

Comparable safety of 2 aspirin desensitization protocols for aspirin exacerbated respiratory disease

Teresa Pelletier, MD^a, Gigia Roizen, MD^a,
Zhen Ren, MD, PhD^b, Golda Hudes, MD, PhD^a,
David Rosenstreich, MD^a, and Elina Jerschow, MD, MSc^a



Clinical Implications

- Diagnosis and initiation of the treatment for aspirin exacerbated respiratory disease requires confirmation through an oral aspirin challenge. A 1-hour dose-escalation protocol suggested in 2015 has not yet been widely accepted. This study supports the safety of the shorter, 60-minute desensitization protocol.

TO THE EDITOR:

Aspirin exacerbated respiratory disease (AERD) is an acquired syndrome characterized by the triad of asthma, nasal polyps, and nonsteroidal anti-inflammatory drug (NSAID) sensitivity.¹ Diagnosis and initiation of the treatment for AERD requires confirmation through an oral aspirin challenge.¹ Desensitization to aspirin followed by maintenance therapy has been shown to improve sinopulmonary symptoms.¹ Well-established aspirin desensitization protocols are considered to be safe in appropriate outpatient settings, although it remains difficult to predict how individuals will react.² Patients may experience bronchial, laryngeal, gastrointestinal, naso-ocular, and cutaneous reactions. Bronchial reactions are most concerning, as they could lead to severe bronchospasm.³

Until the early 2000s, a 3-hour desensitization protocol was widely used, but this protocol lasted over 2 days.⁴ Macy et al⁵ described a 90-minute escalation protocol in 2007. In 2010, another protocol was developed that was a combination of oral and intranasal desensitization, shortening the procedure to less than 2 days.⁶ In 2015, a 1-hour escalation protocol was suggested.⁷ However, it has not yet been widely accepted.^{2,3}

Our group shifted from the 90-minute to the 1-hour desensitization protocol in May 2014. We conducted a retrospective study comparing the 2 protocols. A total of 54 patients were desensitized to aspirin in the clinic. Of these, 16 patients followed a 90-minute dose-escalation protocol before May 2014, with 40, 80, 160, and 325 mg of aspirin (diluted Alka-Seltzer) given every 90 minutes. The next 38 patients followed a 60-minute dose-escalation protocol, with identical dosing. Peak expiratory flow rates (PEF), nasal peak flow (NPF), and spirometry were recorded at baseline, every 25-30 minutes, before each dose, after any reaction, and after recovery. Reactions were defined as characteristic sinonasal symptoms and/or a $\geq 15\%$ drop in forced expiratory volume in 1 second (FEV₁). After reactions occurred, patients were treated based on their symptoms with nebulized albuterol and racemic epinephrine, supplemental oxygen, oral famotidine, oral antihistamines, intranasal oxymetazoline, and oral corticosteroids. Desensitization resumed after symptoms resolved.

At baseline, there were no significant demographic or clinical differences between the 2 protocol groups (Table I). There was no significant difference between the 2 groups in patient-recalled time of reaction after NSAID ingestion (typically, the reaction before presentation that alerted them to NSAID sensitivity) (Table I and Figure 1, B).

We compared the severity and timing of the hypersensitivity reactions that occurred during the 90- versus 60-minute escalation protocol. Reaction severity was evaluated based on the

TABLE I. Demographics: comparison of demographic information between individuals undergoing 90-minute protocol vs 60-minute protocol

Variable	90-min protocol (N = 16)	60-min protocol (N = 38)	P value
Age (y), mean $\pm$ SE	40.0 $\pm$ 2.6	44.6 $\pm$ 2.0	.2
Female, N (%)	12 (75)	25 (66)	.8
Race, N (%)			.9
White	3 (19)	8 (21)	
African American	8 (50)	17 (45)	
Hispanic	5 (31)	12 (32)	
Asian	0	1 (2)	
Patient reported time to reaction after NSAID ingestion (min), mean $\pm$ SE	33 $\pm$ 6.9	30 $\pm$ 6.9	.7
Lund-Mackay score, median (IQR)	20 (19-21)	18 (14-21)	.1
FEV ₁ , %-predicted, baseline, mean $\pm$ SE	78 $\pm$ 4.5	83 $\pm$ 3.5	.4
Peak flow (L/min), mean $\pm$ SE	365 $\pm$ 23	386 $\pm$ 17	.5
Nasal peak flow (L/min), mean $\pm$ SE	132 $\pm$ 15	113 $\pm$ 7.7	.3
ACT score, mean $\pm$ SE	18.9 $\pm$ 1.4	18.7 $\pm$ 0.7	.9
High dose ICS use, N (%)	10 (62.5)	21 (55.3)	.8

Lund-Mackay score = radiological severity quantification of chronic rhinosinusitis based on the CT of head and sinuses.

ACT, Asthma control test; CT, computed tomography; ICS, inhaled corticosteroid; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SE, standard error.

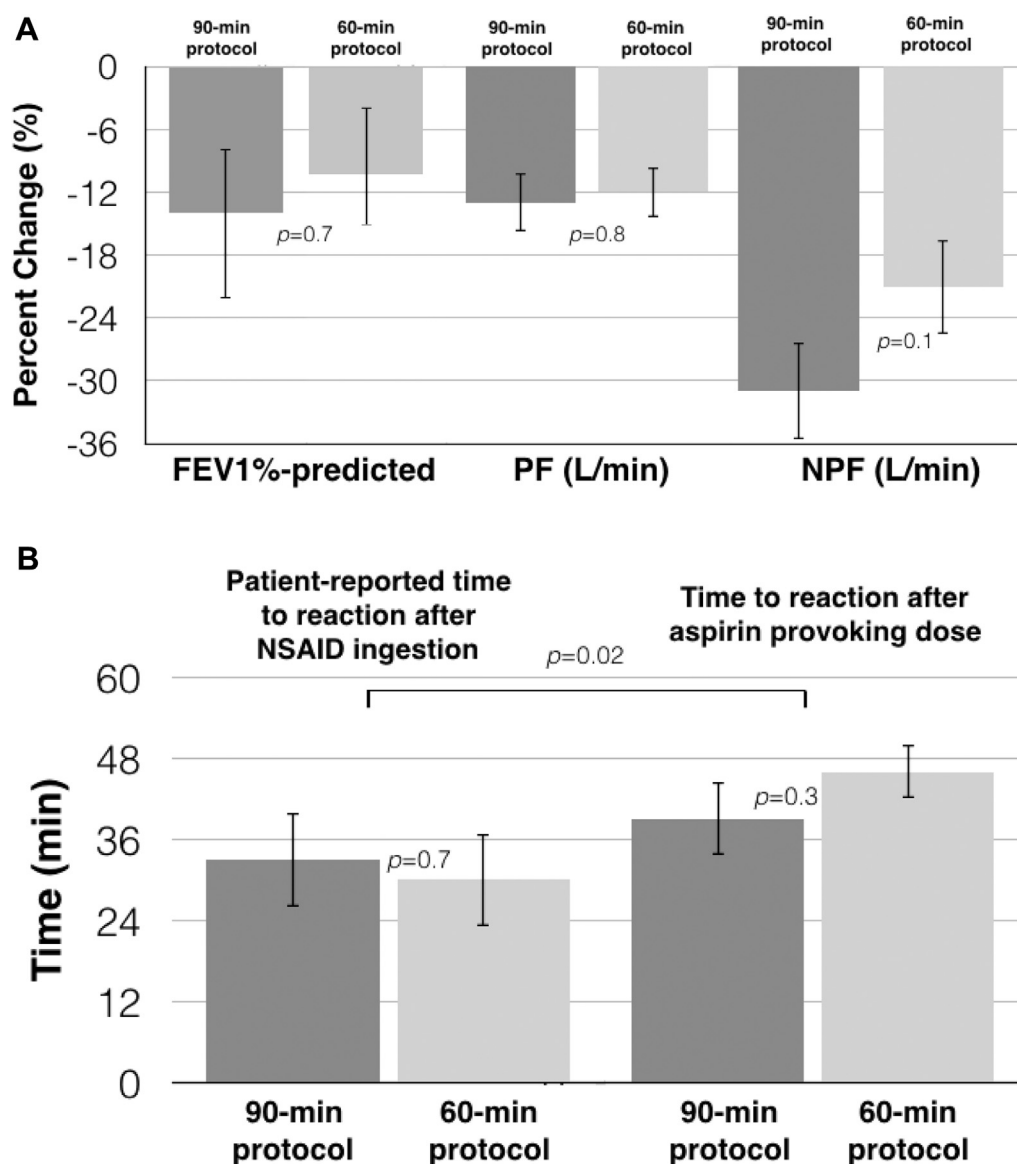


FIGURE 1. **A**, Reaction severity: comparison of percent changes in FEV₁, peak flow (PF), and nasal peak flow (NPF) during hypersensitivity reaction to aspirin challenge between 2 groups. **B**, Reaction timing: comparison of patient-reported time to reaction after NSAID ingestion and time to reaction after administration of the aspirin provoking dose during challenges between 2 groups. FEV₁, Forced expiratory volume in 1 second; NSAID, nonsteroidal anti-inflammatory drug.

percent changes in PF, NPF, and FEV₁. There were no significant differences in average percent changes in FEV₁ (-14% interquartile range [IQR] -22 to -8 for 90-minute protocol group vs -10.3% IQR -15 to -4 for 60-minute protocol group, $P = .7$), PF (-13% $\pm$ 2.8% for 90-minute vs -12% $\pm$ 2.4% for 60-minute, $P = .8$), and NPF (-31% $\pm$ 4.6% for 90-minute vs -21% $\pm$ 4.5% for 60-minute, $P = .1$) (Figure 1, A). There were no significant differences in the percent of individuals who could not complete the challenge because of gastrointestinal symptoms or persistent bronchospasm (3 patients [18.8%] in 90-minute protocol vs 5 patients [13.3%] in 60-minute protocol, $P = .3$). Silent desensitizations occurred more frequently in the 60-minute protocol (3 patients [8%],

with a history of multiple NSAID reactions and/or reaction during desensitization at later time) versus none in the 90-minute protocol, $P = .004$. All patients in both groups completed desensitization in 1 day.

The provoking dose of aspirin was defined as the last dose immediately preceding the reaction. There was no significant difference in time to reaction after the provoking dose, 39 $\pm$ 5.4 minutes for 90-minute and 46 $\pm$ 4.0 minutes for 60-minute ($P = .3$, Figure 1, B). The median provoking dose for both groups was 80 mg (IQR 60-160 for 90-minute vs IQR 40-120 for 60-minute, $P = .4$).

Desensitization to aspirin represents a key treatment for the management of patients with AERD. The severity and timing of

hypersensitivity reactions during these 2 desensitization protocols were compared. Changes in PF, NPF, FEV₁, representing reaction severity, were similar between these 2 protocol groups, supporting the safety of the 60-minute protocol in comparison with the 90-minute protocol.

A provoking dose of 80 mg was shared by both protocols and reported in other studies.⁸ There was no significant difference in the reaction timing after the provoking dose in either protocol. With the 90-minute protocol, it was noticed that the time from provoking dose to reaction was consistently less than 1 hour; 3 patients did react just after 60 minutes, but likely due to delay in recognition of reaction until completion of PF and spirometry assessments during interval (at 60-minute) monitoring. This led us to more readily adapt the shortened 60-minute protocol (with this monitoring at 25 and 55 minutes). We observed a similar decrease in FEV₁ and reaction timing after a provoking dose in the 60-minute protocol group to that reported by Chen et al.⁷

The onset of reaction after provoking dose during the challenges was significantly longer than patients' historical recollection of time to reaction after self-ingestion of NSAID; with protocol groups combined, patient-recalled reaction time was 30 ± 5.6 minutes compared with a reaction time of 44 ± 3.2 minutes during challenge ($P = .02$, Figure 1, B). Patients likely consumed NSAIDs at higher doses than the first/provoking dose of the desensitization. Furthermore, asthma control is optimized before conducting aspirin desensitization.⁵⁻⁷ All study patients received montelukast for a week before the desensitization, including the morning of the challenge, which has been shown to lessen these reactions during a challenge.¹ Lastly, the severity of historical reactions does not predict the reaction severity after aspirin challenge in clinic.⁹

These observations support the safety of a shorter 60-minute escalation desensitization protocol. This protocol reduces the duration of the desensitization by potentially 3 to 4 hours, minimizing patient discomfort and time in clinic while maintaining safety. However, limitations include having a small sample size and being a retrospective, nonrandomized, non-blinded study. It is encouraging that, outside of this study, we successfully applied the 60-minute protocol to our clinical practice during the last 237 aspirin challenges/desensitizations. Yet, a prospective, randomized study is required to confirm these observations. Careful selection of patients for the 60-minute

protocol is advisable, and longer protocols should be used in selected patients.

^aDivision of Allergy & Immunology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York, NY

^bDivision of Allergy & Immunology, Washington University School of Medicine, Barnes Jewish Hospital, St Louis, Mo

Portions of this work were funded by the Stony Wold-Herbert Fund research grant to E.J.

Conflicts of interest: E. Jerschow has received a research grant from Cumberland Pharmaceuticals Inc (not relevant to this study). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 14, 2018; revised July 26, 2018; accepted for publication August 8, 2018.

Available online August 23, 2018.

Corresponding author: Elina Jerschow, MD, MSc, Albert Einstein College of Medicine, Montefiore Medical Center, Hutchinson Medical Center, 1250 Waters Place, Tower 2, 12th Floor, Bronx, NY 10461. E-mail: Elina.Jerschow@einstein.yu.edu.

2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2018.08.004>

REFERENCES

1. Buchheit KM, Laidlaw TM. Update on the management of aspirin-exacerbated respiratory disease. *Allergy Asthma Immunol Res* 2016;8:298-304.
2. Waldram J, Walters K, Simon R, Woessner K, Waalen J, White A. Safety and outcomes of aspirin desensitization for aspirin-exacerbated respiratory disease: a single-center study. *J Allergy Clin Immunol* 2018;141:250-6.
3. Stevenson DD, White AA. Aspirin desensitization in aspirin-exacerbated respiratory disease: consideration of a new oral challenge protocol. *J Allergy Clin Immunol Pract* 2015;3:932-3.
4. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol* 2006;118:773-86.
5. Macy E, Bernstein JA, Castells MC, Gawchik SM, Lee TH, Settipane RA, et al. Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: a practice paper. *Ann Allergy Asthma Immunol* 2007;98:172-4.
6. Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon RA, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2010;105:130-5.
7. Chen JR, Buchmiller BL, Khan DA. An hourly dose-escalation desensitization protocol for aspirin-exacerbated respiratory disease. *J Allergy Immunol Pract* 2015;3:926-31.
8. Schuler C, Baldwin J, Baptist A. Frequency and severity of reactions to a 325-mg aspirin dose during desensitization. *Ann Allergy Asthma Immunol* 2017;118:333-8.
9. Williams AN, Simon RA, Woessner KM, Stevenson DD. The relationship between historical aspirin-induced asthma and severity of asthma induced during oral aspirin challenges. *J Allergy Clin Immunol* 2007;120:273-7.