Sitagliptin-associated Acute Pancreatitis: A Case Report

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Abstract

The most recently-approved class of agents to treat type 2 diabetes in Taiwan is dipeptidyl peptidase-4(DPP-4) inhibitors, most popularly sitagliptin. Commonly reported adverse events with sitagliptin include upper respiratory tract infections, sore throat, headache and diarrhea. Post-marketing surveillance has raised the possibility of acute pancreatitis in association with its use. Here we presented a case of type 2 diabetes with acute pancreatitis after 50 days' use of sitagliptin, which is similar to previous report in time of onset of acute pancreatitis after use of sitagliptin. She has no past history of acute pancreatitis, nor any common inciting factors of acute pancreatitis, including hypertriglyceridemia, gallstones and alcohol abuse. Incretin-based therapy, including the glucagon-like peptide-1 (GLP-1) receptor agonists and DPP-4 inhibitors, lowers serum glucose by increasing serum GLP-1 level. Post-marketing surveillance suggests an association between incretin-based therapy and acute pancreatitis. However, some analysis suggested that acute pancreatitis may be associated with diabetes *per se*. Although the causal relationship of incretin-based therapy and acute pancreatitis is still not clear, we still should be alert to its possible side effects. (J Intern Med Taiwan 2011; 22: 278-282)

Key words: Sitagliptin, Acute pancreatitis, GLP-1 agonist, Type 2 diabetes

Introduction

The most recently-approved class of agents to treat type 2 diabetes in Taiwan is dipeptidyl peptidase-4 (DPP-4) inhibitors, most popularly sitagliptin. Commonly reported adverse events with sitagliptin include upper respiratory tract infections, sore throat, headache and diarrhea. Post-marketing surveillance has raised the possibility of acute pancreatitis in association with its use. Here we presented a case of type 2 diabetes with acute pancreatitis after 50 days' use of sitagliptin.

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Case Report

A 58 year-old woman with a history of type 2 diabetes since 2003, height 150 cm, weight 74 kg and waist circumference 96 cm, used Gliclazide MR 30mg with metformin 1500 mg per day for her glycemic control. Her recent HbA1c level was 7.6-8.1%. Nephropathy with microalbuminuria was also diagnosed. Therefore, Irbesartan 150 mg daily was also prescribed for her microalbuminuria. No apparent diabetic retinopathy was seen on ophthalmological consultation. There was no past history of macrovascular diseases. The patient denied a history of gallstones, pancreatitis or alcohol use. Sitagliptin was added to improve glycemic control. Fifty days later, sudden onset of epigastralgia associated with nausea developed. The characteristics of the pain is dull and fullness in nature and radiate to the back. The patient visited our Emergency Department, where high serum amylase and lipase were noted (Amylase 739 U/L, Lipase 1444 U/L). The remaining biochemical and hematological data was Cr 1.37 mg/dL, ALT/AST 60/45 U/L, WBC 7450 /uL, Hb 12.8 g/dL , Platelet 352K/uL. She was admitted later with suspected acute pancreatitis. Abdominal sonogram revealed fatty liver and a normal pancreas, gall bladder and common bile duct. Only mild hypertriglyceridemia (201 mg/dL) was found. With supportive care with adequate hydration and inhibition of oral intake, serum amylase and lipase declined after two days (Amylase 135 U/L, Lipase 43 U/L). After discharge, sitagliptin was discontinued. Acarbose with gliclazide and metformin were used for the patient's glycemic control. No more acute pancreatitis episodes occurred during the next ten months and the patient's glycemic control improved.

Discussion

The most recently-approved classes of agents used to treat type 2 diabetes are incretin-based therapy, including the glucagon-like peptide-1 (GLP-1) receptor agonists and DPP-4 inhibitors. Post-marketing surveillance of exenatide, the first GLP-1 receptor agonist, has raised the possibility of acute pancreatitis in association with their use[1-4] Sitagliptin is a dipeptidyl peptidase-4 inhibitor, the first DPP-4 inhibitor approved for use in patients with type 2 diabetes. Commonly reported adverse events with sitagliptin include upper respiratory tract infection, sore throat, headache and diarrhea. Sitagliptin is a safe and well-tolerated drug[5]. However ,between October 2006 and February 2009, 88 reports of severe pancreatitis in patients receiving sitagliptin prompted the US Food and Drug Administration (FDA) to issue an alert on this potential adverse reaction[6].

Numerous studies have well described the etiologies of acute pancreatitis[7]. The most common inciting factors are gallstones (35-40%) and alcohol abuse (30%)[8]. Other causes of acute pancreatitis include structural abnormalities, neoplasms, metabolic disorders, drugs, trauma, iatrogenic causes, infections, vascular disorders, genetic and idiopathic conditions. The patient in this case report had none of these risk factors, except minor hypertriglyceridemia (204 mg/dL). Although hypertriglyceridemia is a well-recognized cause of acute pancreatitis, it is usually > 1000 mg/dL when acute pancreatitis occurred. Therefore, this episode of acute pancreatitis was not likely caused by hypertriglyceridemia. In animal studies, use of incretin-base therapies lead to pancreatic acinar inflammation and pyknosis, increased pancreatic ductal turnover and ductal metaplasia, which may increase the risk of acute pancreatitis[9,10].

Acute pancreatitis is a rare side effect of sitagliptin use that has not previously been reported with the use of sitagliptin in Taiwan. In this case report, acute pancreatitis occurred 50 days after initiation of sitagliptin therapy. In Garg's report, acute pancreatitis occurred eight weeks after initi-

ation of sitagliptin[11]. By contrast, in cases with acute pancreatitis induced by exenatide, acute pancreatitis usually developed within 10 days after initiating exenatide[1,3,4]. The reason for the difference in time of onset of acute pancreatitis after use of exenatide and sitagliptin remains unclear.

Only two meta-analysis studies found an association of acute pancreatitis and incretin-based therapy[12,13] The latest analysis used the FDA database of reported adverse events to find those associated with the DPP-4 inhibitor sitagliptin and the GLP-1 mimetic exenatide during 2004-2009. They found that use of sitagliptin or exenatide increased 6-fold the risk of pancreatitis, compared with other therapies. Pancreatic cancer was more commonly reported among patients who took sitagliptin or exenatide than other therapies; patients who took sitagliptin had higher occurrence of all other cancers than those taking other regimens[13].

Patients with type 2 diabetes and a higher incidence of several of the known risk factors also have a higher incidence of pancreatitis than the general population. In a multinational, placebo-controlled clinical trial (FIELD study) involving nearly 10,000 patients with type 2 diabetes, the incidence of pancreatitis in the placebo group was 0.094 per 100 patient-years[14] By contrast, annual incidence rates of pancreatitis in the general population range 0.004 to 0.045 per 100 patient-years[15] In another report, incidence of acute pancreatitis was approximately two times higher in patients with type 2 diabetes[16]. The reasons for the higher risk of pancreatitis in patients with diabetes remain unclear, but may relate to higher rates of known risk factors for pancreatitis, such as obesity, hypertriglyceridemia, age and the greater use of medications potentially associated with pancreatitis in such patients.

The causal relationship of incretin-based therapy and acute pancreatitis is still not clear. However, a recent retrospective observational pharmacy claims analysis found no association of acute pancreatitis with exenatide or sitagliptin in those with type 2 diabetes[17] which is similar to Dore's analysis[18]. In Garg's report, the incidence of acute pancreatitis in a diabetic cohort (0.563 cases per 100 patient-years)[17] was similar to that reported in a claims analysis by Noel et al[16]. That study found an extremely low incidence of acute pancreatitis with exenatide (0.13%) and sitagliptin (0.12%), and a comparable risk of acute pancreatitis for those patients and those taking glyburide and metformin.

The rising incidence of obesity and type 2 diabetes means that more patients are likely to take multiple pharmacotherapy for weight management and glycemic control. Although incretin-based therapy has a promising effect on glycemic control, we should be alert to its possible side effects.

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Sitagliptin 相關的胰臟炎 - 個案報告

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摘 要

在台灣最新被核淮用於治療第二型糖尿病的口服藥是第四型雙胜肽蛋白水解酶的抑制劑 (dipeptidyl peptidase-4 inhibitors)，它常見的副作用是腸胃道方面的症狀及低血糖。然而上市後的追蹤卻發現似乎和急性胰臟炎的發生有所關聯．在這個個案中，我們的病人在使用 sitagliptin 後約 50 天產生了急性胰臟炎；回顧她的病史，過去從沒有急性胰臟炎，同時並沒有急性胰臟炎常見的危險因子，包括很高的高三酸甘油脂血症，膽結石及酒精濫用等，同時其發生的時間與國外的報導相似．腸促胰泌素 (incretin) 類的藥物是最新一類被核淮用於治療第二型糖尿病的藥物，它主要是增加血中類昇糖激素胜肽 (Glucagon-like peptide-1,GLP-1) 而達到降血糖的目的，然而上市之後陸續發現不論是注射的類昇糖激素胜肽類似物或第四型雙胜肽蛋白水解酶的抑制劑都有文獻報導似乎和急性胰臟炎有相關。雖然有些研究認爲急性胰臟炎的發生可能和糖尿病本身有關而不是這類藥物，但此個案報告仍希望能讓臨床醫師在使用這類藥物時多注意是否有急性胰臟炎的發生。