

Outpatient Aspirin Desensitization for Patients With Aspirin Hypersensitivity and Cardiac Disease

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Background: Cardiac disease is common and often treated with aspirin therapy. Patients who develop an immunoglobulin E (IgE) hypersensitivity reaction to aspirin must abort treatment and receive alternative antithrombotic agents. Aspirin desensitization is a therapeutic procedure that may allow patients with a history of hypersensitivity to safely resume aspirin treatment. A variety of inpatient desensitization protocols have been published for IgE-mediated reactions, but outpatient regimens have not been previously reported.

Objective: We aimed to determine the efficacy and safety of a multiday outpatient aspirin desensitization protocol for patients with an IgE-mediated aspirin hypersensitivity.

Methods: We retrospectively assessed the efficacy of a multidose aspirin desensitization protocol performed in a university allergy-immunology clinic between July 2006 and December 2009. Patients were referred for a diagnosis of aspirin hypersensitivity and required aspirin for cardiac disease treatment. The protocol involved 10 or 12 aspirin doses depending on the final dose of 81 or 325 mg. Patients were desensitized over 2 to 3 half-days and were able to return home in between desensitization sessions.

Results: A total of 9 patients with cardiac disease and aspirin hypersensitivity underwent an outpatient multiday aspirin desensitization. Eight patients (89%) were successfully desensitized and 1 patient declined to continue with further desensitization. No adverse reactions requiring inpatient hospital care occurred during desensitization.

Conclusions: This novel outpatient multiday aspirin desensitization protocol was a safe and effective approach for the treatment of aspirin hypersensitivity in patients with cardiac disease who require aspirin therapy. This flexible protocol is convenient for patients by avoiding hospital admission and full-day time commitments.

Key Words: aspirin desensitization, aspirin hypersensitivity, cardiac disease

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Aspirin (also known as acetylsalicylic acid), synthesized in 1897 by Felix Hoffman, is widely used for its antithrombotic effect by inhibiting cyclooxygenase in platelets.¹ Due to its rapid inhibition of thromboxane-mediated platelet aggregation, daily aspirin is a mainstay in the treatment and prevention of cardiac disease and other vascular thrombotic events. Current guidelines recommend indefinite daily oral aspirin therapy for patients with stable coronary artery disease (CAD), as well as those with a history of myocardial infarction and percutaneous coronary intervention (Grade 1A recommendation).^{2–4} Additionally, daily aspirin therapy is a Grade 1A recommendation for patients with moderate risk for a coronary event.⁴ Other indications for aspirin treatment include peripheral

vascular disease, cerebral vascular disease, prosthetic heart valves, and hypercoagulable conditions such as antiphospholipid antibody syndrome. The length and dose of therapy vary based on the clinical indication.

A meta-analysis of randomized trials of antiplatelet therapy found that aspirin was the most widely studied antiplatelet drug for the prevention of death, myocardial infarction, and stroke in high-risk patients.⁵ In 65 published trials, antiplatelet monotherapy with any dose of aspirin had a 23% odds reduction for a vascular event compared with treatment with placebo.⁵ With the great clinical relevance of aspirin treatment, it is important to ensure that patients who require this therapy are able to safely receive this medication.

MEDICATION DESENSITIZATION

Desensitization is a procedure where patients receive incremental doses of a drug to which they have previously experienced a hypersensitivity reaction until the therapeutic target dosage is achieved.⁶ The majority of published medication desensitization protocols have demonstrated safety and efficacy.^{7–9} Due to the risk of allergic reactions and rarely anaphylaxis, desensitization is typically performed by a trained allergist in the inpatient intensive care unit setting. Desensitization is contraindicated in patients who have experienced toxic epidermal necrolysis or Stevens-Johnson syndrome.⁶

ASPIRIN HYPERSENSITIVITY AND DESENSITIZATION

In the general population, hypersensitivity reactions to aspirin range from 0.6% to 2.5% and include aspirin-exacerbated respiratory disease (AERD), idiopathic urticaria and/or angioedema, and immunoglobulin (Ig) E-mediated reactions.¹⁰ In AERD and chronic idiopathic urticaria caused by aspirin, patients typically react to all cyclooxygenase-1 inhibitor medications and are instructed to avoid ingestion of all members of this drug class. These reactions are not considered to be IgE-mediated.¹¹ In contrast, patients who have an IgE-mediated hypersensitivity avoid only that specific medication.

While the actual prevalence of IgE-mediated hypersensitivity to aspirin alone is unknown, aspirin allergy is a frequent concern for both patients and medical practitioners. Clinical experience with aspirin desensitization for Type I immediate hypersensitivity reactions is somewhat limited compared with the well-studied aspirin desensitization protocols for the treatment of AERD.^{12–17} The 2 to 3 days protocols for AERD start with an initial dose of 30 mg with subsequent doses given every 3 hours.^{18,19} In general, 3 doses are given per day with spirometry performed at the time of dosing.^{17,20,21}

For patients with cardiac disease, aspirin desensitization is the only option that will allow these patients to safely receive daily aspirin therapy.^{22–24} We describe a novel outpatient protocol for elective desensitization in patients with Type I immediate hypersensitivity reactions to aspirin who have cardiac disease.

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METHODS

Study Design

We conducted a retrospective analysis of patients who were examined in an outpatient university allergy-immunology center between November 2006 and December 2009 for drug allergy based on an International Classification of Diseases—Ninth Revision code of 995.3 (Allergy, unspecified) and/or 995.27 (Drug allergy, NEC [Not Elsewhere Classified]). The electronic medical record was reviewed to determine if patients were allergic to aspirin and if they had undergone an elective oral desensitization for an immediate hypersensitivity reaction. This study was approved by the Institutional Review Board at our facility.

Study Population

A total of 9 stable outpatients were identified who needed aspirin therapy for pharmacologic treatment of cardiac disease but had experienced an immediate hypersensitivity reaction to aspirin. Our institution-specific clinical algorithm for identifying patients appropriate for this outpatient aspirin desensitization is presented in Figure 1. Baseline clinical and demographic characteristics, including age, gender, type of hypersensitivity reaction, indication for desensitization, and target aspirin dose were recorded (Table 1). The mean age of the patients was 51.8 years and 55.5% were male. The

diagnosis of aspirin allergy was based on a clinical history of a hypersensitivity reaction immediately following oral aspirin ingestion. Patients were classified by the type of historical hypersensitivity reaction, with the majority (88.9%) manifesting cutaneous symptoms such as an erythematous, pruritic rash, and urticaria. A total of 3 patients (33.3%) experienced facial, lip and tongue angioedema. In 1 patient, angioedema was the sole manifestation; the second patient experienced angioedema and urticaria; and the third experienced angioedema, urticaria, and respiratory distress. The mean time from the onset of aspirin hypersensitivity to the time of outpatient desensitization was 277 months as many of these patients had taken aspirin in the past for an alternate indication and had subsequently developed cardiac disease. No patients were taking aspirin at the time of their visit, and all were strictly avoiding this medication. Patients were able to tolerate other members of the NSAID family, further supporting an IgE-mediated mechanism. Patients did not have underlying chronic urticaria or asthma at the time of their evaluation.

Desensitization Protocol

Prior to undergoing oral aspirin desensitization, the benefits and risks of oral desensitization, including anaphylaxis and death, were discussed with patients who provided informed verbal and written consent. At the onset of the desensitization, patients had to be free of any skin rashes. None of the patients was receiving concomitant oral corticosteroids or antihistamines. Moreover, patients were not treated with antihistamines or steroids prior to the procedure. Epinephrine when used to treat anaphylaxis in patients taking beta-blockers may be ineffective or promote undesired alpha-adrenergic and vagotonic effects.^{25–29} Therefore, after discussion with their cardiologist, patients discontinued beta-blockers for at least 48 hours prior to the procedure and resumed this medication following completion of desensitization.

All procedures were performed in the outpatient office setting. Baseline vital signs were obtained before beginning this multistep protocol. Our institutional pharmacy constituted a 1 mg/mL aspirin solution by dissolving a crushed 81-mg aspirin tablet in 81 mL of sterile water per our instructions. This method has been used safely for previous desensitizations to other drugs in our clinic.³⁰ This solution was freshly prepared for each day of the desensitization. Beginning with a 0.1 mg dose, escalating doses were administered orally every 60 minutes in the outpatient allergy office over 2 or 3 partial days (Table 2). Serial vital signs were obtained during the desensitization. At dose 10 or 12, patients received a whole 81

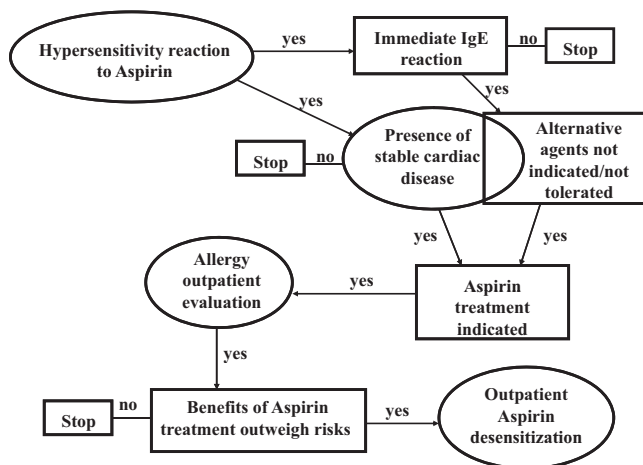


FIGURE 1. Clinical algorithm for outpatient aspirin desensitization.

TABLE 1. Characteristics of Patients Desensitized to Aspirin

Patient	Sex	Age (yr)	Type of Initial Aspirin HSR	Time From Initial Aspirin HSR → DS (mo)	Clinical Indication for Aspirin DS	Target Dose of Aspirin (mg)	Length of DS (d)
1	M	67	Hives	480	CAD	81	3
2	M	32	Hives, angioedema, respiratory distress	204	CAD	325	2
3	M	76	Hives	720	CAD	325	3
4	M	65	Rash	480	CAD	325	3
5	M	23	Hives	100	Aortic valve replacement/SBE	81	2
6	F	33	Rash	276	CAD, APS	81	2
7	F	61	Hives, angioedema	36	CAD	325	2
8	F	47	Rash	65	CAD	325	3
9	F	62	Angioedema	132	CAD	81	2
Mean		51.8		277			2.4

HSR indicates hypersensitivity reaction; DS, desensitization; M, male; F, female; CAD, coronary artery disease; SBE, subacute bacterial endocarditis; APS, antiphospholipid antibody syndrome.

TABLE 2. Aspirin Desensitization Protocol

Dose Number	Aspirin Dose (mg)	Day Number of Protocol
1	0.1	1
2	0.2	1
3	0.5	1
4	1.0	1
5	2.0	1 or 2
6	5.0	2
7	10.0	2
8	20.0	2
9	40.5	2
10	81.0	2 or 3
11	162.0	3
12	325.0	3

Doses 1–8 were an oral aspirin solution with a concentration of (1 mg/1mL); doses 10–12 were an oral aspirin tablet.

Doses were given 1 hour apart.

Dose 5 was given on day 1 or 2; dose 10 was given on day 2 or 3.

Patients were observed for 2 additional hours following the final dose (dose 10 or 12).

or 325 mg aspirin tablet, respectively, depending on their target therapeutic dose. Following the final dose, patients were observed for 2 additional hours in the office prior to discharge. Patients were desensitized over 2- to 3-half day clinical encounters and were able to go home in between desensitization sessions.

On completion of a successful desensitization, all patients were instructed to contact their physicians or go to the ER if they developed any allergic symptoms while taking aspirin. Since most patients will become resensitized to aspirin within 2 to 7 aspirin free days, patients were instructed not to miss a dose of aspirin for more than 24 hours as this would place them at risk for a serious allergic reaction.^{31,32} No formal follow-up visit was scheduled for the patients who completed the desensitization. At 6 months following desensitization completion, the patient's continued tolerance of aspirin was confirmed using the medical record or telephone contact.

RESULTS

A total of 9 oral outpatient aspirin desensitizations for patients with cardiac disease were performed over this time period (between November 2006 and December 2009). Desensitization failure was defined as inability to reach the target dose due to

reactions such as persistent rash or urticaria, respiratory distress, or cardiovascular compromise. Of the 9 patients, 8 (89%) were able to tolerate the whole aspirin dose at completion of the protocol without complications. In 1 patient who did not complete desensitization, he developed an itchy, macular rash on his forearm 15 minutes following the 0.5 mg dose on day 1, which was treated with 10 mg of cetirizine and resolved after 30 minutes. He subsequently received the 1.0 mg dose without incident. On day 2, he tolerated a repeat of the 1.0 mg dose. At the 2.0 mg dose, he developed a single hive on his forearm within 15 minutes, which was treated with 10 mg of cetirizine. The hive resolved but he declined to continue with further desensitization. He did not experience any swelling, throat tightness, difficulty in breathing, or hypotension.

Four other patients (50% of those who successfully completed desensitization) experienced transient cutaneous reactions during desensitization but were able to proceed without problems. Symptoms resolved in 2 of these patients without any pharmacologic treatment: one patient experienced facial itching with the day 1 0.2 mg dose which resolved in 30 minutes and the other patient developed 2 linear hives at the 81 mg dose on day 3, which resolved prior to the 162 and 325 mg doses. A third patient had 2 hives on the chest and facial itching at the 0.1 mg dose which resolved after 10 mg of cetirizine. The fourth patient experienced a rash on the chest and back and itching at the 81 mg dose on day 3. After 10 mg of cetirizine, the symptoms resolved and the patient tolerated the 162 mg and 325 mg doses. No patients experienced respiratory distress, cardiovascular compromise, or required epinephrine treatment during this protocol. All 8 patients (100%) who successfully completed desensitization continued to tolerate aspirin at 6 months following the procedure. The immediate and the 6 months outcomes as well as reactions and treatments during the desensitization are presented in Table 3.

DISCUSSION

Aspirin allergy poses a problem for the acute and long-term treatment of patients with cardiac disease as alternative antiplatelet therapies are somewhat limited. Patients with immediate aspirin hypersensitivity have an increased risk of reactions including respiratory or cardiovascular compromise if they ingest aspirin without undergoing desensitization. It has been observed in our study and previous studies that aspirin desensitization can be a safe method for enabling aspirin allergic patients to receive this medication on a daily basis.

The precise mechanism of desensitization for patients with IgE-mediated reactions is unknown. Repeated and sustained aspirin

TABLE 3. Aspirin Desensitization Clinical Outcomes

Patient Number	Successful DS: Immediate Y/N	Successful DS: After 6 mo Y/N	Reaction During DS Y/N	Dose at Reaction (mg)	Type of Reaction	Treatment During DS Y/N	Treatment Medication, Dose
1	Yes	Yes	Yes	0.1	Hives, facial itching	Yes	Cetirizine 10 mg
2	Yes	Yes	Yes	0.2	Facial itching	No	
3	Yes	Yes	Yes	81	Hives	No	
4	Yes	Yes	No			N/A	
5	No*	N/A	Yes	0.5;2	Rash, hives	Yes	Cetirizine 10 mg × 2
6	Yes	Yes	No			N/A	
7	Yes	Yes	No			N/A	
8	Yes	Yes	Yes	81	Rash, itching	Yes	Cetirizine 10 mg
9	Yes	Yes	No			No	
Total (%)	88.9%	100%	55.5%			33.3%	

*Patient declined to continue with desensitization.

DS indicates desensitization; Y, yes; N, no; N/A, not applicable.

exposure may lead to gradual saturation of anti-aspirin IgE antibody binding sites on basophils and mast cells and possibly depletion of inflammatory cytokines.^{22,33}

In our study, patients were classified as having an immediate IgE-mediated hypersensitivity to aspirin based on their clinical history. Although it was possible that some of the patients who were successfully desensitized may not have had IgE-mediated reactions, commercially available *in vitro* tests were not available to confirm the presence of aspirin specific IgE antibodies.^{34,35} The term desensitization has been used to describe the process of inducing immunologic tolerance to an antigen against which specific IgE antibodies are present.^{35–37} We used the term desensitization to describe our protocol because it involved slowly increasing medication dosages (ie, doubling of the dose every hour) and more total medication doses than a graded challenge. It is possible that some of these patients would have tolerated a graded challenge. However, given that there are no standardized tests to evaluate IgE-mediated aspirin hypersensitivity, we felt that desensitization was safer than a challenge in patients with cardiac disease. Additionally, patients preferred the option of desensitization. Finally, the fact that during desensitization more than half of our patients reacted to subtherapeutic doses of aspirin validated our cautious approach.

Our protocol represents a unique approach to desensitizing patients with aspirin allergy. The previously published protocols were performed in the inpatient hospital setting in contrast to our protocol which is the first published protocol for IgE-mediated aspirin desensitization in cardiac patients performed in the outpatient setting. Our protocol allowed patients to go home in between the half-day sessions, whereas previous protocols were performed continuously in the hospital setting. Although other protocols have been performed on an emergent basis for acute cardiac disease, our outpatient protocol has a novel applicability for elective desensitization in stable cardiac patients who require treatment with aspirin. Our protocol did not require premedication and a lower starting dose of 0.1 mg allowed earlier identification of patients prone to experience hypersensitivity reactions.

There have been several previously published aspirin desensitization protocols for patients with cardiac disease. These protocols have demonstrated heterogeneity in terms of total length of the protocol, total number of aspirin doses, and the final target dose. All of these protocols have involved inpatient admissions of various lengths with the number of patients ranging from 1 to 34. These rapid protocols were performed in continuum over 1.5 to 5.5 hours.

In 2000, Wong et al presented a series of 11 patients with aspirin and/or NSAID induced hypersensitivity who underwent aspirin desensitization. Of the 11 patients, 9 received pretreatment with antihistamines, 1 received steroids and antihistamines, and 1 was not premedicated. The protocol length varied between 100 and 200 minutes, and these procedures were performed on an inpatient basis.³⁸ In 2005, Silberman et al desensitized 16 unstable cardiac patients to aspirin over 2.5 to 3.5 hours in the coronary care unit. The 3.5-hour protocol had a lower starting dose of 1 mg compared with 5 mg in the 2.5-hour protocol. Doses were given every 30 minutes up to 75 to 100 mg. One patient was treated with epinephrine and corticosteroids for angioedema 3 hours after completing the protocol, but was successfully rechallenged 2 days later. Another patient developed shortness of breath and nasal swelling 1 hour after the final dose and was not rechallenged.³⁹ Steg and Neukrich-Stoop updated the Silberman et al case series showing the successful desensitization of an additional 18 patients.⁴⁰ Overall, 33 of 34 patients were successfully desensitized using this protocol.

In 2008, Rossini et al published a rapid aspirin desensitization protocol that was successful in 23 of 26 patients with acute CAD who underwent cardiac catheterization and stent placement. Starting

at 1.0 mg, 6 doses were given over 5.5 hours to a target dose of 100 mg.⁴¹ In 2010, using the Rossini protocol, Fernando and Assaad published a case report of successful aspirin desensitization followed by rapid clopidogrel desensitization 3 days later in a patient with ischemic cerebrovascular disease.⁴²

In 2009, Dalmau et al used a modified rapid oral aspirin desensitization protocol combining the Wong and Silberman protocols in 5 patients with acute CAD who required cardiac stent placement. Starting at 0.1 mg, doses were given at 15 to 20 minute intervals up to 100 mg in the hospital setting.^{38,39,43} In 2010, Ortega-Loayza et al used a modification of the Wong protocol to desensitize 3 patients with CAD in the hospital setting. Starting at 0.5 mg, doubling aspirin doses were given every 30 minutes up to 100 mg over 240 minutes. These patients were premedicated with diphenhydramine.^{38,44}

In the Alijotas-Reig case series, 4 pregnant hospitalized patients with antiphospholipid antibody syndrome were desensitized to aspirin using 8 doses given at 15 minute intervals over a 2 hour period up to 100 or 125 mg. The final dose was repeated 24 hours later.³³ This report suggests the safety of aspirin desensitization even in pregnancy.

Unlike inpatient protocols, our outpatient protocol involved 8 to 10 doses that were given 1 hour apart in 2 to 3 half-days. Patients went home in between sessions and did not require premedication. Approximately 89% of patients (8 of 9) were successfully desensitized, and 100% of those successfully desensitized continued to tolerate aspirin at 6 months. Of our patients, 55% experienced reactions during desensitization that promptly resolved spontaneously or with antihistamine treatment. No patients required epinephrine or corticosteroids before or during our protocol. We are not suggesting that this protocol replace inpatient desensitization for acute treatment of cardiac disease, rather that it be considered as a novel and convenient therapeutic option for stable outpatients. If this outpatient regimen was unavailable at our medical institution, these 9 patients would have necessitated admission for inpatient desensitization. Our study is limited by the retrospective analysis and the small sample size.

CONCLUSIONS

Although this outpatient aspirin desensitization was performed on a small case series, this medical procedure may assist in the management of a particular population who require aspirin to treat cardiac disease. Additional studies with larger subject populations are needed to confirm the safety and efficacy of this desensitization treatment. In an age of dual antiplatelet therapy for treatment of cardiac disease and the success of aspirin desensitization protocols for treating immediate hypersensitivity to aspirin, our outpatient protocol may be a convenient and attractive therapeutic option for some patients. Our study represents the first outpatient desensitization protocol for IgE-mediated allergy to aspirin in stable cardiac patients requiring aspirin therapy.

DISCLOSURES

Nothing to declare.

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