

The relationship between historical aspirin-induced asthma and severity of asthma induced during oral aspirin challenges

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Background: Historical aspirin- or nonsteroidal anti-inflammatory drug (NSAID)-induced reactions might provide predictive information about the severity of reactions in patients with aspirin-exacerbated respiratory disease (AERD) undergoing oral aspirin challenge (OAC).

Objective: We sought to assess the relationship between historical aspirin- or NSAID-induced bronchial reactions and the severity of bronchial reactions during OAC in patients with AERD.

Methods: Data regarding the provoking doses, treatments, and treatment settings of historical aspirin/NSAID-induced reactions were recorded, analyzed, and compared with the provoking doses, maintenance regimens, and observed decreases in FEV₁ that occurred during OAC in 210 consecutive patients referred with suspected AERD.

Results: Of 147 patients who reported seeking acute medical care for their historical aspirin/NSAID-induced asthma attacks, 101 (69%) were treated in an emergency department and released, and 46 (31%) required hospitalization. During OAC in these 147 subjects, 23 (16%) had a 20% to 29% decrease and 14 (10%) had a 30% or greater decrease in FEV₁ values from baseline. Of the 46 patients previously hospitalized for aspirin/NSAID-induced asthma attacks, 9 (20%) had a 20% to 29% decrease and 6 (13%) had a 30% or greater decrease in FEV₁ during OAC. By contrast, of the 63 patients who treated their prior aspirin/NSAID-induced reactions at home, 5 (8%) had a 20% to 29% decrease and 5 (8%) had a 30% or greater decrease in FEV₁ during OAC (*P* = not significant for both).

Conclusion: The severity of the historical aspirin/NSAID-

induced asthma attack was not predictive of asthma severity during OAC.

Clinical implications: These data provide further reassurance regarding the safety of outpatient aspirin desensitization.

(*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Aspirin, nonsteroidal anti-inflammatory drugs, leukotrienes, leukotriene modifier drugs, asthma, aspirin-exacerbated respiratory disease, aspirin challenge, aspirin desensitization, nasal polyposis, chronic rhinosinusitis

Aspirin-exacerbated respiratory disease (AERD) is a syndrome consisting of asthma, nasal polyposis, chronic hyperplastic eosinophilic sinusitis, and nonallergic hypersensitivity reactions to medications that inhibit COX-1, namely aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).¹ These reactions usually occur within 30 minutes to 3 hours after ingestion of therapeutic doses of aspirin or NSAIDs and can consist of a spectrum of respiratory reactions, including rhinitis, conjunctivitis, laryngeal spasm, and asthma, as well as extrapulmonary reactions, such as urticaria, flushing, nausea, vomiting, and abdominal pain.

Clinical confirmation of the diagnosis of AERD has important therapeutic implications. Patients with AERD who have an indication for daily aspirin or NSAID use can be successfully desensitized and, while maintaining the desensitized state with daily ingestion of aspirin, thereafter safely consume these medications. In addition, for patients with AERD with severe or treatment-refractory chronic sinusitis, nasal polyposis, and/or asthma, aspirin desensitization, followed by continued treatment with twice-daily aspirin, can be used therapeutically for the treatment of their underlying inflammatory respiratory disease.^{2,3}

In the United States the currently accepted standard means of establishing the diagnosis of AERD is by means of oral aspirin challenge (OAC).⁴ For patients in whom a sufficiently high clinical suspicion of AERD exists, OAC followed by desensitization is accomplished through a 2- to 5-day graded, escalating-dose protocol.^{5,6} For many clinicians involved in the care of patients with AERD, however, questions regarding the safety of OAC and desensitization remain. However, when conducted as previously reported, we have found this procedure to be relatively safe.⁷

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Presented at the AAAAI Annual Meeting; February 25th, 2007; San Diego, Calif.

Disclosure of potential conflict of interest: A. N. Williams is employed by Scripps Clinic. R. A. Simon is employed by Scripps Clinic and is on the speakers' bureau for Merck, Critical Therapeutics, GlaxoSmithKline, Schering, Novartis, Pfizer, and Sanofi-Aventis. K. M. Woessner is employed by Scripps Clinic and is on the speakers' bureau for Merck, GlaxoSmithKline, and Critical Therapeutics. D. D. Stevenson has consulting arrangements with Portola Pharmaceuticals; has received support from a Skaggs Institutional grant; is employed by Scripps Clinic and the Scripps Research Institute; is on the speakers' bureau for Merck and Critical Therapeutics; and has served as an expert witness for the defense in litigation.

Received for publication February 9, 2007; revised March 20, 2007; accepted for publication March 22, 2007.

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0091-6749/\$32.00

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doi:10.1016/j.jaci.2007.03.020

Abbreviations used

AERD:	Aspirin-exacerbated respiratory disease
ED:	Emergency department
ICU:	Intensive care unit
LTMD:	Leukotriene modifier drug
NSAID:	Nonsteroidal anti-inflammatory drug
OAC:	Oral aspirin challenge

In an attempt to further assess the safety of OAC, we sought to determine whether any correlation could be found between historical aspirin- or NSAID-induced respiratory reactions and those observed after OACs in patients referred with suspected AERD.

METHODS

Participants

Data were obtained and analyzed from 210 consecutive patients who underwent aspirin desensitization between January 2003 and July 2006. All patients had been referred to the Division of Allergy, Asthma, and Immunology at Scripps Clinic with suspected AERD for OAC followed by aspirin desensitization. All patients were required to have had a history of asthma, nasal polyposis, chronic sinusitis, and at least 1 historical respiratory reaction temporally associated with the ingestion of aspirin or an NSAID to be considered for OAC. In addition, patients were not allowed to proceed with challenge and desensitization if their prechallenge baseline FEV₁ was not at least 60% of predicted value or greater than 1.5 L or if their asthma was unstable. Until January 30, 2005, patients undergoing OAC and desensitization were admitted to the General Clinical Research Center of Scripps Clinic. Beginning February 1, 2005, these procedures have been performed on consecutive days in the outpatient allergy clinic. Before undergoing OAC and desensitization, all patients signed Human Research Subjects Committee–approved informed consent documents to undergo OAC followed by desensitization and to allow collection of these data.

Historical reaction severity

At the time of initial evaluation, patients were specifically asked to provide detailed information about the historical aspirin/NSAID-induced reaction, including indication for aspirin/NSAID, medication, dosage, time to onset of reactions, symptoms, treatment, location of treatment (home, physician's office, or emergency department [ED]), and whether hospitalization or intensive care unit (ICU) admission was required. For patients who reported multiple previous reactions to aspirin, NSAIDs, or both, these data were obtained for each reaction. The provocation doses for NSAID-induced reactions were converted to an aspirin equivalence dose as follows: 325 mg of aspirin = 200 mg of ibuprofen = 220 mg of naproxen = 1000 mg of acetaminophen = 25 mg of indomethacin. When reaction symptoms and location of treatment varied between multiple historical aspirin/NSAID-induced reactions, the lowest aspirin dose (or equivalent NSAID dose) and highest intensity-of-care treatment location required were recorded.

Oral aspirin challenges

Aspirin challenges conducted in both the General Clinical Research Center and outpatient clinic were performed in standardized dose-escalating protocols that have been published previously.^{6,7}

Usual controller medications, such as systemic, nasal, and inhaled corticosteroids; leukotriene modifier drugs (LTMDs); long-acting β -agonists; and theophylline, were continued. Short-acting β -agonists, cromolyn, and oral or intranasal antihistamines, decongestants, or both were withheld for at least 48 hours before OAC.

Challenges were begun with 30, 45, or rarely 60 mg of aspirin followed by advancing doses (60, 100, 150, 325, and 650 mg) every 3 hours during daytime/clinic hours. FEV₁ values were measured at baseline and every hour throughout the challenge, and the best of 3 efforts was recorded. Patients were evaluated hourly or more frequently as symptoms prompted for signs of aspirin-induced reactions and changes in vital signs. When reactions occurred, they were confirmed by physician examination, the challenge was suspended, and any symptoms or changes in FEV₁ were managed with medications (eg, inhaled or nebulized short-acting β -agonists, topical nasal decongestants, oral or intravenous ranitidine, or antihistamines). Once symptoms were adequately treated or changes in FEV₁ were adequately reversed, the challenge was continued with administration of the provoking dose, followed by resumption of the dose-escalating protocol to a target dose of either 325 or 650 mg.

Definitions of types of reactions

OAC reactions were characterized and recorded according to organ system involvement: naso-ocular, laryngeal, bronchial, cutaneous, and gastrointestinal. A positive naso-ocular reaction to aspirin challenge was defined by the postchallenge appearance of nasal congestion, rhinorrhea, sneezing, paranasal headache, periorbital edema, or conjunctival itching and/or injection. A positive bronchial reaction was defined as a postchallenge decrease in FEV₁ from a baseline value of 15% or greater. Laryngeal reactions to OAC were defined by stridorous sounds auscultated over the upper chest and trachea. Gastrointestinal reactions consisted of nausea, vomiting, diarrhea, and/or abdominal pain. The development of urticaria, angioedema, pruritis, or flushing was considered to be indicative of a cutaneous reaction. The aspirin challenge dose administered just before the confirmatory reaction was considered the provoking aspirin dose.

Statistical analysis

To be as descriptive as possible, positive bronchial reactions were categorized into 3 groups according to changes in aspirin-induced decreases in FEV₁ compared with prechallenge FEV₁ as follows: 15% to 19% decrease in FEV₁, 20% to 29% decrease in FEV₁, and 30% or greater decrease in FEV₁. Before data analysis, the boundaries of 20% and 30% decreases in FEV₁ were selected on the basis that these were believed to represent clinically important outcomes to OAC. The Fisher exact test was used to compare historical reaction severity to challenge severity, with statistical significance requiring a *P* value of less than .05. Mean differences in decreases from baseline in FEV₁ after OAC were compared by using the χ^2 test. The *t* test was used to compare historical reaction doses with OAC provocation doses.

RESULTS

Complete data were available for analysis of 210 consecutive patients (86 [41%] male and 124 [59%] female patients). The mean age of the cohort was 45.8 years. All but 3 patients had a history of nasal polyposis. One hundred forty-eight (71%) patients had a history of atopy. As would be expected in a cohort of patients with AERD, our study population had a mean of 5.3 sinus infections per year (range, 0–12; SD, 4.0), 3.0 sinonasal

polypectomy operations (range, 0-13; SD, 2.3), and 4.4 ED visits (range, 0-50; SD, 6.9) and 1.6 hospitalizations (range, 0-30; SD, 3.6) for asthma. Only 11 (5%) patients were taking LTMDs at the time of their historical aspirin/NSAID reaction.

The maintenance medication regimen for patients at the time of OAC included LTMDs in 161 (77%) patients, nasal corticosteroids in 157 (75%) patients, inhaled corticosteroids in 173 (82%) patients, and scheduled systemic corticosteroids in 42 (20%) patients.

Historical reaction severity

After a historical respiratory reaction attributed to aspirin or NSAID ingestion, 63 (30%) patients were able to adequately control reaction symptoms without seeking acute medical care. Of the 147 patients who did seek acute medical care for the treatment of their asthma attacks, 101 (69%) were treated and released from the ED, and 46 (31%) required hospitalization.

OAC reaction severity

The observed reactions to OAC by organ system involvement are listed in Table I. AERD was clinically confirmed on the basis of naso-ocular reactions in 188 (89.5%) patients.

Of the 147 patients who reported seeking acute medical care for their historical aspirin- or NSAID-induced reactions, 90 (61%) had a naso-ocular reaction to OAC without a bronchial reaction (<15% reduction in FEV₁ from baseline), 20 (14%) had a 15% to 19% decrease in FEV₁ from baseline, 23 (16%) had a 20% to 29% decrease in FEV₁ from baseline, and 14 (10%) had a 30% or greater decrease in FEV₁ from baseline. In contrast, of the 63 patients who reported self-treating their historical aspirin- or NSAID-induced reactions without acute medical intervention, 46 (73%) had naso-ocular reactions without a significant reduction in FEV₁, whereas 7 (11%) had a 15% to 19% decrease in FEV₁, 5 (8%) had a 20% to 29% decrease in FEV₁, and 5 (8%) had a 30% or greater decrease in FEV₁ during OAC (no significant difference between the 2 groups, Table II). Of the subset of patients who reported requiring hospitalization after their historical aspirin- or NSAID-induced reactions, only 13% had a 30% or greater decrease in FEV₁ during OAC.

Of the 74 patients who had positive bronchial reactions to OAC (defined as $\geq 15\%$ decrease in FEV₁ from baseline), the mean decrease in FEV₁ from prechallenge baseline values in patients who treated their reactions at home was 25% compared with 25% and 24% for patients who were treated in the ED and either released or hospitalized, respectively ($P =$ not significant, χ^2 test).

A total of 19 (9%) patients reacted to OAC with bronchial reactions that consisted of a 30% or greater decrease in FEV₁. These patients were not significantly more likely than those whose bronchial reactions consisted of a less than 30% decrease in FEV₁ to have reported seeking acute medical care for their historical aspirin/NSAID reactions (14/19 [73%] vs 133/191 [70%]; $P =$ not significant, χ^2 test).

TABLE I. OAC reactions

	n (%)
Naso-ocular	188 (90)
Bronchial	74 (35)
15% to 19% decrease in FEV ₁	27 (13)
20% to 29% decrease in FEV ₁	28 (13)
$\geq 30\%$ decrease in FEV ₁	19 (9)
Gastrointestinal	49 (23)
Cutaneous	20 (10)
Laryngeal	16 (8)
Negative OAC	17 (8)

Provoking doses

There were no significant differences in average provoking aspirin or NSAID doses among patients who treated their reactions at home compared with those who sought acute medical care. Importantly, the mean dose of aspirin (or aspirin-equivalent dose) for historical reactions was almost 9 times the provoking dose during OAC: 550 mg for the historical reaction and 62 mg during OAC ($P = .0001$, t test).

DISCUSSION

The beneficial effects of aspirin desensitization and continued treatment with aspirin on the upper and lower respiratory disease process in patients with AERD has been established and recently reviewed.^{1-3,6,8} Our experience suggests, however, that this approach is underused. One potential barrier to more widespread use of aspirin challenge and desensitization involves concerns clinicians might have regarding the safety of performing this procedure. In patients with AERD, the fear of provoking severe and potentially life-threatening reactions might cause clinicians and patients to consider other diagnostic or therapeutic options. Furthermore, these concerns might cause clinicians to limit such procedures to hospital or ICU settings in which the cost, time, or other logistic barriers then become prohibitive. Safety concerns might further be confounded by the commonly held assertion that asthmatic patients with AERD tend to have a more severe and persistent asthma phenotype than asthmatic subjects without AERD.^{6,9}

Our data suggest that OAC is relatively safe, even in patients who report historical respiratory reactions to full therapeutic doses of aspirin or NSAID ingestion severe enough to warrant acute medical care, hospitalization, or admission to the ICU. Specifically, we found that although a majority (70%) of patients seek acute medical care for their historical respiratory reactions to aspirin or NSAIDs, most reactions during outpatient OAC are limited to naso-ocular reactions (65%) or mild (<20% decrease in FEV₁) asthma attacks. In addition, patients requiring acute medical intervention in the ED or hospital for the treatment of historical reactions to aspirin or NSAIDs were not significantly more likely to have a severe bronchospastic

TABLE II. Relationship of OAC bronchial reaction severity to historical aspirin/NSAID reaction treatment location

OAC bronchial reaction severity	Historical reaction treatment location		
	Home (n = 63), n (%)	ED (n = 101),* n (%)	Hospital (n = 46),† n (%)
<20% decrease in FEV ₁	53 (84)	79 (78)	31 (67)
20% to 29% decrease in FEV ₁	5 (8)	14 (14)	9 (20)
≥30% decrease in FEV ₁	5 (8)	8 (8)	6 (13)

P values were determined by using the Fisher exact test.

*Comparison of those who treated reactions at home versus those who went to the ED, *P* = .597.

†Comparison of those who treated reactions at home versus those who required hospitalization, *P* = .116.

reaction to OAC than patients who treated their historical asthmatic attack without seeking acute medical intervention. Furthermore, of those who had a positive bronchial reaction to OAC, the mean OAC decrease in FEV₁ did not differ significantly between patients who treated their historical aspirin reactions at home and those who sought care for their historical aspirin reactions.

There are several factors that might provide some explanation for the observation that patients who sought acute medical care for their historical reactions are not more likely to have severe OAC reactions than those who did not. First, the mean provocation dose for OAC was much less than the dose eliciting the historical reaction (62 vs 550 mg). Previous observations have suggested that aspirin/NSAID sensitivity in AERD is dose dependent.⁶ Whereas most historical aspirin- or NSAID-induced reactions follow ingestion of therapeutic doses of these medications (eg, 325–650 mg of aspirin and 200–600 mg of ibuprofen), virtually all patients who have a positive OAC response react to 100 mg of aspirin or less.

Second, we found a significant difference in the use of LTMDs at the time of the historical reactions compared with OAC (5% vs 77%, respectively). It is becoming increasingly clear that one of the defining pathophysiologic features of COX-1 inhibitor-induced reactions in AERD is the overproduction of cysteinyl leukotrienes.^{10–19} Aspirin challenges in patients with AERD have been associated with significant increases in urinary levels of leukotriene E₄^{11–13} and leukotriene C₄ levels in nasal and bronchial lavage fluid.^{14–17} In addition, recent studies have demonstrated a reduction in the severity of aspirin-induced asthma in patients taking LTMDs.^{5,20,21}

Third, the vast majority of patients in our cohort were receiving maintenance therapy with additional controller therapy, including inhaled corticosteroids and long-acting β -agonists, at the time of OAC. Continuation of these controller regimens might also contribute to reducing the severity of respiratory responses to OAC in patients with AERD.⁵ Because our OAC protocol requires a prechallenge FEV₁ of 60% of baseline values or greater before initiating the challenge, we speculate that the underlying asthma status at the time of challenge was likely to be less labile than that at the time of the historical reactions.

It should be noted that a small number of patients will have respiratory reactions to AERD that involve precipitous decreases in FEV₁ (eg, ≥30% decrease in FEV₁). In this cohort a total of 19 (9%) patients reacted to OAC

with a 30% or greater decrease in FEV₁. These patients were not significantly more likely to have been treated in the ED or hospitalized for their historical reactions. Although none of these patients required transfer to an ICU for their reactions to OAC, the importance of appropriate supervision and early intervention with inhaled β -agonists or epinephrine cannot be overemphasized.

A few limitations of our study should be noted. First, the data obtained from patients about the details of their experiences a number of years prior are subject to recall bias. Second, because of the uncertainty that exists as to the level of asthma control and use of asthma controller medications at the time of patients' historical aspirin- or NSAID-induced reactions, we cannot be certain that this analysis is comparing similar clinical states. Third, the broad application of our findings might be limited by the fact that these challenges were performed at an institution with physicians and nursing staff with a high degree of experience with conducting OACs. Nonetheless, these data provide important and reassuring information regarding the overall safety of OACs in patients with AERD.

In summary, we found that although many patients with AERD report seeking acute medical care for full-dose historical aspirin- or NSAID-induced asthmatic reactions, a minority respond to OAC with severe asthmatic reactions (≥30% decrease in FEV₁). Furthermore, historical reactions that prompt affected patients to seek acute medical care do not predict more severe asthmatic responses to OAC. Our data provide support to the hypothesis that pretreatment with asthma controller therapy, including LTMDs, and the lower aspirin challenge provocation dose compared with historical reaction provocation doses contribute to the overall safety of OACs. OACs should not be avoided solely on the basis of prior aspirin- or NSAID-induced asthmatic reactions that resulted in hospitalization, admission to the ICU, or intubation.

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