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AN UNEXPECTED CAUSE OF SEVERE METABOLIC ACIDOSIS

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ABSTRACT

Introduction: Metabolic acidosis is a potentially serious electrolyte disorder with a variety of potential causes. It can cause serious harm to multiple organ systems with irreversible damage and if untreated it can even cause mortality.

Case description: A 66-year-old man presented at the emergency room of our hospital because of abdominal pain, nausea, and vomiting for 3 days, with no diarrhoea. Physical examination showed a sick, restless, shaking, middle-aged man with a maximal eye-motor-verbal score. He had a history of polycythaemia vera but had been lost to follow-up. He was clinically dehydrated with extremely dry mucous membranes and complaining of thirst. Laboratory investigations showed severe metabolic acidosis with a pH of 7.08 and electrolyte disturbances with hyperkalaemia and hyponatremia. The treatment with a high dose of hydroxyurea had been re-started 14 days before presentation at the emergency room.

Conclusion: We believe that the recent initiation of the treatment with a (too) high dose of hydroxyurea with consequently gastrointestinal complications could have been the underlying cause. In addition to the indirect effect of dehydration resulting from the gastrointestinal side effects of hydroxyurea, another known but rarely reported adverse effect is (tubular) renal dysfunction, which may have contributed to the progression of metabolic acidosis. The exact mechanisms by which hydroxyurea induces metabolic acidosis remain unknown. It is important to recognize hydroxyurea as the culprit of the development of severe metabolic acidosis. If unrecognized, metabolic acidosis can worsen and cause irreversible damage.

KEYWORDS

Metabolic acidosis, hydroxyurea, anion gap

LEARNING POINTS

- Metabolic acidosis is a potentially severe, even lethal metabolic derangement.
- Hydroxyurea can be the causative agent through indirect side effects on the gastrointestinal system causing dehydration.
- In rare instances hydroxyurea can cause direct (tubular) renal failure thus adding to the development of metabolic acidosis.

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INTRODUCTION

Metabolic acidosis is a condition characterized by a decrease in blood pH due to excessive acid accumulation or a significant loss of bicarbonate[1]. A variety of health problems can cause severe metabolic acidosis[1]. Among them are diabetic ketoacidosis, lactic acidosis due to tissue hypoxia, chronic kidney disease, and severe diarrhea. Metabolic acidosis can cause serious harm to multiple organ systems, in particular to the respiratory, cardiovascular, and neurological systems[1]. If detected and treated in time, metabolic acidosis can well be reversible. However, a delay in diagnosis and treatment can cause severe irreversible morbidity and even mortality[1]. Apart from the well-known potential causes of metabolic acidosis some other rare causes have been described. In this report we describe a case of severe metabolic acidosis combined with severe electrolyte disturbances due to an unexpected cause, which, to our knowledge, has not been documented before.

CASE DESCRIPTION

A 66-year-old man presented at the emergency room (ER) of our hospital because of abdominal pain, nausea, and vomiting since 3 days, with no diarrhoea. He had no appetite, and he complained of postprandial vomiting. The stomach content was dark red/black. He felt very weak and suffered from generalized muscle pain and weakness. He had a history of polycythaemia vera, diagnosed 3 years previously, but he had been lost to follow up since approximately 6 months. However, therapy with a high dose of hydroxyurea had been re-started 14 days before presentation at the ER. A few days before presentation he had gone to his family practitioner due to a nosebleed. Since 2 days, he had used flucloxacillin and amoxicillin-clavulanate, prescribed by the family physician because of a suspected skin infection.

Physical examination showed a sick, restless, shaking middle-aged man with a maximal eye-motor-verbal score. The patient was clinically dehydrated with extremely dry mucous membranes and complaining of thirst. The blood pressure was 131/45 mmHg, and the pulse rate 112 bpm. The respiratory rate was 25 rpm, with an oxygen saturation of 99% on room air. The abdomen was soft with normal peristalsis and no pain. Body temperature was 36.3 °C. No skin lesions were observed.

Additional laboratory investigations *(Table 1)* showed severe acidosis with a pH of 7.08, and electrolyte disturbances with hyperkalaemia and hyponatremia. Plasma lactate was 0.9 mmol/l and plasma bicarbonate 6.4 mmol/l with an anion gap of 32.6. The blood urea nitrogen was severely disturbed. In addition, there was pancytopaenia. The electrocardiogram showed a sinus tachycardia of 108 bpm with a QRS time of 192 ms and spikey T tops.

Because of the severe hyperkalaemia the patient was given 30 ml of calcium gluconate and 50 ml of dextrose with 10 IU of insulin aspart. He was admitted to the Intensive Care Unit and treated with intravenous infusion of 2000 ml NaCl 0.9% in 2 hours followed by 2000 ml per 24 hours. In addition, he received 100 ml of sodium bicarbonate 8.4%, 6 doses daily of 5 mg salbutamol inhalers, and pantozol because of potential hematemesis. In accordance with the nephrologist, we decided to continue with conservative treatment to avoid dialysis. Within 4 hours after admission the pH increased to 7.31 and the plasma potassium concentration decreased to 6.2 mmol/l, with an anion gap of 34.5 *(Table 1)*. The plasma sodium concentration increased to 130 mmol/l which was judged as an excessively rapid increase. The time course of the metabolic corrections is shown in *Table 1*.

In the following days electrolytes, bicarbonate levels, anion gap and pH improved significantly *(Table 1)*. However,

	T 0	T 4h	T 1d	T 2d	T 3d	T 4d	T 5d
pH	7.08	7.31	7.27	7.32	7.35	7.44	7.48
Lactate (mmol/l)	0.9	1.3	0.9	1.0	1.5	1.4	1.2
Sodium (mmol/l)	118	130	128	131	132	134	140
Bicarbonate (mmol/l)	6.4	10.5	10.6	10.8	14.2	17.1	26.6
Potassium (mmol/l)	8.2	6.3	6.4	5.9	4.6	4.2	3.2
Anion gap	32.6	34.5	27.4	27.2	28.3	27.9	18.4
Platelets ($\times 10^3/mm^3$)	89	-	56	21	15	34	41
Haemoglobin (Mmol/l)	7.3	-	5.0	4.9	4.5	4.7	4.9
Leucocytes ($\times 10^9$/l)	7.20	-	0.96	0.41	0.12	0.21	0.70
BUN (mmol/l)	77.0	75.2	78.2	74.6	71.9	69.8	53.9
Creatinine (mmol/l)	745	691	768	777	745	713	461

Abbreviations: T, timepoint; h, hours; d, days; BUN, blood urea nitrogen.

Table 1. Laboratory data at the time of admission and during follow up.

the pancytopenia worsened for 4 more days. The clinical condition of the patient improved substantially. The patient was discharged to the internal ward after 5 days.

DISCUSSION

Metabolic acidosis can arise from a variety of causes and has distinct consequences on several organ systems[1]. The pathogenesis of metabolic acidosis can be classified into four primary mechanisms[1,2]:

1. Increased acid production occurs in lactic acidosis due to tissue hypoxia and keto acidosis in case of insulin deficiency;
2. In chronic kidney disease and in distal renal tubular acidosis the kidneys are unable to excrete the excess of H+-ions;
3. Loss of bicarbonate can occur during prolonged diarrhoea. Also, in proximal renal tubular acidosis the kidneys are unable to reabsorb bicarbonate;
4. Aggressive volume resuscitation with isotonic saline causes dilution of serum bicarbonate causing relative acidosis.

Calculation of the anion gap helps in determining the potential cause of metabolic acidosis[3]. The accumulation of unmeasured anions (e.g., lactate, ketones, or toxins) leads to an increased anion gap, which occurs in lactic acidosis, ketoacidosis, renal failure, and ingestion of toxins. If the anion gap is normal, which is also called hyperchloremic acidosis, bicarbonate is lost but chloride is retained, keeping the anion gap normal, which occurs in diarrhoea and in renal tubular acidosis.

In our patient there was no increase in acid production since plasma lactate was normal and ketones were not detected. Also, our patient did not have chronic kidney disease. In addition, there was no history of diarrhoea.

Apart from the actual metabolic disturbances, the medical history as well as the additional laboratory investigations led us to believe that another causative agent, namely, the recent re-starting of treatment with hydroxyurea and consequently the gastrointestinal complications, could have played a role. To our knowledge there is no scientific literature available describing the relationship between the use of hydroxyurea and metabolic acidosis. Hydroxyurea is an antimetabolite drug used in the treatment of polycythaemia vera[4]. The exact mechanism of action is not known although it is believed that the blockade of the ribonucleotide reductase system is the main effect. The usual dose in case of polycythaemia vera is 10-15 mg/kg body which in our patient corresponds to a maximum of 1500 mg per day. In older patients (>65 years) an even lower dose is recommended. Our 66-year-old patient however was treated with 3000 mg per day[4,5].

Side effects of the drug hydroxyurea include nausea, anorexia, general malaise, vomiting, abdominal pain, a variety of skin defects, gastrointestinal mucosal lesions, tubular kidney failure, anaemia, and thrombocytopaenia[5,6]. These were all symptoms and complaints of our patient. We believe that the gastrointestinal symptoms were the consequence of the hydroxyurea use. The blood loss during vomiting was probably the consequence of small intestinal mucosal lesions in combination with thrombocytopaenia. Although we did not see any skin lesions at the time of admission, the family physician had started antibiotic treatment since he suspected a skin infection which was probably skin defects as a side effect of hydroxyurea.

Metabolic acidosis is not a well-known common side effect of hydroxyurea. By direct mechanisms, through (tubular) renal failure, and indirect mechanisms, through gastrointestinal side effects, hydroxyurea can contribute to the development of metabolic acidosis[5,6]. In the setting of renal dysfunction, impaired hydrogen ion excretion and reduced bicarbonate reabsorption may result in metabolic acidosis[7]. In addition, hydroxyurea can cause the tumour lysis syndrome which can lead to metabolic acidosis[8]. Finally, in rare cases, hydroxyurea could cause other metabolic disturbances that might indirectly contribute to acid-base imbalances[8].

Theoretically, the combination of flucloxacillin and paracetamol could also lead to the development of metabolic acidosis. However, our patient had not used paracetamol prior to hospital admission. In addition, flucloxacillin had only been prescribed 3 days earlier, which does not correspond to the severity of the metabolic disturbances.

To our knowledge there are no previous descriptions of the relationship between the use of hydroxyurea and the development of metabolic acidosis.

In general, treatment of the underlying cause is the primary step in managing metabolic acidosis[1]. In cases of severe acidosis (pH <7.1), sodium bicarbonate may be administered to buffer the acidity and raise the pH[1]. However, bicarbonate therapy is controversial in some situations, such as in lactic acidosis, as it can lead to paradoxical worsening of tissue hypoxia[1]. In addition, supportive care in the form of fluid resuscitation, electrolyte correction, and if needed mechanical ventilation, are essential supportive treatments. In our case supportive care was provided and the administration of hydroxyurea was suspended. It is important to recognize hydroxyurea as a potential cause of severe metabolic disturbances, as failure to do so may lead to worsening metabolic acidosis and irreversible damage.

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