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Liraglutide overdose: A case report and an updated review

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Abstract:

Little is known about liraglutide overdose and in particular its association with hypoglycemia. The aim of this study was to report on an accidental case of liraglutide overdose and to review similar cases in the literature. Here, we report a case of a young female presented with an accidental injection of 18 mg of liraglutide subcutaneously. She presented with relative hypoglycemia with gastrointestinal symptoms that resembled pancreatitis. We concluded with several implications and policies targeting accidental injections from the use of such medication and similar subcutaneous medications in clinical practice.

Keywords:

Liraglutide hypoglycemia, liraglutide overdose, liraglutide toxicity

Introduction

Liraglutide, a long-acting glucagon-like peptide (GLP)-1 analog, is an efficient medication for weight reduction and glycemic control. It increases satiety, delays gastric emptying, and enhances insulin secretions of beta cells.^[1,2] An overdose of such medication may result in hypoglycemia. However, liraglutide overdose and its association with hypoglycemia need further elucidation.

Given this background, the present research aimed to report on an accidental case of liraglutide overdose and review the clinical features of such overdose cases from the literature.

Case Report

A 28-year-old female presented to the emergency department (ED) with an accidental injection of liraglutide 18 mg subcutaneously (18 mg/3 ml of pen

injection SAXENDA). She shortly developed epigastric abdominal pain radiating to her back that was associated with nausea, vomiting, and sweating.

Her medical history revealed diabetes mellitus type II in addition to obesity (weight: 109 kg with a body mass index of 40.5 kg/m²). The patient was prescribed metformin 500 mg twice daily, in addition to a daily tablet of multivitamin.

Her vital signs were all within normal, and her blood glucose on arrival was 4.6 mmol/L. Physical examination of the patient revealed normal conscious level with a soft and lax abdomen, and there was no focal tenderness. Venous blood gas revealed normal pH (7.40), PCO₂ of 42 mmHg, normal HCO₃ of 25.2 mEq/L, and normal lactate of 0.6 mmol/L. She showed mild hypokalemia at 3.2 mmol/L, which was due to her vomiting. The rest of the electrolyte and renal panels was within normal. Her pancreatic panel revealed a normal lipase and amylase level as well as her C-peptide level.

The patient was kept under observation for 16 h to monitor her hourly blood glucose

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levels. However, during this phase, the patient suffered from epigastric abdominal pain and persistent vomiting. She received three boluses of dextrose D50% (50 ml) and dextrose 5% and 10% infusion during her stay. Figure 1 illustrates the serum glucose level in relation to dextrose injections during the interval of ED stay. After the observation period with serial glucose, the patient became asymptomatic, her abdominal pain improved, and blood glucose levels were normal at 7.8 mmol/L.

After 15 months, the patient was found to be in good health. She did not continue liraglutide and did not further encounter episodes of hypoglycemia or pancreatitis.

Discussion

The association between liraglutide and hypoglycemia should be considered with respect to side effect and overdose. The side effect point of view, hypoglycemia has been reported for regular daily dose of 3 mg liraglutide.^[3] Those who developed hypoglycemia had a history of overweight/obesity and diabetes mellitus type II. Although confounded by the use of sulfonylurea or insulin, such hypoglycemia incidences were found to be augmented but not mutually exclusive.

On the other hand, patients with liraglutide overdose presented with persistent nausea, vomiting, and diaphoresis in addition to a slight decrease in their blood glucose level.^[4-8] Such presentation resembles hypoglycemia and may trigger the clinician to attempt to treat as such. This temptation is justifiable due to the paucity of information on the overdose of such medication and the fact that such drug is categorized as an antidiabetic medication. However, this raises a question of whether liraglutide-overdosed patients require dextrose infusion for the slight decrease in their serum glucose or whether their serum glucose reflects starvation from persistent vomiting, given that

this drug causes weight reduction in obese diabetic patients. In our patient, we did not start the dextrose infusion until 7 h from the overdose onset and 3 from the gastrointestinal symptoms. The patient glucose was slightly low (4.6 mmol/L); however, the glucose level was numerically stable from the time of injections to the decision of dextrose supplementation. The patient received the first bolus of dextrose 50% after 2½ h from the onset of symptoms, as noted in Figure 1.

It is worth mentioning that, despite the infusion of dextrose 5%, dextrose 10%, and even boluses of dextrose 50%, her gastrointestinal symptoms persisted and her blood glucose did not increase dramatically nor did it fall to lower limits. In agreement, another report revealed that one patient, following an overdose of 18 mg, had blood glucose level of 3.6 mmol/L, and yet, the patient recovered with supportive measures without dextrose supplementation.^[6] This indicates that liraglutide overdose causes relative hypoglycemia, secondary to prolonged and persistent vomiting, and the lack of food intake within such period, rather than their insulin secretogenic properties.

We reviewed all the English-written articles about liraglutide overdose, illustrated in Table 1. The incidence of hypoglycemia in those with liraglutide overdose is 50% ($n = 4$). Only two of four patients required dextrose infusion^[8] and two of the four patients were nondiabetic.^[7,8]

Among those two, the patient who did not require dextrose received glucagon and did have a prior pancreatic insufficiency.^[7] Furthermore, the variability in the amount overdosed from as little as 3 mg^[9] to as high as 72 mg^[5] without hypoglycemia further opposes the notion that liraglutide overdose is the cause of such hypoglycemia from a dose-response point of view and that other factors may have been implicated.

The occurrence of hypoglycemia in nondiabetic patients can be explained by the normal physiological expression of GLP-1 receptors, in contrast to those who were diabetic with similar but fewer receptors.^[8-11]

Moreover, because pancreatic beta cells have an abundant GLP-1 receptor, pancreatic insufficiency may be a protective factor against hypoglycemia as noted in one patient.^[7,12]

We infer that liraglutide causes hypoglycemia secondary to the full activation of GLP-1 receptors when those receptors were normally expressed. This, in part, explains hypoglycemia as a side effect and in overdose cases without diabetes. Besides, whether those receptors were downregulated or simply fewer than it should,

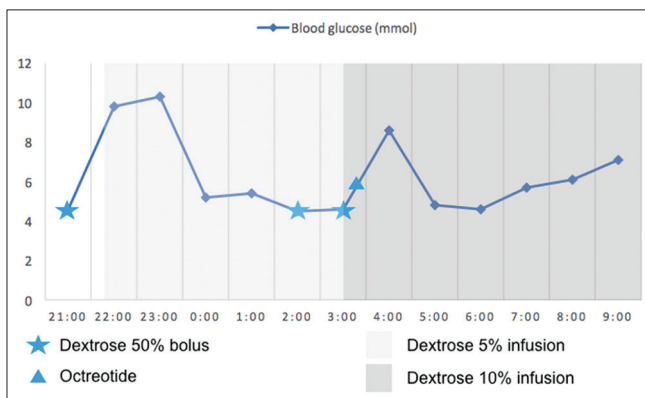


Figure 1: Illustrate the serum glucose level in relation to dextrose injections during the interval of emergency department stay

Table 1: Summary of the reported liraglutide overdose

Study	Dose (mg)	Interval	Hypoglycemia mmol/L	Needed dextrose intervention	Past history of DM II	Accidental/ suicide
Bode <i>et al.</i> (2013)	18	Over 7 months	No	No	Yes	Accidental
NovoNordisk A/S (2010)	17.4	Once	No	No	Yes	-*
Nakanishi <i>et al.</i> (2013)	72	Once	No	No	Yes	Suicide
Elmehdawi <i>et al.</i> (2014)	18	Once	Yes (3.6)	No	Yes	Accidental
Bowler <i>et al.</i> (2014)	36	Once	Yes (5.6)	No	No	Suicide
Solverson <i>et al.</i> (2018)	36	Once	Yes (1.3)	Yes	No	Suicide
Rotella and Wong (2019)	3	Once	No	No	No	Accidental
Our patient	18	Once	Yes (4.6)	Yes	Yes	Accidental

*The mode of injection was not reported.^[10] DM=Diabetes mellitus

as in those with pancreatic insufficiency or those with diabetes, were protective against hypoglycemia from overdose.

Thus, patients with an overdose from liraglutide without an underlying diabetes tend to manifest profound hypoglycemia that mandates treatment. Knowing that such medication is prescribed for diabetic patients, hypoglycemia from accidental injections tends to be mild and improves with only supportive care, mitigating dextrose infusion side effects from extravasation to overwhelming the overused pancreas.

Another important manifestation of liraglutide overdose includes gastrointestinal symptoms similar to the manifestation of pancreatitis. Beyond the previous notion, those symptoms were reported among overdosed and as a side effect.^[4-8,13] Indeed, the association of liraglutide with subclinical pancreatitis has been reported,^[12-14] but not with an overdose.^[15] None of the reported overdose cases had pancreatitis during their acute illness and during their follow-up, as did our patient. Such gastrointestinal symptoms resolve with supportive care, including hydration and antiemetics and electrolyte monitoring.

The role of octreotide in liraglutide overdose remains unclear despite their theoretical effect of targeting insulin secretion similar to sulfonylurea toxicity. Neither symptom improvement nor dextrose level changed in our patient despite the supplementation of octreotide, as shown in Figure 1. Likewise, octreotide did not affect the gastrointestinal manifestation in one patient and did not prevent the second hypoglycemic attack.^[8]

Little is published on the use of glucagon in such toxicity, despite liraglutide suppression of elevated glucagon secretion.^[2] Such suppression needs further evaluation in overdose.

Conclusions

There are several implications that mandate attention. The number of accidental injections was 57.1% ($n = 4$) in all the reported cases. This is due to the unfamiliarity

with the medication route of delivery as reported by our patient, especially to self-administer for the first time.

We urge clinicians prescribing liraglutide to have the first dose administered by the patient in their clinic either under their supervision or that of a health-care provider. Such practical education will overcome communication and transcription errors and will overcome age, educational, language, and social barriers that may prohibit the patients or their watcher from asking further questions. To solidify such recommendation, pharmacist dispensing the drug should be the gatekeeper ensuring such conduct.

We also advocate subcutaneous medications not to be dispensed over-the-counter, especially for first-time users. We believe that such restrictions should be applied to all subcutaneously administered drugs. Overall, the patient's right for practical education and state restrictions on over-the-counter drugs should indeed be a part of the patient's sovereignty over their health.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Author contribution statement

We verify and confirm that each author contributed to every stage of this manuscript equally.

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Conflicts of interest

The authors declare no conflict of interest.

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