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Severe metabolic alkalosis with fludrocortisone therapy—a case report

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Abstract

Background: We present an atypical case of severe metabolic alkalosis, not reported in the literature to date.

Case Presentation: Owing to concerns of apneas and desaturation, a 75-year-old man presented to the emergency department with significantly deranged physiology: bicarbonate level of 63.6 mmol/L, a base excess of 40.6, and a potassium concentration of 1.9 mmol/L. Primary diagnoses included metabolic alkalosis secondary to fludrocortisone therapy with respiratory compensation, hypokalemia, and hypochloremia. He initially received potassium replacement with cardiac monitoring, followed by permissive hypercapnia in the intensive care unit. He received acetazolamide to further improve his acid-base status. The patient had a good outcome with gradual return of his pH and bicarbonate levels to baseline. He was then discharged.

Conclusion: Iatrogenic mineralocorticoid excess should be considered when the patient presents with significantly raised bicarbonate levels. When starting fludrocortisone, renal function needs to be diligently monitored due to risk of hypokalemia metabolic alkalosis.

Keywords: Case report, Electrolyte disorders, Fludrocortisone, Hypokalemia, Metabolic alkalosis

Introduction

This case report describes a severe case of metabolic alkalosis, secondary to fludrocortisone therapy for postural hypotension. This case is unique in the literature in terms of the extent of the alkalosis and its atypical presentation. Metabolic alkalosis is the most common acid-base disorder in intensive care patients.[1] It is defined as a blood pH of greater than 7.45 secondary to a metabolic process.[2] It results in an excess of bicarbonate ion levels in the blood. Mortality increases as pH increases[3]; 2 main causes include metabolic alkalosis with extracellular fluid volume depletion and with extracellular fluid volume expansion.[3] Fludrocortisone is a synthetic mineralocorticoid,[4] which acts at the mineralocorticoid receptors. Fludrocortisone is used as an unlicensed treatment for neuropathic postural hypotension at a dose of 100–400 µg daily.[5] Through this case report, we hope to educate both critical care and emergency medicine physicians in the management of extreme presentations of this common disorder.

Patient information

A 75-year-old man presented to the emergency department of our district general hospital. The patient was brought in by both his full-time caregiver and wife. His key presenting features were apneic episodes leading to desaturation and new confusion over the last few days. On arrival, he was diagnosed with severe metabolic alkalosis and severe hypokalemia. He had respiratory compensation with consequent hypercapnia. His venous blood gas is shown in Table 1.

This patient had the relevant background medical history of cervical spinal cord injury, requiring home ventilation via a non-invasive positive pressure ventilator machine. His home ventilation settings were bilevel positive airway pressure mode with a pressure support of 30, positive end-expiratory pressure of 6, and a backup ventilatory rate of 20 breaths per minute. He had a long-standing right lung collapse secondary to previous microaspirations. He also had a permanent cardiac pacemaker secondary to third-degree heart block, which developed after his spinal cord injury. He had recently been admitted to his tertiary respiratory unit for routine assessment of his ventilation and a percutaneous endoscopic gastrostomy insertion. He had an arterial blood gas during that admission with a pH of 7.46, bicarbonate level of 33.9, a base excess of 8.9, and potassium of 4.5. He was started on fludrocortisone therapy of 100 µg 8-hourly, for postural hypotension which was affecting his ability to be transferred via hoist. A previous blood gas prior to that admission and commencement of fludrocortisone did not show metabolic alkalosis.

Clinical findings

On examination a size 5 Trachoe twist tracheostomy was in situ. It was patent and well sited. There was no air entry on the right side of the chest. He had a blood pressure of 155/67 and a heart rate of 53 with a paced rhythm on electrocardiogram. His heart sounds were normal, with no murmurs. He had peripheral edema noted in both the upper and lower limbs. He was clinically hypervolemic. He communicated via lip reading and mouthing at baseline. His wife reported his answers were confused compared with normal. His capillary blood glucose was normal. He had a catheter in situ, with reported normal urine output over the past few days. He had a soft abdomen, with no

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Table 1

Venous Blood Gas on Presentation

Value	Result	Unit
pH	7.513	—
pCO_2	10.6	kPa
pO_2	4.5	kPa
Hb	100	g/L
sO_2	66.6	%
FCOHb	3.1	%
Na^+	146	mmol/L
K^+	1.9	mmol/L
Cl^-	72	mmol/L
Ca^{2+}	1.17	mmol/L
Glucose	3.9	mmol/L
Lactate	0.7	mmol/L
Base excess	40.6	mmol/L
HCO_3^-	63.6	mmol/L
Anion gap	10.3	mmol/L

stoma output that day but a healthy pink-looking stoma. His mobility was at his baseline of being bedbound and requiring a hoist for transfers.

Diagnostic assessment

The patient had a chest X-ray showing no new changes compared with that during previous imaging. His arterial blood gas was remarkable (Table 1). His formal laboratory blood analysis showed a potassium level of 2 mmol/L and a normal renal function. His magnesium level was normal on admission. He had no markers of infection. His liver function tests were normal.

Therapeutic intervention

The patient was initially examined in the emergency department, and IV potassium replacement was commenced with 40 mmol potassium over 4 hours. He had an arterial line inserted to monitor serial arterial blood gases. The decision was made to admit him to intensive care unit (ICU) for management of his ventilation and cardiac monitoring. On arrival in the ICU, he was transferred from his own ventilator to the intensive care Drager ventilator to allow for finer control of his ventilation. We employed a strategy of permissive hypercapnia to mimic and maintain his normal physiological respiratory compensation for metabolic alkalosis. He was treated with acetazolamide 500 mg intravenously 12-hourly for 3 days. His fludrocortisone was already stopped by his caregiver due to the development of peripheral edema.

Follow-up and outcomes

Over a period of 12 hours, his pH normalized. His bicarbonate levels returned to his baseline over the following 6 days. He unfortunately developed a hospital-acquired pneumonia, but was discharged home upon resolution. He had follow-up arranged with his tertiary care unit prior to discharge. We were saddened to learn that the patient died 5 months after his admission to our unit. We do not know the cause of death.

Discussion

The strengths of this case report are that we had access to high-quality information via the intensive care electronic patient record. This meant that we could review the trends of his blood pH and potassium level. It enabled us to see the time frame over which correction occurred and exactly what medications were given and for how long. The limitations of this case study are that the patient had an unusual mixture of preexisting conditions and treatments. This means that the findings may be less applicable to the general population who present with metabolic acidosis.

We searched for similar cases in the literature and found only one case report, published in 1983 by Burns et al.,[6] which describes a patient who developed severe metabolic alkalosis secondary to unmonitored fludrocortisone therapy. She presented with a bicarbonate of 40.1 mmol/L, potassium of 1.9 mmol/L, and a partial pressure of carbon dioxide of 11.7 kPa. The extent of the metabolic alkalosis was not equivalent to that of our patient. We found no recent cases of a similar presentation or cases involving existing mechanical ventilation or pacemakers.

The usual clinical presentation of metabolic alkalosis involves both neuromuscular and cardiac features. Signs and symptoms are secondary to electrolyte disturbance. They include confusion, paresthesia, muscle weakness, and arrhythmia.[7] This patient presented atypically with hypoxia and apneic episodes. Hypoxia results from a left shift in the oxyhemoglobin curve due to metabolic alkalosis, leading to reduced oxygen delivery to the tissues. Hypoventilation and apneas result from respiratory compensation for metabolic alkalosis with resultant hypercapnia. Our patient was ventilated at home due to his high spinal cord injury, which protected him from severe hypoxia and death, secondary to apnea and hypoventilation. Similarly, he had a permanent pacemaker that protected him from bradyarrhythmias, associated with hypokalemia. Notably, tachyarrhythmias can also occur with hypokalemia[8]; however, a pacemaker would not protect from these. Our patient had no evidence of tachyarrhythmias.

Differential diagnosis of metabolic alkalosis is categorized by the extracellular fluid status. The causes are summarized in Table 2.[3,9–11] Pathogenesis of metabolic alkalosis is a 2-stage process. First, either bicarbonate must be added to or abnormally retained in the extracellular fluid, or hydrogen ions must be lost from it. For the metabolic alkalosis to continue, there must then be an impairment of the usual system for maintaining homeostasis. This impairment can be due to hypovolemia, hypochloremia, hypokalemia, hyperaldosteronism, reduced glomerular filtration rate, or a combination of these factors.[12]

Our patient had significant metabolic alkalosis with respiratory compensation. He had an associated hypokalemia and hypochloremia. We considered possible causes of metabolic alkalosis in this case. Hydrogen ion loss from the gastrointestinal tract was ruled out as this patient had no history of vomiting or high stoma output. He also had features of volume overload, rather than of dehydration. His volume status also made rebound alkalosis following hypercapnia unlikely. Hydrogen ion loss from the kidney is often due to diuretics, and he had no diuretic use change in the preceding days or

Table 2

Causes of Metabolic Alkalosis[3,9–11]

Extracellular Fluid Depletion	Extracellular Fluid Expansion
Vomiting/nasogastric suction	Intravenous fluid administration
Diarrhea	Citrate administration, eg, significant blood transfusion
Thiazide diuretics	Primary aldosteronism, eg, Conn's syndrome
Loop diuretics	Secondary aldosteronism, eg, renal artery stenosis, renal artery vasoconstriction
Bartter syndrome	Exogenous mineralocorticoids
Gitelman syndrome	Congenital adrenal hyperplasia
Cystic fibrosis with severe perspiration	Excessive licorice ingestion
Rebound following hypercapnia	Liddle syndrome

weeks. Bicarbonate gain was considered, but again there was no history of exogenous bicarbonate administration. Primary causes of hyperaldosteronism were considered; however, the most likely cause was bicarbonate retention, secondary to exogenous mineralocorticoid administration. The presence of hypokalemia and a history of recent fludrocortisone commencement supported this diagnosis. Bartter's, Gitelman, cystic fibrosis, and Liddle syndromes are all likely to be diagnosed in childhood; hence, these were not considered as likely causes. Due to the patient's preexisting medical conditions, he had a plethora of regular medicines; however, the only new medication was fludrocortisone. None of his usual medicines had been stopped or had a dose change during the time frame of hypokalemia or metabolic alkalosis development.

Our patient was prescribed fludrocortisone for management of postural hypotension. This is an unlicensed use and is specific to neuropathic postural hypotension. The evidence base for this indication is poor.[13] Fludrocortisone is also indicated for management of adrenocortical insufficiency, including in cases of septic shock.[5] Fludrocortisone is a synthetic mineralocorticoid, which acts at the aldosterone receptor. The aldosterone receptor is a steroid receptor and therefore exerts its effects on gene expression. Aldosterone receptor agonism leads to increased synthesis of epithelial sodium channels (ENaCs), leading to increased numbers in the luminal membranes of the principal cells. These cells are found in the distal convoluted tubules of the kidney. These are coupled channels for sodium entry and potassium exit from the principal cells; therefore, more sodium is reabsorbed from the tubular fluid, and more potassium is lost into it. Aldosterone receptor activation also leads to increased activity of the sodium-potassium ATPase on the basement membrane of the principal cells, which means increased sodium is reabsorbed into the blood, and increased potassium is secreted from it. Sodium retention leads to increased plasma volume and increase in blood pressure. This is the mechanism of treatment of postural hypotension. However, the loss of potassium ions can lead to the side effect of hypokalemia. Hydrogen ions are also excreted.[14] Bicarbonate reabsorption is increased in the proximal and distal tubules in the presence of hypokalemia, resulting in metabolic alkalosis. Other serious or long-term effects of fludrocortisone therapy include hypertension, edema, congestive cardiac failure, raised intracranial pressure, change in behavior, stomach ulcers, gastric perforation, muscle weakness, osteoporosis, pathological fractures, glaucoma, cataracts, and weight gain.[15]

Acetazolamide, the main pharmacological intervention used for our patient, is a carbonic anhydrase inhibitor, which inhibits renal reabsorption of bicarbonate ions. Its use for metabolic alkalosis with acute respiratory failure has been evaluated by systematic reviews.[16,17] Acetazolamide has the known side effect of hypokalemia and hence is contraindicated for use in the presence of low potassium.[18] Use of acetazolamide was successful in this case, as management on the ICU allowed for frequent monitoring of serum potassium and replacement via central access, if required. Upon reflection, a more suitable pharmacological management would have been amiloride, a synthetic pyrazine derivative. It acts upon the ENaCs, found in the luminal membranes of principal cells in the distal convoluted tubules and collecting ducts. Amiloride reversibly blocks these channels, meaning that sodium excretion is reduced. This alters the potential difference across the luminal membrane; hence, it is no longer in favor of potassium and hydrogen ion excretion. Potassium and hydrogen are therefore retained.[19] This diuretic would therefore have been useful in dual management for correction of metabolic alkalosis as well as hypokalemia. Spironolactone could also have been considered as another potassium-sparing diuretic,[20] acting as an antagonist at the aldosterone receptor. Its maximum effect occurs at 2–3 days; it may thus be less useful in the acute setting.[21]

Conclusion

One important conclusion to draw from this case report is to consider iatrogenic mineralocorticoid excess, when the patient presents with significantly raised bicarbonate. It is also important to remember that when starting fludrocortisone, renal function needs to be monitored owing to risk of hypokalemia metabolic alkalosis. Additionally, we caution against correction of secondary hypercapnia, as this is an appropriate physiological compensation, and correction of the hypercapnia can worsen alkalosis. Amiloride is a logical pharmacological intervention for management of extreme hypokalemic metabolic alkalosis; however, in this case, acetazolamide was used successfully.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Williams GSM was the intensive care registrar on call when the patient presented to the hospital. She initiated intensive care management and drafted the article. Hinxman H was the intensive care consultant-on-call when the patient presented to the hospital. She formulated the management plan for the patient and reviewed and edited the article.

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Ethical approval of studies and informed consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. The Health Research Authority decision tool[22] was used to determine if Ethics Committee review was required for this case report; the outcome was that no review was required. Written informed consent was obtained from the patient's wife as the patient lacked the capacity to consent.

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