Treatment of the alcohol intoxications: ethylene glycol, methanol and isopropanol

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Intoxications with ethylene glycol, methanol, and isopropanol are among the most common ingestions, in the treatment of which a nephrologist plays an important role. These three substances have the ideal characteristics for intervention by hemodialysis, and the three parent compounds and their metabolites are readily dialyzable. Two of the three substances, ethylene glycol and methanol, are metabolized to more toxic substances, so that an early treatment strategy that removes the parent compound or blocks its metabolism can prevent the development of many of the adverse events that are often seen in these ingestions. Fomepizole, an inhibitor of alcohol dehydrogenase, slows the metabolism of these substances and is now approved by the US Food and Drug Administration for use in ethylene glycol intoxication. The present review addresses recent advances in the diagnosis and treatment of intoxication with ethylene glycol, methanol and isopropanol. Curr Opin Nephrol Hypertens 9:695–701.

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Abbreviations

CNS	central nervous system
FDA	US Food and Drug Administration
NAD	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide, reduced form
TESS	Toxic Exposure Surveillance System

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Introduction

Intoxications with methanol, ethylene glycol, and isopropanol have substantial morbidity and significant mortality. Toxicity from these alcohol moieties is treatable, if instituted early and rapidly, because no other toxins share characteristics of small volume of distribution, lack of protein binding, and the rapid equilibration with the intravascular space, which renders these agents dialyzable. In addition to the use of dialysis, however, recent advances have increased the armamentarium available for effective treatment. The present review addresses these advances and outlines the current strategy for the treatment of ethylene glycol, methanol, and isopropanol intoxication.

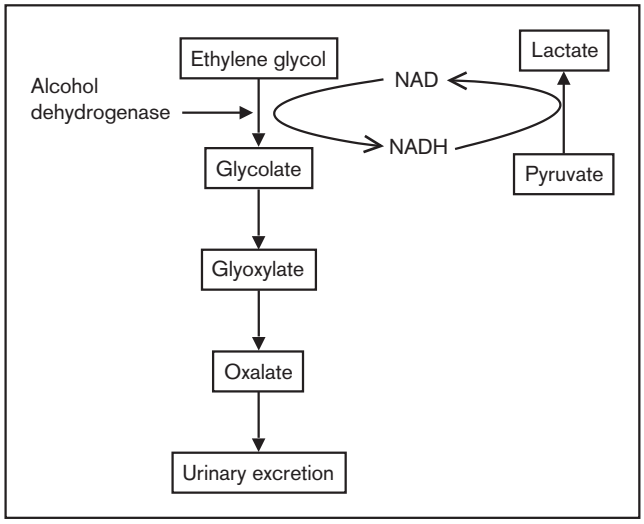
Ethylene glycol

Ethylene glycol is a sweet-tasting substance that is a common constituent of antifreeze. Because of its sweet taste and its ability to intoxicate, it is sometimes used as a substitute for ethanol. It is also often found as an accidental ingestion in children, or as a suicidal agent, accounting for approximately 0.3% of all exposures and 3.0% of all deaths due to poisonings. In 1998 alone, 6281 exposures to ethylene glycol and 27 deaths were reported to the Toxic Exposure Surveillance System (TESS) [1]. The estimated minimum lethal dose for adults is approximately 100 ml, but a number of patients have survived ingestions of over 2000 ml. In a case report by Johnson *et al.* [2•], one patient who underwent rapid treatment with ethanol infusion and hemodialysis in the emergency room survived an ingestion of 3000 ml without sequelea. The ethylene glycol level was found to be 1889 mg/dl. There have been other similar reports [3,4•].

Pharmacokinetics

Ethylene glycol reaches a peak serum level 2–4 h after ingestion. It is water-soluble and has a volume of distribution that is equal to that of total body water (0.6 l/kg). It has a molecular weight of 62 g/mol. Fig. 1 shows the metabolism of ethylene glycol to its end products. Ethylene glycol is oxidized by alcohol dehydrogenase in the presence of nicotinamide adenine dinucleotide (NAD) to glycoaldehyde, which is then rapidly oxidized to glycolate [5••]. Ethanol and fomepizole slow the metabolism of ethylene glycol by inhibiting the enzyme alcohol dehydrogenase. Glycolate is the toxic metabolite and produces the high anion gap acidosis. Some part of the acidosis stems from the production of lactate and is due to the reduction of NAD to nicotinamide adenine dinucleotide, reduced form

Figure 1. Metabolism of ethylene glycol



NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide, reduced form.

(NADH), which drives the conversion of pyruvate to lactate (Fig. 1).

Without treatment the elimination half-life of ethylene glycol is 3–8 h. Ethanol at a concentration of 100 mg/dl will prolong the half-life fivefold to 15–20 h. A recent study by Brent *et al.* [6••] examined the use of femopizole (4-methylpyrazole) as an alcohol dehydrogenase inhibitor in ethylene glycol intoxication. Those investigators administered femopizole to 19 patients with ethylene glycol intoxication and plasma levels greater than 20 mg/dl. They found that a 5 mg/kg loading dose of fomepizole followed by a 10 mg/kg dose every 12 h was sufficient to inhibit the metabolism of ethylene glycol and increase its half-life to 20 h.

Symptomatology

The clinical course of ethylene glycol intoxication can be divided into three phases. The first phase occurs less than 1 h after ingestion and is characterized by mental status depression, similar to that of alcohol intoxication. In severe intoxication, coma, seizures, and respiratory depression can complicate this phase. This stage lasts about 12 h as the ethylene glycol is oxidized to glycoaldehyde and glycolate [7•].

During the second phase, glycolate has a toxic effect on the cardiopulmonary system. In severe intoxications, patients can develop acidosis, heart failure, pulmonary edema or adult respiratory distress syndrome [7•]. The timing of this stage depends on the metabolism of the ethylene glycol to glycolate, and usually starts approximately 12 h after ingestion, but will be delayed by alcohol coingestion. Review of data from TESS suggests that most deaths occur during this stage [1].

The final stage occurs 24–72 h after ingestion and is characterized by flank pain, acute tubular necrosis, hypocalcemia, and renal failure. During this stage, the production of oxalate leads to calcium oxalate precipitation in the kidney and other tissues, and hypocalcemia. The renal toxicity is probably due to a combination of hydronephrosis from calcium oxalate crystals and a direct toxic effect from the metabolites of ethylene glycol. Most renal damage is reversible and renal recovery, which may take a few months, is the norm, even after anuria [8].

There is very little correlation between serum ethylene glycol and clinical outcome. Indeed, patients may present after their serum levels have begun to decrease and the ethylene glycol has been converted to its toxic metabolites. There is better correlation between the arterial pH, serum bicarbonate or glycolate level and the clinical outcome. A number of studies of patients treated with fomepizole have shown that those who present without acidosis or a high glycolate level do well [6••,9].

Laboratory abnormalities

Ethylene glycol intoxication is characterized by a high anion gap acidosis, osmolar gap, and hypocalcemia. The anion gap acidosis is due to both the production of glycolate and the reduction of NAD to NADH during the oxidation of ethylene glycol to glycolate. A patient may have no acidosis soon after ingestion before the ethylene glycol has been converted to glycolate. The gap will grow as the ethylene glycol is metabolized.

Ethylene glycol will also form an osmolar gap because it is osmotically active and has a relatively small molecular weight. The osmolar gap is the difference between the calculated osmolarity and the osmolarity, as measured by freezing point depression [10]. There are a number of different equations that can be used to calculate the serum osmolarity, each one giving a slightly different value. An equation that is easy to use for calculating osmolarity is as follows:

$$2(Na^+) + \text{glucose (mg/dl)}/18 + \text{BUN(mg/dL)}/2.8 + \text{ethanol(mg/dL)}/4.6$$

where BUN is blood urea nitrogen. The osmolar gap is advantageous because it can be found quickly and add evidence for an intoxication. An osmolar gap greater than 10 mOsm/kg is suggestive of intoxication with ethylene glycol, methanol, isopropanol, ethylene oxide, or acetone [11]. In ethylene glycol intoxication, the serum level of the toxin can be estimated by multiplying the osmolar gap by 6.2.

The osmolar gap lacks the sensitivity and specificity to be an ideal screening test for intoxication. Glycolate does not contribute to the osmolar gap so that, as the ethylene glycol is metabolized to glycolate, the osmolar gap will in fact fall. Therefore, patients who present late after an ingestion may have a normal osmolar gap. Another factor that lowers the sensitivity of the osmolar gap is the considerable variation in the normal osmolar gap in the general population. Indeed, patients may have an increased gap that is still below 10 mOsm/kg [12•]. Thus, a high osmolar gap is supportive of ethylene intoxication, but a normal gap does not rule it out. On the other hand, the osmolar gap can also be falsely elevated. Patients who are critically ill may have an elevated gap because of the presence of endogenous substances such as amino acids. Patients with hyperlipidemia or hyperproteinemia will have spurious hyponatremia, leading to an elevated gap. There is also an accumulation of osmotically active substances in chronic renal failure [7•].

The urine may contain two forms of calcium oxalate crystals in ethylene glycol intoxication. The dumbbell-shaped monohydrate forms are more common, but the octahedral-shaped dihydrate form is more specific for ethylene glycol intoxication. Individuals who ingest a large amount of vitamin C or urate-containing foods may have monohydrate calcium oxalate crystals in their urine. The dihydrate form requires higher oxalate concentrations for its formation, and therefore is more indicative of intoxication with ethylene glycol [5••].

Treatment

Supportive treatment includes airway protection, circulatory support, correction of metabolic abnormalities and control of seizures. Bicarbonate is indicated for patients with pH below 7.3. Asymptomatic hypocalcemia is generally not treated because of the risk of increasing the formation of calcium oxalate crystals. Seizures may be due to hypocalcemia, but should be treated first with standard anticonvulsants. There is no role for the use of activated charcoal, cathartics or gastric lavage in the treatment of ethylene glycol intoxication [5••]. Alcoholic persons and patients who are likely to be malnourished should be given thiamine and pyridoxine.

There are two currently used antidotes that inhibit the metabolism of ethylene glycol. The indications for the use of an antidote have been outlined by the American Academy of Clinical Toxicology [5••]. These indications include a plasma ethylene glycol concentration >20 mg/dl, a recent ingestion of ethylene glycol and an osmolar gap >10 mOsm/kg or a high clinical suspicion, and two of the following: pH <7.3, serum bicarbonate <20 mmol/l, osmolar gap >10 mOsm/kg, or urinary oxalate crystals.

Ethanol has been used as an inhibitor of alcohol dehydrogenase in ethylene glycol intoxication for 50 years, but has not been approved by the US Food and Drug Administration (FDA). The standard loading dose is 0.6 g ethanol/kg, followed by a constant infusion to keep the blood alcohol level between 100 and 200 mg/dl. The average maintenance dose is 100 mg/kg per h, but is significantly higher for alcoholic persons and for patients on dialysis. Blood alcohol levels should be checked every 1–2 h until a steady state has been reached, and then every 2–4 h. The potential adverse effects of ethanol include central nervous system (CNS) depression, hypoglycemia, respiratory depression, and aspiration.

Fomepizole was recently approved by the FDA as an antidote in ethylene glycol intoxication. It has a number of potential advantages to the use of ethanol. It is easier to dose with more predictable kinetics, and therefore does not require blood monitoring. Furthermore, it has fewer side effects and does not cause CNS depression. Finally, some patients treated with fomepizole may not need observation in an intensive care unit if they are otherwise stable [9].

Fomepizole should be given at a loading dose of 15 mg/kg followed by 10 mg/kg every 12 h for 48 h. After 48 h, the dose should be increased to 15 mg/kg every 12 h. Fomepizole should be continued until the serum ethylene glycol level is <20 mg/dl and the patient is asymptomatic with a normal pH. Fomepizole is dialyzed and therefore needs to be dosed every 4 h during dialysis [13].

Hemodialysis

Hemodialysis is very effective at clearing ethylene glycol and its metabolites. The clearance rate of ethylene glycol ranges between 200–250 cm^3/min, depending on the filter and blood flow. Glycolate, which is the major toxic metabolite, has a half-life of up to 18 h without hemodialysis, but the half-life is reduced by a factor of six with hemodialysis [14]. Patients with acidosis may therefore still benefit from hemodialysis even in the face of a low serum ethylene glycol level.

The indications for hemodialysis include those patients who have, or who are likely to develop the major sequelae of ethylene glycol ingestion. These include patients with metabolic acidosis (pH <7.3) or deteriorating clinical status with respiratory failure or hypotension. Patients with acute renal failure and a metabolic derangement that is unresponsive to standard therapy should be considered for hemodialysis also. In the past, an ethylene glycol level of 50 mg/dl was considered an indication for hemodialysis. Recent experience suggests that patients with normal renal function and no acidosis

may be treated with fomepizole without hemodialysis, even in the setting of an ethylene glycol level greater than 50 mg/dl [9,15•]. These patients require close monitoring for the development of renal insufficiency or acidosis.

Dialysis should be continued until the ethylene glycol level is less than 20 mg/dl, the acidosis has resolved and there are no signs of systemic toxicity, or until the ethylene glycol level is undetectable. Prolonged dialysis may be required for very high ethylene glycol levels and severe acidosis. Both fomepizole and ethanol are cleared during dialysis. The addition of ethanol to the dialysate has been shown to maintain blood alcohol levels during dialysis [4•]. The use of fomepizole during hemodialysis is more straightforward and only requires an increase in the frequency of the doses to every 4 h to maintain adequate levels [6••].

Methanol

Methanol is a highly toxic alcohol that is found in a variety of commercial products, including antifreeze, windshield wiper fluid, paint thinner, and rubbing alcohol. There were 2862 exposures to methanol and 19 deaths reported to TESS in 1998 [1]. This represents 0.1% of all exposures and 2.0% of all deaths due to poisoning. The estimated minimum lethal dose for adults is approximately 10 ml, but there are reports of patients surviving ingestions greater than 400 ml without sequelea [16••].

Pharmacokinetics

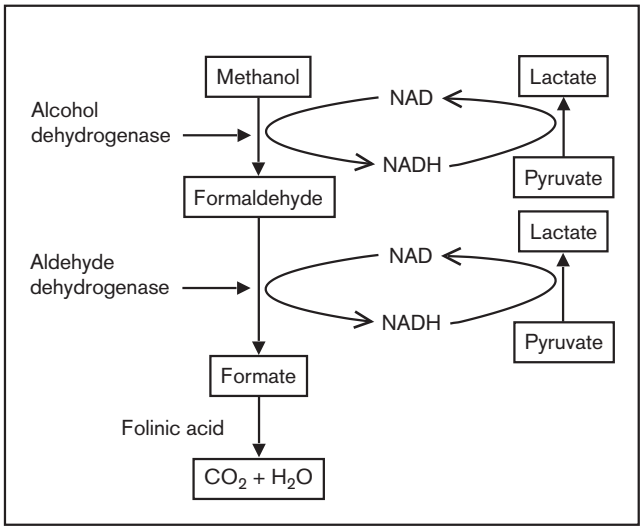
Methanol is rapidly absorbed after ingestion. It has a volume of distribution of 0.6 l/kg and a molecular weight of 32 g/mol. The metabolism of methanol to its end products is displayed in Fig. 2. Methanol is oxidized by alcohol dehydrogenase in the presence of NAD to formaldehyde. Formaldehyde is then quickly oxidized to formate. Formate produces much of the toxic effect as well as the high anion gap acidosis. As with ethylene glycol, some of the acidosis is due to the formation of lactate. Pyruvate is metabolized to lactate because of the reduction of NAD to NADH during the oxidation of methanol [17•]. As with ethylene glycol metabolism, ethanol and fomepizole will once again slow the oxygenation of methanol by inhibiting alcohol dehydrogenase.

The elimination half-life of methanol is 14–18 h without treatment. Ethanol at a concentration of 100 mg/dl will prolong the half-life to 40–50 h. Recent use of fomepizole in methanol intoxication shows that it also prolongs the half-life by fourfold to sixfold [18].

Symptomatology

Most of the clinical effects of methanol intoxication are due to the accumulation of formate. The major clinical effect of methanol before it is metabolized is CNS depression. This is of short duration and is followed by a latent period. The latent period is caused by the time it takes for formate to accumulate, and lasts 14–18 h or longer with ethanol or fomepizole treatment [19].

Figure 2. Metabolism of methanol



NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide, reduced form.

The latent period is followed by a number of systemic findings as formate accumulates. Metabolic acidosis can be severe, and a pH below 7.0 has been found to be the strongest predictor of mortality. Patients with a pH below 7.0 have 20 times the mortality as compared with patients with pH greater than 7.0 [16••]. CNS effects in this stage can include headache, lethargy, convulsions, delirium, and coma. Patients who present with seizure or coma have over 10 times the mortality as patients without these signs [20].

Ocular findings can be prominent and may include photophobia, central scotoma, visual field defects, fixed pupils, and difficulty with light adaptation. Pupillary dysfunction has also been shown to be a strong predictor of mortality. Funduscopic signs include hyperemia, disk edema, and possible optic atrophy [21]. The ocular findings are due to the direct cytotoxic effect of formate on the retina. Other systemic findings may include nausea, vomiting, diaphoresis, and abdominal pain. The abdominal pain is often due to pancreatitis [22].

Laboratory abnormalities

As stated above, the accumulation of formate produces a high anion gap metabolic acidosis. Some of the anion gap is from the increased lactate production. A patient that presents early after an ingestion or later after a

coingestion with both methanol and ethanol may have little or no acidosis, making the diagnosis of methanol intoxication much more difficult. These same patients receive most benefit from alcohol dehydrogenase inhibition, because the ingested methanol still needs to be metabolized to formate to have its toxic effect [17•].

Methanol also produces an osmolar gap. A serum level of 32 mg/dl increases the measured serum osmolarity by 10 mOsm/kg. A high serum methanol level should therefore cause a gap between the calculated serum osmolarity and the measured osmolarity by freezing point depression [10]. However, patients with methanol intoxication may have a normal gap (<10 mOsm/kg) if they present late after ingestion and the methanol has been converted to formate. Formate does not contribute to the serum osmolarity because it is balanced by sodium, which is included in the calculated osmolarity. For this reason, the osmolarity gap should be used to help support the diagnosis of methanol intoxication, but lack of a gap is not sufficiently sensitive to rule out intoxication [17•].

Treatment

Supportive treatment for methanol intoxication is similar to that for ethylene glycol, and includes airway protection, circulatory support, correction of metabolic abnormalities, and control of seizures. Bicarbonate is indicated for patients with pH below 7.3. The use of folate has not been rigorously studied in humans, but has been shown to increase the metabolism of formate to carbon dioxide and water. It can be given as a 50 mg intravenous dose every 4 h for five doses, then once a day [18]. Symptomatic patients should be given one dose of 1 mg/kg folinic acid intravenously.

The main objective of treatment of methanol intoxication is to limit the accumulation of formate. This is done with the same inhibitors of alcohol dehydrogenase as are used in ethylene glycol intoxication. Both ethanol and fomepizole have been shown to be effective in the treatment of methanol intoxication [15•,23]. The regimen for each treatment is similar to that for ethylene glycol intoxication. They should be used in any patient with a methanol serum level >20 mg/dl, an anion gap acidosis and a recent history of methanol ingestion, or in any symptomatic patient with a recent history of a methanol ingestion. The treatment should be continued until the level is undetectable, or both symptoms and acidosis resolve and the level is below 20 mg/dl.

Hemodialysis

Hemodialysis will remove both methanol and formic acid efficiently and will help to correct the acidosis. It should be considered in any patient with a methanol level greater than 50 mg/dl, a history of consuming more than 30 ml methanol, severe acidosis or high formate levels, seizures or visual, funduscopic or mental status changes [24]. Clearance constants with high-efficiency membranes have been as high as 200 cm^3/min for both formate and methanol [25]. Hemodialysis can hinder the maintenance of adequate ethanol levels, and a number of authors have described the use of ethanol-enriched dialysate solutions [26•]. Hemodialysis should be continued until the serum methanol level is undetectable, or until the patient is asymptomatic with a normal serum pH and the serum methanol level is below 20 mg/dL.

Isopropanol

Isopropanol is a colorless liquid with a bitter taste. It is used in the manufacture of acetone and glycerin. It is often used as the solvent in rubbing alcohol. Most rubbing alcohol contains 70% isopropanol.

There were 11 216 exposures to isopropanol and three deaths reported to TESS in 1998 [1]. This represents 0.6% of all exposures and 0.3% of all deaths due to poisoning. It has a much small percentage of deaths per exposure as compared with either ethylene glycol or methanol. The estimated minimum lethal dose for adults is approximately 100 ml, but patients have survived ingestions of over 1000 ml.

Pharmacokinetics

Isopropanol reaches a peak serum level 15–30 min after ingestion. It is water-soluble and has a volume of distribution that is equal to that of total body water (0.6 l/kg). It has a molecular weight of 60 g/mol. Isopropanol is oxidized by alcohol dehydrogenase to acetone. The elimination half-life of isopropanol is 3–7 h, but is prolonged with ethanol coingestion [27]. The elimination of acetone is much slower and is due to excretion in the breath and urine [28].

Symptomatology

Unlike ethylene glycol and methanol, most of the clinical effects in isopropanol intoxication are due to the parent compound. Acetone causes only mild CNS depression [10]. The clinical signs of isopropanol intoxication will occur within 1 h of ingestion, and include effects on the central nervous, gastrointestinal, and cardiovascular systems. The CNS effects include ataxia, confusion, stupor and coma. The gastrointestinal effects include nausea, vomiting, abdominal pain, and gastritis. Patients with severe intoxication can present with hypotension due to cardiac depression and vasodilatation [29]. Hypotension is the strongest predictor of mortality [30]. Many patients will have 'fruity' breath from the acetone elimination via respiration.

Laboratory abnormalities

A serum level of isopropanol equal to 60 mg/dl will increase the serum osmolarity by 10 mOsm/l. A high serum level should therefore produce a gap between the calculated serum osmolarity and that measured by freezing point depression [31]. Acidosis is rare after isopropanol ingestion, because neither the parent compound nor its metabolites are organic acids. Therefore, a finding of a high serum or urine acetone level without acidosis is suggestive of recent isopropanol ingestion [27]. Renal failure can occur in the setting of significant hypotension. Hypoglycemia can result from the interference of gluconeogenesis by isopropanol [10].

Treatment

Supportive treatment includes circulatory support with fluids or vasoconstrictors in patients with hypotension. Inhibition of alcohol dehydrogenase is not indicated because acetone is less toxic than isopropanol. Hemodialysis is indicated for patients with an isopropanol level greater than 400 mg/dl and significant CNS depression, renal failure or hypotension [30]. Hemodialysis will remove both isopropanol and acetone effectively [32]. High-efficiency membranes can produce clearance constants greater than 200 cm^3/min for both acetone and isopropanol.

Conclusion

Early treatment by a nephrologist for intoxications with ethylene glycol, methanol, and isopropanol can have a profound impact on outcome in these poisonings. These compounds are readily dialyzable and antidotes exist to prevent the metabolism to more toxic compounds. Recently, the FDA has approved fomepizole in ethylene glycol intoxication, and it appears to be just as effective in the treatment of methanol ingestion. For all three of these toxins, the newer hemodialysis filters can remove the parent compound and its metabolites very efficiently. These toxins are unique in their characteristics, which allow for rapid and effective treatment that can significantly reduce the adverse effects after ingestion.

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