

Investigation vignette

A 66 Year old Woman with a Severe Lactic Acidosis and Unusual Anion Gap Following Resuscitation from an Asystolic Cardiac Arrest

CASE REPORT

A 66 year old woman was admitted to the accident and emergency department following a witnessed cardiac arrest at home. Her past medical history included hypertension (treated with perindopril, atenolol and felodipine) and anxiety (treated with alprazolam). The paramedical team arrived to find that she was in asystole, which responded to intubation, mechanical ventilation and 2 mg of adrenaline intravenously. During her transport to the hospital she required a further three doses of 0.5 mg of adrenaline i.v. to maintain her pulse. When she arrived at the accident and emergency department she was non responsive to pain, in sinus rhythm at 84 beats per minute with a blood pressure of 120/70 mmHg.

She was admitted to the critical care unit where she remained unconscious, requiring mechanical ventilation and an intravenous adrenaline infusion

varying between 10 and 30 µg/min. A central venous cannula was inserted into the right subclavian vein and an arterial cannula was inserted into the right radial artery.

Arterial blood specimens were simultaneously sent for blood gas analysis (ABL 725, Radiometer, Copenhagen, Denmark) and plasma biochemistry using a sequential multiple analyser with computer (Roche/Hitachi 917, Hoffmann La Roche, Basel, Switzerland). The arterial blood gas analysis (Figure 1) revealed a lactic acidosis with the change in base excess caused predominantly by the increase in plasma lactate. However, the anion gap of 16.9 mEq/L indicated that the normal anion difference in this patient was inordinately low (i.e. 3.9 mEq/L).

Name	Age	Sex
Mrs. A. B.	66	F

PO ₂	654	mmHg	(80 - 105)
PCO ₂	23	mmHg	(35 - 45)
pH	7.19		(7.35 - 7.45)
Calculated HCO ₃ ⁻	8	mmol/L	(21 - 28)
BE	-18	mmol/L	(-3 - 3)
Haemoglobin	108	g/L	(115 - 160)
SaO ₂	100	%	(94 - 99)
Total O ₂	16.7	vol%	(15.7 - 20.5)
P ₅₀	31.7	mmHg	(23.8 - 29.4)
Sodium	138	mmol/L	(135 - 145)
Potassium	2.9	mmol/L	(3.2 - 4.3)
Chloride	116	mmol/L	(99 - 109)
Calcium (Ionised)	1.08	mmol/L	(1.15 - 1.30)
Lactate	13	mmol/L	(< 2)
Anion gap	16.9	mEq/L	(8 - 16)

Figure 1. Blood gases, electrolytes and lactate measured from an arterial specimen on admission to the critical care unit

Diagnosis: Lactic acidosis without a commensurate increase in the anion gap due to an inaccurately measured increase in plasma chloride.

Chemical compounds in solution may either remain intact (i.e. undissociated), in which case they are called non-electrolytes (e.g. glucose, urea), or dissociate to form ions (which carry an electrical charge), in which case they are called electrolytes. Ions with a positive charge are attracted to a negative electrode or cathode, and hence are called 'cations'. Conversely, ions with a negative charge travel towards a positive electrode or anode and are called 'anions'. To maintain a solution's electrical neutrality, the number of anions must equal the number of cations.

The plasma 'anion gap' is calculated from the formula: $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$, where Na^+ , K^+ , Cl^- and HCO_3^- are measured in mmol/L (i.e. mEq/L). It is an index of the gap between the 'unmeasured cations' (e.g. Ca^{2+} 5 mEq/L and Mg^{2+} 1.5 mEq/L) and the 'unmeasured anions' (e.g. plasma proteins 15 mEq/L, phosphate 2 mEq/L, sulphate 0.5 mEq/L, lactate, citrate and ketones 3 mEq/L). Albumin has a molar equivalent of 18, (i.e. 18 mEq for each 6.9 g), therefore a normal albumin level of 4.2 g is responsible for 11 of the 15 'plasma protein' milliequivalents.¹ The unmeasured cations total 6.5 mEq/L and the unmeasured anions total 20.5 mEq/L, therefore the normal mean anion gap is 14.0 mEq/L.

In any individual, the normal 'gap' ranges between 8 and 16 mEq/L, although with ion-selective electrode systems this may be 2 mEq/L lower due largely to an upward shift of the measured chloride values.² An increased anion gap (i.e. > 16 mEq/L) may be due to:³

1. a non-carbonic, non-hydrochloric, metabolic acidosis (e.g. D- or L- lactic acidosis, ketoacidosis), poisoning (e.g. ethylene glycol, methanol, ethanol, paraldehyde, salicylate, paracetamol), or renal failure (due to phosphate and sulphate anions),
2. therapy with sodium salts of strong acids (e.g. acetate, citrate, lactate),
3. high dose penicillin therapy (i.e. excess penicillin anion),
4. alkalaemia (due to an increased protein anion equivalent,⁴ of 0.01 mEq/L per g/L of protein for each increment in pH of 0.10 units),⁵
5. hypernatraemia (by unknown mechanisms),¹ or
6. hyperalbuminaemia (due to an increase in anion equivalent) or ECF volume contraction (due to a higher net anionic charge on plasma proteins or an increase in anions that are restricted to the intravascular compartment).⁶

A decreased anion gap (i.e., < 8 mEq/L) may be due to:³

1. technique-dependent error, for example:
 - a. bromide toxicity occurs with plasma levels greater than 500 mg/L (6.25 mEq/L) and in severe toxicity levels up to 2000 mg/L (25 mEq/L) may occur. As the colorimetric and ion-selective methods used to estimate chloride are more sensitive to bromide, the chloride level is artificially elevated with high plasma bromide levels and the anion gap is reduced.⁷
 - b. high plasma lipid levels (i.e. hyperlipidaemia) interfere with some of the methods used to measure chloride, causing an artificial elevation of the plasma chloride and a decrease in the anion gap.⁸
2. miscellaneous effects, for example:³
 - a. reducing the albumin level by half will reduce the anion gap by 5.5 mEq/L (one study documented a decrease in the anion gap by 2.5 mEq/L for each 10 g/L reduction in albumin - as measured by bromocresol purple - below 44g/L).⁹
 - b. increasing the unmeasured cations of calcium and magnesium,¹⁰ has been reported to reduce the anion gap by up to 2 - 4 mEq/L. However, one study found that an increase in serum magnesium concentration in pre-eclamptic patients managed with intravenous magnesium sulphate and an average serum magnesium concentration of 2.05 mmol/L (i.e. 4.1 mEq/L), was not associated with a significant decrease in the anion gap.¹¹
 - c. an increase in serum lithium lowers the serum anion gap by the commensurate increase in serum lithium level.^{11,12}
 - d. paraproteinaemia with high levels of IgG (a cationic protein) may reduce the anion gap,¹³ whereas patients with high levels IgA (an anionic protein) may have a normal or increased anion gap.¹⁴
 - e. water excess, due to unknown mechanisms, will cause a decrease of the anion gap approximately twice that which would be expected from dilution alone.¹⁵

The anion gap is often used to detect a high anion gap metabolic acidosis (e.g. keto- or lactic acidosis). In a high anion gap metabolic acidosis caused by a single acid anion, the increase in the anion gap (in mEq/L) and decrease in base excess (in mmol/L) should approximate the increase in the acid anion (e.g. lactate, beta-hydroxybutyrate and acetoacetate) in mmol/L. If the decrease in base excess is greater than

the increase in anion gap then both a high anion gap and normal anion gap (i.e. HCO_3^- losing) metabolic acidosis may coexist, whereas if the decrease in base excess is less than the increase in the anion gap, the patient may have both a high anion gap metabolic acidosis and a metabolic alkalosis.

However in the patient described in the case report, the increase in the acid anion lactate (13 mmol/L) while approximating the decrease in the base excess (-18 mmol/L), the anion gap increase by 13 - 18 mEq/L indicated that the patient's normal anion gap would be very low (e.g. -1.1 to 3.9 mEq/L).

However, the simultaneously measured sodium, potassium, chloride and bicarbonate using a sequential multiple analyser with computer (Roche/Hitachi 917, Hoffmann La Roche, Basel, Switzerland) revealed a sodium 139 mmol/L, potassium 2.9 mmol/L, chloride 109 mmol/L, bicarbonate 9 mmol/L, albumin 32 g/L and an anion gap of 24 mEq/L (rather than the 16.9 mEq resulting from the electrolytes measured by the blood gas analyser - ABL 725, Radiometer, Copenhagen, Denmark). Both machines use ion-selective potentiometry. The reduced anion gap reported in the blood gas analysis was caused largely by an artifactual increase in measured plasma chloride (e.g. 116 mmol/L cf. 109 mmol/L) due to an error caused by the reference electrode in the blood gas analyser, as the result was corrected when the reference electrode was replaced.

While laboratory testing is often valuable in the understanding and management of the critically ill patient, abnormal results caused by technical failure should always be considered when the results cannot be easily explained.

K. DESHPANDE

Department of Critical Care Medicine, Flinders Medical Centre, Bedford Park, SOUTH AUSTRALIA

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