CASE REPORT

Two gaps too many, three clues too few? Do elevated osmolal and anion gaps with crystalluria always mean ethylene glycol poisoning?

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SUMMARY

A 60-year-old African-American man with a medical history significant for heavy alcohol abuse, hypertension, delirium tremens, nephrolithiasis and seizure disorder was brought to the hospital with altered mental status. He was found to have high anion gap metabolic acidosis with significantly elevated lactate along with an elevated osmolal gap and calcium oxalate crystals in his urine. With this combination of findings, ethylene glycol poisoning was high in the differential. This case report describes why ethylene glycol poisoning was not the diagnosis in this patient despite the presence of these three classic laboratory findings, therefore emphasising the fact that these findings should not be taken at face value because they can be seen collectively in a patient yet each have a different cause.

BACKGROUND

Patients who present with altered mental status often cannot provide significant medical history and therefore pose a challenge to diagnosis. In such patients, clinical clues will have to be obtained from vital signs, physical examination, blood tests and imaging.

A constellation of elevated osmolal gap, high anion gap along with calcium oxalate crystals in the urine often directs towards the diagnosis of ethylene glycol poisoning. We present a diagnostic dilemma in which the patient had elevated osmolal gap, high anion gap as well as calcium oxalate crystals in the urine, all of which have been explained by causes other than ethylene glycol ingestion. This reiterates that these findings do not always mean ethylene glycol poisoning and they are only suggestive, not pathognomonic, of it.

CASE PRESENTATION

A 60-year-old man with a medical history significant for heavy alcohol abuse, delirium tremens, seizure disorder, nephrolithiasis and hypertension was presented with altered mental status that had started 3 hours prior to admission. His last alcohol consumption was the night before admission. His family reported no recent falls, trauma or change in medications.

The patient takes aspirin, lisinopril, levetiracetam and valproic acid. He had a history of ureteral stent placement about 4 years earlier. He had been smoking two packs per day for 25 years and drinks

heavily per the family. There was no reported illicit drug use.

On presentation, his blood pressure was 134/100 mm Hg with a regular heart rate of 125 beats/min. Oxygen saturation was normal with a respiratory rate of 17/min. His body temperature was recorded as 37°C. On physical examination, he was found to be lethargic and not following commands. Pupils were normal in size and reacting to light. Examination was negative for Kernig's or Brudzinski's sign. He was moving all extremities symmetrically and was withdrawing to painful stimulation. Deep tendon reflexes were sluggish and plantar reflexes were downgoing. As he had a Glasgow Coma Scale of 7/15, he was intubated for airway protection.

INVESTIGATIONS

Complete blood count

White cell count of 20.2 K/ μ L, haemoglobin of 10.4 g/dL and platelets of 165 K/ μ L.

Comprehensive metabolic profile

Sodium of 155 mEq/L, potassium of 3.7 mEq/L, chloride of 117 mEq/L, carbon dioxide of 14 mEq/L, blood urea nitrogen of 19 mg/dL, creatinine of 2.8 mg/dL, anion gap of 24 mEq/L, calcium of 8.2 mg/dL, alanine aminotransferase of 22 U/L, aspartate aminotransferase of 108 U/L and alkaline phosphatase of 184 U/L.

Additional blood workup

Lactate of 13.9 mmol/L, creatine kinase of 1016 U/L, valproic acid level of 39 μ g/mL, ammonia of 69 μ g/dL and measured osmolality of 340 mOsm/kg (calculated osmolality of 325 mOsm/kg). Blood cultures showed no growth.

Urine microscopy and culture

More than 100 red blood cells/high power field (HPF), >100 white blood cells/HPF, 1+ bacteria and a few calcium oxalate crystals. Urine culture showed no growth.

Lumbar puncture

Lumbar puncture revealed 2 mm³ white blood cells, 100% polymorphonucleocytes, 0% macrophages and 10 red blood cells. Clarity was clear and colourless. Glucose was 99 mg/dL and protein 46 mg/dL. Cerebrospinal fluid culture showed no growth.

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Toxicology workup

Blood sample tested negative for methanol, ethylene glycol, acetone levels, ethanol, acetaminophen and salicylates. Urine drug screen tested negative for opiates, barbiturates, amphetamine, cocaine, benzodiazepine, tetrahydrocannabinol and oxycodone.

Imaging

Chest X-ray showed no acute lung process with normal heart, mediastinum and pulmonary vascularity. CT of the head showed no acute intracranial haemorrhage, mass effect or midline shift. Electroencephalogram showed no epileptiform activity.

DIFFERENTIAL DIAGNOSIS

The two major differential diagnoses initially considered were the following:

1. Ethylene glycol poisoning, suggested by elevated osmolal gap, high anion gap and calcium oxalate crystals in the urine.
2. Postictal encephalopathy with seizures secondary to non-compliance, suggested by multiple previous admissions and subtherapeutic valproate levels.

TREATMENT

In light of severe rhabdomyolysis and acute kidney injury, the patient was started on intravenous fluids. He was given anti-epileptics as valproate levels were subtherapeutic. Also, he was started on haemodialysis as soon as ethylene glycol intoxication was suspected. As our pharmacy did not carry fomepizole, ethanol drip was ordered but it was not started. By the time the patient completed a session of haemodialysis and was transported to the intensive care unit, the ethylene glycol level was reported negative. So, there was no more an indication for ethanol drip as negative levels suggested that even if it was a case of ethylene glycol intoxication, the parent molecules would have already metabolised by then.

OUTCOME AND FOLLOW-UP

The patient's mentation improved over the next couple of days and he started following commands. His creatinine normalised eventually. He was later successfully extubated. He denied any consumption of products containing toxic alcohols. The patient was discharged home in good condition and is currently doing well.

DISCUSSION

The most important clues to the diagnosis of ethylene glycol intoxication are obtained from the history of its ingestion or from the available circumstantial evidence. On initial presentation to a hospital, most often, the patients are not in a state to provide the history nor is the circumstantial evidence readily available. The confirmatory test for ethylene glycol poisoning is measuring its levels in the blood. Most laboratories do not have this test readily available and, therefore, there is usually a delay in confirmation.

While awaiting confirmation, it is recommended to initiate treatment with haemodialysis and an alcohol dehydrogenase inhibitor (fomepizole or ethanol) even with mere suspicion of ethylene glycol intoxication. As ethylene glycol intoxication is an emergency and can cause multiorgan damage, laboratory findings of elevated osmolal gap, high anion gap and calcium oxalate crystalluria are often relied on to 'diagnose' ethylene glycol intoxication. This case report describes why ethylene glycol poisoning was not the diagnosis in this patient despite the presence of the triad, emphasising the fact that these findings should not be taken at face value because they can be seen collectively in a patient yet each have a different cause.

An osmolal gap is the difference between the measured osmolality and calculated osmolality. The former is obtained from the blood sample and the latter is obtained using the formula¹⁻⁴:

Calculated osmolality: $(2 \times \text{sodium}) + \text{glucose}/18 + \text{blood urea nitrogen}/2.8 + \text{ethanol}/3.7$

The osmolal gap should not be significant in the absence of other solutes in high concentrations and a gap of 6–10 mOsm/kg is considered acceptable.²⁻⁶ If the difference exceeds 10 mOsm/kg, it implies there are additional solute particles contributing to the osmolality.

When a substance containing ethylene glycol is ingested, the ethylene glycol molecules add solute particles to the plasma, thereby causing an osmolal gap. As ethylene glycol begins to metabolise (figure 1), it is converted into glycolic acid and oxalic acid, which cause the anion gap. Therefore, as metabolism proceeds, there is a gradual drop in the osmolal gap and a rise in the anion gap.⁷⁻¹⁰

The confirmatory test for ethylene glycol intoxication is the measurement of its levels in the blood. The patient in discussion eventually tested negative for ethylene glycol poisoning. Despite the fact that the levels were negative, there was concern that this was because ethylene glycol molecules had metabolised by the time the blood sample was drawn. As described above, the ethylene glycol molecules, and not the metabolites, cause the osmolal gap. Therefore, ethylene glycol intoxication can have negative serum levels and a normal osmolal gap,¹⁰⁻¹¹ but cannot have negative serum levels in the presence of an elevated osmolal gap. This also reiterates that no specific cut-off in the osmolal gap can be used to rule in or rule out ethylene glycol poisoning, as they can be high or normal depending on the timing of its consumption and metabolism. In this case, the labs were not consistent with ethylene glycol intoxication.

The next diagnostic challenge then was to explain what could be causing the high osmolal gap if it was not ethylene glycol. The causes of elevated osmolal gap with anion gap metabolic acidosis are listed below.¹²

1. Diabetic/alcoholic ketoacidosis.
2. Chronic kidney disease.
3. Lactic acidosis.
4. Toxic alcohol ingestions like methanol and ethylene glycol.

Figure 1 Explains the metabolism of ethylene glycol marking the cause of the osmolal gap, anion gap and the calcium oxalate crystals.

5. Propylene glycol infusion.

6. Paraldehyde ingestion.

Among the causes listed, the most likely explanation of this patient's elevated osmolal gap is lactic acidosis. Laboratory findings, including creatine kinase (CK) of 1016 U/L, aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio close to 5 and a lactate of 13.9 mmol/L, suggest that the patient had significant rhabdomyolysis. With lactic acidosis, there is a significant cellular and tissue breakdown which causes the release of glycogen breakdown products that are osmotically active.^{5 12 13} These products contribute to the osmolal gap.

Lactic acidosis secondary to convulsion usually resolves within a short period of time. Lactate is primarily cleared by the liver and about 10%–20% by the kidneys.¹⁴ Lactate clearance by the liver is impaired at higher concentrations of lactate as well as with severe acidosis, both of which were present in this patient. In addition, the patient in this case also had severe rhabdomyolysis and acute kidney injury. With impaired liver and renal clearance, the lactate levels in this patient normalised as soon as he underwent dialysis. No recurrence of elevated lactate levels were noted on subsequent laboratory investigations after dialysis.

Of note, there can be elevated lactate levels with ethylene glycol intoxication which can either be a true elevation from glycolic acid interfering with cellular aerobic respiration or a spurious elevation due to discrepancies between the methods used for testing. True elevation of lactate levels in ethylene glycol intoxication are usually not high and do not account for the level of acidosis caused due to the presence of organic acid metabolites.⁸ It however is not so in this case where the lactate levels were high enough to account for the level of acidosis. Also, point of care analysers estimate lactic acidosis by detecting the metabolites of lactate using the L-lactate oxidase-based system. In ethylene glycol intoxication, glycolate is structurally similar to the metabolites of lactate which cannot be differentiated by the point of care analysers causing the spurious elevation of lactate.^{15 16} In this case, lactate levels were measured using laboratory analyser instead of point of care analyser making it unlikely for it to be a spurious elevation.

Finally, what explains the calcium oxalate crystals in the urine? Different morphologies and causes have been described for calcium oxalate crystals, of which calcium oxalate monohydrate crystals are most commonly associated with ethylene glycol poisoning. However, contrary to this common knowledge, both monohydrate and dihydrate crystals can be associated with it.^{7 17} Also, both kinds of crystals are present in commonly consumed plant tissues.^{9 18 19} Therefore, identification of calcium oxalate crystals in the urine is a very non-specific finding and does not necessarily mean ethylene glycol poisoning. In addition, a patient with daily alcohol abuse likely has chronic dehydration and therefore is prone to develop oxalate crystals. The patient in this case had a history of nephrolithiasis as well. In this setting, it is more likely that the findings of crystalluria was not new for him making ethylene glycol the less likely cause of the crystals.

With these explanations, ethylene glycol was no longer considered as the diagnosis. The patient's altered mental status was attributed to postictal encephalopathy. The elevated CK of 1016 and AST:ALT ratio of close to 5 clearly suggest significant rhabdomyolysis from seizure activity. Also, subtherapeutic valproate levels of 39 µg/mL suggest that the patient had a seizure activity likely secondary to non-compliance with his medication.

Eventually, the patient's mentation improved, and he denied consumption of any abnormal products. No circumstantial evidence to support ethylene glycol poisoning was ever found. He had multiple prior post seizure admissions due to non-compliance, and he later stated he had not been taking his valproate for the past few days.

Learning points

- Elevated osmolal gap, high anion gap and calcium oxalate crystals are findings suggestive of ethylene glycol poisoning, but are not pathognomonic of it.
- No specific cut-off in the osmolal gap can be used to rule in or rule out ethylene glycol poisoning, as they can be high or normal depending on the timing of its consumption and metabolism.
- Lactic acidosis should be considered as a cause of osmolal gap.
- No morphology of calcium oxalate crystals is specific for ethylene glycol intoxication, as both monohydrate and dihydrate crystals develop in ethylene glycol intoxication and are present in commonly consumed plant tissues as well.

Contributors MG: primary resident taking care of patients, reviewed the literature and wrote the manuscript. RKV: secondary resident, reviewed the literature and wrote the manuscript. AK: primary care physician, reviewed the literature and the manuscript. EAS: attending, reviewed the literature and wrote the manuscript.

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REFERENCES

- 1 Rasouli M. Basic concepts and practical equations on osmolality: biochemical approach. *Clin Biochem* 2016;49:936–41.
- 2 Choy KW, Wijeratne N, Lu ZX, et al. Harmonisation of Osmolal Gap - Can We Use a Common Formula? *Clin Biochem Rev* 2016;37:113–9.
- 3 Rasouli M, Kalantari KR. Comparison of methods for calculating serum osmolality: multivariate linear regression analysis. *Clin Chem Lab Med* 2005;43:635–40.
- 4 Pursell RA, Pudek M, Brubacher J, et al. Derivation and validation of a formula to calculate the contribution of ethanol to the osmolal gap. *Ann Emerg Med* 2001;38:653–9.
- 5 Schelling JR, Howard RL, Winter SD, et al. Increased osmolal gap in alcoholic ketoacidosis and lactic acidosis. *Ann Intern Med* 1990;113:580–2.
- 6 Lynd LD, Richardson KJ, Pursell RA, et al. An evaluation of the osmole gap as a screening test for toxic alcohol poisoning. *BMC Emerg Med* 2008;8:5.
- 7 Jacobsen D, Hewlett TP, Webb R, et al. Ethylene glycol intoxication: evaluation of kinetics and crystalluria. *Am J Med* 1988;84:145–52.
- 8 Gabow PA, Clay K, Sullivan JB, et al. Organic acids in ethylene glycol intoxication. *Ann Intern Med* 1986;105:16–20.
- 9 Eder AF, McGrath CM, Dowdy YG, et al. Ethylene glycol poisoning: toxicokinetic and analytical factors affecting laboratory diagnosis. *Clin Chem* 1998;44:168–77.
- 10 Steinhart B. Case report: severe ethylene glycol intoxication with normal osmolal gap - "a chilling thought". *J Emerg Med* 1990;8:583–5.
- 11 Ammar KA, Heckerling PS. Ethylene glycol poisoning with a normal anion gap caused by concurrent ethanol ingestion: importance of the osmolal gap. *Am J Kidney Dis* 1996;27:130–3.
- 12 Kraut JA, Xing SX. Approach to the evaluation of a patient with an increased serum osmolal gap and high-anion-gap metabolic acidosis. *Am J Kidney Dis* 2011;58:480–4.
- 13 Inaba H, Hirasawa H, Mizuguchi T. Serum osmolality gap in postoperative patients in intensive care. *Lancet* 1987;1:1331–5.
- 14 Consoli A, Nurjhan N, Reilly JJ, et al. Contribution of liver and skeletal muscle to alanine and lactate metabolism in humans. *Am J Physiol* 1990;259:E677–84.
- 15 Verelst S, Vermeersch P, Desmet K. Ethylene glycol poisoning presenting with a falsely elevated lactate level. *Clin Toxicol* 2009;47:236–8.

Reminder of important clinical lesson

- 16 Porter WH, Crellin M, Rutter PW, *et al.* Interference by glycolic acid in the Beckman synchron method for lactate: a useful clue for unsuspected ethylene glycol intoxication. *Clin Chem* 2000;46:874–5.
- 17 Jacobsen D, Akesson I, Shefter E. Urinary calcium oxalate monohydrate crystals in ethylene glycol poisoning. *Scand J Clin Lab Invest* 1982;42:231–4.
- 18 Seo JW, Lee JH, Son IS, *et al.* Acute oxalate nephropathy caused by ethylene glycol poisoning. *Kidney Res Clin Pract* 2012;31:249–52.
- 19 Leth PM, Gregersen M. Ethylene glycol poisoning. *Forensic Sci Int* 2005;155:179–84.

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