Reminder of important clinical lesson

Successful outcome of accidental ethylene glycol poisoning despite delayed presentation

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Summary

A 69-year-old man presented to the emergency department after being found unconscious by his son. He had experienced headache the previous day but had been otherwise well. Investigations revealed a severe metabolic acidosis, raised lactate and acute kidney injury. The calculated anion and osmolar gap were both elevated at 37.7 and 39.3, respectively. Due to his reduced Glasgow coma score (GCS) he was intubated and a CT scan performed: only a small, mature pontine infarct was found of uncertain significance. Further questioning of the family revealed accidental ingestion of 150 ml of a 'blue liquid' 24 h earlier (later identified as car screenwash). With ethylene glycol (EG) poisoning suspected, he was given intravenous ethanol, fomepizole (a competitive inhibitor of alcohol dehydrogenase) and haemofiltration. Despite the delayed presentation, prompt recognition and treatment of EG poisoning led to a successful discharge in this case.

BACKGROUND

It is not unusual to be faced with an unconscious adult in the emergency department (ED). This case demonstrates the importance of considering poisoning as a cause of neurological depression in a patient presenting with profound metabolic acidosis; more specifically ethylene glycol (EG) ingestion with a high anion gap, high osmolar gap metabolic acidosis (confirmatory blood EG levels were not available until 3 days into admission). This case highlights that even delayed presentation can benefit from treatment with fomepizole.

CASE PRESENTATION

A 69-year-old Czech man was admitted on a Saturday via the ED with reduced consciousness and a history of headache. Initially the only available history was of the patient being found slumped on the sofa by his son. It was later discovered that he had drunk approximately 150 ml of a blue liquid from a mineral water bottle 24 h earlier. Our patient was unaware the water bottle was actually used to store screenwash for car windshields (the original container or product labels were never found). His initial neurological examination revealed a Glasgow coma score GCS of 6, with sluggish pupils and globally reduced muscle tone with absent plantar reflexes. Apart from tachypnoea, the rest of the clinical examination was otherwise unremarkable. There was no medical, psychiatric or family history of note. He was not taking any regular medications. He was on holiday in the UK visiting his son and was planning on returning home shortly.

INVESTIGATIONS

His admission arterial blood gas (on 8 litres of oxygen) revealed a severe metabolic acidosis with pH 7.113, PO₂ 25.15 kPa, PCO₂ 1.01 kPa, bicarbonate 2.4 mmol/litre, base excess -24.1 mmol/litre and lactate 6.6 mmol/litre.

A full blood count showed haemoglobin 16.5 g/dl, white cell count 30.7×10⁹ cells/litre, neutrophils 28.7 ×10⁹ cells/litre, platelets 240×10⁹ cells/litre. Sodium was 138 mmol/litre, potassium 7 mmol/litre, urea 14.1 mmol/litre, creatinine 254 µmol/litre.

Liver function tests showed bilirubin 6 µmol/litre, alkaline phosphatase (ALP) 89 IU/litre, alanine aminotransferase (ALT) 28 IU/litre. C reactive protein was 13 mmol/litre, chloride 105 mmol/litre.

An anion gap was calculated as follows: (sodium+potassium)-(bicarbonate+chloride)=37.6 mmol/litre (range: 12–16 mmol/litre).

An osmolar gap is the difference between measured and calculated osmolality. Osmolality was calculated as follows: 2(Sodium) + glucose + urea = 297.7 mmol/litre. The measured osmolality was 337 mOsm/kg giving a gap of 39.3.

A CT scan of the head was performed on admission to exclude intracranial causes of neurological depression. It revealed a left-sided mature pontine infarct.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of an increased anion gap, osmolar gap metabolic acidosis, EG poisoning, or methanol poisoning

TREATMENT

The patient was transferred to the intensive care unit (ITU) and intubated and ventilated. He was fluid resuscitated with normal saline and 1.26%/8.4% sodium bicarbonate. After excluding gross intracerebral pathology by CT and in view of the blood results poisoning was suspected. Intravenous ethanol was given empirically after serum samples were saved for toxicology. Once information on ingestion of an unknown liquid became available we became highly suspicious and contacted the National Poisons Unit in Cardiff, UK. Fomepizole was suggested for suspected EG poisoning

(although there is no evidence of efficacy 8 h post ingestion) as he still had a high osmolar gap indicating the ongoing presence of alcohols, not just the toxic metabolites. Initially we could only treat with intravenous ethanol, until fomepizole was couriered in from Cardiff (treatment started 19 h post admission). He was also given haemofiltration (HF) in the ITU within 5 h of admission due to ongoing acidosis and anuria. We were unable to perform haemodialysis in our ITU. We used a modified regime of fomepizole (10 mg/kg every 8 h) as dose adjustment is required as it is dialysable (a protocol was only available for haemodialysis, not HF and so a regime was decided with the poisons unit). An episode of supraventricular tachycardia was treated with amiodarone and he was successfully extubated at the second attempt and was subsequently discharged to the ward to continue haemodialysis.

OUTCOME AND FOLLOW-UP

A total of 72 h of fomepizole was given. Metabolic acidosis was corrected by day 3 post admission (pH 7.4, HCO_3^- 25 mmol/litre, base excess (BE) 1.5 mmol/litre). Admission EG levels of 100 mg/litre (level of detection 80 mg/litre) became available on day 3 confirming EG poisoning (serum levels by day 2 post admission were undetectable). A CT scan of the head was repeated as he failed to maintain his airway on first attempt at extubation. It showed extensive bilateral basal ganglia infarct involving internal and external capsule as well as a stable pontine lesion (findings in keeping with exogenous poisoning). He was successfully extubated on day 7 and discharged to the renal ward. He developed a hospital-acquired pneumonia, which was treated with Tazocin. He was passing good volumes of urine by day 25 and dialysis was stopped with a creatinine 515 $\mu\text{mol/litre}$ and urea 26.3 mmol/litre. He failed a trial without catheter, was recatheterised and was discharged on day 30. He was last reviewed 6 weeks post discharge and he was feeling very well with no neurological deficit evident, good urine output and clinically euvolaemic.

He remained dialysis independent until the time he was lost to follow-up due to returning to the Czech Republic 12 weeks post admission.

DISCUSSION

EG poisoning is a relatively common form of poisoning. However the presentation in this case was slightly unusual because it is rare for adults to ingest EG unknowingly; it is more often seen in cases of attempted suicide or deliberate ingestion as a cheap substitute for alcohol. EG is a major ingredient of automobile antifreeze. It is highly toxic but odourless and colourless with a sweet taste. A fluorescein dye is often added to help diagnose radiator leaks in automobiles: this can be exploited clinically as the patient's urine may fluoresce under ultraviolet light.

After ingestion, EG is rapidly absorbed with peak levels 1–4 h after ingestion. EG itself only causes an initial alteration in mental status similar to ethanol ingestion; the real toxicity is due to metabolite production via alcohol dehydrogenase pathway (see figure 1, pathophysiology of EG). Once metabolised, the accumulation of glycolic acid causes a severe metabolic acidosis with significant effects on cardiorespiratory function; most commonly tachycardia, tachypnoea, hypertension and congestive cardiac failure. Death most often occurs in this stage 12–36 h post ingestion. After 24–36 h post ingestion, renal failure may develop due to combination of oxalate crystal deposition and cardiovascular instability.

The fact that we did not know what our patient had ingested, even after the son brought in the bottle (it was unlabelled) made the diagnosis challenging. To differentiate between the causes of metabolic acidosis the anion gap, as in this case, can be useful to establish the presence of additional non-measured acids (see figure 2). The presence of an osmolar gap in combination with an anion gap is virtually diagnostic for the presence of EG or methanol.

The most reliable method of diagnosing EG toxicity is measuring blood EG concentration. However, most hospital

Figure 1 Pathophysiology of ethylene glycol poisoning.

The anion gap is the difference between the plasma concentrations of measured cations and anions. As standard electrolyte tests do not measure all anions present in the serum, an anion gap may exist.

High Anion Gap

- Lactic acidosis
- Ketoacidosis
- Renal Failure – urate, phosphate
- Ingestion – salicylate, methanol, ethylene glycol, paraldehyde, sulphur, metformin
- Massive rhabdomyolysis (release of H⁺ and organic anions from damaged muscle)

Non-anion gap

- Loss of HCO₃ eg GI diarrhea or renal (type 2 RTA)
- Pancreatic fistula
- Renal dysfunction
- Hypoaldosteronism (type 4 RTA)
- Hyperventilation
- Ingestions – ammonium chloride, acetazolamide

Osmolar gap

The normal osmolar gap is 10-15. The gap is the measured plasma osmolality minus calculated osmolality. Osmolality is determined by all active substances including ionic and non-ionic such as serum ion, glucose and urea as well as other substances such as alcohols and lipids.

- Elevated osmolar gap indicates methanol or ethylene glycol ingestion

Figure 2 Differential diagnosis of metabolic acidosis.

laboratories are unable to perform this analysis. In our case, the sample had to be sent to Birmingham and the results were only available on day 3 of admission. The general consensus is that in the presence of a high index of suspicion treatment should be given empirically while awaiting EG levels in order to avoid the associated morbidity and mortality.¹ After resuscitation and stabilisation of the patient, treatment with an antidote should be given as soon as possible. As previously mentioned, EG is metabolised through the hepatic enzyme alcohol dehydrogenase. This enzyme has a stronger affinity for ethanol rather than EG and so intravenous ethanol can be used as a competitive substrate for this enzyme, preventing metabolism of EG.² However, it is technically difficult to administer, it can cause neurological depression due to intoxication, as well as hypoglycaemia and therefore careful monitoring of levels are required be prevent under or over dosing. Fomepizole directly inhibits alcohol dehydrogenase and is considered superior to ethanol for a variety of reasons. Firstly, its ease of administration with fixed dosing without the need to monitor levels.³ Secondly, Fomepizole, if used early enough, can avoid the need for haemodialysis.¹ Haemodialysis is often used in addition to an antidote to enhance the removal of unmetabolised EG as well as correct acidosis. EG is renally excreted therefore if the production of metabolites are prevented with fomepizole, the need to enhance EG removal is negated. In our case, we had great difficulties obtaining fomepizole on

a Sunday afternoon, which led us having to use intravenous ethanol initially until fomepizole was delivered from Cardiff poisons unit.

The estimated lethal dose of EG poisoning is 1.4 ml/kg; our 80 kg patient ingested around 150 ml of liquid but the exact concentration of EG in the liquid was not known and unfortunately our earliest serum EG level was beyond 24 h (a peak value was never available). EG and its principle metabolites are eliminated slowly via the kidneys but rapidly metabolised. EG can therefore be difficult to detect after 24–48 h.⁴ The presence of EG in the patient's blood, even at a low level (100 mg/dl) eventually confirmed our initial diagnosis.

Due to the delayed presentation, the persistence of an osmolar gap in this case was important as it implied the continuing presence of an osmotically active substance such as EG or methanol rather than just its metabolites. The poisons unit felt that an ongoing osmolar gap was justification for the use of fomepizole to prevent further harmful metabolite production.

A similar case of a 90-year-old⁵ who accidentally ingested EG has been reported. Her treatment consisted of ethanol infusion and haemodialysis, given 18 h post ingestion. Our case differs since our patient presented to the ED 24 h after ingestion and his treatment was given 28 h after ingestion, consisting of HF and intravenous fomepizole. This case highlights that, despite age and presenting in a comatose state, a good outcome is achievable.

Learning points

- ▶ It is important to consider metabolic disturbances as a cause of neurological depression.
- ▶ Once a metabolic acidosis is established, the anion and osmolar gap should be calculated to help differentiate the diagnosis further.
- ▶ Important to send an admission blood sample for ethylene glycol (EG) levels as it is rapidly metabolised to acids we do not measure and so it may go undiscovered.
- ▶ Fomepizole may not be readily available and each trust should have clear guidance on how to obtain it in an emergency (<http://toxbase.org> has suggested contacts for this). Discussion with a poisons unit is mandatory.
- ▶ Despite delay in presentation, presenting over the weekend and delay in obtaining fomepizole a good outcome can be achieved with good collaboration between the intensive care unit and medical teams.

Competing interests None.

Patient consent Obtained.

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