

Aspirin as a cause of pancreatitis in patients with aspirin-exacerbated respiratory disease

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Hoyte et al¹ presented 3 cases of acute pancreatitis appearing in patients with aspirin-exacerbated respiratory disease (AERD) who recently underwent aspirin challenge/desensitization. The editors of the *Journal of Allergy and Clinical Immunology* invited us to review drug-induced pancreatitis and to comment on these cases.

Most pancreatitis is caused by bile duct stones occluding the pancreatic duct or chronic alcoholism, with 10% to 25% of cases having no readily identified cause and termed idiopathic.² Large gallstones can be readily diagnosed. Microstones, so-called biliary sludge, can evade detection by means of computed tomographic scanning or ultrasonography yet can still occlude pancreatic ducts.^{3,4} Accurate identification of drug effects, particularly in a setting of polypharmacy or other known causes of pancreatitis, is sometimes impossible.⁴ Although rechallenge with a suspect drug is the best evidence available for cause and effect, it is not proof. Many patients with idiopathic pancreatitis or microlithiasis have recurrent attacks of acute pancreatitis. Therefore stopping and starting a drug with recurrence of pancreatitis might be a coincidence and not a cause-and-effect relationship.⁴

Attempts to provide guidelines on drug/pancreatitis associations have been published.^{5,6} In one study a drug was assigned to class I if greater than 20 prior case reports of drug association with pancreatitis had been reported and at least 1 positive rechallenge result with the suspect drug had been documented.⁵ All the statins and 1 nonsteroidal anti-inflammatory drug, sulindac, are in class I. Ten or more case reports without any rechallenges were less probable (class II), and all others, with less than 10 case reports, were classified as possible (class III).⁵ In another classification, patterns of latency from the start of drug therapy to the onset of pancreatitis were added.⁶ Class I included drugs in which at least 1 case report described a recurrence of acute pancreatitis after rechallenge with the same drug. Class II included drugs in which there was a consistent latency in 75% or more of the reported cases. Class III was 2 or more case reports, but neither a rechallenge nor consistent latency was observed. Class IV was similar to class II, but only 1 prior case report had been published.⁶

The 3 patients in the letter by Hoyte et al¹ provided 3 different associations and time latency to onset of abdominal pain. Patient 1 had typical AERD and was taking a number of medications, including simvastatin and montelukast. On the basis of history, after ingesting nonsteroidal anti-inflammatory drugs, he had experienced respiratory reactions with associated gastrointestinal pain, which was attributed to gastroesophageal reflux disease. The current oral aspirin challenge induced a typical respiratory reaction, which was associated with rapid onset and severe abdominal pain and was diagnosed as pancreatitis.¹

Because pancreatitis can lead to morbidity and death, physician-initiated rechallenge is potentially dangerous and not the standard of care. Most rechallenges have been patient initiated.⁷ Hoyte et al¹ assumed that the prior nonsteroidal anti-inflammatory drug reactions and aspirin challenge a year ago were actually nonsteroidal anti-inflammatory drug- and aspirin-induced pancreatitis, except pancreatic enzymes were not measured. The authors could not exclude simvastatin-induced pancreatitis,⁷ some unknown interaction between simvastatin and salicylate,⁸ or recurrent pancreatic duct occlusion by microlithiasis.^{3,4} The authors hypothesized that a surge of recently synthesized leukotrienes might have caused the pancreatitis. Such a theory might potentially assign special susceptibility to patients with AERD. If COX-1 inhibition initiated leukotriene synthesis and induced pancreatitis, it is curious that only 1 strong inhibitor of COX-1, sulindac, has been identified in class I⁵ and that the weakest COX-1 inhibitor, acetaminophen, includes more than 10 case reports and meets the criteria for a class II drug.⁵ In addition, statins do not inhibit COX-1 and appear to be the most common and accepted class of drugs that have been reported to induce pancreatitis.^{5,6} These observations suggest to us that specific drugs, including sulindac, acetaminophen, and statins, induce pancreatitis directly.

Patient 2 was only taking montelukast during his reported oral aspirin challenge.¹ A year before, an oral aspirin challenge performed at another institution induced a respiratory reaction with abdominal pain on day 3, at which time aspirin was discontinued. Pancreatic enzymes were not drawn. He was treated with proton-pump inhibitors, recovered, and avoided aspirin for a year. He then underwent his second aspirin challenge.¹ Unlike patient 1, abdominal pain and increased pancreatic enzyme levels occurred 48 hours after the aspirin-induced respiratory reaction. Furthermore, during his hospitalization for pancreatitis, an ultrasound revealed small biliary calculi, which could have induced both episodes of abdominal pain. Alternatively, he might have had aspirin-induced gastritis previously and now microlithiasis-induced pancreatitis. If the leukotriene theory were to be applied, urinary leukotriene E₄ levels spike during aspirin-induced reactions and return to baseline before 48 hours.⁹ Nevertheless, case 2 is temporally associated with one drug (aspirin), with documented pancreatitis during his second episode.

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This could be the first case of aspirin-induced pancreatitis (class III⁵ or IV⁶).

For patient 3, our interpretation is that aspirin caused gastritis. Abdominal pain was mild and started 4 days after aspirin desensitization treatment. Rather than going directly to the emergency department, she waited 3 weeks until her scheduled return visit and then told her doctors. Lipase and amylase enzyme levels were marginally increased. Hospitalization included extensive workup, including computed tomography and ultrasonography, which revealed no other known cause for pancreatitis. While continuing aspirin at a lower dose of 81 mg/d, her abdominal pain disappeared, which is characteristic of aspirin-induced gastritis. Repeated pancreatic enzyme levels returned to lower values. To conclude that this patient had aspirin-induced pancreatitis, one would have to believe that moderate doses of aspirin, with a latency of 4 days, can cause pancreatitis but that very low doses cannot. Her story was also burdened by polypharmacy, including concomitant clopidogrel, vitamin D, rosuvastatin,¹⁰ alendronate, and montelukast. Did the rosuvastatin cause her pancreatitis, and was this drug discontinued? Or was microlithiasis with temporary pancreatic duct occlusion the cause of transient low-grade pancreatitis? Or were the minimal enzyme levels increased from another source, such as the salivary glands, and was her epigastric pain caused by aspirin-induced gastritis?

If aspirin-induced pancreatitis occurs during oral aspirin challenges,¹ we should find more aspirin-desensitized patients with increased pancreatic enzyme levels. This is the authors' valid position: if you do not look for something, you will never find it. In our 2007 study,¹¹ 210 consecutive patients with AERD had positive oral aspirin challenge results, and 49 (23%) experienced both respiratory reactions and abdominal pain. All received ranitidine, cleared their gastrointestinal symptoms, completed aspirin desensitization, and were transitioned to daily aspirin treatment. In 228 patients undergoing ketorolac/modified aspirin challenge/desensitizations over the past 5 years,¹² 17 (7.5%) had abdominal pain during their respiratory reactions. All were treated as above, cleared their abdominal symptoms rapidly, completed aspirin desensitization, and ingested daily aspirin at 650 or 325 mg twice daily. Currently, 11 of 17 are free of abdominal pain. Three discontinued aspirin because of epigastric pain, and 3 could not be contacted. Recently, we tested 3 patients with AERD who had moderately severe abdominal pain during aspirin desensitization. Pancreatic enzyme levels were normal, and all 3 proceeded to a pain-free successful aspirin desensitization.

Although we are not convinced that the authors are presenting the first case, or perhaps 2 cases, of aspirin-induced pancreatitis, if the authors are correct, were such reactions linked to AERD and aspirin desensitization? Our reasoning is that such a linkage seems very unlikely. Furthermore, if aspirin and pancreatitis are uncoupled from AERD, many other cases of aspirin-induced pancreatitis should have occurred and been reported. In the United States 12 million patients have coronary artery disease,¹³ and the standard of care for cardioprophylaxis is daily aspirin. In addition, up to 1000 mg of aspirin is consumed at one time by millions of headache sufferers around the world. Despite this massive exposure to aspirin, a Medline search is curiously devoid of believable case reports of aspirin-induced pancreatitis.⁸

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