TOXIC ALCOHOLS
Mark B. Mycyk

Alcohol poisoning can result in metabolic acidosis, renal failure, blindness, central nervous system (CNS) injury, pulmonary edema, or death. Ethylene glycol is present in antifreeze solutions, deicing solutions, foam stabilizers, and chemical solvents. Methanol is a component of windshield-washing solutions, gas-line antifreeze solutions, solvents, and brake cleaners. Isopropyl alcohol is found in rubbing alcohol, aerosols, and other cosmetic products. Propylene glycol is commonly found as a diluent in parenteral medications such as phenytoin, diazepam, and lorazepam. The other toxic glycols can be found in various household and industrial cleaners, paints, resins, and solvents.

More than 35,000 toxic alcohol exposures are reported yearly to the American Association of Poison Control Centers. Most cases are individual poisonings. However, contamination of beverages or pharmaceutical products has resulted in epidemic poisonings, including two significant outbreaks, in India and in Haiti in the 1990s, from diethylene glycol that affected hundreds of victims.

Definitive laboratory confirmation of toxic alcohol poisoning is usually not immediately available to the emergency physician. However, early recognition of poisoning and emergency department (ED)–initiated interventions significantly improve patient outcomes and reduce the occurrence of alcohol-specific complications.

PATHOPHYSIOLOGY

Most toxic alcohol poisonings occur by oral ingestion. Significant methanol poisoning has also been reported to occur by inhalation of brake cleaning products, and isopropanol poisoning has occurred through transcutaneous absorption in children treated for fevers at home with rubbing alcohol baths. Complete absorption is rapid by any route, each alcohol has a small volume of distribution (0.5 to 0.8 L/kg), and metabolism to toxic organic by-products occurs through hepatic alcohol dehydrogenase (ADH) (Figs. 151.1 and 151.2).

Toxicity from the parent products is limited to local mucous membrane irritation and CNS depression. The term toxic is specifically related to the production of different toxic by-products (oxalic acid and formic acid) by each of these alcohols. Ethylene glycol metabolism results in renal failure from deposition of oxalic acid in renal tubules. Methanol...
Toxic Alcohols

obtunded on presentation or may become obtunded during ED evaluation. The level of inebriation does not correlate with peak serum concentrations of the parent product or the accumulation of metabolic by-products. Other clinical findings range from mild to life-threatening, depending on the type of alcohol and the dose consumed. Because the clinical toxicity from these alcohols results from the accumulation of specific toxic metabolites, some patients may appear relatively asymptomatic before the manifestation.

Because the rate of metabolism through ADH varies by alcohol type and by individual variability in cytochrome P-450 genetic expression, clinical onset of worrisome symptoms can be delayed by 1 to 36 hours. Furthermore, the concomitant presence of ethanol may delay metabolism to the toxic by-products because ethanol has a higher affinity for ADH than the toxic alcohols and competitively inhibits metabolism of these alcohols to toxic by-products until the serum ethanol concentration drops to less than 100 mg/dL.

Isopropanol is unlike ethylene glycol and methanol in that it is not metabolized to an organic acid. Instead, it is metabolized to acetone, an osmotically active CNS depressant, which leads to profound inebriation (Fig. 151.3).

**PRESENTING SIGNS AND SYMPTOMS**

**CLASSIC OR TYPICAL**

Most patients poisoned with a toxic alcohol demonstrate some level of CNS depression consistent with inebriation (Table 151.1). Patients who arrive in the ED either shortly after a large ingestion or later after an ingestion, such that systemic accumulation of toxic metabolites has occurred, may be obtunded on presentation or may become obtunded during ED evaluation. The level of inebriation does not correlate with peak serum concentrations of the parent product or the accumulation of metabolic by-products.

Other clinical findings range from mild to life-threatening, depending on the type of alcohol and the dose consumed. Because the clinical toxicity from these alcohols results from the accumulation of specific toxic metabolites, some patients may appear relatively asymptomatic before the manifestation.

**Table 151.1 Symptoms and Signs of Toxic Alcohol Poisoning**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered mental status</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Headache</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Nausea</td>
<td>Dysrhythmias</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Hypoventilation</td>
</tr>
<tr>
<td>Weakness</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Unsteady gait</td>
<td>Nystagmus</td>
</tr>
<tr>
<td>Visual blurring</td>
<td>Sluggish pupils</td>
</tr>
<tr>
<td>Skin flushing</td>
<td>Hyperemic optic disk</td>
</tr>
<tr>
<td>Seizures</td>
<td>Coma</td>
</tr>
</tbody>
</table>

Fig. 151.1 Ethylene glycol metabolism pathway.

Fig. 151.2 Methanol metabolism pathway.

Fig. 151.3 Isopropanol metabolism pathway.
of significant symptoms. Hypotension with reflex tachycardia is common in significant ingestions because of the vasodilatory effects common to all alcohols. In patients with ethylene glycol or methanol poisoning, routine laboratory analysis classically shows anion gap metabolic acidosis and an enlarged osmol gap. Patients with isopropanol poisoning typically have only an enlarged osmol gap, because isopropanol is not metabolized to any organic acids. Patients poisoned with the other toxic alcohols, such as diethylene glycol or butyl ethers from household cleaning products, have acidosis of varying degrees and inconsistently demonstrate an enlarged osmol gap.

**TYPICAL VARIATIONS**

Ethylene glycol poisoning that progresses to significant organic acid accumulation can cause Kussmaul respirations from severe acidosis, cerebral edema, and seizures. Multiple reports have described various self-limited cranial nerve palsies associated with ethylene glycol. Tubular necrosis from local oxalate deposition and renal failure are common. Because oxalic acid precipitates calcium, dysrhythmias and tetanic spasms secondary to hypocalcemia have been reported.

Metabolism of methanol to formic acid gives rise primarily to neurologic and ophthalmologic findings. Patients who are not obtunded may have severe headache, vomiting, dizziness, and amnesia. Cerebral edema, necrosis, and infarcts have been identified on intracranial imaging. Visual disturbances range from simple blurring to “snowstorm” vision to blindness. Worrisome eye findings include sluggish nonreactive pupils, papilledema, a hyperemic optic disk, and retinal edema.

Isopropanol ingestion is associated with a fruity breath odor from acetone accumulation and CNS depression that is reportedly two to four times more profound than would be expected from an equivalent dose of ethanol. Vomiting and hemorrhagic gastritis have also been reported in patients with isopropanol ingestion.

Propylene glycol is metabolized to lactic acid. This poisoning typically occurs iatrogenically from the diluent present in parenteral medications such as phytonin and various benzodiazepines. Accumulated lactate in these cases has been associated with profound hypotension and cardiac dysrhythmias.

Diethylene glycol and the other butyl ethers have been associated with renal tubular necrosis, hepatitis, and pancreatitis.

**DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING**

The differential diagnosis mnemonic “A CAT MUD PILES” should be used for any patient in whom ED evaluation demonstrates an anion gap acidosis (Box 151.1). Many of the possible conditions in the list can be easily excluded with a basic metabolic profile (e.g., uremia) and rapidly obtainable serum quantitative tests (e.g., salicylate). Although alcoholic ketoacidosis looks like toxic alcohol poisoning, it improves rapidly with only intravenous fluids and dextrose supplementation, whereas acidosis from a significant toxic alcohol exposure does not improve without antidotal treatment or enhanced elimination with hemodialysis, or both. In children, disorders of organic acid metabolism should be considered when poisoning is unlikely or has been excluded.

**BOX 151.1 Metabolic Acidosis with Elevated Anion Gap: “A CAT MUD PILES”**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Cyanide, carbon monoxide</th>
<th>Alcohol</th>
<th>Toluene</th>
<th>Methanol, metformin</th>
<th>Uremia</th>
<th>Diabetic ketoacidosis</th>
<th>Paraldehyde</th>
<th>Iron, isoniazid</th>
<th>Lactic acidosis</th>
<th>Ethylene glycol</th>
<th>Salicylates, strychnine</th>
</tr>
</thead>
</table>

Laboratory testing in all patients with potential poisoning should include a basic metabolic profile to determine baseline renal function and acid-base status and to calculate the anion gap and osmol gap. In calculation of the osmol gap, the measured osmolality must be obtained at the same time as the basic metabolic panel (see “Facts and Formulas” box). The osmol gap value should be interpreted with caution because it is an imperfect screening test. The traditionally accepted normal value for an osmol gap is less than 10 mOsm/L. Unfortunately, an individual’s normal gap may range between −14 and +10 mOsm/L, so the osmol gap by itself is imperfect and not diagnostic.

**FACTS AND FORMULAS**

### Anion Gap

- **Anion gap** = $\text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-)$ [normal anion gap = 8-12 mEq/L]
- **Osmol gap** = measured osmols − calculated osmols
- **Calculated osmols** = $(2\text{Na}^+ + \text{BUN}/2.8 + \text{glucose}/18 + \text{ethanol}/4.6)$ [normal osmol gap < 10 mEq/L]

* $\text{BUN}$, Blood urea nitrogen; $\text{HCO}_3^-$, bicarbonate.

Additional serum tests include the following: (1) an ethanol measurement, to enable accurate calculation of the osmol gap and determine the need for additional ADH inhibition; and (2) measurement of the calcium level, which can be depressed in cases of ethylene glycol poisoning and may lead to prolonged QT, cardiac dysrhythmias, and tetany. Arterial blood gas measurements should also be obtained to determine the level of acidosis.

Urinalysis should be performed to look for crystals: monohydrate (spindle-like) or dihydrate (envelope-shaped) crystals are present in 50% to 60% of cases of ethylene glycol poisoning and suggest significant poisoning. However, the absence of these crystals does not reliably exclude poisoning. Some authorities have suggested examining the urine under a Wood

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Fig. 151.4  Mountain schematic. Patients who present early may have elevated osmols without an anion gap (A). Patients who present late may have an elevated anion gap without an elevation of osmol gap (B).

Although ED clinical decisions depend mostly on clinical suspicion and interpretation of imperfect laboratory data such as the anion gap, osmol gap, and urinalysis, cases of suspected toxic alcohol poisoning require that measurements of serum concentrations of ethylene glycol, methanol, and isopropanol be ordered as soon as possible. These measurements are the only definitive means of confirming the diagnosis and guiding duration of both antidotal therapy and hemodialysis. Unfortunately, most hospital laboratories are not equipped to run these tests and must send the specimens to an off-site reference laboratory.1\(^{1}\) Except when the patient arrives with the appropriately labeled product that was ingested in hand, a practical initial strategy is to order serum concentration measurements of all three of these alcohols because patients often do not know exactly what they ingested. Confirming the units of measure when these results are available is also important because different laboratories use different units, and management decisions may be significantly affected if test results are interpreted incorrectly. Serum concentration measurements for toxic alcohols other than ethylene glycol, methanol, and isopropanol are not routinely available; even if obtainable, test results do not guide management decisions.1\(^{1}\)

In cases of ethylene glycol poisoning, a baseline electrocardiogram should also be obtained because of the potential for dysrhythmias resulting from hypocalcemia.

**TREATMENT**

Treatment decision making for the patient with toxic alcohol ingestion is easiest when the patient arrives with the ingested product in hand. Because this is an uncommon occurrence, definitive laboratory diagnosis is usually delayed by the need to send serum samples to off-site reference laboratories.6,11 ED treatment in these cases should not be delayed and must be based on a presumptive clinical diagnosis. Attention to the airway in cases of CNS depression should be the first priority. Intravenous fluids should be administered to treat hypotension and maintain renal perfusion in all cases of toxic alcohol poisoning.

Because alcohols are so rapidly absorbed, gastric emptying procedures are not necessary in patients with toxic alcohol poisoning. In cases of suspected ethylene glycol or methanol poisoning, immediate ADH inhibition should be considered to block continued metabolism of the ethylene glycol to toxic acids.6 ADH inhibition is most effective when it is administered as early as possible after exposure and before significant acidosis develops.11 This treatment should be considered in cases of a witnessed ingestion, when this agent is highly suspected from the history, in the presence of an elevated osmol gap alone with appropriate clinical suspicion, in the patient with both an elevated osmol gap and anion gap acidosis, or when the serum concentration of a toxic alcohol exceeds 20 mg/dL.

ADH inhibition can be achieved with either ethanol or fomepizole.2,3,14 Until 1999, ethanol was the only clinically available antidote. Its affinity for ADH is higher than that of ethylene glycol and methanol, it is inexpensive, and it is readily available. An ethanol level of 100 mg/dL has been the accepted goal for ensuring complete ADH inhibition; after intravenous loading, ethanol levels must be checked regularly until the measured ethylene glycol or methanol concentration
is lower than 20 mg/dL. An ethanol load may be administered orally or with an intravenous infusion (see “Facts and Formulas” box). Treatment difficulties associated with ethanol therapy include (1) iatrogenic inebriation of the patient and inability to monitor mental status, (2) potential occurrence of hypoglycemia in pediatric patients, and (3) difficulty maintaining a therapeutic level because of individual variability in ethanol metabolism and clearance.14

In cases of ethylene glycol poisoning, supplemental thiamine and pyridoxine should be administered to decrease the accumulation of oxalic acid (see “Facts and Formulas” box). In cases of methanol poisoning, supplemental folate should be given to enhance the elimination of formate by converting it to carbon dioxide and water. Although this approach is theoretically beneficial and has been found to be useful in some animal models, no human data demonstrate a clear benefit of cofactor administration.

Hemodialysis should be initiated in any patient with a significant ethylene glycol or methanol concentration and significant acidosis because it helps remove both the parent product and the resultant toxic acids.17-19 When a serum concentration is not immediately available, hemodialysis should be initiated in patients with clinical indicators of significant toxicity, such as pH less than 7.30 despite aggressive intravenous fluid resuscitation, creatinine concentration indicative of renal failure, or other electrolyte abnormalities unresponsive to conventional therapy.2,3,17 Hemodialysis should also be initiated soon after presentation in patients in whom ADH inhibition cannot be used because of antidote unavailability or a contraindication. Hemodialysis should also be considered to shorten the duration of antiodote requirements and of hospitalization when acidosis has not occurred but the serum concentration of the toxic alcohol is extremely high.17,18 For example, the half-life of methanol has been reported to be as long as 54 hours in patients receiving ADH inhibition, and these patients may require several days of hospitalization and antidotal therapy if hemodialysis is not performed as well (Fig. 151.5).

Management of the other toxic alcohol poisonings requires aggressive supportive therapy, attention to the medical complications of acidosis, and hemodialysis only in the presence of significant renal insufficiency or other electrolyte abnormalities.13 Despite the similarity of its name to ethylene glycol, diethylene glycol does not produce oxalic acid, and any benefit from ADH inhibition in cases of diethylene glycol poisoning is uncertain.20

The use of fomepizole, which was approved by the U.S. Food and Drug Administration in 1999, is an easier form of ADH inhibition than the use of ethanol.14-16 Dosing is weight based, and unlike ethanol, fomepizole does not require a constant infusion (see “Facts and Formulas” box). Fomepizole is given every 12 hours in patients not receiving hemodialysis or every 4 hours in patients undergoing hemodialysis, it does not cause inebriation, and it does not require monitoring of serum levels to ascertain therapeutic efficacy.14 Fomepizole should not be given when ethanol concentrations are significantly elevated because ethanol works as an ADH inhibitor, and fomepizole’s higher affinity for ADH will prolong the half-life and the clinical inebriation by the ethanol. Fomepizole is not available in all hospitals because of its high cost.6

In cases of poisoning with any of the toxic alcohols, the addition of a sodium bicarbonate infusion should be initiated when acidosis is severe. Alkalization of serum is helpful in keeping acids in their ionic form. In patients with methanol poisoning, alkalization of serum enhances the renal clearance of formate and may prevent formic acid from entering the CNS and affecting the optic nerves.

### FACTS AND FORMULAS

#### Antidotes for Toxic Alcohols

**Fomepizole**
- Loading dose: 15 mg/kg IV (≤1 g)
- Maintenance therapy: 10 mg/kg IV every 12 hr for four doses, then 15 mg/kg every 12 hr (during hemodialysis, increase frequency to every 4 hr)

**Ethanol**
- Goal: Maintain ethanol level of 100-150 mg/dL until ethylene glycol or methanol level is ≤20 mg/dL, pH normalizes, and patient is asymptomatic.
- 5% solution: 15 mL/kg IV load, then 2-4 mL/kg/hr
- 10% solution: 7.5 mL/kg IV load, then 1-2 mL/kg/hr
- 50% solution: 2 mL/kg oral load, then 0.2-0.4 mL/kg/hr

#### Cofactor Supplementation

- Folate: 50 mg IV every 6 hr until acidosis resolves (methanol only)
- Thiamine: 100 mg IV every 6 hr until acidosis resolves (ethylene glycol only)
- Pyridoxine: 50 mg IV every 6 hr until acidosis resolves (ethylene glycol only)

### TIPS AND TRICKS

- Consult your local poison center: 800-222-1222.
- Refer to the Mountain schematic (see Fig. 151.4) to help interpret anion gap and osmol gap results.
- If long delays until definitive laboratory confirmation of the ingested substance are expected, consider repeating the basic metabolic profile or measure arterial blood gases.
- If alcohol dehydrogenase has not been blocked by fomepizole or ethanol, acidosis should worsen despite standard intravenous fluid resuscitation if ethylene glycol or methanol is present.
- Treatment difficulties associated with ethanol therapy are (1) iatrogenic inebriation and inability to monitor mental status, (2) potential occurrence of hypoglycemia in children, and (3) difficulty maintaining a therapeutic level because of individual variability in ethanol metabolism and clearance.
Suspected toxic alcohol poisoning

Airway management as needed, fluids for hypotension

Obtain chemistry panel, serum osmols, calcium, magnesium, ABG, UA for crystals, ethanol level, and toxic alcohol levels; consider salicylate and acetaminophen if coingestants possible

Anion gap acidemia? (anion gap may be normal if early arrival)

No

Osmol gap >10? (osmol gap may be normal if late arrival but patient should have had an anion gap)

No

Yes

Confirm stat toxic alcohol level order (result may not be available), ECG, and initiate treatment

ADH blockade with ethanol or fomepizole (see “Facts and Formulas” box)

Yes

No

Toxic alcohol level > 20 mg/dL?

Yes

No

Disposition based on any other factors/other potential diagnoses and need for psychiatric eval

ADH blockade with ethanol or fomepizole (see “Facts and Formulas” box)

Sodium bicarbonate for severe acidosis (pH ≤ 7.2)

Consult toxicology

Consult renal service to evaluate for hemodialysis

Cofactor supplementation (thiamine and pyridoxine for ethylene glycol and folate for methanol, see “Facts and Formulas” box)

Admit

Fig. 151.5  Treatment algorithm for toxic alcohol poisoning.  ABG, Arterial blood gas measurements; ADH, alcohol dehydrogenase; ECG, electrocardiography; UA, urinalysis.

DISPOSITION

Patients without acidosis and with a toxic serum alcohol level less than 20 mg/dL may be discharged home if clinical findings and renal function are normal. Any patient receiving an ADH antidote must be admitted to the hospital until a definitive serum alcohol concentration is available. Patients with significant mental status depression or acidosis, patients who are receiving an intravenous ethanol infusion, or patients who need hemodialysis should be admitted to the intensive care unit because laboratory values must be checked frequently. Patients who arrive early after a significant ingestion may be considered for treatment in a setting other than the intensive care unit; these patients are given fomepizole therapy alone if no acidosis was detected before administration of the antidote.

In cases of intentional ingestion, appropriate psychiatric evaluation is warranted after the patient’s medical issues are treated. In cases of unintentional poisoning, especially in children, appropriate poison prevention counseling for all caregivers is required before discharge.21
SECTION XV  TOXICOLOGIC EMERGENCIES

**DOCUMENTATION**

**History**
- Any history of psychiatric illness or earlier suicidal ingestions
- Time lapse since ingestion if known
- History of renal or cardiac disease or other illnesses that will exacerbate the complications of toxic alcohols

**Physical Examination**
- Does the patient look ill? Pale? Febrile? Mental status?
- Cardiac status (blood pressure, arrhythmias)?
- Respiratory and airway status
- Visual acuity if concern exists for methanol poisoning
- Urine output
- Repeated examination while patient is in the emergency department

**Studies**
- Laboratory tests and time the samples were obtained (serum osmol should be done at the same time as blood chemistry panel)
- Availability of toxic alcohol levels

**Medical Decision Making**
- Decision to begin treatment or delays
- Consultations and times that contacts were made

**Treatment**
- Availability of antidotes, time antidote was ordered, and any delays to treatment

**Patient Instructions**
- Document discussion with patient regarding diagnosis, warning signs, what to do, follow-up, and when to return
- With accidental ingestions in children, document poison prevention counseling

**RED FLAGS**

- Urinalysis: The absence of crystals or fluorescence does not exclude poisoning.
- The absence of an osmol gap in patients with severe acidosis does not exclude toxic alcohol poisoning; it may be the result of a delayed presentation.
- The absence of an anion gap in patients who present early does not exclude toxic alcohol poisoning.
- Be prepared to have definitive laboratory confirmation delayed by 8 to 24 hours, depending on the individual hospital’s access to an outside reference laboratory. Empirical treatment should be started if indicated.
- Renal specialists should be consulted early, to prevent complications.
- Be wary of the potential for hypoglycemia in patients treated with intravenous ethanol.
- Do not give ethanol with fomepizole. Both agents compete for alcohol dehydrogenase, and their use together may reduce antidotal effectiveness.
- Because metabolism varies by alcohol type and by individual variability, clinical onset of symptoms can be delayed by 1 to 36 hours.

**REFERENCES**

References can be found on Expert Consult @ www.expertconsult.com.

REFERENCES


