Editorial

Aspirin Desensitization: Faster Protocols for Busy Patients

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In a patient with aspirin-exacerbated respiratory disease (AERD), aspirin desensitization and cross-desensitization with antipyrine were reported in 1922.[1] However, it was not until 1980[2] that a therapeutic use for daily aspirin treatment, after desensitization, was discovered. The effectiveness of this treatment has been confirmed in patients with AERD at numerous centers[3-5] all of which measured improvement in rhino-sinus outcomes. Improvements in asthma outcomes were documented in some, but not in all studies. In the last 38 years, details of aspirin desensitization, followed by daily aspirin treatment, have evolved to the point where this therapeutic intervention is accepted as the standard of care for patients with AERD.

The process of identifying patients with AERD involves 3 steps: (1) AERD only occurs in patients who have rhinosinusitis and asthma; (2) a careful nonsteroidal anti-inflammatory drug (NSAID) exposure and reaction history; and (3) a positive oral aspirin challenge. If the patient gives a history of ingesting a COX-1 inhibiting NSAID, followed by respiratory symptoms, there is a greater than 80%[6] chance that the patient has AERD (positive oral aspirin challenge). If NSAID ingestion is associated with respiratory symptoms and occurred 2 or more times, with the same or 2 different NSAIDs, the chances of a positive oral aspirin challenge increase to 89%.[6]

During a recent meta-analysis, the prevalence of AERD among all asthmatics was found to be 7.2%, and if the asthma was severe, the prevalence increased to 14.9%.[7] Nineteen million asthmatics in the United States × 7.2% equals 1,368,000 patients who have AERD. Many patients are hiding in plain sight because physicians did not take an NSAID + symptom history and therefore failed to screen patients or refer them for definitive diagnosis via an oral aspirin challenge.[8]

After 1980, in the General Clinical Research Center at Scripps Clinic, a full day of placebos, followed by oral aspirin challenges, with escalating doses every 3 hours, using special capsules containing 30, 60, and 100 mg on day 2 and 150, 325, and 650 mg on day 3 was the protocol. When a reaction occurred, doses were paused, treatment rendered, and then doses were repeated to achieve desensitization. Valuable information was gathered during these years, but the leisurely pace consumed at least 3 days of hospital time (if challenges were negative) and was unsustainable because of cost and time. Williams et al[9] provided important data that showed that there was no correlation between historical reactions to full therapeutic doses of NSAIDs (aspirin 650 mg) with large asthmatic reactions and oral aspirin challenges (average provoking dose of 60 mg of aspirin) with easily treated asthmatic responses. Outpatient aspirin challenge turned out to be perfectly safe, with enormous savings in scheduling and cost. Modifications using pill cutters of available aspirin doses (81 and 325 mg) began to appear in the late 1990s with 40.5, 60.75, 101.25, 162, and 325 mg doses approximating the dosage schedule above and the 650 mg dose was discarded because no patient with AERD ever reacted to 650 mg of aspirin.[10] The mean provoking dose in all studies was approximately 60 mg, with provoking doses on either side of a bell-shaped curve.[10] During oral aspirin challenges, pretreatment with montelukast significantly prevented excessive bronchospasm, and this pretreatment is now standard.[11] Before montelukast was available, severe bronchospasm occurred infrequently. To our knowledge, oral aspirin challenges have not resulted in any deaths as observed by us, reported in the literature, nor brought to our attention via access to litigation records.

Aspirin challenge procedures have also evolved. In 2007, an international expert committee,[12] based on opinion rather than data, changed the interval between escalating doses of aspirin from 180 to 90 minutes. Despite shortening this time between doses, adverse consequences or safety concerns have not surfaced. Outside the United States, where aspirin lysine is available for use in humans, nasal and bronchial inhalation challenges are routinely used to establish a diagnosis of AERD. In the United States, using liquid ketorolac,[13] similar diagnostic studies have been reported. But, because of the need to convert to oral aspirin, 60 mg × 2 during the first afternoon and then 150 and 325 mg during the next morning, the average length of nasal challenge plus oral desensitization is a day and half. Chen et al[14] came up with a new screening criterion. If patients' historical reactions to full therapeutic doses of an NSAID were within 60 minutes, they changed the interval between escalating doses to 60 minutes. Forty percent of their 57 challenge subjects finished desensitization during the first day. Sixty percent spilled over into the second day but were usually finished by noon. The disadvantage of both studies was the cost of an extra hotel night for out-of-town patients, time for patients, and increasing costs for clinic time and personnel. The advantages were safety for both groups, with the ketorolac protocol inducing less bronchial and gastrointestinal responses, but more laryngospasm.

Two studies in this issue of *J Allergy Clin Immunol Pract* focus on reducing the time to completion of aspirin desensitization.

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Pelletier et al[15] present a retrospective observational study of 2 groups of patients with AERD. A baseline group of 16 patients with 90-minute intervals between oral aspirin challenges was contrasted with a new group of 38 patients with 60-minute intervals between escalating doses. Doses of aspirin (diluted Alka-Seltzer), used for both groups, were 40, 80, 160, and 325 mg (skipping the 60 mg dose used in prior protocols). All reactions occurred after the 80 mg dose of aspirin. Both groups provided similar historical information with elapse times from dosing to reactions of <36 minutes. For the 90-minute group, aspirin-provoked reactions occurred at 39 minutes, and for the 60-minute interval group, at 46 minutes. All reactions occurred with intervals well within the 60 minutes. Extreme bronchospastic responses never occurred in either group. When you look at the minimal recorded declines in forced expiratory volume in 1 second values during aspirin-induced reactions, respiratory safety is obvious for the 16 and 38 reported patients.

However, outliers occur and larger studies will be necessary to incorporate delayed or severe reactions. Equally concerning, the authors reported a desensitization failure rate of 3 patients (18.8%) in the 90-minute group and 5 (13.3%) in the 60-minute group. The reader is not provided any details about these 8 of 54 (15%) patients who failed aspirin desensitization. In our experience, failure to achieve acute desensitization is very uncommon. We recently reported safety outcomes for 167 consecutive aspirin desensitization procedures using our ketorolac/oral aspirin protocol. We identified 23 of 167 (14%) patients with severe reactions that required multiple dosing before aspirin desensitization was completed. Yet, all 167 subjects advanced to a dose of 325 mg of aspirin, without symptoms, and thus achieved the state of aspirin desensitization. For the 167, the average time to completion of desensitization was 1.67 days, but the subgroup of patients with gastrointestinal reactions averaged 2.29 days. All 167 patients left the clinic taking daily aspirin treatment.[16] The inability to successfully complete aspirin desensitization might be due to patient decision to stop the challenges or secondary to the speed of the protocol itself. Patients should be warned that a faster protocol might be associated with the disadvantage of not completing aspirin desensitization and/or that further days may be needed to complete desensitization. We suggest that "failure to desensitize" should be a primary endpoint in studies claiming improved protocol variations, not only in this but future protocols.

In a second study, DeGregorio et al[17] presented their outcomes with the use of a 90-minute dosing interval intended to complete the desensitization in 1 clinic day. Their study included challenge doses of 40.5, 81, and 161 and a mandatory 3-hour observation after onset of reactions. This addition is important, as most studies reporting desensitization protocols do not include the time necessary to treat the inevitable reactions. This study included a typical AERD population without regard to reaction type or timing. One of the 44 subjects could not be desensitized and 2 other patients required a second day to complete desensitization. Thus, the majority (93%) were able to complete desensitization in 1 day with 1 failure in a gastrointestinal reactor. This study is to be commended for completing desensitization in 43 of 44 patients. An important difference with this protocol, compared with other 90-minute protocols, is that the first dose was 40.5 mg, advancing to 81 mg for the second dose. In addition, the protocol ended after the patient repeated the provocative dose and tolerated 1 subsequent escalated dose. Thus, the protocol could end before 325 mg of aspirin was administered. These adjustments made it feasible to plan on a 1-day aspirin challenge/desensitization for almost all patients. Although this is an attractive option for patients, the average time to completion was 9.5 hours. If the first dose were administered at 8 am, the average patient would not be discharged until 5:30 PM with some patients requiring 12 hours. Some outpatient clinics might be unable to monitor and staff the procedure properly with this potential obligation. Nonetheless, the point that the procedure can be safely and successfully completed in 1 clinic day is impressive and clearly deserves application to a larger cohort of potential patients with AERD.

As AERD gains a foothold in the diagnostic mainstream, more referrals and desensitization centers for aspirin challenge and desensitization will be needed. An estimation of 1,368,000 patients with AERD in the United States is probably low, given the fact that typical patients are ignored or overlooked.[18] The demand for oral aspirin challenge centers to diagnosis and treat AERD is already needed and increasing. Safety, reduction of symptoms during reactions, and time to completion for all challenged patients continue to drive innovations in new protocols.

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