CASE REPORT

Saxagliptin-induced Recurrent Acute Pancreatitis

Chien-Feng Lee, Meng-Shun Sun and Yen-Kuang Tai

Abstract

Although dipeptidyl peptidase-4 (DPP-4) inhibitors have been implicated in the development of acute pancreatitis, the causality of this phenomenon is not well established. We herein report the case of an 85-year-old woman who presented with epigastric pain after taking saxagliptin for five months. A high serum lipase level with characteristic computed tomography findings confirmed the diagnosis of acute pancreatitis. The patient’s symptoms rapidly resolved after admission, although they recurred when she resumed treatment with saxagliptin for 18 days after discharge. In the absence of any identifiable causes of pancreatitis and considering the temporal sequence of events, the saxagliptin therapy was highly suspected to be the triggering factor. Although drug-induced pancreatitis is rare, treatment with DPP-4 inhibitors should be included as a potential etiology of acute pancreatitis.

Key words: dipeptidyl peptidase-4 inhibitor, drug-induced pancreatitis, incretin-based therapy, pancreatitis, saxagliptin

(Intern Med 53: 1351-1354, 2014)
(DOI: 10.2169/internalmedicine.53.1913)

Introduction

Between October 2006 and February 2009, 88 postmarketing reports of acute pancreatitis in patients receiving the first dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin, prompted the US Food and Drug Administration to issue an alert regarding a potential adverse reaction (1). Thereafter, several large retrospective studies investigating the causal relationship between the administration of incretin-based therapy and acute pancreatitis showed conflicting results (2-4). However, cases of acute pancreatitis associated with treatment with glucagon-like peptide-1 (GLP-1) agonists or DPP-4 inhibitors continue to be reported worldwide (5-11). Among the DPP-4 inhibitors, the suspected offending drugs include sitagliptin and vildagliptin. While this rare adverse effect is considered to be a class effect of DPP-4 inhibitors, saxagliptin has never been reported to cause acute pancreatitis in the medical literature. A recently published randomized controlled trial also found no increased risk of acute pancreatitis in patients treated with saxagliptin (12). We herein present, to our knowledge, the first case of recurrent acute pancreatitis in a patient receiving saxagliptin.

Case Report

An 85-year-old woman with a history of type 2 diabetes lasting for more than 30 years presented to our emergency department with severe epigastric pain radiating to the back. She denied any history of pancreatitis, smoking or alcohol use. She had received a permanent pacemaker due to atrioventricular block 10 years earlier; however, she denied a history of abdominal trauma, invasive procedures or surgery. There was also no family history of pancreatitis. The patient had been treated with antidiabetic therapy, including gliclazide (160 mg twice daily) and metformin (500 mg twice daily), for more than five years. Treatment with insulin glargine once daily had been initiated 15 months prior to admission. In order to further improve the patient’s glycemic control, saxagliptin (5 mg/d) had been prescribed five months before presentation.

On a physical examination, the patient was not found to be obese (body mass index: 26.3 kg/m²), although she experienced tenderness on palpation of the epigastrium. A recent laboratory study showed a serum lipase level of 6,720 U/L (reference range: ≤55), a white blood cell count of 11.1×10³/μL, a hemoglobin level of 11.1 g/dL, a hematocrit
level of 34.0%, a C-reactive protein level of 3.8 mg/L, a creatinine level of 0.9 mg/dL, a calcium level of 8.7 mg/dL, a triglyceride level of 80 mg/dL, an alanine aminotransferase level of 17 U/L, an aspartate aminotransferase level of 18 U/L and a total bilirubin level of 0.68 mg/dL. Abdominal computed tomography (CT) revealed an enlarged pancreatic head with increased infiltration around the pancreas and along the small bowel mesentery and right retroperitoneum, consistent with a diagnosis of acute grade C interstitial pancreatitis (Figure). There was no evidence of gallstones or biliary tract abnormalities. The patient was therefore admitted to the department of gastroenterology for treatment of acute pancreatitis.

In addition to glucose-lowering agents, the patient’s regular medications included rosuvastatin (5 mg twice weekly), irbesartan (150 mg daily), diltiazem (30 mg twice daily), indapamide (1.5 mg daily) and aspirin (100 mg daily). Except for the use of irbesartan for 21 months, all medications had been prescribed for more than five years. All oral medications were discontinued upon admission, and the serum lipase level rapidly declined to 131 U/L two days later. With supportive care, the patient’s symptoms resolved by the fourth hospital day, and she was discharged home on day 7. However, medication was not suspected as a possible cause of the acute pancreatitis; therefore, the patient resumed taking the medications prescribed at the diabetes clinic after discharge.

Eighteen days later, persistent epigastric pain recurred. This time, the patient was sent to another hospital, where the serum amylase (2,120 U/L, reference range: 30-160) and lipase (2,940 U/L, reference range: 13-60) levels were again found to be markedly elevated. After admission, the fasting lipid profile was unremarkable, with a triglyceride level of 97 mg/dL. The immunoglobulin G4 (IgG4) value was 20.0 mg/dL (reference range: 3-200). Abdominal ultrasound showed no evidence of gallstones or biliary tract abnormalities. After discontinuing the oral medications again, the patient’s symptoms resolved three days later, and she was discharged without any complications on the seventh hospital day. Based on a thorough review of her medication history, the recently prescribed DPP-4 inhibitor, saxagliptin, was highly suspected to be the triggering factor for the repeated episodes of acute pancreatitis. Therefore, the patient was told to continue all medications, except for saxagliptin. Five weeks later, the follow-up serum levels of pancreatic enzymes were normal (amylase: 37 U/L and lipase: 23 U/L). There has been no recurrence of acute pancreatitis for three months after the cessation of saxagliptin treatment.

Discussion

To the best of our knowledge, this is the first published case report of saxagliptin-associated acute pancreatitis. This case is also the first well-documented case of acute pancreatitis caused by a DPP-4 inhibitor with a positive rechallenge. Based on the modified classification of drug-induced acute pancreatitis proposed by Badalow et al., saxagliptin should be considered a class I drug, as there is at least one case report of a rechallenge with the drug (13). The Naranjo Adverse Drug Reaction Probability Scale indicated a highly probable relationship between the onset of acute pancreatitis and the use of saxagliptin in this patient (14).

Drug-induced acute pancreatitis is a rare entity, accounting for 0.1% to 2% of cases (15, 16). Although more than 500 medications have been implicated as causes of acute pancreatitis, many case reports suffer from a combination of inadequate criteria for the diagnosis of acute pancreatitis, the failure to exclude other common causes and/or the lack of a rechallenge with the medication. In the present case, the diagnosis of acute pancreatitis was confirmed based on the patient’s typical clinical presentation, serum lipase and/or amylase levels ≥ three times the upper limit of normal and characteristic findings of acute pancreatitis on a CT scan. Although only the serum lipase level was measured on the first admission, serum lipase is a more sensitive and specific marker than amylase in the diagnosis of acute pancreatitis. In addition, a contrast-enhanced CT scan of the abdomen confirmed the presence of acute inflammation involving the pancreas and peripancreatic fat in this case.

Gallstones and alcohol use are the most common causes of acute pancreatitis. Other uncommon etiologies include hypertriglyceridemia, hypercalcaemia, structural abnormalities, trauma, iatrogenic invasive procedures, infection and medications. In the present case, CT and ultrasonography did not disclose any gallstones or biliary tract diseases. In addition, the normal serum lipid profile and calcium level observed on admission excluded the possibility of metabolism-related pancreatitis, and detailed history-taking ruled out other causes of acute pancreatitis, including alcohol use, abdominal trauma, infection or previous invasive procedures, such as endoscopic retrograde cholangiopancreatography. Furthermore, the patient had no past history of recurrent abdominal pain from childhood; therefore, the presence of a congenital pancreatic anomaly, such as pancreatic
divisum, was unlikely. Negative results for antinuclear antibodies and the normal level of serum IgG4 also contradicted a diagnosis of autoimmune pancreatitis. Therefore, acute pancreatitis possibly induced by treatment with saxagliptin was highly suspected.

A number of medications used by the present patient have been implicated in the development of acute pancreatitis, including metformin, rosuvastatin and irbesartan. Metformin and rosuvastatin had been used in this case for more than five years, and treatment with irbesartan was initiated 21 months before the first episode. Metformin has previously been reported to cause acute pancreatitis in patients with acute renal failure (17, 18). However, our patient did not suffer from acute renal failure on either of the two episodes of disease exacerbation. Among drugs causing acute pancreatitis with positive rechallenges, the latency period measured between the initiation of treatment and the onset of acute pancreatitis for statins and angiotensin II receptor blockers is six months and less than seven days, respectively. In general, the latency period in reported cases involving rechallenges is less than one year (13). Chronic use of the above-mentioned medications without a recent increase in the dose made an association with these drugs unlikely in the present case.

On the other hand, the patient’s symptoms occurred five months after the initiation of treatment with saxagliptin and resolved after saxagliptin was withdrawn on admission. In addition, the patient’s symptoms recurred 18 days after resuming saxagliptin therapy. Furthermore, when we counseled the patient to stop taking saxagliptin after the second discharge, her symptoms did not recur. In the absence of an identifiable cause of the pancreatitis and considering the temporal sequence of events, the details of this case strongly suggest a causal link between the administration of saxagliptin and the development of acute pancreatitis.

In the literature, there are seven previously reported cases of acute pancreatitis in patients receiving DPP-4 inhibitors (Table). Although the DPP-4 inhibitors, sitagliptin and vildagliptin, were suspected by the authors to be the triggering factors for acute pancreatitis, common risk factors, such as gallstones or mild hypertriglyceridemia, were also present in some cases. In addition, there were no re-challenges in any of the previously reported cases. The latency period in these seven cases ranged from three weeks to eight months. In the present case, the latency period was five months, which is similar to that observed in two Japanese cases and one Indian case (8-10). Although there is no confirmed mechanism to explain the induction of acute pancreatitis by DPP-4 inhibitors, a hypersensitivity reaction or the accumulation of toxic metabolite(s) has been supposed (13). The inconsistency of the latency period among reported cases potentially implicates a genetic role in the individual susceptibility to drug-induced pancreatic injury.

Animal studies have provided biochemical and histological evidence linking the use of incretin-based therapy to pancreatitis based on the detection of pancreatic acinar inflammation and pyknosis, ductal metaplasia and increased pancreatic ductal turnover (19, 20). A large population-based case-control study also revealed that the administration of incretin-based therapy is associated with an increased risk of hospitalization for acute pancreatitis (4). In addition to the findings of previous reports, the present case reinforces the potential for DPP-4 inhibitors to induce acute pancreatitis.

In conclusion, the present case report alerts clinicians to the possibility of pancreatitis in patients receiving DPP-4 inhibitors. Despite the low incidence of drug-induced pancreatitis, the use of DPP-4 inhibitors should be included as a potential etiology of acute pancreatitis.

The authors state that they have no Conflict of Interest (COI).

References


| Table. Reported Cases of Pancreatitis Associated with DPP-4 Inhibitors |
|----------------|----------------|----------------|----------------|----------------|
| Reference | Age (years)/sex | Associated drug (mg/d) | Latency | Outcome |
| 5 | 53/Female | Sitagliptin (100) | 8 wk | Recovery |
| 6 | 61/Female | Vildagliptin (100) | 5 wk | Recovery |
| 7 | 76/Female | Sitagliptin (100) and exenatide [5 mcg/d] | a few wk | Fatal |
| 8 | 68/Male | Vildagliptin (50) | 7 mo | Recovery |
| 9 | 42/Male | Vildagliptin (50) | 6 mo | Recovery |
| 10 | 55/Male | Sitagliptin (50) | 8 mo | Recovery |
| 11 | 49/Male | Vildagliptin (100) | 3 wk | Recovery |

DPP-4 : dipeptidyl peptidase-4


