The occasional toxic alcohol ingestion

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INTRODUCTION

Toxic alcohol ingestions – most commonly methanol and ethylene glycol – are time-sensitive emergencies with potentially serious consequences, including vision loss, renal failure, severe metabolic acidosis and death.[1] These alcohols are found in everyday products such as windshield fluid, antifreeze and paint thinner. Exposures to toxic alcohols may be intentional or unintentional, and outbreaks affecting multiple individuals have been reported worldwide.[2,3]

Toxic alcohol poisoning presents a clinical challenge for providers in all practice settings, both in diagnosis and management. These challenges may be particularly pronounced in rural healthcare settings due to limited availability of diagnostic testing, treatment modalities, and/or speciality services, as well as the need to transport patients over long distances. Rural generalists and emergency medicine providers must therefore be familiar with the clinical presentations of toxic alcohol poisoning, have a structured approach to ordering and interpreting diagnostic tests and be prepared to initiate treatment, when appropriate, based on reasonable clinical suspicion.

PATHOPHYSIOLOGY

Like other simple alcohols, toxic alcohols are rapidly absorbed and reach peak serum concentration shortly after ingestion.[1] Methanol poisoning through inhalation or dermal absorption can also occur.[1] Although methanol and ethylene glycol themselves are relatively non-toxic in their parent forms, they undergo hepatic metabolism to highly toxic compounds, initially through alcohol dehydrogenase [Figure 1]. Consequently, the onset of clinical toxicity is typically delayed, with symptoms emerging only after the parent compounds have been converted to their toxic metabolites [Table 1]. In the absence of diagnosis and treatment, ingestion of these alcohols can lead to irreversible neurological, cardiopulmonary and renal damage within 72 h.[1]

Formate – the primary toxic metabolite of methanol – inhibits mitochondrial function, eventually leading to cellular hypoxia and an accumulation of lactic acid. Additionally, formate is particularly toxic to retinal and optic nerve tissues and can cause retinal injury leading to blindness.[4] Formate is also toxic to neurons in the basal ganglia, and patients have developed parkinsonism after poisoning.

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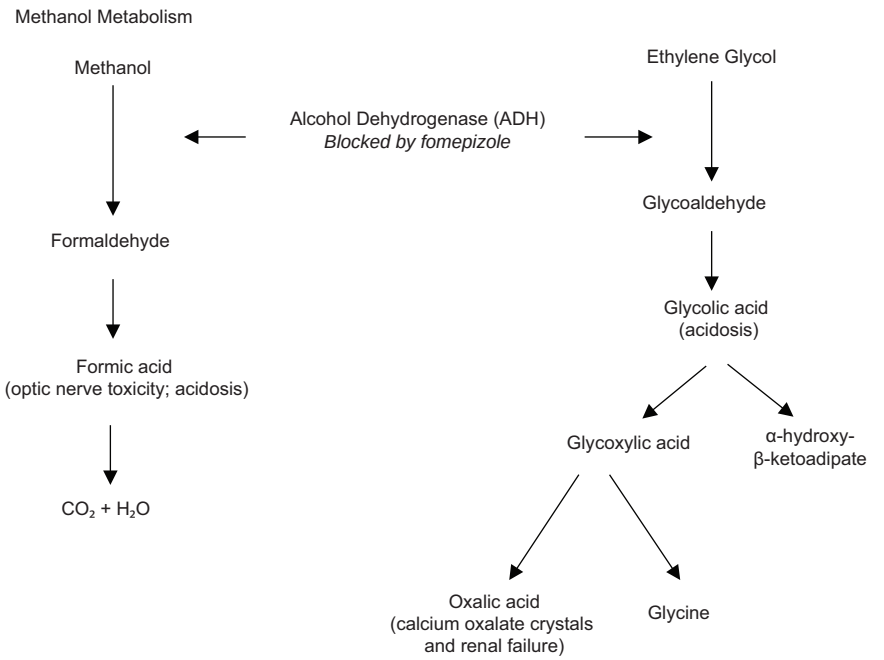

Figure 1: Mechanistic pathway of toxic alcohol metabolism and its inhibition by fomepizole. Fomepizole inhibits alcohol dehydrogenase, preventing conversion of toxic alcohols into their toxic metabolites and limiting the progression to high anion gap metabolic acidosis (based on Kraut and Mullins, 2018).

Table 1: Common toxic alcohols and their effects

Alcohol	Source examples	Toxic metabolite	Clinical features[1]
Methanol	Windshield-washer fluid	Formate	Visual disturbances, leading to blindness
	Camp stove fuel		CNS depression
	Adulterated ethanol		High anion-gap metabolic acidosis
	Paint thinner		
Ethylene glycol	Antifreeze solution	Glycolic acid, oxalic acid	Acute kidney injury
	Engine coolants		Hypocalcaemia
	Deicing fluids		CNS depression
			High anion-gap metabolic acidosis

CNS: Central nervous system

Glycolic acid – the primary toxic metabolite of ethylene glycol – accumulates and causes a high anion gap metabolic acidosis that impairs cellular function and contributes to central nervous system (CNS) depression.[5] Oxalic acid, another metabolite of ethylene glycol, can form calcium oxalate crystals that deposit in multiple tissues including kidneys, heart and lungs and lead to organ dysfunction.[1]

In both methanol and ethylene glycol ingestions, the accumulation of toxic acid metabolites causes a high anion gap metabolic acidosis to develop.[6] The resulting acidaemia allows formate to cross the blood–brain barrier, further worsening CNS toxicity. Importantly, while ingestion of isopropyl alcohol from products such as hand sanitiser or rubbing alcohol can present in a manner similar to methanol or ethylene glycol poisoning, it does not contribute to a high anion gap metabolic acidosis and follows a different, more conservative, course of treatment.[7]

CLINICAL PRESENTATION

History and physical

Collecting a good history, when possible, is the starting point for managing patients with suspected toxic alcohol poisoning. Attempt to gather the following pertinent information from the patient:

- The suspected substance, the route of ingestion, quantity taken and timing

- Whether any coingestants – such as ethanol – were taken, which can delay toxicity onset
- Intent of the exposure – to achieve intoxication versus self-harm.

Patients with toxic alcohol poisoning may present with a wide range of clinical features, depending on the time elapsed between exposure and presentation. Early in the course, when the parent alcohol predominates in circulation, patients may exhibit signs of inebriation, which are often subtle in cases of methanol ingestion. With delayed presentation, clinical manifestations reflect the toxic effects of metabolic by-products. The presence of severe symptoms such as coma, seizures, hyperpnoea (deep rapid breathing) and/or hypotension suggests that a significant portion of the parent alcohol has already been metabolised into its toxic by-products.[8] In such cases, specific physical examination findings may help identify the particular toxic alcohol involved.[8]

- Methanol-specific findings
  - Afferent pupillary defect
  - Mydriasis
  - Retinal oedema
- Ethylene glycol-specific findings
  - Cranial nerve palsies
  - Tetany
  - Oliguria/haematuria.

Once a history and physical examination have been performed, ordering laboratory tests is the next step.

LABORATORY TESTS

Laboratory evaluation is central to the diagnosis of toxic alcohol poisoning. The diagnostic gold standard is measurement of serum methanol or ethylene glycol concentrations; however, these assays are typically available only through specialised toxicology laboratories, often at large referral centres.

In settings where direct measurement of toxic alcohols is unavailable, the following laboratory studies should be obtained at presentation in patients with clinical suspicion of toxic alcohol poisoning:

1. Blood gas (venous or arterial)
2. Serum lactate
3. Basic metabolic panel and additional chemistries, including sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, amylase or lipase, glucose, calcium, magnesium and phosphate
4. Measured serum osmolality
5. Serum ethanol concentration (required for calculation of the osmolar gap).

Depending on the clinical context, additional laboratory testing may be appropriate, including:

- Beta-human chorionic gonadotropin
- Serum acetaminophen and salicylate concentrations
- Alanine aminotransferase, aspartate aminotransferase, international normalised ratio
- Urinalysis.

Urine microscopy demonstrating calcium oxalate crystals lacks sufficient sensitivity and specificity to reliably diagnose ethylene glycol exposure.

Speak to the receiving tertiary care hospital and draw the appropriate extra tube of blood that can be sent with the patient, if they are transferred, to allow for testing the levels of methanol or ethylene glycol initially present.

In the absence of serum osmolality and ethanol levels, clinicians should rely on the anion gap, exposure history and clinical findings to guide diagnosis.

Interpretation of laboratories

When toxic alcohol ingestion is suspected, calculation of the osmolal gap and anion gap can assist in both diagnosis and management. These calculations are available in medical calculator applications, but careful attention must be paid to the units used.

The osmolal gap is used to assess the presence of unmeasured osmoles in the bloodstream, including parent toxic alcohols such as methanol or ethylene glycol. It is calculated using the following formula,[9] in which all concentrations are expressed in mmol/L:

$$Osmolal\ gap = Measured\ osmolality - [2 \times Na + glucose + urea + 1.25\,(ethanol)]$$

A useful mnemonic to remember this calculation is 'measured osmolality minus two salts

and a sticky bun with a drink'. A normal osmolal gap typically ranges from –10 to 10 mOsm/kg H_2O. Although an elevated osmolal gap is neither sensitive nor specific for toxic alcohol ingestion, a normal osmolal gap likewise does not exclude the presence of a toxic alcohol. An osmolal gap >50 mmol/L is most commonly explained by the presence of a toxic alcohol, such as methanol or ethylene glycol. Ingestion of isopropyl alcohol may also produce an elevated osmolal gap, reflecting the presence of the parent compound. However, isopropyl alcohol is metabolised to acetone, a ketone that does not generate an anion-gap metabolic acidosis.[7]

An elevated anion gap is a key diagnostic finding in toxic alcohol poisoning and reflects the accumulation of acidic metabolites, such as formic acid or glycolic acid, produced when parent alcohols are metabolised by alcohol dehydrogenase (ADH). It is calculated as:

$$Anion\ gap\ (mmol/L) = [Na] - ([Cl] + [HCO3])$$

An anion gap >12 mmol/L is considered elevated. In addition to other causes of a high anion gap metabolic acidosis, such as lactic acidosis and ketoacidosis, toxic alcohol exposure must be considered.

Interpretation of the osmolal gap and anion gap in the setting of a toxic alcohol exposure varies based on the time elapsed since the exposure. Shortly after ingestion, the osmolal gap is elevated due to the presence of the unmetabolised parent alcohol. It subsequently declines as metabolism ensues.[1] In contrast, the anion gap is usually normal early in the course, and rises later, as the toxic metabolites begin to accumulate.[9]

In a patient presenting early, after ingestion of methanol or ethylene glycol, the osmolal gap may be high while the anion gap remains normal [Figure 2]. With delayed presentation, the osmolal gap may normalise as the anion gap increases. Although an elevated anion gap is an important diagnostic clue, its absence does not exclude toxic alcohol poisoning. The anion gap may remain normal in early presentations or in cases of concomitant ethanol ingestion, as ethanol competitively inhibits ADH and delays metabolism of the toxic alcohol.

Once substantial metabolism of the parent alcohol has occurred, venous blood gas analysis typically demonstrates a metabolic acidosis,

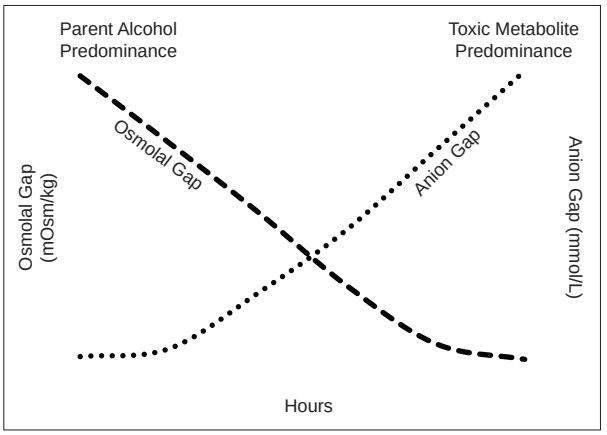

Figure 2: Evolution of the osmolal and anion gaps after toxic alcohol ingestion. The osmolal gap is initially high due to parent alcohol predominance and declines as metabolism occurs, while the anion gap increases as acidic metabolites accumulate (based on Kraut and Mullins, 2018).

characterised by a pH <7.35 and serum bicarbonate <22 mEq/L. The pCO_2 may be decreased (reflecting appropriate respiratory compensation) or normal, depending on the adequacy of ventilatory response.

In resource-limited or rural settings where direct measurement of serum osmolality is unavailable, clinicians should rely on the anion gap, exposure history and clinical findings to guide diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in a patient with simultaneous elevation of both the osmolal gap and the anion gap is relatively limited. Although a high anion gap metabolic acidosis alone has a broad differential, summarised by the GOLDMARK mnemonic (glycols, oxoproline, L-lactate, D-lactate, methanol, acetylsalicylic acid, renal failure and ketoacidosis), the concurrent presence of an elevated osmolal gap substantially narrows the possibilities.

Toxic alcohols, most notably methanol and ethylene glycol, are the principal causes of concurrent elevations in both gaps: the parent alcohol increases the osmolal gap, while its acidic metabolites raise the anion gap. Other conditions may produce overlapping laboratory findings but are typically distinguishable. Diabetic or alcoholic ketoacidosis is characterised by the presence of ketones in blood or urine, with only modest increases in the osmolal gap.[10] Lactic acidosis does not meaningfully elevate the osmolal gap.[11] Renal failure

is generally accompanied by elevated creatinine and clinical uraemia rather than a significant osmolal disturbance.[12] In the absence of these features, toxic alcohol ingestion should be strongly considered.

It is important to reiterate that either gap may be normal depending on the timing of presentation. Serial measurements and characteristic clinical features of toxic alcohol poisoning [Table 1] provide additional diagnostic clues.

TREATMENT

The management of toxic alcohol poisoning relies on early recognition, prompt initiation of antidote therapy, correction of metabolic derangements and initiation of dialysis when appropriate. In settings where confirmatory testing cannot be obtained, therapy should be initiated based on suspicion. The goals of treatment are three-fold: (i) inhibit alcohol dehydrogenase, (ii) correct the acidosis and (iii) enhance elimination of parent alcohols and toxic by-products and provide supportive care to prevent end-organ damage.

Initial management and stabilisation

- Contact the regional poison centre for additional guidance
- Consult nephrology if severe symptoms – marked high anion gap metabolic acidosis, a significantly elevated osmolal gap or, when available, elevated serum toxic alcohol concentrations
- Place the patient on continuous cardiac monitoring with hourly vitals and neurologic checks
- Place 2 large bore intravenous catheters (IVs)
- Correct severe acidaemia (pH <7.00 or HCO_3 <8) with IV sodium bicarbonate boluses and infusions to goal of a minimum of pH >7.2
- Provide supportive care, including monitoring for compensatory hyperventilation and administering IV fluids for hypotension.

Antidotal therapy

- Fomepizole is a competitive antagonist of alcohol dehydrogenase and the first-line antidote
  - Dose: 15 mg/kg IV followed by 10 mg/kg IV every 12 h for at least 4 doses. In patients undergoing dialysis, the dosing interval should be adjusted to account for clearance of fomepizole.[13]
- Fomepizole is generally very well tolerated, though expensive[14]
  - Fomepizole is sometimes avoided due to cost in resource-limited settings (~$1000/vial, with an average of 4 vials needed per patient), but this cost can be offset by potential avoidance of transfer or intensive care unit admission.[15]
- If fomepizole is unavailable, ethanol can be used to reduce the production of toxic metabolites, with dosing titrated to maintain serum ethanol of 22 mmol/L[16] (requires frequent monitoring of ethanol levels). Consultation with a regional poison centre is suggested to discuss dosing and administration, since IV ethanol is unavailable in Canada
- If, in conjunction with the poison experts, isopropyl alcohol toxicity is suspected, rather than methanol or ethylene glycol, do not administer fomepizole as it can prolong isopropanol elimination by inhibiting ADH-mediated metabolism. In this case, treatment is primarily supportive.

Cofactor therapy

- If methanol poisoning is suspected
  - Folic acid 50 mg IV every 4 h to enhance formate metabolism to carbon dioxide and water.
- If ethylene glycol poisoning is suspected
  - Thiamine 100 mg IV every 8 h
  - Pyridoxine 50 mg IV every 6 h to facilitate conversion of glyoxylate into non-toxic metabolites.
- If unsure which toxic alcohol was ingested, folic acid, thiamine and pyridoxine should all be given.

Continued treatment and indications for haemodialysis

- Monitor vital signs and repeat laboratories frequently
  - If fomepizole has been started, repeat laboratories q12 h

- If the patient is on dialysis, repeat q4 h
- If methanol/ethylene glycol levels are not available and fomepizole is not given, repeat laboratory intervals are determined on a case-by-case basis in consultation with a toxicologist
- If the patient requires a bicarbonate infusion, electrolytes and VBG should be monitored q2 h.

- Continue fomepizole and cofactor therapy until the serum concentration of ethylene glycol or methanol falls below 3–5 mmol/L or 6–9 mmol/L, respectively.

In cases of severe poisoning, initiate transportation to a medical centre that can provide haemodialysis.

STOPPING RULES

Once initiated, review indications for stopping therapy with your local poison centre.

CONCLUSION

Toxic alcohol ingestion is a time-critical emergency that can be particularly challenging to diagnose in rural and resource-limited settings where key laboratory investigations may not be immediately available. Toxic alcohol ingestion should be high on a clinician's differential diagnosis when a patient presents with symptoms of intoxication, or altered level of consciousness (LOC), and has an unexplained high anion gap metabolic acidosis. Clinicians should initiate empiric therapy with fomepizole (or ethanol if unavailable) and cofactors, correct the acidaemia and consult with a regional poison centre. Some patients may require urgent transfer to a haemodialysis centre. Early recognition and rapid treatment can prevent catastrophic outcomes, including blindness, renal failure and death.

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