Received: 2010.12.16
Accepted: 2011.02.18
Published: 2011.03.22

A patient with exenatide-associated acute-on-chronic renal failure requiring hemodialysis

Anastazia Kei, Evangelos Liberopoulos, Kostas Siamopoulos, Moses Elisaf

Department of Internal Medicine, University of Ioannina Medical School, Ioannina, Greece

Summary

Background: Exenatide is an adjunctive therapy for adults with type 2 diabetes. Rarely, exenatide has been associated with acute renal failure.

Case Report: A 66-year-old diabetic woman on exenatide was admitted to our hospital due to persistent nausea and vomiting. Her baseline serum creatinine was 1.4 mg/dL (107 μmol/L, estimated glomerular filtration rate 40 mL/min/1.73 m²). Laboratory tests revealed acute-on-chronic renal failure [serum creatinine 8.4 mg/dL (641 μmol/L)]. After 2 sessions of hemodialysis and aggressive hydration over the next 15 days, she was discharged. One month later, renal function returned to baseline level. This is the first published report for an exenatide-associated renal failure requiring hemodialysis.

Conclusions: Renal function deterioration may complicate exenatide treatment, especially in the presence of severe nausea and underlying chronic kidney disease.

key words: **exenatide • hemodialysis • nausea • renal failure**

Full-text PDF: http://www.cardiovascularcontinuum.eu/fulltxt.php?ICID=881605

Word count: 1232
Tables: 1
Figures: –
References: 12

Author's address: Evangelos N. Liberopoulos, Lecturer of Internal Medicine, University of Ioannina Medical School, 45 110 Ioannina, Greece, e-mail: vaglimp@yahoo.com

Background

Exenatide is a synthetic incretin analog approved by the FDA (US Food and Drug Administration) in April 2005 as adjunctive therapy for adults with type 2 diabetes mellitus [1]. Glucagon-like peptide 1 (GLP-1) is the endogenous human incretin hormone and exenatide via GLP-1 receptor activation enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion and slows gastric emptying [2,3]. Nausea and vomiting are the most common adverse events observed in about 20% of patients treated with exenatide [3,4]. Less frequently, exenatide has been associated with pancreatitis [5,6]. Furthermore, FDA has received 78 reports of altered kidney function in patients on exenatide.[7] Some cases occurred in patients with pre-existing kidney disease or with one or more risk factors for developing kidney dysfunction. However, in most of these cases the renal failure was mild without requiring hemodialysis [7]. The European Medicines Agency (EMEA) has also reported cases of exenatide-associated altered renal function, including increased serum creatinine, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis [6]. Reported herein is a case of a 66-year-old woman on exenatide who developed severe acute-on-chronic renal failure requiring hemodialysis.

Case Report

A 66-year-old Caucasian woman was admitted to our hospital due to anorexia, nausea and episodes of vomiting appearing 1 h after meal for the past 1 week. The patient also reported oliguria. She denied hematuria, fever, sorethroat or receiving any over-the-counter medication, including non steroid anti-inflammatory drugs. She was conscious and well orientated. Clinical examination revealed only mild tremor of upper limbs and diaphoresis.

The patient had been diagnosed with type 2 diabetes 15 years ago and had known diabetic retinopathy and nephropathy [baseline serum creatinine 1.4 mg/dL (107 µmol/L), Modification of Diet in Renal Disease estimated Glomerular Filtration Rate (MDRD eGFR) 40 mL/min/1.73 m^2) plus proteinuria (1.5 g total proteins/day)]. She had a body mass index (BMI) of 32 kg/m^2 and was on metformin (1000 mg bid), glimepiride (2 mg od) and exenatide (started with 5 µg bid and uptitrated to 10 µg bidm 6 months ago). She recalled that anorexia, mild nausea and subsequent weight loss (overall 10 kg) had started simultaneously with the onset of exenatide treatment. She had arterial hypertension and was on amlodipine (10 mg od), valsartan (160 mg od) and indapamide (1.5 mg od). Furthermore, she was treated with rosuvastatin (40 mg od) and clopidogrel (75 mg od). There had been no changes in her medication for the last 11 months.

On admission, biochemical analysis revealed elevated serum creatinine [8.4 mg/dL (641 µmol/L)] and blood urea nitrogen (BUN) [108 mg/dL (38.6 mmol/L)], hypoglycemia [plasma glucose 22 mg/dL (1.2 mmol/L)] plus mild hyperkalemia (K^+ 5.7 mmol/L), while the rest of the biochemical parameters were within normal range. Blood gas analysis revealed metabolic acidosis with increased anion gap [pH 7.18, HCO_3^- 8.3 mmol/L, pCO_2 23 mmHg, Na^+ 130 mmol/L, Cl^- 103 mmol/L, anion gap 19 mmol/L (reference values 5–16 mmol/L)] (Table 1). Urine analysis demonstrated highly concentrated urine (specific gravity 1.032, reference range 1.016–1.028) with low sodium concentration (Na^+ <10 mmol/L) but no casts. An abdominal ultrasound examination demonstrated fat deposition in the liver without other abnormalities.

All medications were discontinued and the patient was immediately treated with intravenous glucose, bicarbonate and normal saline. Normal glucose levels [122 mg/dL (6.8 mmol/L)] were reached 24 h after admission. However, serum creatinine went up to 9.2 mg/dL (702 µmol/L) despite aggressive hydration, leaving no choice but hemodialysis. After 2 sessions of hemodialysis her creatinine decreased to 5.2 mg/dL (397 µmol/L). No further hemodialysis was required and the patient continued receiving normal saline intravenously. Additionally, she was started on insulin. Serial biochemical values over this period showed normalization of the potassium value and a fall of creatinine and BUN (Table 1). Proteinuria remained at the baseline level (1.5 g/day) throughout the whole period of patient's hospitalization. At day 15 after admission, creatinine value went down to 2.9 mg/dL (221 µmol/L) and she was discharged. One month later creatinine value returned to baseline level [1.4 mg/dL (107 µmol/L)] (Table 1).

Discussion

To the best of our knowledge this is the first published case report of exenatide-associated severe acute-on-chronic renal failure requiring hemodialysis. Cases of 4 patients (3 male and 1 female) with exenatide-induced renal failure who presented with nausea and vomiting have been recently published.[8] All patients had type 2 diabetes mellitus with or without microalbuminuria plus hypertension and were on angiotensin converting enzyme (ACE) inhibitors and diuretics. In our case the raise of serum creatinine was very profound compared with the rest literature reports [9.2 *vs.* 2.9 mg/dL (702 *vs.* 221 µmol/L), respectively]. In contrast to our patient, none of the others required hospitalization or hemodialysis. The time between onset of exenatide therapy and diagnosis of renal failure ranged from 2 to 9 months, while in our case the renal failure occurred 12 months after exenatide commence and 6 months after dose uptitration [8].

Why did our patient experience this dramatic renal function deterioration? In general, patients with underlying chronic kidney disease are prone to develop acute-on-chronic renal failure due to nephrotoxic insult, compared with healthy subjects. Our patient already had chronic kidney disease (eGFR 40 ml/min/m^2 plus proteinuria). Moreover, as was previously referred, nausea and vomiting are very common exenatide's side effects [3]. Nausea led our patient to decreased fluid intake. Vomiting and concomitant use of indapamide caused a significant loss of fluids. Moreover, GLP-1 induce natriuresis and potentially decrease renal perfusion [9,10]. Exenatide as a GLP-1 receptor agonist may also share the same effect. Of note, exenatide has been associated with blood pressure decrease independently of weight loss [11]. Subsequently, the combination of reduced fluid intake and increased fluid loss caused volume contraction. Furthermore, valsartan by inhibiting the renin-angiotensin cascade and subsequently aldosterone formation deprived the patient from an important volume depletion homeostatic mechanism. These

Table 1. Patient's laboratory values.

	Reference range	Baseline	On admission	On 2nd day (after hemodialysis)	On discharge	1 month after discharge
Fasting glucose, mg/dL (mmol/L)	70–125 (3.9–6.9)	110 (6.1)	22 (1.2)	181 (10)	269 (14.9)	120 (6.7)
Creatinine, mg/dL (μmol/L)	0.6–1.2 (46–92)	1.4 (107)	8.4 (641)	5.2 (397)	2.9 (221)	1.4 (107)
BUN*, mg/dL (mmol/L)	6–27 (2.1–9.6)	30 (10.7)	108 (38.6)	52 (18.6)	50 (17.9)	32 (11.4)
K^+, mmol/L	3.5–5.3	4.5	5.7	3.8	3.6	3.9
pH	7.37–7.43	7.41	7.18	7.26	7.44	7.42
HCO^-_3, mmol/L	22–26	23	8.3	8.4	23	23

* BUN – blood urea nitrogen.

mechanisms, combined with a background of diabetic nephropathy led to such profound acute renal failure. Another mechanism is that uremia per se is associated with nausea, thus resulting in a vicious circle that led to further renal function deterioration [12]. Other contributory risk factors for altered kidney function, such as cardiac insufficiency, pancreatitis, rhabdomyolysis, urinary tract infection, postinfectious glomerulonephritis and IgA nephritis were excluded based on patient's medical history, clinical appearance and laboratory results even though, no renal biopsy was performed. Moreover, the possibility of metformin-associated lactic acidosis was ruled out due to the low levels of plasma lactate (2 mmol/L, normal values 0.7–2.1 mmol/L). Of note, a renal biopsy performed in a patient with exenatide-associated acute renal failure revealed ischemic glomeruli with moderate to severe interstitial fibrosis, tubular atrophy and early diabetic nephropathy [8]. These findings are consistent with the hypothesis that exenatide caused prerenal acute failure and is not associated with direct toxic impact on kidneys [8].

Conclusively, before subscribing or increasing the dose of exenatide baseline renal function and concomitant medication (especially diuretics and renin-angiotensin cascade inhibitors) should always be taken under consideration. Moreover, patients should be well informed in order to distinguish the usual exenatide-induced anorexia and nausea from the cases when these symptoms are becoming harmfully intense. Finally, patients who develop severe nausea and vomiting need renal function assessment.

Acknowledgements

This case report was written independently; no company or institution supported it financially. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies.

References:

1. Exenatide (marketed as Byetta) Information. Available from: *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm113705.htm.* Last assessed 5 Feb, 2011
2. Zinman B, Hoogwerf BJ, Duran Garcia S et al: The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med, 2007; 146: 477–85
3. Robles GI, Singh-Franco D: A review of exenatide as adjunctive therapy in patients with type 2 diabetes. Drug Des Devel Ther, 2009; 3: 219–40
4. EMEA Byetta *http://www.ema.europa.eu/humandocs/PDFs/EPAR/byetta/H-698-en6.pdf.* Last assessed 5 Feb, 2011
5. Byetta; official FDA information. Available from: *http://www.drugs.com/pro/byetta.html.* Last assessed 5 Feb, 2011
6. Byetta (exenatide)-renal failure. Available from: *http://www.ema.europa.eu/humandocs/PDFs/EPAR/byetta/H-698-en8b.pdf.* Last assesed 5 Feb, 2011
7. Byetta (exenatide)-renal failure. Available from: *http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm188703.htm.* Last assessed 5 Feb, 2011
8. Weise WJ, Sivanandy MS, Block CA et al: Exenatide-associated ischemic renal failure. Diabetes Care, 2009; 32: 22–23
9. Gutzwiller JP, Tschopp S, Bock A et al: Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. J Clin Endocrinol Metab, 2004; 89: 3055–61
10. Gutzwiller JP, Hruz P, Huber AR et al: Glucagon-like peptide-1 is involved in sodium and water homeostasis in humans. Digestion, 2006; 73: 142–50
11. Okerson T, Chilton RJ: The cardiovascular effects of GLP-1 receptor agonists. Cardiovasc Ther 2010; doi: 10.1111/j.1755-5922.2010.00256 [Epub ahead of print]
12. Kang JY: The gastrointestinal tract in uremia. Dig Dis Sci, 1993; 38: 257–68