Drug-Induced Pancreatitis
A Potentially Serious and Underreported Problem
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INTRODUCTION
There have been many published reports of potential cases of drug-induced pancreatitis (DIP).1-3 When I was in my Doctor of Pharmacy training in Boston, the medical residents used the mnemonic FATSHEEP to remember the causes of DIP—Furosemide, Azathioprine/Asparaginase, Thiazides/Tetracycline, Statins/Sulfonamides, Hydrochlorothiazide (a little overlap here), Estrogens, Ethanol, and Pentamidine. Although the latter two agents are rarely used today, the mnemonic was a good one because I still remember it after all these years.

Some of the more common culprits for DIP include valproic acid, calcium-channel blockers, antipsychotic agents, sulindac (Clinoril, Merck), methyldopa, octreotide (Sandostatin, Novartis), 6-mercapto purine, 5-aminosalicylic acid compounds, metronidazole (Flagyl, Pfizer), isoniazid, and corticosteroids.1,3,4 Also implicated are the angiotensin-converting enzyme (ACE) inhibitors (the topic of the first Pharmacovigilance Forum column in the March issue of P&T); glucagon-like peptide-1 (GLP-1)–based therapies such as liraglutide (Victoza, NovoNordisk) and exenatide (Byetta, Bydureon, Amylin); and the dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin (Januvia, Merck) and linagliptin (Tradjenta, Boehringer Ingelheim).3,5,6 In fact, sitagliptin was the focus of an FDA alert on September 25, 2009.7 This alert provided an update to the prescribing information and warnings related to 88 postmarketing cases of acute pancreatitis reported between October 2006 and February 2009, including two cases of hemorrhagic or necrotizing pancreatitis.7

Besides drugs, some disease states and characteristics predispose particular populations to the development of pancreatitis, for example:1,8

- female, elderly, or very young patients.
- immunosuppressed patients with conditions such as inflammatory bowel disease.
- transplant recipients.
- patients taking immunomodulators for immune-related conditions.

Patients with HIV infection or AIDS are also at risk for DIP because of their compromised immune system and their intake of some medications, particularly the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine (Videx) and stavudine (Zerit), both made by Bristol-Myers Squibb. In addition, the agents used to treat opportunistic infections, such as ketoconazole (Nizoral, Janssen), sulfonamides, pentamidine, metronidazole, isoniazid, and corticosteroids, may also play a role.

HIV/AIDS patients with cytomegalovirus, cryptosporidiosis, and mycobacterial infections are also at an increased risk. Hypertriglyceridemia, biliary disease, gallstones, alcohol consumption, and low CD4 counts also predispose these patients to DIP.9-11 The incidence of DIP in patients with HIV is at least 40%, much higher than that in the general population.11

Didanosine has been implicated in more than 800 reported cases, as confirmed by rechallenge,11 the definitive method of proving causality of an adverse drug reaction (ADR). Pentamidine has also been implicated in at least 79 confirmed cases of acute pancreatitis. Other AIDS therapies implicated in DIP include abacavir (Ziagen, GlaxoSmithKline), efavirenz (Sustiva, Bristol-Myers Squibb), indinavir (Crixivan, Merck), nelfinavir (Viracept, Agouron), ritonavir (Norvir, Abbott), saquinavir (Invirase, Roche), tenofovir (Viread, Gilead), and zidovudine (Retrovir, Viiv/GlaxoSmithKline/Pfizer).

Hyperparathyroidism, trauma, endoscopic retrograde cholangiopancreatography (ERCP), pancreatic tumors, and surgery are common causes of non–drug-induced pancreatitis.11

PATHOPHYSIOLOGY
Several mechanisms of DIP appear to be involved, including immune-mediated or hypersensitivity reactions, direct toxic effects, bradykinin-induced inflammatory reactions, and mitochondrial toxicity.1,3 There is limited evidence that intrinsic toxicity, which causes damage in a dose-dependent manner, causes DIP.

Only three drugs—acetaminophen, erythromycin (Ery-Tab, E-Mycin, Abbott), and carbamazepine—have been associated with pancreatitis in the setting of a drug overdose; therefore, it is more likely that idiosyncratic reactions occur in most patients with DIP.9 These reactions are unpredictable; they are not dose-dependent, and the incidence is low. They can be further classified as hypersensitivity reactions and those that occur with the accumulation of toxic metabolites or an intermediary damaging substance. Direct immunological effects are usually observed within the first month of drug exposure, whereas toxic effects are noted after a few months of treatment. Indirect mechanisms of pancreatitis include ischemia, an increase in the viscosity of pancreatic enzymes, and intravascular thrombosis.11

INCIDENCE
In the non-HIV/AIDS population, the incidence of DIP is 1.4% to 5%.11 However, because adverse drug events (ADEs) are underreported, the validity and severity of DIP are not known. Although DIP is potentially rare and usually mild in appearance, mortality rates approach 30% in a small number of patients who develop severe complications of this disease.11 Otherwise, most reactions (85%–90%) are...
reversible and resolve on their own within 3 to 7 days after the initiation of treatment and after the offending agent has been discontinued.

**DIAGNOSIS**

DIP is usually an acute illness, but it can be life-threatening. Although many drugs are reported to cause pancreatitis, causality is often difficult to confirm. Initial symptoms are often nonspecific and include mild-to-severe epigastric pain that can radiate to the back, chest, flank, or lower abdomen. Other symptoms may include nausea, vomiting, fever, abdominal tenderness, jaundice, or hypotension; hyperglycemia may also occur.

Within a few hours of its onset, amylase and lipase levels are usually elevated to more than three times the upper limit of normal (ULN). Lipase levels decline more slowly over 7 to 14 days, whereas amylase levels usually decline over 48 to 72 hours. Although amylase levels are elevated in pancreatitis, they may also be elevated in other conditions and therefore must be considered with other diagnostic criteria. Lipase levels are more specific in the diagnosis of acute pancreatitis. A clinical diagnosis of acute pancreatitis necessitates the presence of two out of three criteria. These criteria include:

- serum amylase and lipase elevations at least three times the ULN.
- epigastric abdominal pain often radiating to the back that is not aggravated by movement, respiration, or coughing and that is more severe in the supine position. (The pain may be decreased if the patient leans forward in a sitting position.)
- typical radiological features.

Imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), ERCP, magnetic resonance cholangiopancreatography (MRCP), or transabdominal ultrasound might be informative when the diagnosis is in doubt, when pain is severe, or when a given study might provide specific information.

**TREATMENT**

DIP is usually managed with supportive therapy, including intravenous (IV) hydration to maintain intravascular volume, parenteral pain management, supplemental oxygen as needed, bowel rest, correction of electrolyte and metabolic abnormalities, and nutritional support. Antibiotics should be used if an infection is present. Alcohol cessation, removal of gallstones to restore biliary drainage, or other surgery may be necessary, and attempts should be made to identify and discontinue the offending agent.

The following patients were seen at our institution over the past few months.

**CASE STUDIES**

**Case 1**

A young man with type-2 diabetes mellitus, hypertension, morbid obesity, and hypertriglyceridemia arrived at the emergency department (ED) with complaints of sharp abdominal pain. His rating on the Visual Analogue Scale (VAS) was 10 out of 10. He also reported nausea and vomiting. His history included three prior bouts of pancreatitis, the most recent being 10 weeks earlier, and a 6-day stay in the intensive-care unit. The gastroenterology team diagnosed acute pancreatitis and associated duodenal inflammation, probably secondary to high triglyceride levels. Medications on admission included insulin glargine (Lantus, Sanofi-Aventis) 40 units at bedtime, losartan (Cozaar, Merck) 100 mg daily, insulin aspart (Novolog, NovoNordisk) 20 units subcutaneously (SQ) three times daily before meals, gemfibrozil (Lopid, Pfizer) 600 mg twice daily, sitagliptin (Januvia, Merck) 100 mg daily, and metformin (Glucophage, Bristol-Myers Squibb) 1,000 mg twice daily. In the ED, metformin and sitagliptin were discontinued and hydration with IV normal saline was administered. Pain relief was provided with morphine sulfate 2 mg SQ every 4 hours as needed. He was placed on nothing-by-mouth (NPO) status and was started on heparin 5,000 units SQ every 12 hours to prevent deep vein thrombosis (DVT).

The patient was admitted to the surgical service and was found to have an infected right foot. He received wound care with follow-up care on subsequent hospital days.

On the second hospital day, he still complained of epigastric pain. IV hydration was continued and NPO status was maintained.

On the fourth hospital day, the patient was much improved and was discharged to follow up with outpatient MRCP to evaluate the biliary and pancreatic ducts. The gastroenterology team concluded that the pancreatitis was probably not a result of alcohol use. Of note, the patient had been taking sitagliptin at home, but it was discontinued on admission. The hospital staff and attending physician were informed by the clinical pharmacist that sitagliptin and hypertriglyceridemia could also cause pancreatitis. The final outcome of the patient’s diabetes treatment was not known.

**Case 2**

A middle-aged man with hypertension, type-2 diabetes, hyperlipidemia, anxiety, depression, and obstructive sleep apnea was admitted with dull periumbilical pain. His VAS rating was 8 out of 10. He was receiving multiple medications, including daily sitagliptin 100 mg and colesvelam (Welchol, Sankyo Pharma) 3,750 mg.

The patient was started on ciprofloxacin (Cipro, Bayer) and metronidazole IV (Flagyl) because of abdominal pain and an elevated white blood cell count in triage. Amylase and lipase levels were elevated. Metformin and sitagliptin were withheld. Blood glucose levels were tested, and he received sliding-scale regular insulin (e.g., Novolin R, Novo Nordisk; Humulin R, Eli Lilly) and fingersticks four times daily.

On the second day, colesvelam was also withheld when the staff realized it might cause pancreatitis. A surgeon recommended hydration with IV fluids and NPO status. Morphine was recommended for pain. No surgical intervention was warranted.

On the third hospital day, the patient had only low-level pain and a VAS rating of 1 out of 10. Amylase and lipase levels returned to normal, and his white blood cell count decreased.

The next day, the patient was discharged. Metformin and sitagliptin, but not colesvelam, were restarted. The clinical pharmacist informed the attending physician and staff of the possibility of sitagliptin-induced pancreatitis because the patient had been taking this drug at home. The patient was discharged and resumed taking sitagliptin. The final outcome was not known.

**Case 3**

A middle-aged woman with type-2 diabetes, hypertension, chronic obstructive pulmonary disease (COPD), asthma, sleep apnea, anxiety, osteoarthritis, neuropathy, disc herniation, and morbid obesity presented to the ED with a 1-week history of abdominal pain and nausea. She also had polyuria, shortness of breath, and anxiety.

She had been taking sitagliptin 100 mg daily but had stopped 4 days earlier be-
cause she ran out of medication. Other diabetes agents included insulin glargine 38 units in the morning and 38 units in the evening, metformin 1,000 mg twice daily, and pre-meal insulin aspart. Her home fingerstick glucose values ranged from 200 to 300 g/dL. Her amylase level was 154 U/L (normal, 23–85 U/L), and her lipase level was 485 U/L (normal, 0–160 U/L).

The patient was admitted for hyperglycemia and pancreatitis. She received two doses of regular insulin (10 units) and continued her home dose and regimen of insulin glargine. Her blood glucose levels were tested, and she received sliding-scale regular insulin and fingersticks four times daily. Insulin aspart, metformin, and sitagliptin were withheld. Her other drugs were continued.

On the second hospital day, an ultrasound showed gallstones, and amylase and lipase levels showed a downward trend. Glycosylated hemoglobin was 13.4 g/dL. By the third day, her symptoms resolved and she was discharged with a scheduled follow-up appointment for the next week.

CONCLUSION

Underreporting of drug-induced pancreatitis (DIP) is often a result of a low index of suspicion, mild cases with unrecognized subclinical enzyme elevations, missing the time frame for drug-related exposures, and erroneous classification. It takes an astute clinician to diagnose DIP. Knowing which agents are the likely culprits improves management. DIP is often misclassified as being related to alcohol or biliary disease by default, even when it is drug-induced. Because patients receive nothing by mouth, the offending agent is inadvertently discontinued, leading to a missed diagnosis of DIP, as shown in the case reports. DIP should be considered in the differential diagnosis of patients with epigastric pain. All patients with acute pancreatitis should be asked about their use of medications (prescribed and over-the-counter), herbs, and supplements, followed by appropriate management.

REPORTING ADVERSE DRUG REACTIONS

All ADRs should be reported to MedWatch at 1-888-INFO-FDA, 1-888-463-6332, or online. The FDA 3500 Voluntary Adverse Event Report Form can be accessed online at www.fda.gov/Safety/Medwatch/HowToReport/ucm085568.htm. The FDA is interested in serious reports that include any of these patient outcomes: death; a life-threatening condition; initial hospitalization; prolonged hospitalization; disability or permanent damage; congenital anomalies or birth defects; and other serious conditions for which medical or surgical intervention is needed to prevent one of the aforementioned outcomes. The FDA is also interested in any unlabeled ADRs for new drugs (usually those approved within the previous 2 years).

REFERENCES