Metformin and alcohol binge drinking: a dangerous synergy

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Abstract

Background: Alcoholic ketoacidosis (AKA) is an under-recognised presentation seen in chronic alcoholics with a recent history of binge drinking. Metformin- associated lactic acidosis (MALA) is a rare complication of biguanide treatment which is generally induced by overdose or reduced clearance. Both can present with a significant high anion gap metabolic acidosis and hyperlactataemia.

Case report: A 52-year-old man with a background history of chronic alcoholism and type 2 diabetes mellitus (T2DM) treated with metformin only (latest HbA_{1c} 7% / 53 mmol/mol) presented to the hospital with vomiting. He was hypotensive and had acute kidney injury (AKI) stage 3. This presentation occurred after an episode of binge drinking 12 hours prior. He had had three similar episodes in the past, two episodes occurring within 24 hours of binge drinking. Venous blood gas measurement on presentation showed a pH of 6.934, lactate of 16 mmol/L and glucose of 21.7 mmol/L, and bedside ketones were 3.2 mmol/L. He was treated according to the hospital diabetic ketoacidosis (DKA) protocol.

Discussion: In the presence of a recurrent history of DKA in a patient with chronic alcoholism, AKA should be considered. The mechanism of AKA is complex and occurs in the setting of insulin deficiency and excess glucagon release. Excess ethanol metabolism favours the formation of beta-hydroxybutyrate ketoacid. Counter-regulatory hormones and volume depletion drive lipolysis and ketosis. Repeated episodes of binge drinking-induced renal impairment may have caused metformin accumulation, resulting in hyperlactataemia.

Conclusion: We should consider both AKA and MALA in binge drinkers who present with recurrent severe acidosis.

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Introduction

We present a case of a patient with alcoholic ketoacidosis (AKA) which was misdiagnosed as diabetic ketoacidosis (DKA). As well as AKA, he presented with significant hyperlactataemia, which prompted an associated diagnosis of probable metformin toxicity. The pathophysiological mechanisms underlying this phenomenon are discussed.

Case history

A 52-year-old White British male presented to the emergency department after waking up feeling unwell the morning after an isolated binge drinking episode over the long weekend. His capillary blood glucose was 6.5 mmol/L, and he took his usual 2 g metformin. A few hours later, he experienced acute abdominal discomfort, nausea and vomiting and he was taken to the hospital by ambulance after a 111 call. On arrival in the emergency department, he was found to be markedly hypotensive with a systolic blood pressure of 65 mmHg. He was alert with a Glasgow Coma Score of 15/15 but was tachypnoeic, with a respiratory rate of 28 breaths per minute. His oxygen saturation was 97% on room air and his temperature was 36.6 degrees Celsius.

His electrocardiogram showed tall T waves, reflecting an elevated serum potassium of 6.7 mmol/L. Further blood tests showed results which met the criteria for DKA (Table 1). He was promptly transferred to the intensive care unit, where he received vasopressor support along with initiation of the hospital's DKA management protocol, which included administration of 0.9% sodium chloride solution and a fixed-rate soluble insulin infusion.

He had a raised serum amylase level on presentation suggestive of acute pancreatitis, but no imaging had been performed. His amylase recovered to a normal level four days later.

On review of his medical records, it transpired that he had been admitted three times previously for treatment of DKA. The previous episodes consistently happened less than 12 hours following binge drinking. The biochemistry results from each admission were reviewed electronically (Table 1). Figure 1 shows recurrent raised serum creatinine and neutrophilia during each admission episode.

The patient was diagnosed with type 2 diabetes (T2DM) in

Table 1. Compiled biochemistry results of his recurrent emergency department admissions, which demonstrated high anion gap acidosis complicated by ketosis and severe lactic acidosis

Admissions	4th admission	3rd admission	2nd admission	1st admission
Date	26/5/2024	25/11/2023	03/04/2023	11/12/2021
Blood gases				
Blood pH (7.320-7.430)	6.934	7.000	6.924	7.174
Base excess (-3.2 – 1.8 mmol/L)	-27.0	-23.6	-25.8	-19.0
HCO_3^-(20 – 28 mmol/L)	7	8.6	7.5	11.0
Glucose (3.6 – 5.3 mmol/L)	21.7	22.7	30	17.5
Lactate (0.6 – 1.4 mmol/L)	16	11.7	13.0	3.3
Ketone (<0.6 mmol/L)	3.2	2.3	2.4	3.5
Anion gap (4-12 mmol/L)	25.2	20.4	23.5	32.0
Blood serum				
Haemoglobin (115-165 g/L)	135	140	149	157
Mean corpuscular volume (80-99 fL)	97	99	105	102
White cell count (4-11 $x10^9$/L)	33.2	33.1	28.3	51.1
Neutrophil count (1.5-7.5 $x10^9$/L)	25.33	27.47	24.30	30.66
Platelet count (140-400 $x10^9$/L)	389	423	425	523
Sodium (133-146 mmol/L)	137	133	134	137
Potassium (3.5-5.3 mmol/L)	6.7	5.9	6.6	4.3
Urea (2.5-7.8 mmol/L)	7.0	4.5	4.3	5.6
Creatinine (60-120 umol/L)	263	184	129	129
eGFR (>90 ml/min/1.73m^2)	23	36	55	56
Bilirubin (0-21 umol/L)	7	8	8	5
Alanine aminotransferase (10-49 U/L)	35	19	19	31
Alkaline phosphatase (30-130 U/L)	85	73	74	72
Albumin (35-50 g/l)	46	47	42	56
Total protein (57-82 g/L)	75	77	60	85
Salicylate	Negative			
Amylase (40-140 U/L)	878	159		60
Serum ethanol (0-50 mg/dL)	<10			

2012 and was taking 2 g metformin daily. His body mass index (BMI) was 27.5 kg/m^2 and the most recent HbA_{1c} of 7.0% / 53 mmol/L indicated good glycaemic control. During his fourth hospital admission, his C-peptide level was measured and was 1801 pmol/L, indicating well-preserved endogenous insulin production. Key laboratory parameters such as metformin concentration, acetoacetate and beta-hydroxybutyrate were unfortunately not assessed during any of his admissions, which complicated the diagnostic process. To obtain additional insights, further investigations, including serum amino acids, urine organic acids and vitamin levels, were requested, with the results presented in Table 2.

On further questioning the patient admitted to drinking approximately 14-18 units of vodka per week (35-40% alcohol by volume, ABV). After reviewing his previous admissions' electronic records, all presentations occurred within 24 hours of experiencing abdominal pain following binge drinking, and on three of the four admissions he had associated vomiting. He admitted that he had indulged in overnight binge drinking with an average of half a bottle of vodka (about

Figure 1. Recurrent episodes of AKI and neutrophilia. Each admission is marked by a red triangle

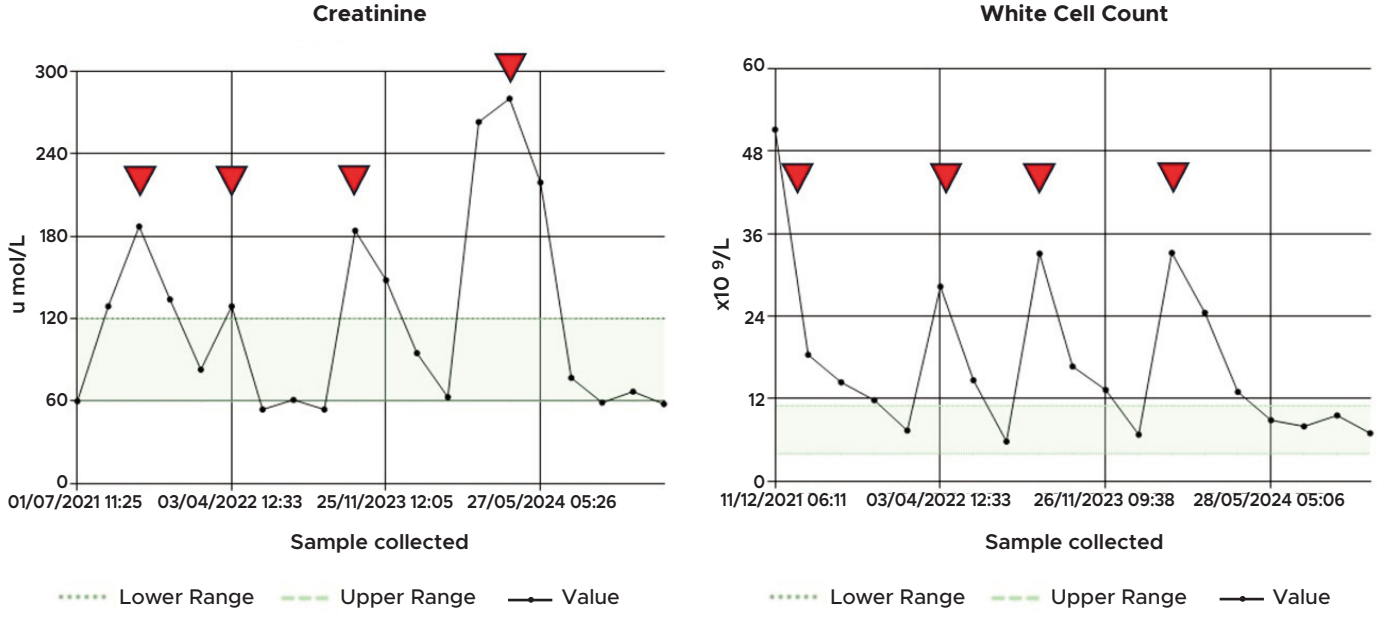

Table 2. Serum amino acids, urine organic acid and vitamins screen during his fourth admission

Serum amino acids (ion-exchange chromatogram)	
No significant abnormalities detected	
Urine organic acid	
Moderate secretion of p-hydroxyphenyllactate (p-HPLA) and p-hydroxy-phenylpyruvate (p-HPPA)	
Vitamins	
Vitamin B2 (Riboflavin) (174-471 x10^9/L)	251
Vitamin B6 (Whole blood) (44-168 nmol/L)	82
Vitamin B1 (Thiamine) (66-200 nmol/L)	122
Plasma acyl & free carnitine	
Free carnitine (15-53 x10^9/L)	35.0
No abnormality detected on plasma acyl level	

20 units of alcohol) prior to his three most recent admissions. He had also taken metformin prior to each presentation.

After a two-day stay in the intensive care unit, the patient was deemed stable enough to be transferred to the general ward. Metformin was not restarted; he was discharged home on Abasaglar insulin 6 units at bedtime with a follow-up appointment arranged in the diabetes outpatient clinic.

Discussion

We believe that this patient suffered from recurrent episodes of alcoholic ketoacidosis (AKA) rather than DKA, complicated by a degree of metformin toxicity. The essential tests (acetoacetic acid and beta-hydroxybutyrate) to differentiate the two conditions are not commonly performed and were not checked in this case. However, the patient's clinical presentation and history offer substantial support for the diagnosis of AKA.

Although it is common, AKA is a less well-known medical emergency compared to DKA. Differentiating the two conditions often relies on patient history. Patients with DKA usually have type 1 diabetes (T1DM) and can present with severe hyperglycaemia. AKA, in contrast, often occurs in patients with a history of longstanding alcohol use and low calorie intake. Patients often present with low or normal glucose levels, although some can present with hyperglycaemia.[1] The serum ethanol level can be low or zero at presentation.[1] Unlike DKA, the management of AKA typically does not require intravenous insulin infusion. Instead, the primary treatment involves rehydration with 5% dextrose and electrolyte (potassium, magnesium and phosphate) replacement. Additionally, thiamine is commonly administered to prevent the development of Wernicke's encephalopathy.[1]

The main precipitating factors behind AKA include a state of insulin deficiency and excess glucagon secretion driven by a higher NADH/NAD^+ ratio, counter-regulatory hormones release and starvation.[2] Excessive ethanol metabolism can also contribute to ketone generation in AKA by increasing acetyl-CoA, a key precursor for ketone body synthesis, and further elevating the NADH/NAD^+ ratio.

A raised NADH/NAD^+ ratio results in preferential acetoacetate (AcAc) conversion to beta-hydroxybutyrate (BOHB),[3] which becomes the predominant ketoacid in alcoholic ketoacidosis. Notably, the ratio of BOHB:AcAc on admission is significantly higher in patients with AKA compared to those with DKA (7:1 vs. 3:1, $p<0.01$).[4] Measurement of the two ketoacids can be considered a part of the diagnostic method to differentiate AKA and DKA in clinical practice, although treatment should not be delayed.

Significant intravascular and extravascular volume depletion following recurrent vomiting can significantly increase counter-regulatory hormones (glucagon, cortisol, catecholamines and growth hormone), which can contribute to ketosis by increasing the availability of free fatty acids. High cortisol can enhance mobilisation of fatty acids, while raised growth hormone stimulates lipolysis.[5] Significant catecholamine release suppresses pancreatic insulin release while intensifying hepatic ketogenesis.[6]

A decreased insulin-to-glucagon ratio can indirectly reduce inhibition of carnitine acyltransferase (CAT), a mitochondrial enzyme responsible for free fatty acid transport into the mitochondria.[7] This can allow more free fatty acids to undergo B-oxidation, resulting in more ketoacid generation. Excess glucagon and epinephrine release may have driven both glycogenolysis and gluconeogenesis, resulting in the hyperglycaemia seen in this patient.

The significant high anion gap metabolic acidosis seen on each admission was not just due to ketoacids but also due to hyperlactataemia. Both type A and type B mechanisms for lactic acidosis would have co-existed, with hypovolaemia causing type A lactic acidosis and several mechanisms (discussed below) causing type B lactic acidosis. In the setting of a raised NADH / NAD^+ ratio, lactate is synthesised rather than pyruvate. Reduced availability of NAD^+ can lead to decreased pyruvate dehydrogenase activity, which can block the utilization of pyruvate within the Krebs cycle – thus causing more substrate for lactate formation.[8]

Recurrent AKI on presentation on all his admissions would have reduced metformin clearance. Metformin is widely used as a first-line agent for the management of T2DM. Rarely, it can be associated with the development of metformin-associated lactic acidosis (MALA), which is a serious and potentially life-threatening adverse event. It is reported to carry an incident rate of 3-10 per 100,000 patients,[9] with a high expected mortality rate of 30 to 50%.

The proposed mechanism for the elevated lactate levels observed in metformin toxicity is related to the inhibition of mitochondrial respiration in tissues.[10-12] This can expedite lactate production. Furthermore, increased ethanol metabolism due to binge drinking exacerbates the issue by generating NADH and increasing the NADH / NAD^+ ratio. As a result, the lactate dehydrogenase reaction favours lactate formation, since NADH is a necessary coenzyme for the conversion of pyruvate to lactate.[8]

An inborn error of metabolism is considered unlikely in this patient given his age, with no previously known childhood disorders and no known family history. In the presence of lactic acidosis and DKA, thiamine deficiency was excluded as a cause: he had a normal level, as shown in table 2.

Key messages

- Consider alcoholic ketoacidosis in patients with a history of binge drinking and recurrent DKA admissions
- If metformin toxicity is suspected, metformin level should be assayed, and we recommend that metformin should not be restarted on discharge

Conclusion

This case highlights important learning opportunities for healthcare professionals managing acute presentations. Distinguishing between DKA and AKA can be challenging since these conditions may exhibit similar biochemical profiles. Obtaining a detailed alcohol consumption history is pivotal when AKA is suspected. Early assessment of the patient's metformin level would have been crucial, as excessively high concentrations can be corrected through renal replacement therapy. Additional biochemical tests measuring acetoacetate and beta-hydroxybutyrate levels can offer valuable diagnostic insights. In summary, the synergistic interaction between alcoholic ketoacidosis and metformin toxicity can result in the development of severe and potentially life-threatening metabolic acidosis.

Conflict of interest None.
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