Osmolal Gap without Anion Gap in a 43-Year-Old Man

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CASE DESCRIPTION

A 43-year-old man presented to the emergency department (ED)² 2 h after ingesting 10 oz of antifreeze mixed with Gatorade in a suicide attempt. The antifreeze was green, of an unknown brand, and purchased at a local gas station. He subsequently confessed to his wife, who brought him to a community hospital ED. He denied abdominal pain, nausea, vomiting, urinary symptoms, or visual changes. Initial laboratory tests (Table 1) were clinically relevant for the following: arterial whole-blood pH, 7.34; \( P_{CO_2} \), 33 mmHg (4.4 kPa); serum bicarbonate, 18 mmol/L; serum ethanol, 10 mg/dL (2.17 mmol/L); and serum anion gap, 18 mmol/L. The serum osmolal gap (75 mOsm/kg) was calculated as follows: osmolal gap = freezing-point depression osmometer value – \((2 \times [Na^+] + [glucose]/18 + [blood \text{ urea nitrogen}]/2.8 + [ethanol]/4.6)\), where the \([Na^+]\) concentration is in millimoles per liter and the glucose, blood urea nitrogen, and ethanol concentrations are in milligrams per deciliter.

With the advice of the local Poison Control Center, the patient was given 15 mg/kg fomepizole intravenously. He was placed on suicide precautions and transferred to a tertiary care center for further evaluation and treatment. On arrival at the tertiary care ED 8 h after ingestion and 3 h after fomepizole administration, the patient had a normal mental status and normal vital signs. Thiamine (100 mg), folic acid (50 mg), and pyridoxine (50 mg) were administered intravenously as cofactors for secondary metabolic pathways. At that time, laboratory test results (Table 1) were clinically relevant for the following: arterial whole-blood pH, 7.39; \( P_{CO_2} \), 28 mmHg (3.7 kPa); serum bicarbonate, 18 mmol/L; creatinine, 1.1 mg/dL (97.2 μmol/L); lactate, 5.3 mmol/L; anion gap, 14 mmol/L; and osmolal gap, 72 mOsm/kg. No crystals were visible in the urine.

Given the improving anion gap and the lack of clinically relevant acidemia, there was debate about whether this patient had actually ingested ethylene glycol (EG) or had instead ingested propylene glycol (found in “safer” antifreezes) or isopropyl alcohol. Therefore, a test for the serum concentration of EG was ordered for confirmation. The sample for measurement of EG by gas chromatography had to be sent by courier to the closest clinical laboratory offering the test, with the results expected in 4 – 8 h. While the sample was en route for testing by gas chromatography, the hospital pathologist performed a modified version of a commercially available veterinary enzymatic assay. This test had been validated by our laboratory, and the results of these studies have been published (1). The serum concentration of EG (Table 1) measured by enzymatic assay was 308 mg/dL (49.6 mmol/L). On the basis of this information, the patient was continued on fomepizole, and plans were made for hemodialysis. Ten hours after admission, the gas chromatography result indicated an EG concentration of 315 mg/dL (50.9 mmol/L), in close agreement with the results of the enzymatic assay (the gas chromatography results were negative for methanol and isopropyl alcohol). After hemodialysis was performed, the patient’s postdialysis serum showed an osmolal gap of 6 mOsm/kg and an EG concentration of 50 mg/dL (8.2 mmol/L). After a second hemodialysis course, the EG concentration according to the enzymatic assay was 1.4 mg/dL (0.2 mmol/L); the fomepizole treatment was then discontinued. The patient’s renal function remained normal, and he recovered completely. He was discharged from the hospital to a psychiatric treatment facility.

QUESTIONS TO CONSIDER

1. What are the major ingredients found in antifreeze that can contribute to toxicity after ingestion?
2. In a patient with an increased osmolal gap and normal anion gap, can EG poisoning be ruled out?
3. What are some factors that may cause a normal anion gap in EG poisoning?
4. Can a normal osmolal gap be used to determine when fomepizole therapy should be discontinued?

CASE FOLLOW-UP

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¹ Nonstandard abbreviations: ED, emergency department; EG, ethylene glycol.
DISCUSSION

EG is a sweet-tasting, colorless liquid found in anti-freeze and airplane-deicing solutions. EG ingestions led to 6241 calls to US Poison Control Centers in 2011, including 7 deaths (2). The toxicity of EG is due to the production of the organic-acid metabolites glycolic acid, glyoxylic acid, and oxalic acid. The first, and rate-limiting, step in this metabolic pathway is catalyzed by alcohol dehydrogenase, the same enzyme responsible for ethanol metabolism (3). As these acids accumulate, an anion gap metabolic acidosis ensues, with subsequent organ and metabolic dysfunction. In addition to severe acidemia, oxalic acid combines with calcium to form calcium oxalate crystals, which deposit in the renal tubules to lead to renal injury and hypocalcemia.

The diagnosis of EG toxicity is made via a combination of the patient’s history, the clinical picture, and a laboratory analysis showing an anion gap metabolic acidosis with an increased osmolal gap. The analysis of the laboratory findings requires consideration of the time of ingestion and the interval between ingestion and presentation to the ED (4). There is a delay between the time of ingestion and the development of the anion gap metabolic acidosis, because the anion gap reflects the presence of the organic-acid metabolites. In addition, the osmolal gap, a reflection of the presence of the parent compound, can be diminished if the patient presents late and has already metabolized most of the parent compound into its organic-acid metabolites. Therefore, the diagnosis can be confusing when a patient presents very early or very late, owing to the time-dependent nature of the anion and osmolal gaps. Confirmatory serum concentrations can be obtained via gas chromatography; however, the lack of this capability in most hospital clinical laboratories often leads to diagnostic delays.

In addition to confirming the diagnosis, serum EG concentrations are useful to guide treatment. The mainstay of treatment for EG toxicity is to inhibit alcohol dehydrogenase with fomepizole (5, 6, 7). Hemodialysis is often used to enhance the elimination of the parent compound and its toxic metabolites and to correct the acidemia. Traditionally, these treatments are continued until the EG concentration decreases to <10 mg/dL (<1.6 mmol/L). Because of the difficulty in obtaining EG concentrations, an osmolal gap of <10 mOsm/kg is often used as a surrogate marker for when it is safe to stop treatment. Such values can be misleading, however, because a “normal” osmolal gap of 10 mOsm/kg can represent a potentially toxic EG concentration of up to 75 mg/dL (12.1 mmol/L) (8, 9). In the present case, the patient’s osmolal gap was 5 mOsm/kg after the first hemodialysis session, but the enzymatic EG concentration was 50 mg/dL (8.2 mmol/L), still far greater than the concentration considered safe to stop.

Table 1. The patient’s laboratory results on presentation, after transfer to the tertiary care center, and on hospital day 2 after hemodialysis.*

<table>
<thead>
<tr>
<th></th>
<th>Initial presentation</th>
<th>Tertiary ED (3 h later)</th>
<th>Actual, day 2 (after hemodialysis)</th>
<th>Expected, day 2 (if untreated)</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mmol/L</td>
<td>140</td>
<td>138</td>
<td>141</td>
<td>Normal</td>
<td>137–145</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.0</td>
<td>4.2</td>
<td>3.6</td>
<td>Normal</td>
<td>3.6–5.0</td>
</tr>
<tr>
<td>Chloride, mmol/L</td>
<td>104</td>
<td>106</td>
<td>103</td>
<td>Normal</td>
<td>98–107</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>18</td>
<td>18</td>
<td>32</td>
<td>Low</td>
<td>22–30</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>11</td>
<td>10</td>
<td>3</td>
<td>High</td>
<td>9–20</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.13</td>
<td>1.1</td>
<td>0.6</td>
<td>High</td>
<td>0.5–1.2</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>106</td>
<td>107</td>
<td>138</td>
<td>Normal</td>
<td>75–110</td>
</tr>
<tr>
<td>Anion gap, mmol/L</td>
<td>18</td>
<td>14</td>
<td>6</td>
<td>High</td>
<td>8–20</td>
</tr>
<tr>
<td>pH</td>
<td>7.34</td>
<td>7.39</td>
<td>7.46</td>
<td>Low</td>
<td>7.35–7.45</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>Unavailable</td>
<td>5.3</td>
<td>1.7</td>
<td>High</td>
<td>0.5–2.0</td>
</tr>
<tr>
<td>Serum osmoles, mOsm</td>
<td>367</td>
<td>358</td>
<td>296</td>
<td>Normal to high</td>
<td>275–295</td>
</tr>
<tr>
<td>Osmolal gap, mOsm/kg</td>
<td>75</td>
<td>72</td>
<td>6</td>
<td>Normal to high</td>
<td>0–10</td>
</tr>
<tr>
<td>EG (gas chromatography), mg/dL</td>
<td>Unavailable</td>
<td>315</td>
<td>Unavailable</td>
<td>High</td>
<td>Nondetectable</td>
</tr>
<tr>
<td>EG (enzymatic assay), mg/dL</td>
<td>Unavailable</td>
<td>308</td>
<td>50</td>
<td>High</td>
<td>Nondetectable</td>
</tr>
</tbody>
</table>

* For conversion to the SI unit of measure: blood urea nitrogen, 1 mg/dL = 0.36 mmol/L; creatinine, 1 mg/dL = 88.4 μmol/L; lactate, 1 mg/dL = 0.11 mmol/L; EG, 1 mg/dL = 0.16 mmol/L.

b BUN, blood urea nitrogen.

Clinical Case Study
treatment. If treatment had then been discontinued, the patient could have developed acidemia and acute kidney injury. Furthermore, when our laboratory had previously performed a validation study for an internal reference interval for normal values for the osmolal gap, the highest osmolal gap we obtained among 40 healthy outpatients was only 2 mOsm/kg. This finding suggests the published clinical threshold of 10 mOsm/kg is an overestimate.

Confirmatory testing of serum EG concentrations is traditionally performed via gas chromatography with flame ionization detection or mass spectrometry at specialized laboratories (1). Depending on distances and courier availability, results can take hours to return, potentially delaying diagnosis and management. An alternative method that uses a modified veterinary enzymatic assay has been developed and validated (1). This veterinary enzymatic assay had been rejected for use with human samples because of concern over interference by propylene glycol and various butanediols, some of which may be increased in chronic alcohol users (10). The development in 2011 of a modified assay that uses kinetic rate analysis has improved the assay’s analytic specificity and has eliminated most false-positive results. This modification also decreased the labor time by 85% and the turnaround time by 10 h (1). The availability of the enzymatic assay in the present case allowed the treating team to rapidly verify the diagnosis and to direct treatment in a safe and efficient manner.

The patient in this case ingested a toxic and dangerous amount of EG. Because he presented early, the initial test results showed a large osmolal gap, but the patient had not yet developed an anion gap acidosis. If the history had been obfuscated, the correct diagnosis would likely have been missed, especially given that serum osmolality tests are often ordered only when there is a high suspicion of toxic-alcohol ingestion or an unexplained anion gap acidosis. The appropriate treatment would have been delayed, and the patient would have developed clinically important renal injury. In properly caring for this patient, we found the availability of an assay that not only measured the EG concentration but also had a rapid turnaround time to be very helpful in confirming the diagnosis and determining the duration of therapy.

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References