An Alternative Aspirin Desensitization Protocol for Patients with Aspirin-Exacerbated Respiratory Disease

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Introduction

Aspirin-exacerbated respiratory disease (AERD) is composed of a triad of respiratory reactions including chronic rhino sinusitis (CRS), nasal polyposis, and asthma as the result of immunological sensitivity to aspirin, or acetylsalicylic acid, and other COX-1 inhibiting NSAIDs[1,2,3,4]. While consuming NSAIDs triggers AERD, the intrinsic inflammatory condition begins and manifests independently of drug ingestion [5]. The reaction to aspirin and other NSAIDs is actually an atypical biochemical response to COX-1 inhibition, rather than an IgE-mediated or true allergic response. According to Woessner and White, the major symptoms of the reaction include rhinorrhea, nasal congestion, ocular tearing and injection, periorbital swelling, and bronchoconstriction anywhere between 30 minutes to 3 hours following ingestion [3,4].

The true prevalence of AERD is hard to determine, but may affect anywhere between less than 5% to up to 40% of asthmatics [4]. However, a recent meta-analysis by Rajan concluded that the prevalence of AERD among asthmatics was much lower at 7.15% (range 5.5% to 14.89%) [6]. AERD diagnosis is dependent upon a provocative challenge with aspirin or another COX-1 inhibiting NSAIDs. While an asthma attack following aspirin ingestion and Samter’s triad (i.e. nasal polyps, chronic sinusitis, and asthma) are suggestive of AERD, it does not necessitate a positive oral aspirin challenge result [7].

Current practice for the treatment of AERD is restricted to two options: abstaining from all COX-1-inhibiting drugs or completing an “aspirin desensitization” protocol so daily aspirin use can be resumed [2]. However, there is evidence that aspirin itself improves a patient’s quality of life by reducing nasal polyps and sinus infections, as well as the subsequent complications with those conditions [4,8]. Because of aspirin’s critical role in treating nasal symptoms, aspirin desensitization is an important treatment option for controlling AERD symptoms [4].

While there are many versions of the oral aspirin desensitization, the standard protocol adheres to the rationale and research published by Hope et al. at the Scripps Clinic. The standard protocol entails administration of a small starting dose of aspirin followed by an incremental increase in oral doses every three hours. Typical completion of the protocol occurred in 2.5 days. While it was found

Abstract

Background: Aspirin exacerbated respiratory disease (AERD) affects up to 5% to 15% of asthmatics. While aspirin desensitization is a safe treatment option and allows for aspirin to be used to control AERD symptoms, not all patients diagnosed with AERD are able to complete the standard desensitization protocol.

Objective: For patients who cannot complete the standard desensitization protocol, we sought to create an alternative method that allows patients to reach a therapeutic maintenance dose of aspirin.

Methods: We retrospectively analyzed patients that underwent AERD desensitization, identifying 5 patients that failed the standard desensitization protocol and 6 that elected to complete the alternative aspirin desensitization. Subjects started at a dose lower than their reaction dose and subsequently increased their dosage by 40.5 mg every 2 to 4 weeks, with the goal of reaching a dose of 325 mg BID.

Results: Among the five patients that initially failed the standard desensitization protocol, our alternative desensitization protocol took an average of 6.1 months to reach a maintenance dose of 307 mg BID with an increase of 47.5 mg aspirin every two weeks. Of the six patients who elected to complete our alternative protocol, it took an average of 4.6 months to reach a maintenance dose of 244 mg BID with an increase of 38.7 mg every two weeks. Six patients successfully increased their aspirin dosage to 325 mg BID by following the alternative protocol.

Conclusion: Based on the data, it seems possible that a graduated approach to the administration of aspirin could benefit a majority of those who fail or do not wish to complete the standard desensitization protocol.

Keywords: Asthma; Aspirin-induced diagnosis; Aspirin-induced immunology; Aspirin-induced therapy; Allergens immunology; Desensitization immunologic methods; Oral administration; Acetylsalicylic acid dose; Adult

Conclusion

Aspirin exacerbated respiratory disease (AERD) affects up to 5% to 15% of asthmatics. While consuming NSAIDs triggers AERD, the intrinsic inflammatory condition begins and manifests independently of drug ingestion [5]. The reaction to aspirin or other NSAIDs is actually an atypical biochemical response to COX-1 inhibition, rather than an IgE-mediated or true allergic response. According to Woessner and White, the major symptoms of the reaction include rhinorrhea, nasal congestion, ocular tearing and injection, periorbital swelling, and bronchoconstriction anywhere between 30 minutes to 3 hours following ingestion [3,4].

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While there are many versions of the oral aspirin desensitization, the standard protocol adheres to the rationale and research published by Hope et al. at the Scripps Clinic. The standard protocol entails administration of a small starting dose of aspirin followed by an incremental increase in oral doses every three hours. Typical completion of the protocol occurred in 2.5 days. While it was found
that most reactions occurred at 45 mg to 100 mg of aspirin, a dosage of 650 mg can be taken without an adverse reaction [9].

However, not all patients diagnosed with AERD are able to complete this rapid desensitization protocol. For patients who fail or cannot follow the usual protocol of 2.5 days, there is no alternative, standardized protocol to achieve a maintenance dose of 325 mg of aspirin twice a day that Lee et al. established as improving AERD symptoms [10]. We sought to prolong the desensitization with the goal of reaching this maintenance dose. Recent discoveries pertaining to the physiological mechanism behind aspirin desensitization may lend support to our alternative method [11].

Methods

Data collection

For this retrospective chart study, IRB approval was obtained through MedStar Union Memorial Hospital. The protocol number appointed to the project was 2014-177. Patient data was retrieved from the Asthma Allergy Sinus Centers in White Marsh and Baltimore, MD. A total of eleven patients with stable asthma were identified to have completed our alternative protocol. All eleven patients were taking Montelukast for at least two weeks prior to initiating aspirin desensitization. All the patients were considered for aspirin desensitization because of their history of AERD and not for any other indication. Patients 1-5 completed the alternative protocol only after failing the standard desensitization protocol, while Patients 6-11 elected to follow the alternative protocol without a previous failure of the standard desensitization protocol.

Subject groups

There were two, mutually exclusive, patient groups identified in this study. The first group of patients were identified during an initial desensitization attempt using the in-office standard protocol as published by Hope et al. at the Scripps Clinic. For Patients 1-5, the initial desensitization failure dose was recorded during this protocol application. Failure of the standard protocol was defined as a decrease of 20% or greater in the FEV1 value. We did not use a refractory period after the positive challenge because the patients chose to come back after a few weeks for continuing their aspirin desensitization.

The second group of patients did not reach a decrease of 20% or greater in the FEV1 value or an allergic reaction as a result of the dose. Patients 6-11 experienced either a decrease of 10-15% in their FEV1 value or nasopharyngeal/periorbital symptoms. These patients elected to discontinue the standard protocol. Follow-up notes were analyzed to determine the dosage increase for each patient. The duration of treatment was determined by their scheduled visits to the office.

Alternative protocol

The diagnosis of AERD in our study participants was made following the administration of an oral aspirin challenge or upon the presentation of a history suggestive of AERD in addition to a documented reaction to NSAIDs. A subset of AERD patients who had failed the oral aspirin challenge was then treated using the standard desensitization protocol. Patients 1-5 of our study failed to complete the standard desensitization protocol and were subsequently treated using our alternate protocol. Patients 6-11 of our study elected to undergo the alternative protocol without a failure in the standard desensitization, as described under the Methods subheading of Subject groups. The alternate protocol consisted of initiating the standard aspirin desensitization, discontinuing when patients reacted to the largest dose (reaction dose). Next, patients were instructed to begin aspirin ingestion the following day with a dose lower than their reaction dose (the daily dose). If no reaction occurred to that daily dose, the daily dose was increased by 40.5 mg every two to four weeks, alternating the increases in the morning or evening. Each initial increased dose was administered in the office. Once patients reached 160 mg BID, their doses were increased 40.5 mg to 81 mg every two to four weeks. Beyond 160 mg BID, patients were instructed to increase their doses at home. If a patient experienced a reaction, the patient was advised to return to the previous daily dose amount.

As a safety precaution, dosage was increased on a BID basis by splitting the dosage increase between the morning and evening hours, rather than ingesting the whole of the increased dose once daily. For example, if a patient prescribed 81 mg BID were to increase their dose by 40.5 mg, the new dose would be added to only the morning regimen. The patient would take 120 mg in the morning and 81 mg in the evening for two weeks. At the start of the third week, the patient would increase the evening dose, resulting in 120 mg BID.

Results

Six of 11 patients were successfully desensitized to 325 mg BID aspirin with our alternative protocol (Tables 1 and 2). Patient 1 was raised from a starting dose of 120 mg to a final dose of 325 mg BID in 6.2 months, and Patient 3 was increased from 81 mg to 650 mg BID in 5.9 months. Patient 5 was raised from 160 mg to 325 mg BID in 6.0 months. Patient 8 was raised from a starting dose of 81 mg to a final dose of 325 mg BID in 7.1 months, and Patient 9 was raised from a starting dose of 120 mg to 325 mg BID in 6.0 months. Patient 11 successfully reached 325 mg BID from a starting dose of 120 mg/d in 4.4 months.

Table 1: Patients who followed alternative protocol due to previous failure on standard protocol.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Desensitization Failure Dose (mg)</th>
<th>Starting Dose (mg/d)</th>
<th>Final Dose (mg BID) Days (Months) Treated</th>
<th>Bi-weekly Dosage Increase (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>155</td>
<td>120</td>
<td>325</td>
<td>186 (6.2)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>162</td>
<td>81</td>
<td>162</td>
<td>235 (7.7)*</td>
</tr>
<tr>
<td>Patient 3</td>
<td>140</td>
<td>162</td>
<td>143 (7.7)Δ</td>
<td>182 (6.0)</td>
</tr>
<tr>
<td>Patient 4</td>
<td>115</td>
<td>162</td>
<td>185 (6.1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient 5</td>
<td>162</td>
<td>162</td>
<td>182 (6.0)</td>
<td>185 (6.1)</td>
</tr>
</tbody>
</table>

*Patient elected to discontinue an increase in dosing as described in the results. ΔPatient discontinued due to urticaria.
did not wish to continue increasing their dose to 325 mg BID, because they were concerned about gastrointestinal complications related to long-term, high doses of aspirin. These four patients opted to continue taking their final dose, as specified in Tables 1 and 2, as a therapeutic measure for AERD.

Among Patients 1-5 who failed the standard desensitization protocol, the average failure dose was 147 mg. While adhering to our alternative protocol, it took an average of 6.1 months to reach a maintenance dose of 307 mg BID with an increase of 47.5 mg aspirin every two weeks (Table 1). Of Patients 6-11 who elected to complete the Alternative Protocol without a previous failure, it took an average of 4.6 months to reach a maintenance dose of 244 mg BID. The average increase was about 38.7 mg every two weeks (Table 2).

### Table 2: Patients who opted into alternative protocol without previous failure.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Starting Dose (mg/d)</th>
<th>Final Dose (mg BID)</th>
<th>Days (Months) Treated</th>
<th>Bi-weekly Dosage Increase (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 6</td>
<td>81</td>
<td>81</td>
<td>42(1.4)*</td>
<td>27</td>
</tr>
<tr>
<td>Patient 7</td>
<td>120</td>
<td>243</td>
<td>91(3.0)*</td>
<td>56.5</td>
</tr>
<tr>
<td>Patient 8</td>
<td>81</td>
<td>325</td>
<td>217(7.1)</td>
<td>36.7</td>
</tr>
<tr>
<td>Patient 9</td>
<td>120</td>
<td>325</td>
<td>182(6.0)</td>
<td>40.8</td>
</tr>
<tr>
<td>Patient 10</td>
<td>120</td>
<td>162</td>
<td>171(5.6)*</td>
<td>16.4</td>
</tr>
<tr>
<td>Patient 11</td>
<td>120</td>
<td>325</td>
<td>135(4.4)</td>
<td>55</td>
</tr>
<tr>
<td>Average</td>
<td>107</td>
<td>244</td>
<td>140(4.6)</td>
<td>55</td>
</tr>
</tbody>
</table>

*Patients elected to discontinue an increase in dosing as described in the results.

### Discussion

Our retrospective data suggests that an incremental administration of low-dose aspirin over duration of about 4-6 months could greatly benefit patients that fail or do not wish to complete the standard desensitization protocol. The alternative method allows more AERD patients to benefit the therapeutic effects of aspirin. Based on our results, we suggest patients who require or desire an alternative aspirin desensitization protocol begin their aspirin regimen at a dose lower than their failure dosage and increase their dosage 40.5 mg to 81 mg every 2-4 weeks. We recommend three hours of supervision before the patient is allowed to return home, covering the aspirin half-life. About half of our patients achieved a 325 mg BID dose of aspirin using this method.

No other study has performed such a gradual, incremental increase of daily aspirin in a desensitization method. On the contrary, other studies have shown and advised front-loading initial doses of aspirin after a standard desensitization protocol [8] For example, Lee et al. instructed patients ingest doses as high as 650 mg BID for one month, only decreasing the dose to 325 mg BID if there was a significant improvement in upper and lower airway symptoms [10]. While we advised our patients to achieve a dose 325 mg BID or above as described in past studies, little is known about the optimal, therapeutic dose of aspirin for specific AERD patients. In fact, it has been difficult to pinpoint a therapeutic dose for the treatment of AERD, and there even may be no significant difference in patients’ symptoms when they take 325 mg BID or 625 mg BID [8]. A more recent study has found that even 300 mg/d controlled the upper airway aspects of AERD in patients with the disease [8]. According to that study, all but two of our patients achieved a maintenance therapeutic dose of aspirin to control their AERD symptoms [12].

An important aspect of our alternative protocol included splitting the increases in aspirin doses between the morning and evening. Based on the short half-life of aspirin in plasma [13] we felt that once patients had ingested their evening dose, the majority of the morning dose had been cleared. The graduated increases in aspirin doses spread between the morning and evening should potentially decrease the risk for reaction in patients.

Although failure to an oral challenge is defined as either a decrease of 20% or greater in the FEVI1 value or an allergic reaction as a result of the dose, only Patients 1-5 adhered to that definition. Patients 6-11 did not “fail” during the standard desensitization protocol, because they were not pushed to a full 20% decrease in FEVI1. Instead, those patients only experienced a 10-15% decrease in FEVI1 or discontinued the standard desensitization protocol due to other reactions such as nasal and sinus symptoms. To avoid the discomfort of completing the standard protocol, Patients 6-11 elected to complete our alternative desensitization protocol.

The physiological mechanism behind our alternative protocol may lie in the recent discovery of elevated IFN-γ and IL-10 expression in CD4+ T lymphocytes of AERD patients. IFN-γ and IL-10 expression in CD4+ T lymphocytes were significantly elevated in AERD patients as opposed to healthy controls, while levels of both were similar in both groups 1-month following aspirin desensitization treatment. These results suggested that IFN-γ and IL-10 expression play a likely role in the disease and its treatment through aspirin desensitization [10] other studies have demonstrated associations between augmented IFN-γ expression and autoimmune diseases as well [14,15].

Our study demonstrates a patient-centered, economic, and practical advantage to an alternative aspirin desensitization protocol. Our method reduces the patient’s time spent in the office and reduces the intensity of the supervision necessary of the healthcare staff. An important aspect of our modified protocol is acceptability to patients. Many patients do not feel comfortable when symptoms are provoked, even in a controlled clinical setting. Furthermore, some patients do not wish to repeat the procedure the next day or cannot repeat it due to barriers to care. Typically, a standard desensitization protocol takes more than 2 days of constant, patient monitoring by the physician and the office staff. With the alternative protocol, patients are only required to come to the office in order to administer the dosage increase, approximately every 2 to 4 weeks. After only two hours of supervision, the patient is allowed to return home, where the patient could safely continue taking maintenance doses. Furthermore, once patients increased their daily aspirin amount to above 160 mg BID; we administered increased doses at home. That decision was in accordance to the study performed at Scripps Clinic, which demonstrated that only 3% of initial aspirin reactions occurred after 150- or 325-mg doses [9].

The limitations in our study are intrinsic to retrospective chart review. A larger, more controlled prospective study should be conducted to validate our results. If an alternative aspirin desensitization protocol proves effective for a larger, more diverse
group of patients that have failed or do not wish to complete the standard protocol, our slow, graduated alternative aspirin desensitization protocol may assist AERD patients in achieving a therapeutic maintenance dose of aspirin. While our study aimed to merely establish an alternative desensitization protocol, we followed the dosage standards set forth by other studies. Future studies must determine the dosages that are the most efficacious in AERD treatment.

REFERENCES