HPI: A 55 yo woman with unknown PMH was brought to BHC after she found with AMS in a hotel room. The patient was reportedly found sitting behind her bed with an empty bottle of “Unisom” at her side. She was ataxic, with multiple bruises on her face, chest, and extremities, and with blood on her lips. EMS was called and she was brought to the ER. On presentation to the AES, she was nonverbal, refusing to answer any questions.

PMH/PSH/Meds/All/SH/FH : unobtainable
PE: VS – T93.8, HR 99, BP 150/102, RR 24, O2 sat 100%
Gen: alert, opening eyes spontaneously, but refusing to talk
HEENT: frontal and bilateral peri-orbital ecchymoses, EOMI, PERRL, dry oral mucosa
Neck: supple, no JVD
CV: tachycardic, nl S1, S2, no m/g/r
Chest: CTAB
Abd: soft, NT, ND
Ext: no edema, multiple hematoma/bruises
INITIAL LABS

Anion Gap: >26

ABG: 7.07/ <20/ 228/ 3.1/ 100%, Lactate >14
VBG: 7.00/ 23/ 35/ 5.5/ 67%, Lac 34

ETOH level <10
Salicylate level < 1.0
Tyelnol level < 10
Measur ed Serum osm: 319
Calculated Serum osm: 289
Osmolar gap: 30

U-tox: negative
UA: large blood, pH 5, protein
>300mg/dl, small LE, WBC 15-30,
RBC packed field, many bacteria,
many CaOx crystals
DIFFERENTIAL DIAGNOSIS

• **High osmolar gap WITH anion gap:**
  - **Methanol** -> metabolized to formate, which causes retinal injury, potential blindness
  - **Ethylene glycol** -> metabolized to glycolate, glycoxylate, and oxalate, which can cause renal failure, ca oxalate crystals
  - Diabetic ketoacidosis, lactic acidosis, and renal failure can also cause increase in osmolar gap, but usually to smaller degree

• **High osmolar gap WITHOUT anion gap:**
  - **Ethanol**
  - **Isopropyl alcohol** -> metabolized to acetone; both are CNS depressants; no risk of renal failure or retinal toxicity; +ketones
  - Severe hyperproteinemia or hyperlipidemia, infusions of sorbitol or mannitol
ETHYLENE GLYCOL TOXICITY
ETHYLENE GLYCOL

- Major industrial chemical, found in anti-freeze, brake fluid, and other solvents
- Poisoning results from ingestion of such substances for suicide attempts, ethanol substitution, or pediatric accidental ingestion
- In 2007, there were 5,731 reported cases of possible ethylene glycol poisoning in the United States (in 2008, there were 5763 cases)
  - Likely gross underestimate as reporting of these cases is not mandatory
CLINICAL MANIFESTATIONS

- Central nervous system depression
- Severe metabolic acidosis
- Renal failure
- Oxalate crystalluria
- Hypocalcemia
- Seizures

- EG itself causes very little toxicity except for inebriation similar to ethanol
- The clinical manifestations are due to its toxic metabolites, rather than the parent compound
Ethylene glycol

\[ \text{OH} \quad \text{OH} \]
\[ \text{H} - \text{C} = \text{C} - \text{H} \]
\[ \text{H} \quad \text{H} \]

Inhibition of alcohol dehydrogenase by fomepizole

Glycoaldehyde

\[ \text{H} - \text{C} = \text{C} - \text{H} \]

Glycolic acid

\[ \text{H} \quad \text{O} \quad \text{O} \]
\[ \text{H} - \text{C} = \text{C} - \text{OH} \]

Glyoxylic acid

\[ \text{O} \quad \text{O} \]
\[ \text{H} - \text{C} = \text{C} - \text{OH} \]

Oxalic acid

\[ \text{O} \quad \text{O} \]
\[ \text{HO} - \text{C} = \text{C} - \text{OH} \]

Urinary excretion

Inhibition by fomepizole

Ethylene glycol → Glycoaldehyde → Glycolic acid → Glyoxylic acid → Oxalic acid

Metabolic acidosis

Calcium oxalate crystals

Urinary excretion
KINETICS

- Ethylene glycol is rapidly and completely absorbed after oral ingestion
- Peak serum concentrations are reached within 1-2 hrs
- Elimination follows first-order kinetics in the absence of treatment
- Estimated serum half-life between 3 to 9 hrs
- If ADH is inhibited, elimination becomes almost entirely renal, with a half-life of 14 to 20 hrs in the absence of renal failure
- META study: 19 patients, treated with ADH-inhibition +/- dialysis
  - Mean elimination half-life of 19.5 hrs
  - 16.8 hrs in patients with normal renal function
- Recent study in 2012 in larger group of pts, all without renal failure, reported half life of 14 hrs
LABORATORY FINDINGS

- **Anion gap:**
  - From the accumulation of the metabolites, glycolic acid, glycoxilic acid, and oxalic acid

- **Osmolar gap:**
  - From the accumulation of ethylene glycol
  - The osmolar gap estimates the molar quantity of uncharged molecules, and therefore is a surrogate measure of ethylene glycol itself
  - The metabolites exist primarily in a dissociated or charged form at physiologic pH; since these anions must be accompanied by a cation (usually Na), they are accounted for in the calculated osmolarity and therefore do not result in a gap
  - The osmolar gap is therefore insensitive in late presentations
MORE LAB FINDINGS

- **Urinary oxalate crystals**
  - From increased oxalic acid, the final metabolite
  - Late and non-specific finding
  - Needle-shaped monohydrate or envelope-shaped dihydrate

- **Lactate**
  - Elevation in serum lactate from a misinterpretation of some laboratory instruments that cannot differentiate between lactate and glycolate:

\[
\begin{align*}
\text{Lactate} & : \quad \text{Glycolate} \\
\text{COO}^- & : \quad \text{COO}^- \\
\text{HO} - \text{C} & : \quad \text{HO} - \text{C} \\
\text{CH}_3 & : \quad \text{H}
\end{align*}
\]
RENAL TOXICITY

• Traditionally attributed to the accumulation of calcium oxalate crystals in the proximal tubular lumen, leading to physical blockage of flow by compression

• Now thought to also be secondary to direct cytotoxic effect of oxalate on the PT cells, leading to tubular necrosis
  • Showed that HPT cells had the same amount of cytotoxicity when exposed to NaOx as CaOx

• The renal failure associated with EG toxicity is usually, oliguric-anuric, and reversible (often recovers over a period of days to months)
• Ethylene glycol levels (with turnaround time <2hrs) and Glycolic acid levels are available at only a few large tertiary care centers
• In centers without these tests readily available, we rely on AG, osmolar gap, and pH as surrogates
• A study of 40 pts found both AG >20 and acidosis with pH < 7.3 predicted AKI (with sensitivity of 96% and 100%, respectively and specificity of 94% and 82%)
• No correlation between EG level and AG, pH, and bicarbonate
**TREATMENT: OVERVIEW**

- Inhibition of Alcohol dehydrogenase
  - Ethanol
  - Fomepizole (4-Methylprazolone) - approved for use in EG toxicity since 1997

- Hemodialysis
  - Effective at removing EG and its toxic metabolites

- Administration of sodium bicarbonate
  - Leads to deprotonation of the toxic metabolites, making them less likely to penetrate end-organ tissues and be excreted in urine

- Administration of cofactors
  - Pyridoxine and thiamine are involved in minor elimination pathways of glycolate
  - Unknown if they help accelerate metabolism along the pathways
Prospective cohort study of 19 patients with ethylene glycol toxicity to study the efficacy of Fomepizole

Pts received a loading dose of Fomepizole 15mg/kg IV followed by 10mg/kg q12 hr x 48hr then 15mg/kg q12hr

Treated until EG level was <20mg/dl

17/19 patients also underwent HD

End points: development of renal injury, additional production of EG metabolites, and the development of cranial neuropathies
• Pts received an average of 3.5 doses of fomepizole (range 1 to 7) over an average of 17.8 hrs (range 5 to 58)
• 18/19 pts survived; the pt who died had a pH of 7.05 and had an acute MI
• None of the pts had cranial neuropathy
• 9 pts had high Cr at presentation; all had further increases in Cr
  • They presented later and had more severe acidosis than those without renal failure, and all had high glycolate levels
  • 6/9 fully recovered renal function by the end of tx
• No signs of renal injury developed in any patient whose initial glycolate level was low, or whose initial Cr was normal
Treatment should be continued until the plasma ethylene glycol concentration is below 20 mg/dl (3.2 mmol/L)
HEMODIALYSIS

- Glycolic acid is a small (MW = 76 daltons), water-soluble molecule that should diffuse across a dialysis membrane.
- It has a small volume of distribution (0.55 L/kg), indicating it remains in the vascular compartment where it can be removed by dialysis.
- The extent of protein binding is unknown.
- A study that measured pre- and post- HD GA levels found:
  - The half-life was reduced from 10 hrs (endogenous GA elimination) to 2.5 hrs with HD.
  - Clearance of 170 ml/min with dialysis flow rates of 250-400 ml/min.
- Peritoneal dialysis and CVVH have not been found to be effective.
HEMODIALYSIS

• Indication:
  • Significant metabolic acidosis (pH < 7.3)
  • Renal failure
  • Ethylene glycol level > 50 mg/dl

• Duration:
  • Traditional endpoint is an undetectable serum EG level OR EG < 20 mg/dl and the disappearance of acid-base abnormalities and signs of systemic toxicity
  • Correction of AG metabolic acidosis and osmolar gap are considered adequate endpoints for dialysis if the pt is receiving Fomepizole and serum EG and GA levels are unavailable
  • Serum osm and AG need to be monitored for 12 hrs after discontinuation of dialysis to ensure there is no rebound and need for reinitiation
BACK TO THE CASE...

- In the ER, she was given a loading dose of Fomepizole 15mg/kg, followed by 10mg/kg q12 x 2 doses.
- Also given Thiamine, Folate, Pyridoxine and started on empiric ABX given leukocytosis, pyuria, and elevated lactate.
- Repeat Lab revealed worsening renal function, so decision made to initiate HD:

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REFERENCES

THANK YOU!