

Ethylene glycol poisoning: mind the gap

Joevy Lim, Anna Mearns, Chip Gresham

We report a case of unknown ethylene glycol (EG) ingestion and discuss a pitfall from point of care (POC) laboratory testing—a falsely reported elevated lactate level that potentially delayed the diagnosis in a critically ill patient with limited medical history. We show how this pitfall may be used to potentially identify EG toxicity. A brief and limited review of EG's mechanism of toxicity, diagnosis and treatment is included.

Case report

A 40-year-old female with no significant past medical history presented to our tertiary hospital emergency department (ED) via ambulance with vague symptoms that included a headache and abdominal pain. She was accompanied by her two sons. Upon arrival, her nursing assessment documented a Glasgow Coma Scale (GCS) score of 15, vital signs (VS) of: heart rate 110 beats/minute, respiratory rate 18 breaths/minute, blood pressure 110/79mmHg, temperature 36.4°C, oxygenation saturation 91% on room air. She reported feeling well the evening prior to presentation. She denied any infective symptoms and her history had no suggestion of trauma. Within the hour of her arrival, her GCS score began to decrease, and she became unresponsive. Re-assessment noted no significant change in her VS, finger-stick blood glucose of 9.3mmol/L, pupils that were equal and reactive and no focal neurology or seizure activity. Further collateral history from her two children revealed a recent marital argument and no background of alcohol or recreational drug use.

A venous blood gas (VBG) was obtained and analysed in the ED on a point of care (POC) analyser. Results were notable for a pH of 7.035, anion gap (calculated) of 31.8 and lactate of >31mmol/L. A full blood count showed a white blood cell count of $14.1 \times 10^9/L$ but was otherwise unremarkable.

Her basic metabolic panel revealed normal electrolytes, renal function and a bicarbonate of <8mmol/L. Her liver function tests were normal. Her ethanol (ETOH) and paracetamol levels were negative. An electrocardiogram showed a narrow complex sinus rhythm with normal QRS and QT intervals.

Prophylactic antibiotics were administered and due to a GCS score of 4 and severe metabolic derangement, she was intubated and hyperventilated. A CT scan of her brain showed no acute intracranial abnormality. She was admitted to the intensive care unit (ICU) for urgent extracorporeal purification therapy (ECPT) to correct her acidaemia. Further standard intensive care continued, including a brief period of vasopressor support.

When further laboratory investigations were obtained in the ICU to monitor her progress, it was noted that the main laboratory (Roche Cobas c502) lactate was significantly lower (12mmol/L) than that measured on the POC blood gas machines (Radiometer ABL 800 flex) in ED and the ICU (>31mmol/L). This discovery prompted urine microscopy, which confirmed the presence of oxalate crystals. The findings of a serum 'lactate gap' and urinary crystals suggested a diagnosis of EG poisoning, which was later confirmed with a positive glycolic acid spot test followed by a quantified EG level of 3473mg/L, after treatment had begun. A laboratory serum osmolality was not obtained.

Treatment was initiated with an ETOH IV infusion, thiamine, pyridoxine and ECPT in the form of sustained low efficiency dialysis (SLED) along with standard ICU care. Over the next three days, her condition improved significantly with a reducing lactate, normalisation of serum blood levels, improving conscious level and correction of polyuria. She was extubated on day three of her ICU admission, and she was able to confirm ingestion of EG, in the form of anti-freeze,

as a self-harm attempt. She was seen by Psychiatry during her admission and was assessed to be stable for discharge home on day seven of admission.

Discussion

EG is a colourless, odourless and sweet tasting liquid, and while it is most commonly used as the active ingredient in anti-freeze, it is also found in other domestic and industrial products such as hydraulic brake fluids, paints, detergents and cosmetics. While exposures leading to significant morbidity or mortality are rare, the National Poisons Centre in New Zealand reported 587 ingestions (20% paediatric) from 2002 to 2018; these varied from splashes to the mouth to significant intentional ingestions. Sixty percent of all exposures/ingestions were referred to an ED (Figure 1).¹

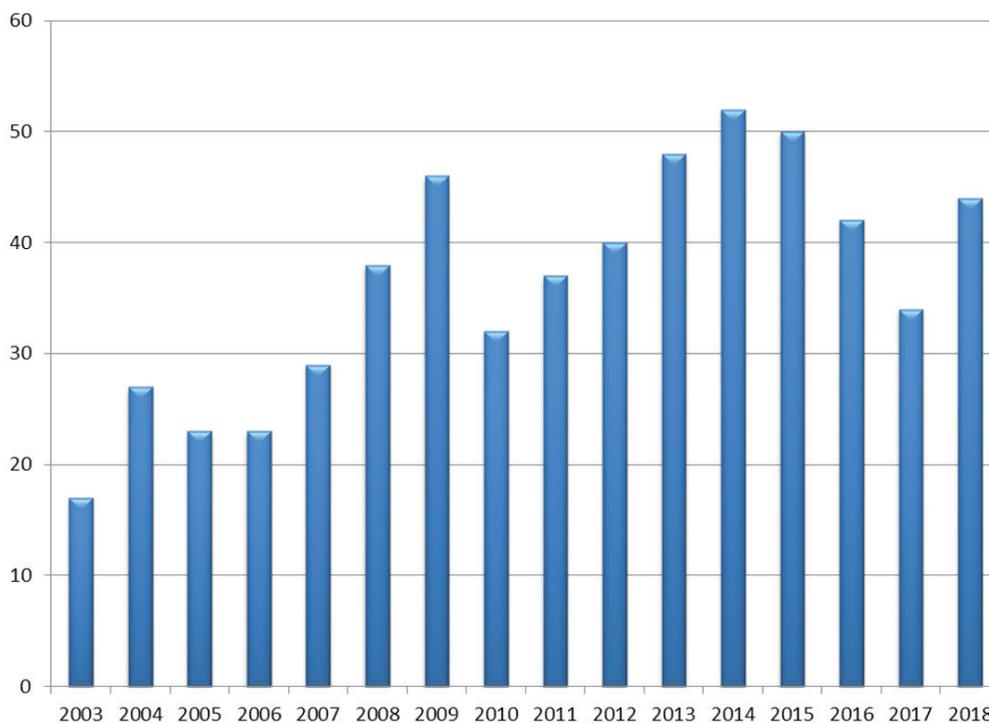
EG is rapidly absorbed after ingestion with peak serum levels reached in 1–4 hours. It causes dose dependent inebriation very similar to ETOH. EG is metabolised in the liver by alcohol dehydrogenase (ADH) to form glycoaldehyde which is then further metabolised to glycolic acid, glyoxylic acid

and oxalic acid by aldehyde dehydrogenase (Figure 2).^{2,3} It is these metabolic products that are responsible for the severe metabolic acidosis (glycolate) and acute kidney injury (oxalic acid forming oxalate crystals) that occurs with EG toxicity.²

EG poisoning is rare in New Zealand, and likely sits low on a differential diagnosis. This presents a significant diagnostic challenge without a clear history from the patient, who may already have an altered mental status at the time of presentation. Clinical and laboratory findings will vary depending on dose and time since ingestion. The hallmark laboratory finding, though not specific to EG, is a metabolic acidosis with an elevated anion gap; however, if the patient presents soon after ingestion, the anion gap may be normal with only an elevated osmolal gap, due to the presence of external solute.^{2,4} As EG is metabolised to acidic metabolites, the anion gap will rise and the osmolal gap will fall (Figure 3).²

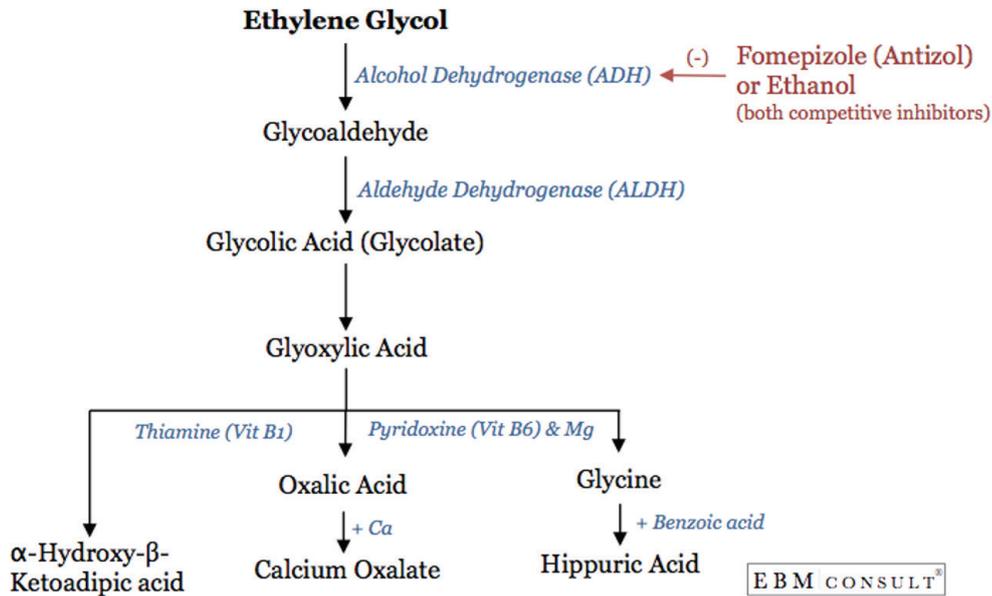
The initial POC laboratory results showed a metabolic acidosis, elevated anion gap with a lactate >31mmol/L. This initially clouded our diagnostic picture. When the

Figure 1: Ethylene glycol exposures reported to the National Poisons Center 2003–Nov 2018.



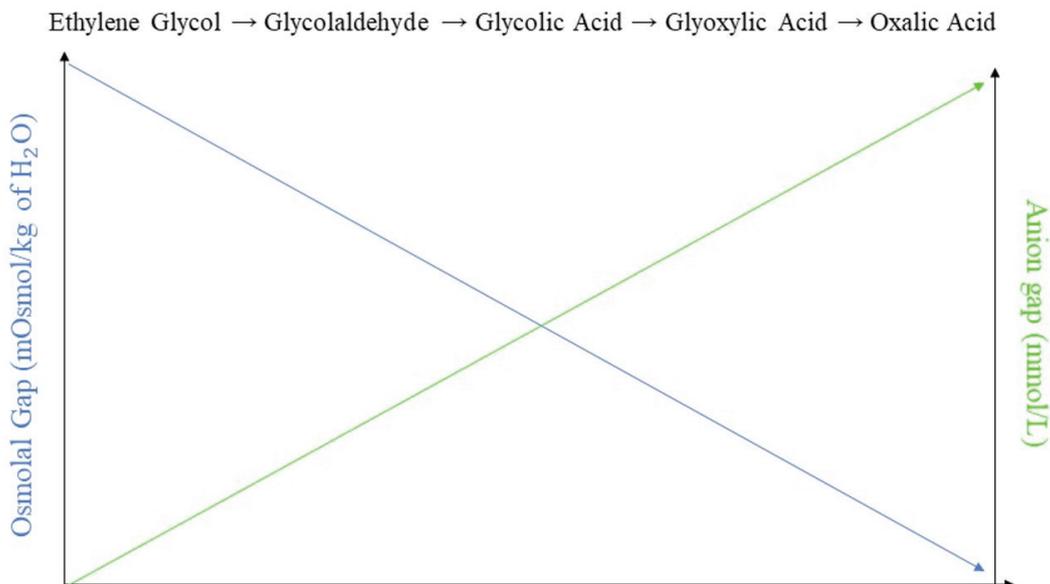
Ethylene glycol exposures reported to the National Poisons Centre: 2001–Nov. 2018. Robin Slaughter. The National Poisons Centre.¹

Figure 2: Metabolic pathway of ethylene glycol.



Ethylene Glycol (EG) is metabolised by alcohol dehydrogenase (ADH) to form glycolaldehyde which is then further metabolised to glycolic acid, glyoxylic acid and oxalic acid, the metabolic products that are responsible for the severe metabolic acidosis and acute kidney injury that occurs with EG toxicity. Antidotes, fomepizole and ethanol, both target ADH, competitively inhibiting it, and therefore preventing the formation of toxic metabolites.²
 Note: Figure retrieved from <http://www.ebmconsult.com>
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Figure 3: Changes in the serum osmolal gap and anion gap with time after ingestion of ethylene glycol.²



repeat lactate obtained from our main hospital laboratory was significantly lower, resulting in what is known as a 'lactate gap', EG moved to the top of our differential, and was verified by urine microscopy, confirming the presence of oxalate crystals. The 'lactate gap' occurs due to the structural similarities between lactate and glycolate (a metabolite of EG) as both substances act as a substrate in the lactate oxidase method used by many POC testing devices, resulting in an erroneously high lactate reading if there is a high blood glycolate level, which occurs in EG toxicity.⁵ So, while a falsely elevated lactate level on its own may be misleading, detection of a 'lactate gap' may be used to potentially diagnose EG poisoning, especially when an EG test is not readily available.⁵⁻⁷ Sending blood to an off-site laboratory for an EG level may not be feasible given the time critical nature of the disease progression and the need for timely intervention.

Treatment

EG is metabolised in the liver by ADH, and if this is prevented then EG is excreted unchanged by the kidneys; hence the mainstay of therapy for EG poisoning is prevention of this metabolism.² This may be accomplished in two ways. The first, and preferable way, is with intravenous (IV) Fomepizole.^{2,8,9} This FDA-approved drug, which does not cause inebriation, inhibits ADH, preventing the metabolism of EG to its toxic metabolites.⁸ Fomepizole has recently been approved for use in New Zealand, however it is not yet readily available. The second line treatment is with ETOH, either IV or orally.^{2,9} ADH has a higher affinity

for ETOH, so when ETOH is available for metabolism, this 'inhibits' the metabolism of EG (and other toxic alcohols). Only pharmaceutical grade ETOH should be given IV and administered through a central venous line. Oral ETOH may be administered as commercially prepared spirits, such as 80 proof vodka. Whichever route is chosen, the goal is to keep the serum ETOH level >100mg/dL.^{2,9} If fomepizole is unavailable and there is any delay in IV ETOH administration, oral ETOH should be given. ECPT is the definitive treatment, though this is being used less in some cases when early fomepizole administration is possible.⁹

Conclusion

This report demonstrates a case of unknown EG poisoning (at time of the original presentation) with an erroneously elevated reported lactate level measured by a POC blood gas analyser. It should serve as a reminder that markedly elevated lactate levels from a POC analyser should be measured against the hospital laboratory analyser, and if a 'lactate gap' is noted, especially in the presence of a metabolic acidosis with an elevated anion gap, the possibility of ethylene glycol toxicity must be considered and treatment initiated early with fomepizole, if available, or ETOH, either intravenously or orally. Early involvement of a clinical toxicologist and/or the National Poisons Centre should be considered as well.

We encourage the readers of this report to discuss the concept of the 'lactate gap' with their hospital's laboratory director; as laboratory and POC analysers may vary across New Zealand.

Competing interests:

Nil.

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