ethanol, methanol, ethylene glycol intoxications

ethylene glycol intoxication

general

commercial products with ethylene glycol:

"Permanent" antifreeze
Paints and lacquers
Polishes and detergents
Inks
Cosmetics
Hydraulic brake fluids
Solar collector fluids
Car wash fluids

- Ethylene glycol is a clear, colorless, almost odorless, sweet-tasting, viscous liquid that is commonly used as the main constituent in most formulations of permanent automotive antifreeze. It also finds use in a variety of commercially available automotive fluids and paint products and it is used industrially as a solvent and synthetic precursor.
- Based on limited anecdotal data, the lethal dose in humans has been estimated at 1 to 2 mL/kg, but there are case reports of fatalities after lower doses and survival after higher doses.
- the parent compound possesses only minor toxic potential compared with its metabolites

clinical manifestations

- The initial effects involve the CNS and typically manifest within 30 minutes to 12 hours after ingestion. These can range from effects that are similar to those seen with acute ethanol intoxication, such as excitement, confusion, disorientation, and ataxia, to signs of CNS depression, such as lethargy, stupor, or coma.
- Nausea, vomiting, myoclonus, and seizures can also occur.
- Cranial nerve deficits, including nystagmus, ophthalmoplegia, facial palsy, dysarthria, and dysphagia have been reported.
- Classically, the second phase manifests 12 to 24 hours after ingestion and consists of cardiorespiratory effects, which may include dyspnea and a Kussmaul respiratory pattern secondary to metabolic acidosis or pulmonary edema. The latter can result in frank respiratory failure necessitating endotracheal intubation and mechanical ventilation.
- Tachycardia, hypotension, frank circulatory shock, coma, and death can also occur during this phase.
- The third phase, which usually takes 1 to 3 days to manifest, consists of renal failure, either oliguric or nonoliguric, due to acute tubular necrosis. Flank pain can also occur.

laboratory manifestations

- Detection of ethylene glycol in serum provides definitive evidence of the diagnosis; however, levels may not be high when presentation is late.
- Acidosis may be severe and is principally caused by glycolic acid accumulation. Dissociation of this acid results in the accumulation of glycolate, which leads to an increase in the serum anion gap.
- Lactate levels also may be artifactually elevated to a substantial degree, because of the cross-reactivity of glycolate with lactate in certain automated lactate analyzers.
- The serum osmole gap may be elevated due to high blood levels of ethylene glycol and its metabolites.
- There are two notable laboratory findings that may be seen in ethylene glycol poisoning; these are findings that are not observed in methanol poisoning. The first is calcium oxalate crystalluria. Oxalate produced by ethylene glycol metabolism chelates calcium, forming crystals and potentially producing hypocalcemia in the process
- The other potential finding is fluorescence of the urine on exposure to ultraviolet radiation. This occurs when the formulation of ethylene glycol ingested contains fluorescein, a fluorescent dye added to many automotive antifreeze solutions to facilitate identification of cooling system leaks

treatment

Decreasing absorption:

(i) Gastric lavage
- may have some efficacy, but only if it is performed within 1 hour after the ingestion.

(ii) Activated charcoal
- is not effective

Decreasing production of toxic metabolites

- Ethanol or fomepizole is administered to slow conversion of the glycol to toxic intermediates (recommended if the serum ethylene glycol concentration is greater than 20 mg/dL; however, inhibitor treatment should be initiated while awaiting definitive identification of the glycol if there is presumptive evidence of intoxication.

Hemodialysis

- Dialysis is conventionally recommended for all patients with serum ethylene glycol levels greater than 50 mg/dL.
- Hemodialysis is indicated for all patients with renal dysfunction and for patients with metabolic acidosis or other toxic manifestations.
- The conventional endpoint for dialysis is a serum ethylene glycol concentration lower than 20 mg/dL in conjunction with normalization of the anion gap, indicating clearance of toxic metabolites.

Vitamins

- glyoxylate may be metabolized to nontoxic products by enzyme systems that rely on pyridoxine (vitamin B6) and thiamine. Providing supplements of pyridoxine (e.g., 50 mg i.v. every 6 hours) and thiamine (e.g., 100 mg i.v. every 6 hours) could hasten elimination of toxic intermediates, although evidence of efficacy is quite limited.

Electrolytes

- Magnesium is a necessary cofactor for the enzymatic degradation of glyoxylate, and supplemental magnesium should be given if there is hypomagnesemia.
- Routine intravenous administration of calcium salts was advocated at one time as a therapeutic means of lowering oxalate levels in body fluids in cases of ethylene glycol poisoning. However, precipitation of calcium oxalate in vital organs is probably more likely to have harmful effects.
- Routine therapeutic administration of calcium to correct hypocalcemia is no longer advised unless the hypocalcemia is severe enough to cause manifestations.

ethanol intoxication

pharmacology

- Ethanol is rapidly absorbed by the gastrointestinal tract and distributed throughout body water
- Between 2% and 10% of ingested ethanol is excreted intact by the kidneys and lungs, but the major fraction is metabolized by the liver
- Ethanol elimination generally follows zero-order kinetics, with elimination rates of 5 to 10 g/hour in nonhabituated subjects, corresponding to a fall in blood ethanol concentration of 10 to 25 mg/dL/hour.
- This rate can more than double in individuals who are chronically habituated to high daily doses of ethanol.

manifestations

complications of intoxication or withdrawal

Alcoholic hepatitis	Hypoglycemia
Aspiration pneumonitis	Hypothermia
Circulatory shock (due to dehydration or hemorrhage)	Infections (e.g., pneumonia, meningitis)
Cirrhosis	Intracranial hemorrhage (e.g., subdural hematoma)
Coagulopathy	Pancreatitis
Dehydration	Peripheral neuropathy
Drug overdose or other toxic ingestion	Psychosis
Electrolyte derangements	Rhabdomyolysis
Gastrointestinal hemorrhage (due to gastritis, peptic ulcer disease, esophageal varices, hemorrhoids, or Mallory-Weiss tear)	Seizures Sepsis
Head injury	Thrombocytopenia
Heat stroke	Vitamin deficiency (folate, thiamine, other B vitamins)
Hepatic encephalopathy	Wernicke-Korsakoff syndrome

Blood Ethanol Concentration (mg/dL)	Clinical Manifestations
<30	Little demonstrable effect
30-50	Mild euphoria, minimal central nervous system effects, subjective sensation of cutaneous warmth
50-80	Relaxation, jocularity, gregariousness, cutaneous flushing, prolongation of reaction time
80-100	Statutory intoxication in many jurisdictions
100-200	Loquacity, animation, exuberance, exaggerated emotional responses, uninhibited behavior, impaired judgment
200-300	Sedation interrupted by periods of boisterous or antisocial behavior, nausea, emesis, dysarthria, horizontal nystagmus, impaired visual pursuit, diplopia, ataxia
300-400	Unstable station and gait, incoherent speech, somnolence, impairment of protective airway reflexes, incontinence, obtundation, stupor
>400	Coma, loss of protective reflexes, respiratory depression, death

laboratory findings:

- Numerous blood test abnormalities can be seen in intoxicated subjects, particularly in patients with chronic ethanol abuse, including hyponatremia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoglycemia, hypertriglyceridemia, leukopenia, thrombocytopenia, and coagulopathy.
- Elevated activities of various circulating enzymes, including amylase, lipase, creatine phosphokinase, transaminases, and g-glutamyl transpeptidase, can occur as a reflection of alcohol-induced pancreatitis, rhabdomyolysis, hepatitis, or cirrhosis. The latter can also result in hyperbilirubinemia and hypoalbuminemia.
- In chronic alcoholic subjects, a blood ethanol concentration lower than 250 mg/dL is an unlikely explanation for alterations in consciousness and should prompt a search for an alternative cause.

treatment

- The treatment of severe ethanol intoxication is largely supportive.
- Parenteral thiamine (50 or 100 mg) is given during the initial phase of management, regardless of the level of sensorium, to prevent or treat Wernicke-Korsakoff syndrome.
- folate and vitamin B12 administration are better delayed until the complete blood count can be assessed, so that specific vitamin assays may be obtained if macrocytic anemia is present.
- Hydration is necessary in many intoxicated patients.
- Dextrose administration is traditionally preceded by thiamine dosing.
- Patients with hypoglycemia require rapid intravenous injection of dextrose followed by a continuous dextrose infusion titrated to the results of frequent serial blood glucose tests.
- Hypokalemia, hypomagnesemia, and hypophosphatemia should be corrected with the use of appropriate oral or parenteral supplementation.
- Patients with anemia or a suggestive history or physical findings may require further investigation for gastrointestinal hemorrhage.

methanol intoxication

general

- Methanol is widely used in laboratories and industry as a solvent and synthetic precursor. It is also a constituent in numerous commercially available products for residential use
- The minimum lethal dose of methanol is highly variable, reportedly ranging from less than 10 mL to more than 500 mL. This variability may result from multiple factors, including the degree of concomitant ethanol intoxication, the presence of folate deficiency, and perhaps other factors.

commercial products containing methanol

Denatured alcohol	Gasoline (some forms of gasohol)
Windshield washer fluids	Dyes
Windshield deicers	Duplicating fluids
Sterno ("canned heat")	Carburetor cleaners
Antifreeze	Adhesives
Paints and paint removers	Glass cleaners
Wood stains	Dewaxing preparations
Shellacs and varnishes	Pipe sweetener
Lacquer and paint thinners	Embalming fluids
Furniture refinishers	Various other solvents and cleaners
Dry gas	

pathophysiology

- Other than its inebriant and mucosal irritant effects, methanol per se is nontoxic. However, it is metabolized slowly to formaldehyde and then rapidly to formic acid
- Formic acid production results in metabolic acidosis.
- Independent of the acidosis, formic acid inhibits cytochrome oxidase and has direct neurotoxic effects, particularly affecting the retina and optic nerves.

clinical manifestations

- Delayed CNS manifestations occur 12 to 24 hours after ingestion and are attributable to production of formic acid.
- They can include cerebral edema, seizures, signs of meningeal irritation, and cerebral infarction (particularly infarction of basal ganglia).
- However, the most specific clinical findings are ocular and range from mildly blurred vision, to visual field defects or tunnel vision, to complete and sometimes permanent blindness. Other possible ocular findings include scotomata, scintillations, papilledema, and loss of pupillary light reflexes.
-. In the most severe cases of poisoning, profound acidosis, respiratory failure, and circulatory shock intervene. Severe global brain injury and brain death can also occur.

laboratory manifestations

- The clinical laboratory can be helpful by providing clues to the diagnosis in cases of occult intoxication and by corroborating cases with a clear history of methanol ingestion.
- The dissociation product of formic acid, formate, is negatively charged and can widen the serum anion gap. Arterial blood gas analysis can corroborate the presence of metabolic acidosis.
- A potentially useful screening test for recognition of methanol exposure early in its course is the serum osmolality gap.
- A number of other exogenous compounds besides methanol cause an increased osmolar gap including ethylene glycol, acetone, isopropanol, propylene glycol, and acetonitrile, all of which have been reported to increase osmolality and the osmole gap.
- False-positive results have been described in cases of circulatory shock, DKA or AKA, the hyperosmolar hyperglycemic nonketotic dehydration syndrome, chronic renal failure, and multiple organ system failure.
- False-negative results can occur if the ingestion involved a small, but still potentially lethal, volume of methanol.
-. Some clinical chemistry laboratories assay serum osmolality by the dew point or vapor pressure method. For technical reasons, this method yields spuriously low osmolality readings in the presence of ethanol, methanol, and other volatile alcohols, and therefore it should not be used to assess the osmole gap.
- Methanol assays are available in many clinical chemistry laboratories and provide a direct assessment of methanol concentration in serum samples. This test is not definitive, because patients who present late after methanol intake may have metabolized much or all of the ingested alcohol, although the toxic byproducts may be present in appreciable concentration.

treatment

Decreasing absorption
- Gastric lavage is unlikely to be of value unless the patient presents within 1 hour after ingestion.
- Activated charcoal is not useful

Decreasing production of toxic metabolites

(i) ethanol
- Ethanol has been the conventional form of antidotal pharmacotherapy for methanol intoxication. The principle is that alcohol dehydrogenase and aldehyde dehydrogenase have higher affinity for ethanol than for methanol, and ethanol thereby serves as an effective competitive inhibitor.
- As a result, conversion of methanol to formaldehyde and formate is significantly slowed in the presence of ethanol, allowing methanol to be excreted by the kidneys and lungs, and by hemodialysis if that modality is employed.

(ii) Fomepizole
- Fomepizole (4-methylpyrazole) is a newer therapeutic alternative to ethanol.
- Like ethanol, fomepizole inhibits alcohol dehydrogenase, but it is considerably more costly than ethanol. Nevertheless, fomepizole has the potential advantage of being easier to dose and titrate, and it has no sedative effects.
Frequent serial blood ethanol assays are avoided.
- Compared with oral dosing of ethanol, there is no risk of nausea, vomiting, gastritis, or abdominal pain with fomepizole .

(iii) sodium bicarbonate
- There also is evidence that undissociated formic acid is more toxic than the dissociation product, formate; increasing the extracellular fluid pH favors conversion of formic acid to formate.
- Therefore, sodium bicarbonate is recommended for subjects with an arterial pH less than 7.30, although intentional alkalemia is not advocated.

haemodialysis
- Methanol is excreted by the kidneys and lungs, but only slowly. Hemodialysis can effectively and more rapidly remove methanol and its toxic metabolites from the body.
- Charcoal or resin hemoperfusion techniques are not effective, and peritoneal dialysis is recommended only if hemodialysis is not available.
- Hemodialysis is recommended as a supplement to ethanol or fomepizole in patients with serious degrees of methanol intoxication.

vitamins
- In humans and certain nonhuman primates, formate is only slowly metabolized, allowing the development of acidosis and ocular pathology if substantial amounts of methanol are ingested. Monkeys given large doses of folinic or folic acid before or after methanol administration had lower formate levels and less toxicity than control animals.
- Based on these and other experimental data, large doses of folic or folinic acid are recommended in clinical methanol poisoning. Typical recommendations are to administer 50 mg of folinic or folic acid i.v. every 4 to 6 hours.