

Clinical Communications

Intranasal ketorolac-induced pancreatitis as a complication of modified oral aspirin desensitization in a patient with aspirin-exacerbated respiratory disease

Kathleen T. Luskin, MD^a, John V. Bosso, MD^b, and Ronald A. Simon, MD^a

Clinical Implications

- This represents the first case of pancreatitis associated with intranasal ketorolac and is a potential adverse effect of the modified aspirin desensitization procedure that clinicians should be aware of.

TO THE EDITOR:

There are published case reports on patients with aspirin-exacerbated respiratory disease (AERD) with aspirin-induced pancreatitis associated with desensitization.^{1,2} There have been 2 cases of pancreatitis due to intramuscular ketorolac in patients without AERD.^{3,4} We present a case of intranasal ketorolac-induced pancreatitis that occurred during aspirin desensitization, which to our knowledge is the first case that has been associated with the modified intranasal ketorolac/aspirin challenge protocol.

A 42-year-old man was referred for asthma, nasal polyps, and ibuprofen sensitivity. One year earlier, he began experiencing frequent sinus infections, anosmia, wheezing, dyspnea, and chest tightness. Six months later, he noticed worsening asthma within 10 minutes of ibuprofen ingestion on 2 occasions; he had previously tolerated ibuprofen. Chest computed tomography demonstrated mucous impaction and scattered atelectasis, and sinus computed tomography revealed diffuse pan-sinusitis with nasal polyps. Despite fluticasone/salmeterol, montelukast, and tiotropium, he still required daily maintenance and intermittent bursts of systemic corticosteroids. He underwent his first sinus surgery without significant improvement postoperatively. Because of significant polyp regrowth 6 months later, he underwent revision surgery and his medications were changed to fluticasone/vilanterol and zileuton; his other medications included omeprazole, vitamin D₃, and budesonide sinus rinses. Two months after the second sinus surgery, because his prednisone could not be tapered below 20 mg daily, the patient presented for desensitization with the intranasal ketorolac and oral aspirin protocol.⁵ This was his first exposure to ketorolac. Forty minutes after the fourth intranasal ketorolac dose (7.56 mg), he developed severe abdominal pain and wheezing. His bronchospasm responded to albuterol nebulizers; however, the epigastric pain did not improve despite 4 doses of intramuscular epinephrine, intravenous H1 and H2 antihistamines, and fluids. Abdominal examination was notable for epigastric tenderness without rebound. His

pain was alleviated with intravenous hydromorphone. Stat blood draws demonstrated elevated amylase 1444 U/L (normal, 25-125 U/L) and lipase 5180 U/L (normal, 10-140 U/L) and he was hospitalized with acute pancreatitis. Comprehensive metabolic panel, triglycerides, and blood glucose were normal. Abdominal ultrasound with Doppler was negative for gallstones, sludge, and cholecystitis. He denied alcohol/recreational drug use, previous similar abdominal pain, insect bites, abdominal trauma, dyslipidemia, or hypercalcemia. He had no recurrence of respiratory symptoms; his amylase decreased to 424 U/L and he was discharged the next day. His abdominal symptoms completely resolved within 3 to 4 days.

Acute pancreatitis is characterized by pancreatic inflammation. Drug-induced pancreatitis (DIP), which occurs in 0.1% to 2% of cases of acute pancreatitis, should be considered after more common causes are ruled out.⁶ DIP diagnosis can be challenging; it is a diagnosis of exclusion, timing between drug administration and symptoms is variable (onset immediately to several months later, depending on underlying mechanism), and the diagnosis is based on case reports with suspected, but unproven, pathogenic mechanisms.⁶ A classification system for DIP sorts medications into classes on the basis of the number of case reports and rechallenge data, with I having the most and IV the least supportive data; this classification system is detailed elsewhere.⁶

The mechanisms of DIP can be variable, including hypersensitivity, metabolite accumulation, and intrinsic toxicity. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with DIP; sulindac (class I) has the strongest evidence, but cases associated with ketorolac (class III), naproxen (class III), diclofenac (class IV), and rofecoxib (class IV) have also been reported.^{3,4,6} It is suspected that NSAID-induced pancreatitis is mediated by COX-1 inhibition and decreased prostaglandin production. Prostaglandins alter pancreatic secretion and assist with pancreatic cell membrane stabilization.⁶ Specifically, **prostaglandin E1** causes a decrease in Sphincter of Oddi (SO) pressure and motility, and **prostaglandin E2** (PGE2) causes gallbladder contraction and SO relaxation.⁷ NSAID-induced decrease in prostaglandin synthesis would thereby result in increased SO pressure. Animal models have demonstrated that aspirin increases pancreatic duct permeability and pancreatic calcium secretion, which is a marker of pancreatic damage.⁶ Although prostaglandin-mediated SO dyskinesia can cause pancreatic duct obstruction and subsequent pancreatitis, edema-induced papillary stenosis can act similarly. NSAIDs cause angioedema via decreased PGE2, thereby potentially causing local swelling and duct obstruction leading to DIP.⁶

The correlation between aspirin and pancreatitis is of particular interest in the AERD population, who have different immune regulation and inflammation compared with most individuals ingesting NSAIDs. In AERD, patients' symptoms may be mediated by baseline decreased PGE2 levels and mast cell prostaglandin D2 overproduction. They may be exquisitely sensitive to prostaglandin inhibition due to low protective PGE2 and local adaptation to chronically high prostaglandin levels, although the role of prostaglandin D2 in pancreatitis has not

been fully elucidated. Previous reports of pancreatitis associated with aspirin desensitization were confounded by polypharmacy, biliary sludge, and unclear diagnosis of gastritis versus pancreatitis.^{1,2,8} The paucity of strong data on NSAID-induced pancreatitis has been raised in an editorial response⁸; however, there may be underreporting because NSAID-associated abdominal pain is often attributed to gastritis without pursuing pancreatitis as a diagnosis. Abdominal pain is a common finding in patients with AERD who ingest aspirin, and occurred along with respiratory reactions in 7.5% to 23%, as seen in our patient and 2 of the 4 previous case reports.^{1,2,5,9}

Like previous AERD DIP case reports, our patient was on medications that have been associated with pancreatitis, notably prednisone and vitamin D. However, he did not have hypertriglyceridemia nor hypercalcemia as is typically found with pancreatitis due to these medications, and he continued on both these medications without symptom recurrence.⁶ Previous case reports have noted an onset of 2.5 hours after the start to 4 days after the completion of desensitization; in this case, our patient's appearance of symptoms was fairly rapid (130 minutes after the first dose of ketorolac), which is consistent with a previous case report of symptom onset 2 hours after ketorolac administration and consistent with prostaglandin effects (alteration of SO tone, gallbladder motility, edema) rather than a memory immunologic response.^{1-3,7} This mechanism is also reinforced by this patient's reactions to multiple NSAIDs (ketorolac and ibuprofen), indicating underlying susceptibility to COX-1 inhibition. His reaction with the first exposure to ketorolac at the typical threshold dose for COX-1-mediated reactions (5-7.5 mg) also supports COX-1 rather than immunologically-mediated etiology. The concomitant bronchospasm could indicate loss of PGE2-induced bronchodilation (and decreased PGE2-induced SO relaxation), further supporting the role of prostaglandins in this patient's presentation. Symptom resolution a few days after last ketorolac exposure is consistent with previous reports noting pancreatitis improvement within 3 to 7 days of stopping the offending medication.^{1-3,6} Our patient did not have previous nor recurrent symptoms, making microlithiasis/biliary sludge missed by ultrasound less likely. In this patient's case, he did not appear to have any other medical, anatomic, or pharmacologic etiologies for his pancreatitis. The temporal relationship between the administration of a medication in a drug class known to cause pancreatitis

and symptom resolution upon drug withdrawal make ketorolac the most likely cause of his pancreatitis.

In summary, acute pancreatitis is a potential adverse reaction that can occur during aspirin desensitization for AERD. Clinicians should be aware of this rare potential complication and be prepared to diagnose and treat it appropriately.

^aDivision of Allergy, Asthma and Immunology, Scripps Clinic, San Diego, Calif

^bPenn Medicine, Penn AERD Center, Philadelphia, Pa

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication August 8, 2019; revised September 24, 2019; accepted for publication October 10, 2019.

Available online ■ ■

Corresponding author: John V. Bosso, MD, Hospital of the University of Pennsylvania-Perelman Center for Advanced Medicine, 3400 Civic Center Blvd, 3 South OTO, Philadelphia, PA 19104. E-mail: John.Bosso@pennmedicine.upenn.edu.

2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2019.10.006>

REFERENCES

1. Hoyte FC, Weber RW, Katial RK. Pancreatitis as a novel complication of aspirin therapy in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2012;129:1684-6.
2. Durrani SR, Kelly JT. Pancreatitis as a complication of aspirin desensitization for aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2013;131:244-6.
3. Goyal SB, Goyal RS. Ketorolac tromethamine-induced acute pancreatitis. *Arch Intern Med* 1998;158:411.
4. Famularo G, Bizzarri C, Nicotra GC. Acute pancreatitis caused by ketorolac tromethamine. *J Clin Gastroenterol* 2002;34:283-4.
5. 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.
6. Hung WY, Abreu Lanfranco O. Contemporary review of drug-induced pancreatitis: a different perspective. *World J Gastrointest Pathophysiol* 2014;5:405-15.
7. Martinez E, Sarles JC. Effect of prostaglandins E1, E2, and F2 alpha on the electric activity of the sphincter of Oddi in living rabbit. *Eur Surg Res* 1983;15:322-7.
8. Stevenson DD, White AA, Simon RA. Aspirin as a cause of pancreatitis in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2012;129:1687-8.
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.