Aspirin Allergy Desensitization in Cerebrovascular Disease

A Report of Two Cases, Literature Review and Management Guide for the Neurointerventionalist

SCOTT L ZUCKERMAN, DAVID B SEDER, CRYSTIANA TSUJIURA, DEBORAH CUSHING, HOLLY GALLUP, J MOCCO, RICHARD A HANEL, ROBERT D ECKER

Department of Neurosurgery, Vanderbilt University Medical Center, Nashville, TN, USA

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Summary

Aspirin (ASA) is the mainstay of treatment in cerebrovascular and systemic vascular disease. ASA hypersensitivity can pose a challenge to achieving optimum medical management prior to and after neurointerventional treatment. Desensitization to ASA is well described in the allergy and cardiovascular literature, but there are no similar discussions specific to neurointervention. The purpose of our study was to describe our experience with ASA hypersensitivity management and review the relevant literature.

Two cases of patients with symptomatic cerebrovascular disease requiring neurointervention who were successfully desensitized to their ASA hypersensitivity prior to treatment are described. The subsequent literature is reviewed. Several ASA desensitization protocols exist and have been proven to successfully treat ASA hypersensitivity and allow for ASA therapy to be safely initiated. We describe several previously published protocols.

ASA desensitization is a safe and simple way to manage ASA hypersensitivity. We provide comprehensive management guidelines for the neurointerventionalist engaging in ASA desensitization.

Introduction

There are now multiple commercially available oral drugs that inhibit the ADP receptor/P2Y₁₂ including, clopidogrel, prasugrel, ticlopi-

dine, cangrelor, elinogrel and ticagrelor. However, aspirin (ASA), an irreversible inhibitor of cyclooxygenase-1 (COX-1), remains unique pharmacologically and a pillar of cerebrovascular and systemic vascular disease management.

ASA hypersensitivity can pose a challenge to optimizing medical management in cerebrovascular patients both prior to and after neurointerventional treatment.

Hypersensitivity to ASA can be grouped in three categories: (1) respiratory, (2) cutaneous, and (3) systemic. In a recent systematic literature review, the prevalence of ASA hypersensitivity reactions in the general population ranged from 0.3% to 0.9%¹.

A second study found that 26 out of 1014 patients (2.6%) undergoing cardiac catheterization had a self-reported history of ASA allergy².

Desensitization to ASA is well described in the allergy and cardiovascular literature, but similar discussions to neurointervention are lacking²⁻⁶.

Protocols for desensitization vary widely from those that desensitize patients in hours to days or weeks. Two cases of patients with symptomatic cerebrovascular disease requiring neurointervention who were successfully desensitized to their ASA hypersensitivity prior to treatment are described, and the literature is reviewed. We then provide comprehensive management guidelines for the neurointerventionalist engaging in ASA desensitization.

Figure 1 A) Pre-angioplasty of right vertebral stenosis with basilar pseudo-occlusion. B) Post-angioplasty with resolution of pseudo-occlusion.

Methods

Patients were identified based on a retrospective review of prospectively maintained clinical databases at both Maine Medical Center and Mayo Clinic Jacksonville. IRB approval was obtained based on an expedited review of a minimal risk study. MEDLINE and PubMed records were searched to identify all studies pertaining to ASA hypersensitivity and desensitization in the neurointervention literature. The proceeding terms were used as Medical Subject Heading terms and text words: aspirin, ASA, allergy, ASA hypersensitivity, ASA desensitization, dual anti-platelet management. The reference lists of these articles were examined to identify additional relevant research.

Case 1

A male in his late seventies presented to an outside hospital with acute gait difficulty, ataxia and visual field loss. His medical history revealed a heavy smoking history thirty years prior, esophageal cancer treated with chemotherapy and surgery and hypercholesterolemia treated with a statin. His allergies included both iodinated contrast and ASA with a history of respiratory difficulty and severe polypsis requiring surgery. By the time the patient was evaluated in the emergency department

his symptoms had improved save for gait instability and new hoarseness. Neurological examination revealed a reduced gag reflex and palatal sensation, and severe gait ataxia. MRI/MRA revealed a shower of emboli in the occipital lobes, left thalamus, and bilateral cerebellar hemispheres. Both of his V3 segments had severe atherosclerotic changes just prior to the take-off of the posterior inferior cerebellar arteries. After pretreatment with corticosteroids, cerebral angiography confirmed severe bilateral V3 stenosis with the left vertebral artery with a Mori III lesion that ended in PICA without contribution to the basilar artery. The right vertebral artery was slightly less stenosed and provided some flow to the mid-basilar artery, providing a visual “pseudo-occlusion” of the mid basilar artery (Figure 1A). The dominant flow to the basilar apex was off very small bilateral posterior communicating arteries that provide delayed flow to the posterior circulation.

Four weeks after initial presentation, the patient had improved to his neurologic baseline, and given his allergy to ASA and prior naïveté to antiplatelet medication, was sent out on clopidogrel (Plavix) monotherapy in addition to his statin as medical management. Two weeks later he re-presented with double vision from a new intranuclear ophthalmoplegia (INO) and return of his gait ataxia. Repeat MRI/MRA revealed no new diffusion

Figure 2 A) Recurrent vs. residual ophthalmic aneurysm. B) Unsubtracted image at treatment. C) Follow-up at three months with residual aneurysm filling.

abnormality. The inpatient Allergy Service was consulted and felt the patient to be appropriate for ASA desensitization. On day one the patient was given montelukast (Singulair) 10mg orally. Four hours later he was given 20.25 mg of ASA, three hours later he was given 40.5 mg ASA, two hours later 60.75 mg ASA and then four hours later 81 mg ASA. Then three hours later he took 162 mg ASA, followed by 324 mg ASA. The following morning he was given 325 mg ASA and then brought to neurointervention.

The left vertebral artery was felt to be too diseased to try angioplasty and/or stenting and given the contribution to PICA alone likely not to improve the symptoms. A 5-Fr envoy was brought into the right vertebral artery and hooked to a 10,000 unit flush bag of heparin. The lesion was crossed with a synchro 14 wire (Stryker Neurovascular, Freemont, CA, USA) and a 2×9 mm Gateway balloon (Stryker Neurovascular, Freemont, CA, USA) was used to perform three sequential angioplasties. The technical result at this point was excellent with a smooth 2 mm lumen that now contributed robustly to the posterior circulation with complete resolution of the “pseudo-occlusion” (Figure 1B). It was felt that a stent would be unnecessary. The patient was dismissed to rehabilitation and one week later his gait had normalized and by two weeks his INO had resolved.

Case 2

A female in her early fifties presented with recurrent ophthalmic segment of right internal carotid artery aneurysm. Two years before, she had undergone coil embolization for a ruptured right internal carotid ophthalmic segment aneurysm at an outside hospital. Her medical history revealed previous intracranial hemorrhage. Her allergies included ASA with a history of respiratory difficulty and rash after taking ASA. Neurological examination was intact. MRA revealed a 6mm recurrent versus remnant aneurysm filling at the base of the coil mass. Cerebral angiogram confirmed the MRA findings, in addition to small left middle cerebral artery and left internal carotid artery aneurysms (Figure 2A).

Therapeutic options included observation, microsurgical clipping and endovascular repair. She underwent left craniotomy for clipping of the left-sided lesion with complete aneurysm occlusion. For the right-sided lesion, the decision was made to use a pipeline embolization device (Covidien, Mansfield, MA, USA) for her recurrent right-sided ophthalmic segment aneurysm, Figure 2b.

One month after craniotomy, she was started on appropriate ASA desensitization. Her protocol lasted for a total of nine days. For the first three days of therapy, she was on 20.25 mg ASA, followed by three days of 40.5 mg ASA, three days of 60.75 mg ASA and then 81 mg ASA

daily. Clopidogrel (Plavix) 75 mg daily was also started with the ASA regimen. Aspirin and Clopidogrel (Plavix) function test (Verify Now, Accumetrics) were checked and found to be therapeutic. The procedure was performed under local anesthesia and conscious sedation. A 7-Fr groin sheath was placed. A 6-Fr guide catheter was advanced into the right internal carotid artery. Thirty-five hundred units of heparin were given. A Marksman (Covidien, Mansfield, MA, USA) microcatheter was advanced over a synchro 14 wire (Stryker, Freemont, CA, USA) up to the M1 segment of the right middle cerebral artery, and a Pipeline embolization device, 4 mm×16 mm, was advanced and successfully deployed covering the neck of the aneurysm. The patient was kept on a dual antiplatelet regimen for three months. Clopidogrel (Plavix) was then discontinued. She remains on ASA 81mg daily. Follow-up cerebral angiogram three months post Pipeline demonstrated residual aneurysm filling (Figure 2C). The patient remains on ASA therapy without problem.

Discussion

The combination of dual antiplatelet therapy has been borrowed from the cardiac experience and broadly applied to neurointervention⁹. Dual antiplatelet therapy of ASA and Clopidogrel (Plavix) is most commonly used. With multiple drugs now working at the ADP receptor/P2Y₁₂, Clopidogrel (Plavix) allergy is relatively easily managed. Unlike the ADP receptor/P2Y₁₂ family of drugs, there are no alternative drugs to ASA, which makes ASA sensitivity a challenge to achieving optimal antiplatelet therapy in patients requiring neurointervention. We describe two cases where an ASA allergy was encountered and successfully managed by ASA desensitization. It is our hope that from our experience, neurointerventionalists will be more likely to utilize ASA desensitization when indicated and proceed to optimal antiplatelet therapy. We briefly discuss the literature on ASA allergies, the importance of ASA therapy, desensitization protocols, and how all pertain to the neurointerventionalist's practice.

Aspirin Hypersensitivity Mechanisms and Desensitization

Non-steroidal anti-inflammatory (NSAID) sensitivity, of which ASA was the first drug, is

generally broken down into three categories: (1) asthma, rhinitis, nasal polyposis, (2) cutaneous sensitivity with rash, hives or angioedema, (3) systemic sensitivity with anaphylactoid reaction. The mechanism for NSAID hypersensitivity is generally not IgE-mediated, thus standard skin testing is of little utility, making a good medical history critical to the diagnosis of ASA hypersensitivity¹⁰. Oral challenges have been reported and performed in a protected setting⁴. At least 10% of patients with a history of asthma will have NSAID hypersensitivity¹⁰. The triad of ASA sensitivity, asthma, and nasal polyposis has been called Samter's triad since the seminal paper in 1968¹¹. The more modern term of aspirin exacerbated respiratory disease (AERD) is used today to refer to the asthma, although worsened by ASA, is generally a progressive process over life. NSAID desensitization improves asthmatic control and decreases airway inflammation⁸.

Aspirin desensitization is more often successful in patients with AERD than those with urticaria and angioedema¹². Some authors recommend monitoring the forced expiratory volume (FEV1) during desensitization, with a decrease of 15% grounds for administering repeat equivalent doses until the FEV1 stabilizes¹³. Albuterol can be used to treat symptoms during desensitization. Desensitized patients remain desensitized as long as they continue taking ASA daily – typically a 325 mg daily dose protects against all NSAID reactions. If ASA doses are missed for more than three days, the full desensitization procedure must typically be repeated.

ASA desensitization is common in the cardiac literature. De Luca et al.⁶ encountered 43 patients with ASA hypersensitivity that required coronary angioplasty. Over the course of 4.5 hours and with eight gradual doses from 1 mg to 250 mg, 42 of 43 patients were successfully desensitized. Cortellini et al.¹⁵ evaluated 61 patients with ASA hypersensitivity prior to coronary stenting. Thirty patients had a history of mild reactions to ASA (low risk), and underwent a tolerance test in five steps; 29/30 achieved uneventful desensitization, with one patient developing urticaria. Thirty-one patients had a history of severe reactions to ASA (high risk), and underwent slow desensitization in 12 steps; only three patients did not tolerate and discontinued the test, with 28/31 achieving successful desensitization. Fajt et al.⁵ examined nine patients who, in the course of treatment for cardiac disease,

developed ASA sensitivity⁵. Using a unique outpatient approach that either consisted of ten doses in two days or twelve doses in three and a half days, the authors were able to desensitize eight of the nine patients; the one patient that was not fully desensitized opted to discontinue treatment. Other studies have shown near-perfect sensitization success rates (Table 1). Furthermore, we provide a summary of common ASA desensitization protocols utilized in the cardiac literature (Table 2).

Aspirin Hypersensitivity and Clinical Practice

Aspirin discontinuation or non-compliance can lead to catastrophic complications. Sibon and Orgogozo¹⁹ reported that 4.49% of strokes were related to discontinuation of an antiplate-

let agent, all cases occurring six to ten days after cessation. Maulaz et al.²⁰ conducted a case-control study with 309 patients previously on ASA who suffered an ischemic stroke or transient ischemic attack (TIA). Compared to a control group, ASA interruption yielded an odds ratio for stroke or TIA of 3.4 [1.08-10.63]. The cardiac literature tells a similar story. A recent meta-analysis showed that non-compliance or withdrawal from ASA was associated with a three-fold higher risk of major adverse cardiac events (OR 3.14 [1.75-5.61])²². The risk was magnified in patients with stents. Aspirin is the mainstay in the treatment of cerebrovascular pathology.

Several studies prove the efficacy of dual antiplatelet therapy, both in the neurointervention²³⁻²⁵ and cardiac²⁶⁻²⁹ literature. However, in

Table 1 **Aspirin desensitization studies and outcomes in the cardiac literature**

Study	N	Reason for Desensitization	Results
Cortellini et al., 2012 ¹⁵	61	Percutaneous coronary intervention	<i>Low risk</i> : 29/30 successful long-term desensitization <i>High risk</i> : 28/31 successful long-term desensitization
Silberman et al., 2005 ³	16	Percutaneous coronary intervention	15/16 successful long-term desensitization
De Luca et al., 2012 ⁶	43	Coronary angioplasty	42/43 successful long-term desensitization; all successful stenting
Fajt et al., 2011 ⁵	9	Cardiac disease treatment with aspirin	8/9 successful desensitization; 1 patient opted to discontinue treatment
Rossini et al., 2008 ²	26	Coronary catheterization	23/26 successful long-term desensitization
Wong et al., 2000 ⁴	11	CAD; pulmonary embolism(1) refractory chronic sinusitis/ asthma(1)	9/11 successful long-term desensitization; 2 with urticaria and/or angioedema independent of ASA allergy

Table 2 **Summary of commonly used aspirin desensitization protocols**

Protocol	Dosing Interval	Aspirin Dose (mg)	Total Time	Aspirin Form
Silberman et al. ³				
Protocol 1	30 min	1, 2, 4, 6, 8, 16, 32, 64, 100	4.5 hrs	Oral
Protocol 2	30 min	5, 10, 20, 40, 75	2.5 h	
Wong et al. ⁴	10-20 min	0.1, 0.3, 1, 3, 10, 30, 40, 81, 162, 135	3 h	Oral
Low risk	45 min	10, 25, 25, 50, 50	4.75 hrs	Oral
High risk	20 min	0.1, 1, 1.5, 2, 3, 4, 5, 10, 15, 25, 35, 50	4.75 hrs	
Rossini et al. ²	30 min (3 doses) 120 min (2 doses)	1, 5, 10, 20, 40, 100	5.5 h	Oral

most cases where ASA hypersensitivity is encountered, and dual antiplatelet management is indicated, the cardiac literature often resorts to Clopidogrel (Plavix) monotherapy¹⁸. However, there is no direct evidence to support Clopidogrel (Plavix) monotherapy. Aspirin desensitization then becomes an overlooked management strategy in high-risk patients¹⁸. Reinforcing this underutilization, the neurointerventional literature is devoid of prospective samples, retrospective studies, or even case reports describing ASA desensitization protocols. Thus, a need exists for a straightforward ASA desensitization protocol for the neurointerventionalist.

Though a unified, standardized ASA allergy protocol would be convenient, in reality, allergic desensitization methods are called for in a wide range of clinical settings. Table 2 summa-

rizes several highly cited protocols to be used in the immediate setting, with excellent results. Rather than providing a single formula, we leave this up to the neurointerventionalist managing the ASA allergy. We have reported successful intervention with a short and long protocol recommended by our inpatient Allergy Service, in addition to several highly cited protocols, to each be used when clinically appropriate. It is our hope that these protocols help facilitate successful ASA desensitization, and furthermore, ASA challenge protocols become the mainstay of treatment in managing this small high-risk subset of cerebrovascular patients. Aspirin desensitization provides the opportunity for medical and endovascular treatment in patients thought to be excluded due to ASA allergy.

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Scott L Zuckerman, MD
 Dept of Neurosurgery - T-4224 Medical Center North
 Vanderbilt University Medical Center
 1211 Medical Center Drive
 37212 Nashville, Tennessee, U.S.A.
 E-mail: zuckerman.scott@gmail.com