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CASE REPORT

Intractable Normal Anion Gap Metabolic Acidosis in a Patient with Diabetic Ketoacidosis

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ABSTRACT

High anion gap metabolic acidosis (HAGMA) is a hallmark of Diabetic Ketoacidosis (DKA). Occasionally, a Normal Anion Gap Metabolic Acidosis (NAGMA) can be seen, especially during the treatment phase. In this case report, a 55-year-old lady with diabetes mellitus who presented with a 2-day history of fever, lethargy and multiple episodes of vomiting and diarrhoea. Initial laboratory investigations revealed: capillary blood glucose as 27 mmol/L, urine ketone as 3+, blood ketone as 3.5 mmol/L, serum bicarbonate as 14 mmol/L, and serum chloride as 95 mmol/L. She was treated with intravenous normal saline fluid resuscitation and constant rate insulin infusion which was fortunately accompanied by stabilization of blood glucose and normalization of blood ketone to 0.2 mmol/L. However, despite normalization of her anion gap (25 to 14), she remained unwell with acidotic breathing due to refractory hyperchloraemic NAGMA with bicarbonate at 11 mol/L and chloride of 112 mmol/L. It was then decided to administer 100 mL of 8.4% Sodium Bicarbonate solution. The next day, she was no longer tachypneic as her bicarbonate and carbon dioxide improved to 21 mmol/L and 32 mmHg respectively. The presence of NAGMA in DKA should prompt clinicians to conduct a thorough search for possible underlying causes, such as gastrointestinal fluid loss, sepsis and chloride load from aggressive fluid resuscitation with normal saline. Sodium bicarbonate should only be considered in intractable cases to correct a NAGMA and not routinely used in the treatment of DKA.

INTRODUCTION

Diabetic Ketoacidosis (DKA) is an acute life-threatening medical emergency that can be observed in patients with both type 1 and type 2 diabetes mellitus. It is characterized by the presence of hyperglycaemia, ketonaemia and a high anion gap metabolic acidosis (HAGMA)[1]. The accumulation of beta-hydroxybutyrates and acetoacetate leads to a high anion gap metabolic acidosis (HAGMA) in DKA. Interestingly, HAGMA can be changed to NAGMA during recovery and treatment phase. One of the reasons for developing NAGMA could be due to the loss of bicarbonate ions during the urinary excretion of ketones. The second reason could be the development of hyperchloremic metabolic acidosis (HMA)[2]. During recovery from diabetic ketoacidosis (DKA), many patients may eliminate the organic anions (through increased renal clearance and utilization) faster than their acidosis resolves. The clinical picture can resemble a normal anion gap acidosis. Excessive fluids with isotonic chloride levels may contribute to this acidemia[3].

CASE PRESENTATION

A 55-year-old lady with long-standing diabetes mellitus presented with a 2-day history of fever, lethargy, multiple episodes of vomiting and diarrhoea. Her diabetes had been managed with metformin and insulin due to poor glycaemic control. Other histories including travel history, sick contacts, family history, social history were largely unremarkable. On examination, she is alert, tachypneic, appeared ill, dehydrated and lethargic with a rapid heart rate (120 beats per minute, sinus tachycardia), and fever (temperature 38°C) Her peripheries were cold, and her mucous membranes were dry due to dehydration. Her initial laboratory investigations revealed: capillary blood glucose as 27 mmol/L, urine ketone as 3+, blood ketone as 3.5 mmol/L, serum bicarbonate as 14 mmol/L, and serum chloride as 95 mmol/L.

With the diagnosis in mind, she was transferred to a high dependency unit for close monitoring and further treatment. She was promptly treated with intravenous normal saline fluid resuscitation followed by a constant rate insulin infusion which fortunately accompanied by stabilization of blood glucose and normalization of blood ketone to 0.2 mmol/L. However, despite normalization of her anion gap (28 to 14), she remained unwell with acidotic breathing due to refractory hyperchloraemic NAGMA with bicarbonate 11 mmol/L and chloride of 112 mmol/L (Table 1). It was then decided to administer 100 mL of 8.4% sodium bicarbonate solution. The next day, she was no longer tachypneic as her bicarbonate and carbon dioxide improved to 21 mmol/L and 32 mmHg respectively.

Table 1 Blood investigation report of the patient

	Upon admission	Day 1	Day 2	Day 3	Day 4	Day 5
Sodium (mmol/L)	137	139	137	135	137	137
Potassium (mmol/L)	3.9	3.4	3.9	3.0	3.6	4.0
Chloride (mmol/L)	95	108	112	106	105	107
Hc03 (mmol/L)	14	15.3	11	18.3	21.6	23.4
Ph	7.21	7.29	7.32	7.49	7.48	7.50
Anion gap (mmol/L)	28	16	14	11	10	7

She was discharged well after 2 weeks of hospitalization upon completion of antibiotics for *Escherichia coli* bacteraemia which was cultured in peripheral blood. In-patient ultrasonography of the abdomen did not reveal any intraabdominal abscesses or collection secondary to *Escherichia coli* bacteraemia. She was well with good glycaemic control when she was reviewed back again at our outpatient clinic. Repeated blood gases were all in normal ranges.

DISCUSSION

DKA is classically linked to a HAGMA. However, a variable degree of NAGMA can occasionally be observed, more commonly during the treatment phase or among patients with DKA presenting late in the disease course[4]. The proposed mechanism of NAGMA in DKA is twofold. Firstly, in patients with DKA, there is a net urinary loss of bicarbonate in the form of keto-anions. In the early stages of less severe disease, most of these keto-anions are reabsorbed in the kidneys and metabolized to bicarbonate. This phenomenon is lost in severe cases or delayed presentations[5]. Secondly, during the treatment phase, NAGMA is aggravated by aggressive fluid resuscitation with normal saline[6]. Despite being widely used in fluid resuscitation, various studies have demonstrated that administration of large volumes of normal saline is associated with hyperchloraemia and hyperchloraemic metabolic acidosis.[6, 7].

We believe that the presence of NAGMA in DKA should prompt clinicians to conduct a thorough search for possible underlying causes, such as ongoing gastrointestinal fluid loss, sepsis and chloride load from aggressive fluid resuscitation with normal saline. This patient had multiple episodes of vomiting and diarrhoea that did not resolve until day 4 of admission. She was in sepsis secondary to *Escherichia coli* bacteraemia. Besides, she was initially resuscitated with large volumes of normal saline which led to the increment of serum chloride levels from 95 mmol/L to 112 mmol/L. The anion gap has normalised, however, she remained in metabolic acidosis. After administration of sodium bicarbonate solution, the metabolic acidosis has completely resolved. In another case report of a 21-year-old male, presented with DKA and subsequently progressed into hyperchloraemic NAGMA after being administered with aggressive fluid resuscitation of normal saline. In view that he remained in refractory metabolic acidosis, sodium bicarbonate was then administered. The next day, the acidosis has resolved[4]. In another retrospective analysis, delta ratio was calculated for all patients to study the metabolic acidosis. A delta ratio between 0.4 – 1 signifying mixed HAGMA and NAGMA, while a delta ratio of less than 0.4 signifying a pure NAGMA[5]. Calculation of the delta gap will help to identify concomitant metabolic alkalosis. Intravenous sodium bicarbonate is indicated when acidosis is due to a change in bicarbonate level (normal anion gap acidosis)[8].

Serum bicarbonate should not be used as a sole marker of DKA resolution as overzealous fluid resuscitation in the setting of refractory acidosis can lead to complications and adverse patient outcome. A retrospective analysis showed that even after the anion gap is closed with insulin therapy, NAGMA can persist. It would be prudent to use bicarbonate therapy in these situations[3]. NAGMA also can occur in the excretion of ketoacid in the urine, hence it can no longer be converted back into bicarbonate. Administration of sodium bicarbonate in this case is a logical therapy for NAGMA because this reflects a bicarbonate deficiency.

CONCLUSION

This case report demonstrated an uncommon but important phenomenon of DKA, which is a common medical condition. Physicians should focus on various mechanisms that might lead to a NAGMA in patients of

DKA. Clinicians need to be aware of this phenomenon to ensure an early diagnosis, better treatment and patient outcome.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this article.

CONSENTS

Written consent was obtained from the patient to publish the case. A copy of the written consent is available for review by the Chief Editor.

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