Management of diabetic ketoacidosis

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Abstract

Although the mortality of diabetic ketoacidosis (DKA) has decreased substantially in the developed world, high mortality rates still prevail in South Africa, thus making this an important condition to recognise early and manage well. This review discusses the treatment of DKA, with emphasis on the controversial aspect of initial fluid replacement therapy. Current guidelines recommend the use of normal saline. The concern is that normal saline, when used in large volumes, leads to the development of a hyperchloraemic metabolic acidosis which is of uncertain clinical significance. This hyperchloraemic acidosis is better quantified using Stewart's model, as opposed to the "traditional" Henderson-Hasselbalch equation. Ringer's lactate is an alternative choice for initial fluid resuscitation, but may exacerbate the high lactate to pyruvate ratio in patients in DKA, and may cause hyperkaleamia. Insulin therapy, prevention of electrolyte abnormalities, and the replacement of bicarbonate and phosphate, are other important considerations in the management of the patient with DKA.

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Introduction

Diabetic ketoacidosis (DKA) continues to be a frequent cause of admission to the medical ward. In the developed world, the overall mortality rate of adult patients in DKA has been reduced to < 1%.[1] However, in the South African setting, mortality rates remain between 6.8-9%,[2,3] positioning DKA as an important condition that requires correct recognition and management. Furthermore, as the incidence of type 1 diabetes mellitus appears to be increasing in almost all populations worldwide,[4] it is likely that more patients will present in DKA in the future. In addition, awareness is needed of the recently defined entity of ketosis-prone diabetes in patients of African origin, who present in DKA, but who have the clinical and metabolic features of type 2 diabetes.[5] This review will focus on the treatment of DKA, with special emphasis on fluid therapy.

Fluids

Fluid replacement and intravenous insulin administration are the primary and most critical initial treatments of diabetic ketoacidosis (DKA). While it is accepted that fluid resuscitation is a crucial factor, the exact type of fluid to be used remains controversial. The fluid lost in DKA is predominantly due to osmotic diuresis, caused by glycosuria, with minor contributions from vomiting, pyrexia and hyperventilation.[6] The osmolality of the fluid lost is similar to half-normal saline, making it a relatively hypotonic fluid. Half the fluid loss in DKA is derived from the intracellular compartment, and the other half from the extracellular compartment.[6] Although fluid is lost from all body fluid compartments, patients present clinically with hypovolaemia, i.e. depletion of the intravascular compartment. In managing a patient who presents in DKA, the first priority should be to restore the circulating volume and improve tissue perfusion so that insulin may be adequately delivered to the sites of action.[7]

Colloid versus crystalloid solution

Colloid solutions are more effectively retained in the intravascular compartment than crystalloid solutions, and are most efficient for rapid resuscitation. However, a recent systematic review comparing colloid and crystalloid fluid resuscitation across a wide variety of clinical conditions (but not including DKA), failed to show a mortality benefit in favour of using colloid solutions.[8] Crystalloids are preferred as they are readily available and inexpensive compared to colloid solutions. Unlike colloid solutions, they also don't carry the risk of anaphylaxis. With regard to crystalloid solutions, choices include hypotonic solutions such as half-normal saline, or isotonic solutions like normal saline or Ringer's lactate. Table I compares the constituents of normal saline and Ringer's lactate.

Table I: Composition of intravenous fluids, based on one-litre bags

	Normal saline	Ringer's lactate
Na^+ mmol/l	154	130
K^+ mmol/l	0	4
Cl^- mmol/l	154	109
Ca^{2+} mmol/l	0	2.7
HCO_3^- mmol/l	0	0
Lactate mmol/l	0	28
pH	5.0	6.5
Osmolality	308	273

Isotonic versus hypotonic fluid

Since the fluid lost in DKA is hypotonic, should our initial choice of fluid replacement be isotonic or hypotonic?

Hypotonic solutions do not remain intravascular, and for that reason are not ideal for the purposes of initial resuscitation. However, they do manage to restore total body fluid losses with distribution to all three compartments. On the other hand, isotonic fluids are more efficient at restoring circulatory volume.[6] For every litre of infused isotonic saline, a quarter normally remains in the circulatory volume.[6] Because isotonic saline remains largely confined to the extracellular compartment, it does not provide free water to replace intracellular losses. Isotonic fluids are mainly distributed to the interstitial space, and if administered in excess, may lead to peripheral and pulmonary oedema when the interstitial compartment becomes overexpanded.[6]

Normal saline versus Ringer's lactate

Current guidelines from the USA and the UK recommend intravenous isotonic fluid replacement in the management of DKA. A recent consensus statement from the American Diabetes Association[9] advocates the use of isotonic saline as the initial fluid therapy in the absence of cardiac compromise. The Association of British Clinical Diabetologists' guideline[10] agrees. In fact, early studies on DKA in the 1970s used normal saline,[11] and its use continues to be advocated in modern textbooks.[12]

Over the past decade, a number of articles have compared two different approaches to interpreting acid-base disorders.[13,14] The "traditional" approach uses the Henderson-Hasselbalch equation to describe and classify metabolic acidosis. A shortcoming of the traditional approach is that it doesn't allow a distinction between the various possible causes of metabolic acidosis. The "modern" approach is Stewart's physical chemical approach: a model more useful for quantifying acid-base disorders. In Stewart's analysis, there are only three independent variables that determine pH:

- Partial CO_2 tension (PCO_2).
- Total concentration of weak acid (ATOT). In plasma, these consist of albumin and inorganic phosphate.
- Strong ion difference (SID). The SID describes the difference between the concentrations of the strong cations (Na^+, K^+, Mg^{2+}, and Ca^{2+}) and strong anions (Cl^-, lactate, ketoacids, sulphate and others) in a fluid compartment, and may be calculated using the complex equation below.

Any change in pH must be because of a change in one or more of these independent variables, or in the dependent variables, such as hydrogen ion concentration (H^+) and bicarbonate concentration (HCO_3^-).

Calculation of strong ion gap (SIG)

$$SIG = [(Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + lactate^-)] - (2.46 \times 10^{-8} \times PCO_2/10^{-pH} + [albumin\ (g/dl)] \times (0.123 \times pH - 0.631) + [PO4^-\ (mmol/l)] \times (pH - 0.469)]$$

The concern is that administration of large volumes of normal saline is associated with the development of a hyperchloraemic metabolic acidosis in the majority of patients.[15] This acidosis may be more accurately described as a strong ion acidosis.[16] A problem arises when clinicians use the base deficit in preference to the anion gap to document an improvement in the DKA. The base deficit, although an accurate measure of the total metabolic component of an acidosis, cannot differentiate between coexistent causes like ketosis and hyperchloraemia. Hyperchloraemia, if not explicitly recognised as giving rise to acidosis, may mask resolution of the ketoacidosis. The unwary clinician may erroneously interpret the low bicarbonate as being due to ongoing ketosis or hypovolaemia, and this may prompt an unnecessary alteration in therapy: either a change in insulin dose and/or increased fluid administration.

This is where Stewart's theory comes into play. The "traditional" Henderson- Hasselbalch model assumes that bicarbonate is an independent variable and is not influenced by chloride, hence it cannot satisfactorily explain the mechanism of the hyperchloraemic acidosis. However, Stewart's strong ion approach provides a mechanistic explanation for hyperchloraemic acidosis by using a set of equilibria that describes the chemistry of plasma.[17]

Besides the development of hyperchloraemic acidosis, the administration of large volumes of normal saline may theoretically cause hyperkalaemia through an extracellular shift of K^+ ions caused by acute changes in blood H^+ ion concentration, which occurs secondary to the hyperchloraemic acidosis.[15] A few small studies have suggested that normal saline administration may be detrimental to renal function.[15]

What about the use of Ringer's lactate in DKA? There are arguments against its use for several reasons. Patients in DKA have a high lactate to pyruvate ratio, and the 28 mmol/l of lactate in Ringer's lactate could exacerbate this.[18] Secondly, a litre of Ringer's lactate contains 4 mmol of potassium, which may be life-threatening for a patient who is initially hyperkalaemic. Another consideration is the cost. One litre of Ringer's lactate costs R33.72, as opposed to R12.77 for a litre of normal saline.[19]

Therefore, the question of which fluid replacement is optimal in DKA still remains unanswered. No randomised controlled trials are currently available to support the superiority of one fluid over another. Endocrinologists advocate normal saline, whereas critical care specialists argue against it due to the likelihood of saline causing a hyperchloraemic acidosis. Yet, there is no evidence in the literature that this is clinically significant or dangerous to patients. More prospective studies in this area are needed.

How much fluid to replace?

The average fluid deficit in an adult presenting in DKA is five-to-ten litres,[20] or 100 ml/kg. The fluid deficit may be calculated using the following formula:

Total body water deficit
= (0.6 x body weight in kg) x (1-140/serum Na^+)[21]

Corrected Na^+
= serum Na^+ + 1,6 x [(plasma glucose in mmol/l – 5.551)/5.551]

Patients should receive 1-1.5 l of fluid in the first hour,[9] and thereafter 250-500 ml per hour. The aim is to replace 50% of the fluid deficit during the first 12 hours of presentation, and the remainder within the next 12-16 hours.[22] Since hyperglycaemia is corrected faster than ketoacidosis,[23] dextrose-containing fluids should be used once the glucose falls to < 14 mmol/l to prevent hypoglycaemia.

Insulin therapy

Insulin remains the main component of DKA management. The most common way of administering regular insulin is via the intravenous route, either by continuous infusion, or by hourly administration of a bolus. A landmark randomised controlled trial in patients in DKA demonstrated that insulin is effective, irrespective of the route of administration.[24] In this trial, the group receiving insulin intravenously displayed the most rapid fall in plasma glucose and ketones, when compared to the groups receiving either subcutaneous or intramuscular insulin.[24] Subcutaneous insulin was found to have a delayed onset of action and prolonged half-life. Thus, if carefully titrated, continuous intravenous infusion of regular insulin remains the preferred route of therapy because of its short half-life and ease of titration.

Current treatment guidelines recommend an initial intravenous bolus of regular insulin of 0.1 u/kg, followed by an intravenous infusion of 0.1 u/kg/hour.[9] A more recent randomised controlled trial compared the use of this regimen to intravenous infusions of insulin without the use of a bolus.[25] The findings showed that a bolus dose of insulin was unnecessary if a slightly higher insulin infusion rate of 0.14 u/kg/hour was used.

Since the advent of the insulin analogues, studies have showed that subcutaneous administration of the insulin analogues is an effective alternative to regular insulin administered by the intravenous route in patients presenting in DKA. Patients with mild-to-moderate DKA were treated out of the intensive care unit (ICU) with subcutaneous insulin aspart every one or two hours.[26] This regimen was found to be as safe and effective as an intravenous insulin infusion administered in ICU. In this study, there was no mortality, no difference in length of hospital stay, and no difference in total dose of insulin used. There was approximately 30% less cost with the use of insulin analogues in the general ward, versus intravenous insulin infusions used in ICU. The use of insulin analogues by the subcutaneous bolus route may be a safe, effective and cost-saving alternative in patients with mild, uncomplicated DKA in the general ward setting. However, in our setting, patients are infrequently admitted to ICU and receive hourly regular insulin boluses in the general ward.

Potassium replacement

It is important to measure serum potassium levels before initiating insulin therapy. Patients in DKA usually present with mild-to-moderate hyperkalaemia. In these patients, serum potassium levels are an unreliable indicator of total body potassium, which is usually depleted. If the initial electrolyte panel shows a K^+ of < 3.5 mmol/l, potassium replacement should commence before initiating insulin therapy to avoid the risk of hypokalaemia. Insulin therapy and correction of acidosis cause potassium to move into cells, and may precipitate severe hypokalaemia with arrhythmias and muscle weakness complications. Thereafter, four-hourly monitoring of electrolytes should guide the need for further potassium replacement as shown in Table II. Potassium levels should be maintained within the normal range.

Table II: Guide to potassium chloride replacement

Serum K^+	Replacement
< 3 mmol/l	40 mmol KCl per litre
3.1-4.0 mmol/l	30 mmol KCl per litre
4.1-5.0 mmol/l	20 mmol KCl per litre
> 5 mmol/l	Omit KCl

Bicarbonate therapy

The use of bicarbonate in the treatment of DKA is controversial. A study on both human and animal subjects in DKA showed that administration of bicarbonate augments ketosis and markedly increases blood acetoacetate and B-hydroxybutyrate levels.[27] Bicarbonate therapy actually led to delayed improvement of blood ketones when compared to control subjects, despite more rapid correction of acidaemia. [27] A prospective randomised study in 21 patients showed no beneficial or deleterious effects in those receiving bicarbonate therapy for pH between 6.9-7.1.[28]

In both prospective and retrospective studies of patients in DKA, treated with or without sodium bicarbonate, there were no differences in cardiac or neurologic function, incidence of hypokalemia or hypoglycemia, or rate of recovery from ketoacidosis.[28,29,30] Therefore, no clinical benefit has been demonstrated by the administration of bicarbonate to treat DKA.

There are no prospective randomised studies that have used bicarbonate in patients with a pH < 6.9. Despite a paucity of data on such patients, in an attempt to err on the side of caution, bicarbonate use is advocated in these instances. The rationale is that the administration of sodium bicarbonate in patients with severe acidaemia will increase serum pH, thereby eliminating the potentially deleterious effects of acidaemia. Severe acidaemia causes a decrease in myocardial contractility, [31] a fall in cardiac output and a fall in blood pressure. It also sensitises the myocardium to arrhythmias. Acidaemia reduces the binding of norepinephrine to its receptors. Protons bind to intracellular proteins, as well as extracellular proteins, especially albumin and haemoglobin. Thus, acidaemia may adversely affect important cell functions such as enzymatic reactions, generation of ATP, fatty acid biosynthesis, and bone formation and resorption.[32] On the positive side, a decrease in pH reduces the affinity of haemoglobin for oxygen, thereby enhancing delivery of oxygen to tissues: also known as the Bohr Effect.

Current recommendations support the use of bicarbonate in patients in DKA with an admission pH < 6.9.[9] Patients should receive 100 mmol of 8.4% sodium bicarbonate in 400 ml of water, together with 20 mmol of potassium chloride administered at a rate of 200 ml per hour until the venous pH is more than 7.0. This infusion may be repeated until the pH reaches > 7.0.

It is important to remember that sodium bicarbonate therapy is not without potential harm. The sodium load may worsen hyperosmolarity and cause hypernatraemia. Administration of bicarbonate to humans and animals increases blood lactate, as well as ketone bodies.[27] A number of in vitro studies show that alkalinisation hastens cell death, i.e. acidosis has been shown to protect cells against hypoxic injury in a variety of organs, including the heart, lung and liver. [33,34,35] Potassium shifts into cells as pH rises, sensitising the heart to arrhythmias. It is important, when using bicarbonate, to carefully monitor and replace potassium. Serum ionised calcium concentration is reduced by sodium bicarbonate infusion.

In a study where normal human volunteers were made acidaemic with acetazolamide, and then corrected with sodium bicarbonate, the acute correction of the pH caused increased haemoglobin affinity for oxygen that worsened oxygen delivery to tissues. This effect lasted approximately eight hours.[36]

In summary, many potentially detrimental effects of bicarbonate administration have been identified, but whether these observations are all clinically relevant to humans in DKA is unknown. Further prospective controlled studies are required.

Phosphate replacement

Patients in DKA typically present with hyperphosphataemia, despite whole body deficits in phosphate. However, up to 90% of patients will become acutely hypophosphataemic within six to twelve hours of beginning therapy.[37,38] The hypophosphatemia, resulting from the treatment of DKA, may be attributed to transcellular shifts resulting from a number of factors, including fluid resuscitation, correction of acidosis, insulin therapy, and use of bicarbonate, which lower serum phosphate levels.[38,39]

Symptomatic hypophosphataemia is usually observed when plasma phosphorus falls below 0.32 mmol/l. The clinical manifestations of a low serum phosphate are diverse, and include altered mineral metabolism, disorders of skeletal and cardiac muscle, and respiratory depression. Rhabdomyolysis may complicate severe hypophosphataemia.[40] Another consequence of phosphate depletion is respiratory muscle weakness. This may delay the recovery of patients receiving mechanical ventilation.[41]

Wilson et al showed that the routine use of phosphate therapy does not affect the duration of DKA, dose of insulin required, rate of fall of glucose, morbidity or mortality.[42] However, a number of studies conducted in settings other than DKA show an association between hypophosphataemia and increased mortality.[43,44] It is unclear as to whether the hypophosphataemia contributes to the increased mortality, or whether it is just a marker of severity of illness.[45]

It is generally recommended that patients with severe hypophosphataemia (< 0.3 mmol/l) are treated to avoid potential detrimental consequences, especially if the patients are critically ill, intubated, or are symptomatic.

In patients who require it, 20-30 mmol/l of K_2PO_4 can be added to the replacement fluid.[9] The infusion rate should not exceed 20 mmol per hour of K_2PO_4.[45] Hypocalcaemia may be precipitated by the use of phosphate in the treatment of DKA.[46]

Conclusion

The successful management of a patient in DKA requires careful attention, not only with regard to the abovementioned points pertaining to correction of dehydration, hyperglycaemia and electrolyte imbalances, but also to identification of the precipitating event that gave rise to the DKA, and management of sepsis. Frequent patient monitoring and vigilance for possible complications are vital.

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