Teaching Point
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Severe hyperlactaemia in the setting of alkalaemia

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Introduction

Alcoholic patients may present with a range of metabolic derangements due to malnutrition, chronic liver disease and renal tubular dysfunction. In the case presented here, we describe a patient in whom the effects of alcohol abuse and complications of previous gastrointestinal surgery combined to cause a number of biochemical abnormalities. The most striking of these were observed in the arterial blood gases, which revealed severe hyperlactaemia (lactate 23 mmol/l) in the setting of significant alkalaemia (pH 7.64); this is a highly unusual finding and in our discussion of the case, we have attempted to explain the possible underlying causes for this. Hyperlactaemia most likely occurred due to a combination of factors including hypoxia, hypovolaemia, vitamin deficiency, increased gastrointestinal production of lactate and impaired removal of lactate by the liver and kidney. Evidence exists to support the concept that an alkalaemic state can significantly potentiate a rise in serum lactate concentration under anaerobic conditions, presumably in order to minimize changes in plasma pH.

Case history

A 59-year-old man was admitted to hospital with increasing limb weakness over the course of several weeks. He had been unable to mobilize and had been lying in bed for at least 24 h prior to admission. Past medical history included resection of a carcinoma of the rectum several years previously with formation of a colostomy. He had subsequently developed both entero-cutaneous (thought to be originating from the large bowel) and recto-vesical fistulae, which had been partially treated with a de-functioning ileostomy. The patient had a long history of alcohol abuse. Prior to admission, oral intake had been very poor whilst the output from the ileostomy was high. He strongly denied vomiting and was not taking diuretics; regular medication consisted only of codeine phosphate.

On examination, the patient appeared thin and malnourished, with significant muscle wasting. He had clinical evidence of volume depletion with reduced skin turgor, low jugular venous pressure and poor peripheral perfusion. Blood pressure was low at 80/40 mmHg. Carpopedal spasm could be induced in the upper limb upon inflation of a blood pressure cuff (Trousseau’s sign). The remainder of the examination was unremarkable.

Blood tests were performed and revealed evidence of acute kidney injury [AKI—serum creatinine 209 μmol/l (2.38 mg/dl)] and a number of other significant abnormalities in venous blood (Table 1), including severe hypophosphataemia, hypocalcaemia, hypokalaemia and hypomagnesaemia. Liver enzymes were elevated, INR was prolonged and the platelet count was low; all findings were consistent with chronic liver disease due to alcohol. Creatine kinase was elevated at 2732 U, most likely due to rhabdomyolysis secondary to immobility.

Treatment was commenced with intravenous saline (NaCl) to restore the circulating volume and improve tissue perfusion and to correct the metabolic alkalosis. The patient was also given intravenous potassium, magnesium and calcium, and intramuscular vitamin D for the electrolyte disturbances, with continuous cardiac monitoring. Appropriate therapy was instituted to treat the symptoms of alcohol withdrawal, including vitamin B supplements. Following an initial worsening of the renal function [with a peak creatinine level of 400 μmol/l (4.55 mg/dl)], the patient made a gradual recovery. Twelve days after admission, his biochemical profile had improved significantly and the lactate and bicarbonate levels had returned to normal. The patient was discharged shortly afterwards.
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Discussion

In the case described here, an alcoholic patient presented with multiple problems, including AKI (due to hypovolaemia and rhabdomyolysis), chronic liver disease and significant electrolyte disturbances (secondary to malnutrition, gastro-intestinal losses and alcoholic renal tubular toxicity). However, the most striking and unusual abnormalities were observed in the arterial blood gases, which revealed severe hyperlactaemia in the presence of significant alkalaemia (due to combined metabolic and respiratory alkalosis). This is a rare finding and, to the best of our knowledge, such a high level of lactate has not previously been described in an alkalaemic patient, in the absence of prolonged vomiting. We will now attempt to explain the underlying causes of these acid–base disturbances, and review the theoretical reasons why an alkalaemic state may actually potentiate a rise in serum lactate concentration under anaerobic conditions, which can occur in a critically ill patient.

Our patient had evidence of a mild primary respiratory alkalaemia, with a slightly reduced PCO₂ in the absence of an acidemic state. Acute respiratory alkalosis is commonly observed on abrupt withdrawal of alcohol in dependent patients due to hyperventilation [1]. In addition, experimental evidence exists to suggest an association between hyperlactaemia and hyperventilation (even in the absence of a metabolic acidosis), which may have been relevant in this case [2].

Metabolic alkalaemia is less commonly observed in alcoholics, who more typically present with a ketotic metabolic acidosis due to ethanol metabolism and malnutrition. When alkalaosis is encountered in these patients, it is usually attributed to prolonged vomiting. We believe that the metabolic alkalaemia in our patient was most likely caused by chronic deficiency of potassium and chloride, combined with a contraction of extracellular fluid volume (so called ‘contraction alkalaosis’). There was no history of alkali ingestion or prolonged vomiting, and an increase in renal acid excretion was unlikely in the context of significant AKI. Hypokalaemia causes metabolic alkalaemia by shifting hydrogen ions from the extracellular to the intracellular space [3] and possibly also by increasing renal ammonia secretion [4]. Unfortunately, due to technical reasons, serum chloride was not measured before the institution of saline therapy on this admission. However, evidence was found of chronic hypochloraemia on repeat blood tests performed 3 months later, which revealed a serum chloride of 82 mmol/l (95–106). ‘Contraction alkalaosis’ refers to an increase in bicarbonate concentration that occurs when the volume of extracellular fluid in which the bicarbonate ions are dissolved is lowered. It is maintained to an extent by increased renal reabsorption of bicarbonate. Furthermore, under these circumstances, a rise in venous bicarbonate concentration may also occur due to increased intracellular production of carbon dioxide, secondary to increased extraction and usage of oxygen from blood that is moving sluggishly through peripheral tissues. This excess carbon dioxide can then react with water to promote the formation of intracellular bicarbonate ions, which can leave cells in exchange for chloride ions [5]. These changes are reversible upon restoration of a normal extracellular fluid volume.

Hyperlactaemia has a variety of causes, which are usually divided into type A (related to hypoperfusion of tissue and/or hypoxia) and type B (elevated serum lactate in the presence of normal tissue perfusion and oxygenation). Examples of type B hyperlactaemia include inborn errors of metabolism, mitochondrial cytopathy and cyanide poisoning. Lactate is formed from pyruvate in the following simplified equation, catalysed by lactate dehydrogenase (LDH):

\[
\text{Pyruvate} + \text{NAD}^- \leftrightarrow \text{lactate} + \text{NAD}^+
\]

It therefore follows that compromise of mitochondrial respiratory chain function (e.g. due to hypoxia) can promote the formation of lactate in two ways. Firstly, by causing a build up of pyruvate, due to impaired usage as a metabolic fuel for oxidative phosphorylation, and secondly, by leading to decreased oxidization of mitochondrial NADH at complex I, which (indirectly) also push the cytosolic NAD pool into a more reduced state, leading to an increased NADH/NAD⁺ ratio. When oxidative phosphorylation is impaired, cells become dependent on anaerobic glycolysis for ATP production. The formation of lactate from pyruvate at the end of the glycolytic process regenerates NAD⁺, which is required for the earlier stages of glycolysis.

The elevated level of lactate observed in our patient was most likely due to hypoxia and hypoperfusion (type A). This situation may have been compounded by a dietary deficiency of vitamins important for normal aerobic metabolism; for example, B1 (thiamin), B2 (riboflavin) and B6 act as cofactors for the normal oxidization of pyruvate. These must therefore be replaced promptly in patients with malnutrition and hyperlactaemia. Biotin is required for the usage of lactate for gluconeogenesis; therefore, biotin

<table>
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<tr>
<th>Table 1. Venous blood results on admission</th>
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<tr>
<td>Sodium 141 mmol/l (135–150)</td>
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<tr>
<td>Potassium 3.1 mmol/l (3.5–5.3)</td>
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<tr>
<td>Urea 7.3 mmol/l (2.5–7.5)</td>
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<td>Creatinine 209 μmol/l (190–250)</td>
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<td>Creatine kinase 2732 U (25–100)</td>
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<td>Corrected calcium 1.43 mmol/l (2.1–2.5)</td>
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<tr>
<td>Phosphate 0.48 mmol/l (0.8–1.4)</td>
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<tr>
<td>25-OH vitamin D 10 nmol/l (20–110)</td>
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<tr>
<td>Magnesium 0.28 mmol/l (0.7–1.1)</td>
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<td>Albumin 31 mmol/l (35–50)</td>
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<th>Table 2. Arterial blood gas values on admission (on room air)</th>
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<tr>
<td>pH 7.64 (7.35–7.45)</td>
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<tr>
<td>PO₂ 7.87 kPa (&gt;10.6)</td>
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| Bicarbonate 36.4 mmol/l (24–30) |...
deficiency will also tend to cause a build up of lactate. Given the extensive history of gastrointestinal surgery in our patient, excess production of lactate by gut bacteria (via fermentation) and subsequent reabsorption into the blood stream may also have contributed to the aetiology of hyperlactaemia. This scenario can occur when colonic bacteria are exposed to high levels of carbohydrate, either due to overgrowth of organisms in the small bowel or due to abnormal delivery of carbohydrates to the colon (e.g. following malabsorption of sugars in the small bowel) [6]. It may lead to increased production of either the D- or L-isomer of lactate, depending on the type of bacteria. Consumption of large amounts of fruit and/or vegetables can present both an alkali and lactate load; however, our patient was not a vegetarian and was generally malnourished. Uptake and breakdown of plasma lactate normally occur in the liver and kidney, both of which were functionally impaired to a significant extent in our patient, which almost certainly contributed significantly to the development of hyperlactaemia.

Lactate can leave cells in exchange for OH− ions and act as an organic acid in the extracellular fluid. Hyperlactaemia is therefore typically associated with metabolic acidosis, and only rarely with metabolic alkalosis [7,8]. Some authors have postulated that the low frequency of occurrence in the literature may be artefactual, due to the fact that lactate is infrequently measured in the setting of metabolic alkalosis [8]; however, most modern blood gas analysers now measure lactate as a matter of routine.

Although hypoxia and hypovolaemia alone can cause significant hyperlactaemia, there are several theoretical reasons why an alkalaemic state may potentiate a rise in serum lactate concentration, which could explain why such a high lactate level was observed in our patient. Firstly, an increase in pH will shift the oxygen–haemoglobin dissociation curve to the left, leading to a decrease in oxygen release in the tissues, causing an increase in anaerobic respiration [9]. Secondly, in patients with lactic acidosis treated with sodium bicarbonate, a rise in serum lactate concentration can occur, independent of an increase in lactate production, due to a pH-dependent redistribution of intracellular lactate into the extracellular compartment [10]. Thirdly, intracellular production of lactate via anaerobic glycolysis is thought to be increased by a rise in pH. Experiments performed on isolated cells in the 1960s revealed that 6-phosphofructokinase (PFK), a key rate-limiting enzyme in glycolysis, is pH dependent [11]. An increase in pH (alkalaemia) increases the activity of the enzyme, whilst a decrease in pH (acidemia) has the opposite effect. Therefore, under anaerobic conditions, an alkalaemic state will potentiate the formation of lactate in cells, whilst an acidic state will inhibit it. It has been postulated that this therefore provides a negative feedback loop, whereby the production of lactate is adjusted according to alterations in the acid–base balance, in order to minimize changes in cellular pH (for a detailed discussion of this hypothesis see [12]). Further evidence for the existence of this feedback mechanism comes from experimental work on lactate production during exercise in human volunteers, which was found to be increased by the artificial induction of metabolic alkalosis [13], but decreased by induction of metabolic [14] or respiratory acidosis [15]. Presumably, the teleological advantage of this feedback mechanism is maintenance of normal pH under anaerobic conditions, in order to allow optimal functioning of intracellular enzymes during times of metabolic stress. However, this is potentially at the cost of a decrease in glycolytic ATP production in an acidic milieu. Indeed, it is noteworthy that exercise studies in humans have demonstrated a longer endurance at peak performance in alkalotic conditions artificially induced with sodium bicarbonate, than in acidic conditions induced with ammonium chloride [13]. Lactate production in red blood cells may be particularly sensitive to changes in pH [16], as these cells do not contain mitochondria and rely entirely on anaerobic metabolism for ATP production.

In summary, we have presented an alcoholic patient with previous gastrointestinal surgery who developed marked acid–base disturbances, including the interesting and rare finding of severe hyperlactaemia in the presence of alkalaemia. We have discussed the possible underlying mechanisms leading to this scenario. We proposed that a combination of malnutrition, gastro-intestinal losses and renal tubular wasting lead to hypokalaemia, hypochloraemia and contraction of extracellular fluid volume, which in combination most likely caused a chronic metabolic alkalosis. Both an acute respiratory alkalosis (secondary to alcohol withdrawal and hyperventilation) and an acute hyperlactaemic metabolic acidosis (probably due to a combination of hypoperfusion of tissues, hypoxia, vitamin deficiency, increased gastrointestinal lactate production and impaired lactate breakdown by the liver and kidney) were superimposed on this state. We have reviewed the theoretical reasons why an alkalaemic state may potentiate a rise in the serum concentration of lactate under anaerobic conditions, contributing to such severe hyperlactaemia in this case. It has been postulated previously that this could be an appropriate response to minimize the effect of either a respiratory or metabolic alkalosis on the serum pH, and consequently on the function of cellular enzymes that are sensitive to changes in hydrogen ion concentration.

Teaching points

1. Bicarbonate concentration can be affected by changes in extracellular fluid volume, which therefore needs to be assessed clinically in patients with metabolic alkalosis.
2. Hypovolaemia and reduced tissue perfusion may lead to an increase in intracellular PCO2 in the peripheries, which in turn can cause an increase in venous bicarbonate concentration.
3. Alkalaemia can potentiate a rise in serum lactate concentration, which may then act as a feedback mechanism to minimize changes in pH.
4. Removal of lactate from extracellular fluid may be impaired in the presence of liver and/or kidney dysfunction.
5. Patients with malnutrition and lactic acidosis require an infusion containing B vitamins (including B1, B2 and B6) at the beginning of therapy.
Conflict of interest statement. None declared.

References


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