

CASE REPORT

Is it safe to acutely discontinue insulin therapy in patients with chronic hyperglycaemia starting GLP-1R agonists?

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Accepted 30 May 2017

SUMMARY

We report two patients with chronic hyperglycaemia secondary to type 2 diabetes who developed severe vomiting on d. The first patient was diagnosed with a mixed picture of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) and the second, with DKA. They were on insulin therapy which was discontinued on commencing d because of inefficacy and weight gain. The HHS patient developed dehydration secondary to vomiting and had lactic acidosis but no other precipitant could be found in either case. It appears that the abrupt insulin discontinuation coupled with vomiting and dehydration led to the metabolic derangements. Subsequent C-peptide levels were found to be low in both patients. In view of the predisposition of patients with chronic hyperglycaemia to glucagon-like peptide 1 receptor (GLP-1R) downregulation and the lag time to optimal efficacy of GLP-1R agonists, we propose that patients should have C-peptide levels measured to determine the risk of ketosis and whether insulin should be continued with dose adjustments when starting a GLP-1R agonist.

BACKGROUND

The effects of glucagon-like peptide 1 receptor (GLP-1R) agonist therapy on glycosylated haemoglobin HbA1c (HbA1c) reduction, weight loss and hyperglycaemia are well documented^{1–3} and there has been much in the literature about the risks of pancreatitis, pancreatic and thyroid malignancies.^{1,2,4} The licensing as a second-line, or subsequent agent after metformin is entirely supported by the literature.¹ However, the typical patients for these agents are those experiencing chronic hyperglycaemia with higher body mass index (BMI). These are the subgroup of the diabetic population that are more likely to be GLP-1R resistant and currently there is no test for this resistance developed for use in routine clinical practice. In the event of resistance, the GLP-1R agonist will not be optimally effective and will have a significant delay to efficacy. This potentially puts patients at risk of hyperglycaemia which is more pronounced if another glucose-lowering agent such as insulin is withdrawn in order to allow introduction of the GLP-1R agonist. This is an especially vulnerable period for those with ketosis-prone type 2 diabetes who are difficult to identify prior to any such manipulation of medication. Should we therefore

wean such individuals off insulin or other hypoglycaemics to allow for the lag time to efficacy of the GLP-1R agonist or should we test for GLP-1R resistance prior to commencing these agents or should we at least give ketone metres to these individuals and be vigilant for this problem?

CASE PRESENTATION

The two patients referenced in this report share a very similar profile (table 1) and both presented with a 2-day history of polyuria, polydipsia, nausea, vomiting, poor oral intake and fatigue. A day before their symptoms started, they had received their first dose of dulaglutide (1.5 mg) subcutaneously and on the same day, their insulin was discontinued. They had both been on insulin for a minimum of 5 years.

Case 1 is about a female aged 66 years with a BMI of 29.1 kg/m² and a 13-year history of type 2 diabetes, which had progressively become more difficult to control on several antihyperglycaemic agents. Her most recent HbA1c was 95.6 mmol/mol. Prior to commencing dulaglutide, she was on metformin 850 mg three times a day and Humulin M3, 25 units in the morning and 20 units in the evening. She had been trialled on liraglutide 0.6 mg 2 years prior, and apart from the beneficial effect of weight loss, her blood glucose readings remained erratic and at that time she was maintained on insulin as well as liraglutide. The latter was stopped 2 years before this presentation. On admission to the emergency department, she had a Glasgow Coma Scale (GCS) of 15/15, was severely dehydrated clinically and her blood pressure was 82/43 mm Hg with a pulse of 112 beats/min. Her temperature was 34.6°C and oxygen saturation was 100% on room air. The rest of her clinical examination was unremarkable. Her medical history included systemic hypertension, chronic kidney disease and hypercholesterolaemia and apart from metformin and dulaglutide, she was also on treatment with candesartan, bisoprolol, doxazosin, lercanidipine, atorvastatin, aspirin and esomeprazole.

Case two is about a male aged 74 years with a BMI of 34.5 kg/m² and an 11-year history of type 2 diabetes. He also had a long history of very difficult to control glycaemia and his most recent HbA1c was 88 mmol/mol. He had also been on metformin 500 mg two times a day and Humulin M3 18 units in the morning and 10 units in the evening, prior



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To cite: Okiro JO, Mc Hugh C, Abdalla A. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220437

Table 1 Case characteristics

Characteristics	Case 1	Case 2
Age (years)	66	74
Gender	Female	Male
Years since diagnosis of diabetes	13	11
Haemoglobin A1c (<42 mmol/mol)	95.6	88
Body mass index (kg/m ²)	29.1	34.5
Comorbidities	Hypertension, hypercholesterolaemia, chronic kidney disease	Hypertension, hypercholesterolaemia
Current diabetic treatment	Metformin Discontinued Humulin M3 and commenced on 3 days prior to presentation	Metformin Discontinued Humulin M3 and commenced on d 3 days prior to presentation
Presenting symptoms	Nausea, vomiting, poor oral intake, fatigue, polyuria, polydipsia	Nausea, vomiting, poor oral intake, heart burn, fatigue, polyuria, polydipsia

to commencing dulaglutide. He had been trialed on linagliptin in the past with poor response. On presentation to the acute assessment unit, he was lethargic with a GCS of 15/15. His vital parameters were within normal limits as was his clinical examination.

He had a history of systemic hypertension and hypercholesterolaemia and apart from metformin and dulaglutide he was also on treatment with telmisartan, hydrochlorothiazide, bisoprolol, doxazocin, ezetimibe and aspirin.

Both patients had never had diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS).

Table 2 Investigations

Parameters and normal values	Case 1	Case 2
Creatinine (<84, <104 µmol/L)	233	85
Urea (2.8–7.2 mmol/L)	24.6	6.2
Sodium (133–145 mmol/L)	126	138
Sodium adjusted for hyperglycaemia	143.1	144.5
Potassium (3.3–5.1 mmol/L)	6.2	4.2
eGFR >90 mL/min/1.73 m ²	20	82
pH (7.35–7.45)	6.99	7.27
HCO ₃ (23–27 mmol/L)	4.2	14.3
Lactate (<1.4 mmol/L)	5.7	1.9
Glucose (4.6–6.4 mmol/L)	65	28
Ketones (<0.6 mmol/L)	5.6	7.7
Osmolality (285–295 mOsm/kg)	350	318
Anion gap (3–10 mEq/L)	47.8	32.7
HbA1c mmol/mol	95.6	88
CRP (<5 mg/L)	10	3
WCC (4–11 × 10 ⁹ /L)	26	11.15
Urine culture	No growth	No growth
Blood culture	No growth	No growth
CXR	No abnormality detected	No abnormality detected
Serial troponin <14	43/141/215/88 (over a 2-day period)	17

CRP, C reactive protein; CXR, chest X-ray; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; WCC, white cell count.

INVESTIGATIONS

Please see table 2 for ease of reading and our laboratory reference ranges.

Case 1 had a blood glucose of 65 mmol/L and a serum osmolality of 350 mOsm/kg. Her blood ketone level was 5.6 mmol/L, serum lactate was 5.7 and her pH was 6.99. She had an acute-on-chronic kidney injury with a creatinine of 233 µmol/L and a urea of 24.6 mmol/L, values of which were significantly off her baseline (creatinine of 92 and urea of 8.0 2 weeks prior). Her serum sodium appeared low at 126 mmol/L but when corrected for her hyperglycaemia it was normal at 143.1 mmol/L. She had a leucocytosis of 26 × 10⁹/L with an elevated neutrophil count of 22.14 × 10⁹/L, but her C reactive protein (CRP) was only mildly elevated at 10 mg/L. Septic screen was undertaken including a chest X-ray, urine and blood culture all of which were normal. A high-sensitivity troponin was initially 43 ng/L (please see table 2) and her ECG was normal. Subsequent coronary angiogram was normal.

For case 2, blood glucose was 28 mmol/L with a blood ketone of 7.7 mmol/L and a serum osmolality of 318 mOsm/kg. His renal profile was normal as were his complete blood count and septic screen. A high-sensitivity troponin was elevated to 17 ng/L but an ECG was normal.

DIFFERENTIAL DIAGNOSIS

The presentation and blood indices of case 1 met the Joint British Diabetes Societies Inpatient Care Group definition of HHS with a mixed picture of DKA⁵ (blood glucose 65 mmol/L, blood ketones 5.6 mmol/L, serum osmolality 350 mOsm/kg and HCO₃ 4.2 mmol/L) and case 2, DKA (blood glucose 28 mmol/L, blood ketones 7.7 mmol/L, serum osmolality 318 mOsm/kg and HCO₃ 14.3 mmol/L).⁶ While the diagnosis were self-evident, the precipitating factors were less so. A source of sepsis was not identified clinically, biochemically or radiologically in either case. In case 1, the CRP of 10 and white cell count of 26 × 10⁹/L respectively can be induced by the metabolic abnormalities alone. High-sensitivity troponin T was elevated in case 1 with an estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73 m² on presentation. Troponin T normalised with resolution of the renal abnormality and coronary angiogram was subsequently normal. She also had a lactic acidosis (5.7 mmol/L), which was more likely caused by hypoperfusion or less likely secondary to metformin therapy with acute kidney injury.

TREATMENT

Both patients were treated with intravenous 0.9% saline and intravenous insulin infusion as per the British Diabetic Association Guidelines for DKA.⁶ In addition to the above treatment, case 1 required norepinephrine for inotropic support and intravenous ceftriaxone empirically for suspected sepsis. Metformin was discontinued until her eGFR was >30 mL/min/1.73 m² at which point it was reinstated. She was nursed in the intensive care unit for 1 day. In both cases, d was discontinued and insulin therapy was resumed indefinitely.

OUTCOME AND FOLLOW-UP

Following admission, both patients made a full recovery and were discharged from hospital at days 6 and 4, respectively. Neither was restarted on dulaglutide. Subsequent investigation of insulin reserve showed that both cases 1 and 2 had low 2 hours post-prandial C-peptide concentrations of 0.13 µg/L (0.043 nmol/L) and 0.97 µg/L (0.32 nmol/L), respectively (our local reference range 2–9 µg/L).

At follow-up visits, both patients continued to have suboptimal BMIs (29.8 and 34.9 kg/m² for cases 1 and 2, respectively) and elevated HbA1c concentrations (81 and 62 mmol/mol, respectively). Both continued to be on the mixed twice-daily insulin regime and neither will consent to a reintroduction of dulaglutide.

DISCUSSION

With an overall mortality of 0.2%–2% and 10%–20%, respectively,^{7,8} DKA and HHS remain feared complications of diabetes and one of the aims of diabetes management is to prevent these potentially fatal events by ensuring availability of insulin, reducing its resistance in tissues and impairing glucagon secretion. GLP-1R agonists control blood sugar by employing these mechanisms.³ They exert their effects by binding to GLP-1R on pancreatic beta-cells but studies have shown that in chronic hyperglycaemia there is downregulation of GLP-1R.^{9,10} Rajan *et al* found that there was internalisation of GLP-1R when rodent beta-cells were subjected to chronic hyperglycaemia.⁹ They also showed that when liraglutide was administered to young db/db (diabetic) mice exposed to moderate hyperglycaemia, the GLP-1R agonist was much more potent compared with older db/db mice subjected to more severe hyperglycaemic states and proposed that intensive insulin therapy to normalise glucose levels before induction of GLP-1R mimetics may improve their efficacy in individuals with type 2 diabetes.⁹ However, there was no suggestion of whether age influenced the poorer liraglutide efficacy in the older group of mice or whether the main factor was their more severe hyperglycaemia.

This case report demonstrates two patients with chronic hyperglycaemia in whom insulin therapy was substituted with dulaglutide. They then experienced nausea and vomiting, which is a recognised side effect of dulaglutide and presented with an episode of HHS and DKA.

It appears that the insulin withdrawal was the turning point in the cases outlined. But there is no guidance as to whether one should continue insulin when starting GLP-1R agonists and with the weight gain associated with insulin therapy it is often desirable to discontinue insulin in favour of the better weight profile of GLP-1R agonists. Both cases had low C-peptide levels which were not measured pre-GLP-1R agonist treatment. Had they been, it would perhaps have been apparent that they needed insulin. But again, there is no national guidance on the necessity for this. Iwao *et al* studied predictors of successful switching from insulin to liraglutide in Japanese patients with type 2 diabetes. They measured fasting and postprandial C-peptide in 39 patients who were successfully switched from insulin to liraglutide and 30 patients who were not successfully switched. They found significantly higher postprandial C-peptides in those patients who were successfully switched. Their study concluded that postprandial C-peptide is a useful parameter when assessing which patients may be successfully switched from insulin to liraglutide.¹¹

Jones and Hattersley reported that C-peptide may identify patients on insulin who have good reserve of their beta-cell function and who can be safely switched from insulin to other anti-hyperglycaemic agents. They concluded that C-peptide levels of <0.2 nmol/L predicts patients who may require insulin long term.¹²

Should insulin be weaned off while the GLP-1R agonist is introduced? A study performed by Højberg *et al* reported that 4 weeks of near normalisation of blood glucose would improve beta-cell response to GLP-1R agonists.¹³ Both cases were at risk

of GLP-1R downregulation by virtue of the chronicity of their hyperglycaemia, so the dulaglutide was likely to take a while to reach optimal efficacy in any event. Further studies in humans are needed to determine if patients should receive 4 weeks of intensive insulin therapy to induce relative normoglycaemia prior to GLP-1R agonist therapy. But what then? Should clinicians omit insulin or wean it off as the GLP-1R agonist begins to become active?

The clinical picture of dehydration and vomiting may well have precipitated events and the metformin in case 1 may have reached toxic levels inducing a lactic acidosis. The increased insulin requirement of this metabolic picture was not met by the omission of insulin. We postulate that in chronically hyperglycaemic patients who are already established on insulin, GLP-1R agonists may be introduced but insulin should be continued with dose adjustments pending C-peptide result (allowing for the non-availability of GLP-1R testing in clinical practice) as these patients might be at risk of ketosis if their insulin is stopped abruptly. Similarly, ketone metres if available should be given to patients and/or patients should be educated as to the risks.

Learning points

- ▶ Patients with type 2 diabetes who have chronic hyperglycaemia may have a substandard or at best delayed response to glucagon-like peptide 1 receptor (GLP-1R) agonists.
- ▶ Postprandial C-peptide levels could be measured to identify patients who are at risk of metabolic complications if their insulin is abruptly discontinued during GLP-1R agonist induction.
- ▶ Patients should be counselled about the risks of ketosis and ketone metres provided.
- ▶ In patients with poorly controlled type 2 diabetes who are already established on insulin consider maintaining and titrating insulin when introducing GLP-1R agonists.

Acknowledgements We would like to acknowledge members of the diabetes team who were involved in managing the two cases. Dr Wilma Lourens. Consultant Diabetologist. Sligo University Hospital and our team of Diabetic Clinical Nurse Specialists, Majella Toomey, Kelley Hennihan, Ann Ferguson and Patricia Murray.

Contributors JOO and CMH are both first authors. JOO contributed in writing summary, background, case presentation, investigations, discussion and learning point. CMH oversaw the preparation of this article and contributed in writing summary, background, differential diagnosis, outcome, discussion and learning point. AA contributed in writing background, case presentation, differential diagnosis, discussion and referencing.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Reminder of important clinical lesson

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