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LETTER TO THE EDITOR

A PHYSICOCHEMICAL ACID-BASE APPROACH FOR MANAGING DIABETIC KETOACIDOSIS

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INTRODUCTION

Diabetic ketoacidosis (DKA) is one of the most serious acute metabolic complications of diabetes. It is characterized by the biochemical triad of hyperglycemia, ketonemia/ketonuria, and an increased anion gap (AG) metabolic acidosis. Unless it is relatively mild, DKA is usually managed in the intensive care unit (ICU), and treatment involves a continuous infusion of intravenous (IV) insulin, correction of water and electrolytes deficits, and treatment of the underlying precipitating factors. Patients are commonly discharged from the ICU when criteria of DKA resolution are met (glucose < 200 mg/dl, serum bicarbonate ≥ 18 mEq/l, venous pH > 7.3 and calculated AG ≤ 12 mEq/l)[1] and an IV insulin infusion is no longer necessary. However, serum bicarbonate levels have serious limitations as a surrogate of underlying metabolic disturbances (due to an interdependence with pCO_2 and it does not reveal, *per se,* the main acid responsible for the acidosis).[2] Because hyperchloremic acidosis is a frequent complication of the treatment of DKA,[1] it is not surprising that hyperchloremia retards the increase in bicarbonate and pH and, consequently, tends to prolong IV insulin infusion time and ICU stay. Taking a physicochemical approach to acid-base disorders could be useful in this setting because this approach allows for the quantification of circulating, unmeasured anions as well as the strong ion difference (SID). As a result, it becomes easier to detect the moment that DKA has been resolved and the magnitude of hyperchloremic acidosis (see below).

We describe the case of a young female patient admitted to our ICU with DKA and demonstrate how useful the physicochemical approach was in the management of her case.

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CASE HISTORY

A 21-year-old female presented to the emergency department with a history of weight loss, polyuria and polydipsia over the past 20 days and nausea, dizziness, prostration on the day of admission.

Upon arrival to the hospital (10:00 a.m.), she was conscious, alert and dehydrated. Her blood glucose level was 320 mg/dl on admission, with massive glycosuria and ketonuria. Venous blood gas analysis showed a high AG ($AG = Na^+ - Cl^- - HCO_3^-$) metabolic acidosis (Tables 1 and 2). No significant hyperlactemia was present. A diagnosis of DKA was made. Fluid challenge was initiated with 1 liter of normal saline. Five units of regular insulin were given intravenously as a bolus, and a continuous infusion of 5 units/hour was started. The patient's hyperglycemia was rapidly corrected, and a solution with 5% glucose plus potassium was introduced. Around 3:00 p.m., a new venous blood gas assessment revealed no significant improvements in the severity of her metabolic acidosis (Table 1).

The patient was transferred to the ICU around 6:00 p.m. already receiving 2.5 units/hour of IV regular insulin and had a blood glucose level of 222 mg/dl. New exams revealed that there was still no significant improvement in her metabolic acidosis (Table 1) However, a significant increase in chloremia and decrease in the AG was appreciated. By 11:00 p.m., her clinical condition was stable, with only small alterations in the infusion of IV insulin. In addition, she was able to eat and had no abdominal complaints. A new set of exams revealed a small improvement in the degree of metabolic acidosis (Table 1). However, there was still significant hyperchloremia, though her AG had decreased

Table 1 - Biochemical and acid-base variables during the course of diabetic ketoacidosis treatment

Day	04/15		//		04/16			
Time	10:00 a.m.	03:00 p.m.	06:00 p.m.	11:00 p.m.	07:00 a.m.	12:00 p.m.	06:00 p.m.	11:00 p.m.
Blood gas sample	venous	venous	arterial	arterial	venous	arterial	arterial	arterial
pH	7.14	7.17	7.22	7.24	7.26	7.39	7.45	7.46
pO_2 (mmHg)	22.9	41.7	108.7	70.2	45.1	109.1	108.8	71.2
pCO_2 (mmHg)	24.5	21.4	19.5	25.2	32.4	25.4	31.5	34.2
$SatO_2$ (%)	21.6	57.9	96.4	89.0	71.2	98.0	98.4	95.0
Bicarbonate (mEq/l)	8.2	7.6	7.9	10.6	14.3	15.0	21.4	23.6
BE (mEq/l)	-19.1	-19.0	-17.4	-14.8	-11.4	-8.0	-1.5	0.4
Na^+ (mEq/l)	133	-------	134	132	137	135	-------	138
K^+ (mEq/l)	5.0	2.8	4.0	4.0	3.2	3.7	-------	2.9
Mg^{2+} (mEq/l)	1.7	-------	1.4	1.4	1.2	1.2	-------	1.3
Ca^{2+} (mEq/l)	2.7	-------	-------	2.6	2.6	2.4	-------	2.3
Cl^- (mEq/l)	96	-------	110	109	112	105	-------	100
Lactate (mEq/l)	1.8	2	1.8	2.1	3	3	3.9	1.6
Albumin (g/dl)	-------	-------	-------	3.6	-------	3.3	-------	3.3
Phosphate (mg/dl)	3.1	-------	1.1	0.8	1.9	2.7	-------	3.1
Creatinin (mg/dl)	0.9	-------	-------	0.5	-------	-------	-------	0.6
Glucose (mg/dl)	320	-------	-------	203	-------	-------	-------	185

Table 2 - Traditional and Stewart acid-base variables during the course of diabetic ketoacidosis treatment

Day	**04/15**	**//**	**04/16**			
Time	**10:00 a.m.**	**06:00 p.m.**	**11:00 p.m.**	**07:00 a.m.**	**12:00 p.m.**	**11:00 p.m.**
pH	7.14	7.22	7.24	7.26	7.39	7.46
SIDa (mEq/l)*	44.6	30.2	28.9	29.0	34.3	42.9
SIG (mEq/l) #	25.8	12.4	8.5	5.0	8.5	8.0
AG (mEq/l) F	28.8	16.1	12.4	10.7	15	14.4
Cl^- / Na^+	0.72	0.82	0.83	0.82	0.78	0.72
Weak acids (mEq/l)Y	10.6	9.9	9.8	9.7	10.8	11.3
BE (mEq/l)	-19.1	-17.4	-14.8	-11.4	-8.0	0.4
Bicarbonate (mEq/l)	8.2	7.9	10.6	14.3	15.0	23.6

*SIDa= $[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [lactate^-]$ (see table 1)
# SIG= SIDa - [weak acids] - [bicarbonate]
FAG= $[Na^+] - [Cl^-]$ - [bicarbonate] (see table 1)
Y weak acids= [(10 x albumin (g/dl)) * (0.123 x pH – 0.631)] + [(phosphate (mmol/l)) * (0.309 x pH – 0.469)] (see table 1)

even more. At 7:00 a.m., although there was an increase in lactatemia, her metabolic acidosis continued to improve due to normalization of AG with persistent hyperchloremia. To accelerate the correction of the non-AG metabolic acidosis, a continuous infusion of 8.4% sodium bicarbonate (150 ml every six hours) was prescribed at 10 a.m. Two hours later, her pH, base excess (BE), bicarbonate and AG increased; both natremia and chloremia decreased (Table 1). At 6:00

p.m., her pH, BE and bicarbonate had increased even more, indicating an improvement in metabolic acidosis although there was a parallel increase in lactatemia. Based on a bicarbonate level > 18 mEq/l (in addition to glucose < 200 mg/dl and pH > 7.3), five units of regular insulin were given subcutaneously; one hour later, IV insulin was stopped. The bicarbonate infusion was suspended around 9 p.m., and at 11 p.m., the last set of labs revealed complete resolution of the metabolic acidosis, hyperlactatemia and hyperchloremia. The patient was discharged from the ICU to a general ward the next morning and left the hospital two days later with a prescription of mixed, subcutaneous, intermediate and short-acting insulin.

A review of the case using a physicochemical acid-base approach

According to the physicochemical approach to acid-base disturbances proposed by Stewart[3] and then modified by Figge et al [4], only three independent variables can change the blood pH: a SID, weak acids (mainly phosphate and albumin), and pCO_2. A SID represents the net balance between strong positive ions (cations) and strong negative ions (anions) according to the following formula (all concentrations in mEq/l):

$$SID = (Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + lactate^-).$$

Therefore, decreases in SID lead to increases in the dissociation of water (to maintain electroneutrality) and a fall in pH. This equation, however, does not account for the weak acids present in blood; therefore, we call this the "apparent" SID (SIDa). The "effective" SID (SIDe) is represented by the sum of the charges of the weak acids according to the following equation:

$$SIDe = [12.2 \times (pCO_2\ (mm\ Hg)/(10^{-pH}))] + [(albumin\ (g/l)) \times (0.123 \times pH - 0.631)] + [(phosphate\ (mmol/l)) \times (0.309 \times pH - 0.469)].$$

Unmeasured anions are represented by the strong ion gap (SIG) - the "gap" between SIDa and SIDe, as shown in the following formula:

$$SIG = SIDa - SIDe.$$

In healthy humans, a normal SID value is around 40 mEq/l, and SIG is around zero, (i.e., there are no unmeasured anions).[2]

At the moment of hospital admission, our patient had significant metabolic acidosis, a diagnosis easily made by simply looking at pH, BE and bicarbonate levels (Table 1). The acidosis could be entirely attributed to an increased SIG (Table 2) and possibly attenuated by an increased SID due to hypochloremia.

Upon ICU admission, no significant improvement had occurred in pH, BE or bicarbonate values. However, the level of metabolic acidosis was kept constant due to proportional decreases in SIG (fewer unmeasured anions) and SID (increased chloride) (Table 2). The first blood gas sample (taken at 11:00 p.m.), which showed a small improvement in pH, BE and bicarbonate, had a SID similar to that from the ICU admission, but less SIG was present. At 7:00 a.m., a venous blood sample revealed significant improvement in BE and bicarbonate, which could again be attributed to decreases in SIG. At that moment, although the patient's pH was less than 7.3 and her bicarbonate < 18 mg/dl, metabolic acidosis was almost exclusively due to a decreased SID (essentially hyperchloremia). As a result, the physicians prescribed sodium bicarbonate to correct the acidosis. The next two blood gas analyses showed complete resolution of the acidosis as a result of the correction of the SID with only a transitory increase in SIG and lactate. Curiously, increases in SID following the sodium bicarbonate infusion were accompanied by a reduction in chloremia and not increases in natremia. No relevant changes in weak acid concentration occurred during the entire course of treatment.

DISCUSSION

The main objective of this case report was to demonstrate that the bicarbonate and pH levels are useful for diagnosing DKA, but they should not be used as markers of its resolution because hyperchloremia is common during the treatment of ketoacidosis and frequently retards the correction of acidemia. Before treatment, hypochloremia is common and seems to be a compensatory response to high AG metabolic acidosis in DKA.[5] The use of normal saline or even 0.45% NaCl (solutions with an SID of zero) during DKA treatment as recommended by current guidelines[1] may counteract this compensatory effect and actually worsen the degree of metabolic acidosis. Based on physicochemical principles, solutions with higher SID (such as Lactated Ringer´s) should be more appropriate for hydrating these patients.

The guidelines from the American Diabetes Association (ADA) consider DKA resolved when blood glucose is less than 200 mg/dl, bicarbonate is equal to or greater than 18 mEq/l, and venous pH is greater than 7.3.[1] Less emphasis is given to AG, a useful tool in quantifying unmeasured anions. The AG includes weak acids, lactate and unmeasured anions. In our case, weak acid concentration was stable

throughout the ICU stay, and lactate saw only minor increases; thus, decreases in the AG reflected decreases in unmeasured anions (mainly ketoacids). The case described above shows that the AG normalizes (< 12 mEq/l) well before the pH reaches 7.3 or bicarbonate reaches 18 mEq/l. AG was not adjusted for albumin because albumin was near normal throughout the case. In more critical cases, when hypoalbuminemia is expected, AG should be adjusted to increase its sensitivity in detecting unmeasured anions.[6] Therefore, albumin should be measured frequently, especially in the most critical cases. Considering SIG as a surrogate of circulating ketoacids, there was already a significant improvement in diabetic ketoacidosis upon ICU admission; this improvement could not be appreciated by looking at pH, BE or bicarbonate. Although normal SIG should be near zero,[2] this value is infrequent in critically ill patients, even upon discharge from the ICU (Maciel et al., J Crit Care 2009, in press). In the present case, SIG reached a value near 8 mEq/l a few hours after admission to the ICU; this value was similar to the value at ICU discharge. Some authors already consider a "normal" SIG as 8 ± 2 mEq/l;[7] therefore, this may be a reasonable value to indicate DKA resolution. It is important to emphasize that the normal value of SIG probably differs from lab to lab due to differing techniques for measuring electrolytes.

Because SIG calculation involves a number of complex mathematical equations, some authors have proposed using the chloride:sodium ratio (Cl^-/Na^+) to determine the etiology of metabolic acidosis.[8] One study found that a Cl^-/Na^+ ratio less than 0.75 indicated the presence of a significant amount of unmeasured anions and/or lactate and that a ratio greater than 0.79 excluded their presence. In this case report, the initial Cl^-/Na^+ ratio was 0.72. Because lactate was normal, this ratio implied that unmeasured anions were largely responsible for the metabolic acidosis at hospital admission. Although bicarbonate was the same at both the hospital and ICU admissions, suggesting no metabolic improvement, the Cl^-/Na^+ ratio increased from 0.72 to 0.82, which may indicate nearly complete resolution of ketoacidosis.

Using gamblegrams, (Figure 1), it was possible to imagine that the excess of unmeasured anions originally present at admission corresponded to the deficit of bicarbonate. In the first hours of treatment, the excess unmeasured anions were rapidly substituted with chloride excisions, resulting in little changes in bicarbonate. The next step was a progressive substitution of excess chloride for bicarbonate. In the end, the initial excess of unmeasured anions was converted back into bicarbonate. This fast conversion of a predominant SIG acidosis into a SID acidosis has been described in other post-resuscitation situations.[9]

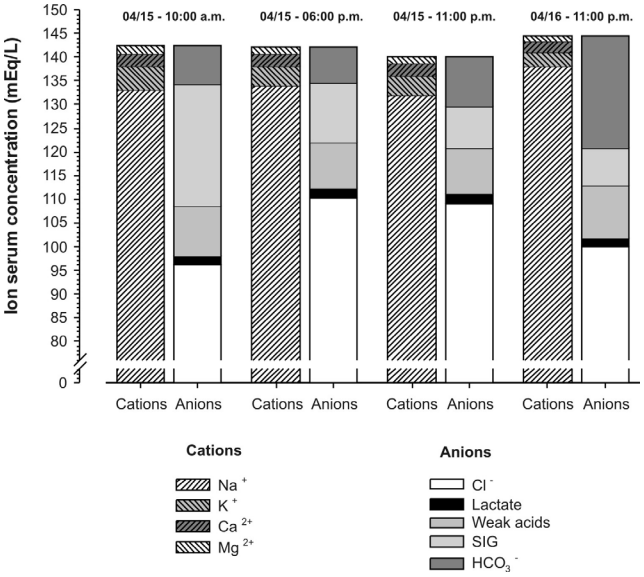

Figure 1 - Evolutive gamblegrams during the course of diabetic ketoacidosis treatment

ADA guidelines do not recommend bicarbonate therapy for patients in DKA with a pH greater than 7.0.[1] This recommendation is due to possible side effects related to the infusion of bicarbonate, such as worsened hypokalemia, worsened intracellular acidosis due to increased carbon dioxide production, delay of ketoanion metabolism, and development of a paradoxical central nervous system acidosis.[1] Hence, bicarbonate infusion in the present case was questionable and, as a general rule, should be avoided. In fact, a transitory increase in SIG and lactate as well as hypokalemia occurred after administration. On the other hand, sodium bicarbonate infusion is used to treat hyperchloremic acidosis because it is a solution with a high SID.[10] In the case reported, sodium bicarbonate was given to correct a SID acidosis and not DKA because SIG was already at low levels. Bicarbonate seemed to accelerate the correction of hyperchloremic acidosis because a rapid decrease in chloremia occurred after its administration. In the presence of normal renal function, SID acidosis could be corrected without the need of a bicarbonate infusion, but it would occur more slowly and would take longer to increase the bicarbonate levels to 18 mEq/l and the pH to 7.3. The question that remains is, "Should we wait until bicarbonate reaches 18 mEq/l and pH reaches 7.3 if SIG and AG are already corrected?" Even before the now-common use of Stewart acid-base principles, it was common practice to use AG to quantify unmeasured anions. However, we should keep in mind that AG is the sum of dissociated, non-volatile weak acids (albumin and phosphate), lactate and unmeasured anions. Therefore, to quantify unmeasured anions properly, the AG should be adjusted for weak acids (mainly albumin) and lactate should be subtracted.[11] For this reason, we believe

that AG, SIG or even the Cl^-/Na^+ ratio should be used to determine the moment of DKA resolution as opposed to using pH or bicarbonate. SIG seems to be the most precise method for quantifying unmeasured anions; however, its calculation is burdensome. As such, the AG or Cl^-/Na^+ ratio may be more easily calculated and useful at the bedside. Traditional approaches to acid-base disorders fail to identify significant changes in the origin of metabolic acidosis, which seems to be very dynamic during the course of the condition. Ketoacids are the main cause of metabolic acidosis only in the first hours of treatment and decrease well before significant alterations in pH or bicarbonate occur. Therefore, changes in the approach to acid-base calculations during DKA treatment has not only therapeutic but also economic implications, as increases in the time the patient receives IV insulin mean increased time spent in the ICU.

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