Advances in Clinical Medical Research and Healthcare Delivery

Volume 1 | Issue 2 Article 5

2021

A Case of Elevated Anion Gap

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Recommended Citation

Pandey R, Rai D, Silver S, Bress J. A Case of Elevated Anion Gap. *Advances in Clinical Medical Research and Healthcare Delivery*. 2021; 1(2). doi: 10.53785/2769-2779.1015.

ISSN: 2769-2779

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Keywords

Pseudoacidosis, Elevated Anion Gap

The Clinical Dilemma

A 56-year-old woman with a past history of cerebrovascular accident, hypertension, and hypothyroidism was referred for persistent metabolic acidosis. Medications included aspirin, atorvastatin, famotidine, levothyroxine, and lisinopril. She was a chronic smoker but denied alcohol or illegal drugs. She rarely used analgesics. She was asymptomatic, and the physical exam was unremarkable. For six years, multiple outpatient chemistries showed serum CO_2 between 10 and 17 mmol/L with an elevated anion gap (Table 1). Glucose, calcium, renal function, glucose, and calcium were normal throughout each year. Most recently, CO_2 was 10mEq/L, and anion gap 23 mEq/L. She was referred to the Nephrology clinic for further evaluation. The questions to be solved for are: 1.) What can cause a high anion gap metabolic acidosis?; 2.) What other tests are indicated?; and 3.) What explains these findings?

Table 1. Trend of the laboratory work up from 2014-2020.

	Normal value	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**
Sodium, mEq/L	135-145	136	141	141	141	142	139	138
Potassium, mEq/L	3.5-5.1	4.4	4.4	4.7	4.2	4.4	4.3	4.7
Chloride, mEq/L	98-108	103	110	114	110	109	110	105
CO2, mEq/L	20-31	15	13	17	11	10	11	10
Anion Gap mEq/L	4-16	18	18	10	20	23	18	23
BUN, mg/dL	8-20	12	10	11	14	17	16	18
Creatinine, mg/dL	0.5-0.9	0.8	0.6	0.8	1	0.8	0.8	0.83
Glucose, mg/dL	65-100	85	92	125	93	120	98	95
Calcium, mg/dL	8.5-10.4	9.2	9.5	9.1	9.6	9.1	9.2	9.3
Phosphorus, mg/dL	2.5-4.5	3.5	3.5	3.7	3.4	3.7	3.5	3
Total Protein, g/dL	6.4-8.5	8.8	7.3	7.5	7.5	7.8	8	7.8
Albumin, g/dL	3.2-4.8	3.8	4.1	3.7	4.4	3.9	4	4.3
Globulin, g/dL	2.4-4.3	5	3.2	3.3	3.1	3.4	3.5	
Magnesium, mg/dL	1.6-2.6	1.8	1.9	2.1	2	2.1	1.9	1.8

Discussion

What can cause a high anion gap metabolic acidosis? The primary difference between measured cations (sodium and potassium) and anions (chloride and boicarbonate) is defined as aniona gap. Causes of elevated anion gap is shown in Table 2.[1] Toxic alcohols, severe salicylate intoxication, lactic acidosis, d-lactic acidosis, and ketoacidosis are unlikely causes of persistent acidosis in an asymptomatic outpatient; tests for these were negative. Pyroglutamic acidosis can occur in malnourished women who habitually take acetaminophen, but urine pyroglutamate was negative.

Table 2. Etiology of high anion gap metabolic acidosis

GOLDMARK
Glycols (ethylene glycol, propylene glycol)
Oxoproline (pyroglutamic acid, the toxic metabolite of excessive acetaminophen or paracetamol)
L-Lactate (standard lactic acid seen in lactic acidosis)
D-Lactate (exogenous lactic acid produced by gut bacteria)
Methanol (this is inclusive of alcohols in general)
Aspirin (salicylic acid)
Renal Failure (uremic acidosis)
Ketones (diabetic, alcoholic, and starvation ketosis)

What other tests are indicated? High anion gap acidoses increase urine ammonium excretion, resulting in a high urine osmolar gap. When our patient's urine osmolar gap was nil, blood gases were obtained. Serum CO_2 and calculated bicarbonate should agree closely, given the relationship of pH, pCO_2, HCO_3, in the Henderson-Hasselbach equation. When the CO_2 measured by autoanalyzer was 10 mmol/L, concurrent venous blood gas analysis revealed pH 7.37, PCO_2 53 mm Hg, and calculated bicarbonate 24 mmol/L. We concluded that our patient did *not* have metabolic acidosis.

Conclusion

What explains these findings? The anion gap is used to detect pathological concentrations of acid anions. Spurious CO_2 or abnormal concentrations of other charged particles in the serum can misleadingly increase or reduce the gap (Table 3).[2] In our patient, an artifactually low CO_2 concentration spuriously raised the anion gap. CO_2 is measured enzymatically in autoanalyzers, and severe hypertriglyceridemia causes interference with the assay and has been reported as causes of pseudoacidosis.[3, 4] Our patient's paraproteins and triglycerides were normal. The serum CO_2 remained low after ultracentrifugation of the serum to extract interfering lipids or proteins. Like one previously reported patient,[5] the cause of the spuriously low serum CO_2 in our patient remains unknown. The final diagnosis is Idiopathic pseudoacidosis.

Table 3. Etiology and mechanism of increased anion gap not associated with acidosis

Etiology	**Spurious elevation (Yes/No)**	**Mechanism**
Hypertriglyceridemia	Yes	Interference of the enzymatic reaction used in the autoanalyzer by the lipid particles spuriously decreases the CO_2 levels.
Pseudoacidosis	Yes	Idiopathic substances interfering with the autoanalyzer assay can lead to change in the anion gap.
IgA Paraproteinemia	No	IgA paraproteins behave as anions as they have isoelectric points below physiologic pH, leading to the increased anion gap
Metabolic alkalosis	No	Alkalosis leads to albumin releasing hydrogen ions and thereby increasing the net negative charge on each albumin. Alkalosis increases the generation and accumulation of organic acids.
Hyperalbulinemia	No	Excess accumulation of anions on albumin can lead to pseudoelevation of the anion gap
Hyperphosphatemia	No	Excess accumulation of phosphate anions can lead to pseudoelevation of the anion gap

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