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Acid-Base and Electrolyte Teaching Case

Approach to the Treatment of Diabetic Ketoacidosis

Kamel S. Kamel, MD, FRCPC,[1,2] Martin Schreiber, MD, FRCPC,[1] Ana P.C.P. Carlotti, MD,[3] and Mitchell L. Halperin, MD, FRCPC[1,2]

Diabetic ketoacidosis (DKA), a common cause of severe metabolic acidosis, remains a life-threatening condition due to complications of both the disease and its treatment. This Acid-Base and Electrolyte Teaching Case discusses DKA management, emphasizing complications of treatment. Because cerebral edema is the most common cause of mortality and morbidity, especially in children with DKA, we emphasize its pathophysiology and implications for therapy. The risk for cerebral edema may be minimized by avoiding a bolus of insulin, excessive saline resuscitation, and a decrease in effective plasma osmolality early in treatment. A goal of fluid therapy is to lower muscle venous P_{CO_2} to ensure effective removal of hydrogen ions by bicarbonate buffer in muscle and diminish the binding of hydrogen ions to intracellular proteins in vital organs (such as the brain). In patients with DKA and a relatively low plasma potassium level, insulin administration may cause hypokalemia and cardiac arrhythmias. It is suggested in these cases to temporarily delay insulin administration and first administer potassium chloride intravenously to bring the plasma potassium level close to 4 mmol/L. Sodium bicarbonate administration in adult patients should be individualized. We suggest it be considered in a subset of patients with moderately severe acidemia (pH $<$ 7.20 and plasma bicarbonate level $<$ 12 mmol/L) who are at risk for worsening acidemia, particularly if hemodynamically unstable. Sodium bicarbonate should not be administered to children with DKA, except if acidemia is very severe and hemodynamic instability is refractory to saline administration.

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INDEX WORDS: Diabetic ketoacidosis (DKA); cerebral edema; acidemia; hypokalemia; metabolic acidosis; type 1 diabetes mellitus (T1DM).

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting either the diagnosis or treatment of acid-base and electrolyte disorders.

INTRODUCTION

A life-threatening complication of type 1 diabetes mellitus is diabetic ketoacidosis (DKA), which develops when there is a lack of insulin actions and unopposed effects of glucagon. DKA may be the initial presentation of type 1 diabetes mellitus or occur when a patient with diagnosed type 1 diabetes mellitus fails to administer insulin. A severe illness such as pneumonia or myocardial infarction causes elevated levels of hormones opposing insulin (eg, adrenalin and glucocorticoids) and may precipitate DKA.

In this Acid-Base and Electrolyte Teaching Case, we emphasize important complications of DKA, their pathophysiology, and our recommendations for treatment (detailed reviews of the pathophysiology of DKA are available[1,2]).

CASE REPORT

Clinical History and Initial Laboratory Data

A 17-year-old boy, who previously weighed 50 kg, developed flu-like symptoms 2 weeks before presentation. Subsequently, he noted increased thirst, for which he drank large volumes of sweetened soft drinks, and his urine output increased markedly. Thirty-six hours before presentation, he changed to drinking mostly water. He lost 4 kg in 2 weeks. He was brought to the hospital confused and drowsy.

On examination, the patient was tachypneic, breathing deeply, and his breath smelled of acetone. Blood pressure was 90/60 mm Hg, heart rate was 110 beats/min, and jugular venous pressure was flat.

Laboratory results are shown in Table 1. The patient had metabolic acidosis with a high plasma anion gap of 30 mEq/L, plasma glucose level of 50 mmol/L, positive serum ketones, plasma β-hydroxybutyrate level of 12 mmol/L, and plasma potassium level of 3.5 mmol/L.

Diagnosis

Diabetic ketoacidosis, with severe hyperglycemia, metabolic acidosis, increased plasma anion gap, positive serum ketones, and elevated β-hydroxybutyrate level in plasma.

Clinical Follow-up

The patient was carefully resuscitated with potassium chloride and 0.9% saline, ensuring that the effective plasma osmolality did

From the [1]Renal Division, St Michael's Hospital and University of Toronto, Ontario, Canada; [2]Keenan Research Center in the Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada; and [3]Division of Pediatric Critical Care Medicine, Department of Pediatrics, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil.

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Address correspondence to Kamel S. Kamel, MD, FRCPC, University of Toronto, Division of Nephrology, St. Michael's Hospital, Toronto, Ontario, M5B 1W8, Canada. E-mail: kamel.kamel@utoronto.ca

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Table 1. Laboratory Results

Parameter	Value
pH	7.25
P_{CO_2} (arterial), mm Hg	25
P_{CO_2} (venous), mm Hg	50
HCO_3^-, mmol/L	10
Na^+, mmol/L	130
K^+, mmol/L	3.5
Cl^-, mmol/L	90
Anion gap, mEq/L	30
Albumin, g/L	50
Glucose, mmol/L	50
Creatinine, μmol/L	190
eGFR, mL/min/1.73 m^2	45
SUN (urea), mmol/L	20
Hematocrit	0.50
β-Hydroxybutyrate, mmol/L	12
L-Lactate, mmol/L	2

Note: Conversion factors for units: glucose in mmol/L to mg/dL, ÷0.05551; creatinine in μmol/L to mg/dL, ÷88.4; SUN in mmol/L to mg/dL, ÷0.357.

Abbreviations: eGFR, estimated glomerular filtration rate; SUN, serum urea nitrogen.

not decrease. Insulin was later added, with correction of the ketoacidosis and the hyperglycemia.

DISCUSSION

Two major treatment concerns were raised. First, the patient's plasma potassium level was low compared with the usual levels in patients with DKA, posing a risk for severe hypokalemia with insulin administration. Second, his young age put him at risk for cerebral edema during therapy.

Cerebral edema is the main cause of mortality and morbidity in children and adolescents with DKA, with an incidence close to 0.5% to 1%.[3] Most cases of cerebral edema occur between 3 and 13 hours after starting therapy,[4] so changes in the initial therapeutic approaches may be needed.[5]

Factors that contribute to cerebral edema act by increasing the intracellular fluid (ICF) volume of brain cells or brain extracellular fluid (ECF) volume.[6] Effective osmoles are those largely restricted to either the ICF or ECF compartment. Water travels swiftly across cell membranes to equalize total concentrations of effective osmoles on both sides. ICF volume expands due to an increase in the number of ICF effective osmoles and/or a decrease in the concentration of ECF effective osmoles.

Activation of the sodium/hydrogen ion exchanger 1 (NHE1) in cell membranes may increase the amount of effective osmoles in brain cells as sodium ions enter brain cells while exported hydrogen ions are bound to ICF proteins and thus are not effective osmoles. These sodium ions may then be exported by the adenosine triphosphatase sodium/potassium pump (Na^+/K^+-ATPase) and replaced in brain cells by potassium ions that are also effective osmoles. Insulin treatment directly activates NHE1. During DKA, β-hydroxybutyric acid and acetoacetic acid enter brain cells on the monocarboxylic acid cotransporter, then dissociate into hydrogen ions and ketoacid anions. An increase in intracellular hydrogen ion concentration in the submembrane area near NHE1 may also result in its activation.[7] Analogues of amiloride that are selective inhibitors of NHE1 may be of benefit to decrease the risk for cerebral edema.[7,8]

Water may also enter brain cells due to a decrease in concentration of effective osmoles in the ECF compartment, reflected by a decrease in plasma effective osmolality. Plasma effective osmolality in patients with DKA is calculated as shown in the following equation (urea is not an effective osmole because it is transported across cell membranes and achieves equal concentrations in ECF and ICF; glucose is an effective osmole for brain cells, when there is a relative lack of insulin. Plasma effective osmolality $= 2\ (P_{Na}) + (P_{glucose})$ (mmol/L), where P_{Na} is plasma sodium level and $P_{glucose}$ is plasma glucose level. A decrease in plasma glucose level and/or a gain of electrolyte-free water will decrease plasma effective osmolality. A rapid decrease in plasma glucose level is largely due to glucosuria when glomerular filtration rate increases after effective arterial blood volume expansion. Sources of electrolyte-free water include hypotonic saline administration or intravenous dextrose administration in water solutions to prevent neuroglycopenia when plasma glucose level decreases. Electrolyte-free water may also be added from fluid previously ingested by the patient but retained in the stomach because hyperglycemia slows gastric emptying.[9] Water absorbed from the gut is added to portal venous blood, returned to the heart, and pumped to the body, potentially causing a decrease in arterial plasma effective osmolality, to which the brain is exposed.[10] This may not be detected initially in measurements in brachial venous blood.[11]

The ECF interstitial compartment expands with higher capillary hydrostatic pressure or lower plasma oncotic pressure. Both may occur following a large intravenous saline infusion.

Hyperkalemia (plasma potassium of ~5.5 mmol/L) occurs in most patients with DKA despite renal potassium losses, leading to a large total-body potassium deficit.[12,13] This suggests a potassium shift out of cells, primarily because of insulin deficiency and hyperglycemia-induced hyperosmolality.

The low plasma potassium level in our patient (3.5 mmol/L) implies severe potassium depletion. Insulin administration is likely to lower the plasma potassium level, which may cause cardiac arrhythmias. Both the American Diabetes Association and