CASE REPORT

The 'gap' in the 'plasma osmolar gap'

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SUMMARY

Ethylene glycol poisoning is a medical emergency that presents challenges for clinicians and clinical laboratories. If left untreated, it may cause morbidity and death, but effective therapy is available if diagnosed in time. The diagnosis of ethylene glycol poisoning is not always straightforward and the commonly quoted 'plasma osmolar gap' is not sufficiently sensitive to exclude a small ingestion and has been reported to be normal in a number of serious exposures. The 'plasma osmolar gap' cannot distinguish among ethanol, isopropyl alcohol, methanol or ethylene glycol. Thus, the measurement of serum ethylene glycol and, ideally, glycolic acid, its major toxic metabolite in serum, is definitive. This also holds true for methanol and its metabolite formic acid. Ethylene glycol metabolites target the kidney and lead to reversible oliguric or anuric injury, which in turn slows the elimination of ethylene glycol. The therapeutic options include reversal of metabolic acidosis, inhibition of alcohol dehydrogenase and early haemodialysis.

BACKGROUND

Poisoning with ethylene glycol and methanol is not common, but when it does occur, it can be severe and is one of the most common reasons for referral to a National Poisons and Information Service (NPIS).

Toxic alcohol and glycols, such as ethylene glycol and methanol, are present in a number of commercial products that are readily available to the public, including antifreeze, brake fluid and wallpaper stripping, as well as window-cleaning and windscreen-washing solutions. If ingested accidentally or deliberately, they can cause severe toxicity, including metabolic acidosis, coma, seizures, renal failure (especially for ethylene glycol) and blindness (methanol). Severe sequelae can be prevented by appropriate clinical management including administration of an antidote, either ethanol or fomepizole, together with appropriate use of haemodialysis. Episodes of severe poisoning are sometimes difficult to manage because of difficulties in obtaining the required laboratory analyses or in locating supplies of antidotes.

Little is known about the epidemiology of this relatively infrequent poisoning in the UK, although the complexity of patient management leads to this being one of the most common types of poisoning requiring referral to NPIS consultant clinical toxicologists for advice on its management. A prospective audit of toxic alcohol and glycol cases reported through telephone enquiries to the NPIS was therefore conducted during the 2010 calendar-year¹ to provide information on the frequency, current

management and outcomes of systemic toxic alcohol poisoning. The main aim was to provide information on which to base the planning of clinical services for this type of poisoning, including appropriate availability of assays and antidotes. During the year, there were a total of 608 enquiries to the NPIS involving toxic alcohols and glycols, relating to 488 individual exposures. Of these, 250 originated from non-hospital sources.

The vast majority of incidents (431) occurred in the home and most were acute ingestions. There were 89 cases involving children aged 5 years or less. Accidental exposures accounted for 328 cases, 119 were intentional exposures and four were described as recreational use. Of the people involved, 409 had no or minor symptoms only at the time of the call and 71 had moderate or severe symptoms (see figure 1). Ninety-nine of these required an antidote and 33 patients required haemodialysis and/or haemofiltration. Difficulties were often encountered in obtaining the specialist assays and antidotes required for optimal management of this type of poisoning.

Some of the difficulties encountered by clinicians in managing this relatively uncommon but potentially serious poisoning included a lack of availability of laboratory assays for toxic alcohols, inadequate stock of antidotes, and inadequate access to facilities for haemodialysis. The decision to use a specific antidote in ethylene glycol toxicity may have to be taken before the assay result becomes available. Similarly, the decision to stop using the antidote may be delayed if the analytical results are not available promptly. This may result in suboptimal clinical management, a prolonged admission to hospital and a poor use of clinical and financial resources.

Individual hospitals encounter clinically important systemic poisoning with toxic alcohols and glycols infrequently. As a result, they may not be well prepared to manage cases when they do occur, since stocking of appropriate antidotes and availability of specialist assays may not be considered a priority. NPIS data, however, indicate that there is an average of at least two severe cases each week nationally. To manage these more effectively, NHS hospitals need to consider how they can improve the local availability of assays and antidotes.

CASE PRESENTATION

A 42-year-old Caucasian man was brought to the emergency department by the ambulance in the early morning hours with a low Glasgow Coma Score (GCS) of 8. His physical examination was unremarkable, his capillary glucose was 10 mmol/L and there were no ketones in the urine. His vital

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* blocked by ethanol and fomepizole.

Figure 1 Ethylene glycol metabolism.

signs were normal apart from a temperature of 35.8°C.

Initial arterial blood gas showed: PH 7.2, lactate 4.9 mmol/L, bicarbonate 12 mmol/L, base excess of -16 mmol/L.

The chest X-ray was clear and the relevant laboratory results were:

- ▶ Creatine kinase 800 U/L
- ▶ Na 131 mEq/L
- ▶ Cl 108 mEq/L

- ▶ Calculated anion gap of 11 mmol/L ($\text{Na} - (\text{Cl} + \text{HCO}_3)$).
- ▶ C reactive protein 8
- ▶ Urea 11 mmol/L
- ▶ Creatine 90 mmol/L

From his previous discharge summaries, it was gathered that he was a primary schoolteacher and had a background of a non-specified 'fit disorder' but was not on any regular medication apart from PRN codeine and diazepam for his back pain. The

serum ethanol was <10 mg/dL and the standard toxicology screen confirmed his usual medications (benzodiazepine and codeine); the serum paracetamol and salicylate levels were below detection limits.

A provisional diagnosis of a 'post ictal' state was made and an intensive care opinion was sought due to his persistently low GCS. He was eventually intubated and the CT head excluded any acute intracranial event. He was not given any anti seizure medication as the history was not clear and he did not have any further fit after admission.

He was monitored in the intensive care unit (ICU) and received fluids due to his high lactate and negative base excess. Over the next 24 h, the acidosis and lactate failed to improve and he developed an acute kidney injury with the creatine rising from 90 to 170 mmol/L. Possibility of a tricyclic antidepressant overdose was raised, but he had no access to it and his ECG showed normal sinus rhythm. Collateral history from his wife and friends failed to elicit history of any illicit drug or recreational drug ingestion, but she did confirm that he was not at home for 1 day prior to being admitted to the hospital. The patient's general practitioner when contacted failed to add any more detail and the 'fit disorder' was a single episode of seizures that occurred 2 years ago, and the CT and EEG were normal at that time.

After 2 days of deliberation, the case was discussed with the National Poisons and Information Service (NPIS) and a blood toxicology screen specifically requested for volatile acids surprisingly showed an ethylene glycol level of 24 mg/L, despite the fact that the osmolar gap was 9 mOsm/kg (calculated serum osmolality of 291 mOsm/kg—measured ($2 \times \text{Na} + \text{urea} + \text{glucose}$) serum osmolality ($2 \times 131 + 9 + 11 = 281$ mOsm/kg)).

This was the only sample with an ethylene glycol level and it was 2 days post ingestion, not at the time when the serum osmolar gap was calculated initially. NPIS guidance is usually to discontinue the antidote once the levels are <50 mg/L, but the advice was to initiate treatment in this situation because of uncertainty over timing and the persistence of acidosis. This also makes the point about an 'early rise in osmolar gap' and 'late rise in anion gap' due to metabolism.

He was started on an absolute alcohol infusion with pabrinex (intravenous B-complex preparation) supplementation for ethylene glycol toxicity as the centre did not use fomepizole. The patient developed massive polyuria the next day with urine output in excess of 4–5 L a day, which were attributed to a recovering acute tubular necrosis (ATN) or perhaps the osmotic effects of alcohol. He eventually ended on haemodiafiltration (CVVHDF) alongside the alcohol infusion with an even fluid balance (box 1).

His kidney function and mental state recovered slowly over 3 days and the serum creatine at discharge was 94 mmol; the urine was reported to be too dilute for an accurate oxalate analysis, but his 24 h urinary calcium was normal. He made a complete recovery but had a significant memory lapse to be able to put things in order as regards his curious presentation, but he was recently made redundant from his job and had ongoing domestic issues.

DISCUSSION

The established hallmark of any toxic alcohol poisoning is a combination of a high anion gap metabolic acidosis and an osmolar gap. However, the increase in the serum osmolal gap and metabolic acidosis can occur either together or alone depending on several factors, including the baseline serum

Box 1 Aid to diagnosis, treatment and haemodialysis indications

Diagnosis

- ▶ Arterial blood gas (to determine extent of acidosis)
- ▶ Routine chemistry (to determine anion gap and renal function)
- ▶ Serum and calculated osmolality (to help determine osmolar gap)
- ▶ Serum ethanol concentration (to exclude confounding factors)
- ▶ Serum calcium concentration (to rule out ethylene-glycol associated hypocalcaemia)
- ▶ Serum ethylene glycol (to establish diagnosis)
- ▶ Urinalysis (for oxalate crystals)

Treatment

- ▶ Block alcohol dehydrogenase with *fomepizole*
- ▶ If fomepizole is unavailable or the patient has a known allergy, block alcohol dehydrogenase with ethanol
- ▶ Administer *sodium bicarbonate* for patients with pH below 7.3
- ▶ Administer *thiamine*, 100 mg IV, and administer *pyridoxine*, 50 mg intravenously
- ▶ If the diagnosis is uncertain but clinical suspicion is high, the clinician should initiate antidote treatment with alcohol dehydrogenase blockade and consultation for haemodialysis

Haemodialysis is indicated in severe toxicity

- ▶ Unresolving metabolic acidosis, regardless of drug level
- ▶ Elevated serum ethylene glycol levels (>50 mg/dL), unless arterial pH is above 7.3
- ▶ Evidence of end-organ damage (eg, renal failure)

osmolal gap, molecular weight of the alcohol, and stage of metabolism of the alcohol.²

Ethylene glycol is rapidly absorbed from the gut. Peak concentrations occur 1–4 h after ingestion. It is metabolised to glycolaldehyde, then to glycolic, glyoxylic and oxalic acids, which are responsible for the majority of its toxic effects. Glycolic acid is cleared by the kidney and is largely responsible for the marked acidosis seen in severe cases. There is increasing evidence that calcium oxalate monohydrate crystals are the cause of cerebral oedema and renal failure.

Ethylene glycol elimination appears to follow first-order kinetics in the absence of treatment, with an estimated serum half-life of between 3 and 9 h through various metabolic pathways, but elimination after alcohol dehydrogenase inhibition (figure 2) becomes almost entirely renal, with a half-life of 17–20 h.³

Given that most hospitals do not have the means to measure the specific toxin in plasma, the osmolar gap, however small, still serves as a rapid diagnostic test for detecting the presence of osmotically active substances like ethylene glycol in plasma,⁴ despite the fact that the osmolar gap measurement is incomplete and inaccurate at times.^{5 6}

Osmolar gap has widely been used as a screening test for the presence of exogenous substances, but reviews⁷ show that its clinical utility remains hypothetical; having been theoretically extrapolated from the non-poisoned population, the serum in

Figure 2 National Poisons and Information Service audit data re the toxicity 'burden'.

itself is not an 'ideal' solution as the osmotic activity of a substance is not proportional to the number of the solute particles contained.⁸

The plasma osmolar gap estimates the molar quantity of uncharged molecules and therefore increases only in the presence of the parent alcohol (ethylene glycol). The toxic acid metabolites of ethylene glycol (glycolate, glyoxylate and oxalate) exist primarily in a dissociated (ie, charged) form at physiological pH; since these anions must be accompanied by a cation (mostly sodium), they do not contribute to the calculated osmolar gap. As a result, the plasma osmolar gap is insensitive in late presentations, since most of the parent alcohol has already been metabolised.⁹

Some patients with ethylene glycol poisoning present with elevated lactate levels, but the rise in lactate is insufficient to account for the degree of acidosis and is likely to be caused by the misinterpretations of some laboratory instruments that cannot differentiate between lactate and glycolate

(metabolite of ethylene glycol), which is structurally similar to lactate.^{10 11}

Treating with cofactors (folic acid, thiamine and pyridoxine) to optimise non-toxic metabolic pathways (figure 1) helps in the elimination of the parent alcohol or its metabolite.^{12 13}

Early treatment with an antidote will prevent the production of toxic metabolites and prevent the rise in the anion gap. Haemodiafiltration is less effective than dialysis, but high flow haemodiafiltration should be considered if haemodialysis is unavailable. Haemofiltration does not remove ethylene glycol or its metabolites as effectively as haemodialysis (or haemodiafiltration).

Haemodialysis is effective in removing ethylene glycol, glycolaldehyde and glycolate (metabolites) and can shorten the duration of poisoning in addition to correcting the metabolic abnormalities. The half-life of ethylene glycol during haemodialysis is reduced to around 3 h. Haemodialysis may therefore be preferred to prolonged antidotal treatment.¹⁴

Learning points

- ▶ The practice of categorically ruling out ethylene glycol exposure on the basis of a 'plasma osmolar gap' of less than 10 units is unjustified. Osmolar gap is insensitive in late presentations.
- ▶ Patients will develop a high osmolar gap as they absorb the glycol over the first few hours. Thereafter, as the glycol is metabolised to acids, the osmolar gap will fall while the patient's anion gap will climb and the acidosis worsen. A severely poisoned patient can present early with a normal anion gap and a normal pH; their osmolar gap is usually high.
- ▶ The ideal approach is to measure the serum concentration of the specific alcohol early in order to quantify the absorbed dose and predict the clinical course. Measure the ethylene glycol concentration (at least 2 h after ingestion) and *start an antidote* while waiting for the results if the clinical suspicion is high.
- ▶ Elevated lactate in ethylene glycol toxicity is not reflective of a shocked state and should be interpreted with caution.
- ▶ Serum ethanol, if present, would add to the osmolar gap and inhibit the hepatic metabolism of ethylene glycol, obscuring signs of toxicity.

Competing interests None.

Patient consent Obtained.

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