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Case Report .

Liraglutide: Unusual Drug Reaction

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ABSTRACT

Liraglutide effectively improves glycemic control in individuals with type 2 diabetes, when used as monotherapy or in combination with one or more selected oral anti-diabetic drugs. 58 years old Egyptian male living in Makkah presented on follow up diabetes clinic with feeling unwell and nausea. He was diabetic since almost 10 years, morbidly obese, ex-smoker, IHD on treatment and post MI with 5 stents in right coronary. He was on glargine insulin 50 units/day and aspart insulin 50 units' t.i.d pre-meals. Also on Metformin XR 2250 mg/ day as well as sitagliptin 100 mg/ day and Lipitor 80 mg/day, ASA 81 mg/ day. Inspite of these combinations above his A_1C was 8.3%, which led us to add for him other medication which will help him to lose weight, adjust his A_1C, lower the insulin requirements and improve his CVD risk, putting in mind his history of CAD and the 5 stents he had in the right coronary. Therefore, it was decided to start him on Liraglutide injection. Drug induced-hepatotoxicity with raised liver enzymes due to liraglutide was suspected as this was the only new agent added to patient's treatment plan. We advised him to stop liraglutide immediately and to hold metformin and statin therapy till liver enzymes and creatinine back to normal levels. Liver enzymes and creatinine were back to normal levels after stoppage of liraglutide.

We report this case to raise the attention regarding the importance of having baseline pancreatic enzymes as amylase, liver enzymes and creatinine before starting patients on GLP-RA medication and on follow up visits.

Keywords: Liraglutide, Hepatotoxicity, Morbid Obesity, Drug Reaction.

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INTRODUCTION

Incretin hormones are two naturally occurring hormones that play a role in the maintenance of glycemic control: Glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide (GLP-1), both of which have a short half-life because of their rapid inactivation by dipeptidyl peptidase 4 (DPP-4).[1]

Incretin hormones are responsible for 50-70% of total insulin secretion after oral glucose load. GLP-1 has multiple physiological effects that make it an attractive candidate for type 2 diabetes therapy. It increases insulin secretion while inhibiting glucagon release, but only when glucose levels are elevated[2], thus offering the potential to lower plasma glucose while reducing the likelihood of hypoglycemia. Furthermore, gastric emptying is delayed[3] and food intake is decreased after GLP-1 administration.

Preclinical studies revealed other potential benefits of GLP-1 receptor agonist treatment in individuals with type 2 diabetes, which include the promotion of –b-cell proliferation[4] and reduced b-cell apoptosis.[5]

Liraglutide is a GLP-1 analog that shares 97% sequence identity to native GLP-1.[6,7] The addition of a C16 fatty acid side chain enables once-daily dosing of liraglutide by prolonging its duration of action to over 24 h. This protraction is achieved through reversible binding to albumin and increased stability through heptamer formation mediated by the fatty acid side chain.[6,7]

Data from the Liraglutide Effect and Action in Diabetes (LEAD) trials[8,9] have demonstrated that liraglutide effectively improves glycemic control (up to a 1.5% decrease in A_1C) in individuals with type 2 diabetes, when used as monotherapy or in combination with one or more selected oral anti-diabetic drugs. Results from this trial revealed that liraglutide provided significantly greater reduction in mean A_1C compared with exenatide (-1.12 vs. 0.79%; P, 0.0001).[10] As a result, greater proportion of patients with type 2 diabetes reached the ADA A_1C target (< 7.0%) with liraglutide compared with exenatide (54 vs. 43%;P = 0.0015).[10]

The effects on body weight were similar with both liraglutide and exenatide (23.24 vs. 22.87 kg, respectively), with a similar proportion of patients losing weight in both treatment groups (78% with liraglutide vs. 76% with exenatide).[10] In addition to their effects on glycemic control and body weight, the long-acting GLP-1 receptor agonists have been shown to reduce systolic blood pressure in patients with type 2 diabetes, ranging from - 4.7 mmHg after 15 weeks with exenatide LAR to- 6.7 mmHg after 26 weeks with liraglutide.[9]

Adverse effects of liraglutide have been reported mainly nausea, vomiting and diarrhea. However very rare side effects such as increased serum creatinine, acute renal failure, worsening chronic renal failure, hypersensitivity reactions (anaphylactic and angioedema), acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis have been reported in less than 1% of cases. In addition, hepatic and renal impairment have been reported very rarely.[11]

CASE REPORT

This is a 58 years old male Egyptian patient living in Makkah and he is diabetic since more than 10 years. His BMI is 51.59 kg/m^2. His blood pressure is 130/75, pulse rate is 90 beats/minute, , O_2 saturation is 96%. Patient was on glargine insulin 50 units/day and aspart insulin 50 units' t.i.d pre-meals. Also he was on Metformin XR 2250 mg/ day as well as sitagliptin 100 mg/ day and Lipitor 80 mg/day, Acetylsalicylic acid (ASA) 81 mg/ day.

Inspite of these combinations of therapy, his glycated haemoglobin level (A_1C) was 8.3%, which led us to add for him other medication which could help him to lose weight, adjust his A_1C, lower the insulin requirements and improve his cardiovascular disease (CVD) risk, putting in mind his history of CAD and the 5 stents he had in the right coronary.

After discussion of his case scenario, we decided to start him on Liraglutide injection.

We enlighten him about the possible adverse effects of the medication as well as the different suspicions and cautions around its use regarding pancreatitis, pancreatic cancer and medullary cell carcinoma. Family history of the later was negative.

Patient accepted to start on liraglutide knowing that he has to tolerate the unavoidable severe nausea at the start especially the first two weeks. His baseline amylase was 67u/l (N 25-115), aspartate transaminase (AST) was 18u/l (N 15-37), alanine transaminase (ALT) was 42 u/l (N 16-63), creatinine was 1mg/dl (N 0.6-1.3), blood urea nitrogen (BUN) was 13 mg/dl (N7-18), random blood glucose (RBS) was 245 mg/dl, low density lipoprotein (LDL) was 82 mg/dl, and Triglyceride was180 mg/dl.

For the first month after therapy, his blood glucose started to improve and he decreased his total insulin dose by 50 units and he was feeling much better.

In the second month, he attended to diabetic clinic for follow up and he was complaining of sense of feeling unwell and severe intolerable nausea but no abdominal pain.

Liver enzymes, creatinine and amylase were done for him as well as he was asked to decline the dose of liraglutide to 1.2 mg/day till having the result of the laboratory tests. He couldn`t tolerate the nausea and was advised to stop liraglutide till results come back. Results showed amylase of 81 u/l (N25-115), AST of 153u/l (N15-37), ALT of 250 u/l (N16-63), creatinine of 1.4 mg/dl (N0.6-1.3), BUN of 23 mg/dl (N7-18), random triglyceride of 562 mg/dl and RBS of 181mg/dl. He was advised to stop Liraglutide, metformin, statin and sitagliptin till the situation of raised liver enzymes and creatinine will be clarified.

Patient was admitted as query drug induced hepatitis in King faisal general hospital for observation. Patient was observed during admission for any signs of liver or renal function deterioration. He was nil per os (NPO) and on intravenous fluid (IVF).

His nausea improved after stopping the suspected agent progressively. Table 1 show that his liver and renal functions were returned to normal after two weeks of admission. Patient's general condition became better and he returns to his prior insulin dose. Now, patient is on regular follow up and planning to restart metformin and statin progressively increasing the dose. Also sitagliptin planned to be restarted.

Table 1: Hepatic and renal functions of the patient during two weeks of hospital admission.

Test	Day of hospital admission			
	1st Day of admission	2nd Day of admission	5th Day of admission	2 weeks later
AST	153	34	44	20
ALT	250	145		53
Creatinine	1.4	1.0	1.3	0.9
BUN	23	14	18	12

DISCUSSION

In the present case report, the patient's history and laboratory findings were suggestive of Liraglutide unusual hepatic as well as renal impairment.

Human studies assessing the effect of Liraglutide on the liver have been limited to rare case reports,[12,13] case series[14] and uncontrolled retrospective studies.[15] In light of these limited experiences, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) did not recommend not using of Liraglutide in patients with mild, moderate and sever liver injury. The efficacy and safety of this group of drugs in liver disease, therefore, remain unproven.[16]

A meta-analysis was performed to assess the safety and efficacy of liraglutide on liver parameters and proved that 26 weeks' treatment with liraglutide 1.8 mg/day is well tolerated, safe to use and even results in significant improvements in liver enzymes in patients with type 2 diabetes and asymptomatic liver impairment.[16] Additionally, it has been reported that the efficacy of 26-week liraglutide on liver enzymes is dependent on dosage of the drug and appears to be mediated by its effect on weight change and glycaemic control.[16] In the current case, elevated liver enzyme were observed after two months (~8 weeks) of treatment with liraglutide.

Liraglutide has not been found to be directly nephrotoxic either in animal studies or clinical trials, post-marketing reports of acute renal failure and worsening of chronic renal failure sometimes requiring dialysis have been observed. A majority of these reports occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.[17] In the present case, creatinine level has increased from 1 mg/dl at baseline to 1.4 mg/dl and BUN has raised from 13 mg/dl to 23 mg/dl after two months of initiating Liraglutide therapy. Moreover, these two parameters returned to their normal level after two weeks of stopping of Liraglutide

(0.9 and 12 mg/dl for creatinine and BUN, respectively). This could indicate renal impairment as a result of Liraglutide therapy.

Up to our knowledge, this patient presents the first reported case of hepatic and renal impairment associated with liraglutide. However, in the literature, we did not find a clear explanation for that.

In conclusion, we report this case to raise the attention regarding the importance of having baseline pancreatic enzymes as amylase, liver enzymes (AST and ALT), and renal parameters (creatinine and BUN) before starting patients on GLP-RA medication and on follow up visits for the possible impairment of these parameters as a result of Liraglutide therapy and having a better chance to stop therapy earlier.

We report this case to raise the attention of the hepatotoxicity of incretin analogue, a class effect with a long latency period.

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