TOXINZ POISONS INFORMATION

Ethylene Glycol

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DESCRIPTION

SUBSTANCE NAME

Ethylene Glycol

SUBSTANCE CLASS

Glycol

PHYSICOCHEMICAL PROPERTIES

Colorless, odorless, sweet-tasting, hygroscopic liquid

Molecular Weight	62.07[1]
Melting Point	-13 degrees C[1]
Specific Gravity (water = 1)	1.1274[1]
Flash Point	115 degrees C[1]
Solubility	Water: miscible[1] Ethanol: miscible[1] Glycerol: miscible[1] Acetic acid: miscible[1] Acetone: miscible[1] Ether: slightly soluble[1] Benzene: insoluble[1] Chlorinated hydrocarbons: insoluble[1] Petroleum ether: insoluble[1] Oils: insoluble[1]

USES

Ethylene glycol is predominantly used as a deicer or antifreeze in cooling systems. It is also used in hydraulic brake fluids, as a solvent, a chemical intermediate, and as an industrial humectant. It may also be used as a glycerin substitute in commercial products including paints, detergents, and cosmetics.

INTERVENTION CRITERIA

INTERVENTION LEVEL

Child

Medical assessment and observation in an emergency department is recommended for:

- Ingestions greater than a witnessed lick or exploratory taste of ethylene glycol
- Symptomatic ingestions
- Symptomatic eye exposures (other than mild resolving symptoms following flushing)
- Significantly symptomatic patients (more than mild irritation) following skin or inhalation exposure

Adult

Medical assessment and observation in an emergency department is recommended for:
- Ingestions greater than 10 mL of ethylene glycol
- Symptomatic ingestions
- Symptomatic eye exposures (other than mild resolving symptoms following flushing)
- Significantly symptomatic patients (more than mild irritation) following skin or inhalation exposure
- Exposures with intent to self-harm

OBSERVATION PERIOD

Observation at Home

If the patient does not require medical observation they can be monitored at home for 8 hours in the care of a reliable observer.

The patient should be medically assessed if any symptoms develop, including:
- Nausea
- Vomiting
- Drowsiness
- Slurred speech
- Stumbling or difficulty in moving
- Confusion
- Decreased urine output

Medical Observation

If medical observation is required, patients with an undetectable serum ethanol should be monitored until 8 hours post-exposure for the onset of symptoms or biochemical evidence of evolving toxicity. Patients co-ingesting ethanol should be monitored until 12 hours post-exposure.

If the patient is asymptomatic at the end of the observation period, with normal serum pH, bicarbonate, and creatinine concentrations and their serum (or breath) ethanol concentration is undetectable they may be:
- Discharged into the care of a reliable observer, or
- Referred for psychological assessment if the overdose or exposure was with intent to self-harm

INVESTIGATIONS

Patients, particularly children, presenting within an hour of suspected ethylene glycol ingestion or those who have concurrently co-ingested ethanol may not have any abnormal surrogate markers of poisoning. In these instances, close observation and serial monitoring of acid-base profile and renal function status should be performed. Any development of early metabolic acidosis would be highly suggestive of recent ethylene glycol exposure.

Serum ethylene glycol concentration (where available)
Serum ethanol concentration (required for osmolar gap calculation)
Osmolar gap (elevated in early stages of poisoning)
Serum electrolytes including:
- Sodium (required for anion gap calculation)
- Chloride (required for anion gap calculation)
- Bicarbonate (required for anion gap calculation)
- Calcium
- Potassium

Anion gap (elevated in later stages of poisoning)
Blood gas analysis including:
- Serum pH

Creatinine and BUN
Urine output
Urinalysis including:
- Proteinuria
- Hematuria
- Examination under UV light (Wood's lamp) for fluorescence (present in many antifreeze solutions and with urinary elimination the urine will fluoresce when expose to UV light). A negative result does not completely rule out ethylene glycol exposure.
- Microscopic examination for crystalluria (calcium oxalate crystals)

If a serum ethylene glycol concentration measurement is not available a presumptive diagnosis of poisoning may be based on:

either

A history or suspicion of ethylene glycol ingestion plus any 2 of the following;[2] [3]
- Arterial pH < 7.3
- Serum bicarbonate < 20 mmol/L (20 mEq/L)
- Osmolar gap > 10 mOsm/L
- Presence of urinary oxalate crystals

or

A history or suspicion of ethylene glycol ingestion within the last 1 hour and osmolar gap > 10 mOsm/L

A serum ethylene glycol is the preferred investigation, but is often not readily available. A significant ethylene glycol ingestion may be inferred from an increased osmolar gap (in the early stages of intoxication) indicating a solute (glycol) load. However, a normal osmolar gap cannot rule out ethylene glycol exposure. Once the glycol is metabolized the osmolar gap will drop and may be replaced by an increased anion gap, indicating an increased organic acids (glycol metabolites) load, with an accompanying metabolic acidosis.

Presence in the urine of either fluorescein or calcium oxalate crystals indicates ethylene glycol exposure, but their absence does not exclude this poisoning. Calcium oxalate crystals may not be present until the later stages of intoxications. Fluorescein is rapidly eliminated by the kidneys and may have already been excreted prior to presentation. Also, the ingested ethylene glycol may not contain fluorescein. Care must be exercised when checking for fluorescence as plastic containers may exhibit some degree of fluorescence under a UV light. A glass container is preferable and previous experience with visualizing fluorescein containing urine is useful.

ADMISSION CRITERIA

Admission to an intensive care environment is recommended when:
- Ethylene glycol concentrations are > 20 mg/dL (3.2 mmol/L)
- Those receiving antidotal therapy
- Following symptoms occur
  - Coma
  - Seizures
  - Kidney injury
  - Hypotension

Ensure the receiving hospital is able to provide:
- The specific antidotes (Ethanol or Fomepizole)
- Advanced care/ICU facilities, and
- Hemodialysis

TREATMENT

TREATMENT SUMMARY

Initial management includes airway protection and adequate minute ventilation, administration of IV fluids, treating seizures with benzodiazepines or barbiturates, and correcting hypoglycemia (unless rapid glucose screen indicates otherwise); concurrently administer thiamine and pyridoxine to support metabolism of ethylene glycol to less toxic products. Nasogastric aspiration may be performed within 1 hour of ingestion provided the airway is protected. Ethanol and fomepizole are effective antidotes and should be administered to patients as early as possible.[3] Hemodialysis is effective in excreting glycols and their toxic metabolites and should be considered in acute renal failure, severe metabolic acidosis, or if other indications are present. Doses of ethanol and fomepizole need to be increased during hemodialysis.[4] [5]

Severe acidosis is ideally managed using extracorporeal techniques (e.g. hemodialysis). Intravenous sodium bicarbonate may be considered as an adjunctive treatment for severe acidosis. Hypocalcemia should only be reversed if cardiac dysrhythmia occurs (particularly QT prolongation), or seizures prove unresponsive to management. Hypoglycemia, hyperkalemia, and hypomagnesemia should be corrected. Calcium oxalate crystals may form in any organ with resultant multiorgan dysfunction/failure. The kidneys are often afflicted, resulting in acute kidney injury. There is also a risk of lung injury, and fluid balance will require careful monitoring. Stupor or coma indicates metabolic encephalopathy or cerebral edema.[6] Cranial nerve palsies may occur some 5 to 20 days following ingestion and usually spontaneously resolve over weeks to months without specific therapy.[7] [8] [9] [10]

Eye exposures require a 15 minute irrigation with saline or water and if more than mild, resolving symptoms are present following irrigation, an ophthalmologic examination should be undertaken, including slit lamp examination and fluorescein staining. If there is evidence of injury an ophthalmologist should be consulted. Treatment should follow standard protocols for the management of eye irritation.

- Emergency Stabilization
  - Ensure adequate cardiorespiratory function
  - Hypotension
  - Seizure
  - Hypoglycemia
  - Emergency monitoring
- Decontamination
  - Ingestion
    - Nasogastric aspiration
  - Eye
    - Irrigate immediately
  - Inhalation
    - Fresh air, oxygen
  - Skin
    - Irrigate
- Antidote(s)
  - Ethanol
  - Fomepizole
  - Pyridoxine
  - Thiamine
- Enhanced Elimination
  - Hemodialysis
  - Urinary alkalinization
- Supportive Care
  - Monitoring
  - Metabolic

- Metabolic acidosis

Renal

- Acute kidney injury

Fluid and electrolytes

- Hypocalcemia
- Hypomagnesemia
- Hyperkalemia

Neurologic

- CNS depression
- Seizure
- Neurotoxicity

Cardiovascular

- Hypotension

Hepatic

- Hepatotoxicity

Respiratory

- Acute respiratory distress syndrome (ARDS)
- Pulmonary edema

EMERGENCY STABILIZATION

ENSURE ADEQUATE CARDIOPULMONARY FUNCTION

Airway

Ensure the airway is protected (intubation may be required), and administer oxygen. Establish secure intra-venous access.

Hypotension

Hypotension may be present due to gastrointestinal fluid loss and alcohol-induced vasodilation, and in such cases fluid replacement with a crystalloid should be performed, having regard to adequate urine output.

CHILD

Hypotension in children is determined by age and systolic blood pressure

Age	Hypotension if Systolic Blood Pressure (mm Hg) is:
0 to 28 days	< 60
1 to 12 months	< 70
1 to 10 years	< 70 + (age in years x 2)
> 10 years	< 90

Administer an isotonic crystalloid fluid

10 mL/kg IV over 5 to 10 minutes

If the systolic blood pressure does not return to the normal range, give a further 10 mL/kg body weight of the isotonic crystalloid over 5 to 10 minutes.

The intraosseous route can be used if IV access is difficult or delayed.

ADULT

Administer a bolus of isotonic crystalloid fluid if systolic blood pressure is less than 100 mmHg.

Isotonic crystalloid fluid dose:

20 mL/kg IV over 5 to 10 minutes

If the systolic blood pressure does not return to the normal range, give a further 10 mL/kg body weight normal saline over 5 to 10 minutes.

The intraosseous route can be used if IV access is difficult or delayed.

SEIZURE

Administer a benzodiazepine as first-line treatment to patients with seizure activity.[11]

Blood glucose concentration should be promptly determined. If the result indicates hypoglycemia, or is unobtainable, supplemental dextrose should be administered IV.

Check for hypoxia and electrolyte disturbances. Correct acid base and metabolic disturbances. Seizures due to ethylene glycol intoxication may prove unresponsive to standard management unless hypocalcemia is corrected.

HYPOGLYCEMIA

IV dextrose is indicated (even if blood glucose cannot be quickly measured) in patients with altered mental status, unusual behavior, coma, or seizures. Hypoglycemic patients may present with focal neurological deficits.[12] However, these may also be due to cerebral ischemia.

Thiamine

Must be administered to adult patients considered alcohol-dependent or malnourished.[3][13]

Thiamine dose

ADULT
100 mg IV, which may be repeated every 8 hours, if needed.

EMERGENCY MONITORING

Blood pressure
ECG
Respiratory rate
Oxygen saturation
Serum ethylene glycol concentration (if available)
Serum ethanol concentration (used in calculation of osmolar gap)
Osmolar gap (elevated early in poisoning)
Electrolytes including:
- Sodium (required for anion gap calculation)
- Chloride (required for anion gap calculation)
- Bicarbonate (required for anion gap calculation)
- Calcium
- Potassium

Anion gap (elevated later in poisoning)
Blood gas analysis including:
- Serum pH

Creatinine and BUN
Urine output
Urinalysis including:
- Proteinuria
- Hematuria
- Microscopic examination for crystalluria

Blood glucose

Liver function

DECONTAMINATION

INGESTION

Nasogastric Aspiration

Nasogastric aspiration is recommended if the quantity of liquid ingested is both systemically toxic and in sufficient volume to aspirate. As this procedure may increase the risk of vomiting and pulmonary aspiration, the airway must be protected in all patients. Accurate placement of the nasogastric tube must also be ensured in all patients.

Nasogastric aspiration is recommended if the patient has presented early (within 1 hour) following ingestion of ethylene glycol.

Single Dose Activated Charcoal

Activated charcoal is not considered an effective decontaminant for this ingestion as ethylene glycol is rapidly absorbed from the gastrointestinal tract and has poor binding affinity for activated charcoal. Unless there is concern for coingestants, there is little benefit from activated charcoal administration in ethylene glycol ingestions.

EYE

Remove contact lenses. Irrigate immediately with water or saline for at least 15 minutes. If the eye is contaminated with solid particles, the eyelid should be completely everted and any solid material removed as quickly as possible whilst continuing to irrigate. A topical anesthetic may be necessary in some patients, especially children, to enable the patient to open the lids sufficiently for effective irrigation.

If, following irrigation, any of the following are apparent:
- Ocular pain (other than mild and resolving)
- Redness (other than mild and resolving)
- Decreased visual acuity
- Ocular discharge/crusting

The patient should receive a full ophthalmologic examination, including slit lamp examination and fluorescein staining. If there is evidence of injury an ophthalmologist should be consulted.

INHALATION

Remove the patient from the exposure. If respiratory symptoms such as shortness of breath are present, administer oxygen and provide additional support if necessary.

SKIN

Remove any contaminated clothing or jewelry. Wash the affected area thoroughly with soap and water until all of the contaminant is removed.

ANTIDOTE(S)

Appropriate use of antidotes in glycol poisoning is essential. Ethanol has long been regarded as an effective intervention, is cheap and available but requires longer periods of monitoring due to the risk of ethanol intoxication. Fomepizole has proven efficacy,[14] but suffers the disadvantage of expense and may not be immediately available. Both effectively act (via different mechanisms) by inhibiting the role of alcohol dehydrogenase in ethylene glycol metabolism, thus reducing the metabolic conversion of

glycol to toxic metabolites (including glycolic, glyoxylic, and oxalic acid).[15]

Thiamine and pyridoxine may be indicated as therapeutic adjuncts. Theoretically, they act as cofactors in the formation of non-toxic metabolites of ethylene glycol. No data exists to support this assumption, but they may benefit those with a history of ethanol abuse or inadequate nutrition (e.g. vitamin deficient patients).[3]

Ethanol
Fomepizole
Pyridoxine
Thiamine

ETHANOL

Indications

Ethanol is indicated if:[3]

- Reliable history of ingestion of a toxic quantity of ethylene glycol; or
- Plasma ethylene glycol concentration is greater than 3.2 mmol/L (20 mg/dL) or;
- History or clinical suspicion of ethylene glycol poisoning and at least two of the following:
  - Arterial pH < 7.3
  - Serum bicarbonate < 20 mmol/L (20 mEq/L)
  - Osmolar gap > 10 mosm/L
  - Presence of urinary oxalate crystals

Dose and Administration

For acceptable efficacy, the blood ethanol concentration should be maintained between 22 and 33 mmol/L (100 to 150 mg/dL).[3] To achieve this both a loading dose and maintenance infusion are required. Either 100% ethanol diluted for intravenous use may be infused, or liquor (e.g. vodka, gin) may be administered orally.

Prior to use of ethanol therapy a blood ethanol determination should be made to identify if the patient has an existing ethanol concentration requiring a modification of the loading dose. Monitoring in an intensive care setting is required during administration. Because of the large inter-individual variability in ethanol metabolism, serum ethanol concentrations should be monitored every 1 to 2 hours if this is available.

Ideally effectiveness of blocking can be monitored by analysis of metabolite concentrations, or blood gases if metabolite and ethanol analyses are not available.

As ethanol may depress respiration, mechanical hyperventilation is recommended in those with reduced level of consciousness.[16]

Loading Dose

Oral ethanol loading dose

Intravenous ethanol loading dose

Oral Ethanol Loading Dose

To calculate the loading dose of oral ethanol from common concentrations in spirits use the appropriate calculation below. The dose should be administered as a 20% or less solution (e.g. diluted with water or fruit juice).

Ethanol %	Dose (mL)

37/37.5%	body weight x 2.5
40%	body weight x 2.3
42%	body weight x 2.2
45%	body weight x 2.04

If the concentration of spirits does not match those in the above table the dose can be calculated by clicking here.

Note: The term "proof" describing alcohol content of beverages should be halved to obtain the proper % v/v value (e.g. 60 proof = 30% v/v ethanol).

Intravenous Ethanol Loading Dose

Concentrated ethanol solutions need to be diluted with isotonic 5% glucose (dextrose) to prevent vascular damage. To convert concentrated ethanol formulations to 5 or 10% click here.

To reach the desired blood ethanol concentration of 22 to 33 mmol/L (100 to 150 mg/dL) administer:

5% v/v ethanol:

15 to 22 mL/kg over 30 minutes

10% v/v ethanol:

8 to 11 mL/kg over 30 minutes

10% solution are hyperosmolar and irritant and should be administered via a central venous line

If you have w/v formulations please click here to convert to v/v

Maintenance Dose

The doses suggested below are only a starting point. Maintenance doses should be titrated aiming to achieve the desired blood ethanol concentration of 22 to 33 mmol/L (100 to 150 mg/dL); this is best guided by frequently repeated measurements of serum ethanol concentrations (ideally every 1 to 2 hours).

Oral ethanol maintenance dose

Intravenous ethanol maintenance dose

Oral Ethanol Maintenance Dose

Ethanol %	Children (mL/h)	Adults (non-alcohol dependent) (mL/h)	Adults (alcohol dependent) (mL/h)
37%	0.61 x body weight	0.41 x body weight	0.82 x body weight
40%	0.57 x body weight	0.38 x body weight	0.76 x body weight
42%	0.54 x body weight	0.36 x body weight	0.72 x body weight
45%	0.5 x body weight	0.33 x body weight	0.67 x body weight

This should be administered as a 20% or less solution (e.g. diluted with water or fruit juice).

If the concentration of spirits does not match those in the above table the dose can be calculated by clicking here.

Intravenous Ethanol Maintenance Dose

Concentrated ethanol solutions need to be diluted with isotonic 5% glucose (dextrose) to prevent vascular damage. To convert concentrated ethanol formulations to 5 or 10% click here.

5% v/v solution:
- CHILD
  - 4.5 mL/kg/h
- ADULT
  - Non-alcohol dependent:
    - 2 to 3 mL/kg/h
  - Alcohol dependent:
    - 4 to 6 mL/kg/h

10 % v/v solution:
- CHILD
  - 2.25 mL/kg/h
- ADULT
  - Non-alcohol dependent:
    - 1 to 1.5 mL/kg/h
  - Alcohol dependent:
    - 2 to 3 mL/kg/h

10% solution are hyperosmolar and irritant and should be administered via a central venous line

If you have w/v formulations please click here to convert to v/v.

Dosing requirements will change if hemodialysis is required. See enhanced elimination section.

Antidote Endpoint

Ethanol administration may be discontinued if ethylene glycol concentrations can no longer be detected or are less than 3.2 mmol/L (20 mg/dL) with a normalized arterial pH and resolved signs of systemic toxicity - this is likely to take 2 to 3 days given ethylene glycol's typical elimination half-life of around 17 to 18 hours in the presence of ethanol, if hemodialysis is not applied.[3]

Precautions

Hypoglycemia may occur, especially in children.[17] Once an infusion has been commenced blood glucose concentrations must be determined on a frequent basis (every 1 to 2 hours). It may be necessary to add dextrose to intravenous solutions, or give glucose if ethanol is being administered orally.

It is recommended that patients receiving ethanol therapy be monitored in an intensive care setting and any decline in respiratory drive countered with hyperventilation.[16]

FOMEPIZOLE

While availability is limited by purchase price, fomepizole appears preferable to ethanol. It is more particularly indicated in those with altered mental status, patients suffering hepatic disease, pregnant women, or those critically ill but lacking confirmation of poisoning. Its administration to pediatric patients avoids the disadvantages of ethanol (e.g. inebriation, hypoglycemia).[3]

Indications

Fomepizole is indicated if:[3]

- Plasma ethylene glycol concentration greater than 3.2 mmol/L (20 mg/dL) or;
- Recent ingestion of a toxic amount of ethylene glycol and presence of osmolar gap greater than 10 mosm/L or;

- History or clinical suspicion of ethylene glycol poisoning and at least two of the following
  Arterial pH < 7.3
  Serum bicarbonate < 20 mmol/L (20 mEq/L)
  Osmolar gap > 10 mosm/L
  Presence of urinary oxalate crystals

Particular indications:[3]
- Altered mental status
- Co-ingestion of other drugs that may cause CNS depression (e.g. opioids, sedatives, antidepressants, anticonvulsants, antihistamines, hypnotics, muscle relaxants)
- Patients taking disulfiram or metronidazole
- Hepatic disease
- Critically ill patients lacking confirmation of ethylene glycol toxicity
- Pregnancy
- Pediatric patients (avoids the inebriation and hypoglycemia that may occur with ethanol administration)
- Inability of local laboratory to measure repeated ethanol concentrations
- Lack of local availability of a facility to monitor the patient closely such as an intensive care unit

Dose and Administration

Child and Adult

Loading dose[4]

- 15 mg/kg diluted in 100 mL of normal saline or 5% dextrose in water and administered by IV infusion over 30 minutes

Maintenance doses[4]

- 10 mg/kg should be administered every 12 hours for 4 doses, then;
- 15 mg/kg every 12 hours thereafter if indicated

Maintenance fomepizole should be administered in the same fashion as the loading dose. Dosing requirements will change if hemodialysis is required – as outlined in the enhanced elimination section.

Antidote Endpoint

Fomepizole may be discontinued when ethylene glycol plasma concentrations are either undetectable, or below 3.2 mmol/L (20 mg/dL) in patients with a normal pH and resolved signs of systemic toxicity.[4]

Adverse Effects

Abdominal pain, skin rash, nausea, headache, dizziness, and drowsiness have been reported following fomepizole use.[4]

PYRIDOXINE (VITAMIN B6)

Pyridoxine acts as a co-factor in the conversion of glyoxylic acid to the non-toxic metabolite glycine. While the clinical benefit of pyridoxine administration for the treatment of ethylene glycol poisoning has not been demonstrated in healthy individuals, it is recommended for use in malnourished or alcohol dependent patients who may have vitamin deficiencies.[3]

Dose and Administration

The formulation should be diluted at least 1 to 5.

ADULT
- 50 to 100 mg pyridoxine given as an IV infusion over 15 to 30 minutes every six hours
- Continue for two days[18]

Precautions

Profound peripheral neuropathy may occur after very large single doses[19] or a series of doses (for example a total of > 2 g/kg pyridoxine over a three day period).[20] The sensory (if not motor) disturbances are potentially irreversible.[21]

THIAMINE

Thiamine acts as a co-factor in the conversion of glyoxylic acid to the non-toxic metabolite alpha-hydroxy-beta-ketoadipate. While the clinical benefit of thiamine administration for the treatment of ethylene glycol poisoning has not been demonstrated in healthy individuals, it is recommended for use in malnourished or alcohol dependent patients who may have vitamin deficiencies.[3]

Dose and Administration

ADULT
- Administer 100 mg IV or IM thiamine every six hours
- Continue for two days[18]

ENHANCED ELIMINATION

HEMODIALYSIS

Hemodialysis is a highly effective method to enhance excretion of glycols and their toxic metabolites, reducing duration of antidote use and enhancing patient outcome. The approximately 6-hour elimination half-life of ethylene glycol may be reduced to 2.5 to 3.5 hours with hemodialysis.[22][23][24] In severe poisonings it can be life-saving. If dialysis is prolonged monitor for and treat hypophosphatemia.

Hemodialysis is indicated where:[3]

Clinical signs are deteriorating despite intensive supportive care or;
Metabolic acidosis with pH < 7.25 unresponsive to therapy or;
Acute kidney injury or;
Serum ethylene glycol concentration > 8.1 mmol/L (50 mg/dL) in those not receiving fomepizole therapy.

Ethanol Maintenance

This therapy should continue during hemodialysis. As ethanol is dialysed, infusions must be increased (approximately doubled during intermittent hemodialysis) or 95% ethanol added to the dialysate. Further infusion rates must be guided by regular measurement of serum ethanol concentration.

Ethanol should be continued in those receiving hemodialysis until:

Measured serum ethylene glycol concentration is < 3.2 mmol/L (< 20 mg/dL), and renal function is restored, and acidosis resolved,[5]
or
Osmolar gap, anion gap, electrolyte concentrations, acid-base, and renal function have normalized.

Fomepizole Maintenance

The dose of fomepizole must be increased during hemodialysis to compensate for losses from the procedure. If hemodialysis is started six or more hours after the last administration of fomepizole, the next scheduled dose should be given at the commencement of the procedure. All patients should then receive additional fomepizole doses every four hours for the duration of the hemodialysis run.[4]

Fomepizole should be continued in those receiving hemodialysis until:[25] [4]

- Acid-base and renal function have normalized;
- Signs of systemic toxicity have disappeared, and;
- Serum ethylene glycol concentration are 3.2 mmol/L (20 mg/dL) or less.

Fomepizole treated patients should continue this therapy following hemodialysis. If a dose has been administered within the last hour a further dose is not required. Those not having received a dose within 1 to 3 hours should be administered half their next scheduled dose at the completion of dialysis; while those who have not received fomepizole for more than 3 hours should receive their full dose. All should maintain 12 hourly dosing thereafter during the monitoring period.[4]

Post-hemodialysis monitoring

Patients may suffer acute kidney injury as a result of their poisoning and require hemodialysis for some weeks. It is usual (but not inevitable) that full renal function will return.

SUPPORTIVE CARE

MONITORING

Level of consciousness
Blood pressure
ECG
Respiratory rate
Oxygen saturation
Serum ethylene glycol concentration (if available)
Serum ethanol concentration (used in calculation of osmolar gap)
Osmolar gap (elevated early in poisoning)
Electrolytes including:
- Sodium (required for anion gap calculation)
- Chloride (required for anion gap calculation)
- Bicarbonate (required for anion gap calculation)
- Calcium
- Potassium

Anion gap (will be increased in later stages of poisoning)
Blood gas analysis including:
- Serum pH

Creatinine and BUN
Urine output
Urinalysis including:
- Proteinuria
- Hematuria

Microscopic examination for crystalluria
Blood glucose
Liver function
Head CT (if neurological abnormality)

METABOLIC

Metabolic Acidosis

Increased anion gap metabolic acidosis results from the metabolism of ethylene glycol to acidic metabolites, predominantly glycolic acid. In severe acidosis, use of hemodialysis in addition to an antidote to halt production of acidic metabolites is necessary. Intravenous sodium bicarbonate may be considered as an adjunctive treatment in cases of severe metabolic acidosis.

Monitor:
- Blood gases
- Plasma lactate

Manage metabolic acidosis following standard treatment protocols.

Early use of hemodialysis must be considered for any patient with metabolic acidosis.

RENAL

Acute Kidney Injury

Renal injury may occur due to the toxic metabolites of ethylene glycol crystallizing in the presence of calcium and being deposited in the kidneys. Acute tubular necrosis, cortical edema, and other direct toxicity is possible.[26] [27] Signs and symptoms of renal insufficiency predominate at 2 to 3 days post ingestion.[28] [29] [30] Urine output should be closely monitored. Hemodialysis is indicated in the presence of renal failure.[3]

Patients should be monitored for the onset of acute kidney injury:
- Urine output
- Serum creatinine
- Blood urea nitrogen (urea)
- Proteinuria

Manage acute kidney injury following standard treatment protocols.

FLUID AND ELECTROLYTES

Hypocalcemia

Calcium is recommended for patients continuing to seize despite standard anticonvulsant management, or in the presence of cardiac dysrhythmia – particularly prolonged corrected QT interval (greater than 500 ms). Available ionized calcium will rise with increasing acidosis (due to release from plasma proteins) and fall with return to normal serum pH. Prophylactic calcium or treatment of asymptomatic hypocalcemia is not recommended due to the risk of further precipitation of calcium oxalate in the tissues.[3]

Monitor for onset of hypocalcemia with:
- Observation for signs and symptoms of hypocalcemia
- Serum ionized calcium
- Serum electrolytes (hypomagnesemia and hyperkalemia are often also present)

Hypocalcemia may be managed following these recommendations.

Hypomagnesemia

Magnesium is a cofactor with thiamine in the metabolic detoxification of ethylene glycol metabolites. Serum magnesium concentrations should be monitored and hypomagnesemia corrected.[18]

Monitor:
- Serum magnesium
- Nausea and vomiting

Lethargy, weakness, fatigue
Tremor
Hyperreflexia

Manage hypomagnesemia following standard treatment protocols.

Hyperkalemia

Hyperkalemia can occur in association with metabolic acidosis due to the formation of acidic metabolites. To prevent worsening acidosis, an antidote (ethanol or fomepizole) and bicarbonate should be administered and hemodialysis performed to correct potassium concentrations.[31]

Monitor:
- Serum potassium
- Blood gas analysis
- ECG for changes suggestive of hyperkalemia including
  - Peaked T waves (tenting)
  - Flattened P waves
  - Prolonged PR interval (first-degree heart block)
  - Widened QRS complex
  - Deepened S waves and merging S and T waves
  - Idioventricular rhythm
  - Sine-wave formation
- VF and cardiac arrest

Hyperkalemia may be managed following these (hyperlinked) recommendations.

NEUROLOGIC

CNS Depression

Drowsiness, ataxia, slurred speech, and stupor are common early signs of ethylene glycol intoxication.[26] Ethylene glycol metabolites, namely glycoaldehyde, glycolic acid, and glyoxylic acid, may contribute to CNS depression.[3]

Closely monitor level of consciousness.

Manage depressed level of consciousness following standard treatment protocols.

Seizures

Seizure activity unresponsive to standard management is typically indicative of hypocalcemia, particularly in the presence of calcium oxalate crystalluria, or following administration of sodium bicarbonate (which can lower ionized serum calcium). Calcium is recommended for patients continuing to seize despite standard anticonvulsant management.[3] Seizure-related hypoxic encephalopathy may also occur.[18]

Observe the patient closely for onset of seizure activity.

Toxic seizure may be managed following these (hyperlinked) recommendations.

Neurotoxicity

Cranial nerve defects occur in the subacute phase of ethylene glycol toxicity. This may occur within 5 to 20 days and may persist for weeks or months.[7][8][9][10] The exact mechanism in ethylene glycol poisoning is unknown.[7]

Closely monitor patients for onset of neurotoxicity.

Manage neurotoxicity following standard treatment protocols.

CARDIOVASCULAR

Hypotension

Profound hypotension has been reported due to critical circulatory failure.[32] The exact mechanism is unknown.

Monitor:
- Heart rate/rhythm
- Blood pressure
- ECG
- Level of consciousness
- End-organ perfusion

Manage hypotension following standard treatment protocols.

HEPATIC

Hepatotoxicity

Acute liver dysfunction may develop with significant toxicity. Elevated ALT and bilirubinemia has been reported.[33] [34]

Hepatic monitoring should include:
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- International normalized ratio (INR)
- Serum bilirubin
- Blood or plasma glucose
- Serum lactate

Manage acute hepatotoxicity following standard treatment protocols.

RESPIRATORY

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome has been reported in the presence of normal cardiac function. It is speculated that it may be due to direct toxic effect from ethylene glycol metabolites. Respiratory support with mechanical ventilation and positive end-expiratory pressure may be required.[35]

Monitoring for acute respiratory distress syndrome should include:
- Oxygen saturation
- Blood gas analysis
- Chest X-ray
- Heart rate
- Blood pressure
- ECG
- Urine output
- Fluid balance
- Serum electrolytes
- Level of consciousness

Treat using standard protocols for management of acute respiratory distress syndrome (ARDS).

Pulmonary Edema

Pulmonary edema may occur in severe ethylene glycol poisoning. Death can occur within 24 to 72 hours.[26]

Pulmonary edema usually manifests with desaturation, tachypnea, and pulmonary crepitations. Occasionally frothy, pink sputum may be apparent.

Monitoring for this condition should include:
- Chest auscultation
- Oxygen saturation
- Blood gas analysis
- Chest x ray

Manage pulmonary edema following standard treatment protocols.

DISCHARGE CRITERIA

All asymptomatic patients should be observed until appropriate investigations have been carried out, serum pH is normal, venous bicarbonate concentration is greater or equal to 20 mmol/L (mEq/L), and serum (or breath) ethanol concentration is undetectable. If treatment is not required they may be:
- Discharged into the care of a reliable observer, or
- Referred for psychological assessment (if the overdose was intentional)

Symptomatic patients may be considered for discharge once ethylene glycol concentrations are undetectable, or when all of the following criteria are met: serum pH is normal, venous bicarbonate concentration is greater or equal to 20 mmol/L (mEq/L), serum (or breath) ethanol concentration is undetectable, toxic sequelae have resolved, and ethylene glycol serum concentrations have declined to below 3.2 mmol/L (20 mg/dL). In some cases, patients may exhibit transient renal failure, requiring continuing dialysis. Furthermore, ongoing cranial nerve palsies may occur, but typically resolve within weeks to months. Rehabilitation may be required during this time.

FOLLOW UP

Standard protocols should be used for follow-up of patients suffering renal failure or CNS effects. Psychiatric intervention may be necessary depending on the circumstances of the exposure.

PROGNOSIS

Those patients surviving an initial severe acidosis may face oliguric renal failure and require regular hemodialysis for weeks to months.[18][31] Fortunately, recovery is expected and very few cases lead to permanent renal failure. The return of renal function is usually signified by an increase in urine output and concomitant decrease in serum creatinine.

Those who develop severe CNS manifestations, including seizures and coma, can recover full neurologic function. Cranial nerve palsies may occur in nerves II, V, VII, VIII, IX, and XII, typically resolving over weeks to months[9] though ongoing mild defects may persist.[7]

SIGNS AND SYMPTOMS

Symptoms following ethylene glycol ingestion can be divided into three acute stages or phases.[30][28][7][36] The severity of these stages and their progression from one to the other often depends on the amount ingested and other circumstances (e.g. ethanol co-ingestion). Death can occur in any of the

acute stages but most commonly the second stage.[18] Ethanol co-ingestion can delay the onset of toxic effects.[32] Low serum pH, decreased base excess, hyperkalemia at admission, seizures, and coma usually indicate a poor prognosis.[31]

Initial symptoms of ethylene glycol intoxication (0.5 to 12 hours after ingestion) are due to the direct toxicity of ethylene glycol. CNS effects predominate and include inebriation (without the alcohol odor on the breath), slurred speech, drowsiness, somnolence, hypotonia, hyporeflexia, ataxia, myoclonic jerks, and gastrointestinal upset. Mild metabolic acidosis may occur. In severe cases, seizures and coma may develop.[33] [30] [28] [37] [38] [39] [40] [28] [41]

In subsequent cardiopulmonary phases of intoxication (12 to 36 hours after ingestion), accumulation of acidic metabolites of ethylene glycol are responsible for the presenting abnormalities including high-anion gap metabolic acidosis and cardiopulmonary symptoms.[42] [30] [28] [39] The anion and osmolar gaps are usually increased, but may be within normal parameters in some patients.[29] [36] [39] In significant poisonings, severe metabolic acidosis with compensatory hyperventilation or Kussmaul respirations can develop.[7] [26] [43] Tachycardia, mild hypertension followed by hypotension, pulmonary edema, and congestive heart failure are all believed to be due to the deposition of calcium oxalate crystals within the vascular tree, myocardium, and the lung parenchyma.[28] [44] [45]

The renal phase of intoxication, beginning 24 to 48 hours after ingestion, is marked by oliguria, flank pain acute tubular necrosis, renal failure, and occasionally bone marrow suppression.[40] [26] [33] Hematuria and proteinuria are also possible.[33] [46] In severe poisonings, renal failure may appear early and progress to anuria.[40] [3] Renal symptoms may last up to 45 days or more.[18] Acute renal failure may prove permanent in a minority of cases.[32] Subacute cranial nerve palsies usually occur within 5 to 20 days and may persist for weeks to months.[7] [8] [9] [10]

Inhalation of ethylene glycol can cause upper respiratory tract irritation. Systemic effects are not expected unless it has been heated or aerosolized.[47]

Eye exposure to vapors or direct contact with the liquid may lead to eye irritation;[48] significant eye injury would not be expected.

Brief or occasional skin exposure is unlikely to cause harm to the skin but prolonged or repeated exposure may lead to significant irritation and sensitivity.[49] Skin absorption is limited, and systemic effects are unlikely to develop.[50]

Routes of Exposure

Symptoms predominantly occur following ingestion of ethylene glycol. However, toxicity is also possible via intravenous and intramuscular routes.

Onset/Duration of Symptoms

There are three acute stages[28] [41] [29] and one sequelae stage[9] [51] [52] [53] [36] [7] that may occur following ethylene glycol ingestion. Most deaths are reported in stage II but can occur at any of the stages.[54] The severity of these stages and their progression from one to the other often depends on the amount ingested and other circumstances (e.g. ethanol co-ingestion).

Stage I: Neurological Phase
- 0.5 to 12 hours post-ingestion
  - Inebriation
  - Nausea
  - Vomiting/hematemesis
  - Metabolic acidosis/elevated anion gap/elevates osmolar gap
  - Hypocalcemia
  - Calcium oxalate crystalluria

CNS depression
Coma
Stage II: Cardiopulmonary Phase
12 to 24 hours post-ingestion
Hypertension
Tachycardia
Tachypnea
Severe metabolic acidosis
Pulmonary edema
Congestive heart failure
Stage III: Renal Phase
24 to 72 hours post-ingestion
Proteinuria
Oliguria
Anuria
Acute tubular necrosis
Renal failure
Sequelae
Onset several (5 to 20) days after ingestion
Cranial nerve neuropathies

Severity of Poisoning

Mild Ethylene Glycol Toxicity	*Moderate Ethylene Glycol Toxicity*	*Severe Ethylene Glycol Toxicity*
Nausea Vomiting Ataxia Slurred speech Confusion Drowsiness	Mild metabolic acidosis Tachycardia Hypertension Hypocalcemia Calcium oxalate crystalluria Oliguria Hematuria Proteinuria	Pulmonary edema Anuria Hyperventilation/Kussmaul respirations Hyperkalemia Elevated anion and osmolar gaps Severe metabolic acidosis Seizures Acute kidney injury Multiple organ failure Cranial nerve defects Coma Death

ACUTE EFFECTS (ROUTE OF EXPOSURE)

INHALATION

Exposures via inhalation are rare due to the low vapor pressure of ethylene glycol at normal temperatures. However, when heated or aerosolized, exposures may occur. Upper respiratory tract irritation and cough have been reported.[47] Chronic inhalation has caused nystagmus, periods of unconsciousness, and lymphocytosis.[55]

SKIN

Ethylene glycol is slightly irritating to the skin.[56] [57] Repeated skin exposures may result in sensitivity including erythema and edema.[49] Dermal absorption is limited; acute contact is unlikely to produce systemic effects.[50]

EYE

There are limited human reports involving eye exposures to ethylene glycol. However, in animal

studies, direct eye contact may result in immediate eye irritation with temporary conjunctival inflammation and swelling. Significant corneal damage would not be expected.[48]

ACUTE EFFECTS (ORGAN SYSTEM)

NEUROLOGIC

Ataxia[58] [59] [26] [40] [60] [31] [33]
Slurred speech[58] [26] [9] [7] [60]
Confusion[58] [61] [38] [33] [62]
Somnolence[26] [63] [33] [31] [64]
CNS depression[30] [18]
Disorientation[60] [33] [58]
Agitation[62]
Dizziness[7] [33]
Strabismus[33] [30]
Headache[33] [51]
Dysarthria[65]
Hyporeflexia[33] [66]
Myoclonus[62]
Myoclonic jerks[33]
Hypotonia[43] [67]
Nystagmus[40] [26] [33] [9]
Dysthymia[58] [9]
Absent reflexes (deep tendon and plantar)[27] [67]
Acute Parkinson's syndrome[58] [30]
- Bradykinesia
- Cogwheel rigidity

Defects of cranial nerves V, VII, VIII, IX, X[9] [7] [53] [52] [36] [62] [26] [51]
- Dysphagia[58] [7] [53] [9]
- Hearing loss[53] [36]
- Ophthalmoplegia[9] [33]
- Strabismus[33] [30]
- Facial weakness/diplegia[9] [52] [36] [7] [9]
- Anisocoria (unequal pupil diameters)[68] [9]
- Absent gag reflex[53] [9]

Permanent deficit in gross and fine motor skill[29]
Cerebral edema[64]
Encephalopathy[18] [27]
Quadriparesis[40]
Seizures[33] [26] [37] [61] [29] [40] [27] [64] [30] [34] [31] [69]
Coma[7] [37] [40] [70] [34] [31] [27] [29] [43] [66] [33] [39] [36] [69]

METABOLIC

Metabolic acidosis (increased anion gap)[66] [67] [63] [38] [62] [61] [60] [29] [67] [32] [43] [46] [37] [39] [33] [18] [58] [70] [26] [69] [27] [40] [64]
Increased osmolar gap[31] [67] [63] [38] [61] [7] [59] [60] [18] [58] [70]
Hyperthermia[33] [46] [71]
Hypothermia[37] [34]
Hypoglycemia[37] [43]

NB. A normal anion or osmolar gap does not rule out ethylene glycol ingestion.[36] [29]

NB: With certain ethylene glycol assays, some metabolites can produce falsely elevated serum lactate

levels.[72]

RENAL

Elevated BUN[7] [43] [46] [36] [33] [63] [40]
Elevated creatinine[7] [43] [36] [40] [51]
Oliguria[27] [30] [60] [7] [32] [46] [31] [36] [39] [70]
Anuria[33] [73] [40] [37] [36] [39] [62] [7] [32] [34] [31] [26] [67] [27] [53]
Calcium oxalate crystalluria[29] [59] [63] [61] [37] [38] [39] [60] [33] [18] [26] [71] [74] [31] [70] [58] [27] [68] [64]
Hematuria[38] [30] [33]
Proteinuria[26] [46]
Albuminuria[30]
Dysuria[33]
Azotemia[33]
Incontinence[33]
Urinary tract infection[30]
Acute renal failure[32] [40] [62] [31] [26] [69] [71] [33] [63] [70] [9] [64]

RESPIRATORY

Hyperventilation/tachypnea[29] [30] [67] [65] [61] [60] [7] [67] [37] [33] [43] [46] [31] [66] [26] [27] [53] [63] [18]
Kussmaul respirations[7] [29] [37] [33] [43] [66] [26] [40]
Wheeze[39] [68]
Bradypnea[63] [39]
Hypoxia[71]
Pneumonia[33] [32]
Adult respiratory distress syndrome[35]
Non-cardiogenic pulmonary edema[32] [62] [33]

CARDIOVASCULAR

Tachycardia[61] [7] [43] [26] [59] [39] [62] [60] [33] [30] [67] [74] [71] [27] [40]
Hypertension[69] [38] [59] [62] [7] [29] [32] [31] [26] [37] [65] [33] [27]
Hypotension[34] [39] [32] [46] [37] [33] [30] [71] [40]
Bradycardia[18] [68]
QRS widening[34]
Cardiogenic pulmonary edema[71]
Cardiorespiratory arrest[43]

FLUID AND ELECTROLYTES

Hyperkalemia[31] [7] [43] [46] [67] [62] [33] [26]
Hypocalcemia[29] [32] [37] [60] [26] [51] [64]
Hyponatremia[62]
Hypernatremia[40]
Hypobicarbonemia[67]

GASTROINTESTINAL

Nausea[33] [63] [7] [46]
Vomiting[33] [65] [63] [30] [62] [7] [53]
Hematemesis[30]
Sialorrhea[58]
Abdominal pain[33] [62] [7] [46] [36]

OCULAR

Mydriasis/poorly reactive pupils[29] [74] [69] [75] [9] [33] [67] [39] [62] [67] [46] [27] [9]
Decreased visual acuity[75] [51]
Blurred or edematous optic discs[33] [75] [51] [9]
Miosis[43]

MUSCULOSKELETAL

Myalgia (muscle pain)[26] [33]
Increased creatine kinase (CK)[26] [71]
Rhabdomyolysis[66]

HEPATIC

Elevated ALT[34]
Bilirubinemia[33]

HEMATOLOGIC

Leukocytosis[43] [30] [40] [64]
Anemia[70] [33]
Thrombocytopenia[70]
Methemoglobinemia[46]
Bone marrow arrest[40]
Disseminated intravascular coagulation[34]

CHRONIC EFFECTS

GENERAL EFFECTS

Chronic exposures to ethylene glycol vapor may result in nystagmus, unconsciousness, and lymphocytosis.[55]

TOXICITY

HUMAN

ACUTE

The toxic dose is variable in humans. The minimum lethal dose is considered approximately 90 to 100 mL, although cases of death were reported with just 30 mL of the concentrate in adults,[57] and survival occurring with ingestions of 3 to 4 litres.[63] [38] [76]

Ethylene glycol serum concentrations are not a predictor of toxicity due to metabolism to more toxic metabolites. Patients with low arterial blood pH, severe metabolic acidosis, hyperkalemia, seizures, and/or coma are at a high risk of death.[31] Co-ingestion of ethanol may delay toxic effects.[32]

Medical assessment is warranted for any ingestion of pure ethylene glycol greater than a witnessed lick or taste in a child or more than a 'swallow' (10 to 30 mL) in an adult. For ingestions of lower concentration products (<20%), any ingestion greater than 0.1 mL/kg of pure substance equivalent warrants referral.[77]

CASE STUDIES

Child

100 mL ethylene glycol(ingested)
- 2 year male: initially vomited and found unconscious the following morning. On arrival was semi-conscious, hyperventilation, tachycardia, and hypotension. Hematemesis, oliguria, hematuria, albuminuria, decreased serum bicarbonate, metabolic acidosis, and elevated BUN occurred. Later developed seizures and had athetoid movements
  - Supportive care, including IV calcium gluconate, ethanol infusion, frusemide, peritoneal dialysis, diazepam, and phenobarbitone
    - Recovered after 17 days[30]

Unknown amount of antifreeze(ingested)
- 6 year female: presented with metabolic acidosis, responsive to pain only, tachycardia, tachypnea, hypertension, emesis, and crystalluria. Elevated anion gap, lactate, sodium, chloride, and glucose were present. Nystagmus developed following fomepizole administration. Polyuria developed at 18 hours. Serum ethylene glycol concentration was 13 mg/dL 3 hours post-admission.
  - Supportive care, including oxygen, IV saline, sodium bicarbonate, IV cefotaxime, pyridoxine, thiamine, fomepizole, hemodialysis, and electrolyte supplementation
    - Recovered and discharged after 2 days[78]

Adult

29.5 mL Antifreeze(ingested)
- 17 year male: dizziness, incoordination, confusion, dysuria, nausea, abdominal pain, emesis, tenderness in upper right quadrant, and calcium oxalate crystals in urine. Impaired renal function with elevated BUN developed on day 3. On day 7 developed azotemia, acidosis, and anemia
  - Supportive care
    - Recovered and discharged after 7 days[33]

~30 mL Ethylene glycol(ingested)
- 33 year male: inebriation, slurred speech, hallucinations, vomiting, unconscious, pale, cyanosis, miosis and failed to react to light, hypotension, nystagmus, fever, and anuria
  - Supportive care, including blood transfusion, nicetamide, sympatol, and strophantin
    - Fatal after 48 to 60 hours[57]

~30 mL Ethylene glycol(ingested)
- 42 year male: vomiting, pupils failed to react to light, anuria, coma, Kussmaul respiration, hypotension, and absent reflexes
  - Supportive care
    - Fatal after 144 hours[57]

59 mL Ethylene glycol(ingested)
- 17 year male: disorientation, unable to ambulate, urinary incontinence, and calcium oxalate crystals in urine. On day 3 developed elevated BUN
  - Supportive care
    - Recovered and discharge after 9 days[33]

100 mL antifreeze solution(ingested)
- 13 year old female: within 30 minutes developed tachycardia, hypertension, and elevated pO2. Ataxia and dysarthria also developed. Urinalysis revealed calcium oxalate crystals. Serum ethylene glycol concentration was 103 mg/dL
  - Supportive care, including IV ethanol, orotracheal intubation, and IV fomepizole
    - recovered and discharged after three days[59]

88 to 118 mL Ethylene glycol(ingested)
- 17 year female: Within 36 hours presented with confusion, seizures, semi-comatose state, vomiting, metabolic acidosis, and hyperkalemia. Later developed cyanosis, hypotension, mild tachycardia, tachypnea with Kussmaul respirations, myoclonic jerks, mydriasis and pupils unreactive to light, papilledema, hypoactive deep tendon reflexes, and pulmonary edema
  - Supportive care, including oxygen, IV dextrose, hemodialysis, ascorbic acid, and methylene blue

Fatal after 47 hours[33]

118 mL Ethylene glycol(ingested)

17 year male: Within 48 hours developed fatigue, headache, blurred vision, nausea, confusion, ocular palsy, anuria, bilateral ophthalmoplegia, and hypertension. Later developed bronchopneumonia, renal failure, and calcium oxalate crystals deposits

Supportive care, including lumbar puncture, potassium, sorbitol, and hemodialysis

Fatal after 17 days[33]

150 mL ethylene glycol windscreen wash solution(ingested)

69 year male: GCS of 6, sluggish pupils, reduced muscle tone, tachypnea, severe metabolic acidosis, elevated BUN, elevated creatinine, increased anion and osmolar gap, anuria, and supraventricular tachycardia. Serum ethylene glycol concentration was 100 mg/dL

Supportive care, including intubation, ventilation, IV fluids, sodium bicarbonate, IV ethanol, IV fomepizole, hemofiltration, and amiodarone

Recovered and discharged on day 30.[67]

450 mL antifreeze solution(ingested)

60 year old male: coma, Kussmaul respirations, hypotension, hypothermia, hyperglycemia, metabolic acidosis, hyperventilation, hypertension, hypocalcemia, calcium oxalate crystals in urine, aspiration, anuria, elevated creatinine, and seizure

Supportive care, including IV saline and glucose, sodium bicarbonate, oxygen, resuscitation, intubation, ventilation, insulin, dobutamine, crystalloid & colloids, epinephrine (adrenaline), norepinephrine (noradrenaline), calcium chloride, mannitol, frusemide, ethanol infusion, hemofiltration, diazepam, and phenytoin

Fatal[37]

1,000 mL antifreeze solution(ingested)

48 year male: dysarthria, emesis, hypertension, tachypnea, hypoxia, and increased anion gap. Serum ethylene glycol concentration was 700 mg/dL

Supportive care, including oxygen and fomepizole

Recovered and discharged after 4 days[65]

3,000 mL antifreeze solution(ingested)

36 year male: nausea, vomiting, increased drowsiness, somnolence and became progressively lethargic and bradypneic. Increased anion gap and osmolar gap developed. Urinalysis revealed moderate calcium oxalate crystals. Mild pulmonary edema and non-oliguric acute kidney failure developed after 72 hours. Serum ethylene glycol concentration was 1,889 mg/dL

Decontamination and supportive care, including gastric lavage with activated charcoal and magnesium citrate, IV administration thiamine, pyridoxine, magnesium sulfate, sodium bicarbonate, ethanol infusion, and hemodialysis

Recovered and discharged after 3 days[63]

3,785 mL antifreeze and an unknown amount of ethanol(ingested)

33 year male: mildly intoxicated. Serum ethylene glycol concentration was 706 mg/dL

Supportive care, including fomepizole

Recovered and discharged after 4 days[76]

~4,500 mL antifreeze solution(ingested)

58 year old male: confusion, metabolic acidosis with increased anion and osmolar gap, decreased BUN, and calcium oxalate crystals in urine. Serum ethylene glycol concentration was 791 mg/dL

Supportive care, including activated charcoal, IV ethanol, intubation, and hemodialysis

Recovered after 3 to 5 days[38]

ANIMAL

ACUTE

Ethylene glycol poisoning in animals is relatively common as it has a sweet taste and looks like water. Relatively low amounts of water drained from radiators containing ethylene glycol may cause toxicity.

Symptoms in animals are similar to those seen in humans and follow similar stages of toxicity, although

excluding the neurological sequelae of poisoning seen in humans. Symptoms in cats and dogs include ataxia, vomiting, diarrhea, disorientation, bradycardia, hypothermia, metabolic acidosis, and acute kidney injury.[79] In birds, ataxia, weakness, depression, and flaccid paralysis can occur. Calcium oxalate deposits in the renal tubules have also been noted.[80] [81]

In dogs, peak plasma ethylene glycol concentrations occur 2 hours post-ingestion.[79] Peak glycolic acid plasma concentrations occur at 4 hours.[79]

The sooner antidotal therapy is commenced, the better the outcome.[82] Cats have the best chance of survival following a lethal dose if the antidote is started within 3 hours of ingestion,[83] whereas dogs can have the antidote started within 6 to 8 hours of ingestion.[79] Recovery may take 3 to 5 days.[83] The antidote is only effective at blocking ethylene glycol metabolism, therefore, there is no benefit of administering it if the ethylene glycol is already metabolized or if the animal has renal failure. Prognosis is poor if the animal presents in the final stage of poisoning, with symptoms of renal failure or coma.[82] Hemodialysis can be considered in severe cases.[84]

Ethylene Glycol:

LD50 Oral, Rat	4,000 to 10,020 mg/kg[85] [1]
LD50 Oral, Mouse	5,500 to 8,350 mg/kg[85]
LD50 Oral, Guinea pig	6,610 mg/kg[1]
LD50 IP, Rat	5,010 mg/kg[85]
LD50 IP, Mouse	5,614 mg/kg[85]
LD50 SC, Rat	2,800 mg/kg[85]
LD50 IV, Rat	3,260 mg/kg[85]

BIOLOGICAL LEVELS - TOXIC

SI Unit Conversion

To convert an ethylene glycol concentration expressed in mg/dL into mmol/L:
Multiply the mg/dL by 0.1611

To convert an ethylene glycol concentration expressed in mmol/L into mg/dL:
Multiply the mmol/L by 6.2070

Units: 1 dL = 0.1 L
1 ug/L = 0.1 ug/dL
1 ug/dL = 10 ug/L

Toxic Plasma Level

Plasma Ethylene Glycol Concentration

Serum ethylene glycol concentrations at admission are not predictive of outcome. Low serum pH, high anion gap, and low base excess, indicative of accumulation of toxic metabolites, do predict outcome.[31]

Ethylene Glycol Toxic Plasma Concentrations from Case Reports

103 mg/dL (1 hour post ingestion)
After approximately 120 mL of antifreeze orally, a 13 year old female had ataxia, dysarthria, and calcium oxalate crystals in urine[59]
700 mg/dL (time of ingestion unknown)
After approximately 1,000 mL of antifreeze orally, a 48 year old male had dysarthria, emesis, and metabolic acidosis with a

high anion gap[65]

888 mg/dL (3 hours post ingestion)

After an unknown amount of ethylene glycol was ingested a 28 year old male was comatose with hyperventilation, calcium oxalate crystals in urine, and acute renal failure[18]

1,889 mg/dL (5 hours post ingestion)

After approximately 3,000 mL of antifreeze orally, a 36 year old male had nausea, emesis, lethargy, bradypnea, metabolic

acidosis, calcium oxalate crystals in urine, and acute kidney failure[63]

Osmolar Gap

The osmolar gap represents the difference between the measured osmolality (osmoles per kilogram solvent) and calculated osmolarity (osmoles per liter of solution).[86] [3] When positive, it may indicate the presence of low molecular weight compounds such as alcohols and glycols. A normal osmolar gap does not reliably rule out the presence of a toxic alcohol in the blood stream.

OSMOLALITY

Serum osmolality is generally in the range 270 to 290 mOsm/kg H2O, and should be measured by freezing point depression.[38]

OSMOLARITY

The osmolarity may be calculated using SI units or using Mass (traditional) units.

Osmolarity Calculation Using SI Units

Osmolarity = 2 x sodium[mmol/L] + glucose[mmol/L] + urea[mmol/L] + ethanol[mmol/L]

Urea = BUN (blood urea nitrogen)
Include ethanol if found on serum measurement

Osmolarity Calculation Using Mass (traditional) Units[87]

Osmolarity = (2 x sodium[mEq/L]) + (glucose[mg/dL] /18) + (BUN[mg/dL]/2.8) + (ethanol[mg/dL]/4.6)

BUN = urea
Include ethanol if found on serum measurement

These equations should also include other compounds such as ethanol or mannitol, if present. This calculation should be undertaken in the earlier phases of intoxication prior to the metabolic removal of alcohols and glycols.

OSMOLAR GAP CALCULATION

Osmolar gap = Measured Osmolality - Calculated Osmolarity

The mean normal osmolar gap has been determined to be approximately < 10 or 15 mOsm/kg H2O (though this range will vary between laboratories).[38] However, there exists considerable variation in osmolar gaps between individuals. Hence, a 'normal' osmolar gap does not rule out the presence of an alcohol or glycol.[87] The osmolar gap is most useful in suggesting the presence of suspected glycol or alcohol ingestion when it is significantly elevated (usually > 20 to 30 mOsm/kg).

Anion Gap

The anion gap represents the difference between the sum of measured cations and the sum of

measured anions. An elevated anion gap indicates the presence of unmeasured organic acids (including products of the metabolism of alcohols or glycols).

ANION GAP CALCULATION[88]

Anion gap = [([sodium]) − ([bicarbonate] + [chloride])]

Potassium is normally omitted from the calculation because its range is relatively small and constant.

All units should be expressed as mmol/L.

A "normal" anion gap may be considered to be within the range of 3 to 15.[88]

REPRODUCTION

PREGNANCY

There are limited studies of ethylene glycol in pregnant women. A 26 week pregnant patient who ingested ethylene glycol underwent a cesarean section due to fetal asphyxia. Following birth the neonate was intubated and required artificial lung ventilation. The child had metabolic acidosis and was treated with forced diuresis and replacement transfusion. The baby was extubated at 2 weeks and discharged after 3.5 months with no significant neurological complications.[69] Pregnant female workers potentially exposed to industrial mixtures containing ethylene glycol ethers had increased risk of spontaneous abortion and subfertility.[89]

In animal studies the metabolite glycolic acid is responsible for developmental toxicity in rats rather than ethylene glycol itself.[90] Low level exposures of ethylene glycol do not saturate glycolic acid metabolism so have a low risk of development effects.[91] Both ethylene glycol and glycolic acid decreased fetal body weights and axial skeleton malformations in rats.[90]

Ethylene glycol has been shown to be teratogenic in animals. Teratogenicity was observed in the absence of maternal toxicity in both rats and mice. Effects in mice include reduced number of live pups, decreased pup weight, and skeletal malformations (fused ribs, abnormally-shaped or missing vertebrae, and twisting of the spine).[92] Similar effects were noted in rats receiving doses of 2,500 to 5,000 mg/kg/day.[93] [92] At these doses, severe malformations including craniofacial abnormalities, neural tube defects (anencephaly, meningomyelocele), and visceral malformations were observed.[92]

LACTATION

It is unknown whether this compound is excreted in human breast milk.

TOXIC MECHANISM

The major toxic agent in ethylene glycol poisoning is not the parent compound, but the metabolites produced by the action of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH).[94]

Ethylene glycol is rapidly metabolized via ADH into glycoaldehyde, which is rapidly converted into glycolic acid by ALDH. The rate-limiting step in the metabolism of ethylene glycol is the formation of glyoxylic acid from glycolic acid via lactate dehydrogenase or glycolic acid dehydrogenase. Glyoxylic acid can be either metabolized into non-toxic alpha-hydroxy-beta ketoadipate and glycine via thiamine and pyridoxine-dependent ways respectively, or into oxalate.[95] [18]

The etiology and pathophysiology of the CNS, metabolic, cardiopulmonary, and renal toxicity are primarily due to the formation and accumulation of toxic intermediary metabolites, especially glycolic acid (produces metabolic acidosis)[44] and to a lesser but histologically important extent, oxalate production, and excretion.[45] [44] [28] Calcium oxalate crystals may form in tissues, in particular the

renal tubules, lungs, and the meninges of the brain, and excreted in the urine.[44] [28]

KINETICS

ABSORPTION

Oral Absorption
Rapid
Onset of Action
CNS effects may occur within 30 minutes[28]
Time to Peak Plasma Levels
1 to 4 hours[41]

DISTRIBUTION

Volume of Distribution
During hemodialysis: 0.5 to 0.67 L/kg[38] [24]

METABOLISM

Metabolism
Hepatic[2]
Metabolites
Glycoaldehyde[41]
Glycolic acid[41] [94]
Glyoxylic acid[41]
Oxalate[41]
Major Metabolic Pathways
Parent:
Via alcohol dehydrogenase to glycoaldehyde[41] [2]
Glycoaldehyde :
Metabolized to glycolic acid with subsequent conversion to glyoxylic acid and oxalate[41] [2]

ELIMINATION

Excretion
Urine
20% excreted unchanged in urine[2] [3]
Half-life
Overdose
Ethylene glycol: 3 to 3.79 hours[23] [38]
Ethylene glycol with ethanol: 17 to 18 hours[23] [38]
Ethylene glycol with hemodialysis: 2.5 to 3.5 hours[23] [38]
Ethylene glycol with fomepizole: 11 to 20 hours[96] [25] [76]
Potential for Accumulation
Calcium oxalate crystals can accumulate in the kidney leading to renal damage and renal failure[41]

IDENTIFICATION

OTHER NAME(S)

Common Names

1,2-Ethaandiol	1,2-Ethandiol	1,2-Ethanediol
2-Hydroxyethanol	Antifreeze	Athylenglykol
Coolant	Deicer	EG
Etandiol	Ethane-1,2-diol	Ethylene alcohol
Ethylene dihydrate	Ethylene glycol	Ethylenglycol
Etilenglicol	Etilenglikol	Etilenoglicol
Etyleeniglykoli	Glicole etilenico	Glikol etylenowy
Glycol	Glycol alcohol	Glycolmonomer
Lutrol-9	M.E.G	Monoethylene glycol
Radiator fluid	Ramp	Ucar 17

Chemical Name

Ethylene Glycol:
1,2-Ethanediol

CODES

CAS NUMBER

Ethylene Glycol:
107-21-1

MOLECULAR FORMULA

Ethylene Glycol:
$C_2H_6O_2$

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