CASE REPORT

EXENATIDE INDUCED ACUTE KIDNEY INJURY

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Exenatide is an incretin mimetic. It was approved by the federal drug authority in 2005 for the treatment of type-2 diabetes. Since it is a relatively new medicine clinicians have limited experience with regards to its side effects and safety profile. We report a 47 year old lady who presented with exenatide associated acute kidney injury. She had type-2 diabetes for 10 years with mild micro albuminuria and normal renal functions. She was also taking a stable dose of metformin, gliclazide, angiotensin converting enzyme inhibitor and diuretic for over a year and there was no history of any recent use of non-steroid anti-inflammatory medications. One week after starting exenatide, she developed severe vomiting, followed by hypotension. She presented with acute renal insufficiency and severe lactic acidosis and had to be dialyzed on emergency basis. To our knowledge this is probably the first case reported in the local United Arab Emirate (U.A.E) population.

Keywords: Exenatide, renal failure, incretin mimetics, complication

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INTRODUCTION

Exenatide is gaining increasing popularity in managing uncontrolled type-2 Diabetes. Clinicians should be well aware of the fact that exenatide should be used with caution not only in patients with renal insufficiency but also in patients with normal renal functions.

Exenatide is gaining popularity in diabetics who are mostly at a risk of Reno-vascular disease. These patients are frequently using a combination of potentially nephrotoxic drugs namely metformin, angiotensin converting enzyme inhibitors and diuretics. Since nausea, vomiting and gastro intestinal upset are a frequent side effect of this medicine, so patients who are on the above combinations should have frequent monitoring of their renal functions and the dose of the drug should be reduced or stopped before development of overt kidney injury. More over in my opinion a review of the drug specific information leaflets should be done with special emphasis on its renal side effects in order to increase the physicians and patients awareness of its renal side effects.

CASE REPORT

We report a case of 47 year old Emirati lady who was known diabetic since past 10 years. She had been taking maximum dose of gliclazide, i.e., 120mg once daily, metformin 850mg twice daily and was started on exenatide 5mcg subcutaneously twice daily since her blood sugars were not under control. Her lab parameters prior to starting exenatide therapy: Urea 12mg/dl, Creatinine 0.7mg/dl, HBA1C 7.8%, Urine micro albuminuria 31.5 mg/24 hours (<30mg/24 hours).

After three injections she started having symptoms of intolerance to the medicine in form of nausea, vomiting and poor appetite. Patient continued to take the medicine since she had been counselled about the side effects of this injection and thought that these symptoms would disappear with time. After taking 12 injections the symptoms became worse and she had copious vomiting (12/13 episodes per day, loss of appetite and presented to the emergency of our hospital :

On examination she was dehydrated, tachycardiac, blood pressure was initially maintained (110/60), she was afebrile and maintaining saturations on room air. Systemic examination was unremarkable.

Laboratory parameters confirmed the diagnosis of acute renal failure. (serum sodium 132mmol/l, potassium 4.6mmol/l, bicarbonate 12mmol/l, urea 124mg/dl, Creatinine 6.6mg/dl, serum lactate 15.1 mmol/l), serum amylase 640U/L septic screen was negative, Urine analysis was normal. Blood culture and urine cultures revealed no growth. Chest x ray was unremarkable.

After admission (i.e., in the next 8 hours she became hypotensive, developed low urine output, and acidotic breathing. Her repeat laboratory work up revealed worsening of acute renal failure and acidosis (Urea 172 mg/dl, Creatinine 8.1 mg/dl, Arterial blood gases(on 4l oxygen):PH 6.795, PCO2 12.6, PO2 130,Bicarbonate 1.8mmol/l).

An urgent nephrology opinion was sought. She was shifted to intensive care unit and an emergency dialysis was done and the offending anti diabetic medications was removed. She was given bicarbonate infusion (@10-20mmol/hour), intravenous fluids and iniotropic support. After one session of dialysis her urine output started improving, her laboratory parameters over successive days progressively improved.

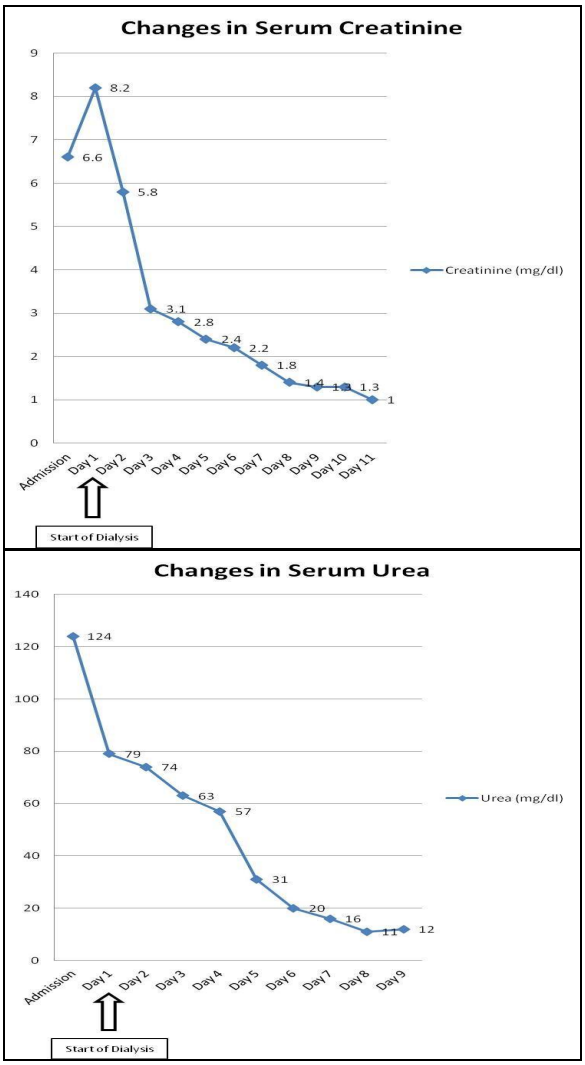

Figure 1 a): Serum urea and Creatinine

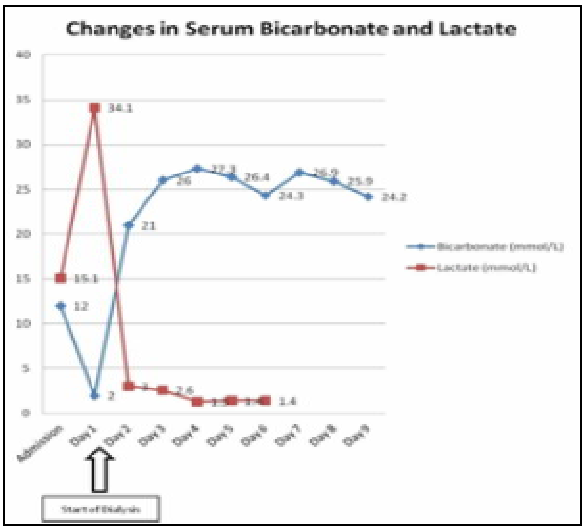

Figure-1 b): Serum Bicarbonate and lactate pre and post-dialysis

Her renal functions started to stabilize after dialysis; hence she was shifted to the general medical ward and subsequently discharged on insulin lispro and glargine

DISCUSSION

Glucagon like peptide 1 (GLP-1) is produced in intestinal L-type cells and released into the bloodstream in response to ingested food**.** Exendin-4 (GLP-1 analogue) was initially isolated from the salivary glands of the Gila monster (Heloderma suspectum), a poisonous lizard which is inhabitant of the deserts of Arizona and it is currently registered as the anti-diabetic agent named exenatide.

Exenatide is a synthetic peptide. It is known to stimulate insulin release, inhibit glucagon secretion and it delays gastric emptying. It can be used with metformin alone or in combination with sulfonylurea urea and metformin to achieve normo glycemia in type-2 diabetics. It causes weight loss and enhances recovery of beta cell function. Nausea and vomiting are one of the most common side effects (as we see in this patient), but in most of the patients it dis appears with time.[1] However in as many as 14% patients it may lead to discontinuation of the medicine.[1] These side effects are reported to disappear if the dose of the drug is significantly reduced or stopped.[2]

According to United States food and Drug Administration (FDA) statistics, from April 2005 to October 2008, 78 cases of altered kidney functions have been reported (62 cases of acute renal failure and 16 cases of renal insufficiency), in patients using Byetta (exenatide).[3] Some of the cases have occurred in patients with pre-existing kidney disease or in patients with one or more risk factors for developing renal disease.[4] New cases have also been reported in 2009.[2] The patient we have presented was moderately obese (BMI 36), type-2 diabetic, with hypertension, who had mild to moderate micro albuminuria and stable renal functions. There were no classical signs or symptoms suggestive of acute pancreatitis. Although the mild to moderate raise in serum amylase can be attributed to acute kidney injury, however a bout of mild self-limiting pancreatitis cannot be excluded completely.

In the background of a high risk reno-vascular profile, it has been reported that renal insufficiency usually takes about 2–9 months to develop after starting exenatide therapy.[2] However, our patient came with symptoms of acute kidney injury within one week of starting exenatide therapy rather than months.

It is seen that renal insufficiency responds to a dose reduction of the medicine while others require a cessation of the offending drug. However there is no evidence that exenatide is directly nephrotoxic.[2] It

causes nausea, vomiting and extra cellular volume contraction. When combined with diuretic and angiotensin converting enzyme inhibitors (Ace -1) or angiotensin receptor blockers (ARB) it leads to an exaggerated decline in renal functions[4] and glomerular filtration rate. Hypovolemia and volume contraction may lead to ischemic renal failure.[5]

However if there is deterioration in renal functions in the absence of other causes of acute kidney injury such as dehydration and hypotension then acute tubule interstitial nephrites should be suspected in patients.[6] In such case a biopsy would be required before starting steroid which may reveal extensive tubule interstitial damage and fibrosis, together with tubular atrophy.[2] This particular patient we are reporting had acute renal failure in the back ground of normal renal functions, overt diabetic nephropathy could be excluded because of normal urine analysis and absence of urine sediments. Since renal functions normalized after dialysis, the renal biopsy was not recommended by the nephrologist.

Glucagon like peptide (GLP1) analogues cause natriuresis and decrease renal perfusion in normal healthy subjects and obese men with insulin resistance (25% of whom are diabetics).[7] This effect is also shared by exenatide. This diuretic effect can be delirious in the setting of dehydration and volume depletion.

United States food and drug Administration (FDA) recommendations for patients who are started on Byetta (exenatide) are.[3]

1. It is not recommended in patients with severe renal impairment (creatinine clearance <30 ml/min) or end-stage renal disease.
2. In patient with moderate renal impairment (i.e., creatinine clearance between 30-50 ml/min caution should be exercised when initiating or increasing doses of Byetta (exenatide) from 5–10 mcg.
3. It is recommended that health care professionals should monitor patients carefully for the development of renal dysfunction and re-evaluate the need for Byetta (exenatide) if kidney dysfunction is suspected while the patient is using this product.

Our patient had severe lactic acidosis at presentation, in the setting of absence of infection. The cause of raised lactic acid is multi factorial; this could be explained by metformin, and later on in the course of the illness by volume depletion and hypotension. Exenatide itself is known to decrease proton excretion and hence causes acidosis. Reports suggest that the incidence of metformin induced lactic acidosis with normal renal functions is 0.05/1000 patient years.[8] Severe dehydration complicated by acute renal injury, sepsis, alcoholism or hypoxia can contribute to life threatening lactic acidosis.

It has been previously reported that food and water intake were diminished with continuous glucagon like peptide infusion in patients suffering from type 2 diabetes mellitus[9] which may be one of the reasons for causing dehydration and volume depletion in our patient. Exenetide also causes a 6% decrease in glomerular filtration rate.[9]

Gut incretins in addition to insulin tropic actions cause natriuresis which is accompanied by diminished proton excretion from the kidneys. They cause a dose dependent increase in urinary sodium excretion and a decrease in urinary hydrogen excretion. This is also accompanied by an increase in urinary calcium and chloride excretion It is also known to have a direct effect on the Na+/H+ exchange pump at the proximal tubule.[9] These effects are mediated by binding with the plasma membrane receptor of the G protein-coupled receptor family (GLP-1R). This receptor is expressed not only in the pancreatic -cell but also in the brain, the kidneys, the lungs, the pituitary gland, the heart, the stomach, the small intestine, and major blood vessels.[10]

In summary it is seen that Glucagon like peptides exert a variety of biological actions which till to date are not very well understood.

CONCLUSION

A dose adjustment is needed according to the pharmacokinetics and tolerability, and renal functions.

Hence, patients on exenatide only or exenatide together with other anti-diabetic medications namely metformin should have meticulous monitoring of their renal function test.

REFERENCES

1. Zinman B, Hoogwerf BJ, Durán García S, Milton DR, Giaconia JM, Kim DD, *et al*. The effect of adding exenatide to a thiazolidinedione in sub optimally controlled type 2 diabetes: a randomized trial. Ann Intern Med.2007; 146:477–85.
2. Weise WJ, Sivanandy MS, Block CA, Comi RJ. Exenatide associated ischemic renal failure. Diabetes Care. 2009;32:22–3.
3. Food and Drug Administration. Safety Alerts for Human Medical Products [updated 2010 Feb5;].Available from www.fda.gov/Safety/MedWatch/Safety Information/Safety AlertsforHumanMedicalProducts/ucm188703.htm
4. Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med.2007;357:797–805.
5. Lopez-Riuz A, del Peso-Gilsanz C, Meoro-Aviles A, Soriano-Palao J, Andreu A, Cabezuelo J,et al.Acute renal failure when exenatide is co-administered with diuretics and angiotensin ii blockers. Pharm World Sci 2010;32(5):559–61
6. Nandakoban H, Furlong TJ, Flack JR. Acute tubulointerstitial nephritis following treatment with exenatide. Diabet Med 2013;30(1):123–5.

7. Gutzwiller JP, Tschopp S, Bock A, Zehnder CE, Huber AR, Kreyenbuehl M, *et al* .Glucagon-Like Peptide 1 Induces Natriuresis in Healthy Subjects and in Insulin-Resistant Obese Men JCEM .2004;89:3055–61
8. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis.Arch Intern Med 2003,163:2594–02
9. Gutzwiller JP, Drewe J, Göke B, Schmidt H, Rohrer B, Lareida J, *et al.* Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol 1999;276:1541–4.
10. Johansen OE, Whitfield R. Exenatide may aggravate moderate diabetic renal impairment: a case report. Br J Clin Pharmacol 2008;66:568–9.

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