Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis

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Background: A definitive diagnosis of aspirin-exacerbated respiratory disease (AERD) requires a positive oral aspirin challenge (OAC), but predicting which patients will have positive challenges is often difficult.

Objective: To analyze information about historical aspirin- and nonsteroidal anti-inflammatory drug (NSAID)–associated respiratory reactions and clinical characteristics as potential markers to predict positive OACs.

Methods: A total of 243 patients underwent OACs. Data related to previous reactions and clinical characteristics of patients were correlated with the result of the OACs.

Results: Without prior exposure to aspirin or NSAIDs, the chance of a positive OAC was 5 in 12 (42%) but was 198 in 231 (86%) for those with a history of aspirin- and NSAID-associated asthma attacks. Sex, atopy, number of sinus infections per year, and number of sinus surgical procedures were not associated with positive OACs. Patients with 2 or more prior aspirin- and NSAID-associated respiratory reactions had an 89% chance of having a positive OAC vs single reactors (80%; $P = .04$). Mild or moderate prior reactions were associated with 84% or 80% positive OACs, whereas 100% of the 45 patients with severe prior reactions had positive OACs ($P = .007$). Except for hospitalizations, treatment locations of prior reactions (home or emergency department) did not seem to make any difference. Logistic regression identified age, sense of smell, and multiple prior reactions as independent risk factors associated with positive OACs.

Conclusions: Age younger than 40 years, poor sense of smell, multiple prior respiratory reactions, and severe prior asthmatic reactions associated with aspirin and NSAIDs significantly increased the chances of a positive OAC.

Ann Allergy Asthma Immunol. 2008;100:420–425.

INTRODUCTION

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are used extensively throughout the world because of their analgesic and anti-inflammatory effects. However, these drugs cause a variety of adverse reactions.[1] Of particular interest is the aspirin- or NSAID-induced respiratory tract reaction, which is seen in patients who have underlying asthma, recurrent sinonasal polyps, and chronic rhinosinusitis. In these patients, after ingestion of aspirin or NSAIDs, bronchospasm, rhinorrhea, sneezing, nasal congestion, watery-itchy eyes, and sometimes systemic symptoms of flushing, hives, abdominal cramps, and hypotension can occur. If not recognized and treated rapidly, aspirin and NSAIDs can cause severe reactions and even death from asthma, particularly when full doses of aspirin or NSAIDs are ingested and the individual is away from an acute care medical facility.[2]

Aspirin desensitization followed by daily treatment with aspirin for most patients with aspirin-exacerbated respiratory disease (AERD) has been documented to be effective in peer-reviewed publications.[3] The efficacy of this long-term treatment for AERD has been demonstrated.[4–7] Therefore, accurate diagnosis of AERD is important in the selection of patients who might respond to this and other treatment options.

A multicenter European study found that 15% of asthmatic patients, undergoing routine oral aspirin challenges (OACs), tested positive but had previously been unaware that aspirin or NSAIDs could have caused respiratory reactions.[8] In fact, many patients with asthma are avoiding aspirin and NSAIDs either because they do not need them or because physicians have warned them not to take them. In a large survey of pharmacy-reported reactions to analgesics in asthmatic patients, the prevalence of AERD was listed as 3% in adults and 2% in children.[9] In a large population (sample size of 12,971) of Polish citizens with asthma, based on patient observation, 4.3% identified themselves as being sensitive to aspirin.[10] These low prevalence figures are contrasted with a meta-analysis of 15 studies, using prospective OACs in patients with underlying sinusitis, nasal polyps, and asthma. The combined prevalence of AERD was 21% (range, 14%–29%) for adults and 5% (range, 0%–14%) for children.[9] These data clearly indicate that AERD regularly occurs in the general

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Disclosures: Authors have nothing to disclose.

Received for publication September 25, 2007; Received in revised form November 8, 2007; Accepted for publication December 6, 2007.

asthmatic population but is often not recognized by patients and physicians, including specialists.

Not only is underdiagnosis of AERD a problem, but overdiagnosis is also encountered. Sometimes, patients experienced asthma attacks after ingestion of aspirin or NSAIDs, but the asthma attack was due to another provoking factor. In a study of 50 asthmatic patients with nasal polyps and sinusitis who gave a prior history of aspirin- or NSAID-associated respiratory reactions, 8 of 50 patients (16%) did not react to aspirin during the OAC.[11] Furthermore, in this early study, there was no attempt to look more closely at the details of the historical aspirin- or NSAID-associated respiratory reactions to see if some histories of prior asthma attacks were more likely to predict a positive OAC.

With a large population of asthmatic patients referred to our clinic for aspirin desensitization, we had an opportunity to look more carefully at the question of whether characteristics of patients and prior reactions could predict accurately the diagnosis of AERD. Furthermore, we evaluated the probability that patients with a certain clinical profile would or would not ultimately undergo positive OACs.

METHODS

Study Population

Historical data were analyzed from consecutive patients referred to the Division of Allergy, Asthma and Immunology of the Scripps Clinic and The Scripps Research Institute for the purpose of aspirin challenges and desensitization. All patients signed Human Research Subjects Committee–approved and written informed consent before answering historical questions and undergoing OACs. Information relevant to this study included recall by patients of historical events, records from referring physicians, questioning patients about sense of smell, number of sinus infections per year and sinus surgical procedures, and the results of OACs. Medical records rarely included copies of emergency department (ED) or hospitalizations for prior asthma attacks. Listed below are details of data collection.

Severity of Previous Reactions

At the time of prechallenge evaluation, patients described the severity of previous asthmatic reactions associated with aspirin or NSAIDs and were classified into 3 groups: mild (responded to albuterol treatments with asthmatic episode lasting less than an hour), moderate (partial response to albuterol but episode lasting longer than an hour), and severe (poor response to albuterol and requirement for medical intervention up to intubation). For patients who had multiple previous reactions, the most severe episode was recorded.

Definitions of Single vs Multiple Reactors

If patients recalled 1 historical asthma attack associated with aspirin or NSAIDs, they were identified as single reactors. If 2 or more historical reactions were noted, patients were classified as multiple reactors.

Treatment Locations of Previous Aspirin- or NSAID-Associated Reactions

According to the patient's memory, treatment locations for prior asthma attacks associated with aspirin or NSAIDs were identified as home, ED, and hospital admission. If the reaction was treated in a physician's office, it was placed in the ED category. Home was used for all reactions that were not treated in the physician's office, ED, or hospital. For patients who experienced multiple previous reactions, the highest intensity of care treatment location was recorded.

Symptoms Scores for Sense of Smell

Subjective symptoms were classified as follows: 0 indicated no sense of smell; 1, intermittent partial sense of smell; 2, intermittent complete sense of smell; 3, partial sense of smell most of the time; 4, complete sense of smell most of the time; and 5, perfect and continuous sense of smell. The determination was made at the time the patient was about to start the OAC.

Oral Aspirin Challenge

All challenges were performed in standardized dose-escalating protocols in the outpatient department.[1] Patients were allowed to take their usual controller medications such as systemic, inhaled, and nasal corticosteroids, leukotriene modifier drugs (LDs), long-acting β-agonists, and theophylline. Montelukast was the only LD used in the study population. The use of oral and intranasal antihistamines, decongestants, short-acting β-agonists, and cromolyn was discontinued 48 hours before challenges. Challenges were initiated with 30, 45, or 60 mg of aspirin followed by advancing doses (60, 100, 150, 325, and 650 mg) every 3 hours during daytime. Patients were evaluated hourly or more frequently if signs of aspirin-induced reactions occurred. When reactions occurred, they were confirmed by physician examination. A positive reaction was defined as classic reactions (decline in forced expiratory volume in 1 second [FEV_1] of at least 15% combined with naso-ocular reaction), pure lower respiratory tract reactions (related symptoms with 20% decline in FEV_1), and naso-ocular reactions only. Some patients also experienced extrapulmonary signs or symptoms during positive OACs.

Statistical Analysis

Statistical analysis was performed using SPSS statistical software, version 13.0 for Windows. Nominal values were expressed as number (percentage), and results were expressed as mean (SEM) (95% confidence interval [CI]). The χ^2 analysis or Fisher exact test and analysis of variance test were used to compare severity, numbers, and treatment locations of previous historical reactions in OAC-negative and OAC-positive patients. All directional P values were 2-tailed, and significance was assigned to values less than .05. Logistic regression analysis was performed to establish the factors that were associated with positive OACs. We examined the following variables: age; sex; atopy; number of sinus infections per year; number of sinus surgical procedures; smell score; severity, number, and treatment locations of previous histor-

ical reactions; and LD use at the time of challenge on positive OACs. Logistic regression equation was defined as $P(Y) = 1/1 + e^{-Z}$, where Z was the usual regression equation: $Z = \beta_0 + \beta_1 X_1 + \beta 2 X_2 .. + \beta kXk$. A P(Y) value greater than 0.50 indicated that patient would have a positive OAC. Odds ratios (ORs) and their CIs were also estimated with exp(β) and 95% CI, respectively.

RESULTS

Of the 243 patients, 231 (96.3%) remembered having historical reactions to aspirin and/or other NSAIDs and constituted the study population. One hundred sixty-three patients (71%) had a history of atopy. The mean number of sinus infections per year and history of sinonasal surgery was 5.28 (0.27) (95% CI, 0–12) and 3.02 (0.15) (95% CI, 0–13), respectively. Most patients (84%) had poor or absent sense of smell. Nobody had completely normal sense of smell (score of 5). OAC was positive in 198 patients (85.7%). Reactions were pure naso-ocular in 116 (59%), pure bronchial in 3 (1%), and combined in 79 (40%). The maintenance therapy at the time of OAC included nasal steroids in 171 (74%), inhaled steroids in 190 (82%), LDs in 174 (75%), and systemic steroids in 46 (20%). The clinical characteristics according to historical reactions are summarized in Table 1. Of the 243 patients, 12 patients were avoiding aspirin and NSAIDs because their physicians told them to avoid these drugs or they had no need for them. Therefore, they had no prior history of asthma attacks associated with aspirin or NSAIDs and were referred because of nasal polyps, chronic sinusitis, and asthma. OACs were positive in only 5 of 12 (42%) (1 pure naso-ocular and 4 combined reactions of upper and lower respiratory tracts) of these patients. This group was too small to evaluate multiple variables with statistical analysis.

When examining the study population, a significant difference was observed in positive OACs between patients with poor or absent and good sense of smell (89% vs 69%; $P = .02$). In addition, if one had 2 or more prior reactions, chances of a positive OAC were 89.4% vs 80% if one had had only 1 prior reaction ($P = .04$). If the historical reactions were severe, 45 of 45 patients (100%) had a positive OAC ($P = .007$). Patients with a single mild reaction had only a 79% chance of having a positive OAC. This was contrasted with mild reactions occurring on 2 or more occasions, for which the percentage of positive OACs increased to 88%. For moderate prior reactions, although this difference (73% vs 86%) appeared to be significant, the *P* value was not statistically significant. With respect to treatment location of prior reactions, except for hospital treatment (positive OAC in 23 of 23 patients), no predictive value was found if home or ED was used for treatment during prior reactions, even analyzing single vs multiple reactors (home, 76% and 90%; ED, 79% and 87%). It was associated with a negative OAC for 10% to 24% of those patients not treated in the hospital for their

Table 1. Characteristics of the Study Population Historically Associated With Respiratory Reactions After Ingesting Aspirin or NSAIDs

Characteristics	Single reactors (n = 90)	Multiple reactors (n = 141)	All reactors (n = 231)
Sex, No. (%)			
Female	60 (66)	80 (57)	140 (61)
Male	30 (34)	61 (43)	91 (39)
Age, mean (SD), y	46.3 (1.3)	46 (0.9)	46.1 (0.7)
Skin test result, No. (%)			
Positive	62 (68)	101 (73)	163 (71)
Negative	28 (32)	40 (27)	68 (29)
No. of sinus infection per year, mean (SD)	4.9 (0.4)	5.5 (0.4)	5.3 (0.3)
No. of sinus surgical procedures, mean (SD)	2.8 (0.2)	3.1 (0.2)	3 (0.1)
Smell score, No. (%)			
0	57 (63.3)	86 (61)	143 (61.9)
1	15 (16.7)	25 (17.7)	40 (17.3)
2	5 (5.6)	8 (5.7)	13 (5.6)
3	8 (8.9)	16 (11.3)	24 (10.4)
4	5 (5.6)	6 (4.3)	11 (5.4)
Severity of historical reactions, No. (%)			
Mild	28 (31.1)	49 (34.8)	77 (33.3)
Moderate	44 (48.9)	65 (46.1)	109 (47.2)
Severe	18 (20)	27 (19.1)	45 (19.5)
Treatment location of historical reactions, No. (%)			
Home	37 (41.1)	61 (43.3)	98 (42.4)
ED	42 (46.7)	68 (48.2)	92 (47.6)
Hospital	11 (12.2)	12 (8.5)	23 (10)
OAC result, No. (%)			
Negative	18 (20)	15 (10.6)	33 (14.3)
Positive	72 (80)	126 (89.4)	198 (85.7)

Abbreviations: ED, emergency department; NSAIDs, nonsteroidal anti-inflammatory drugs; OAC, oral aspirin challenge.

reactions (208). All associations for positive OACs are summarized in Table 2.

On multivariate analysis, factors associated with the risk of having a positive OAC were age ($P = .03$), smell score ($P = .002$), and multiple previous historical reaction ($P = .048$). The age was inversely associated with a positive OAC. Patients 40 years or younger had significantly greater risk of a positive OAC than those older than 40 years (OR, 2.67; 95% CI, 1–7.11; $P = .049$). Patients with impaired sense of smell (smell score of 0 to 2) had a greater risk of positive OACs (OR, 4.123; 95% CI, 1.7–9.98). Having multiple previous historical reactions yielded a 2.19-fold (95% CI, 1–4.76) greater risk of having a positive OAC (Table 3). Based on these results, the model to estimate for having a positive OAC was calculated as follows:

$Z = 3.193 - (0.039 \times \text{age}) + (1.417 \times \text{sense of smell}) - (0.785 \times \text{reaction number})$,

with 1 used for a smell score of 0 to 2, 0 used for a smell score of 3 to 5, 1 used for a single reactor, and 0 used for multiple reactors.

If the $P(Y) = 1/1 + e^{-Z}$ value is found to be greater than 0.50, patients will have a positive OAC. The model correctly classified 86% of all cases and 99.5% of cases with positive OACs.

DISCUSSION

This study demonstrates the value of the history in patients with chronic sinusitis, nasal polyps, and asthma in estimating their chances of having a positive OAC and thus a secure diagnosis of AERD. At 1 of the 2 extremes, patients whose prior reactions, associated with full dose of aspirin or NSAIDs, were classified as severe reactors experienced positive OACs in 100% (45/45) of the patients. At the other extreme, patients with nasal polyps, sinusitis, and asthma who did not recall a prior aspirin- or NSAID-associated respiratory reaction or never used these drugs during the time when they had their inflammatory respiratory disease had a 42% chance of having a positive OAC. In our small sample, the percentage of positive OACs is slightly higher than prior studies. Weber et al[12] conducted OACs in 38 patients with nasal polyps, sinusitis, and asthma who did not recall having been exposed to aspirin or NSAIDs and found that 13 of 38 (34%) had positive OACs. Delaney[13] also challenged 45 patients with nasal polyps, sinusitis, and asthma without prior history of aspirin- or NSAID-associated asthma attacks and found that 9 of 45 (20%) had positive OACs. Thus, in the absence of a history of aspirin- or NSAID-associated respiratory reactions, the likelihood of a positive OAC is lower than those of patients with a prior history of an asthma attack after ingesting NSAIDs but still must be kept in mind. This group represents the main area where underdiagnosis of AERD is likely to occur.

Despite historical reactions that sound convincing, a substantial number of patients (33 of 231 [14%]) have been previously diagnosed as having AERD but do not have this disease (negative OACs). These data are also interesting from another standpoint. Despite one change in prechallenge protocols since 1983, the addition of LDs during OACs, the percentage of patients in our current study who thought they had AERD but had a negative OAC was 33 of 231 (14%), which is similar to that reported in 1983, namely, 8 of 50 (16%).[11]

Although none of the patients in our current study were taking LDs at the time of their historical reactions, 175 of 231 (76%) were taking LDs during their OACs. We cannot exclude the possibility that a small number of patients had false-negative OACs because they were taking LDs at the time of the OAC. Most patients had naso-ocular reactions, with or without an associated bronchial reaction, even while taking LDs. LDs are known to not block aspirin-induced upper respiratory tract reactions,[14] and therefore, the only potential false-negative reactions to aspirin might occur in patients who have pure lower airway reactions but were taking LDs that block the lower airway from participating in

Table 2. Historical Factors Associated With Positive Oral Aspirin Challenge

Factors	Single reactors, No. (%) (n = 90)	Multiple reactors, No. (%) (n = 141)	Whole group, No. (%)	*P* value
Smell score				
0–2	65 (84)	109 (92)	174 (89)	
3–4	7 (54)	17 (77)	24 (69)	.02[a]
Severity of historical reactions				
Mild	22 (79)	43 (88)	65 (84)	
Moderate	32 (73)	56 (86)	88 (80)	.007[b]
Severe	18 (100)	27 (100)	45 (100)	
Treatment location of historical reactions				
Home	28 (76)	55 (90)	83 (84)	
ED	33 (79)	59 (87)	92 (84)	.11[b]
Hospital	11 (100)	12 (100)	23 (100)	

Abbreviation: ED, emergency department.

[a] Smell score of 0 to 2 vs 3 to 4 by χ^2 analysis.

[b] Among 3 groups by analysis of variance.

Table 3. Multivariate Analysis Using Logistic Regression Model Based on Positive OAC[a]

Characteristics	OR (95% CI) for positive OAC	*P* value
Age ≤40 y	2.67 (1–7.11)	.049
Sex		.44
Atopy		.69
No. of sinus infections per year		.15
No. of sinus surgical procedures		.22
Smell score of 0–2 vs 3–4	4.123 (1.7–9.98)	.002
Severity of previous reaction		.61
No. of previous reactions		
Single vs multiple reaction	2.19 (1–4.76)	.048
Treatment location of previous reaction		.71
Leukotriene modifier use at time of challenge		.53

Abbreviations: CI, confidence interval; OAC, oral aspirin challenge; OR, odds ratio.
[a] Only the ORs that have significant *P* values are listed in the table.

the aspirin-induced asthma attack. In a previous 1983 study, 3 of 50 patients with potential AERD (6%) underwent OACs and had pure bronchial reactions.[11] In another study we showed that only half of the bronchial reactions were blocked by LDs.[14] Although the potential for only bronchial reactions occurring during OAC in our study population is estimated to be no more than 6% (14/231 patients), we observed pure bronchial reaction only in 3 patients. Thus, we infer that less than 1% of patients could have had false-negative OACs. Even if these 3 patients would have had positive OACs if we had withheld montelukast, the percentage of positive OACs would have only increased from 86% to 87% for the 231 patients.

These data provide prechallenge probability that the OAC will be positive and that aspirin desensitization should be undertaken. It has been demonstrated for most patients with AERD that aspirin desensitization has efficacy in reducing upper airway congestion, reducing polyp formation, and improving asthma control. The alternative to OAC and aspirin desensitization continues to be avoidance of all NSAIDs combined with controller therapy, including LDs and topical and systemic steroids. For patients who need aspirin for cardiac prophylaxis, pain management, or other indications, aspirin challenges would be appropriate.[3] Therefore, using data from this study, the physician can better discuss the probability of a positive OAC with patients who need aspirin for any of these indications. Young patients with multiple reactions and poor sense of smell will be particularly good candidates for aspirin desensitization.

Upper airway involvement is a key part of AERD, and the best indicator of this is impaired sense of smell.[1] Thus, we focused on whether absence of smell might be a good clinical predictor of a positive OAC. Poor sense of smell regardless of the number of sinus infections per year, the number of sinus surgical procedures, and the number, severity, and treatment location of historical reaction were significantly related to positive OACs.

The logical criticism of this study is that it relies on the memory of patients with respect to the details of their prior reactions to aspirin or NSAIDs. However, when we discussed this issue with patients, they consistently told us that prior historical reactions to aspirin ASA and NSAIDs were frequently traumatic enough so that details were strongly imprinted in their minds. Even events of 20 years ago were remembered in detail. We had medical records from referring physicians. For the most part these reports also relied on the patients' recall of past events but nevertheless were consistent with current recall of these events. In a medical care provision system in which ED records could be kept electronically and retrieved for studies such as this, it might be possible to corroborate patient's memory about these events. However, although ED records might record presence of an asthma attack and treatment rendered, busy ED physicians may not necessarily discover or link aspirin or NSAID ingestion with asthma attacks that they are treating in the ED.

In conclusion, if patients had severe asthma attacks associated with aspirin or NSAID ingestion and/or were admitted to the hospital for these reactions, they had a 100% chance of having a positive OAC and thus having AERD and would be eligible for aspirin desensitization. If a patient had a mild or moderate prior asthma attack associated with aspirin or NSAIDs, they had a 73% to 79% chance of having AERD with 1 prior reaction and an 88% to 86% chance with multiple prior reactions. Poor sense of smell was a strong predictor of having AERD (89%) when compared with a good sense of smell (69%). Without prior exposure to aspirin or NSAIDs, even in the presence of nasal polyps, asthma, chronic sinusitis, and poor sense of smell, one's chances of having AERD is only approximately 20% according to Delaney,[13] 34% according to Weber et al,[12] and 42% based on our current study. In addition, to estimate the probability of having positive OACs, the statistical model that includes age, sense of smell, and prior reaction numbers seems easy to use in clinical practice. We think this information will be useful in giving clinicians the data with which to inform patients and other physicians about the likelihood of having AERD and thus having the potential option of undergoing aspirin desensitization treatment.

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