

CASE REPORT

A Case of Acute Pancreatitis Due to Liraglutide

Noe Quesada-Vazquez, Jose Such, Pascale Anglade

Cleveland Clinic Abu habi, Al Falah Street, Al Maryah Island - Abu Dhabi, United Arab Emirates

ABSTRACT

Context Liraglutide is a long-acting glucagon-like peptide-1 (GLP-1) analog which has an important role in the management of glucose metabolism. Liraglutide also decreases caloric intake due to a reduction of appetite effect. As a result of such effects, liraglutide was developed for the treatment of type 2 diabetes and weight management. Observational studies and clinical trials data suggest an association between GLP-1 agonist use and acute pancreatitis and it has been suggested that acute pancreatitis is a potential complication of liraglutide therapy. **Case report** We present a case of acute pancreatitis occurred in a patient treated with liraglutide for weight management. All others potential causes of acute pancreatitis were ruled out. **Conclusions** Although more studies are needed to demonstrate the direct cause effect relation between liraglutide and acute pancreatitis, the trend of results found in the literature has positioned liraglutide as a potential risk factor of acute pancreatitis.

INTRODUCTION

Liraglutide is a long-acting glucagon-like peptide-1 (GLP-1) analog, obtained by derivatizing GLP-1 with a fatty acid side chain [1, 2]. Like native GLP-1, liraglutide has a glucose-dependent stimulation of insulin secretion effect resulting in a regulation of glucose metabolism [2, 3, 4, 5]. Liraglutide also produces an inhibition of small bowel motility [6] and gastric emptying [7], and lowers body weight through decreased caloric intake due to a reduction of appetite effect [4, 8]. As a result of its dual effects on appetite/weight and glucose regulation, liraglutide was developed for the treatment of type 2 diabetes and weight management. Liraglutide 3.0 mg is currently approved for weight management in Australia, Canada, the European Union, Mexico and the USA.

Observational studies and clinical trial data suggest an association between GLP-1 agonist use and acute pancreatitis. At least 13 cases of acute pancreatitis due to liraglutide have been reported [9]. According with this background, has been suggested that acute pancreatitis is a potential complication of liraglutide therapy so that, liraglutide should be used cautiously in patients at risk of pancreatitis. Furthermore, the U.S. Food and Drug Administration (FDA), on its warnings and precautions advices to do not restart liraglutide anymore if pancreatitis is confirmed.

CASE REPORT

A 44-year-old female (height 164 cm, weight 86 Kg, BMI 31.97) who arrived at the Emergency Department (ED) with a new-onset intolerable abdominal pain in the epigastrium radiated to her back and accompanied with nausea and vomiting. The pain appeared suddenly and lasted two to three hours.

At ED, her serum lipase concentration was found to be extremely elevated (8,150 units/L; normal, 20–90 units/L), as was his serum amylase concentration (958 units/L; normal, 73–393 units/L) and the patient was diagnosed of acute pancreatitis (AP) based on two out three AP diagnostic criteria: characteristic abdominal pain, amylase and/or lipase \geq 3ULN and/or characteristic findings on pancreas imaging (**Figure 1**).

No medical conditions other than hypertension. Her previous history was otherwise unremarkable; she did not report any acute or chronic pancreatic disease and denied alcohol use, smoking, toxic habits or taking any other medications, including over-the-counter medications or herbal remedies, potentially associated with pancreatitis. Her home medications included amlodipine 5 mg orally daily but discontinued one year ago because of her blood pressure has been normalized since that time. She had no known medication allergies. No medical history among her family. No history of acute pancreatitis or pancreas disorders in her family. Six months before admission, liraglutide (1.2 mg/day) had been started for the aim of losing weight.

The patient was fully alert and oriented, afebrile and had normal vital signs; physical examination yielded normal findings apart from a tender epigastrium. No rebound tenderness. A baseline comprehensive metabolic panel (CMP) and complete blood count (CBC) were performed upon her admission to the hospital. All

Received December 11th, 2017 - Accepted January 10th, 2018
Keywords Acute Disease; etiology; Glucagon-Like Peptide 1; Liraglutide; Pancreatitis
Correspondence Noe Quesada-Vazquez
Cleveland Clinic Abu habi, Al Falah Street
Al Maryah Island - Abu Dhabi
United Arab Emirates
Tel +971 2 501 9000
E-mail quesadan@clevelandclinicabudhabi.ae

laboratory test values were within normal limits except for an elevated blood lipase and amylase (described above). Alanine aminotransferase (ALT) (44 IU/L; reference range 10-36 U/L), aspartate aminotransferase (AST) 27 IU/L (normal range 10-36 IU/L), and total bilirubin 4.2 $\mu\text{mol/L}$ (normal range 5-21 $\mu\text{mol/L}$); γ -glutamyltransferase, alkaline phosphatase, electrolytes, hematological variables, cholesterol, triglycerides, renal function tests, and blood gases were normal. She did not report any melena, hematochezia, or changes in his bowel habits. An abdominal ultrasound was done in the ED and revealed a normal pancreatic gland and a normal gallbladder without gallstones (**Figure 2**). Non-dilated common bile duct. Viral hepatitis and an autoimmunity (Ig G 1-4) screening were also negative. The BUN was normal, there were no SIRS criteria, there was no pleural effusion on chest X-ray, mental status was normal with a Glasgow score of 15 and regarding the patient's age, she didn't meet any BISAP (Bedside Index of Severity in Acute Pancreatitis) score criteria.

Liraglutide was discontinued indefinitely and the patient was treated conservatively with bowel rest, intravenous fluids and analgesia for pain.

Over the duration of the patient's hospital stay, her amylase and lipase levels were monitored daily. On hospital day 4, her serum amylase and lipase concentrations were normalized. On hospital days 4-7, the patient's amylase and lipase levels remained normal, and her symptoms ceased. A re-challenge test was not performed for safety reasons.

DISCUSSION

Although diabetic patients (most population evaluated using GLP-1 agonist) have an increased base-line rate of pancreatitis as compared to the general population [10], safety concerns have been proposed due to the possible increased risk of pancreatitis related to drugs that act through the GLP-1 pathway such as liraglutide, exenatide and sitagliptin.

An hypersensitivity or a metabolic idiosyncratic reaction triggered by liraglutide seems to be the most likely mechanism of pancreatic injury in the cases reported in the literature since none of the studies in animals have shown pancreatic damage in subjects using extremely high dose of GLP-1 agonist [11, 12, 13]. Nonetheless, a secondary analysis of pooled data from the SCALE Clinical Development Program, a randomized, parallel group trial with 3,731 participants, found an unknown increased amylase and lipase level in blood in patients using GLP-1 analogs; however the authors suggested that GLP-1A causes subclinical pancreatic inflammation leading to enzyme elevation. The absolute risk of AP in the SCALE program was low, but numerically higher in the liraglutide group compared to the placebo group [14, 15]. In addition, a study from the French Pharmacovigilance Database showed that compared with other antihyperglycemic agents, the use of GLP-1 analogs is associated with an increased risk of acute pancreatitis [16].

Therefore, studies suggesting that type 2 diabetes patients receiving GLP-1 analogs are not exposed to an elevated risk of pancreatitis have relevant analysis limitations such as the low prevalence of GLP-1 analogs users and the lack of a clear distinction between therapy groups with GLP-1 receptor agonists and other antidiabetic treatments [14, 17, 18, 19].

CONCLUSION

In our case no concomitant medication was reported. Furthermore, he had no prior history of acute or chronic pancreatic disorders and alternative causes of acute pancreatitis such as gallstones, alcohol use, hypertriglyceridemia, tobacco, autoimmunity or an active viral infection were ruled out upon history, clinical presentation and laboratory studies.

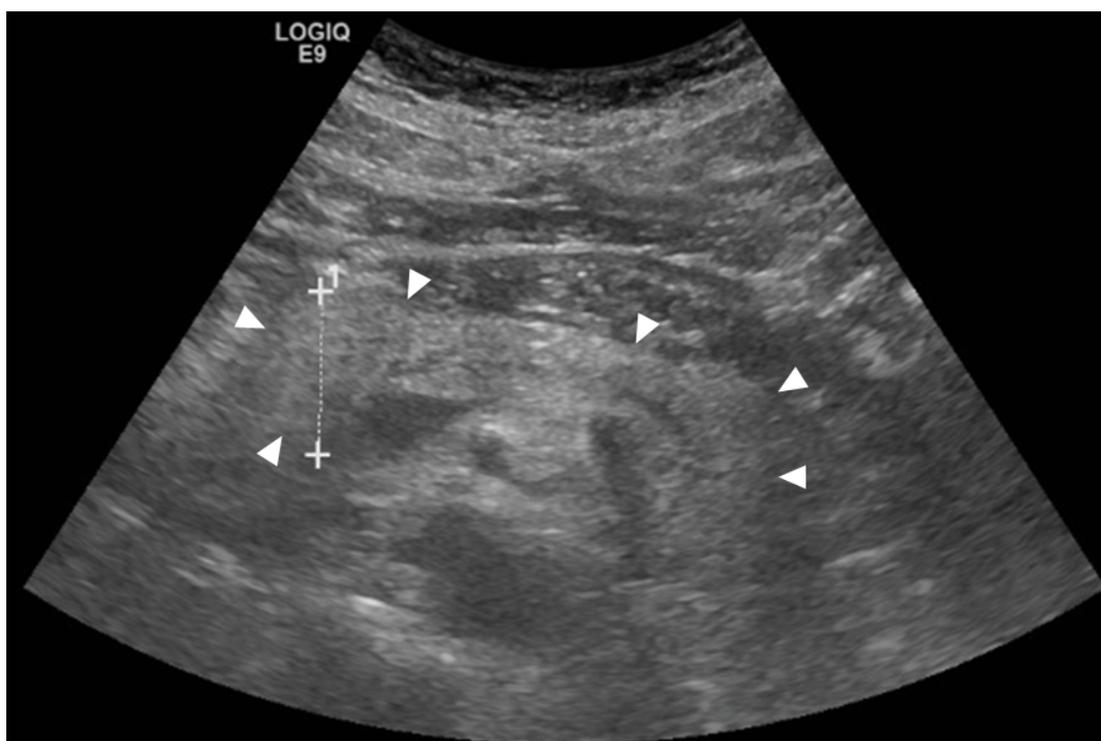


Figure 1. Normal pancreatic gland.

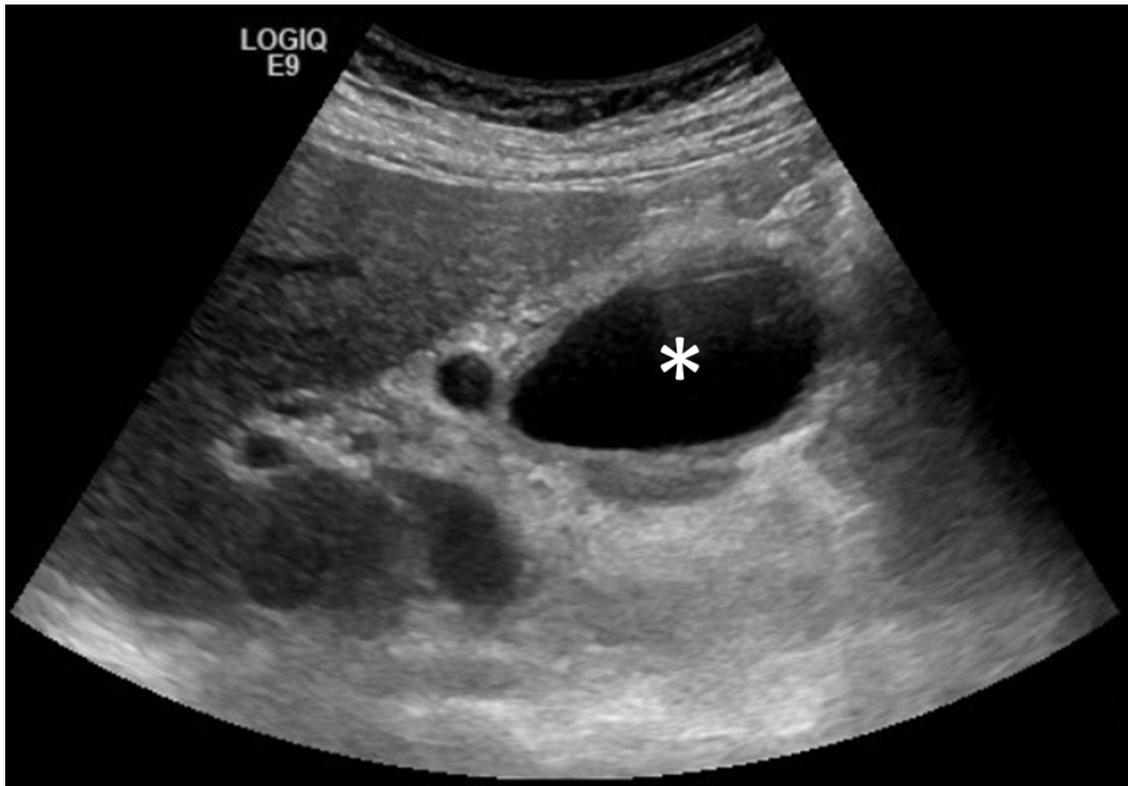


Figure 2. Normal appearance of the gallbladder without gallstones (asterisk).

Using the Naranjo algorithm probability scale for adverse drug reactions, a probable causative relationship was established between liraglutide and the acute pancreatitis in this case (score of 7). Moreover, the temporal relationship between liraglutide initiation and symptoms associated with acute pancreatitis, as well as symptoms resolution and normalization of laboratory test values after liraglutide discontinuation supports a causative role in this probable adverse event. The absence of type 2 diabetes mellitus in our patient and the absence of other risk factors of acute pancreatitis as well, make liraglutide into the unique causative agent of AP in this case. However, the potential causal relationship between liraglutide and acute pancreatitis will be further investigated.

Acknowledgement

This case was reported to the Food and Drug Administration's MedWatch program.

Conflict of Interest

None of the authors have any conflict of interest to disclose related to this article.

References

1. Wilding JPH, Overgaard RV, Jacobsen LV, Jensen CB, le Roux CW. Exposure-response analyses of liraglutide 3.0 mg for weight management. *Diabetes Obes Metab* 2016; 18:491-9. [PMID: 26833744]
2. Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, et al. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 1996; 379:69-72. [PMID: 8538742]

3. Barrera JG, Jones KR, Herman JP, D'Alessio DA, Woods SC, Seeley RJ. Hyperphagia and Increased Fat Accumulation in Two Models of Chronic CNS Glucagon-Like Peptide-1 Loss of Function. *J Neurosci* 2011; 31:3904-13. [PMID: 21389245]
4. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest* 1998; 101:515-20. [PMID: 9449682]
5. Flint A, Raben A, Ersbøll AK, Holst JJ, Astrup A. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. *Int J Obes Relat Metab Disord* 2001; 25:781. [PMID: 11439290]
6. Amato A, Baldassano S, Liotta R, Serio R, Mulè F. Exogenous glucagon-like peptide 1 reduces contractions in human colon circular muscle. *J Endocrinol* 2014; 221:29-37. [PMID: 24443715]
7. Nauck MA, Niedereichholz U, Ettl R, Holst JJ, Orskov C, Ritzel R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol* 1997; 273:E981-988. [PMID: 9374685]
8. Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, et al. Determinants of the Impaired Secretion of Glucagon-Like Peptide-1 in Type 2 Diabetic Patients. *J Clin Endocrinol Metab* 2001; 86:3717-23. [PMID: 11502801]
9. Giorda CB, Sacerdote C, Nada E, Marafetti L, Baldi I, Gnani R. Incretin-based therapies and acute pancreatitis risk: a systematic review and meta-analysis of observational studies. *Endocrine* 2015; 48:461-71. [PMID: 25146552]
10. Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 2009; 32:834-8. [PMID: 19208917]
11. Nakamura T, Ito T, Uchida M, Hijioka M, Igarashi H, Oono T, et al. PSCs and GLP-1R: occurrence in normal pancreas, acute/chronic pancreatitis and effect of their activation by a GLP-1R agonist. *Lab Invest J Tech Methods Pathol* 2014; 94:63-78. [PMID: 24217090]
12. Gier B, Matveyenko AV, Kirakossian D, Dawson D, Dry SM, Butler PC. Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras(G12D) mouse model. *Diabetes* 2012; 61:1250-62. [PMID: 22266668]

13. Franks AS, Lee PH, George CM. Pancreatitis: a potential complication of liraglutide? *Ann Pharmacother* 2012; 46:1547–53. [PMID: 23136352]
 14. Jensen TM, Saha K, Steinberg WM. Is there a link between liraglutide and pancreatitis? A post hoc review of pooled and patient-level data from completed liraglutide type 2 diabetes clinical trials. *Diabetes Care* 2015; 38:1058–66. [PMID: 25504028]
 15. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med* 2015; 373:11–22. [PMID: 26132939]
 16. Faillie JL, Babai S, Crépin S, Bres V, Laroche ML, Le Louet H, et al. Pancreatitis associated with the use of GLP-1 analogs and DPP-4 inhibitors: a case/non-case study from the French Pharmacovigilance Database. *Acta Diabetol* 2014; 51:491–7. [PMID: 24352344]
 17. Steinberg WM, Buse JB, Ghorbani MLM, Ørsted DD, Nauck MA, LEADER Steering Committee, et al. Amylase, Lipase, and Acute Pancreatitis in People With Type 2 Diabetes Treated With Liraglutide: Results From the LEADER Randomized Trial. *Diabetes Care* 2017; 40:966–72. [PMID: 28476871]
 18. Funch D, Gydesen H, Tornøe K, Major-Pedersen A, Chan KA. A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. *Diabetes Obes Metab* 2014; 16:273–5. [PMID: 24199745]
 19. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30:239–45. [PMID: 7249508]
-