

Three ileus cases associated with the use of dipeptidyl peptidase-4 inhibitors in diabetic patients

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ABSTRACT

Dipeptidyl peptidase (DPP)-4 inhibitors are a new class of antidiabetic drugs that increase incretin hormone levels to enhance blood sugar level-dependent insulinotropic effects, suppress glucagon action, and reduce bowel motility. These incretin effects are ideal for blood sugar control. However, the safety profile of DPP-4 inhibitors is not yet established. Herein, we present three cases of ileus, considered to be closely related to the use of DPP-4 inhibitors, in diabetic patients. Each of the three patients exhibited some risk of a deficiency in bowel movement; the onset of ileus was within 40 days after strengthened inhibition of DPP-4. The use of a DPP-4 inhibitor could be safe, although the cases presented herein enable us to inform the scientific community to some of the potential adverse effects of the use of DPP-4 inhibitors in select populations. (*J Diabetes Invest*, doi: 10.1111/jdi.12095, 2013)

KEY WORDS: Adverse drug reaction, Complication, Dipeptidyl peptidase-4, Niveau

INTRODUCTION

Dipeptidyl peptidase (DPP)-4 inhibitors enhance the activity of endogenous incretin hormones¹, which are important prandial stimulators of insulin secretion, and exhibit other physiological actions, such as reducing bowel motility^{1,2}. In addition to their glucose-lowering effects, DPP-4 inhibitors have potential adverse effects due to their diverse and pleiotropic actions³. Herein we present three cases of ileus in diabetes patients that may be associated with the use of a DPP-4 inhibitor.

CASE REPORT

Case 1

The first patient was a 70-year-old Japanese man with a >10-year history of diabetes without diabetic nephropathy or retinopathy. He had undergone surgery for appendicitis. In addition, the patient had been treated for Parkinson's disease with levodopa-carbidopa tablets for 2 years, and his condition was stable with mild rigidity. The patient presented at the hospital complaining of persistent nausea, vomiting, and diarrhea for 2 days. The patient had been taking mitiglinide for approximately 20 months to treat his diabetes, but had been prescribed alogliptin (25 mg/day) instead of mitiglinide 11 days prior to

his presentation at hospital. Abdominal X-ray and computed tomography (CT) revealed air–fluid levels in his intestines. After admission, the patient passed multiple diarrheal stools and his air–fluid levels subsequently resolved without intervention. He was discharged 11 days later.

Case 2

The second patient was a 61-year-old Japanese woman with myeloperoxidase anti-neutrophil cytoplasmic antibody (ANCA)-positive rapidly progressive glomerulonephritis being treated with prednisolone. The patient was in a stable condition (estimated glomerular filtration rate [eGFR] 29 mL/min per 1.73 m²). The patient had undergone surgery for early gastric cancer (Ic) 25 years previously. She had a >10-year history of type 2 diabetes and her diabetes had been treated with mitiglinide and sitagliptin; miglitol (150 mg/day) was added to her antidiabetes regimen to control post-prandial hyperglycemia, and the sitagliptin was discontinued. The patient's average HbA1c over 6 months was 7.7% (NGSP⁴). The patient refused insulin and had been treated instead with a half-dose of vildagliptin (50 mg/day) in addition to mitiglinide (30 mg/day) and miglitol (225 mg/day) for 4 months. The patient's prednisolone dose was decreased to 10 mg/day (from 15 mg/day) and she was eventually prescribed a full dose of alogliptin (25 mg/day) instead of vildagliptin (50 mg/day). Thirty-eight days later, she experienced intermittent abdominal pain and vomiting. She had experienced difficulty in emptying her bowel for the past month. She was identified with air–fluid levels in her colon and was admitted to the surgical unit for further assessment. X-Ray and

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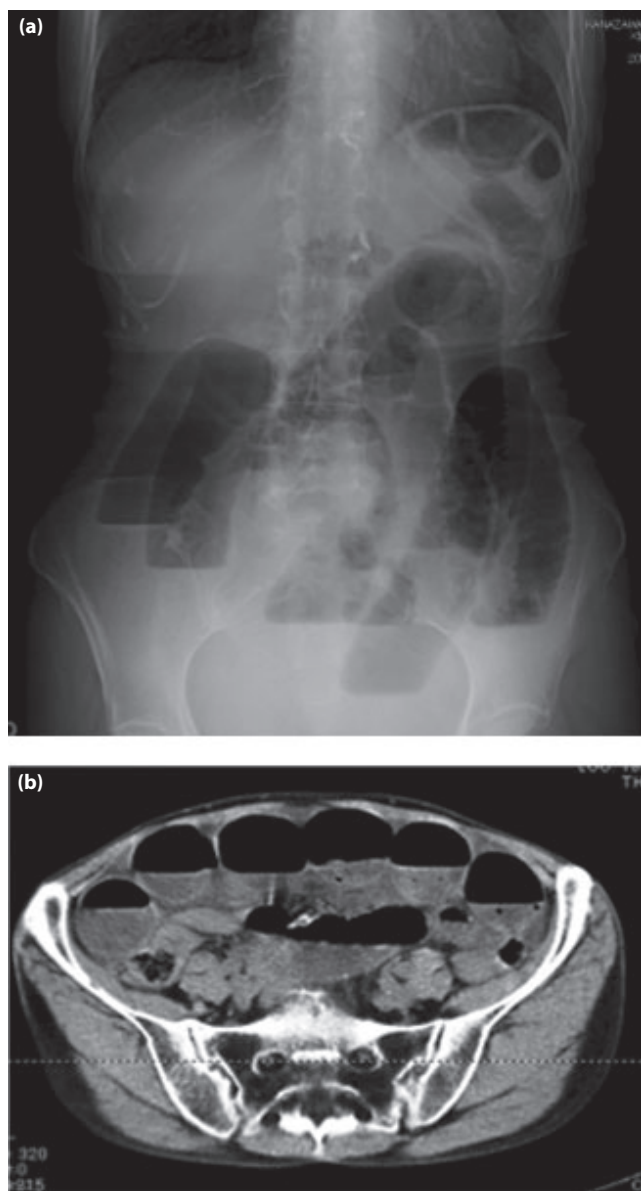


Figure 1 | Results of abdominal X-ray and computed tomography (CT) imaging in Case 2. An upright abdominal X-ray (a) and CT scan (b) demonstrate small bowel obstruction. Note that multiple air–fluid levels can be seen in both panels.

CT imaging indicated that her ileus was becoming worse (Figure 1). Gastrointestinal decompression was performed via a nasogastric tube; however, this was not effective. So, 3.5 days later, surgical decompression and reconstructive surgery were performed for a collapsed small intestine, which revealed an internal hernia.

Case 3

The third patient was a 78-year-old Japanese man with a >10-year history of type 2 diabetes. This patient's right leg had been

amputated 11 years ago because of atherosclerosis obliterans. The patient had chronic kidney disease (eGFR 46 mL/min per 1.73 m²). The patient had undergone total gastrectomy with partial pancreateosplenectomy and left adrenalectomy 12 years ago for advanced gastric cancer. He had had an ileus that was resolved with conservative treatment 5 years ago. One day prior to admission, the patient experienced intermittent lower left abdominal pain with nausea and vomiting. X-Ray and CT scans revealed air–fluid levels in his intestines. The patient was admitted to hospital for his ileus. Gastrointestinal decompression via a nasogastric tube was successful and the patient was discharged 3 weeks after admission. His diabetes had been treated with glargine, metformin (500 mg/day), miglitol (225 mg/day), repaglinide (0.75 mg/day), and sitagliptin (50 mg/day). The patient was also taking amlodipine, aliskiren, calcium polystyrene sulfonate, camostat mesilate, liver hydrolysate, and mosapride citrate hydrate. His diabetes was relatively stable, with an HbA1c of 8.0% (NGSP⁴), but random sampling revealed blood sugar levels >300 mg/dL. A diabetologist had asked the patient to use rapid insulin instead of an oral hypoglycemic agent, but the patient did not like the idea of multiple insulin injections. Thirty-three days prior to his admission for the ileus, the patient was prescribed a full dose of vildagliptin (100 mg/day) instead of sitagliptin (50 mg).

DISCUSSION

Herein we present three cases of ileus in diabetic patients treated with DPP-4 inhibitors. Case 1 presented as a first-time user of a DPP-4 inhibitor. In Cases 2 and 3, a DPP-4 inhibitor had been used chronically and had subsequently been changed for strengthened DPP-4 inhibition^{5,6}. These two patients had also been treated with miglitol, possibly inducing defects in gastrointestinal movement. There was no clear information regarding either diabetic gastroenteropathy or neuropathy in any of the cases. Two cases had a history of major abdominal surgery; one of these patients also had a history of ileus. Two of the three patients had other chronic diseases, namely ANCA-associated vasculitis⁷ and Parkinson's disease^{8,9}, which could potentially affect the motility of the gastrointestinal system, although quantitative evaluations for bowel motility had not been performed. Despite the fact that a causal relationship between ileus and the use of a DPP-4 inhibitor was unclear, in all patients the onset of ileus occurred within 40 days after strengthened DPP-4 inhibition (see Figure S1 available as Supplementary Material to this paper). In all three cases, the DPP-4 inhibitors were discontinued: Case 1 was treated with miglitol only, Case 2 was prescribed insulin detemir with repaglinide, and Case 3 was given insulin glulisine three times per day and basal glargine.

The glycemic-lowering action of incretin-associated drugs results from their insulinotropic effects, as well as reduced bowel motility^{1,2,10}. However, the incretin-associated drug effects on reduced bowel motility could be harmful if produced in excess through interactions with underlying conditions, such

as a history of abdominal surgery, microangiopathy in the gastrointestinal system, or autonomic defects. All three patients in the present series were given a stronger DPP-4 inhibitor before the onset of ileus, indicating pathological interactions between defects in basal bowel movement and DPP-4 inhibitor-reduced bowel motility. There is no case report in the literature describing an association between the use of DPP-4 inhibitors and ileus.

The three cases presented herein demonstrate the potential for adverse effects of DPP-4 inhibitors in certain populations. Thus, further long-term safety monitoring is required.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Clinical course of the patients in the present series.