An unusual case of drug-induced acute pancreatitis

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ABSTRACT

We report a rare case of drug-induced pancreatitis in a patient receiving repaglinide anti-diabetic therapy. A patient with type 2 diabetes mellitus presented with severe abdominal cramping, nausea, and vomiting. Three months prior to symptoms, repaglinide was added to the patient's current regimen of metformin. The patient was diagnosed with acute pancreatitis, treatment was initiated, and repaglinide discontinued. There was no history of pancreatitis or other risk factors such as history of gallstones, alcohol abuse, or hypertriglyceridemia. The patient reported resolution of symptoms following discontinuation of repaglinide. Considering the temporal relationship of his symptoms to the addition of repaglinide to his existing anti-diabetic regimen, this case strongly suggests a possible causal link between repaglinide and the etiology of acute pancreatitis in this patient.

INTRODUCTION

Oral insulin secretagogues are anti-diabetic medications that have been reported to be causally linked to acute pancreatitis (Blomgren & Sudstrom, 2002). Meglitinides are a class of insulin secretagogues that act in a glucose-dependent manner to increase pancreatic insulin secretion. They work specifically by closing adenosine triphosphate (ATP)-dependent potassium channels on the β-cell, causing calcium channels to open and thereby, increasing calcium influx and insulin secretion (Stein, Lamos, & Davis, 2013). We will consider the effects of a meglitinide analog, repaglinide, by presenting a case of likely drug-induced pancreatitis in a patient who was started on repaglinide.

CASE PRESENTATION

A 40-year-old male with a past medical history of type 2 diabetes mellitus, diabetic nephropathy, obesity, and hypertension presented to the emergency room with 2 weeks of severe, cramping epigastric pain that radiated to the back. Pain was intermittent, severe, and associated with non-bilious, non-bloody vomiting and non-bloody diarrhea. The patient denied a history of gallstones, hypertriglyceridemia, pancreatitis, recent alcohol consumption, fevers, night sweats, or weight loss. His medication regimen included metformin 500 mg PO BID, lisinopril, metoprolol XL, as well as repaglinide 2mg PO before each meal that had been initiated three months prior, for optimal glycemic control. On admission, vital signs were temperature of 98.5 °F, blood pressure of 164/103 mmHg, pulse of 79 beats/min, respiratory rate of 20 breaths/min. On abdominal exam, the left upper quadrant was tender, without rebound, guarding, or organomegaly. Sclera and skin were anicteric, and the remainder of the physical exam was unremarkable.

Laboratory analysis revealed serum lipase 132 U/L (reference range 16-58 U/L), amylase 19 U/L (reference range 34-131U/L), glucose 423mg/dL (reference range 74-200mg/dL), creatinine 2.5mg/dL.
(reference range 0.6-1.2mg/dL), calcium 8.9 mg/dL (reference range 8.7-10.0mg/dL), triglycerides 216mg/dL (reference range <250mg/dL), and HbA1c 12.3%. The remaining laboratory values, including WBC and LFTs were unremarkable. Imaging was obtained, and abdominal computed tomography (CT) revealed focal pancreatitis around the head and uncinate of the pancreas (Figure 1), and ultrasound showed no evidence of cholelithiasis. Abdominal ultrasound showed no evidence of cholelithiasis. The patient was diagnosed with acute pancreatitis, made NPO, and given IV fluids. An insulin sliding scale, morphine, and ondansetron were initiated, and repaglinide was stopped. On hospital day three, the patient’s symptoms resolved, and serum lipase and amylase decreased to 21 U/L and 16 U/L, respectively. He tolerated a PO diet and was discharged home symptom free, on metformin and insulin for glycemic control.

DISCUSSION

To date, there are 525 different medications in the WHO database that can induce acute pancreatitis (Nitsche, Jamieson, Lerch, & Mayerle, 2010). Overall, drugs remain a relatively rare causative factor for acute pancreatitis, with an incidence between 0.1% and 2% of pancreatitis cases (Nitsche et al, 2010). The elderly may be especially susceptible to drug-induced pancreatitis due to polypharmacotherapy and mixed drug interactions (Nitsche et al, 2010). Although we know that activation of trypsin can lead to pancreatic autodigestion and, consequently, acute pancreatitis, the mechanisms by which certain drugs can induce pancreatitis is not known (Blomgren & Sudstrom, 2002). One theory is that some drugs known to diffuse into the pancreas, such as metronidazole, can exhibit a direct toxic effect; another is that drugs can lead to an accumulation of toxic metabolites (Nitsche et al, 2010). Unfortunately, data for drug-induced pancreatitis remain sparse and most are collected from case reports and case-control studies.

A review of the literature shows that some anti-diabetic medications have been linked with pancreatitis. In a case-control study, Blomgren and Sudstrom (2002) found an increased risk of first-time acute pancreatitis among diabetic patients taking glyburide. Interestingly, insulin and long-term metformin use were found to be associated with a decreased risk of acute pancreatitis. Long term sulfonylureas, however, were found to increase this risk (Gonzalez-Perez, Schlienger, & Rodriguez, 2010). An analysis of the FDA adverse event reporting system (AERS) by by Elashoff, et al. (2011) found that two GLP-1 agonists in particular, exenatide and liraglutide, have a six-fold increased risk of pancreatitis as compared to other therapies. Because of this correlation, as seen in several case reports, liraglutide is recommended to be used cautiously in diabetic patients with a history of pancreatitis (Franks, Lee, & George, 2012). In animal models, exenatide administration resulted in focal proliferation of the exocrine pancreas, which is a well-recognized component of chronic pancreatitis in humans (Gier et al., 2012). Similarly, Matveyenko et al. (2009) showed that rats treated with rats treated with sitagliptin, another GLP-1 agonist, also had evidence had evidence of increased pancreatic ductal proliferation. Although a clear causal relationship between anti-diabetic medications and pancreatitis has not yet been established, studies showing the temporal relationship of drug use and symptom onset, combined with resolution of symptoms following drug discontinuation, suggest that such an association cannot be excluded.

Our patient’s history and clinical findings link repaglinide as the etiologic agent of acute pancreatitis in this case. Though we cannot rule out an occult etiology for his condition, he had no major risk factors for pancreatitis. There are presently no previously reported cases of repaglinide-induced acute pancreatitis, and a plausible mechanism for anti-diabetic drug-induced pancreatitis has yet to be found. Because initiation of repaglinide presumably corresponded to an episode of acute pancreatitis in our patient and discontinuation resulted in resolution of symptoms, repaglinide is strongly suggested to be the cause to be the cause. This is an unusual and rare case of repaglinide-induced pancreatitis, and we recommend precaution when prescribing repaglinide to patients with a history of pancreatitis. Therefore, physician recognition and patient awareness of possible side effects of repaglinide, could decrease morbidity and shorten overall hospital stay.
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REFERENCES


Figure 1. Focal pancreatitis around the head and uncinate of the pancreas.