidal anti-inflammatory drugs. *Immunol Allergy Clin North Am* 2001;21:745–768.
14. Kowalski ML, Grzelewska-Rzymowska I, Szmidi M, Rozniecki J. Clinical efficacy of aspirin in “desensitized” aspirin-sensitive asthmatics. *Eur J Respir Dis* 1986;69:219–225.
15. Ferreri NR, Howland WC, Stevenson DD, Spiegelberg HL. Release of leukotrienes, prostaglandins, and histamine into nasal secretions of aspirin-sensitive asthmatics during reaction to aspirin. *Am Rev Respir Dis* 1988;137:847–854.
16. Bosso JV, Schwartz LB, Stevenson DD. Tryptase and histamine release during aspirin-induced respiratory reactions. *J Allergy Clin Immunol* 1991;88:830–837.
17. Juergens UR, Christiansen SC, Stevenson DD, Zuraw BL. Inhibition of monocyte leukotriene B_4 production following aspirin desensitization. *J Allergy Clin Immunol* 1995;96:148–156.
18. Arm JP, O’Hickey SP, Spur BW, Lee TH. Airway responsiveness to histamine and leukotriene E_4 in subjects with aspirin-induced asthma. *Am Rev Respir Dis* 1989;140:148–153.
19. Daffern P, Muilenburg D, Hugli TE, Stevenson DD. Association of urinary leukotriene E_4 excretion during aspirin challenges with severity of respiratory responses. *J Allergy Clin Immunol* 1999;104:559–564.

Requests for reprints should be addressed to:

Donald D. Stevenson, MD

Scripps Clinic and The Scripps Research Institute

10666 North Torrey Pines Road

La Jolla, CA 92037

E-mail: Stevensn@Scripps.edu