

Long-term assessment of aspirin desensitization shows successful bridging with non-aspirin nonsteroidal anti-inflammatory drugs for procedures

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ABSTRACT

Background: Aspirin (ASA) desensitization and continuous daily ASA therapy is the criterion standard treatment for ASA-exacerbated respiratory disease (AERD). However, the optimal maintenance dosage of ASA and safety of “bridging” patients with AERD and with alternative cyclooxygenase-1 inhibitors for surgery have not been determined and require further investigation.

Objective: This study was designed to compare the long-term effects of different maintenance doses of ASA and to assess the success of bridging subjects with AERD for surgery without losing desensitization.

Methods: We retrospectively assessed 36 subjects with AERD who successfully underwent ASA desensitization from 2011 to 2017. We performed comprehensive medical record reviews and subsequent telephone interviews with a questionnaire.

Results: Of 36 subjects, the average age was 52.8 years, with an average of 3.2 years since desensitization, and 65% were women. The subjects reported a decrease in frequency of nasal symptoms ($p < 0.001$), asthma symptoms ($p = 0.016$), and sinus infections ($p < 0.001$) after desensitization. Improvements were reported in sense of smell, taste, quality of sleep, and quality of life ($p < 0.001$) in all dosage groups. Thirteen subjects required stopping of ASA for surgeries. Six subjects (46%) were bridged with ibuprofen on an average of 5.9 days before surgery and restarted ASA on an average of 1.3 days after surgery, with no incidence of major adverse events or loss of desensitization. Seven subjects (54%) were not bridged, with three subjects restarting ASA after surgery without symptoms and four subjects losing desensitization.

Conclusion: There did not seem to be a difference of benefits between 325 mg once or twice a day compared with 650 mg once or twice a day, but our small subject numbers made this conclusion difficult to prove. Desensitization improved subjective reporting on sleep quality as well as quality of life. Bridging the subjects with AERD who required surgery by using ibuprofen seemed to be safe and effective in maintaining ASA desensitization.

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Aspirin-exacerbated respiratory disease (AERD) is characterized by aspirin (ASA) sensitivity, asthma, rhinitis, and chronic sinusitis with nasal polypsis. This constellation of findings is often referred to as the Samter triad but is more accurately referred to as a pentad.^{1–3} The literature is clear that ASA is an effective therapeutic intervention for AERD with improvement in associated rhinitis, sinusitis, and asthma, and for a decrease in nasal polyp formation.^{1,2,4–8} De-

spite years of advancements in treatment for AERD, several questions remain. First, what is the optimal dose of ASA that is well tolerated? Second, before surgery or aggressive dental work, what is the best way to bridge ASA desensitization without losing the desensitized state? Currently, some surgeons discontinue ASA for a week and then patients have to re-desensitize at a later time. Third, because severe nasal congestion associated with AERD can disturb sleep, can ASA desensitization improve quality of sleep?

METHODS

Study Design

This was a retrospective study of subjects with AERD who successfully underwent rapid 2-day ASA desensitization from 2011 to 2017 at Hershey Medical Center. Ethics approval was obtained by the Penn State Office for Research Information Systems and the Office for Research Protections. The Human Subjects Protection Office of the Penn State College of Medicine approved this study. We performed comprehensive medical record reviews of the subjects and subsequent

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Table 1 Demographics of the study subjects

Characteristic	
Age at chart review, mean, y	50.9
Range	27–80
Age at desensitization, mean, y	49.1
Range	21–77
Sex, <i>n</i> (%)	
Men	13 (36)
Women	23 (64)
Race	
White	31 (86)
Black or African American	2 (5.6)
Other	2 (5.6)
Unknown	1 (2.8)

telephone interviews with the use of a questionnaire (Table 1) to include quality of life and quality of sleep, and also queried about the dose of ASA, symptom improvement, success of “bridging” for surgery, and tolerance of ASA.

Currently, there is no standard protocol for bridging, for surgical procedures, patients with AERD who are on continuous daily ASA. For this reason, we devised the following protocol as noted in Table 2. We used ibuprofen and stopped it 24 hours before surgery based on an article by Goldenberg *et al.*,⁹ which demonstrated that ibuprofen only affected platelets for 24 hours because ibuprofen is a competitive cyclooxygenase-1 (COX-1) inhibitor and does not acetylate the COX-1 enzyme as ASA is known to do.

Inclusion Criteria

Male and female patients who were ≥ 18 years old, with a history of AERD, and who successfully underwent rapid ASA desensitization at Milton Hershey Medical Center during the years 2011–2017 were eligible for inclusion. Subjects were identified by using the Milton Hershey Medical Center i2b2 data base.

Exclusion Criteria

Subjects who were unable to comprehend or speak English, or provide oral consent to participate in the study, and those considered part of a vulnerable population (< 18 years old, pregnant women, and prisoners) were excluded from the study.

Statistical Analysis

The sample size of this study was based on convenience. Subject stratification was based on a clinical diagnosis of AERD or recurrent nasal polyps. The subjects with AERD were further divided into those successfully desensitized, desensitized with successful bridging, desensitized with unsuccessful bridging, and

desensitized with subsequent termination of daily ASA. The mean of the paired difference and paired *t*-test analyses were used to compare symptoms before and after desensitization.

RESULTS

Demographics

The subjects were 64% women, 86% white, with an average age of 49.1 years at the start of desensitization and 50.9 years at chart review. All the subjects had undergone at least one surgery for nasal polyp removal, with an average age of 39.8 years at the first polyp surgery. All 36 subjects underwent successful 2-day ASA desensitization, with 67% ($n = 24$) still maintained on therapy and 33% ($n = 12$) who discontinued daily ASA. Of those who were still maintained on daily ASA, 36% ($n = 13$) required bridging for surgical procedures.

Desensitization and Adverse Events

ASA desensitization was achieved over a 2-day procedure with incremental exposure, spirometry, observation, and, if required, medical intervention for symptoms. Of the 36 subjects, 32 (88.9%) experienced a mild-to-moderate adverse event during desensitization. The first dose in which the subjects demonstrated an adverse event was at 10 mg ($n = 1$ [2.8%]), 20 mg ($n = 1$ [2.8%]), 40 mg ($n = 12$ [33.3%]), 80 mg ($n = 12$ [33.3%]), and 120 mg ($n = 5$ [14.9%]). Twenty-two subjects (61.1%) experienced a second adverse event during desensitization. Four subjects (11%) experienced no adverse reactions in the desensitization process. Severe bronchial constriction or nasal-ocular symptoms to ASA exposure that threatened the termination of the desensitization procedure were rarely observed ($n = 3$) and resolved with pharmacological intervention.

The characteristics of first adverse reactions during desensitization were assessed. Twenty-eight subjects (77.8%) demonstrated nasal-ocular symptoms, such as conjunctival injection, tearing, rhinorrhea, nasal congestion, sneezing, and pruritus. Sixteen subjects (44.4%) had bronchial symptoms, and 10 (27.8%) demonstrated throat tightness symptoms. One subject (2.8%) had cutaneous symptoms (urticarial, angioedema, pruritus, erythema). During desensitization, if the subjects had a first symptom, their second adverse symptom on a higher subsequent dose were nasal-ocular ($n = 9$ [25%]), bronchial ($n = 7$ [19.4%]), and laryngeal throat symptoms ($n = 5$ [13.9%]).

Maintenance ASA Dose

We assessed the initial and current maintenance ASA dosing. Thirty subjects (83.3%) were initially maintained on 325 mg twice a day (b.i.d.) or 650 mg every

Table 2 Preoperative ASA bridge for patients

Days	Protocol
5–7 Days before surgery	Stop ASA and start ibuprofen 200–400 mg t.i.d.
Day of surgery	No ibuprofen
Day after surgery	Restart ibuprofen 200–400 mg t.i.d.
2–3 Days after surgery or when bleeding risk is minimal	Restart the usual dose of ASA

ASA = Aspirin; t.i.d. = three times a day.

Table 3 Reason for aspirin discontinuation after desensitization

Subject No.	Dose (mg)	Reasons for Discontinuation	Treatment
21	325 q.d.	Gastrointestinal symptoms	Proton-pump inhibitor
22	324 b.i.d.	Stopped (no improvement of AERD symptoms)	None
23	325 b.i.d.	Asthma bronchial symptoms	β_2 -agonist
24	325 b.i.d.	Gastrointestinal symptoms	Proton-pump inhibitor antacid
25	325 b.i.d.	Stopped (pregnant)	None
26	325 q.d.	Bruising	None
27	325 q.d.	Gastrointestinal symptoms	None

q.d. = Every day; AERD = aspirin-exacerbated respiratory disease; b.i.d. = twice a day.

day (q.d.). Only three (8.6%) and two subjects (5.7%) were maintained on 325 mg q.d. and 650 mg b.i.d., respectively. At the time of the study, the maintenance dose of the subjects ($n = 24$) was reevaluated. Twelve subjects (50%) were maintained on 325 mg q.d., 11 (46%) were on 325 mg b.i.d. or 650 mg q.d., and one (4%) was on 650 mg b.i.d. Fourteen subjects (58%) had a decrease in the daily ASA maintenance dose compared with the initial dose. Only one subject reported an increase in the maintenance dose. Reasons for a decrease in daily maintenance dosage was due to either a good response ($n = 4$ [29%]), adverse events ($n = 7$ [50%]), or unknown reason per subject ($n = 3$ [21%]).

Adverse Reactions on Maintenance ASA Dose

Adverse events from the subjects who were desensitized and maintained on ASA ($n = 24$) at the time of the study were assessed. Seven subjects (29%) reported mild easy bruising, and six subjects (25%) had bleeding symptoms, from epistaxis or minor cuts. Four subjects (16%) reported gastrointestinal symptoms, such as nausea, vomiting, gastric pain, and heartburn. One subject (4%) experienced nasal-ocular symptoms (conjunctival injection, tearing, rhinorrhea, nasal congestion, sneezing, or pruritic). One subject (4%) experienced cutaneous symptoms (urticarial, angioedema, pruritus, or erythema). Of the 12 subjects who reported at least one adverse event, 2 required pharmacological intervention. These two subjects had gastrointestinal symptoms, which were managed with proton-pump inhibition medications.

Reason for Discontinuation of the Maintenance Dose

Twelve subjects were desensitized to ASA but eventually discontinued their daily maintenance dose. Four subjects (33%) lost desensitization after stopping daily maintenance for surgery and failure to bridge. Five subjects (42%) discontinued ASA due to reported adverse effects, including three with gastrointestinal symptoms, one with bronchial symptoms, and one with easy bruising (Table 3). One subject (8%) discontinued the maintenance dosage due to pregnancy, and another (8%) stopped due to no improvement of symptoms.

Comparison of Before and After ASA Desensitization Symptoms

The subjects of the study ($N = 36$), including those who discontinued daily ASA maintenance, reported a decrease in the frequency of nasal, asthma, and sinus infection symptoms per month (30 days) after ASA desensitization. For nasal symptoms, such as rhinorrhea and sneezing, the subjects reported an average and standard deviation of $\bar{x} = 14.1 \pm 4.8$ days per month and $\bar{x} = 3.7 \pm 5.1$ days per month before and after desensitization, respectively. The mean difference of post- and prenasal symptoms was -10.4 ($-12.6, -0.1$; $p < 0.001$). For asthma symptoms, such as wheezing, coughing, and shortness of breath, the subjects reported $\bar{x} = 5.8 \pm 6.3$ days per month and $\bar{x} = 3.2 \pm 5.4$ days per month before and after desensitization,

Table 4 Bridging subjects with AERD after desensitization

Subject No.	Days Before Procedure, Stopping ASA	Days After Procedure, Beginning ASA	Medication	Daily Dose (mg)	Total Dose (mg)	Adverse Event
16	7	1	Ibuprofen	400 b.i.d.	800	
17	7	3	Ibuprofen	500 q.d.	500	
18		1	Ibuprofen			Asthma
19						
Procedure 1	4	1	Ibuprofen	200 b.i.d.	400	
Procedure 2	4	1	Ibuprofen	200 b.i.d.	400	
Procedure 3	4	1	Ibuprofen	200 b.i.d.	400	
31	7	1	Ibuprofen	300 q.8 hr	900	
34						
Procedure 1	7	1	Ibuprofen	200 b.i.d.	400	Ocular pruritus
Procedure 2	7	1	Ibuprofen	200 b.i.d.	400	
Average	5.9	1.2			500	

AERD = Aspirin-exacerbated respiratory disease; ASA = aspirin; b.i.d. = twice a day; q.d. = every day; q.8 = every 8 hr.

respectively. The mean difference for asthma symptoms after and before desensitization was -2.6 (-4.6 , -0.5 ; $p = 0.016$). The subjects reported $\bar{x} = 8.6 \pm 6.0$ days per month with symptoms of sinus infections before and $\bar{x} = 1.8 \pm 2.7$ days after desensitization. The mean difference of sinus infections was -6.8 (-9.3 , -4.41 ; $p < 0.001$).

Subjective ratings, from 0–10 (0 being no symptoms and 10 being intense symptoms), demonstrated an improved sense of smell, taste, quality of sleep, and quality of life. The subjects reported a mean difference of 3.3 (1.5, 5.1; $p < 0.001$) in sense of smell before ($\bar{x} = 1.9 \pm 2.7$) and after ($\bar{x} = 5.2 \pm 3.3$) desensitization. Sense of taste improved by a mean of 2.4 (1, 3.8; $p = 0.002$) between before ($\bar{x} = 3.9 \pm 3.4$) and after (6.3 $\pm$ 2.6) desensitization. Quality of sleep improved by a mean of 2.6 (1.6, 3.7; $p < 0.001$) between before ($\bar{x} = 5.1 \pm 2.7$) and after ($\bar{x} = 7.7 \pm 2.1$) desensitization. Quality of life improved by a mean of 3.4 (2.3, 4.4; $p < 0.001$) between before ($\bar{x} = 4.8 \pm 2.8$) and after ($\bar{x} = 8.2 \pm 2.0$) desensitization.

Of the subjects who have been desensitized and maintained on daily ASA ($n = 24$) at the time of the study, 100% reported an overall decrease in frequency of nasal and asthma symptoms, and improvements in subjective quality of sleep and life. Approximately 81% of the subjects strongly agreed that the benefits of desensitization outweighed the risk of adverse effects from the procedure. Also, 81% of the subjects strongly agreed that desensitization outweighed the cost of time required for the 2-day procedure. All the subjects agreed that they would repeat a desensitization procedure should it be required, due to the overall benefits they experienced from the procedure.

Bridging for Procedures with Risk of Bleeding

Thirteen subjects needed to stop daily ASA maintenance therapy for a medical or surgical procedure due to a high risk of bleeding (Table 4). Six subjects were successfully bridged for a total of nine different surgeries. The subjects were bridged with a total daily average of 500 mg ibuprofen on average 5.9 days before surgery and restarted ASA on average 1.2 days after surgery, with no incidence of major adverse events or loss of desensitization. One subject experienced ocular pruritus, and one had increased symptoms of asthma. Both of these subjects did not require emergency medical intervention. Three subjects were not bridged with alternative medication, but they did not experience any adverse reactions when restarting ASA after surgery. Four subjects reported no bridging with an alternative medication and subsequent loss of ASA desensitization.

DISCUSSION

In this retrospective chart review, we demonstrated that ASA desensitization was significantly and positively associated with improved ASA-exacerbated respiratory disease symptoms and subjective disease ratings, but we also demonstrated significant improvement of sleep. Furthermore, analysis of our data supported the bridging of ASA with ibuprofen for patients after desensitization as a safe and effective measure for surgical procedures.

In 1980, two patients with AERD were desensitized and maintained on either 625 mg or 650 mg of ASA daily.¹ Recent literature focused on long-term effects of ASA desensitization and daily ASA dosage.^{10,11} Benefits of ASA desensitization in patients with AERD have been reported, with studies that showed reductions in steroid requirements, fewer sinus infections, and im-

provements in naso-ocular and asthma symptoms.^{2,5} These findings are consistent with our data. However, we also found an improvement in subjective reporting of sleep among our subjects. Furthermore, we also found that bridging of ASA with ibuprofen for the subjects after desensitization was safe for those who were undergoing surgical procedures, although our numbers were small. Although our subjects reported a decrease in daily ASA maintenance due to adverse events, there is recent literature that a dosage decrease does not improve adverse events.¹¹

Maintaining desensitization by means of daily ASA ingestion presents a challenge in patients who need surgery. Usage of antiplatelet agents, *e.g.*, ASA, may be associated with an increased risk of bleeding during surgical procedures.¹² The risk depends on various factors, including invasiveness and site, and consideration of risks and benefits is crucial for the safest management. A proposed protocol for stopping ASA before surgery is presented in Table 2. Although some studies demonstrated that continuation of ASA does not increase the risk of bleeding during surgery, some surgeons remain concerned of the risk associated with COX-1 inhibitors.^{13–14} For this reason, we developed a “bridge” to remove ASA in ample time before surgery and to replace it with a nonsteroidal anti-inflammatory drug, such as ibuprofen, which only temporarily affects platelets, unlike ASA which affects platelets for the duration of the life of the platelet. This reduced the time off a COX-1 inhibitor to 24 hours and allowed reintroduction of ASA without risk and thus avoided the need for a repeated desensitization procedure. Analysis of our data demonstrated that patients with AERD on daily ASA maintenance therapy could be effectively bridged with ibuprofen before surgical or other invasive procedures.

Limitations of our study ought to be considered. The limited number of patients with AERD who received care at our hospital restricted our study population size. Because this was a single-center study, our results may not be reflective of populations in other regions. Given the retrospective nature of our study, the bridging protocol of the subjects was not standardized, which may have resulted in variability of adverse events observed. However, our study demonstrated that ibuprofen was a viable replacement for ASA in the subjects after desensitization and undergoing surgical procedures. Future studies are needed to confirm this. Because our study was retrospective, recall bias was possible given the length of time from ASA desensitization, bridging, and our questionnaire. Our subjective symptoms, reported on a scale of 1 to 10, were susceptible to reduced interrater reliability. Also, we did not use standardized questionnaires to assess sleep and quality of life. Nonetheless, our study demonstrated that ASA desensitization significantly improved overall sleep, but future studies need to confirm this.

Conclusion

Our study did not demonstrate a difference of benefits between 325 mg once or twice daily compared with 650 mg once or twice daily. ASA desensitization significantly improved overall sleep quality. We showed that bridging the subjects with AERD who required surgery by using ibuprofen seemed to be safe and effective in maintaining ASA desensitization. Additional research on the safety of ibuprofen use in patients after desensitization and who are undergoing surgical procedures should be performed, as well as studies to confirm the overall improvement in sleep in patients with AERD after ASA desensitization.

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