Safety of Aspirin Desensitization in Patients With Reported Aspirin Allergy and Cardiovascular Disease

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ABSTRACT

Background: Aspirin (ASA) is the drug of choice in patients with coronary artery disease for primary and secondary prevention. This poses a problem for those patients reporting hypersensitivity to this drug or class of drugs.

Hypothesis: Desensitization to ASA may be carried out safely and effectively in patients with reported ASA or nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity needing ASA for cardiac indications. Our 7-step protocol is one choice for a rapid desensitization protocol.

Methods: A retrospective chart review was conducted evaluating ASA desensitization in patients with reported ASA or NSAID hypersensitivity and a cardiac indication for ASA.

Results: In 160 evaluations over 15 years, 89 desensitizations were performed in both the inpatient and outpatient setting with only 16 reactions (18%). Eleven of these 16 patients (68.7%) were able to take daily ASA. Twenty-six desensitization procedures were performed with our 7-step rapid desensitization protocol in 10 inpatients and 16 outpatients with 3 reactions (18.75% of reactions). Initial reaction to ASA involving angioedema and reacting to ASA within the past year increased the risk of having a reaction to desensitization.

Conclusions: Desensitization may be safely performed in patients with reported ASA or NSAID hypersensitivity and a cardiac indication for ASA. Our 7-step rapid protocol may be used in both the inpatient and outpatient setting to desensitize these patients. Patients who had angioedema with ASA ingestion or a reaction to ASA within the past year are at higher risk for reaction during the desensitization protocol.

Introduction

Aspirin (ASA) has been shown to be effective at reducing cardiovascular events; unless otherwise contraindicated, it is recommended for both primary prevention in those at risk of cardiovascular disease and secondary prevention for those who already have cardiovascular disease.[1] In the general population, 0.5% to 1.9% experience ASA hypersensitivity[2]; urticarial reactions are reported in about 0.07% to 0.2% and respiratory reactions in up to 10% of asthmatics.[3] Thus, despite the clear benefit of ASA therapy, without some intervention, patients reporting ASA hypersensitivity cannot receive this treatment.

Aspirin hypersensitivity manifests in different clinical patterns. Patients may have ASA-exacerbated respiratory disease (AERD) consisting of asthma (generally severe), chronic rhinosinusitis with nasal polyposis, and respiratory reaction to ASA. Other syndromes include urticaria/angioedema exacerbated by nonsteroidal anti-inflammatory drugs (NSAIDs), multiple NSAID-induced urticaria/angioedema, single NSAID-induced reactions, mixed reactions, or delayed reactions to NSAIDs.[2,4] Because these reactions are not typically related to immunoglobulin E (IgE) production, oral challenge is the only way to objectively prove ASA hypersensitivity; in vitro or in vivo testing is not available.[5,6] In some instances, such as AERD, the introduction of ASA invariably leads to a pulmonary reaction. Thus, in cardiac patients with a convincing history of ASA hypersensitivity (AERD or other), a temporary induction of drug tolerance (oral desensitization) may be preferable to the risk of a reaction to an oral challenge. This temporary induction of tolerance by giving small, incremental doses of medication is referred to in this article as desensitization (DS).

Because of frequent requests for evaluation of patients with reported ASA hypersensitivity and a cardiac indication for ASA, we conducted a retrospective chart review to confirm our clinical experience that DS can be safely carried out in this subset of patients. A secondary objective was to evaluate a 7-step rapid desensitization protocol (7SP) utilized by our clinic in both the inpatient and outpatient settings (Table 1). We compared our 7SP to our other DS procedures to confirm the safety and efficacy of this specific protocol. Our final objective was to evaluate whether any routine historical information was associated with reaction during an ASA DS protocol.

Additional Supporting Information may be found in the online version of this article.

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Table 1. 7-Step Rapid Desensitization Protocol

Volume (mL)[a]	Dosage (mg)[b]	Cumulative Dosage (mg)
0.1	1	1
1	10	11
2	20	31
4	40	71
8	80	151
16	160	311
Entire tablet	325	636
End test		

[a]Dissolve 1 Alka-Seltzer tablet in 32.5 mL water for a 10 mg/mL solution. Use this solution for the first 6 doses. For the last dose, use 1 full Alka-Seltzer tablet. [b]Doses are administered 15 minutes apart.

Methods

Study Population

A retrospective chart review was conducted. We searched our electronic medical record, WUMED (St. Louis, MO), using the terms "aspirin and challenge" and "aspirin and desensitization." Inclusion dates for outpatients were the beginning of the electronic medical record in 2003 to June 30, 2011. Handwritten inpatient consults were reviewed from January 1996 to June 30, 2011.

Patient Selection

Patients included were seen as an inpatient consult or in our outpatient allergy clinic at a tertiary academic institution and had a self-diagnosed history of ASA or NSAID sensitivity who required ASA for coronary artery disease (CAD) or a cardiac procedure. Patients being desensitized specifically to treat AERD were excluded. Patients undergoing DS were evaluated for adverse reactions defined as any change in medical status requiring an alteration of the protocol, or symptoms attributable to ASA up to 1 week after the protocol was completed. Next, DS procedures using 7SP were identified, and adverse reactions were evaluated.

Protocol

In April 2006, we developed our 7SP to use in both the inpatient and outpatient settings using Alka-Seltzer (Bayer HealthCare, Morristown, NJ). Alka-Seltzer is used because it dissolves rapidly and is readily accessible. One Alka-Seltzer containing 325 mg of ASA is dissolved in 32.5 mL of water to create a 10-mg/mL solution, which is further diluted as shown in Table 1. Patients are given doses every 15 to 20 minutes, with the last dose being 1 Alka-Seltzer tablet to ensure tolerability of a full 325 mg of ASA. Total administration time is 90 to 120 minutes. If the patient tolerates DS, 325 mg of ASA is taken daily. If >2 doses are missed, the patient is instructed to return for a repeat DS. Pretreatment with antihistamines is not routinely given prior to initiating this protocol. In addition, β-blockers are not routinely withheld.

Statistical Analysis

Data were extracted from medical records and entered into Microsoft Excel 2007 (Microsoft Corp., Redmond, WA). The following variables were evaluated as predictors for reaction during DS: age, sex, ethnicity, diagnosis of asthma, allergic rhinitis, chronic urticaria or angioedema, presence of nasal polyps, medication with β-blocker, antihistamines, leukotriene antagonists, systemic steroids, use of 7SP, time since last ASA reaction in years, and type of initial reaction to ASA. The initial reaction to ASA was divided into 3 symptom groups: rash or hives, angioedema, and shortness of breath or wheeze. Statistical analysis was performed using SPSS version 20.0 (IBM, Armonk, NY). Procedure outcome data are reported as percentages and mean (SD) unless otherwise indicated. The χ^2 test and Fisher exact test were used to determine if variables were significantly more or less associated with reaction during DS. A P value <0.05 was considered statistically significant, indicating a greater association with reaction.

Investigations were in accordance with the Declaration of Helsinki. Approval for this study was received by the institutional review board at Washington University in St. Louis.

Results

We identified 309 individual patients as needing evaluation for ASA allergy. The distribution of these patients is shown in the Supporting Figure 1. One hundred and fifty patients required ASA for a cardiac indication and were included in our study. Due to overlap, 160 separate patient visits were included in the study. These visits included 133 inpatient and 27 outpatient visits. Diagnostic oral challenge, performed in 34 patients (22.67%), and no procedure in 27 (18%) left 81 patients for whom DS was necessary. Eight of the 150 patients (5.33%) did not have enough information recorded to determine which procedure was chosen. Reasons that no procedure was elected included risk determined to be greater than benefit (9), history not consistent with ASA allergy (9), patient refusal (6), previously unsuccessful DS (1), no need for daily ASA (1), and patient having just received ASA from primary team with no reaction (1).

Eighty-one patients required DS procedures. Seventy-four patients received 1 DS; 6 patients received 2 DS; 1 patient received 3 DS. Demographic information and key characteristics of the DS patients are listed in Table 2. Only 16 patients (19.7%) had a DS reaction. Eleven of these were instructed to continue ASA. Four of the 16 elected not to continue ASA; 1 patient does not have enough documentation to determine if ASA was continued. Characteristics of the patients who had reactions are shown in Table 3.

Of the 81 DS patients, 45 (55.6%) were still on ASA at the time of their most recent clinical evaluation. Only 2 patients (2.2%) had documentation of stopping ASA because of later reactions. One had cough, the other had cutaneous symptoms.

As noted above, 7 patients required ≥1 DS. The reasons for repeat DS were discontinuation of ASA for surgery (3) or colonoscopy (1), reaction to ASA (1), unclear discharge instructions (1), and unclear reasons (2). Hence, there are 89 DS procedures, of which 67 were performed on inpatients and 22 on outpatients. One procedure was aborted in the

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Table 2. Demographic and Key Baseline Characteristics of Patients Undergoing Any Desensitization and the 7SP

Characteristic	All Desensitization Patients, N = 81 (% or SD)	7SP Patients, n = 23 (% or SD)
Sex		
M	31 (38.3)	10 (43.5)
F	50 (61.7)	13 (56.5)
Age	63.85 ± 12.324	62.57 ± 14.148
Race		
White	62 (76.5)	19 (82.6)
Black	17 (21)	3 (13)
Other	1 (1.2)	0 (0)
Asthma	22 (27.2)	6 (26.1)
Polyps	7 (8.6)	1 (4.3)
Allergic rhinitis	13 (16)	9 (39.1)
Chronic urticaria	2 (2.5)	1 (4.3)
Chronic angioedema	1 (1.2)	1 (4.3)
Reported allergy to other medications	54 (66.7)	10 (43.5)
Type of drug initially reacted to:		
ASA	66 (81.5)	17 (73.9)
NSAID[a]	4 (4.9)	2 (8.7)
Initial reaction to ASA involving:[b]		
Rash or hives	41 (50.6)	11 (47.8)
Angioedema	42 (51.9)	11 (47.8)
SOB or wheeze	18 (22.2)	5 (21.7)
Time since last reaction, y		
<1	6 (7.4)	3 (13)
2–5	9 (11.1)	2 (8.7)
6–10	12 (14.8)	2 (8.7)
11–20	15 (18.5)	5 (21.7)
>20	23 (28.4)	6 (26.1)

Abbreviations: 7SP, 7-step rapid desensitization protocol; ASA, aspirin; DS, desensitization; F, female; M, male; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SOB, shortness of breath. [a]Initial NSAID reactions in all desensitization patients were to naproxen sodium in 1 patient and ibuprofen in 3 patients. One patient with an ibuprofen reaction and the patient reacting to naproxen sodium were also in the 7SP group. It was unknown which drug 6 of the patients initially reacted to (7.4%), and 1 patient (1.2%) took ASA and NSAIDS together at the time of initial reaction. [b]Three of the 4 patients reacting to NSAIDs did not have history of reaction to ASA, therefore symptoms were not included in the initial reaction to aspirin column (2 of these are also in the 7SP column). The 1 patient who also later reacted to ASA had his symptoms to ASA included.

Table 3. Characteristics of Patients Having Reactions During Desensitization

Characteristic	No. of Patients, N = 16 (% or SD)
Sex	
M	10 (62.5)
F	6 (37.5)
Age	62.69 ± 12.213
Race	
White	13 (81.3)
Black	3 (18.8)
Asthma	4 (25)
Polyps	1 (6.3)
Allergic rhinitis	2 (12.5)
Chronic urticaria	1 (6.3)
Chronic angioedema	1 (6.3)
Reported allergy to other medications	13 (81.3)
Initial reaction to ASA involving:	
Rash or hives	11 (68.8)
Angioedema	12 (75)
SOB or wheeze	2 (12.5)
Time since last reaction, y	
<1	5 (31.3)
2–5	2 (12.5)
6–10	3 (18.8)
11–20	1 (6.3)
>20	2 (12.5)
DS performed inpatient	11 (68.8)
DS performed outpatient[a]	5 (31.2)
On antihistamines, LTRAs, or systemic steroids at time of procedure	8 (50)
On β-blocker at time of procedure	7 (43.8)
Reaction time after previous dose, h	9.8 ± 1.2
Reaction before next dose (<20 min)	5 (31.25)
Reaction after protocol complete	7 (43.75)
Reaction at dose <105 mg	7 (43.75)
Protocol require adjustment	6 (37.5)
Discharged on ASA	11 (68.8)
Still on ASA	6 (37.5)
Stop ASA later because of reaction	1 (6.3)

Abbreviations: ASA, aspirin; DS, desensitization; F, female; LTRAs, leukotriene antagonists; M, male; SD, standard deviation; SOB, shortness of breath. [a]One of these patients had initial DS as an outpatient and had a reaction; subsequent protocol as an inpatient was completed with no reaction.

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Table 4. Characteristics Evaluated for Increased Association With Reaction During Desensitization

Characteristic	*P* Value
Sex	0.092
Age	0.621
Ethnicity	0.878
Asthma	1
Polyps	0.737
Allergic rhinitis	1
Chronic urticaria	0.575
Chronic angioedema	0.093
Initial reaction to ASA involving:	
Rash or hives	0.262
Angioedema	0.018
SOB or wheeze	0.501
Time since last reaction <1 year	0.006
Setting where DS performed	0.132
On antihistamines, LTRAs, or systemic steroids at time of procedure	0.438
On β-blocker at time of procedure	1
7SP used as protocol	0.102

Abbreviations: 7SP, 7-step rapid desensitization protocol; ASA, aspirin; DS, desensitization; LTRAs, leukotriene antagonists; SOB, shortness of breath.

outpatient clinic and restarted as an inpatient; it is included among the inpatient procedures.

Twenty-six of the 89 (29.2%) procedures used the 7SP. These procedures were performed on 23 patients. Baseline characteristics of these patients are outlined in Table 2. Reactions occurred in 3 patients (13% 7SP patients). Twelve of these patients were still on ASA at the time of their most recent clinical documentation.

Analysis evaluating whether factors were likely to be associated with reaction during DS (Table 4) yielded 2 factors significantly more likely to be associated: time since last reaction if within the past year ($P = 0.006$), and angioedema as an initial reaction to ASA ($P = 0.025$). The use of 7SP did not have increased association with reaction when compared with other DS protocols ($P = 0.102$).

Discussion

Aspirin and NSAID hypersensitivity to multiple members of this class is most often thought to be mediated by inhibition of cyclooxygenase-1 with increased release of leukotrienes; thus, cross-reactivity exists among cyclooxygenase-1 inhibitors. In single-drug reactors, it is possible to have an IgE-mediated reaction to a single agent.[5] Unlike immunotherapy, which induces immunologic tolerance, DS does not alter immune reactivity. Rather, it is thought to render the immune system unable to react; this state is lost quickly if the drug is stopped. Healthcare providers with previous experience performing DS should supervise these procedures.[4] In patients with cutaneous single-drug or cross-reacting multiple-drug reactions needing ASA, DS can generally be completed in 1 day, but patients with AERD typically have reactions during the course of the protocol, necessitating multiday protocols for DS.[7]

There have previously been several small case series demonstrating ASA desensitization in patients with CAD. Most protocols were carried out in an inpatient setting,[8–15] and 1 group used a multiday protocol in an outpatient setting.[16] It is not clear if Christou et al performed desensitization on inpatients or outpatients.[17] The majority of these case series consisted of <20 patients, though 1 European group had 42 patients[15] and another had 26.[10] These protocols have had good outcomes. Wong et al have published a rapid protocol with dosing intervals of 10 to 30 minutes, which is similar to that presented here, but it was used only in the inpatient setting for patients with CAD.[9]

In our patient population, diagnoses for which ASA was required were cardiac in nature and ranged from primary CAD prevention to placement of a drug-eluting stent. As mentioned in Table 2, there were 7 patients with nasal polyps, 22 with asthma, and 18 initial reactions that included shortness of breath or wheezing. Because oral challenges were not conducted for unequivocal diagnosis of ASA allergy, it is possible that some patients actually did have undiagnosed AERD. However, only 5 of the patients with polyps also had asthma and a history of a respiratory reaction to ASA; all tolerated DS without reaction.

When evaluating our DS outcomes, we classified patients as having a reaction if there were any problems during the DS, regardless of whether or not they were felt to be a direct result of ASA. These reactions are characterized in Table 5. The majority of the reactions were mild and cutaneous or gastrointestinal in nature. Eleven of the 16 patients (68.7%) were discharged from either the hospital or clinic with instructions to continue ASA. Five of the 16 reactions (31.2%) occurred in patients receiving DS as an outpatient. No patients died, 1 had his hospitalization prolonged by a few hours, and patient 44 went to the emergency department. Four patients had symptoms that were considered severe. Three of these reactions were not clearly linked to ASA (patients 44, 111, and 131), and patient 125 was noted to be wheezing prior to beginning DS, though it is likely ASA was involved in the reaction. Six of the patients having reactions were documented to still be on ASA during their most recent clinical evaluation. Only 1 patient with a reaction during the protocol later chose to discontinue daily ASA due to a subsequent reaction.

Previously, the only protocol that has been published for outpatient ASA DS requires 3 days.[16] The 7SP presented here was used in the clinic 16 times and in 10 inpatient procedures. Of the 3 reactions with 7SP, 2 occurred in the outpatient setting; all 3 patients had angioedema. Two of the 3 reactions occurred within 24 hours of completing the protocol, and these 2 patients continued ASA therapy. The third elected alternative antiplatelet therapy. When compared with all DS procedures, the use of the 7SP was not significantly more associated with reaction ($P = 0.102$).

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Table 5. Summary of Reactions and Ability to Tolerate ASA

Patient	Symptoms	Cumulative Dose (mg)	Tolerate Daily ASA?
9	Angioedema of fingers	636	Yes
10	Angioedema of lip, itch	31	No
22	Itch	Not documented	No
31	Itch	314	Yes
38	Itch	14	Yes
44	Bronchospasm	311	Yes
52	Hives	836.1	Yes
78	Rash	Not documented	Yes
82	Nausea, vomiting	1	Yes[a]
88	Angioedema of lip	27	Yes
111	Pulmonary edema, wheeze	101.5	Yes
112	Itch, hives	3.25	Yes[b]
125	Epigastric burning, CP, wheeze	325	Not documented[c]
131	CP, diaphoresis, bradycardia	30	No
147	Hives	644	No
148	Facial swelling	631	Yes

Abbreviations: ASA, aspirin; CP, chest pain. [a]Patient 82 had to undergo a new protocol, which was tolerated with no symptoms. [b]Patient 112 chose to stop daily ASA therapy because of "skin symptoms." Several years later, he underwent new DS without reaction and currently tolerates daily ASA therapy. [c]Not enough documentation to determine whether ASA was continued after the reaction was treated.

To our knowledge, this is the first rapid protocol that has been shown to be both safe and effective in the outpatient setting.

Factors that may affect the outcome of desensitization to ASA in cardiac patients have not been previously evaluated. Urticaria and angioedema are typically documented together in discussions of symptoms upon ASA ingestion, as they relate to oral challenge or DS.[3,8] Our data suggest that angioedema alone, with or without urticaria, is more likely to be associated with a reaction during DS ($P = 0.025$) but does not preclude successful DS. Patients who had their last reaction to ASA within the past year also had significantly more reactions during DS ($P = 0.006$). Knowledge of these 2 factors may allow the allergist to better individualize DS protocols.

Study Limitations

Our study does have several limitations. As a retrospective chart review, documentation was at times missing, such as reaction history to other NSAIDs. The study is also subject to recall bias. Reactions were historical and not witnessed, and diagnostic oral challenges were not performed in DS patients due to safety concerns, so it is possible that some of our patients may not have had true ASA hypersensitivity. Follow-up appointments were not routinely scheduled for all patients undergoing DS to ASA for cardiac indications, which decreases the information available. We also recognize the need for future, prospective analysis to determine whether or not angioedema and the length of time since a reaction to ASA can truly be used as predictors for reaction during DS. The patient population presented here does not include patients with diagnosed AERD. Although we do desensitize AERD patients to treat their respiratory disease, none of our AERD population needed ASA for a cardiac indication. Therefore, the 7SP as presented does not apply to this subset of patients. For further reading on ASA DS in patients with AERD, the reader is directed to a review by Lee and Stevenson.[18] Nevertheless, our clinical experience with 81 patients and 89 DS procedures adds to the literature on the safety of ASA DS in non-AERD patients with a cardiac requirement for ASA.

Conclusion

Desensitization may be completed safely in patients with historical reaction to ASA of the single-drug or multidrug type requiring this therapy for cardiac reasons. Our 7SP is safe and effective in this population and may be used in either the inpatient or outpatient setting. Patients with angioedema to ASA or their last reaction to ASA within the past year may be more likely to have reactions during or shortly after DS, though most reactions are mild and do not preclude the subsequent use of ASA in these patients. Prospective studies should be used to replicate these findings and further quantify the nature of ASA hypersensitivity in patients needing ASA for cardiac reasons.

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