

# Ethylene Glycol is a Poison

Ethylene glycol ingestion first affects the central nervous system (CNS). After a characteristic latent period, signs of inebriation may be followed by serious illness and even death, caused by toxic metabolites.

Ethylene glycol is rapidly absorbed from the gastrointestinal tract and slowly absorbed through the skin or lungs. The toxicity of ethylene glycol results from its metabolism to more toxic metabolites. Like ethanol, ethylene glycol is rapidly absorbed in the GI tract, with peak absorption in 30-60 minutes.

Because it is highly water-soluble, ethylene glycol is distributed throughout total body water. Peak tissue levels occur several hours after ingestion. Approximately 24 to 48 hours later, it is difficult to detect ethylene glycol in urine or tissues, thus indicating rapid biotransformation.

The normal serum half-life of ethylene glycol has been estimated to be about 2.5 hours in children and 3-8 hours in untreated adults.

Other than its inebriating effects, ethylene glycol is metabolized in the liver by successive oxidations to a variety of compounds that include

- glycoaldehyde
- glycolic acid
- glyoxylic acid
- oxalic acid

These compounds are more toxic than ethylene glycol itself. Some of these compounds have elimination half-lives of up to 12 hours.

The main toxicity results from hepatic metabolism of ethylene glycol to glycoaldehyde, glycolate, glyoxylate, and oxalate. These metabolites inhibit

- oxidative phosphorylation and cellular respiration
- glucose and serotonin metabolism
- protein synthesis
- DNA replication
- ribosomal RNA formation

The accumulation of organic acid metabolites, especially glycolic acid, results in anion gap metabolic acidosis which affects many cellular functions.

Severe ethylene glycol poisoning may go through three stages: CNS depression, cardiopulmonary toxicity, and renal toxicity

## Stage 1 (CNS depression phase)

CNS depression begins soon after exposure, lasting for up to 12 hours after ingestion. This depression appears similar to ethanol intoxication, but without the characteristic odor of alcohol. Initially, the inebriation, euphoria, slurred speech, sleepiness, and so forth are due to the unmetabolized ethylene glycol.

After the glycoaldehyde forms (at 4-12 hours) and metabolic acidosis begins, CNS depression—if it is a serious intoxication—can lead to the following effects:

- seizures

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- coma
- cerebral edema (in some cases)
- gastrointestinal irritation (nausea and vomiting)

## Stage 2 (Cardiopulmonary toxicity phase)

The following cardiorespiratory symptoms may appear 12-24 hours after ingestion

- tachycardia,
- tachypnea, and
- hypertension or hypotension.

The following conditions may develop in this stage

- pulmonary edema,
- pneumonitis,
- congestive cardiac failure, and
- shock.

Formation of oxalic acid may lead to deposition of calcium oxalate crystals in

- the meninges,
- blood vessel walls,
- lung, and
- myocardium.

These deposits can cause tissue injury. They also may lead to hypocalcemia secondary to calcium oxalate precipitation. Most deaths from ethylene glycol poisoning occur during stage 2.

## Stage 3 (Renal toxicity phase)

Kidney damage usually develops 24-72 hours after exposure. Acidosis and acute renal failure may result from deposition of calcium oxalate crystals in the kidneys.

The following conditions characterize the third phase

- flank pain,
- costovertebral angle tenderness, and
- oliguric renal failure.

Prolonged, rarely permanent, kidney failure is distinguished by

- proteinuria,
- hematuria,
- crystalluria, and
- increased serum BUN and creatinine.

Calcium oxalate crystals may appear in the urine as early as stage 1, but absence of these crystals does not rule out the diagnosis of ethylene glycol poisoning

## Neurologic Effects

The initial phase of ethylene glycol poisoning is characterized by inebriation caused by unmetabolised ethylene glycol. In acute poisoning cases, the following symptoms are common ataxia

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- slurred speech
- drowsiness
- irritation
- restlessness
- disorientation

Possible sequelae of severe poisonings include

- myoclonic jerks
- convulsions
- coma
- death

Cerebral edema and deposition of calcium oxalate crystals in the walls of small blood vessels in the brain contribute to this CNS toxicity. Some studies also documented brain dysfunction with corresponding cranial computed tomography findings after ethylene glycol ingestion.

## Cranial Nerve Damage

Recovery in survivors is usually rapid and complete. However, the following cranial nerve palsies have been reported one or more weeks after acute exposure

- facial palsy
- hearing loss
- dysphagia
- ophthalmoplegia
- visual disturbances

## Respiratory Effects

Inhaled ethylene glycol can irritate the respiratory tract.

- Throat and upper respiratory irritation were the most common complaints following prolonged experimental exposures in humans (4 weeks at concentrations of 1-25 ppm).
- Exposure to 60 ppm aerosolized ethylene glycol caused very noticeable irritation.
- Exposure to 80 ppm aerosolized ethylene glycol was judged “intolerable” because respiratory discomfort developed rapidly.

Pulmonary effects typically occur 12 to 72 hours after ingestion of ethylene glycol. Pulmonary edema and adult respiratory distress syndrome (ARDS) have been reported in ethylene glycol victims.

The following respiratory effects often occur 12 hours or more after exposure in victims of severe ethylene glycol poisoning.

- tachypnea,
- hyperventilation,
- Kussmaul respirations.

Such effects most often reflect physiological compensation for severe metabolic acidosis rather than primary lung disease .

Autopsies of ethylene glycol victims revealed the following

- pulmonary edema with diffuse hemorrhagic exudates,
- bronchopneumonia (probably caused by aspiration), and

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- deposits of calcium oxalate crystals in lung parenchyma.

## Cardiovascular Effects

The following severe cardiovascular effects have been reported in ingestion victims, during stage 2 :

- Congestive heart failure with cardiogenic pulmonary edema
- Circulatory collapse

Severe metabolic and fluid electrolyte abnormalities may cause

- cardiac dysrhythmias
- cardiac arrest

Ingestion of antifreeze may affect blood pressure, causing either

- hypertension or
- hypotension, which may progress to cardiogenic shock.

## Metabolic Effects

Severe ethylene glycol poisoning is characterized by metabolic acidosis.

- Onset occurs within 24 hours after ingestion.
- Acidosis is caused primarily by the accumulation of glycolic and glyoxylic acid. Oxalic and excess lactic acid also contribute.

The metabolic acidosis of ethylene glycol poisoning is characterized as normochloremic with

- low serum bicarbonate level and pH and
- elevated acidemia and anion gap.

Ethylene glycol is a small, osmotically active molecule that

- markedly increases plasma osmolality and
- causes a large osmolal gap.

Osmolality reflects the number of solute particles in a solution. Numerical measures of osmolality express the number of particles present in a given weight of solvent.

Tetany can sometimes occur due to hypocalcemia that results from precipitation of calcium by the oxalate formed during ethylene glycol metabolism.

## Renal Effects

Kidney damage typically occurs during stage 3 of ethylene glycol intoxication.

- Kidney damage manifests as acute oliguric renal failure.
- Costovertebral angle tenderness is the most common physical finding?
- The most characteristic abnormality is the presence of large numbers of “tent-shaped” (octahedral) or needle-shaped oxalate crystals in the urine.
- Absence of oxalate crystals does not rule out the diagnosis of ethylene glycol poisoning .

Other typical urinalysis abnormalities are

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- low specific gravity
- proteinuria
- microhematuria
- pyuria
- elevated serum BUN and creatinine

Disturbed renal function may be mild and short-lived or severe and persistent for several months. Permanent renal insufficiency is uncommon but does occur .

The toxicity of ethylene glycol is linked with two metabolites.

- Glycolic acid, which causes the acidosis.
- Oxalic acid.
  - Oxalic acid is poorly soluble in the presence of calcium.
  - Calcium oxalate crystals in the urine are diagnostic.
  - The precipitation of oxalate crystals in the tubular lumen leads to luminal blockage and compression-induced loss of glomerular filtration (renal failure).

In transformed kidney cells, the oxalate ion induces cytotoxic damage. Another study, however, stated that glycoaldehyde and glyoxylate are the principal metabolites responsible for ethylene glycol nephrotoxicity.

## Key Points

Signs of inebriation are among the first symptoms to appear after ethylene glycol ingestion.

Delays in initiating treatment can result in more severe adverse effects.

The most common cause of tachypnea is uncompensated metabolic acidosis.

Ethylene glycol poisoning through ingestion can cause noncardiogenic pulmonary edema and ARDS.

Ethylene glycol poisoning can cause dysrhythmias and heart failure.

Ethylene glycol exposure is characterized by an osmolal gap and a metabolic acidosis with an elevated anion gap.

Nephrotoxicity is the dominant effect of significant ethylene glycol poisoning.

## How Should Patients Exposed to Ethylene Glycol Be Treated?

Treatment should not be delayed pending results of ethylene glycol serum levels if the patient's condition or history suggests such poisoning. Treatment advice can be obtained from a regional poison control center or medical toxicologist.

When the ingestion is recent, take steps to prevent ethylene glycol absorption.

- Induced emesis or gastric lavage may be useful if
  - ingestion occurred within 2 hours
  - the patient has a normal level of consciousness
- Activated charcoal adsorbs ethylene glycol poorly and is probably not effective in this setting

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Specific treatment for ethylene glycol poisoning includes

- sodium bicarbonate to correct the metabolic acidosis as indicated,
- ethanol or fomepizole (Antizol) to competitively inhibit metabolism of ethylene glycol to its more toxic metabolites, and
- hemodialysis, if indicated, to remove ethylene glycol and glycolic acid.

This treatment strategy is effective in most cases, but renal failure and death can occur if treatment is delayed.