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Persistent Lactic Acidosis - Think beyond Sepsis

Emily Pallister[1] and Thogulava Kannan[2]*

[1]*ST5 Anaesthetics, University Hospitals of Coventry and Warwickshire, UK*

[2]*Consultant Anaesthetist, George Eliot Hospital, Nuneaton, UK*

*Corresponding author: *Emily Pallister, ST5 Anaesthetics, University Hospitals of Coventry and Warwickshire, Coventry, UK*

Introduction

A 79-year-old patient with type 2 diabetes mellitus was admitted to the Intensive Care Unit for management of Acute Kidney Injury refractory to fluid resuscitation. She had felt unwell for three days with poor oral intake. Admission bloods showed severe lactic acidosis and Acute Kidney Injury (AKI).

The patient was initially managed with fluid resuscitation in A&E, but there was no improvement in her acid/base balance or AKI. The Intensive Care team were asked to review the patient and she was subsequently admitted to ICU for planned haemofiltration.

This case presented multiple complex concurrent issues. Despite haemofiltration, acidosis persisted for over 36 hours, prompting investigation for other causes for hyperlactataemia. Ketones were found to be raised, prompting diagnosis of euglycaemic diabetic ketoacidosis. Euglycaemic ketoacidosis with metformin induced lactic acidosis has been described in patients suffering with renal failure [1]. However, in this case acidosis was difficult to manage despite haemofiltration.

Recovery of acidosis was protracted compared to previous case reports.

Concurrent digoxin toxicity manifested as bradycardia, caused by the Acute Kidney Injury. This was not initially recognised, and hence digoxin levels were not checked until 12 hours after admission. Isoprenaline caused deleterious effects and so was discontinued. Eventually, the patient's acidosis improved with addition of 5% dextrose and Actrapid infusions.

Learning points:

- Differential diagnoses for hyperlactatemia beyond sepsis.

- Remember to check ketones in patients taking Metformin who present with renal impairment.

- Recovery can be protracted despite haemofiltration.

- Suspect digoxin toxicity in patients on warfarin with acute kidney injury, who develop cardiac manifestations.

Case Description

The patient presented to the Emergency Department with a 3 day history of feeling unwell with poor oral intake. On examination, her heart rate was 48 with blood pressure 139/32. There was no evidence of pyrexia (temperature 36.4 °C) or hypoxia (SpO_2 94% on room air). After urinary catheterisation, the patient was found to be oliguric. She was alert throughout. ECG lacked P waves in keeping with Slow Atrial Fibrillation (AF).

Admission bloods demonstrated raised white cell counts (white cell count 18.44×10^9/L, neutrophils 16.31×10^9/L). C-Reactive Protein was 33 mg/L. Clotting studies were deranged with INR of 4.3, APTT 1.8 secs and PT 46.3 secs. Acute Kidney Injury (AKI) was noted - potassium 5.6 mmol/L, urea 26.7 mmol/L and creatinine 528 umol/L. Venous random glucose level was 12.6 mmol/L. Paracetamol and Salicylate levels were normal.

Arterial Blood Gas analysis taken in A&E demonstrated a severe lactic acidosis - pH 7.13, Lactate 13.0 mmol/L, Base Excess - 17.6, Bicarbonate 11.3 mmol/L. Chloride level was 100 mmol/L, hence presentation was high anion gap metabolic acidosis (Anion Gap 26.7).

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The patient's medical history included Atrial Fibrillation, 2 previous Myocardial Infarctions, Type 2 Diabetes Mellitus, and previous Transient Ischaemic Attack (TIA). Her drug history comprised omeprazole, warfarin, furosemide, nicorandil, metformin, sitagliptin and a statin.

The patient had been discharged from another hospital 3 months prior for leg sepsis and fast AF. Discharge paperwork was not available from this episode. In 2017, she was investigated for arterial insufficiency and bilateral leg ulcers. MR Angiography demonstrated multi-level vessel disease including complete occlusion of the right superficial femoral artery, narrowing in the proximal left common iliac artery, stenosis in the left common femoral artery and complete occlusion of the left superficial femoral artery.

The patient was admitted to ICU at 03.30 AM for haemofiltration (CVVHDF) for the management of AKI and hyperlactataemia. The deranged clotting profile meant this was delayed whilst advice was sought from the on-call Haematology Consultant. Vitamin K, 2 units of Fresh Frozen Plasma and Octaplex were given, before CVVHDF was instigated through a central venovenous catheter in the right internal jugular vein. Haemofiltration was commenced at 09.30 AM. In the meantime, 100 ml of 8.4% sodium bicarbonate was given for management of acidosis (as per Renal specialist advice) and insulin/dextrose infusion for hyperkalaemia. Blood pressure was maintained without the need of vasopressors or inotropes.

Cardiology Specialists were consulted regarding the patient's presenting bradycardia. Atropine had been given - to a total of 1.8 mg - to no effect. Isoprenaline was commenced, however after receiving only 36 mcg a broad complex tachycardia developed. Cardiology were in attendance at this time, completing a transthoracic echocardiogram. The isoprenaline was discontinued and 2 mmol of Magnesium given. The rhythm converted to sinus. Further investigation of bradycardia was sought - blood biochemistry on the afternoon of admission demonstrated normal TSH (1.63 milliunits/litre) and raised Digoxin level (2.1 ug/mL).

During admission, the patient complained of pain in her legs and had mottled skin to the thighs on examination. In view of the persistently raised lactate, the on call surgical team were asked to review. Peripheral lower limb pulses were palpated. To exclude bowel or leg ischaemia, the patient underwent CT Abdomen and Pelvis. There was no evidence of ischaemic bowel. Extensive atheroma was seen within the vasculature of the lower limbs but no evidence of occlusion.

After 12 hours of haemofiltration, moderate acidosis continued (pH 7.21, lactate 11.3 mmol/L, Base Excess -15.6, Bicarbonate 10.8 mmol/L). Normoglycaemia (9.4 mmol/L) and hyperketonaemia (ketones 5.6 mmol/L) remained. 5% dextrose was given as fluid boluses during the course of the evening, and on day 2 was commenced as an infusion - increased from 25 ml/h to 100 ml/h during the day. Once instigated, an improvement was seen in acidosis. Background Actrapid infusion was started on day 3 of admission.

Thirty-eight hours after haemofiltration started, the patient's acid-base balance normalised, and ketone level fell below 1.5 mmol/L. Digoxin level reduced to 1.5 ug/mL by day 3 of admission. She was discharged to the ward after 6 days on ICU Table 1.

Discussion

This case presented a challenge for ICU staff in terms of multiple complex concurrent issues. Euglycaemic ketoacidosis with metformin induced lactic acidosis (MALA) cases have been described previously in patients suffering with renal failure [1], however in this case acidosis was felt to be difficult to manage effectively despite haemofiltration. Recovery of acidosis was protracted as compared to previous case reports. Provision of carbohydrate substrate with 5% dextrose infusion appeared to contribute to eventual resolution of acidotic state.

Euglycaemic ketoacidosis

Euglycaemic ketoacidosis (EDKA) was first described by Munro, et al. in 1973 [2]. They defined euglycaemic ketoacidosis as a "blood sugar level of less than 300 mg/

Table 1: Acid/Base changes during admission.

Date/Time	pH	Lactate	Ketones	5% Dextrose infusion rate (ml/h)
Day 1 04.00 (Admission to ITU; NaHCO$_3$ given)	7.13	13.0		
Day 1 06.00	7.20	12.0		
Day 1 07.00	7.22	13.0		
Day 1 08.00	6.91	13.4	4.3	
Day 1 11.00 (after CVVHDF commenced)	7.17	10.08	2.9	
Day 1 20.00	7.21	11.3	5.2	100 ml bolus given at 18.00
Day 1 24.00	7.29	11.1		
Day 2 03.00	7.35	7.1	Not tested	25
Day 2 06.00	7.40	5.5		50
Day 2 15.00	7.43	2.9		50

ml and plasma bicarbonate of 10 mEq/L or less". This has since been adapted to include a blood glucose level of less than 200 mg/dl (11.1 mmol/L) [3]. The condition has been reported in typically Type 1 diabetic patients associated with reduced calorie intake [4], alcohol consumption, glycogen storage disorders and chronic liver disease [3].

The pathophysiology of diabetic ketoacidosis is well known - hyperglycaemia results from a relative lack of insulin or increase in counter-regulatory hormones. The body, deficient of insulin, cannot utilise the glucose substrate and resorts to lipolysis, causing production of ketones. In *Euglycaemic* diabetic ketoacidosis, there is an underlying systemic lack of glucose - either due to reduced hepatic glucose production during fasting, or increased urinary glucose losses. Burge, et al. demonstrated that insulin withdrawal in fasted diabetics resulted in lower glucose levels than control subjects [5]. During times of starvation, glucagon predominates and glycogenolysis, gluconeogenesis, lipolysis and ketogenesis prevail. Over time, glycogen stores are depleted, and the body enters starvation state. If DKA then supersedes, the hyperglycaemic state cannot occur, and the patient remains euglycaemic [6]. Often EDKA occurs in diabetic patients who continue to take insulin whilst unwell or in a fasting state, and hence why it is more common in insulin dependent or Type 1 diabetes mellitus. In comparison, dehydration combined with fasting in diabetic patients was shown to cause relatively worse hyperglycaemia [5].

Typically Type 2 diabetic patients do not suffer from insulin deficiency, but relative insulin resistance. Therefore, DKA and EDKA are less common in these patients, as the pathophysiology of the conditions typically dictates a lack of insulin. Reports of EDKA in Type 2 diabetics do exist, but usually in patients on insulin regimes. Yu, et al. [7] described one patient who developed EDKA and was later diagnosed with Type 2 diabetes mellitus. Similar to our patient, poor oral intake was thought to be the precipitant. They postulate that in times of starvation, on a background of poor glycogen stores (e.g. weight loss), blood glucose levels will remain low as the remaining glycogen is depleted. Concurrently, a 'metabolic shift to lipid utilisation' occurs, causing lipolysis and ketoacidosis. This is compounded by increased insulin resistance, especially in times of metabolic stress such as illness. More recently, euglycaemic ketoacidosis has been reported in association with sodium glucose co-transporter inhibitors (SGLT-2) used for the management of type 2 diabetes mellitus [8] superseded with the above conditions.

As per the management of hyperglycaemic diabetic ketoacidosis, EDKA treatment comprises IV insulin and fluid replacement. Insulin infusion manages the relative deficiency seen in DKA, causing suppression of ketogenesis and peripheral utilisation of glucose. In the treatment of hyperglycaemic DKA, when the venous glucose level falls to less than 14 mmol/L, 10% glucose should be infused to prevent hypoglycaemia. The glucose infusion is used as the primary metabolic substrate, stimulated by insulin and hence ketosis is reduced. The same principle can be applied to EDKA.

Metformin associated lactic acidosis

Metformin has long been known to precipitate Type B Lactic Acidosis i.e. lactic acidosis without tissue hypoxaemia. The underlying pathophysiology is thought to be due to the inhibitory action of metformin on pyruvate carboxylase, causing decreased oxaloacetate production and accumulation of pyruvate [9]. This is compounded in renal or hepatic failure when the action of metformin is prolonged. Haemodialysis is a definitive management for metformin associated lactic acidosis (MALA) as metformin is renally excreted. The incidence of MALA is reported as 4.3 cases per 100,000 patient years in patients who take metformin. A retrospective study in Italy by Mariano, et al. [10] found 1.45% of all patients on Renal Replacement Therapy in ICU were due to MALA, with a survival rate of 78.3%. However, Cochrane Review found no evidence of increased risk of lactic acidosis or hyperlactataemia compared to other anti-hyperglycaemic medications [11]. It is possible therefore that MALA occurs due to a combination of hypoxic (i.e. Type A) and non-hypoxic mechanisms [12].

This case is likely to represent a multifactorial cause of lactic and keto- acidosis than just MALA alone. The patient was known to have stenosed lower limb arteries and during admission had mottled and cold legs. In addition to MALA, Type A lactic acidosis due to tissue hypoxaemia probably occurred, possibly from underlying sepsis or tissue ischaemia. The result was a compound hyperlactataemia caused by sepsis, ischaemia and metformin accumulation. However, the acidosis was initially resistant to sepsis management and even several hours of haemofiltration - prompting the investigation of other causes of hyperlactataemia and discovery of superimposed EDKA. Overall, the patient's acidosis did not improve until the instigation of 5% dextrose infusion - demonstrating a state of starvation with ongoing ketone body production. Once the dextrose infusion had commenced, rapid improvement in the patient's acid/base balance was seen.

Acute kidney injury and hyperkalaemia

The patient reported poor oral intake for 3 days prior to her admission. It is not documented whether this included oral fluids as well as food. As outlined previously, dehydration often precipitates hyperglycaemia [5] and yet this was not evident. However, admission bloods demonstrated Acute Kidney Injury which could be in keeping with pre-renal injury from dehydration.

Despite the presence of AKI and EDKA, the patient suffered only mild hyperkalaemia (venous potassi-

um 5.6 mmol/L). Umpierrez, et al. [13] demonstrated a mean potassium result of 5.6 mEq/L (5.6 mmol/L) in patients with DKA. Where acidosis is caused by an organic acid such as lactate or ketones, there is a state of high serum H+ concentration, and low HCO_3. Inhibition of Na^+/H^+ exchange transporters, and Na^+-HCO_3 cotransport occur, causing a fall in intracellular sodium. Na-K-ATPase activity reduces leading to a net loss of intracellular potassium and relative hyperkalaemia [14]. The patient stated that her usual medications included furosemide, although as highlighted later her drug history was somewhat unclear as evidenced by the digoxin that she'd taken but not declared. It is plausible that she had not taken the furosemide. As a loop diuretic, furosemide inhibits the Na-K-Cl transporter within the thick ascending limb of the Loop of Henle. There is net loss of these ions alongside water, leading to hyponatraemia and hypokalaemia. In this case, the potassium balance may have been influenced by acidosis and furosemide, with lactataemia proving prevalent in causing hyperkalaemia.

Use of haemofiltration

In this case, acidosis worsened despite timely implementation of haemofiltration. In our unit, the dialysate solution used is lactate-containing (Prismasol4©, contains 3 mmol/L lactate). Bicarbonate containing dialysate is not available. Plasma lactate is the product of systemic release in to the circulation (primarily anaerobic metabolism production) minus clearance. Clearance of lactate occurs via metabolism in the liver, kidneys and skeletal muscle. In this case, lactate was systemically overproduced whilst the dialysate used in haemofiltration added additional lactate to the systemic circulation. The resulting persistent lactic acidosis demonstrated an imbalance, favouring production over clearance.

The use of lactate-containing dialysate relies upon adequate hepatorenal function to metabolise lactate via gluconeogenesis (70%) and oxidation (30%) to pyruvate. Both processes consume hydrogen ions (attained from water), thereby releasing hydroxyl ions that form bicarbonate [15]. When hepatic function is normal, lactate is rapidly converted to bicarbonate. When patient is unable to convert lactate to bicarbonate at a rate that exceeds lactate production, serum levels of lactate will rise, as witnessed in this patient.

Although commonly used to treat *acute* renal failure, lactate-containing dialysate solutions can exacerbate lactic acidosis. Hilton, et al. [16] described a group of patients that deteriorated with worsening acidosis after commencing haemofiltration. As they explained, small solutes (15-20 kDa) are removed via filtration, including bicarbonate ions at a rate of 37 mmol/h. Failure to replace bicarbonate worsens acidosis. If the dialysate lactate cannot be metabolised, acidosis will also be exacerbated. Levraut, et al. [17] demonstrated that the filter accounted for less than 3% of total lactate clearance, hence could not 'mask' lactate overproduction. A study by Thomas, et al. [18] demonstrated a net gain of lactate of 65 mmol/h from lactate-containing dialysate after 24 hours of haemofiltration.

The Intensive Care Society (ICS) Guidelines on Renal Replacement Therapy (RRT) advocates no difference in the use of bicarbonate versus lactate containing dialysate fluids, as demonstrated by Thomas, et al. in 1997 [18,19]. However, the use of bicarbonate is recommended in severe lactic acidosis (pH < 7.2) or cases of 'lactate-intolerance' i.e. a 'rise in lactate of greater than or equal to 5 mmol/L from baseline' during RRT with a lactate containing dialysate. These recommendations suggest that our patient should have been managed with bicarbonate buffer to reduce lactate load.

Digoxin toxicity

This case had added interest due to digoxin toxicity. The patient had been discharged from a nearby hospital three months earlier but unfortunately IT systems and therefore paperwork is not shared between Trusts. The patient did not list Digoxin in her current medications, hence there was a delay in investigating Digoxin levels. The abnormal cardiac signs of slow AF were not in keeping with the usual presentation of hypovolaemic state, prompting further investigation in liaison with cardiology specialists. Digoxin is not dialysed and is readily accumulated in AKI. No specific treatment was instigated to treat the digoxin toxicity, and levels reduced within the first 36 hours of admission of their own accord.

This patient presented multiple challenges for the admitting team overnight - abnormal clotting precluded the rapid instigation of haemofiltration, management of AKI lead to rapid improvement in renal function but superimposed MALA and EDKA caused a protracted acidosis. Provision of carbohydrate substrate via 5% dextrose infusion eventually improved the body's starvation state. Then, an episode of abnormal bradycardia caused by unrecognised digoxin toxicity and subsequent isoprenaline induced tachycardia, added extra complexity. The patient made an overall good recovery and was discharged to the ward after 24 hours of haemofiltration, and 6 days stay on ICU.

Consent

The patient was asked for consent to publish this case report and agreed willingly.

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