HHS Public Access

Author manuscript

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

J Allergy Clin Immunol Pract. 2015 ; 3(3): 449–451. doi:10.1016/j.jaip.2015.01.007.

Tolerance of chronic low-dose aspirin does not preclude aspirin exacerbated respiratory disease

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Keywords

AERD; Aspirin exacerbated respiratory disease; Aspirin intolerant asthma; Aspirin triad; Asthma; Nonsteroidal anti-inflammatory drug; Samter's Triad; Low-dose aspirin; High-dose aspirin; Eosinophilic nasal polyposis

To the Editor:

Aspirin exacerbated respiratory disease (AERD) is characterized by asthma, eosinophilic nasal polyposis, rhinosinusitis and respiratory reactions to COX-1 inhibitors including aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). AERD patients with symptoms refractory to guideline-based management of asthma, nasal polyposis or rhinosinusitis benefit from aspirin desensitization and treatment with high-dose aspirin[1]. Daily doses of at least 300 mg of aspirin, with some patients requiring up to 1300 mg, are effective in reducing the burden of disease[2,3]. Studies investigating doses lower than 300 mg daily have yielded inconsistent results, with the weight of evidence suggesting that low doses of aspirin are not effective[4,5].

Clinical observation suggests that a subset of patients with AERD report taking daily low-dose (81 mg) aspirin for months to years without clinical history of an adverse reaction to aspirin. These patients come to attention because of recurrent eosinophilic nasal polyposis. When they undergo oral aspirin challenge after holding their daily aspirin for 10 days, they develop stereotypical respiratory reactions. To our knowledge, such patients with AERD have not been previously described in the literature. The goal of the present study is to identify a group of these patients and investigate their characteristics, with attention to their response to treatment with high-dose aspirin.

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We performed a retrospective chart review of 163 subjects with AERD who were referred to Brigham and Women's Hospital or Massachusetts General Hospital for evaluation of possible AERD and who agreed to participate in our AERD registry between September 2013 and August 2014. We identified subjects who were taking 81 mg aspirin daily at the time of AERD evaluation and who reported no clinical history of aspirin hypersensitivity. All subjects who were taking daily low-dose aspirin at the time of AERD evaluation stopped taking aspirin for at least ten days and then underwent aspirin challenge. The electronic medical record was reviewed for all subjects. Comprehensive clinical and questionnaire data were available for 91 subjects.

There were 7 subjects (4.3% of 163) with AERD who had tolerated chronic daily aspirin (81 mg aspirin group). Six of the 7 subjects underwent positive aspirin challenge tests at our institution and developed a characteristic upper and/or lower airway reaction; the seventh reported a positive NSAID challenge done elsewhere. Demographic characteristics are displayed in Table I and aspirin challenge results are displayed in Table II. The dose of aspirin that provoked a clinical reaction was 81 mg or less in 5 of 6 patients. Subjects in the 81 mg aspirin group were significantly older at the time of aspirin challenge than other AERD subjects (59.6 vs 48.3 years, $P < .05$), though there was no significant difference between groups in time between subject-reported onset of nasal polyposis and date of aspirin challenge. There was no significant difference between groups in number of lifetime polypectomies, but fewer subjects in the 81 mg aspirin group had a clinical history of asthma (5/7 vs 83/84, $P < .05$).

Of the subjects in the 81 mg aspirin group, one started taking low-dose aspirin daily prior to the onset of AERD symptoms and another started low-dose aspirin prior to onset of nasal polyps but had had mild intermittent asthma since childhood. Five had symptoms of AERD at the time they started taking daily low-dose aspirin. Of these, three were not taking montelukast and two could not recall their use of montelukast when they initiated daily low-dose aspirin.

Four subjects in the 81 mg aspirin group were desensitized to aspirin and began high-dose aspirin therapy of at least 325 mg twice daily, and have been followed for a mean of 26 months (range 5 to 37 months). Since beginning high-dose aspirin, none have required repeat polypectomy and all report improvement in nasal symptoms. Those with asthma (n=3) report improvement in asthma symptoms with increases in FEV1 of 12.2, 15.3 and 41.4% at the first visit after initiation of high-dose aspirin, which occurred 6, 12 and 6 weeks after aspirin desensitization, respectively. The patient whose FEV1 increased by 41.4% restarted zileuton, which he had temporarily stopped taking, around the same time that he started taking high-dose aspirin. Of the remaining three subjects in the 81 mg aspirin group, two will pursue polypectomy prior to aspirin desensitization and one has elected not to pursue high-dose aspirin therapy.

There are several explanations for why some patients with AERD apparently tolerate daily low-dose aspirin. First, they may initiate daily aspirin early in the clinical course of AERD before they develop aspirin hypersensitivity. However, only one subject in our group began taking baby aspirin prior to the onset of AERD symptoms. Second, the use of montelukast at

the time of aspirin initiation could blunt their reaction, producing a “silent desensitization”[6,7], though the majority of subjects we studied were not taking montelukast when they began taking daily low-dose aspirin. Given our findings, the most likely explanation is that they develop a reaction to their first ingestion of low-dose aspirin, but fail to connect the reaction with their aspirin use and subsequently become desensitized to aspirin through daily use.

Though asthma is a prominent clinical feature of AERD, it is possible to have AERD without asthma[8]. Subjects in our 81 mg aspirin group had significantly lower prevalence of asthma than subjects who had not been taking daily aspirin. AERD patients who have more severe asthma may be less likely to tolerate daily low-dose aspirin without clinically obvious reactions. In our 81 mg aspirin group, the positive reactions elicited during oral aspirin challenge were generally less severe and involved smaller decreases in FEV1 than were observed in other AERD subjects.

This exploratory study identified a group of AERD patients who were able to tolerate low-dose aspirin. A correct diagnosis is clinically meaningful, as the subjects we studied did benefit subjectively and objectively from high-dose aspirin treatment. We believe this group is under-recognized and under-treated. Clinicians must maintain a high suspicion for AERD in patients with recurrent polyposis, even in patients who appear to tolerate low-dose daily aspirin.

Acknowledgements

This work was supported by NIH grants AI007306-27, U19 AI095219-01, 5U19AI070412-06 Opportunity Fund Subaward No 153556/153044, K23HL111113-02 and by generous contributions from the Vinik Family and the Kaye Family.

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Clinical Implications: There is a subset of patients with aspirin exacerbated respiratory disease (AERD) who previously tolerated daily low-dose aspirin. In our cohort, these patients are characterized by older age at AERD diagnosis and lower asthma prevalence, and benefit clinically from high-dose aspirin.

Table I

Demographic and baseline characteristics*

	81 mg Aspirin		No Aspirin		*P* value
	Mean	**n**	**Mean**	**n****	
Female sex – # (%)	3 (42.9)	7	88 (56.4)	156	NS
History of asthma – # (%)	5 (71.4)	7	83 (98.8)	84	<.05
Age of asthma onset – year	25.6	5	33.6	81	NS
Age of nasal polyp onset – year	45.5	6	37.5	82	NS
# lifetime polypectomies	2.86	7	2.46	83	NS
Age at aspirin challenge – year	59.6	7	48.3	66	<.05
Years between nasal polyp onset and aspirin challenge	14.4	6	11.1	66	NS
Baseline FEV1 - % predicted	83.2	5	92.7	61	NS
Maximum % decrease in FEV1 during aspirin challenge (range)	1.04 (−9.4-+9.8)	6***	12.86 (−55.4-+2.8)	55	<.05

FEV1- forced expiratory volume in one second.

No Aspirin- this group is composed of AERD subjects who were not taking daily low-dose aspirin prior to AERD diagnosis.

* Characteristics of subjects who were on low-dose daily aspirin (81 mg Aspirin group) at the time of evaluation and who were not (No Aspirin group) were compared using non-paired two-tailed *T*-test and Chi-square analyses.

** In the no aspirin group, comprehensive data were available for 84 patients. 66 patients underwent aspirin challenge at our institution.

*** One patient underwent NSAID challenge prior to referral to our center.

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Table II

Results of oral aspirin challenge in 81 mg Aspirin subjects

Subject	History of asthma	Pre-challenge FEV1 (L,% predicted)	During Challenge		Provocative dose (mg*)	Time to reaction after provocative dose – Min	Clinical reaction to aspirin challenge	
			Minimum FEV1 (L)	% change in FEV1			Subjective Symptoms	Objective Findings
1	Yes	3.08 (81)	2.79	−9.4	81	90	Nasal congestion	Copious lacrimation, hyponasal speech
2	Yes	2.68 (65)	2.56	−4.5	162	Few		Rhinorrhea, copious lacrimation, conjunctival hyperemia
3	No	2.86 (108)	2.82	−1.4	81	90	Nose tingling, increased nasal congestion	Rhinorrhea, hyponasal speech, facial flushing
4	No	5.08 (129)	5.04	−0.8	40.5	30	Ear pressure, increased nasal congestion	Hyponasal speech
5	Yes	1.56 (61)	1.56	0	81	60		Copious lacrimation, wheezing
6	Yes	1.22 (55)	1.34	9.8	81	60	Nausea, increased nasal congestion	Copious lacrimation, hyponasal speech, conjunctival hyperemia

All subjects underwent our standard aspirin challenge protocol[9].

*The dose that provoked the onset of respiratory symptoms is shown.