

Sitagliptin and Acute Pancreatitis: Cases and Literature Review

Sitagliptin ve Akut Pankreatit: Olgular ve Literatürün Gözden Geçirilmesi

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Geliş Tarihi/Received: 02.09.2010

Kabul Tarihi/Accepted: 07.12.2011

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ABSTRACT Acute pancreatitis is the rapid onset inflammation of the pancreas. Medications are rare but important and rising cause of acute pancreatitis and account for approximately 2% of all cases. Sitagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of patients with type 2 diabetes mellitus and acts by increasing active incretin hormone concentrations. Adverse effects including constipation, nausea, nasopharyngitis, urinary tract infection and dizziness were reported. We reported a case with acute pancreatitis that seems to be induced by sitagliptin.

Key Words: Sitagliptin; incretins; drug toxicity; acute necrotizing pancreatitis

ÖZET Akut pankreatit, pankreasın hızlı gelişen yangısıdır. İlaçlar, nadir, önemli ve gitgide daha fazla dikkat çeken akut pankreatite neden olabilir ve tüm olguların yaklaşık %2'sinden sorumludur. Sitagliptin, tip 2 diabetes mellituslu hastaların tedavisinde kullanılan güçlü ve selektif bir dipeptidil peptidaz-4 (DDP-4) inhibitörüdür ve aktif inkretin hormon konsantrasyonunu artırarak etki eder. Konstipasyon, bulantı, nazofarenjit, üriner sistem enfeksiyonu ve baş dönmesi, bu ilacın bildirilen yan etkileri arasındadır. Bu makalede, sitagliptinin neden olduğu düşünülen bir akut pankreatit olgusu sunulmaktadır.

Anahtar Kelimeler: Sitagliptin; inkretinler; ilaç toksisitesi; akut nekrotizan pankreatit

Türkiye Klinikleri J Med Sci 2012;32(3):859-64

Acute pancreatitis is a severe disease with an overall mortality of approximately 5%, though in subpopulations with necrotizing pancreatitis and infected necrosis, mortality may be as high as 17% and 30%, respectively.¹⁻³ The most common etiologies are excessive alcohol use and gallstone disease, comprising 70-80% of all cases. Other etiologies include autoimmune disease, iatrogenic injury, inflammatory bowel disease, infections, inherited disorders, neoplasia, structural abnormalities, toxins, trauma, ischaemia and drug toxicity.¹⁻⁴ Drug-induced pancreatitis is remarkably rare, given the large number of drugs prescribed. Due to its rarity and the lack of unique clinical characteristics, the true epidemiology and risk factors for drug-induced pancreatitis remain unknown. The diagnosis

of drug-induced pancreatitis is often difficult to make because there are no unique clinical, biochemical or radiological features to distinguish this etiology of pancreatitis from other causes. Furthermore, data regarding the mechanisms through which drugs cause pancreatitis are limited, with few animal studies. The first step is to confirm the diagnosis of pancreatitis. This requires two of the following three features: abdominal pain characteristic of acute pancreatitis, serum amylase and/or lipase levels ≥ 3 times the upper limit of normal range and characteristic findings on computed tomography (CT) scan.^{1,2}

We reported a case of acute pancreatitis, which seems to be due to sitagliptin use.

CASE REPORT

An 82-year-old man with type 2 diabetes for the last 15 years presented with abdominal pain, nausea, vomiting and abdominal distention. His medical history was unremarkable except for coronary artery disease and hypertension. There was no previous history of pancreatitis or gallstones. He denied alcohol use. He was taking metformin 1000 mg po twice a day, atorvastatin 40 mg po at bedtime, irbesartan 150 mg po once daily and sitagliptin 100 mg po once a day. Remarkable findings on examination were abdominal obesity and upper abdominal tenderness. There was no fever or chills. The patient was 173 cm tall and weighed 82 kg. HbA1c level was 7.5%. Biochemical tests revealed glucose 195 mg/dL, creatinine 1.1 mg/dL, aspartate aminotransferase (AST) 51 IU/L and alanine aminotransferase (ALT) 12 IU/L. Serum triglyceride levels were 154 mg/dL, serum calcium 9.1 mg/dL, white blood cell count 18 900 cells/mm³, and hemoglobin 15.4 g/L. Serum amylase and serum lipase levels were 217 IU/L (28-100) and 718 IU/L (21-7), respectively. Total and direct bilirubin levels were normal. Abdominal ultrasonography (US) showed mild dilatation of the common bile duct; the gallbladder was normal. Computed axial tomography (CT) scan of the abdomen revealed increased density of the peripancreatic fat tissue and increased reactive lymph nodes suggesting pancreatitis (Fig-

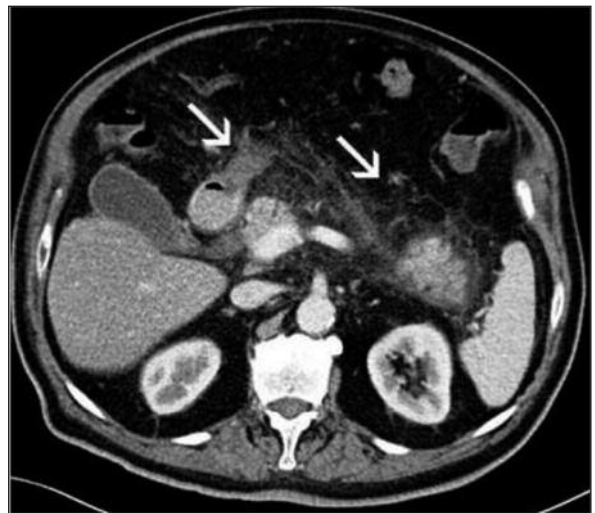
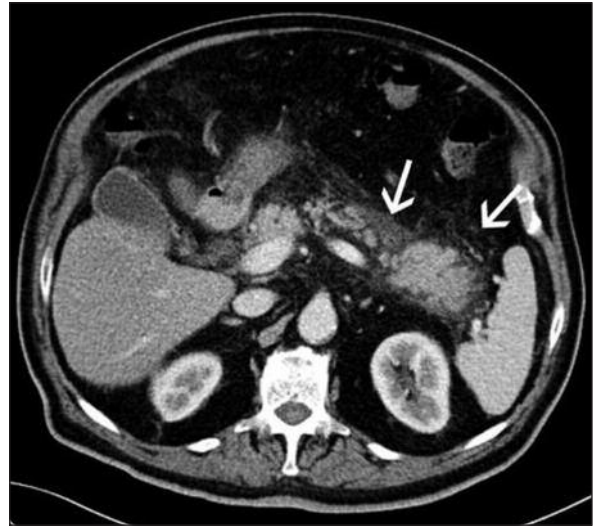


FIGURE 1,2: Acute Edematous Pancreatitis
Increased density of the peripancreatic fat tissue and minimal effusion (arrows).

ure 1 and Figure 2). There was no stone in the choledoc or gallbladder.

We considered acute edematous pancreatitis with these findings and the patient was admitted to the gastroenterology clinic. Serum calcium levels and lipid parameters were normal. Considering the elevation of ALT and gamma-glutamyltransferase (GGT) levels and abdominal US and CT results, endoscopic ultrasonography (EUS) was performed to exclude biliary obstruction and other pathologies. EUS revealed signs of pancreatitis. Due to the normal appearance of the ampulla

and normal findings in the repeated US and CT images and rapid improvement of clinical and laboratory findings, no pathology regarding cholestasis or pancreatitis was suspected. The patient has been using sitagliptin 100 mg po once daily for approximately two months and has had no adverse events. However, he had developed a mid-epigastric abdominal pain radiating to the back. This medical history suggested a drug-induced pancreatitis. Intravenous fluids along with intravenous pantoprazole were initiated. He was advised NPO (nothing to eat) and sitagliptin was stopped. A weight-based sliding scale of insulin was started using aspart and glargine. On subsequent days, the lipase level was 50 IU/l. The abdominal pain resolved by day five. With these findings, this condition was considered acute pancreatitis secondary to sitagliptin.

DISCUSSION

Recently, improved understanding of the incretin effect on the pathophysiology of type 2 diabetes has led to the development of new hypoglycemic agents. The incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, which are released in the presence of glucose or nutrients in the gut. The incretin effect is composed primarily of two peptides, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4), resulting in a very short half-life as minutes.⁵ Both GIP and GLP-1 are endogenous physiological substrates for DPP-4, and chemical inhibition of DPP-4 activity, or genetic inactivation of DPP-4 in rodents, results in increased levels of intact bioactive GIP and GLP-1. Therapeutic approaches for enhancing incretin action include degradation-resistant GLP-1 receptor agonists (incretin mimetics), as exenatide and liraglutide and inhibitors of DPP-4 activity (incretin enhancers), as sitagliptin and vildagliptin.^{5,6}

Sitagliptin has significant antidiabetic effects when given in monotherapy, and results in further improvements of glycaemic control when given in

combination with other antidiabetic agents.⁷⁻¹⁰ The side effect profiles of the DPP-4 inhibitors were recently reviewed by scientists from the Cochrane Institute, who concluded that both vildagliptin and sitagliptin were well-tolerated.^{9,11} A recent meta-analysis suggested that the most common adverse effects reported in slightly higher proportions of patients receiving sitagliptin or vildagliptin were nausea, nasopharyngitis, urinary tract infection, hypoglycemia and headache. Adverse effects of GLP-1 analogues are nausea, hypoglycemia, diarrhea, feeling jittery, dizziness, constipation, sweating, and backache.^{12,13} Recent reports suggest that exenatide has adverse pancreatic effects in some patients, triggering a Food and Drug Administration (FDA) alert.^{9,14} In the postmarketing period, 30 cases of pancreatitis possibly caused by exenatide were reported from the date of the drug approval until 2007.¹¹ The first reported case of acute pancreatitis in which exenatide appeared to be the etiologic agent was in 2006.^{15,16} Pancreatitis has also been reported in clinical trials of the GLP-1R agonist, liraglutide.¹⁷

However a retrospective analysis reported that there was no increased risk of acute pancreatitis associated with the use of incretin-based drugs. The estimated risk of acute pancreatitis during follow-up was 0.13% among patients treated with exenatide and 0.12% for patients treated with sitagliptin. The risk of acute pancreatitis was comparable among initiators of exenatide and sitagliptin when each was compared with their matched comparison cohorts of others. No increased risk of acute pancreatitis associated with the use of exenatide or sitagliptin was reported. However, studies of this type are limited by the data that are available in the claims database, given that the information is collected for payment purposes and not for research.¹⁸

There are several possible explanations for the association of pancreatitis with the use of exenatide.

The first one is the 1- GLP-1 Receptor. The majority of studies examining GLP-1 biology in the pancreas were focused on a- and b-cells within the endocrine pancreas. However, GLP-1 exerts a num-

ber of actions in the exocrine pancreas. GLP-1 Receptor (GLP-1R) agonists induce transdifferentiation of pancreatic exocrine cells to an endocrine cell phenotype *in vitro*.^{8,19} Exenatide increases expression of some proteins in the exocrine pancreas. Mice treated with GLP-1R agonists exhibit an increase in pancreas weight that cannot be attributed solely to increased cell mass.²⁰ Thus, GLP-1R activation induces gene and protein expression in the exocrine pancreas. GLP-1R activation modifies gene expression, enzyme secretion or pancreatic inflammation in the human pancreas.¹⁹

The second explanation is acinar inflammation. One recent study on exenatide and GLP-1 suggested that these products stimulated exocrine and endocrine pancreatic secretion through local and central neurons of the vagus, offering a broad spectrum of effects on the pancreas.²¹ The extended use of exenatide in rats leads to pancreatic acinar inflammation and pyknosis. These data raised important concerns about the pancreatic effects of incretin mimetics.¹⁴ GLP-1 inhibits pancreatic exocrine secretion and gastropancreatic function by inhibiting central parasympathetic outflow.²² It's a putative mechanism associated with the development of pancreatitis, it seems possible that sustained GLP-1 receptor activation will increase the susceptibility for development of pancreatic inflammation.

The last mechanism is ductal metaplasia. A study reported that sitagliptin treatment was associated with increased pancreatic ductal turnover and ductal metaplasia in rat pancreatitis. In that study, although ductal GLP-1 receptor expression was not altered, it was postulated that the pancreatic effects could be related to increased GLP-1 concentrations.^{14,23} Matveyenko et al. encountered marked ductal metaplasia in 25% of high-fat diet-fed *human islet amyloid polypeptide transgenic* (HIP) rats treated with sitagliptin and severe hemorrhagic pancreatitis developed in one sitagliptin-treated animal.

Following those findings, the exocrine effects of sitagliptin were investigated. These latter studies provided some insights into the reported asso-

ciation of GLP-1 mimetic therapy with exenatide or liraglutide and pancreatitis, and they provided some cautions about the potential long-term effects of GLP-1 mimetic therapy, including DPP-4 inhibition in diabetes.^{17,24} Ductal metaplasia was present in three HIP rats treated with sitagliptin. One of the three sitagliptin-treated HIP rats with ductal metaplasia also displayed marked pancreatitis. Ductal replication quantified by Ki-67 immunoreactivity was increased fourfold in untreated diabetic HIP rats versus wild-type controls. Sitagliptin treatment led to an additional three-fold increase in the frequency of ductal cell replication versus untreated HIP rats and a 12-fold increase compared with wild-type rats.²³ GLP-1 receptors were expressed in pancreatic ducts, and exendin-4 treatment increases the number of insulin-producing cells in isolated human pancreatic ducts.²⁵ Direct actions of sitagliptin on the exocrine pancreas could not be excluded. However, because pancreatitis has also been reported in humans treated with GLP-1 agonists it seems likely that the exocrine effects of sitagliptin treatment reported here is a consequence of increased GLP-1 concentrations.^{17,24}

According to the FDA Safety Information and Adverse Event Reporting Program 88 post-marketing cases of acute pancreatitis, including two cases of hemorrhagic or necrotizing pancreatitis in patients using sitagliptin were reported between October 2006 and February 2009.

We reported a case of acute pancreatitis in which sitagliptin appeared to be the etiologic agent. There was no previously reported cases of sitagliptin induced acute pancreatitis in the literature. In this case, the medical history including alcohol use, biliary tract disease or gallstones, abdominal surgery, personal or family history of pancreatitis, recent abdominal trauma, and weight loss and blood tests within the first 24 hours including liver function tests, and calcium and triglyceride levels was questioned. The association of symptoms with the onset and cessation of therapy along with the normalization of laboratory parameters on drug withdrawal implicates

sitagliptin as the cause. We also observed the slow resolution of the symptoms and signs in this case. Could it be one of the important and specific characteristics of the sitagliptin-induced pancreatitis? This paper is a review of the literature revealing the incretin-based treatment induced pancreatitis and potential mechanisms of the sitagliptin-induced pancreatitis.

CONCLUSION

Whether the improvement of *in vivo* β -cell function during incretin-based therapy will persist remains unclear but the available data would indicate that therapy should be started as early as possible in

the clinical course before β -cell function has irreversibly deteriorated. However, these new classes of hypoglycemic agents will require continued evaluation both for long-term efficacy and for safety with controlled trials and in clinical practice to assess their safety profile and to determine their role among the many available and well-established therapies for type 2 diabetes. We suggest that healthcare professionals should monitor patients very carefully for the development of pancreatitis after initiation of sitagliptin. Caution should be exercised when prescribing sitagliptin and it should be contraindicated in patients at high risk for pancreatitis.

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