Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfda-online.com

Case Report

Acute pancreatitis in patients with type 2 diabetes mellitus treated with dipeptidyl peptidase-4 inhibitors

Tzu-Lin Yang [a], Mei-Chiou Shen [a], Ming-Lung Yu [b,c], Yaw-Bin Huang [a,d], Chung-Yu Chen [a,d,*]

[a] Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[b] Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[c] Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[d] School of Pharmacy, Master Program in Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan

ARTICLE INFO

Article history:
Received 18 October 2015
Received in revised form
8 December 2015
Accepted 5 January 2016
Available online 21 February 2016

Keywords:
acute pancreatitis
dipeptidyl peptidase-4 inhibitors
type 2 diabetes mellitus

ABSTRACT

Dipeptidyl peptidase (DPP)-4 inhibitors are approved for use in monotherapy or in combination therapy for patients with type 2 diabetes mellitus for <1 decade. However, numerous reports of DPP-4 inhibitors induced acute pancreatitis were made through the US Food and Drug Administration Adverse Event Reporting System, and this led to a revision in the prescribing information for these drugs. Therefore, this study is designed to evaluate DPP-4 inhibitors induced acute pancreatitis via the spontaneous adverse drug reactions (ADRs) reporting system in a medical center. In four of 2305 ADR cases, it is suspected that DPP-4 inhibitors induced moderate to serious acute pancreatitis. Beyond drugs, other factors also contribute to acute pancreatitis and affect the possibility of ADRs assessed using the Naranjo algorithm. Finally, our results indicate that the incidence of DPP-4 inhibitors induced acute pancreatitis is low.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive illness that requires continuing medical care to prevent acute complications and to reduce the risk of long-term complications, particularly cardiovascular events [1]. According to the recommendations of the American Diabetes Association and the European Association for the Study of Diabetes, the main therapeutic goal in T2DM is the achievement and maintenance of glycemic levels as close to the nondiabetic range as possible [glycosylated hemoglobin (HbA1C) < 7.0%] [2].Traditional antihyperglycemic drugs include insulin and insulin analogues, insulin sensitizers (metformin and

* *Corresponding author*. Number 100, Shihcyuan 1st Road, Sanmin District, Kaohsiung City 80708, Taiwan, ROC.
E-mail address: jk2975525@hotmail.com (C.-Y. Chen).

http://dx.doi.org/10.1016/j.jfda.2016.01.009

thiazolidinediones), insulin secretagogues (sulfonylureas and glinides), and agents that inhibit dietary carbohydrate breakdown (α-glucosidase inhibitors) [3]. Novel antidiabetic drugs, developed on the basis of an improved understanding of the mechanisms that govern glucose homeostasis, include the incretin-based agents, namely, glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase (DPP)-4 inhibitors (also named "gliptins"). These drugs enhance glucose-dependent insulin secretion from pancreatic β cells and glucose-dependent suppression of glucagon release from pancreatic α cells, respectively, by mimicking the glucoregulatory effects of endogenous GLP-1 (GLP-1 receptor agonists or incretin mimetics) or enhancing endogenous GLP-1 concentrations (DPP-4 inhibitors or incretin enhancers) [4].

DPP-4 inhibitors, such as sitagliptin and vildagliptin with metformin, have been approved for use in monotherapy or in combination therapy for patients with type 2 diabetes since 2006 [5]. A large body of evidence indicates that DPP-4 inhibitors as a class have a good safety and tolerability profile, with a low incidence of mostly mild to moderate adverse events. However, numerous reports of DPP-4 inhibitors induced acute pancreatitis were made through the US Food and Drug Administration Adverse Event Reporting System, and it led to a revision in the prescribing information for these drugs [6]. Therefore, this study is designed to evaluate DPP-4 inhibitors induced acute pancreatitis via the spontaneous adverse drug reaction (ADR) reporting system in a medical center.

2. Case Report

ADR cases of DPP-4 inhibitors induced acute pancreatitis in our hospital, which had been reported to the National Reporting Center of Adverse Drug Reaction during January 2009 to December 2014, were collected, and the severity was analyzed using descriptive statistics. Moreover, the prescription amounts of suspected gliptins, sitagliptin, and vildagliptin with metformin, are analyzed to understand the incidence of DPP-4 inhibitors induced acute pancreatitis in the same period. A total of 2305 ADR cases were reported to the National Reporting Center of Adverse Drug Reaction between January 2009 and December 2014, including reports that four of regular follow-up type 2 diabetic patients had come to our emergency department for help with a discharge diagnosis of acute pancreatitis induced suspiciously by gliptins during the same period (Table 1). Because the average length of hospital stay for a patient with acute pancreatitis is approximately 5–6 days [7], one case (Patient 3) was defined as serious ADR because hospitalization lasted more than 7 days until recovery. The other three cases (Patients 1, 2, and 4) were defined as moderate because hospitalization lasted only 2–5 days. After withholding gliptins, medical intervention, nothing by mouth combined with adequate intravenous fluid supply, and medication for symptom relief, all patients achieved clinical recovery (Tables 1 and 2).

Table 1 – Characteristics of reporting cases during 2009 to 2014.

Item	No.	(%)
Case number (total)	2305	100
ADR of DPP-4 inhibitors induced acute pancreatitis	4	0.17
Severity of DPP-4 inhibitors induced acute pancreatitis		
Mild	0	0.00
Moderate	3	0.23
Serious	1	1.35

ADR = adverse drug reaction; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors.

Moreover, the initial data of the four cases, including underlying diseases as defined by *International Classification of Disease, Ninth edition, Clinical Modification* (ICD-9-CM) codes, suspected gliptins, concurrent hypoglycemic agents, HbA1C, duration of gliptins treatment, clinical manifestations, gastrointestinal outcomes, other risk factors, and the Naranjo scale [8], were presented (Table 2). The underlying diseases included T2DM with or without renal or neurological manifestations (ICD-9-CM codes: 250.00, 250.40, 250.60), malignant neoplasm of the thyroid gland (ICD-9-CM codes: 193), hyperlipidemia (ICD-9-CM codes: 272.4), hypercholesterolemia (ICD-9-CM codes: 272.0), hypertension (ICD-9-CM codes: 401.1, 401.9), constipation (ICD-9-CM codes: 564.0), transient disorder of initiating or maintaining sleep (ICD-9-CM codes: 307.41), and hepatitis (ICD-9-CM codes: 573.3). Suspected gliptins were sitagliptin and vildagliptin with metformin. Concurrent hypoglycemic agents were glimepiride, gliclazide, pioglitazone, and insulin. The four patients had been treated by sitagliptin (for 699–1455 days), and three had been further treated by vildagliptin with metformin (for 27–276 days). Before the first dose of gliptins was taken, the level of HbA1C was more than 7% in three cases and one patient's level was equal to 7%. When Patient 3 stopped taking all gliptins, the level of HbA1C was < 7%. Clinical manifestations included abdominal pain (100%), abnormal serum amylase level (100%), abnormal serum lipase level (75%), and computed tomography-proven pancreas lesions (75%). Other risk factors were smoking (50%), alcohol consumption (25%), and obesity (50%). Applying the Naranjo scale, three reports were classified as possible (75%) and one as probable (25%).

By contrast, sitagliptin was prescribed 139,706 times, and the combination product, vildagliptin with metformin, was prescribed 20,631 times in our diabetic outpatient setting at the same time. The incidence of DPP-4 inhibitors induced acute pancreatitis is rare in our hospital during the past 5 years, accounting for approximately < 0.1%.

3. Discussion

Acute pancreatitis is an inflammatory condition of the pancreas characterized clinically by abdominal pain and elevated levels of pancreatic enzymes in the blood [9]. The pathogenesis of acute pancreatitis is not fully understood. Pancreatitis due to medications is rare (0.3–1.4%), although limited data suggest that the incidence may be increasing. Several medications have been associated with drug-induced pancreatitis, and a number of different mechanisms of drug-induced pancreatitis have been proposed [7]. These mechanisms include immunologic reactions, direct toxic effect,

Table 2 – Demographic data, clinical characteristics, and outcome of four suspicious gliptins induced acute pancreatitis patients.

Severity	Age (y)/sex	Underlying disorders (by ICD-9 codes)	Suspected gliptins	Duration of gliptins treatment (d)	Concurrent hypoglycemic agents	HbA1C (4–6%)		Clinical manifestations	Gastrointestinal outcome after gliptins were discontinued	Other risk factors			Naranjo Scale
						Before the first dose of gliptins used	When all gliptins were suspended			Smoking	Alcohol consumption	Obesity (BMI)	
Moderate	60/F	193: malignant neoplasm of thyroid gland 272.4: hyperlipidemia 250.00: type 2 diabetes mellitus 401.1: hypertension	Sitagliptin	Sitagliptin: 699	Glimepiride	7.4	7.8	Abdominal pain		Nonavailable	Nonavailable	BW[a]: 70 kg	3
					Metformin			Amylase: 163 U/L (basal: nonavailable) Lipase: 253 U/L (basal: nonavailable) CT-proven Grade A, B pancreatitis	Amylase: 63 U/L Lipase: 29 U/L				
Moderate	53/F	250.40: type 2 diabetes mellitus with renal manifestations 250.60: type 2 diabetes mellitus with neurological manifestations 401.9: hypertension 272.4: hyperlipidemia 307.41: transient disorder of initiating or maintaining sleep	Vildagliptin with metformin (status post sitagliptin used)	Sitagliptin: 1445 Vildagliptin: 27	Gliclazide	13.1	9.8	Abdominal pain		No	No	Yes (26.9)	4
					Insulin			Amylase: 294 U/L (basal: 16 U/L) Lipase: 18 U/L (basal: 13 U/L)	Amylase: 66 U/L Lipase: 36 U/L				

Serious	68/M	250.00: type 2 diabetes mellitus 272.0: hyperlipidemia	Vildagliptin with metformin (status post sitagliptin used)	Sitagliptin: 980 Vildagliptin: 57	Gliclazide Pioglitazone	7.0	6.9	Abdominal pain Amylase: 379 U/L (basal: nonavailable) Lipase: 684 U/L (basal: nonavailable) CT-proven Grade B pancreatitis	 Amylase: 232 U/L Lipase: 312 U/L Autoimmune pancreatitis was suspected during further clinic visit	Yes	Yes	No (21.2)	5
Moderate	63/M	250.00: type 2 diabetes mellitus 250.60: type 2 diabetes mellitus with neurological manifestations 573.3: hepatitis 272.0 hyperlipidemia 564.0: constipation	Vildagliptin with metformin (status post sitagliptin used)	Sitagliptin: 1355 Vildagliptin: 276	Insulin	8.3	10.3	Abdominal pain Amylase: 1550 U/L (basal: nonavailable) Lipase: 1698 U/L (basal: nonavailable) CT-proven groove pancreatitis	 Amylase: 62 U/L Lipase: 50 U/L	Yes	No	Yes (28.4)	4

BMI = body mass index; BW = body weight; CT = computed tomography; HbA1C = glycosylated hemoglobin; ICD-9 = *International Classification of Disease, Ninth edition, Clinical Modification*.
[a] Only body weight available.

accumulation of a toxic metabolite, ischemia, intravascular thrombosis, and an increased viscosity of pancreatic juice. Acute pancreatitis has been reported in association with DPP-4 inhibitors treatment. However, there are insufficient data to determine if there is a causal relationship at present. In addition, a population-based study on a Taiwanese population had revealed that the risk of acute pancreatitis was not significantly higher among DPP-4 inhibitor users compared with nonusers [10]. Although our study is a simple descriptive one that did not involve a comparison group, it is noteworthy that the incidence, accounting for 0.17% of 5-year ADR reporting data, of DPP-4 inhibitors induced acute pancreatitis is rare in our study.

Second, other factors may also include the etiology of acute pancreatitis beyond drugs [7]. The approach to determine the etiology of acute pancreatitis are the following: previous symptoms or documentation of gallstones, alcohol use, history of hypertriglyceridemia or hypercalcemia, family history of pancreatic disease, prescription and nonprescription drug history, history of trauma, and the presence of concomitant autoimmune diseases. Aside from T2DM, some of our cases had dyslipidemia, some had liver problems, and some were smokers or alcohol users, which may also contribute to acute pancreatitis. These factors are known to affect the possibility of ADRs as assessed by the Naranjo algorithm.

Third, there is no study concluding how long it takes for acute pancreatitis to occur after patients had started taking DPP-4 inhibitors. Intriguingly, even though the underlying conditions and other risk factors varied among patients, all our patients had been taking gliptins for more than 1 year (long term), and all had initial manifestations of accidental abdominal pain with abnormal serum amylase level. Therefore, pancreatitis should be considered in patients with persistent severe abdominal pain (with or without nausea), and DPP-4 inhibitors should be discontinued in such patients, even if they had been in use for a long time. If pancreatitis is confirmed, a DPP-4 inhibitor should not be restarted. In addition, DPP-4 inhibitors should not be initiated in patients with a history of pancreatitis. Furthermore, although further well-conducted studies are needed to prove it, female and elderly DPP-4 inhibitor users had significantly elevated risks of acute pancreatitis development [10]. Our study cannot reflect that sex and age are risk factors for DPP-4 inhibitors users to develop acute pancreatitis, but physicians may pay more attention to these groups.

4. Conclusion

From our results, the incidence of DPP-4 inhibitors induced acute pancreatitis in patients with T2DM is rare. Although physicians should remain attentive for this rare but potential complication, DPP-4 inhibitors are still reasonable options for type 2 diabetic patients who are being monitored for adverse symptoms. Otherwise, because pancreatitis could happen any time during care, patients and their caregivers should be on alert for signs of pancreatitis including severe stomach pain, back pain, very upset stomach, or throwing up. DPP-4 inhibitors should also be discontinued in such patients to prevent irreversible pancreatic harm.

Conflicts of interest

All contributing authors declare no conflicts of interest.

REFERENCES

[1] American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care 2010;33:S11–61.
[2] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203.
[3] Kulasa KM, Henry RR. Pharmacotherapy of hyperglycemia. Expert Opin Pharmacother 2009;10:2415–32.
[4] Tahrani AA, Piya MK, Kennedy A, Barnett AH. Glycaemic control in type 2 diabetes: targets and new therapies. Pharmacol Ther 2010;125:328–61.
[5] Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T, Rosebraugh C. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. N Engl J Med 2014;370:794–7.
[6] FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes. Available from URL: http://www.fda.gov/drugs/drugsafety/ucm343187.htm [accessed 25.03.14].
[7] Van Woerkom RC, Adler DG. Acute pancreatitis: review and clinical update. Hosp Physician 2009; Jan:9–19.
[8] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.
[9] Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1–15.
[10] Lai YJ, Hu HY, Chen HH, Chou P. Dipeptidyl peptidase-4 inhibitors and the risk of acute pancreatitis in patients with type 2 dabetes in Taiwan: a population-based cohort study. Medicine 2015;94:e1906.