Two cases of toxic methanol ingestion, one leading to brain death: case reports and a brief review

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ABSTRACT

Two patients were admitted sequentially to a rural emergency department, then transferred to a tertiary intensive care unit, both with serious methanol poisoning from home-brewed alcohol. They were intubated, mechanically ventilated, and treated with intravenous and nasogastric ethanol and continuous venovenous haemodiafiltration. Although quite similar in presentation, metabolic complications and therapy, one patient became brain dead due to severe cerebral oedema, while the other was discharged without any significant complications. Their course highlights the importance of early treatment of non-ethanol alcohol poisoning.

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Clinical records

Patient 1

A 60-year-old man who was deeply unconscious was brought to a rural hospital emergency department. He had experienced severe vomiting in the past 12 hours. His friend gave the history that he and another friend had consumed home-brewed alcohol 24 hours before. Apart from well controlled type 2 diabetes mellitus, his past history was unremarkable. He was immediately endotracheally intubated for deep unconsciousness and airway protection, and was commenced on noradrenaline (~ 0.3 μg/kg/min) for hypotension and surface warming for hypothermia (core temperature, 33.8°C). Pupils were 4 mm in size bilaterally with no reaction to light.

Arterial blood gas measurement on 0.3 FiO_2 showed a severe metabolic acidosis (pH 7.02; [reference interval (RI), 7.35–7.45]; $paCO_2$, 23 mmHg [RI, 35–45 mmHg]; PaO_2, 135 mmHg; bicarbonate concentration, 6 mmol/L [RI, 22–28 mmol/L]; anion gap, 33 mmol/L [RI, 12–20 mmol/L]). Plasma biochemical analysis showed urea concentration, 7.3 mmol/L [RI, 3.2–7.1 mmol/L]; creatinine level, 254 μmol/L [RI, 55–105 μmol/L]; blood glucose level, 8.4 mmol/L [RI, 3.9–7.8 mmol/L]; lactate concentration, 7.6 mmol/L [RI, 0.5–2.0 mmol/L]; and ketone level, 0.2 mmol/L [RI, < 0.1 mmol/L].

A computed tomography (CT) scan of the brain did not show acute pathological features. An empirical diagnosis of toxic alcohol ingestion was made. Transfer to my tertiary intensive care unit, which is 1 hour away by air, was organised. On arrival, a blood sample was sent for measurement of plasma osmolality and plasma concentrations of ethanol, methanol and ethylene glycol. The patient was then immediately commenced on an intravenous infusion of 10% ethanol to empirically treat poisoning with non-ethanol alcohols and glycols (NEAGs). As per published guidelines,[1] 100% ethanol was diluted in 5% dextrose to a 10% concentration and the infusion dose titrated to target plasma ethanol levels of about 22 mmol/L (100 mg/dL). This was changed to nasogastric ethanol the next morning. Continuous venovenous haemodiafiltration (CVVHDF) was commenced for the dual indications of severe metabolic acidosis and NEAG toxicity.

The biochemical analysis was instructive. The measured osmolality was 411 mmol/L (osmolal gap, 101 mosm/L). The measured plasma lactate concentration was 1.2 mmol/L and plasma ketone concentration was 0.2 mmol/L. Therefore, the osmolal gap was mainly due to an unmeasured osmole such as an alcohol — ethanol, methanol or ethylene glycol. Borderline plasma calcium concentration (1.18 mmol/L [RI, 2.13–2.63 mmol/L]) made ethylene glycol ingestion unlikely. Differentiating between the former two required direct measurement of their concentrations, but it was considered appropriate to empirically treat for methanol ingestion given the serious toxidrome associated with it. Several hours later, the measured ethanol and methanol concentrations were available: < 2.2 mmol/L and 72.7 mmol/L, respectively, confirming the diagnosis of toxic methanol ingestion.

Plasma osmolality and ethanol levels were measured 6-hourly to titrate the infusion dose of ethanol. Sixteen hours after it was first measured, plasma osmolality had decreased to 332 mosm/kg. During the next 24 hours, the patient's pupil size changed from 4 mm to 6 mm (still no response to light). In the setting of supratherapeutic anticoagulation with heparin for CVVHDF for a few hours, intracerebral haemorrhage was raised as a possible cause. A CT scan of the brain was performed; its

Table 1. Clinical and biochemical differences between the two patients

	Patient 1	Patient 2
Time to admission	About 24 hours	About 50 hours
Symptoms on admission	Vomiting, deep unconsciousness	Blurred vision, reduced level of consciousness
Osmolal gap at admission	55 mosm/L	101 mosm/L
Blood methanol concentration	72.7 mmol/L	33.3 mmol/L
Blood ethanol concentration	< 2.2 mmol/L	13.3 mmol/L
Treatment in intensive care unit	Endotracheal intubation for airway protection Mechanical ventilation Intravenous ethanol followed by nasogastric ethanol as per published guidelines Continuous venovenous haemodiafiltration	
Outcome	Brain death	Survived to be discharged home; no significant neurological or visual deficits

findings were reported by the radiology registrar as "subarachnoid haemorrhage", on the basis of which a CT angiogram of the circle of Willis was performed. The radiological diagnosis of subarachnoid haemorrhage was subsequently modified by the radiology consultant as "pseudo-subarachnoid haemorrhage", a well described artefact associated with increased intracranial pressure.[2] The CT scan was formally reported as showing severe cerebral oedema with inferior herniation of the cerebellum.

Two days later, when intravenous ethanol was stopped and ethanol concentration was < 2.2 mmol/L, neurological examination demonstrated evidence of brain death.

However, as the possibility of methanol-induced optic neuritis precluded clinical examination for brain death, a radionuclide HMPOA scan was performed, which confirmed brain death. The patient's family consented to organ donation, with successful transplantation of the liver, both kidneys, heart and both corneas.

Patient 2

Patient 2 was a friend of Patient 1, was 42 years old, and had ingested the home-brewed alcohol at the same time. He presented to the same rural hospital emergency department 26 hours after Patient 1 (ie, about 50 hours after the alleged time of ingestion). He had complained of no significant symptoms in the first 36 hours, but started having blurred vision for a few hours followed by worsening drowsiness.

At presentation in the emergency department, the patient was still answering questions, but was confused and disoriented, due to which visual acuity could not be evaluated. Biochemical analysis revealed a severe high anion gap and high osmolal gap metabolic acidosis. He was intubated to facilitate ethanol therapy and transferred to my tertiary ICU.

After a few days of receiving virtually identical therapy as Patient 1 (mechanical ventilation, CVVHDF, intravenous followed by nasogastric ethanol), he not only survived to be discharged home, but also regained full neurological and visual function (which was surprising, given his delayed presentation with visual symptoms). The significant clinical and biochemical differences are summarised in Table 1.

Discussion

Poisoning from ingestion of NEAGs (methanol, methylene glycol and ethylene glycol) is uncommon in Australia, with the Victorian registry having only 48 confirmed exposures in the past 5 years across the state (as determined by a search of Austin Health's website, http://www.austin.org.au; search term "methanol"). Substances containing NEAGs include antifreeze, canned heating sources, copy machine fluids, fuel additives (octane boosters), paint remover or thinner, shellac, varnish and windshield wiper fluid. Once ingested, NEAGs have excellent bioavailability and undergo first-pass metabolism in the liver by the enzyme alcohol dehydrogenase (ADH) to various acids.

The spectrum of toxicity includes common class effects, namely, metabolic acidosis with a combination of high anion gap (due to the metabolite) and high osmolal gap (due to the parent drug), plus unique end-organ effects due to the parent drug and its metabolite. For instance, methanol causes direct neurotoxicity and ocular changes, such as optic neuritis, which leads to transient or permanent blindness. Direct neurotoxic effects of methanol and its metabolite formic acid include retinal injury with optic disc hyperaemia, oedema, and eventually permanent blindness, as well as ischaemic or haemorrhagic injury to the basal ganglia.[3] These changes are postulated to result from disruption of mitochondrial function.[3] Severe toxic methanol ingestion carries a high mortality (~ 48%) and morbidity (23% blindness in survivors).[4] Poor prognosis was associated with pH < 7, coma on admission and a delay of 24 hours or more from ingestion to admission.[4]

Therefore, prompt institution of specific treatment is key to reducing morbidity, even before confirming the diagnosis. Any patient who presents with a high anion

gap and high osmolal gap metabolic acidosis that cannot be explained by lactic acidosis or ketoacidosis must be assumed to have toxic NEAG ingestion, and specific treatment commenced empirically. Regardless of the specific NEAG consumed, the management principles of toxic NEAG ingestion are similar — initial resuscitation and stabilisation including airway protection, treatment of metabolic acidosis, enhanced elimination of the unmetabolised compound and existing toxic metabolites and inhibition of NEAG metabolism.

Enhanced elimination from the blood is achieved by dialytic therapy, while inhibition of NEAG metabolism is achieved by competitive inhibition of ADH. For many decades, the only available competitive inhibitor was ethanol, administered either enterally or intravenously. Ethanol therapy has significant disadvantages including hypoglycaemia, hypothermia, and, most importantly, neurological depression or agitation from inebriation necessitating airway protection. Dosing is unpredictable due to variations from differences in metabolism and clearance by dialysis. Another antidote, fomepizole (4-methylpyrazole), is now considered the antidote of choice when available. Apart from being 8000 times more potent than ethanol as an ADH inhibitor, its other advantages over ethanol include ease of dosing and the fact that monitoring is not required.[5] Its main drawback is significant cost, especially in dialysed patients, among whom the frequency of dosing is 4-hourly instead of 12-hourly. Hence, it is not readily stocked in most Australian hospital pharmacies. I could not obtain it for these two patients at short notice from the hospital pharmacy or elsewhere, and thus had to use ethanol.

Intravenous ethanol is administered by diluting 100% dehydrated ethanol to 10% to avoid possible damage to central venous catheters. Nasogastric ethanol is administered at 20%–40% strength due to the high risk of gastric mucosal excoriation at higher concentrations. Due to variations in absorption and hepatic enzyme induction, there is no "standard" dose. To achieve effective competitive inhibition of methanol, the recommended target plasma ethanol concentration is 22 mmol/L (100 mg/dL). Infusion rates to achieve this target level could reach 200–250 mL/h. Dosing is further complicated by clearance of ethanol by dialysis. The simplest way is to start with the recommended initial dose, and regularly monitor plasma ethanol concentrations and plasma osmolality. The treatment is ceased on resolution of the metabolic acidosis and when the methanol level is < 6.24 mmol/L (20 mg/dL).

These two cases of methanol poisoning with important differences in presentation and outcome raise several issues.

Patient 1's poor outcome may have been due in part to the delay in instituting treatment of possible methanol poisoning until transfer to the tertiary hospital, despite a presentation that was highly consistent with toxic NEAG ingestion. This was partly a failure on my part as the tertiary intensive care specialist, in not advising the referring rural hospital emergency department to initiate empirical treatment.

The reason for the startling difference in outcome between the two patients was unclear, but the initial biochemistry raises some possibilities. One possible reason is a lower ingested toxin load in Patient 2, as evidenced by lower methanol level and smaller osmolal gap. However, the lower plasma levels could have also been due to greater metabolism of methanol to formic acid as a result of the delayed presentation. Another possibility is that Patient 2 had a significant coingestion of ethanol (admission ethanol levels were much higher than Patient 1, despite the delay in his presentation), which acted as an antidote.

The cause of the cerebral oedema that led to brain death in Patient 1 could have been direct neural toxicity from methanol or its metabolite (formic acid). It also could have been caused or exacerbated by severe osmolal shifts — in Patient 1, plasma osmolality decreased precipitously from 411 mosm/kg to 332 mosm/kg over 16 hours. There were competing forces affecting the osmolality — decrease in osmolality due to clearance of methanol and ethanol by CVVHDF and increase in osmolality due to ethanol and glucose administration, with the net effect being unpredictable. Despite identical treatment, the plasma osmolality in Patient 2 only decreased gradually. I still cannot explain the reason for this occurrence.

Pseudo-subarachnoid haemorrhage is a well recognised entity in patients with severe cerebral oedema, and must be considered whenever radiological findings are inconsistent with the clinical setting, or when radiological findings are not internally consistent.[2] Postulated mechanisms to explain the increased attenuation of the basal cisterns in the setting of diffuse cerebral oedema include vasogenic oedema, and congestion of the superficial pial veins.[2,6] In Patient 1's case, the consultant radiologist noted that the distribution of the subarachnoid blood was disproportionately diffuse, without a concomitant intraventricular haemorrhage.

CT angiogram diagnosis of brain death is not well validated, and requires several specific criteria.[7] Australian and New Zealand Intensive Care Society guidelines on brain death recommend a more validated imaging investigation such as 3- or 4-vessel angiography or radionuclide perfusion scan for confirmation.[7]

Once brain death was confirmed, the suitability of organ donation in the setting of methanol poisoning was raised. Several case reports have described successful

organ donation from such donors,[8,9] and this case adds to that pool.

From this experience, I have several recommendations to make:

- In the setting of high anion gap and high osmolal gap metabolic acidosis, with likely alcohol poisoning, it may be advisable to start treatment early while awaiting confirmation of plasma alcohol levels. The benefits of early treatment with ethanol for a non-ethanol toxic NEAG ingestion outweigh the risks of administering ethanol.
- During treatment of NEAG ingestion poisoning with ethanol, recommended guidelines are only a starting point; the dose must be titrated using frequent monitoring of plasma osmolality and ethanol concentrations in the initial phase of treatment (eg, 2-hourly instead of 6-hourly).
- Although it is not feasible for every ICU to stock fomepizole, consideration could be given to having a centralised stockpile in at least one ICU in each large city, ready to be deployed at short notice where required.
- Intensive care specialists should be aware of the phenomenon of pseudo-subarachnoid haemorrhage in patients with severe cerebral oedema.

Competing interests

None identified.

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References

1 Sivilotti MLA, Winchester JF. Methanol and ethylene glycol poisoning. UpToDate, version 19.1. Jan 2011.
2 Given CA, Burdette JH, Elster AD, et al. Pseudo-subarachnoid hemorrhage: a potential imaging pitfall associated with diffuse cerebral edema. *AJNR Am J Neuroradiol* 2003; 24: 254-6.
3 Sivilotti ML, Burns MJ, Aaron CK, et al. Reversal of severe methanol-induced visual impairment: no evidence of retinal toxicity due to fomepizole. *J Toxicol Clin Toxicol* 2001; 39: 627.
4 Hassanian-Moghaddam H, Pajoumand A, Dadgar SM, Shadnia Sh. Prognostic factors in methanol poisoning. *Hum Exp Toxicol* 2007; 26: 583-6.
5 Jacobsen D. New treatment for ethylene glycol poisoning. *N Engl J Med* 1999; 340: 879.
6 Opeskin K, Silberstein M. False-positive diagnosis of subarachnoid haemorrhage on computed tomography scan. *J Clin Neurosci* 1998; 5: 382-6.
7 Australian and New Zealand Intensive Care Society. ANZICS statement on death and organ donation. Edition 3.1. Melbourne: ANZICS, 2010.
8 Silva JA, Chamorro C, Varela A, et al. Successful bilateral lung transplantation from a methanol-poisoned donor. *Transplant Proc* 2004; 36: 2806-7.
9 López-Navidad A, Caballero F, González-Segura C, et al. Short- and long-term success of organs transplanted from acute methanol poisoned donors. *Clin Transplant* 2002;16:151-62. ❑