

Mind the Gap

An 8-month-old infant with a history of seizure presented to the ED with fever and poor oral intake.

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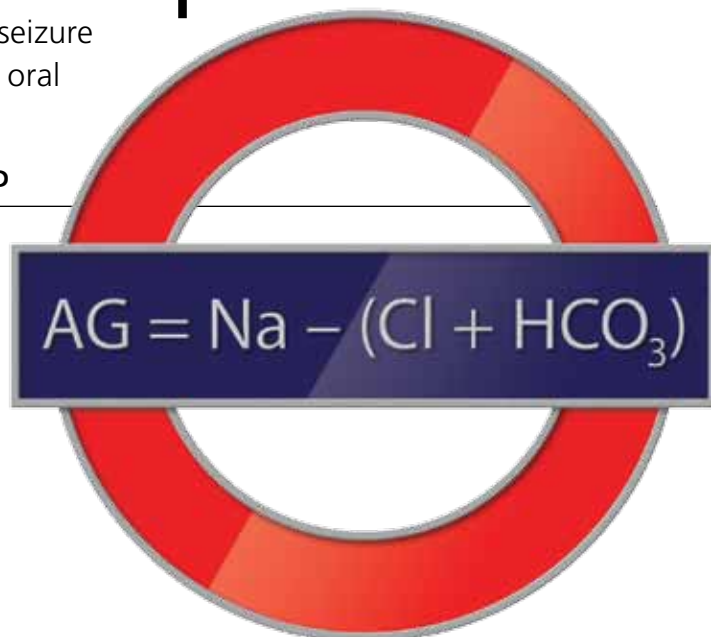
An 8-month-old boy with a history of hypotonia, developmental delay, and seizure disorder refractory to multiple anticonvulsant medications was brought to the ED with a two-week history of intermittent fever and poor oral intake. His current medications included sodium bromide (185 mg bid, orally) for his seizure disorder.

On physical examination, the boy appeared small for his age, with diffuse hypotonia and diminished reflexes. He was able to track with his eyes but was otherwise unresponsive. No rash was present. Results of initial laboratory studies were sodium, 144 mEq/L; potassium, 4.8 mEq/L; chloride, 179 mEq/L; bicarbonate, 21 mEq/L; blood urea nitrogen, 6 mg/dL; creatinine, 0.1 mg/dL; and glucose, 63 mg/dL. His anion gap (AG) was -56.

WHAT DOES THE ANION GAP REPRESENT?

The AG is a valuable clinical calculation derived from the measured extracellular electrolytes and provides an index of acid-base status.¹ Due to the necessity of electroneutrality, the sum of positive charges (cations) in the extracellular fluid must be balanced exactly with the sum of negative charges (anions). However, to routinely measure all of the cations and anions in the serum would be time-consuming and is also unnecessary. Because most clinical laboratories commonly only measure one relevant cation (sodium) and two anions (chloride and bicarbonate), the positive and negative sums are not com-

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pletely balanced. The AG therefore refers to this difference (ie, $AG = Na - [Cl + HCO_3]$).

Of course, electroneutrality exists in vivo and is accomplished by the presence of unmeasured anions (UA; eg, lactate and phosphate) and unmeasured cations (UC; eg, potassium and calcium) not accounted for in the AG (ie, $AG = UA - UC$). In other words, the sum of measured plus unmeasured anions must equal the sum of the measured plus unmeasured cations.

WHAT CAUSES A LOW OR NEGATIVE ANION GAP?

While most health care providers are well versed in the clinical significance of an elevated AG (eg, MUD-PILES [methanol, uremia, diabetic ketoacidosis, propylene glycol or phenformin, iron or isoniazid, lactate, ethylene glycol, salicylates]), the meaning of a low or negative AG is underappreciated. There are several scenarios that could potentially yield a low or negative AG, including decreased concentration of UA, increased concentrations of nonsodium cations (UC), and overestimation of serum chloride.

Decreased concentration of unmeasured anions. This most commonly occurs by two mechanisms: dilution of the extracellular fluid or hypoalbum-

minemia. The addition of water to the extracellular fluid will cause a proportionate dilution of all the measured electrolytes. Since the concentration of measured cations is higher than that of the measured anions, there is a small and relatively insignificant decrease in the AG.

Alternatively, hypoalbuminemia results in a low AG due to the change in UA; albumin is negatively charged. At physiologic pH, the overwhelming majority of serum proteins are anionic and counterbalanced by the positive charge of sodium. Albumin, the most abundant serum protein, accounts for approximately 75% of the normal AG. Hypoalbuminemic states, such as cirrhosis or nephrotic syndrome, can therefore cause low AG due to the retention of chloride to replace the lost negative charge. The albumin concentration can be corrected to calculate the AG.²

Nonsodium cations. There are a number of clinical conditions that result in the retention of non-sodium cations. For example, the excess positively charged paraproteins associated with IgG myeloma raise the UC concentration, resulting in a low AG. Similarly, elevations of unmeasured cationic electrolytes, such as calcium and magnesium, may also result in a lower AG. Significant changes in AG, though, are caused only by profound (and often life-threatening) hypercalcemia or hypermagnesemia.

Overestimation of serum chloride. Overestimation of serum chloride most commonly occurs in the clinical scenario of bromide exposure. In normal physiologic conditions, chloride is the only halide present in the extracellular fluid. With intake of brominated products, chloride may be partially replaced by bromide. As there is greater renal tubular avidity for bromide, chronic ingestion of bromide results in a gradual rise in serum bromide concentrations with a proportional fall in chloride.

However, and more importantly, bromide interferes with a number of laboratory techniques measuring chloride concentrations, resulting in a spuriously elevated chloride, or pseudohyperchloremia. Because the measured sodium and bicarbonate concentrations will remain unchanged, this falsely elevated chloride measurement will result in a negative AG.

WHAT CAUSES THE FALSELY ELEVATED CHLORIDE?

All of the current laboratory techniques for measurement of serum chloride concentration can po-

tentially result in a falsely elevated value. However, the degree of pseudohyperchloremia will depend on the specific assay used for measurement. The ion-selective electrode method used by many common laboratory analyzers appears to have the greatest interference on chloride measurement in the presence of bromide. This is simply due to the molecular similarity of bromide and chloride.

Conversely, the coulometry method, often used as a reference standard, has the least interference of current laboratory methods.³ This is because coulometry does not completely rely on molecular structure to measure concentration; rather, it measures the amount of energy produced or consumed in an electrolysis reaction. Iodide, another halide compound, has also been described as a cause of pseudohyperchloremia, whereas fluoride does not seem to have significant interference.⁴

HOW ARE PATIENTS EXPOSED TO BROMIDE SALTS?

Bromide salts, specifically sodium bromide, are infrequently used to treat seizure disorders but are generally reserved for patients with epilepsy refractory to other, less toxic anticonvulsant medications. During the era when bromide salts were more commonly used to treat epilepsy, bromide intoxication, or bromism, was frequently observed.

Bromism may manifest as a constellation of non-specific neurologic and psychiatric symptoms. These most commonly include headache, weakness, agitation, confusion, and hallucinations. In more severe cases of bromism, stupor and coma may occur.^{3,5}

Although bromide salts are no longer commonly prescribed, a number of products still contain brominated ingredients. Symptoms of bromide intoxication can occur with chronic use of a cough syrup containing dextromethorphan hydrobromide, as well as the brominated vegetable oils found in some soft drinks.⁵

HOW IS BROMISM TREATED?

The treatment of bromism involves preventing further exposure to bromide and promoting bromide excretion. Bromide has a long half-life (10 to 12 days), but in patients with normal renal function, it is possible to reduce this half-life to approximately three days with hydration and diuresis with sodium chloride.³

Alternatively, in patients with impaired renal

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ANSWER

The radiograph shows that the distal femur is medially dislocated relative to the tibial plateau. In addition, the patella is laterally dislocated. No obvious fractures are evident.

Such injuries are typically associated with significant ligament injuries, especially of the medial collateral ligament (MCL), lateral collateral ligament (LCL), and anterior cruciate ligament (ACL). Orthopedics was consulted for reduction of the dislocation, as well as further workup (including MRI of the knee). **CR**



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function or severe intoxication, hemodialysis has been used effectively.⁵

CASE CONCLUSION

The patient was admitted for observation and treated with IV sodium chloride. After consultation with his neurologist, he was discharged home in the care of his parents, who were advised to continue him on sodium bromide (185 mg bid, orally) since his seizures were refractory to other anticonvulsant medications. **CR**

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