

Successful Long-Term Aspirin Desensitization in a Pilot With Aspirin-Exacerbated Respiratory Disease

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ABSTRACT Aspirin-exacerbated respiratory disease (AERD) is a triad of asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and adverse respiratory reactions to the ingestion of aspirin/non-steroidal anti-inflammatory drugs.¹ Patients with AERD are frequently plagued with CRSwNP that is difficult to manage with systemic steroids, nasal steroids, and surgical polypectomy, often requiring multiple endoscopic sinus surgeries and frequent otolaryngology follow-up.^{2,3} There are an abundance of therapies to treat CRSwNP in the setting of AERD, all with varying costs, efficacies, and indications for treatment.⁴ While limited by side effect profile, aspirin desensitization remains an effective, low-cost treatment for patients with CRSwNP and non-steroidal anti-inflammatory drug sensitivity.⁵ We describe a case of an active duty U.S. Air Force pilot with AERD whose CRSwNP was successfully treated with aspirin desensitization without detrimental effect on his flying status.

INTRODUCTION

The U.S. Air Force (USAF) Medical Standards Directory outlines the specific standards that active duty airmen are required to meet for military service. For aviators, health standards are even more stringent, with specific height, weight, and visual acuity requirements that must be met before even being considered for pilot training. Maintenance of flying status is even more rigorous, as there are numerous medical conditions, and their respective treatments, that can adversely impact flying status. Although aspirin-exacerbated respiratory disease (AERD) is not mentioned by name, the USAF Medical Standards Directory lists several disqualifying conditions that are relevant to the active duty patient with chronic rhinosinusitis with nasal polyps (CRSwNP), to include chronic sinusitis causing missed duty (or requiring otolaryngology follow-up more than once annually) as well as nasal polyps resulting in clinical symptoms incompatible with flight.⁶ Repeated courses of antibiotics and/or steroids and frequent otolaryngology follow-up limit an active duty flying airman's ability to fulfill their military duties, as they incur duties not including flying status (DNIF) for the duration of treatment. Thus, it is vital that adequate control of this disease be achieved. Although multiple biologic agents specifically indicated for the treatment of CRSwNP in AERD exist which do not require daily dosing and are highly efficacious, requiring treatment with injectable biologics restricts deployability and can cause pilots to stop flying altogether.^{4,7,8} Conversely, treatment

with aspirin does not significantly impact suitability for flight status or deployability, and many studies demonstrate the efficacy of aspirin desensitization after nasal polypectomy in preventing recurrence of nasal polyps in AERD.⁹ An aspirin-desensitized state can be readily achieved by gradually introducing increased dosages of aspirin in a controlled clinical environment and continuing daily aspirin therapy thereafter. We present a case of AERD with recurrent rhinosinusitis and nasal polyps in an active duty pilot successfully managed with aspirin desensitization, resulting in control of symptoms and maintenance of flying status.

CASE DESCRIPTION

A 32-year-old male fighter pilot with a history of chronic sinusitis with recurrent nasal polyps and non-steroidal anti-inflammatory drug sensitivity status—post-three endoscopic sinus surgeries—was referred for aspirin desensitization to minimize impact on flying status. The patient was frequently removed from flying status because of episodes of sinusitis treated with systemic steroids and/or antibiotics or during recovery from surgical interventions. To reduce the chances of nasal polyp regrowth after his third polypectomy while minimizing the impact of medical treatments on his military career, the patient was chosen for and consented for aspirin desensitization.¹⁰ As the process of aspirin desensitization provokes respiratory symptoms, baseline spirometry was obtained and was normal without bronchodilator response. Desensitization was accomplished using a 2-day intranasal ketorolac tromethamine and modified oral aspirin challenge as described by Lee et al.¹¹ On Day 1 of the protocol, he was given increasing doses of intranasal ketorolac tromethamine which produced minimal upper respiratory symptoms and then introduced to low-dose aspirin which produced lower respiratory symptoms that were successfully treated with oral antihistamines and albuterol via metered dose inhaler (Table I). On Day 2 of the protocol, he was introduced to increasing doses of aspirin which produced minimal

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TABLE I. Response to Intranasal Ketorolac Tromethamine and Oral Aspirin Challenge

Medication and dose	Day of desensitization	Time	FEV1	Symptoms and treatment
Ketorolac tromethamine 1 spray	1	0845	4.79	1/10 Nasal congestion
Ketorolac tromethamine 2 sprays	1	0915		2/10 Nasal congestion
Ketorolac tromethamine 4 sprays	1	0953		4/10 Nasal congestion and sneezing, cetirizine 10 mg given
Ketorolac tromethamine 6 sprays	1	1030	4.37	Wheezing on auscultation, 2 puffs albuterol given
Aspirin 60 mg	1	1130	5.07	2/10 Nasal congestion
Aspirin 60 mg	1	1325	4.81	Asymptomatic
Aspirin 162 mg	2	0830	4.60	1/10 Nasal congestion
Aspirin 325 mg	2	1130	4.49	1/10 Nasal congestion

Patient's FEV1, symptom response, and corresponding treatment (if any) during initial aspirin.

desensitization using an intranasal ketorolac tromethamine and modified oral aspirin protocol.¹¹ Provocation of symptoms with aspirin administration served as confirmation of aspirin sensitivity.

FEV1, forced expiratory volume in 1 s.

upper respiratory symptoms that did not require treatment. Having at this point reached a state of aspirin desensitization, he was subsequently started on aspirin 650 mg twice daily. The patient was prescribed enteric-coated aspirin to mitigate gastrointestinal toxicity from chronic aspirin use. Despite this, he was ultimately weaned to twice daily therapy with aspirin 325 mg within the first 6 months of treatment because of gastrointestinal side effects. After approximately 1 year on twice daily aspirin therapy, because of lack of polyp reformation and patient preference, he was weaned to once daily therapy with aspirin 325 mg (Fig. 1).¹² Aspirin therapy was held before a functional endoscopic sinus surgery to address nasal valve collapse and deviated septum approximately 3 years after

initial desensitization. He was successfully desensitized post-operatively using a 1-day, 90-minute aspirin challenge and desensitization protocol as described by DeGregorio et al., which he tolerated well.¹ Other than the aforementioned pause in aspirin therapy for functional endoscopic sinus surgery, he has remained on 325 mg daily aspirin for over 5 years without regrowth of polyps and with notable reduction in episodes of acute sinusitis in the last 2 years.

DISCUSSION

Our patient has been able to remain free of nasal polyps on daily aspirin therapy, which he has tolerated well, for over 5 years. It is well postulated that interminable nasal polyp formation in AERD is caused by local tissue inflammation, specifically mast cell and eosinophil dysregulation at nasal mucosa.¹³ Biologic agents indicated for CRSwNP in AERD, such as dupilumab, mepolizumab, and omalizumab, inhibit the T-helper 2 immune response and eosinophil activation and migration which reduces polyp formation.⁴ In contrast, the pathophysiologic mechanism of aspirin desensitization for the treatment of CRSwNP in AERD is less well understood. It is known that prostaglandins are key immunologic mediators in the inflammatory pathway. Prostaglandin D2 specifically is a major pro-inflammatory mediator indicated in acute allergic inflammatory responses released by mast cells that cause eosinophil, basophil, and T-helper cell recruitment to local sites.¹⁴ Levels of prostaglandin D2 are suppressed in patients with AERD after aspirin desensitization, which may account for lower levels of local tissue inflammation and, in turn, suggest a mechanism for decreased severity and frequency of nasal polyp formation.¹⁵ Despite only postulations for its pathophysiologic mechanism, aspirin desensitization is still a well-proven and commonly used treatment method to decrease the burden of nasal polyposis in patients with AERD. Regarding treatment choice in the active duty flying population, aspirin therapy offers many advantages over biologic agents. Aspirin only requires a single ground trial with initial use, while biologic injections require a post-injection DNIF after each administration, even once a waiver for retention has been obtained. For dupilumab, this would require DNIF every

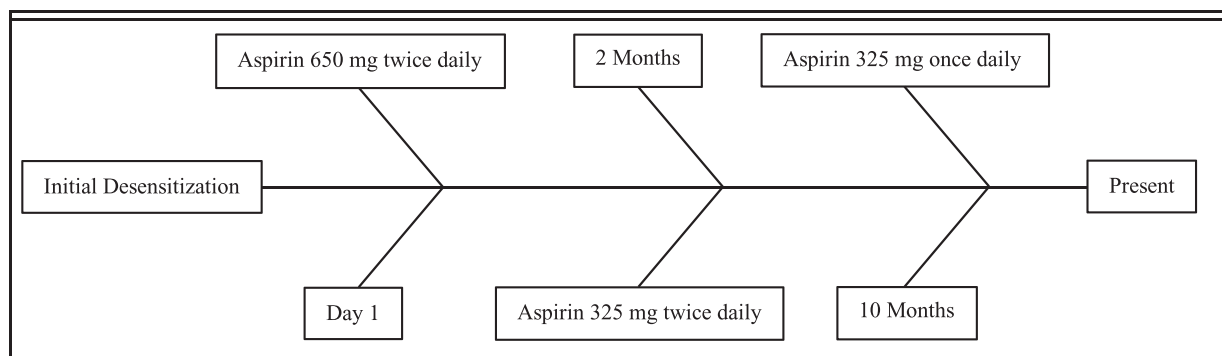


FIGURE 1. Desensitization course. Dose adjustments of aspirin used to maintain desensitization. Dose decreased at 2 months because of gastrointestinal upset and at 10 months because of patient preference. Patient continues on aspirin 325 mg once daily presently.

2 weeks. Biologic agents require careful handling and storage within specific temperature ranges, whereas aspirin is readily available and easily stored. Additionally, certain biologic agents (dupilumab) prohibit administration of live vaccinations, which may further restrict deployability and/or assignment location as many active duty members may require live vaccinations based on command location and/or results of serologic testing for immunity. Aspirin desensitization comes with the added benefit of cross-desensitization to other cyclooxygenase-1 inhibiting non-steroidal anti-inflammatory drugs at comparable doses, which can be used for the treatment of pain and/or inflammatory conditions that are commonly encountered in this patient population.¹⁶ In summary, aspirin desensitization for CRSwNP in patients with AERD remains safe and effective and may be viewed more favorably than biologic therapy in the flight medicine community with regard to suitability for flight status. This case report serves to highlight the successful use of aspirin therapy for CRSwNP in AERD while simultaneously achieving retention of military service and maintenance of flying status in an active duty USAF pilot.

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No personal or financial conflict of interest exists for this work.

CLINICAL TRIAL REGISTRATION

Not applicable.

INSTITUTIONAL REVIEW BOARD (HUMAN SUBJECTS)

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INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT

All authors have read and approved the final manuscript.

DATA AVAILABILITY

No new data were generated or analyzed in support of this research.

INSTITUTIONAL CLEARANCE

It does not apply.

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