
Case report

Failure to maintain an aspirin-desensitized state in a patient with aspirin-exacerbated respiratory disease

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Background: Aspirin desensitization is a useful therapy in patients with aspirin-exacerbated respiratory disease.

Objective: To describe the clinical course of a man with aspirin-exacerbated respiratory disease who was unable to be desensitized to oral aspirin.

Methods: A standard aspirin desensitization protocol was used to achieve a maximum dose of 650 mg of oral aspirin. The patient initially tolerated this dose of aspirin.

Results: Within days of desensitization, the patient began to react to 650 mg of aspirin. Monitored challenge with this dose of aspirin led to marked decrease in forced expiratory volume in 1 second and pronounced nasal and ocular symptoms.

Conclusions: We present a patient with classic aspirin-exacerbated respiratory disease, who despite undergoing a standard aspirin desensitization protocol was unable to maintain his desensitized state.

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INTRODUCTION

Aspirin desensitization is a useful therapy in patients with aspirin-exacerbated respiratory disease. We describe the clinical course of a man with aspirin-exacerbated respiratory disease who was unable to be desensitized to oral aspirin.

CASE REPORT

A 25-year-old man presented for evaluation of asthma, nasal polyposis, and aspirin sensitivity. He had been in good health until 3 years earlier, when ingestion of ibuprofen, 800 mg, produced an acute episode of rhinorrhea, nasal congestion, wheezing, and dyspnea. Similar reactions occurred after taking aspirin, 325 mg, and acetaminophen, 1,000 mg. He had one further exposure to ibuprofen, 800 mg, 18 months later with severe wheezing and dyspnea and thereafter avoided all aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs.

The patient began to experience chronic nasal congestion and postnasal drip. The results of skin testing for aeroaller-

gens were negative. Computed tomography of the sinuses revealed diffuse nasal polyposis and pansinusitis. Shortly thereafter, he underwent the first of 3 polypectomies. The patient had been a competitive athlete until this time, when he started to have episodic wheezing and dyspnea. He responded initially to the use of bronchodilators, but during the next 2 years had gradually deteriorating asthma that required aggressive controller therapy.

Three months after his third polypectomy, he was referred for evaluation. Between asthma exacerbations, he continued to have daily wheezing despite use of fluticasone/salmeterol, 500/50 μ g, inhaled twice daily; montelukast, 10 mg/d; and fluticasone nasal spray. He had been having asthma exacerbations that required systemic corticosteroids monthly. On examination, his nasal membranes were edematous, but polyps were not present and his chest was clear. Baseline forced expiratory volume in 1 second (FEV₁) was 3.96 L or 80% of predicted.

He subsequently returned for aspirin challenge and desensitization. Prednisone in a tapering dose had recently been added to his regimen, and during the aspirin desensitization, he took 60 mg once then 40 mg per day. His FEV₁ was 3.71 L, 75% of predicted. After oral challenge with aspirin, 30 mg, he had a naso-ocular reaction but no significant FEV₁ decline. Aspirin, 30 mg, was repeated with no symptoms. Aspirin, 45 mg, produced a naso-ocular reaction, as well as nausea and vomiting. The next day, he returned and proceeded through doses of aspirin 45, 60, and 100 mg; the last dose resulted in bronchospasm and an FEV₁ decrease of 18%. Since he was participating in an outpatient desensitization program, he

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went home for the weekend, taking aspirin, 60 mg/d, until he could return on Monday to complete aspirin desensitization. He returned the following Monday and received 2 additional doses of aspirin, 100 mg, developing mild chest tightness after each dose. The next day he received aspirin, 150 mg, 325 mg, and 650 mg, with minimal symptoms. He was therefore certified as having achieved acute aspirin desensitization and instructed to take aspirin, 650 mg twice daily; budesonide, 2 inhalations twice daily; salmeterol, 1 puff twice daily; montelukast, 10 mg each evening; fluticasone nasal spray, 1 spray in each nostril twice daily; albuterol as needed; ranitidine, 150 mg twice daily; topiramate, 50 mg twice daily; verapamil, 240 mg/d; amitriptyline, 25 mg each evening; and rizatriptan, 10 mg; as needed for migraine headache. Prednisone use was discontinued.

Within days of completing desensitization, the patient recognized that after each dose of aspirin he would develop wheezing, dyspnea, and cough followed by nasal congestion, tearing, and ocular redness. He adamantly denied any gap in aspirin therapy. These reactions would occur regularly approximately 1 hour after aspirin ingestion and would last for several hours. He would return to baseline several hours after that only to take the second dose of aspirin and repeat the reaction. After bringing these reactions to the attention of his allergist, the patient came to the clinic for observation of a morning dose of aspirin, 650 mg.

Baseline spirometry was stable with an FEV₁ of 81% of predicted. Before aspirin ingestion, the patient had only mild nasal congestion. Thirty minutes after ingesting aspirin, 650 mg, the patient had stable spirometry (FEV₁, 80% of predicted) and no additional symptoms. One hour after aspirin ingestion, the patient developed wheezing, coughing, and dyspnea. His FEV₁ values declined to 42% of predicted (2.1 L). He was treated with albuterol via metered-dose inhaler, but his spirometry measurements continued to fall to an FEV₁ nadir of 1.79 L (36% of predicted). By this point, he had also developed prominent conjunctival injection, epiphora, profuse watery rhinorrhea, sneezing, and complete nasal obstruction. Continued treatment with albuterol led to gradual resolution of his symptoms and a return of his FEV₁ values to baseline. He confirmed that this reaction was similar to the reactions he experienced twice daily since desensitization.

The patient was instructed to discontinue use of aspirin and return to the clinic for follow-up the next day. He returned with a baseline FEV₁ of 86% of predicted. He agreed to undergo a blinded challenge and was given placebo. During the following 2 hours, he experienced no symptoms and no changes in spirometry.

DISCUSSION

Aspirin desensitization for the treatment of aspirin-exacerbated respiratory disease has been shown to improve clinical outcomes and decrease systemic corticosteroid use.¹ It is reserved for those patients with aggressive sinus disease, patients with high corticosteroid requirements, or those patients requiring aspirin or nonsteroidal anti-inflammatory

drugs for another medical condition. The desensitization protocol has been previously published.² The protocol is completed when aspirin, 650 mg, is administered to the patient and no reaction occurs. Patients are then instructed to continue taking aspirin, 650 mg twice daily, for 1 month, followed by 325 mg twice daily thereafter.

Patients are carefully selected before undergoing aspirin desensitization. Unstable asthma (FEV₁ < 60% of predicted) disqualifies a patient for aspirin desensitization. Rarely, patients develop recalcitrant urticaria during aspirin desensitization and cannot complete the protocol. Aside from these rare exceptions, only a few patients cannot complete desensitization. At Scripps Clinic, there has never been a patient who, on reaching the maximum 650-mg dose of aspirin, has not achieved desensitization. To our knowledge, none of the 988 patients desensitized at Scripps Clinic have begun to have reactions to the maintenance dose of aspirin after desensitization was completed. There are only 3 reports of desensitization failure in the medical literature. Interestingly, one occurred in a patient who required high doses of systemic corticosteroid during desensitization to allow desensitization to proceed. The authors suggest that these high doses of systemic corticosteroid increased tolerance to aspirin and, when withdrawn, allowed the reactions to continue.³ The second case involves a patient who successfully underwent desensitization, was treated with daily aspirin without any problems, and 6 months later began to develop asthmatic reactions after each ingestion of aspirin.⁴

The patient we present tolerated 650 mg of aspirin during the desensitization protocol, but within 2 days the patient began to react to aspirin, 650 mg, during maintenance therapy. It is possible that systemic corticosteroids given during the desensitization procedure may have allowed the initial tolerance to 650 mg of aspirin. When prednisone was later withdrawn, the previously "masked" reactions occurred. This finding is unlikely, given that systemic steroids have not been shown to have significant blocking effects on aspirin-induced reactions.⁵ It is possible that this patient had a lapse in aspirin therapy that allowed resensitization to occur. It is unlikely that this occurred, because his reactions to aspirin began 48 hours after undergoing documented aspirin desensitization.

During aspirin desensitization, the initial dose that induces respiratory reactions is termed the *provoking dose*. The provoking dose is always repeated, and in most patients this second dose leads to greatly attenuated symptoms. In many patients, no further reactions occur. During desensitization at Scripps Clinic, many patients receive the provoking dose as the last dose in the afternoon, followed by the second dose the next morning. For our patient, it is unclear why repeatedly taking a provoking dose of aspirin twice daily did not lead to attenuation and desensitization, since this appears to have occurred in every other patient who has undergone desensitization.

The mechanism behind aspirin desensitization is partly understood. Desensitization has been associated with a decrease in airway responsiveness to inhaled leukotriene E₄ but not with a decrease in overall leukotrienes production when

compared with baseline urinary leukotriene E₄ levels.^{6,7} Thus, decreased activity of leukotrienes acting through cysteinyl leukotriene 1 receptors or decreased downstream intracellular signaling provides a plausible mechanism for acute desensitization. Other events include the interruption of histamine and tryptase secretion from mast cells and the blocking of cyclo-oxygenase 1 and 2 in mast cells with termination of synthesis of prostaglandin D₂.⁸ In the long term, expression of cysteinyl leukotriene 1 receptors is reduced in the nasal mucosa of aspirin sensitive asthmatic patients after desensitization.⁹ It is unlikely that this particular patient could be desensitized by even higher doses of aspirin, because no attenuation of reaction occurred after repeated administration of the provoking dose.

In conclusion, we present a patient with classic aspirin-exacerbated respiratory disease who despite undergoing a standard aspirin desensitization protocol was unable to maintain his desensitized state.

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