Aspirin-sensitive asthma and upper airway diseases

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ABSTRACT

Background: Aspirin exacerbated respiratory disease (AERD) consists of nasal polyposis, rhinosinusitis, asthma, and aspirin (ASA) sensitivity.

Objective: This article details how to diagnose and treat AERD and describes the procedures associated with ASA challenge and desensitization, benefits associated with ASA desensitization, and appropriate doses for treatment.

Methods: Criteria for diagnosis of AERD as well as desensitization protocols for oral ASA challenge and combined intranasal ketorolac and oral ASA challenge, are detailed in this article based on literature review.

Results: AERD requires a multidimensional approach to treat the disease given the multiple conditions. With successful ASA desensitization and maintenance of ASA administration, all patients are able to achieve ASA tolerance and select patients are able to achieve improvement in clinical markers such as global scores and reduction in use of topical and systemic corticosteroids.

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Samter and Beers described the association between nasal polyposis, asthma, and aspirin (ASA) sensitivity in 1968.¹ The condition now commonly includes rhinosinusitis and is referred to as aspirin-exacerbated respiratory disease (AERD).² Many, but not all, patients with AERD describe a viral respiratory infection at the beginning of their symptomatic respiratory disease somewhere in their late teens to middle age.³ Thus, a typical history of a patient suffering from AERD includes the usual history of viral upper respiratory infections throughout life with tolerance of cyclooxygenase 1 (COX-1) inhibitors including ASA and nonsteroidal anti-inflammatory drugs (NSAIDs). They eventually describe a clinical progression from persistent symptoms of a viral cold to rhinitis and then development of nasal polyposis, asthma, and anosmia within 1–5 years from rhinitis.⁴ The development of ASA/NSAID sensitivity occurs at any time in the course of their disease.

PATHOPHYSIOLOGY OF AERD

There are several allergic reactions to ASA and NSAIDs including the true allergy to the medication *via* an IgE pathway that can lead to anaphylaxis.⁵ Other reactions include NSAID-induced aseptic meningitis⁶ and hypersensitivity pneumonitis from the cellular immunity pathway as well as worsening chronic urticaria *via* a cross-reaction and arachidonic acid pathway.⁷ AERD is not an allergic or IgE-mediated process; therefore, no *in vitro* testing is available. Although the pathogenesis of AERD is still not clear, abnormalities in arachidonic acid metabolism leading to an increase in proinflammatory markers and a decrease in inflammatory suppressive mediators have been implicated.⁸ Long-term treatment with ASA involves down-regulation of proinflammatory markers.⁸ It should be noted that highly selective COX-2 inhibitors do not cross-react with ASA or other NSAIDs and patients with AERD can tolerate these medications.^{9–11}

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TREATMENT OF AERD

Treatment of AERD requires multiple interventions to target the different components of the disease. Asthma management has multiple goals and treatment modalities should be consistent with the National Asthma Education and Prevention Program: Expert Panel Report 3¹² or Global Initiative for Asthma.¹³ Details of asthma management is beyond the scope of this article but should include education, monitoring, treatment of comorbid conditions, and controlling triggers as well as pharmacotherapy. Likewise, for chronic rhinosinusitis with nasal polyposis, guidelines exist for optimal management^{14–16} and should include therapy to control inflammation and edema, ventilation and drainage of the sinuses, and treatment of infectious microorganisms. For polyposis, patients frequently require multiple polypectomies. For anosmia, in a study on the effect of surgery on olfactory performance, AERD was found to significantly limit olfactory function recovery and unlikely to become normosmic.¹⁷ For ASA sensitivity, avoidance can be practiced; however, ASA challenge protocols aim to diagnose ASA sensitivity as well as simultaneously desensitize the patient. In fact, ASA challenge is the gold standard of diagnosing ASA sensitivity and is an effective treatment modality for AERD.

ASA CHALLENGE HISTORY

In 1976, the paradoxical finding of a 3-day refractory period after oral ASA challenge in patients who had previously reacted to ASA started a search for whether the treatment of patients with ASA sensitivity is possible with the same agent that triggered the symptoms.¹⁸ In 1977, Bianco *et al.* reported six patients with history of reacting to ASA who underwent inhalations of minute amounts of lysine-ASA resulting in a 6- to 7-day relative insensitivity after the challenge. The insensitivity was maintained by ingestion of 500 mg of ASA daily or on alternate days.¹⁹ Many studies since then have been performed to characterize safety of challenge and criteria for a positive challenge, as well as refractory period after initial desensitization. Reliable methods of diagnosing ASA sensitivity have been developed and provocation challenges can be done *via* oral, intranasal, inhaled, and i.v. routes.^{20–24} The Scripps Clinic original protocol²⁵ involves an oral ASA challenge that starts at 30 mg of ASA but increases in doses were tailored for each individual based on historical reaction. The types of reactions that now characterize a positive reaction include respiratory reaction (forced expiratory volume in 1 second [FEV₁] declines >20%) or extrapulmonary, such as naso-ocular, skin (hives),

gastrointestinal (abdominal pain), and hypotension. The refractory period after desensitization for most patients is 2–4 days.²⁶ Current Scripps challenge/desensitization protocol combine diagnosis and desensitization, because significant preparation is required to optimize patients before desensitization. Also, the entirety of the desensitization protocol must be performed to diagnose ASA insensitivity in those patients who do not have reactions to ASA.

Although oral ASA challenge has been the mainstay in the United States, inhaled and nasal provocation with lysyl-ASA challenge has been performed and validated as a diagnostic tool for ASA-sensitive asthma.^{27,28} We present the intranasal provocation data as a precursor to the Scripps Clinic's new protocol of combined inhaled ketorolac and oral ASA protocol. Data for nasal polyposis includes a 1991 study with intranasal desensitization with lysine-ASA corresponding to 20, 200, and 2000 μg of ASA until a maximum dose of 2000 μg weekly was reached. This study proved to be efficacious for 43 patients who had reacted to ASA and were 1 month postpolypectomy when desensitization was started.²⁹ In a 5-year follow-up, recurrent rates of nasal polyps were significantly lower in the ASA-treated group compared with the control group.³⁰ Another randomized double-blind, placebo-controlled, crossover trial of intranasal desensitization with low-dose lysine-ASA (16 mg) administered in 11 ASA-intolerant patients with nasal polyps found poor clinical effect of the intranasal desensitization treatment, but there was significant improvement at the microscopic level.³¹

Intranasal ketorolac combined oral ASA challenge shortens duration of desensitization to 1.9 days when compared with 2.6 days for the ASA only challenge ($p < 0.001$). The combined challenge also attenuated patients' respiratory response as measured by FEV₁ and decreased the percentage of extrapulmonary reactions such as laryngospasm (7% versus 19%; $p = 0.02$) and gastrointestinal reactions (12% versus 33%; $p = 0.01$) when compared with standard oral ASA challenge and desensitization.³²

ASA CHALLENGE AND DESENSITIZATION PROTOCOLS

Before attempting to desensitize patients, the safety of the patients should be ensured by screening for risk factors, as well as appropriate location and resources allocated for where the desensitization will take place. The Aspirin Desensitization Joint Task Force recommends that the procedure should take place where equipment for advanced cardiac care, ventilator support, and constant observation by a supervising physician are available. Patients with risk factors of severe asthma, history of life-threatening ASA or NSAID reaction, β -blocker use, recent myocardial infarction, or any other underlying medical condition or drug treatment regimen that would complicate desensitization should undergo inpatient desensitization. Outpatient desensitizations can be considered for facilities with continuous respiratory and cardiovascular monitoring, pulse oximetry, spirometry, and cardiopulmonary resuscitation is available as well as the physician and staff with experience and capability to handle acute and severe asthma exacerbations. Outpatient desensitization should also be considered for patients with a history of life-threatening ASA or NSAID reaction. The Aspirin Desensitization Joint Task Force published their recommendations before the Scripps study, which showed no correlation between the severity of the historical ASA/NSAID reaction and the challenge reaction.³³

The risks and benefits of the ASA challenge should be discussed with patients and a consent for the procedure obtained and documented in the patient's medical record.

Oral ASA and combined ketorolac/ASA challenges will be detailed.

Oral ASA Challenge Protocol

In 2007, the Aspirin Desensitization Joint Task Force recommended the following protocol.³⁴ One week before challenge, establish airway

stability and optimize asthma therapy by obtaining spirometry. Patients with FEV₁ of $>70\%$ of their prior best (and >1.5 L absolute) are candidates for outpatient desensitization. If asthma is poorly controlled, start or increase systemic corticosteroids and dual-controller therapy. If not already on leukotriene-modifying drug therapy, then starting the medication is recommended. Studies from Scripps Clinic have shown specifically that montelukast can decrease lower respiratory (asthmatic) reaction to oral ASA challenge by 90%.³⁵ Patients should be taken off of antihistamine medications 48 hours before challenge. On day of challenge, the task force recommends placement of i.v. access. However, in unpublished data of patients at Scripps Clinic, we have never needed to use the i.v. access for treatment of reactions to ASA challenge. When ready to begin the challenge, start with 20.25 mg of ASA by mouth followed by 40.5, 81, 162.5 and 325 mg at 90-minute to 3-hour intervals depending on patient's overall disease characteristics as well as possible reactions to each dose. If the patient has a reaction, that dose should be repeated, after the reaction resolves, until the patient tolerates the dose. Then, proceed with the next dose in the protocol mentioned previously.

Intranasal Ketorolac Challenge Protocol

Intranasal ketorolac has been validated as a method for diagnosing AERD.³⁶ For the protocol, 1.26-mg actuation of ketorolac in each spray is first prepared. One spray in one nostril, followed by 2 sprays (1 spray in each nostril given at one time), 4 sprays (2 sprays in each nostril given at one time), and then 6 sprays (3 sprays in each nostril given at one time) in 30-minute intervals. ASA at 60 mg is then given an hour later, followed by another 60-mg dose 90 minutes later. A 150-mg dose is given the next morning, followed by 325 mg 3 hours later.

For both protocols, it is important to evaluate patients clinically and to perform spirometry before each dose and as needed. Positive reactions can include naso-ocular symptoms such as itchy watery eyes, itchy nose, sneezing, and runny nose; naso-ocular and a 15% or greater decline in FEV₁; lower respiratory reaction with $>20\%$ decline in FEV₁; laryngospasm; or systemic reaction such as hives, flushing, gastric pain, or hypotension. A negative reaction is the absence of reactions after the 325-mg dose.

EXPECTATIONS AFTER DESENSITIZATION

ASA desensitization followed by daily ASA treatment (325 or 650 mg twice a day) is more effective in controlling and/or improving upper and lower respiratory symptoms in patients with AERD than just surgical intervention alone.^{37–39} The relapse rate postpolypectomy without ASA desensitization and treatment was as high as 80%.³⁸

In a longitudinal prospective study at Scripps Clinic and the Scripps Research Institute from 1995 to 2000, 172 AERD patients who were desensitized to ASA and treated with 650 mg of ASA twice a day were followed with telephone interviews and questionnaires every month for 6 months and then every 6 months thereafter for up to 6 years.⁴⁰ Seventy-three percent (126/172) of patients completed the study. Of the 126 patients who completed the study, 110/126 (87%) had good-to-excellent response. Responses were rated excellent if patients had improvement in all clinical markers, both global scores, and a reduction in topical and systemic corticosteroids. Good responders were patients who had improvement in some of the clinical markers, at least one of the global, and the same or decrease in corticosteroids. In this responder study population, there was improvement of nasal symptom and olfactory scores ($p < 0.0001$), no recurrence of sinus surgery ($p < 0.0001$), decreased number of sinus infections from five to two a year ($p < 0.0001$), and reduced number of hospitalization and emergency room visits per year. Additionally, this patient population also showed a reduced need for intranasal and oral corticosteroids ($p < 0.0001$ at 12 months follow-up). Improvement with nasal scores, sense of smell, and asthma scores improved

significantly ($p < 0.0001$) and prednisone doses decreased with an average of 10.7–5.9 mg daily ($p = 0.0003$) within as little as 4 weeks.

There were 16/126 patients who were nonresponders. Fourteen of the 16 nonresponders had positive skin test to animal dander, molds, and/or dust mites. Thirteen of 16 nonresponders had positive skin test to animal dander, 11 of whom continued to have animals in the home. None of these nonresponders had or was on concurrent immunotherapy.

It should be noted that chronic ASA therapy has side effects such as gastric pain, gastric bleeding, hives, or nose bleed, and patients are often recommended by their surgeon before a procedure and never restarted ASA treatment postprocedure or because of pregnancy. In fact, out of 46 patients who discontinued ASA during the first 12 months of the study, 29 of them had reported improvement in respiratory symptoms but discontinued the treatment for reasons provided previously.

PREDICTING RESPONSE TO ASA DESENSITIZATION

Predictors of response to ASA desensitization and ASA treatment in AERD patients depend on whether patients have other concomitant diseases. Patients with no concomitant disease have the best outcome with ASA desensitization and ASA treatment. AERD patients who have concomitant atopy (allergic rhinitis and/or asthma), fungal sinusitis, or gastroesophageal reflux have increased risk of nonresponse unless those conditions are well controlled.

MAINTENANCE THERAPY

After ASA desensitization, all patients can maintain desensitization with a minimum of 81 mg of ASA, if that is the goal for prevention of cardiovascular disease. ASA doses of 325 mg/day can keep subjects desensitized to any dose of any other COX-1 inhibitor NSAIDs; however, the dose for AERD has been in some debate.

In one study, for patients with AERD who are post-sinus surgery intervention, 100 mg of ASA taken daily by mouth seemed effective in providing improvement in some symptoms. In a year with a follow-up every 3 months, these patients had no recurrence of nasal polyps (26/30 patients), had marked improvement of their asthma symptoms (9/12), nasal breathing (14/16), and sense of smell (7/11 patients).⁴¹ In an attempt to answer the question of which dose of daily ASA is efficacious in treating patients with AERD, patients who were post-sinus surgery and had a positive ASA provocation test were randomized to either 100 or 300 mg of ASA by mouth daily.⁴² Thirty-seven of these patients were enrolled and followed for an overall median of 27 months. Patients on 100 mg/day did not show improvement. The patients on 300 mg of ASA per day had significant improvement in olfaction and were polyp free for over a period of 12 months. They also did not need revision sinus surgery in the median follow-up period of 27 months. In addition, asthma medication was reduced in three patients and pulmonary function was improved in five patients.

Despite the foregoing encouraging data, in a study at Scripps, the 300-mg dose is inadequate in treating AERD except in a small percent of patients. In patients who had a response to the initial treatment dose of 650 mg twice a day of ASA, after a year, we found ~50% of them continue to require 650 mg of ASA twice a day to maintain the improvements. In the other 50%, we found they could reduce the dose to 325 mg to 975 mg/day without reduction in benefits.⁴⁰

Therefore, Scripps Clinic studied 137 patients who had undergone successful ASA desensitization and randomized them into two groups, 650 mg twice daily versus 325 mg twice daily. After 1 month after randomization, the patients either increased or decreased their dosage based on their symptom control and continued that dosage for the remainder of the year. Fifty-two percent of patients on the 325-mg twice daily dose did require an increase in dosage. After dosage adjustment, both 325-mg twice daily and 650-mg twice daily groups

showed improvements in number of sinus infections, sinus operations, and hospitalizations for asthma ($p < 0.001$). Anosmia, nasal/sinus symptoms, and asthma symptoms improved ($p < 0.03$) and systemic corticosteroid dosages decreased by threefold in the 325-mg twice daily group and fourfold in the 650-mg dose group. Based on these results, it is recommended that the patients begin daily ASA therapy with 650 mg twice daily with subsequent decrease to 325 mg twice daily at the direction of a physician while carefully monitoring symptoms.⁴³

CONCLUSION

After careful screening of patients undergoing evaluation for recurrent sinusitis, asthma, and ASA and/or NSAIDs sensitivity, the approach to treatment of these patients with AERD is multidimensional. In addition to addressing their nasal and sinus pathology, attention also needs to be directed toward reducing their exposure to aeroallergens, asthma control, and desensitizing them to ASA and treatment with daily ASA.

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