

clinical, macroscopic and microscopic features and on sufficient sampling of the tumour tissue.

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Liraglutide-Induced Acute Pancreatitis

Santhosh Jeyaraj, Ananth Samith Shetty, Champat Raj Roopesh Kumar, Arun Nanditha, Satheesh Krishnamoorthy, Arun Raghavan, K Raghavan, Ambady Ramachandran

Abstract

An obese lady of 51 year with Type 2 Diabetes Mellitus for 13 years was prescribed Liraglutide, a glucagon like peptide (GLP-1) analogue (Victoza) for glycaemic control and reduction of weight. She was on gliclazide and Insulin prior to initiation of Liraglutide. Eight weeks after initiation of GLP -1 analogue, she developed severe abdominal pain, nausea and vomiting. She was admitted to a private hospital and evaluated. Biochemical tests and CT scan revealed presence of pancreatitis and she was treated for acute pancreatitis. Liraglutide was withdrawn and symptoms subsided. Subsequent follow-up showed that pancreatic enzyme levels were normal.

Introduction

Liraglutide (Victoza) is a GLP-1 analogue approved by the FDA for the treatment of Type 2 diabetes mellitus (T2DM). It shares 97% structural homology with human GLP-1. However, unlike human GLP-1, which has a half-life of less than 5 minutes, Liraglutide is able to evade degradation by dipeptidyl peptidase IV, which confers on it a half-life of about 13 hours, administered subcutaneously once a day. In clinical studies, treatment with Liraglutide in patients with T2DM reduced haemoglobin A1c by 1% to 1.6%.¹ Liraglutide has also been shown to produce dose-dependent weight loss in obese subjects.² Its main side effects are nausea and vomiting. One of the safety concerns is a possible increased risk of pancreatitis. In the phase 2 and phase 3 trials of Liraglutide, there were 7 cases of pancreatitis reported among the 4257 patients treated with Liraglutide and only one case in the 2381 patients in the comparator group. The small number of events makes it difficult to draw conclusions about causation.³ This case is being reported as there are only few reports of acute pancreatitis due to Liraglutide in the literature.

Case Report

A 51-year-old obese female of high socioeconomic status reported to our hospital with complaints of uncontrolled and fluctuating blood glucose levels. She had (T2DM) for 13 years, and had obesity with hypertension.

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Fifteen days prior to the visit, she was admitted in a local hospital with severe abdominal pain, nausea and vomiting. Her treatment history before the admission included, injection of premixed analogue insulin (Novomix insulin 30/70, 15 units in morning and 10 units in evening), Injection of Liraglutide (1.2 mg once a day), gliclazide (80 mg twice daily), aspirin (150 mg once a day) and prazosin extended release (5 mg twice daily). Initially she was on 0.6 mg of Liraglutide for 1 week and then on 1.2 mg for next 7 weeks. During that admission her random capillary blood glucose was 250 mg/dl. Leucocytes : 15200 cells/cm, Serum Lipase: 420 IU/L, Serum Amylase: 515 IU/L and Triglycerides was 136 mg/dl.

Her CT scan revealed that pancreas was mildly bulky with decreased parenchymal enhancement. There was marked peripancreatic fat strandings, significant peripancreatic fluid extending into lesser sac and left pararenal space with thickening of lateral canal fasciae. Small pockets of fluid were also seen along the greater curvature of body of stomach. No demonstrable necrosis, dilatation or calculi were seen. Mild ascites was present. Features were suggestive of acute pancreatitis.

Based on her clinical presentation, biochemical tests and CT scan of the abdomen, a diagnosis of acute pancreatitis was made. Liraglutide was withdrawn. The patient's oral intake was withheld and managed with antibiotics, intravenous fluids and Insulin. The symptoms subsided in 48 hours and amylase and lipase levels dropped to 106 IU/L and 100 IU/L respectively.

Two weeks after discharge from the local hospital, the patient was admitted in our hospital and her main complaints were uncontrolled, fluctuating blood glucose levels with frequent hypoglycaemia and comorbidities such as obesity and hypertension.

There was no past history of alcohol intake, gall stones, trauma, documented hypertriglyceridaemia or infections. Her body mass index was 31 kg/m², blood pressure was 180/110 mm Hg. She had severe sensory motor neuropathy and mild non-proliferative diabetic retinopathy in both eyes. The random plasma glucose was 220 mg/dl with an HbA1c of 9.7%, proteinuria- 2.0 gms/day. Lipids, serum amylase, serum lipase, liver enzymes (SGOT and SGPT) were normal. The fasting and postprandial C-Peptide levels were 1.59 and 1.70 pmol/ml respectively.

She was treated with basal bolus regimen of insulin, angiotensin receptor blockers and diuretics. Metformin was started (250 mg twice daily). Patient was able to tolerate metformin. Calcium and pancreatic supplements were also given, alpha blocker was continued.

She had no abdominal discomfort. She was

discharged 3 days later. Two weeks later, on follow-up, fasting and postprandial plasma glucose were < 120 mg/dl and < 180 mg/dl respectively. The patient remained asymptomatic with no recurrence of symptoms since Liraglutide was discontinued.

Discussion

To our knowledge, this is the first postmarketing case report of Liraglutide induced pancreatitis from India. The event has occurred within a reasonable period of administration of the drug. There was laboratory and radiological confirmation of acute pancreatitis. The event could not be attributed to any other cause, as there was a complete resolution of the condition on withdrawal of Liraglutide. A rechallenge with the drug was not considered since it was unethical to do so. There was no history of any other risk factors such as severe infection, gall stones, severe hypertriglyceridaemia, trauma and alcohol intake. Therefore as per the WHO-UMC standards⁴ and the Naranjo probability scale,⁵ the adverse event was probably related to Liraglutide.

A retrospective cohort study had concluded that patients with type 2 diabetes have a 2.83 fold increased risk of acute pancreatitis compared to subjects without diabetes.⁶ Adverse events have been reported with use of exenatide and sitagliptin.⁷ It is reported that 0.1-2% of pancreatitis are drug induced.⁶

It is difficult to decide whether the reports of pancreatitis in users of exenatide or gliptins are truly-drug-induced. In phase 2 and phase 3 trials of Liraglutide findings of pancreatitis represented a 4:1 imbalance between the drug and the comparator group.³ It was also suggested that the persistence of nausea and vomiting, common side effects with use of Liraglutide, might be early manifestations of pancreatitis and must be carefully evaluated. In the case described here, these adverse reactions were present.

In the six documented acute cases of Liraglutide-related pancreatitis, daily doses included 1.2 mg (n = 2), 1.8 mg (n = 3), and 3 mg (n = 1). Of the two documented cases of chronic pancreatitis, one of the patients was on 0.6 mg daily and the other on 1.8 mg daily.⁸ While it is not clear that a dose-related effect exists with respect to pancreatitis, in this case report, patient was initiated with Liraglutide 0.6 mg for 1 week and then on 1.2 mg for next 7 weeks. The patient's symptoms resolved with discontinuation of Liraglutide and had not recurred after discharge. Of the other documented cases, 5 of the 6 acute cases resolved and one resolved case among them continued Liraglutide therapy.^{1,8}

Potential serious safety concerns were raised from studies in rodents that use of Liraglutide was

associated with an increased risk of medullary thyroid cancer.⁷ This cannot be considered as a risk for humans, as the experimental drug exposure level in rodents were many times higher than used in humans. The FDA expects to learn more about the drug's safety from the post approval studies and clinical trials.

While the exact mechanism by which the GLP-1 mimetic therapy causes pancreatitis is still unclear, plausible hypotheses have been put forth by several studies. These are reviewed by Butler et al.¹⁰ A potential mechanism of ductal replication rates as found in obesity and type 2 diabetes is proposed. Pancreatitis may be initiated at the level of acinar cells or ductal cells. Aberrations in acinar-ductal systems can lead to local inflammation and acinar cell death and the consequent release of cytokines may trigger signals for chronic pancreatitis. GLP-1 therapy is reported to activate regenerative efforts in the pancreatic ducts with increase in duct cells positive for the transcription factor Pancreatic and duodenal Homeobox-1 (PDX-1). GLP-1 based therapy may also induce pancreatitis by its actions of altering enzyme secretions.¹¹

Animal experiments have demonstrated that GLP-1 receptor activation increases pancreatic mass and modulates the expression of genes associated with pancreatitis.⁹ Further studies are warranted to know whether GLP-1R activation modifies gene expression, enzyme secretion or inflammation in human pancreas.

The temporal relationship between the initiation of Liraglutide and the onset of symptoms of pancreatitis, and the resolution of symptoms and normalisation of laboratory parameters upon its discontinuation clearly indicates a causative role for the drug. Clinicians should use incretin – based therapy cautiously in patients with history of pancreatitis.

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Disseminated Cryptococcosis with Caverno-Oesophageal Fistula in a Case of Idiopathic CD4+ T-Lymphocytopenia

Jairaj P Nair*, Amita U Athavale**, Sonal Gawande***, Unmil Shah*, Milind Baldi***, Vishal Gupta***, Varun Gavali***

*Assistant Professor, **Professor and Head, ***Registrar, Department of Chest Medicine, Seth G.S. Medical College and King Edward VII Memorial Hospital, Mumbai – 400 012
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Abstract

Idiopathic CD4+ T-Lymphocytopenia is a rare immunodeficiency disorder characterised by significantly low absolute CD4 lymphocytes in absence of any viral infections.¹ We present a case of Disseminated Cryptococcosis with Caverno-