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Case Report

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

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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

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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,