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Acid-Base and Electrolyte Teaching Case

Approach to the Patient With a Negative Anion Gap

Michael Emmett, MD, MACP

When anion gap calculation generates a very small or negative number, an explanation must be sought. Sporadic (nonreproducible) measurement errors and systematic (reproducible) laboratory errors must be considered. If an error is ruled out, 2 general possibilities exist. A true anion gap reduction can be generated by either reduced concentrations of unmeasured anions such as albumin or increased concentrations of unmeasured cations such as magnesium, calcium, or lithium. This teaching case describes a patient with aspirin (salicylate) poisoning whose anion gap was markedly reduced (−47 mEq/L). The discussion systematically reviews the possibilities and provides the explanation for this unusual laboratory result.
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INDEX WORDS: Low anion gap; negative anion gap; pseudohyperchloremia; salicylate poisoning; aspirin toxicity; bromism.

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INTRODUCTION

The anion gap (AG) is usually a clue to a variety of metabolic acidoses and the presence of mixed acid-base disorders. When these disorders develop, AG is typically elevated or within the normal range. Less often, the AG is reduced into the low range or even becomes negative. A patient with a markedly negative AG is presented, and a comprehensive review of the differential diagnosis of low and negative AGs follows.

CASE REPORT

Clinical History and Initial Laboratory Data

A 47-year-old Hispanic woman presented 20 hours after a suicide attempt in which she ingested a bottle of aspirin (acetylsalicylic acid [ASA]) and a few beers. At presentation, the patient reported tinnitus, dizziness, dyspnea, palpitations, and nausea with several episodes of emesis. Physical examination showed an anxious-appearing well-developed well-nourished woman who was alert, oriented, and cooperative. She was tachypneic, with a respiratory rate of 33 breaths/min. Other vital signs included temperature of 98.9°F, blood pressure of 120/65 mm Hg, and heart rate of 120 beats/min. Oxygen saturation was 97% on room air. Auditory acuity was reduced, but the examination findings were otherwise unremarkable.

Urinalysis showed clear yellow urine with specific gravity > 1.030, pH 6.0, protein (2+), trace glucose, ketones (2+), 3 to 5 red blood cells, and 0 to 1 white blood cell. Laboratory studies at presentation are shown in Table 1.Of note was a markedly elevated chloride concentration of 170 mEq/L and markedly reduced AG of −47 mEq/L. Salicylate level was 84.6 mg/mL. Serum protein electrophoresis results were unremarkable.

Additional Investigations

The analyzer used to measure the electrolytes employed a chloride ion–selective electrode that was 15 days old (the life cycle for this electrode is ~30 days). Table 2 shows the results when the original serum specimen was reanalyzed with a relatively new electrode and one near the end of its useful life. Also shown are chloride concentration results obtained with a variety of other instruments. When measured with a Buchler-Cotlove chloridometer, the patient's true initial chloride (actually halide) concentration was 98 mEq/L, and the initial AG was recalculated as 25 mEq/L.

Diagnosis

Salicylate poisoning with a triple acid-base disorder: AG metabolic acidosis, metabolic alkalosis, and respiratory alkalosis. The patient also had extreme pseudohyperchloremia due to a salicylate-induced measurement artifact.

Clinical Follow-up

The patient became somnolent, confused, and hypotensive soon after admission, and emergency hemodialysis was initiated. Postdialysis laboratory studies are shown in Table 1. Her salicylate level decreased to 2.2 mg/mL, chloride level increased to 111 mEq/L, and the magnitude of the AG decreased to 3 mEq/L. Her overall condition improved rapidly. A psychiatry consultant arranged follow-up outpatient care, and she was discharged on hospital day 4.

DISCUSSION

ASA poisoning was diagnosed on the basis of the information the patient reported, her physical examination, and her ASA blood level. ASA poisoning typically generates a mixed acid-base disorder. Hyperventilation and respiratory alkalosis is caused by direct stimulation of the central nervous system respiratory centers and peripheral chemoreceptors. This is usually prominent in adult

From the Nephrology Division, Department of Internal Medicine, Baylor University Medical Center, Dallas, TX.

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Address correspondence to Michael Emmett, MD, MACP, Baylor University Medical Center, 3500 Gaston Ave, Rm H-102, Dallas, TX 75246-2096. E-mail: m.emmett@baylorhealth.edu

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Table 1. Laboratory Studies

	At Admission	After Dialysis
SUN, mg/dL	30	17
Cr, mg/dL	1.1	0.5
eGFR,[a] mL/min/1.73 m^2	57	
Na, mEq/L	138	141
K, mEq/L	3.0	3.5
Cl, mEq/L	170[b]	111
HCO_3, mEq/L	15	27
Anion gap, mEq/L	−47[b]	3
Glucose, mg/dL	138	144
Ca, mg/dL	8.6	9.0
Salicylate, mg/dL	84.6	2.2
Arterial blood gas		
pH	7.53	NA
P_{CO_2}, mm Hg	12	NA
P_{O_2}, mm Hg	116	NA
HCO_3, mEq/L	10	NA

Note: Conversion factors for units: Cr in mg/dL to μmol/L, ×88.4; SUN in mg/dL to mmol/L, ×0.357; glucose in mg/dL to mmol/L, ×0.05551; Ca in mg/dL to mmol/L, ×0.2495; salicylate in mg/dL to mmol/L, ×0.0724.

Abbreviations: Ca, calcium; Cl, chloride; Cr, creatinine; eGFR, estimated glomerular filtration rate; HCO_3, bicarbonate; K, potassium; Na, sodium; NA, not available; SUN, serum urea nitrogen.

[a]eGFR calculated using the isotope-dilution mass spectrometry–traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.

[b]True initial chloride was remeasured as 98 mEq/L and initial anion gap was recalculated as 25 mEq/L.

patients, but less pronounced in infants and very young children.[1] Toxic systemic ASA levels also interfere with cellular anion exchange mechanisms, increase mitochondrial proton permeability, cause mitochondrial swelling, and uncouple mitochondrial oxidative phosphorylation. The mitochondrial toxicity often results in modest degrees of lactic acidosis and ketoacidosis, which combine to produce an AG metabolic acidosis.[2,3] High salicylate levels themselves also contribute a few milliequivalents to the AG increase. In addition, other organic acids probably accumulate because the sum of lactate, ketoacid, and salicylate anion levels usually cannot account for the entire AG increase. Toxic salicylate levels can also cause nausea and vomiting. Thus, the

Table 2. Initial Chloride Measurements With Various Analyzers

Analyzer	Chloride, mEq/L
Roche Cobras Integra Analyzer	
3-d-old electrode	103
15-d-old electrode	170
21-d-old electrode	237
Abbot i-Stat	118
Beckman-Coulter Chemistry Analyzer CX	104
AVL analyzer	105
Buchler-Cotlove chloridometer	98

characteristic acid-base disorder in the ASA-poisoned adult is a double (respiratory alkalosis and AG metabolic acidosis) or triple (respiratory alkalosis, AG metabolic acidosis, and metabolic alkalosis) acid-base disturbance.[1-4] This patient clearly had alkalemia and respiratory alkalosis. She also had metabolic acidosis because acute metabolic compensation for her severe acute respiratory alkalosis should only have reduced her bicarbonate level by about 6 to 7 mEq/L, to ∼19 mEq/L. However, her bicarbonate level was reduced to 15 mEq/L (measured as total carbon dioxide in the venous specimen) and was calculated to be 10 mEq/L in her arterial blood gas (Table 1). Very surprisingly, the initial AG was not increased, but markedly reduced to −47 mEq/L.

This teaching case reviews the causes of low and negative AGs and elucidates the mechanisms responsible for this particular patient's unusual laboratory results.

Anion Gap

In any solution containing dissolved ions, the concentration of positive charges (cations) must equal the concentration of negative charges (anions) when these concentrations are expressed as milliequivalents per liter. If only sodium, chloride, and bicarbonate are considered, the sodium (Na) concentration will exceed the sum of the chloride (Cl) and bicarbonate (HCO_3) concentrations. The difference, called the AG, is calculated as:

$$AG = [Na - (Cl + HCO_3)] \qquad \text{(equation 1)}$$

These relationships are shown in Fig 1. The normal range for AG varies from one laboratory to another; therefore, each institution must determine its own reference range (it is generally about 8-12 mEq/L). Note that serum proteins, mainly albumin, make up a large proportion of unmeasured anions. Consequently, when hypoalbuminemia exists, the AG value decreases. In general, AG decreases by about 2.5 to 3 mEq/L for each 1-g/dL decrease in albumin concentration below the normal range. Also, potassium is generally not included and therefore is an unmeasured cation, which means extremes of hypo- or hyperkalemia will affect the calculation.

Besides hypoalbuminemia, other biochemical abnormalities can reduce the value of the AG. As shown in Fig 1, AG can also be calculated as:

$$AG = \text{Unmeasured anions} - \text{Unmeasured cations} \qquad \text{(equation 2)}$$

For purposes of this relationship, unmeasured ions are defined as any ions in the serum other than sodium, chloride, and bicarbonate, and again the concentration of all the ions must be expressed in units of "electrical charge," or milliequivalents per liter. AG will be