Ethylene Glycol Poisoning

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Questions to Answer

- How does ethylene glycol present
- How does the presentation differ from uremia
- How do you treat it?
Outline

- Sources
- Pharmacology
- Metabolism
- Lab Findings
- Diagnosis
- Treatment
Sources

- Antifreeze
- Brake fluids
- Industrial solvents
Pharmacology

- Dihydric alcohol
- Odorless, colorless, water soluble, sweet tasting ("the sweet killer")
- Molecular Weight 62 kDa
Metabolism

- Absorption
- Excretion
Absorption

- Readily absorbed from the GI tract within 30-60 minutes
- Maximal blood concentration reached in 1-4 hours
- 1/2 life is 3-8 hours
- Lethal dose is estimated as 1-1.5 mls/kg or 100mls
Metabolism/ Excretion

- Liver
- Kidney
Liver

- Metabolizes 80% of what is absorbed
- Half life with liver metabolism is 3-8 hours
Liver Continued

- Broken down in the liver by alcohol dehydrogenase to four compounds.
- Glycoaldehyde which is metabolized by aldehyde dehydrogenase to glycolic acid, which is metabolized to glyoxylic acid, which is metabolized to oxalic acid.
Ethanol 4-MP $\rightarrow$ Alcohol dehydrogenase $\rightarrow$ Ethylene glycol $\rightarrow$ NAD$^+$, NADH + H$^+$, Lactate $\rightarrow$ Glycoaldehyde $\rightarrow$ Pyruvate.

Aldehyde dehydrogenase $\rightarrow$ Glycolic acid $\rightarrow$ Metabolic acidosis.

$\ast$ Glyoxylic acid $\rightarrow$ Malate $\rightarrow$ Inhibition of TCA cycle and lactic acidosis.

Oxalic acid $\rightarrow$ Calcium oxalate $\rightarrow$ Tissue deposition.
Liver Continued

- The conversion of glycolic acid to glycoxylic acid is the rate limiting step.

- These metabolites are oxidative phosphorylation toxins that cause CNS depression and cardio-pulmonary and renal failure.
Kidney

- The proximal tubule reabsorbs 80% of what is filtered
- Half life with renal metabolism is 18-20 hours
- The remaining 20% is excreted unchanged from the kidneys
Clinical Presentation

- **Neurologic:** 30 minutes to 12 hours
- **Cardiopulmonary:** 12-36 Hours
- **Renal:** 24-72 Hours
Neurologic

- CNS manifestations: Somnolence, Disorientation, agitation, confusion, ataxia (pt may appear drunk)
  
  - Pathophysiology: Initially a direct effect of ethylene glycol, which in low doses causes euphoria and in high doses causes CNS depression
Deeper CNS Symptoms: Stupor, coma, nystagmus, ocular paresis, myoclonus and focal or universal seizures

- Results from high dose of ethylene glycol
- Results from calcium oxalate desposition in the brain
Cardiopulmonary Cont.

- Leukocytosis
- Seizures
  - Direct effect of the calcium oxalate
  - May also result from hypocalcemia
- Heart failure
  - Arrhythmias result from hypocalcemia and acidosis
Cardiopulmonary Cont.

- **Respiratory Distress**
  - As compensation for metabolic acidosis and from the hypoxia

- **Tachycardia, HTN, Dyspnea, Tachypnea, Kussmaul’s Respiration**
  - As compensation for metabolic acidosis and from hypoxia
Renal

- Will get flank pain, renal tubular necrosis, hematuria, proteinuria, anuria or oliguria
  - Thought to result from calcium oxalate blocking the renal tubules
  - Calcium oxalate is internalized by the proximal tubule causing mitochondrial damage, and resulting in ATN
Renal Continued

- Calcium oxalate monohydrate crystals adhere to the proximal tubule membrane and are endocytosed within 30 minutes.
- Once they enter the proximal cell, calcium oxalate can inhibit the electron transport chain.
COM can also lead to the mitochondrial permeability transition (MPT) which increases the permeability of mitochondria:

- Molecules up to 1500 kDa can enter the mitochondria.
- Causes depolarization, inhibition of ox phos, and ATP depletion.
Cranial Nerve Abnormalities

- Occur with the ingestion of at least 100 cc of ethylene glycol
- Occur 6-18 days after the ingestion of ethylene glycol
- Postmortem studies attribute this to inflammation around the nerve from oxalate microcrystal deposition
Type of treatment is immaterial in terms of

Full recovery may take a year
Laboratory Findings

- High osmolarity with osmolar gap
  - Ethylene glycol and glycoaldehyde increase serum osmolarity
  - Occurs early on, may disappear later as ethylene glycol and glycoaldehyde are metabolized
Ethanol + 4-MP → Alcohol dehydrogenase → Ethylene glycol → Alcohol dehydrogenase → Glycoaldehyde → NAD⁺ → NADH + H⁺ → Pyruvate → Lactate

Glycoaldehyde → Aldehyde dehydrogenase → Glycolic acid → Metabolic acidosis

Glycolic acid → Glyoxylic acid → Malate → Inhibition of TCA cycle and lactic acidosis

Glyoxylic acid → Oxalic acid → Calcium oxalate → Tissue deposition
High anion gap metabolic acidosis

- Partially because of glycolic acid
  - Because the conversion of glycolic acid to glycoxilic acid is the rate limiting step, glycolic acid is able to build up
High anion gap metabolic acidosis

- Partially because lactic acidosis
  - The first two steps in ethylene glycol metabolism cause the reduction of NAD to NADH. The elevated NADH to NAD ration causes the conversion of pyruvate to lactate
Calcium oxalate crystals

- Appear in the urine 4-8 hours after ingestion
- May appear as either an elongated crystal (monohydrate) or octahedral like a pyramid
- Will deposit in almost every tissue of the body including the brain, heart, lungs, kidneys, and urine
FIGURE 3. Calcium oxalate dihydrate crystals.
FIGURE 2. Calcium oxalate monohydrate crystals.
Table 2. Comparison of Laboratory Features Seen in Patients Presenting Early and Later in the Course of Ethylene Glycol Poisoning

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Early</th>
<th>Late</th>
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</thead>
<tbody>
<tr>
<td>Anion gap</td>
<td>Normal or mildly increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Osmolal gap</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum ethylene glycol</td>
<td>Detectable</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Oxalate crystalluria</td>
<td>May be present*</td>
<td>May be present†</td>
</tr>
<tr>
<td>Kidney function</td>
<td>Normal or mild AKI</td>
<td>Severe AKI</td>
</tr>
</tbody>
</table>

*May be seen 4 to 8 hours after ethylene glycol ingestion, up to 40 hours in the absence of acute kidney injury (AKI).
†Present up to 4 days with AKI.
Further Metabolic Abnormalities

- Hypocalcemia:
  - Caused by precipitation of oxalate

- Hyperkalemia:
  - Caused by renal failure
Diagnostic Tests

- Flourescin is added to antifreeze and can be detected by Wood’s light, but is cleared within 4 hours of ingestion.

- Serum ethylene glycol levels can disappear after 5 days, whereas urine ethylene glycol levels persist for 17 days.
Treatment

- Inhibit Absorption
- Correct Acidosis
- Inhibition of Metabolism
- Elimination of parent compound and the metabolites
Inhibit Absorption

- Gastric Treatment:
  - Gastric aspiration followed by lavage useful up to 1 hour after ingestion
  - Syrup of ipecac contraindicated because of aspiration
  - Activated charcoal: Not helpful
Treatment of Acidosis

- **Bicarb drip:**
  - Used to increase the bicarb, but also by increasing the urine pH will promote the excretion of glycolic acid and lactic acidosis
Inhibition of Metabolism

- Fomepizole (4-methylpyrazole)
- Ethanol
- Thiamine
- Pyridoxine
Fomepizole (4-methylpyrazole)

- Mechanism of Action:
  - Competitive inhibitor of alcohol dehydrogenase, alcohol dehydrogenase has 500-1000 times the affinity than for ethylene glycol.
Ethanol → Alcohol dehydrogenase → NAD$^+$
Ethylene glycol → NADH + H$^+$ → Lactate
Glycoaldehyde → Aldehyde dehydrogenase → Glycolic acid → Metabolic acidosis
Glycolic acid → Glyoxylic acid → Malate → Inhibition of TCA cycle and lactic acidosis
Glyoxylic acid → Oxalic acid
Oxalic acid → Calcium oxalate
Calcium oxalate → Tissue deposition
Fomepizole (4-methylpyrazole) Cont.

- Loading dose is 15mg/kg in 100 mls of NS or D5W infused over 30 minutes
- Next 10mg/kg every 12 hours for two days
- Next 15mg/kg every 12 hours until the ethylene glycol level is less than 2 and pt. asymptomatic with a normal pH
Fomepizole (4-methylpyrazole) Cont.

- Dializable so administration interval should be reduced to 4 hours during dialysis

- Adverse effects are dizziness, headache, and nausea
Mechanism of Action:

- Competitive inhibitor of alcohol dehydrogenase, alcohol dehydrogenase has 100 times the affinity than for ethylene glycol
Ethanol
4-MP

Alcohol dehydrogenase

Glycolaldehyde

NAD^+

NADH + H^+

Pyruvate

Lactate

Glyoxylic acid

Malate

Inhibition of TCA cycle and lactic acidosis

Oxalic acid

Calcium oxalate

Tissue deposition

Metabolic acidosis
Ethanol Cont.

Dosing:
- Goal ethanol level of 10-12.5 mg/dl, which is enough to saturate the enzyme
- Loading dose 0.6-0.7 g ethanol/kg, maintenance dose is 66 mg ethanol/kg/hr for nondrinkers and 154 mg/kg/hr for alcoholics
- Goal is to use until the ethylene glycol level is <2
Frequent dose adjustments may be necessary, so the level should be checked every 1-2 hours.

Adverse effects are CNS depression, hepatotoxicity, and hypoglycemia.
Thiamine

- **Mechanism of Action:**
  - Prevents the formation of oxalic acid by facilitating the conversion of glycoxylic acid to alpha-Hydroxy Beta ketoacid.

- **Dose:**
  - 100 mg IV q6 until ethylene glycol can no longer be measured in the serum.
Pyridoxine

- **Mechanism of Action:**
  - Prevents the oxalic acid by converting glycoxylic acid to hippuric acid metabolites and glycine.

- **Dose:**
  - 50 mg IV q6

- **Adverse Reaction:**
  - Can cause a toxic sensory neuropathy
Elimination: Hemodialysis

- **Mechanism of Action:**
  - Removes ethylene glycol and glycolate effectively

- **Indications:**
  - Ethylene glycol concentration $>500\text{mg/L}$ or presence of severe metabolic acidosis, renal failure, severe electrolyte imbalance, or generally deteriorating
<table>
<thead>
<tr>
<th>TABLE 1. Principles of treatment for ethylene glycol intoxication</th>
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<tbody>
<tr>
<td>Indications for treatment of ethylene glycol poisoning with an antidote</td>
</tr>
<tr>
<td>Documented plasma ethylene glycol concentration &gt;20 mg/dL, or</td>
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<tr>
<td>Documented recent (hours) history of ingesting toxic amounts of ethylene glycol and osmolal gap &gt;10 mOsm/L, or</td>
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<tr>
<td>History or strong clinical suspicion of ethylene glycol poisoning and at least 2 of the following criteria</td>
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<tr>
<td>Arterial pH &lt;7.3</td>
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<tr>
<td>Serum bicarbonate &lt;20 mEq/L</td>
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<tr>
<td>Osmolal gap &gt;10 mOsm/L</td>
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<tr>
<td>Urinary oxalate crystals present</td>
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<tr>
<td>Indications for hemodialysis in ethylene glycol toxicity¹⁶</td>
</tr>
<tr>
<td>Deteriorating clinical status despite supportive therapy, metabolic acidosis (arterial pH &lt;7.25–7.30) and/or</td>
</tr>
<tr>
<td>Acute kidney injury with a serum creatinine &gt;3.0 mg/dL (265 mmol/L) or increase in serum creatinine by 1.0 mg/dL (90 mmol/L), or</td>
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<tr>
<td>Acid-base/electrolyte abnormalities unresponsive to standard treatment</td>
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