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The three biological gaps and hyperoxaluria in ethylene glycol poisoning: case presentation and review

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Abstract. – Ethylene glycol is a toxic alcohol which may induce significant toxicity when ingested accidentally or intentionally. The main clinical complications of EG poisoning include central nervous system depression, cardiorespiratory instability and renal failure, which may be lethal if improperly treated. Although the demonstration of high plasma levels of ethylene glycol confirms the intoxication, such measurements are generally not obtained in the acute setting and can be misleading due to the rapid metabolism of EG. This implies the need for alternative, indirect, diagnostic methods, which reflect the metabolic fate of EG. These include an early and transient osmolar gap, followed by an anion gap metabolic acidosis and hyperoxaluria. Another frequent finding is a lactate gap between various methods of lactate measurements. An appropriate knowledge of these laboratory findings is essential for the diagnosis of EG poisoning, and for the initiation of antidote therapy (fomepizole) and hemodialysis in selected cases. These features are illustrated by the presentation of a prototypical case of EG poisoning, in which an incomplete diagnostic workup on hospital admission resulted in an unnecessary laparotomy and a significant delay in the management of the intoxication.

Key Words:
Ethylene glycol poisoning, Anion gap metabolic acidosis, Osmolar gap, Lactic acidosis.

Case Presentation

A woman in her fifties, known for diabetes and hypertension, consulted the emergency department for severe abdominal pain of acute onset. Vital signs and general physical examination were unremarkable. Laboratory data revealed an osmolar gap of 20 mOsm/L (measured and calculated plasma osmolality were 334 and 314 mOsm/L, respectively), lactic acidosis (pH 7.22, HCO_3^- 6.7 mmol/L, lactate 27.8 mmol/l), and a serum anion gap of 37.3 mmol/L (Figure 1). Mesenteric ischemia was suspected, and an emergent laparotomy was decided, which ruled out this diagnosis. The patient was then transferred to the ICU 4h after initial admission. A marked hyperlactatemia (21.6 mmol/L) persisted with no more osmolar gap (7 mOsm/L). Interrogation of the patient's husband revealed he had purchased antifreeze at his wife's request the day before admission, raising the suspicion of ethylene glycol poisoning. The examination of patient's urine with a Wood's lamp disclosed fluorescence. On microscopic examination, large amounts of urinary calcium oxalate crystals were present (Figure 1). The measurement of plasma lactate from the initial blood sampling, using an LDH-based method (Dimension® EXL™ Integrated Chemistry System, Siemens Healthineers, Zürich, ZH, Switzerland), yielded a value of 6.8 mmol/L. In contrast, plasma lactate measured with an oxidase-based method (Cobas 8000® analyzer, Roche Diagnostics, Rotkreuz, ZG, Switzerland), yielded a value of 27.8 mmol/L, resulting in a lactate gap of 21 mmol/L (Figure 1). A diagnosis of ethylene glycol (EG) poisoning was made and intravenous fomepizole was immediately started, together with hemodialysis. Serum EG level, measured 4h after admission, was positive at 64 mg/L. The subsequent course was uneventful, and the patient was discharged from the ICU after 48h.

Discussion

Ethylene glycol (EG: $C_2H_6O_2$) is a toxic alcohol used in industrial solvents and as an anti-freeze[1]. The accidental (due to its sweet taste) or intended (suicide attempt or as a substitute for ethanol) ingestion of EG results in a severe form of metabol-

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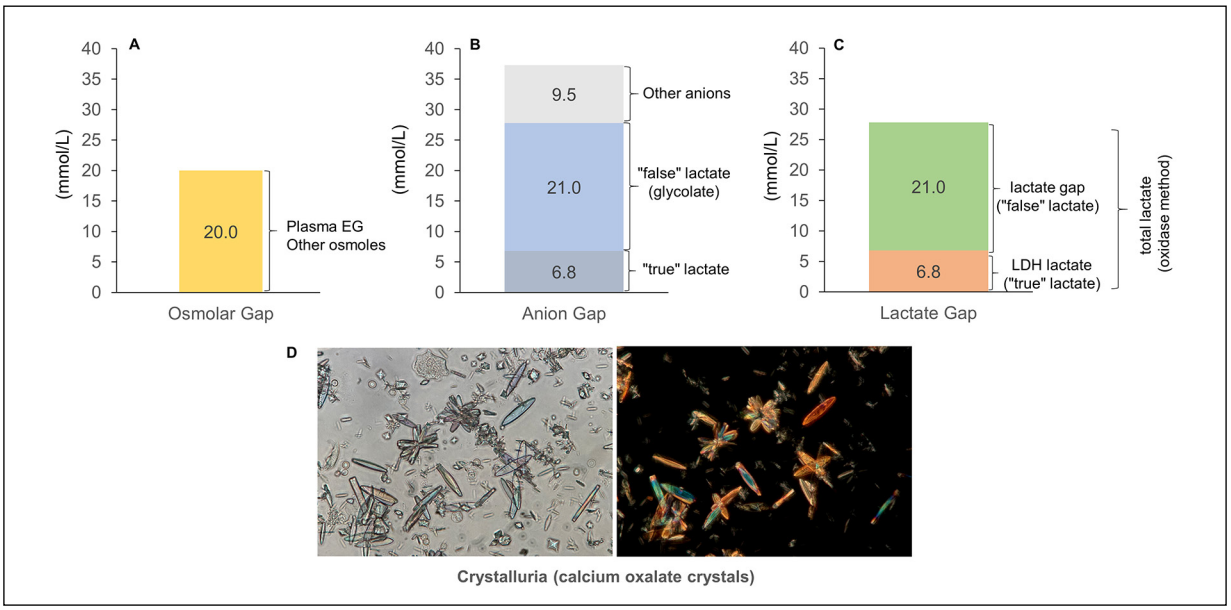

Figure 1. The three biological gaps and hyperoxaluria in ethylene glycol (EG) poisoning. The bar graphs represent the osmolar (**A**), anion (**B**) and lactate (**C**) gaps in the presented case. Photomicrographs (**D**) of calcium oxalate crystals in the patient's urine. Most crystals correspond to needle-shaped monohydrated calcium oxalate crystals (left: contrast phase, right: polarized light; magnification × 400).

ic acidosis and multiorgan failure with significant morbidity and mortality. Severe symptoms occur after the ingestion in excess of 0.1 ml/kg (95% EG solution), and the lethal dose is 1-2 ml/kg (~1500 mg/kg). The absorption of EG is mainly intestinal, with a peak plasma concentration 1-2 h after ingestion, and an elimination half-life of 3-8 h. A plasma concentration of EG > 0.5 g/L is indicative of severe intoxication[2]. However, lower concentrations (as in the case under discussion) do not rule out significant EG intoxication, due to the rapid metabolism of EG.

Early after EG ingestion, a pathological osmolar gap (> 10 mosm/L)[3] develops, due to the accumulation of non-ionized EG[4]. This gap reflects the difference between measured serum osmolarity (using the freezing-point depression), and calculated serum osmolarity, using the formula: [(2 x Na^+) + (Blood urea nitrogen) + (blood glucose)] (in mmol/L)[5]. Rapid metabolism of EG occurs in the liver, through a two-step process involving alcohol dehydrogenase (yielding glycolaldehyde), and aldehyde dehydrogenase (yielding glycolic acid). The latter is responsible for the severe and rapidly progressive metabolic acidosis associated with EG poisoning (Figures 2 and 3)[1,2]. The increase in plasma glycolic acid correlates with a rapid widening of the anion gap (N = 12 ± 2 mmol/L), calculated as: [(Na^+) - (HCO_3^- + Cl^-)] + [0.25 × (40 - serum albumin in g/L)]. The increased anion gap is due to the presence of the glycolate base acting as an unmeasured anion[6], and it is paralleled by a gradual decrease of the osmolar gap, due to EG metabolism (Figures 2 and 3). This inverse relationship implies that the osmolar and anion gaps may be normal of elevated, depending on the stage of intoxication and the level of EG oxidation into glycolic acid[4].

Once formed, glycolic acid is further metabolized into glyoxylic acid and then oxalic acid. The latter is nephrotoxic and may result in hypocalcemia, through its precipitation in renal tubules as calcium oxalate crystals[4]. Although the presence of such oxalate crystals in urinalysis is an important clue to diagnose EG poisoning, their absence does not formally rule out the diagnosis[7]. Urine fluorescence under Wood's lamp examination, as noted in the index case, may be another feature of EG poisoning. It is unrelated to oxaluria, but to the presence of a fluorescent dye added to automotive antifreeze to warn for the presence of leaks[8].

During EG metabolism by alcohol dehydrogenase and aldehyde dehydrogenase, nicotinamide dinucleotide (NAD^+) is reduced to nicotinamide dinucleotide hydride (NADH). NADH promotes the reduction of pyruvate to lactate to regenerate

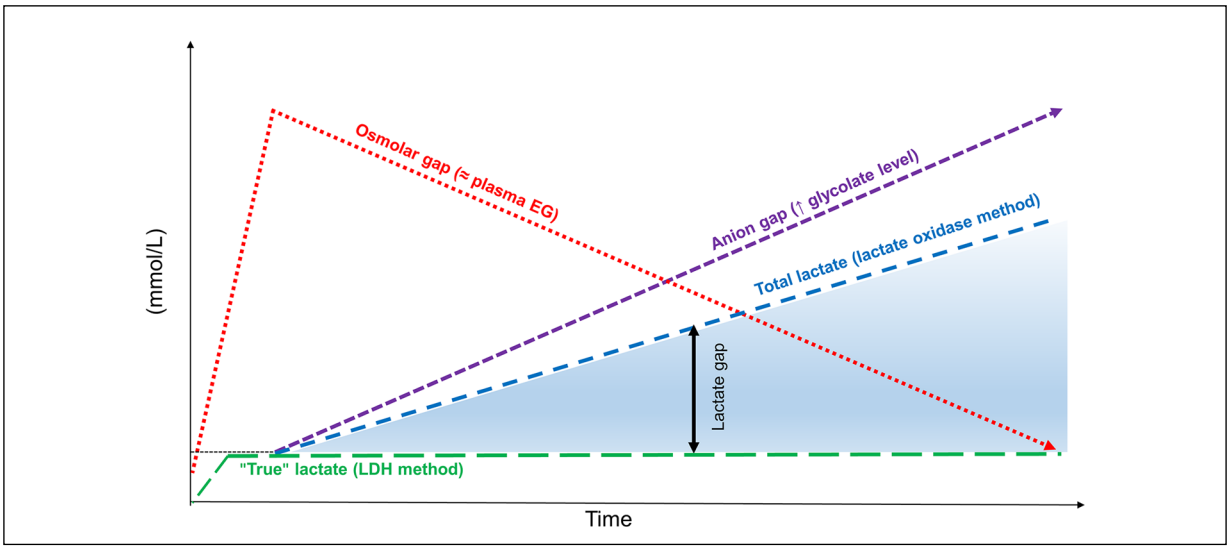

Figure 2. Time course of the osmolar, anion and lactate gaps in ethylene glycol. poisoning. Plasma ethylene glycol (EG) is responsible for the osmotic gap. The metabolism of EG into glycolic acid increases the anion gap due to the glycolate anion. Glycolate also creates the lactate gap, due to its detection by the lactate oxidase method ("false" lactate), while the "true" lactate value is measured by the LDH method.

NAD^+ within the cytosol[9], resulting in a moderate increase of plasma lactate. However, this mechanism cannot account for the marked hyperlactatemia measured in the case presented herein. Lactate can be measured by two distinct methods. The first one uses lactate oxidase (the preferred method for point-of-care lactate measurement), which measures the formation of hydrogen per-

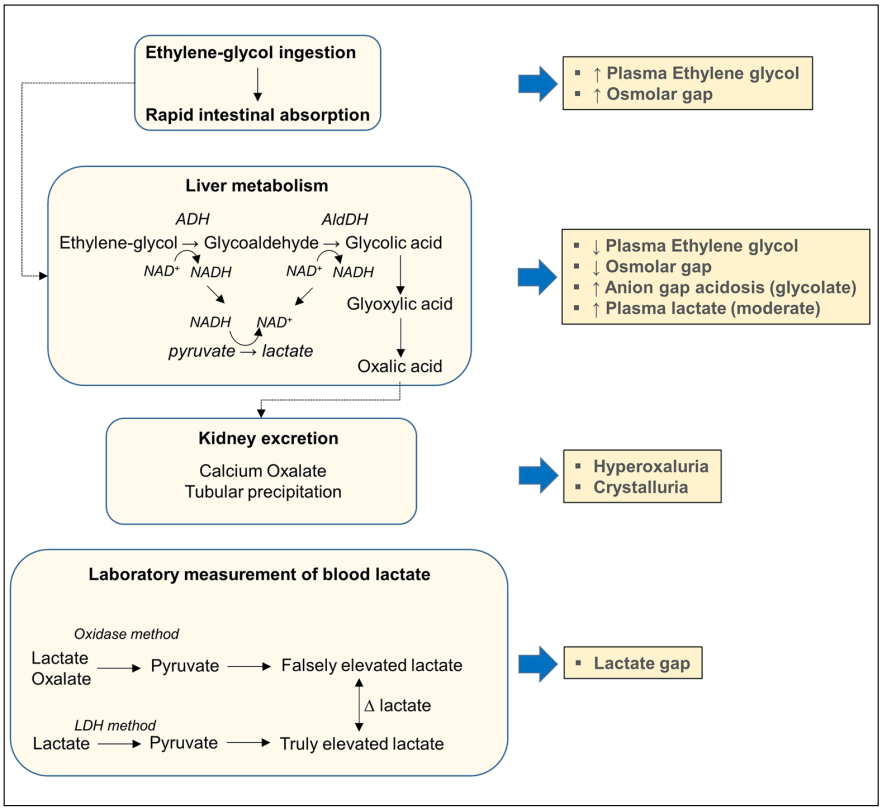

Figure 3. Metabolic fate of ethylene glycol and corresponding biological abnormalities. Following its ingestion and rapid intestinal absorption, ethylene glycol (EG) increases in plasma, creating an osmolar gap. Liver metabolism of EG by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (AldDH) yields glycolic acid, responsible for the anion gap (glycolate anion), with a parallel decrease of the osmolar gap. During EG metabolism, nicotinamide adenine dinucleotide (NAD^+) is reduced to NADH. NADH is oxidized back to NAD^+ via the conversion of pyruvate to lactate, promoting a slight increase of plasma lactate. Glycolic acid formed from EG is further metabolized to glyoxylic acid and oxalic acid, which is excreted by the kidney (hyperoxaluria) and which may precipitate as calcium oxalate crystals. Furthermore, oxalate is falsely measured as lactate when using a lactate oxidase method. This creates a lactate gap by comparison with the specific lactate dehydrogenase method of lactate detection.

oxide during lactate oxidation into pyruvate. The second one uses lactate dehydrogenase, which measures the formation of NADH from NAD^+ during lactate dehydrogenation into pyruvate[9]. Owing to structural similarities between lactate and glycolate, the oxidase-based method not only measures lactate, but also glycolate, leading to falsely elevated values of lactate. In contrast, the specific LDH-based method only measures the low amount of lactate produced during EG metabolism[3] (Figures 2 and 3). The difference between the 2 methods accounts for the typical lactate gap observed during EG intoxication[9,10], as illustrated by our case.

The clinical manifestations of EG poisoning initially comprise abdominal pain (due to gastric irritation), and neurological manifestations. These are characterized by an early state of inebriation, which may be followed by confusion, coma and seizures[7]. After 12-24h, cardiopulmonary complications may develop, including hypertension or hypotension, tachycardia, pulmonary edema, congestive heart failure and circulatory shock. Renal complications usually develop after 24h, due to the precipitation of calcium oxalate crystals in renal tubules, leading to acute renal failure[7]. Finally, a delayed neuropathy, primarily affecting the cranial nerves (facial diplegia, reduced visual acuity, deafness), may develop days to weeks after the intoxication[7].

The treatment of EG poisoning relies on delaying EG metabolism, by inhibiting alcohol dehydrogenase with the antidote fomepizole, and on the removal of toxic metabolites with hemodialysis[4]. Fomepizole should be initiated if plasma EG is above 20-25 mg/dl, or in the presence of a severe and progressive metabolic acidosis (plasma bicarbonate < 15 mmol/L), when a strong suspicion of EG poisoning is present[1,4]. The loading dose is 15 mg/kg, followed by 10 mg/kg q12 hours (q6h in dialyzed patients), for a total of 4 doses or until normalization of the acid-base status[3]. If fomepizole is not available, ethanol may be an alternative to prevent EG metabolism by alcohol dehydrogenase (aiming at an ethanol plasma concentration of 20-25 mmol/L)[4]. However, ethanol is associated with significant adverse effects and is therefore not recommended[11]. Besides fomepizole, hemodialysis is indicated to remove toxic metabolites. It should be initiated in the presence of acute renal failure, significant metabolic acidosis (pH < 7.3), altered mental status, or severe electrolytic disturbances[4]. Additional therapies may also be given to divert EG metabolism towards non-toxic metabolites. These include pyridoxine and thiamine, which favor the formation of glycine and α-hydroxy-ß-ketoadipate, respectively[3].

Conclusions

Ethylene glycol poisoning is a potentially fatal condition, which can be adequately treated with the prompt initiation of antidote therapy (fomepizole) and hemodialysis in selected cases. Knowledge of its prototypical presentation, including (a) a transient osmolar gap followed by (b) a high anion gap metabolic acidosis, (c) a lactate gap between oxidase and LDH-based methods of measurement, and (d) hyperoxaluria, is essential for the early diagnosis and the proper management of ethylene glycol poisoning.

Conflict of Interest

Authors' declaration of personal interests: - Yannis AHMAD. No conflict of interest to disclose with respect to this submission. - Sébastien KISSLING. No conflict of interest to disclose with respect to this submission. - Céline TORRENT. No conflict of interest to disclose with respect to this submission. - Jean-Daniel CHICHE. No conflict of interest to disclose with respect to this submission. - Lucas LIAUDET. No conflict of interest to disclose with respect to this submission. - Zied LTAIEF. No conflict of interest to disclose with respect to this submission..

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Informed Consent

A signed written informed consent for publication has been obtained from the patient presented in this report.

Authors' Contribution

YA: data curation; writing: original draft; SK: provided image data; writing: original draft; CT: provided laboratory data and analyses; JDC: writing: review and editing; LL: writing: final draft, review and editing; figure drawing. ZL: data curation; writing: original draft, review and editing of final draft.

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