

Methanol and ethylene glycol poisoning: a case study and review of current literature

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ABSTRACT

Poisoning is an uncommon but potentially fatal outcome of toxic alcohol ingestion. The toxic alcohols methanol, ethylene glycol and isopropyl alcohol are commonly found in household and commercial products. Because the toxic effects are caused by the metabolites of methanol and ethylene glycol rather than the agents themselves, there is often a substantial delay between ingestion and onset of clinical toxicity. Anion and osmolar gaps are often used for the diagnosis and exclusion of these sometimes subtle overdoses. The pitfalls of using these tests to rule out alcohol ingestion are reviewed. Ethanol infusion is the traditional therapy for such overdoses. In addition to the pathophysiology and clinical findings in poisoning, recent evidence for the use of fomepizole and adjuvant therapies is reviewed.

RÉSUMÉ

L'empoisonnement est une conséquence rare mais potentiellement fatale de l'ingestion d'alcool toxique. Les alcools toxiques comme le méthanol, l'éthylène-glycol et l'alcool isopropylique sont très répandus dans les produits ménagers et commerciaux. Comme les effets toxiques sont causés par les métabolites du méthanol et de l'éthylène-glycol plutôt que par les agents eux-mêmes, il existe souvent un délai important entre l'ingestion et la toxicité clinique. Les écarts anioniques et osmolaires sont souvent utilisés pour le diagnostic et l'exclusion de ces intoxications parfois subtiles. Nous présentons les pièges associés à ces tests utilisés pour exclure l'ingestion. La perfusion d'éthanol est la thérapie couramment utilisée pour traiter ces intoxications. En plus de la physiopathologie de l'empoisonnement et des constatations cliniques, des données récentes suggérant le recours au fomépizole et à des thérapies d'appoint sont passées en revue.

Key words: methanol, ethylene glycol, toxicology, fomepizole, osmolar gap, alcohols, poisoning

Introduction

The toxic alcohols methanol, ethylene glycol and isopropyl alcohol are widely available in household and commercial products that are intentionally abused as ethanol substitutes. Although isopropyl alcohol is relatively benign, both methanol and ethylene glycol have serious, sometimes fatal, effects. Because of the widespread availability of these agents and their potential toxicity, toxic alcohol ingestion

should be considered when a patient presents with a history or clinical picture consistent with such ingestion, associated with acidosis and serum chemistry with a widened anion or osmolar gap.

Case report

Emergency medical services were called to a location where a 38-year-old man was performing cardiopul-

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monary resuscitation on his wife. The woman was asystolic and unresponsive to all resuscitative efforts. The man became increasingly agitated and incoherent. The paramedics noted that he appeared “drunk” but had normal vital signs and oxygen saturation. After transport to hospital, he complained of worsening abdominal pain. At that time, his blood pressure was 110/70 mm Hg, heart rate 72 beats/min, temperature 36°C, respiratory rate (RR) 24 breaths/min and oxygen saturation 97% on room air. Thirty minutes later, his Glasgow Coma Scale score had fallen to 9 (E₂/M₄/V₃) (E = eye opening, M = motor response, V = verbal response), and his RR had increased to 30 breaths/min, but there were no focal neurologic signs, and physical examination was otherwise unremarkable. Fifteen minutes later he began convulsing, and a rapid sequence intubation was performed with midazolam, fentanyl and succinylcholine. The patient then developed pulseless electrical activity, followed by 2 episodes of hypotensive bradycardia. After resuscitation with epinephrine, he received dopamine and transcutaneous pacing while preparations were made for a transvenous pacemaker.

Laboratory results were as follows: sodium (Na⁺) 153 mmol/L, potassium (K⁺) 5.4 mmol/L, chloride (Cl⁻) 108 mmol/L, bicarbonate ions (HCO₃⁻) 5 mmol/L, blood urea nitrogen 5.9 mmol/L, creatinine 174 mmol/L and glucose 6 mmol/L. Arterial blood gas results were as follows: pH 6.49, HCO₃ 5 mmol/L and partial pressure of carbon dioxide (Pco₂) 62 mm Hg. Serum osmolarity was 487 mOsm. The anion and osmolar gaps were 40 and 169 mEq/L respectively.

The severe anion gap metabolic acidosis and widened osmolar gap suggested toxic alcohol ingestion; therefore an ethanol infusion was started. Despite aggressive fluid resuscitation, 8 ampules of sodium bicarbonate, pressor support and transcutaneous pacing, the patient remained hypotensive, which precluded dialysis. Asystolic arrest occurred, and care was withdrawn. Serum methanol levels were positive, and review of a head CT scan done before arrest revealed bilateral globus pallidus ischemia.

Discussion

Methanol, ethylene glycol and isopropyl alcohol are toxic alcohols that may be ingested accidentally or consumed as ethanol substitutes. Like ethanol, all 3 cause intoxication and are metabolized by alcohol dehydrogenase (ADH), a process that creates toxic metabolites. Methanol and ethylene glycol produce the most severe and life-threatening poisonings.

Methanol

Clinical presentation

Methanol is widely used in industry and is found in many North American households. Because of its low freezing point, methanol is a common component in gas line antifreeze, glass cleaner and windshield wiper fluid. Methanol causes intoxication, often associated with nausea, vomiting and abdominal pain. After a latent period of 24 (range 1 to 72) hours, weakness and respiratory difficulty may occur.¹ The latent period may be longer if ethyl alcohol is a co-ingestant or shorter if the volume of methanol is large. Visual disturbances, described as “walking in a snowstorm,” are common. Ocular examination reveals pupillary dilatation, loss of pupillary reflexes, and hyperemia and edema of the optic disk. Coma, seizures and death from cardiorespiratory arrest may occur. Laboratory evaluation may reveal a widened osmolar gap and severe anion gap metabolic acidosis. A pH of less than 7.0 is not uncommon.²

Pathophysiology

The degree of toxicity correlates with the amount of methanol ingested, but not with presenting methanol levels. Latency between ingestion and toxicity occurs because of the time required to convert methanol to toxic metabolites. The toxic effects become apparent when ADH has metabolized methanol to formaldehyde (Fig. 1). Formalde-

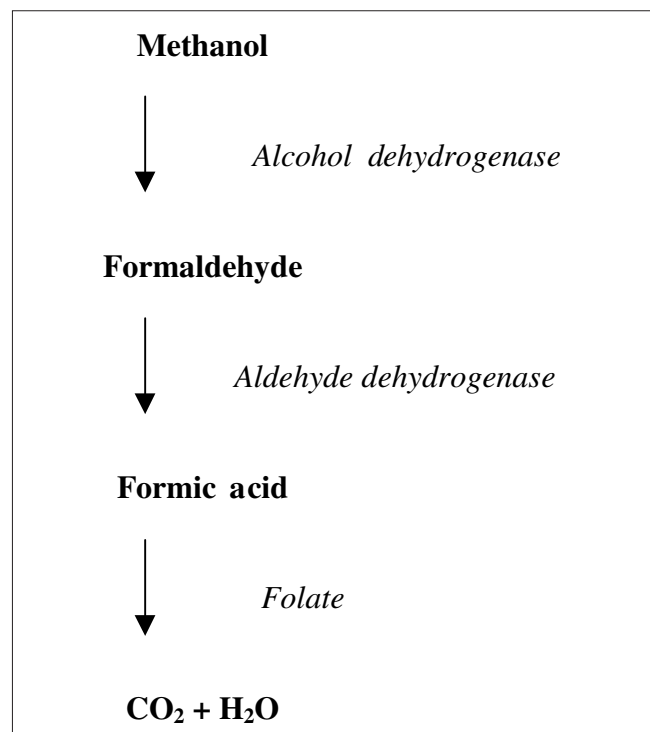


Fig. 1. Methanol metabolism

hyde is highly toxic but is rapidly degraded by aldehyde dehydrogenase and other nonspecific enzymes to formic acid,³ which is responsible for the metabolic acidosis and anion gap. Further metabolism of formic acid to carbon dioxide is dependent on folate.⁴

Visual changes with methanol poisoning are due to microtubule and mitochondrial destruction in the retrolaminar optic nerve.⁵ Survivors may also develop a parkinsonism-like syndrome, which correlates with CT evidence of destruction in the putamen and subcortical white matter hemorrhage.⁶

Ethylene glycol

Clinical presentation

Ethylene glycol is a component of radiator antifreeze, coolants, polishes and cleansers. It is relatively innocuous until metabolized to toxic breakdown products, which explains its 4- to 12-hour latent period.¹ Ethylene glycol toxicity is divided into 3 distinct phases: central nervous system (CNS) depression, cardiorespiratory toxicity and renal toxicity. It is a more potent CNS depressant than methanol and, during the CNS depressant phase (30 minutes to 12 hours

after ingestion), patients exhibit signs of intoxication, stupor, nausea and vomiting, hallucinations and seizures. The cardiorespiratory phase (12 to 24 hours after ingestion) is heralded by the onset of hypotension, tachypnea, congestive heart failure or, occasionally, myositis. The renal stage (24 to 72 hours after ingestion) is marked by flank pain and oxalate crystalluria, followed by the development of oliguric renal failure that may necessitate long-term dialysis.⁴

Pathophysiology

ADH converts ethylene glycol to glycoaldehyde (Fig. 2), which is rapidly converted to glycolic acid.⁷ Glycolic acid is slowly converted to glyoxylic acid, which is then degraded via several pathways. The major pathway is glycolic acid to oxalate, and the next most important involves the creation of glycine via pyridoxine-dependent aminotransferases. Hypocalcemia and severe metabolic acidosis are common laboratory findings, and glycolic acid is the metabolite most responsible for the anion gap metabolic acidosis. Oxalate crystal deposition in tissues is another mechanism of toxicity, and oxalate crystalluria is a hallmark of ethylene glycol poisoning.⁸ Pyridoxine administra-

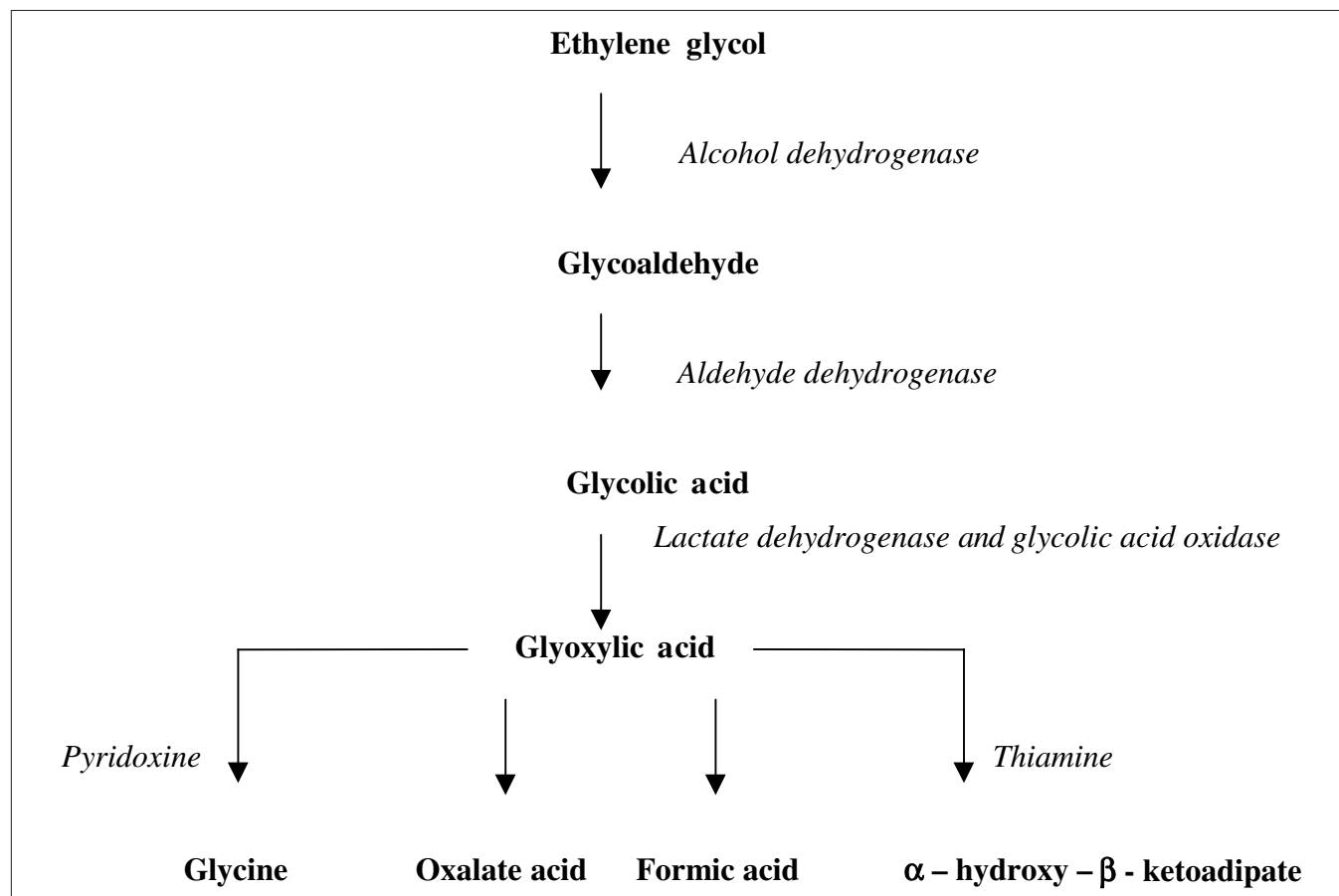


Fig. 2. Ethylene glycol metabolism

tion may shift glycolic acid metabolism away from the production of oxalate and toward the production of glycine, which is less toxic.

Diagnosis of ethylene glycol and methanol poisoning

Rapid recognition and treatment of toxic alcohol poisonings is crucial to reduce the occurrence of morbidity and mortality. The key to diagnosis is a high index of suspicion and a thorough history in patients who appear drunk or who have unexplained acid–base abnormalities. Unfortunately, the early findings, including nausea, vomiting and altered mentation, are nonspecific. Features such as hyperpnea (compensation for metabolic acidosis), visual complaints, pupillary dilation and a latent period between inebriation and more severe symptoms are suggestive of methanol poisoning, whereas calcium oxalate crystalluria, present in 50% of ethylene glycol poisonings, is considered strong enough evidence to begin treatment in appropriate circumstances. Urine that appears fluorescent under a Wood's lamp may be diagnostic, since fluorescein dye is often added to ethylene glycol in radiator antifreeze to help detect radiator leaks. Fluorescein is not added to other compounds containing ethylene glycol, so the absence of fluorescence does not rule out ethylene glycol poisoning.

The anion gap

Because serum is electroneutral, the sum of the positively charged particles (cations) must equal the sum of the negatively charged particles (anions). The routinely measured cations are sodium and potassium and the routinely measured anions are chloride and bicarbonate. The difference between the measured cations and the measured anions is known as the anion gap. It represents unmeasured anions, such as phosphates, sulfates, albumin and organic acids, and unmeasured cations, such as calcium and magnesium. The anion gap actually refers to unmeasured anions – unmeasured cations (Fig. 3).

By convention, potassium is not included in anion gap calculations, so the anion gap is defined as follows: anion gap = sodium – (chloride + bicarbonate). When defined in this way the normal anion gap is 7 ± 4 mEq/L.⁹ An increase in the anion gap is usually due to unmeasured acids and is known as anion gap metabolic acidosis. Unmeasured anions that cause anion gap acidosis may be intrinsic or extrinsic (Table 1). Intrinsic anions include lactate, ketones and the organic acids that accumulate in renal failure. Lactic acidosis is caused by cellular hypoxia from hypoperfusion, toxins that interfere with cellular metabolism or, rarely, inborn errors of metabolism. Ketones accumulate in diabetic, starvation or alcoholic ketoacidosis. An intrinsic

source of anion gap metabolic acidosis can be quickly ruled out by measuring lactate, ketones and renal function. One major exception is that increased lactate levels can also be due to an extrinsic toxin causing cellular hypoxia, as occurs in carbon monoxide poisoning. In the absence of an intrinsic cause, anion gap metabolic acidosis suggests extrinsic poisoning. In this case, a toxin (e.g., acetylsalicylic acid) or a toxic metabolite (e.g., glycolic acid) may be the unmeasured anion (Table 2).

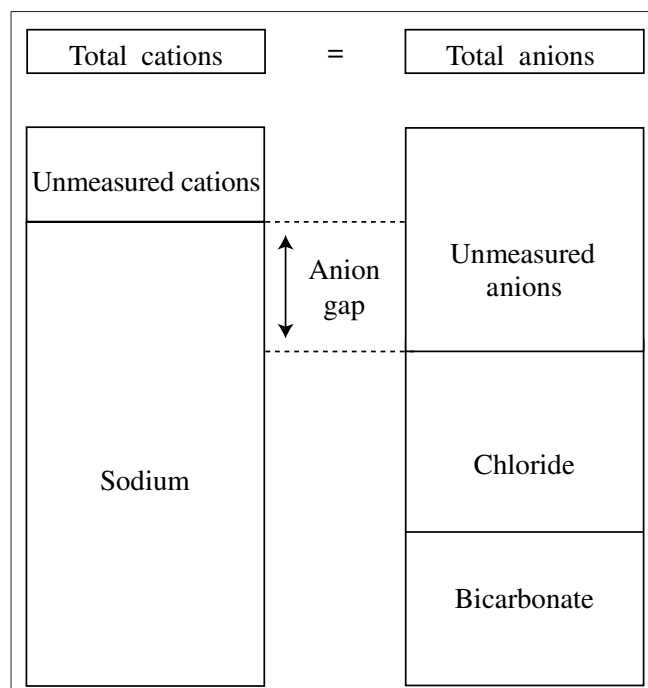


Fig. 3. The anion gap is the difference between the measured cations and the measured anions. It is also equal to unmeasured anions minus unmeasured cations. For the purpose of the calculation, potassium is considered an unmeasured cation.

Table 1. Intravenous and oral ethanol doses¹⁰

Form of ethanol administration*	Loading dose, mL/kg	Infusion rate, mL/kg per hour	
		Patient undergoing dialysis	Patient not undergoing dialysis
10% ethanol IV			
Nondrinker	7.6	2.1	0.8
Chronic drinker	7.6	3.3	2.0
43% ethanol by mouth†			
Nondrinker	1.8	0.5	0.2
Chronic drinker	1.8	0.8	0.5

*Ethanol doses assume a target serum ethanol level of 100 mg/dL and a dialysis time of 6 hours.

†Ethanol is usually diluted to 20% ethanol by volume.

Every widened anion gap should be evaluated. If the cause is transient lactic acidosis, such as occurs after a seizure, it is reasonable to follow the laboratory abnormalities to resolution. If the anion gap is unexplained, then salicylate, methanol and ethylene glycol levels should be measured. In many institutions it is often impossible to perform these assays rapidly enough for the results to be useful in clinical decision-making. Thus, an elevated anion gap not explained by lactate, ketones, renal failure or salicylates may be considered an indication for empiric treatment for toxic alcohol poisoning, pending definitive diagnosis.

Osmolarity and the osmolar gap

Osmolarity is defined as the number of particles in a litre of solution. Serum osmolarity can be approximated by adding the molar concentrations of the most common constituents of serum. The most commonly used formula for calculating osmolarity is as follows: calculated osmolarity = $2 \text{ Na} + \text{urea} + \text{glucose} + \text{ethanol}$ (measured as milliequivalents per litre).

The osmolar gap (OG) is the difference between measured osmolarity and calculated osmolarity: $\text{OG} = \text{O}_m - \text{O}_c$. This difference is normally accounted for by calcium, lipids and proteins, but it may be increased by exogenous compounds such as glycols and smaller alcohols,⁸ including methanol, ethylene glycol, mannitol, glycerol and isopropyl alcohol. Of these, only methanol and ethylene glycol commonly cause severe metabolic acidosis with an elevation of both the anion and osmolar gaps.⁸ Clinicians often believe that an osmolar gap of less than 10 “rules

out” toxic alcohol exposure.^{11,12} Unfortunately, there are problems with this approach, and an osmolar gap within the normal range does not necessarily rule out significant toxic alcohol poisoning.

Caught in the osmolar gap

The normal range for the osmolar gap is wide. One group of investigators found that the mean normal osmolar gap was -2 (standard deviation 6.1) mEq/L.¹³ Assuming that each milliequivalent per litre of ethylene glycol contributes 1 to the osmolar gap, a patient with an osmolar gap of -5 and a toxic ethylene glycol level of 10 mEq/L (64 mg/dL) would have an osmolar gap of 5 mEq/L which would be considered “normal” if 10 mEq/L was considered the upper limit of normal. Furthermore, because the metabolites of ethylene glycol and methanol do not contribute to the osmolar gap, the gap may become normal late in these poisonings, once the primary agent has been metabolized.

Another problem is that different formulae may be used to calculate osmolarity, and their results may differ substantially.¹³ Some laboratories still measure osmolarity by the vapour pressure method, despite its potential inaccuracy.¹⁴ Finally, a widened osmolar gap may occur in lactic acidosis and ketoacidosis.^{15,16} For all these reasons, some authors feel that osmolar gap is of little use in differentiating the causes of anion gap metabolic acidosis.¹⁷ It is most important to re-emphasize that a normal osmolar gap does not rule out a toxic alcohol ingestion.

Other tests

Urine microscopy will reveal calcium oxalate crystals in 50% of ethylene glycol poisoned patients at admission,⁸ and this figure increases with time. Methanol poisoning can be confirmed by determination of serum methanol level, a test that is available in most large hospital laboratories that use gas chromatography. Ethylene glycol determination is less widely available, but elevated urine and serum oxalate levels are helpful adjuncts.

Management of ethylene glycol and methanol poisoning

The management of ethylene glycol and methanol poisonings is similar. Resuscitation, stabilization and decontamination are the initial goals. Gastric lavage, with a standard nasogastric tube rather than the potentially more dangerous Ehrlich tube, may be of benefit within 1 to 2 hours of ingestion. Beyond this, rapid absorption renders the risk of aspiration greater than the possible benefits. Activated charcoal is not helpful unless a poly-drug ingestion is suspected.¹⁸

Dextrose, oxygen, naloxone and thiamine should be

Table 2. Causes of increased anion gap metabolic acidosis

Endogenous causes

Lactate: in shock states, following seizures, as a result of cellular toxins

Ketones: in diabetic ketoacidosis, starvation ketoacidosis or alcoholic ketoacidosis

Organic acids: in renal failure

Exogenous causes*

Salicylates: weak acids responsible for acidosis and anion gap

Nonsteroidal anti-inflammatory agents: weak acids that cause an anion gap

Methanol: anion gap acidosis caused by metabolites (specifically formic acid)

Ethylene glycol: anion gap acidosis caused by metabolites

Toluene: anion gap acidosis caused by metabolites (specifically hippuric acid)

*Many toxins, including cyanide, phenformin, iron and isoniazide, cause anion gap acidosis through accumulation of endogenous anions such as lactate. The most common causes of anion gap metabolic acidosis are ketoacidosis, lactic acidosis and salicylates. If these possibilities have been excluded, toxic alcohol poisoning (with methanol or ethylene glycol) should be considered.

given to obtunded patients. Forced diuresis does not substantially change the rate of excretion and presents the risk of precipitating pulmonary edema — particularly in patients who are developing renal compromise.¹⁹ The 4 major goals in the treatment²⁰ of ethylene glycol and methanol poisonings are as follows:

- 1) inhibition of ADH to prevent toxic metabolite formation,
- 2) correction of the acidosis with bicarbonate,
- 3) use of specific enzymatic cofactors such as folate, thiamine and pyridoxine to modify deleterious metabolic pathways, and
- 4) removal of the toxin and metabolites by hemodialysis.

ADH blockade

The affinity of ethanol for ADH is 100 times that of ethylene glycol and 10 to 20 times that of methanol.¹ As a result, ethanol, given orally or parenterally to achieve concentrations of 20 to 30 mmol/L (100 to 150 mg/dL), will saturate ADH binding sites and prevent it from metabolizing ethylene glycol or methanol.¹⁸ Once the ADH receptors are saturated, serum alcohol levels should be monitored to ensure that therapeutic levels are maintained. Higher doses are necessary in alcoholic patients and those undergoing hemodialysis (Table 1).¹⁰

Indications for ethanol therapy include a history, clinical picture or laboratory evidence suggestive of methanol or ethylene glycol poisoning. It is often prudent to begin therapy before a definitive diagnosis is made.

4-Methylpyrazole (4-MP or fomepizole) is a newly released antidote that reversibly inhibits ADH. 4-MP is rapidly effective, can be administered orally or parenterally, does not cause the inebriation or hypoglycemia seen with ethanol, and has not been associated with serious adverse events.⁸ A prospective evaluation showed that parenteral 4-MP, given as a 15 mg/kg loading dose followed by 10 mg/kg every 12 hours for 48 hours, maintained therapeutic plasma 4-MP levels (≥ 10 $\mu\text{mol/L}$) and was safe and effective for ethylene glycol poisoning.²¹ Although prospective trials have not yet been published,²² a recent case series suggested that fomepizole is a reasonable treatment alternative in methanol poisonings.²³ There is some evidence to suggest that 4-MP may decrease or eliminate the need for dialysis.²⁴

Dialysis

Once ADH is blocked, the half-life of methanol and ethylene glycol become prolonged. Removal is accomplished by means of hemodialysis, which is far more effective than

peritoneal dialysis.²⁵ Indications for hemodialysis in confirmed overdose include metabolic acidosis, renal compromise, visual symptoms (with methanol), or serum concentrations above 4.03 mmol/L for ethylene glycol and above 7.8 mmol/L for methanol.²⁶

Alkalinization

Methanol and ethylene glycol metabolites may generate hundreds of milliequivalents of excess acid per hour.²⁷ Unlike lactic acid, these acid metabolites are not degraded to bicarbonate, and the result is severe metabolic acidosis that is “bicarbonate resistant.” Sodium bicarbonate is indicated if the serum pH falls below 7.2. Bicarbonate may help remove formic acid from the CNS and increase its renal excretion by “ion trapping.” Massive amounts may be necessary, although the risks of hypernatremia and pulmonary edema must be kept in mind.

Co-factors

In cases of ethylene glycol poisoning, thiamine and pyridoxine may decrease oxalic acid formation and shift metabolism to less toxic metabolites. Recommended doses for both thiamine and pyridoxine are 100 mg administered intravenously (IV), daily.²⁸ In methanol intoxication, the degradation of formic acid to carbon dioxide (Fig. 1) is folate dependent. There is evidence that folate (50 mg IV q4h) may enhance the elimination of formic acid, decreasing toxicity.²⁹

Prognostic factors after ingestion of toxins

Liu and colleagues³⁰ found that coma or seizures at presentation and a serum pH less than 7.0 were the factors most closely correlated with death. These authors also found that prolonged acidosis was associated with increased neurologic sequelae and that shorter time to dialysis did not improve survival; however, the latter finding may have been due to a selection bias whereby the sickest patients underwent dialysis most urgently.³⁰

Pregnancy

Limited anecdotal evidence is available to guide the therapy of pregnant patients.³¹ Of note, there is no evidence that standard ethanol therapy adversely affects fetal outcome.

Conclusions

Methanol and ethylene glycol poisonings are common and serious. Ethanol treatment must often begin before the diagnosis is established. While often useful, both the anion

gap and the osmolar gap can be falsely reassuring in attempts to rule out these toxins. Dialysis is the definitive treatment in confirmed poisoning and should be used in conjunction with ethanol therapy. Cofactor strategies (folate, thiamine and pyridoxine) may offer benefit. Recent evidence supports the use of 4-MP in methanol and ethylene glycol poisoning.

Competing interests: None declared.

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