Alcohols, Glycols, & "Cat" cols

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Alcohols and Glycols

- “Iso” means branching of carbon chain
- “Glycol” means 2 hydroxyl groups
  - Ethylene glycol  Antifreeze
  - Propylene glycol  Refrigerant
  - Polyalkylene glycol  Refrigerant oil
- Physiochemical behavior
  - If small hydrocarbon group, acts like water
  - If large hydrocarbon group, acts like the HC-group
Alcohols and Glycols: Glycol Ethers

- Clear, Syrupy liquid; Inoffensive odors; Low Vapor pressure; Non-flammable
- Water & Organic soluble … Very Nice!...”Couplers”!
- Do not bioaccumulate b/c undergo rapid hydrolysis
- Rapid Dermal, inhalation, and oral absorption
  - Molecular Weight $\downarrow \uparrow \uparrow$ Dermal absorption
- Uses: Solvents
  - Household cleaning products (windows)
  - Humectant and plasticizer
  - Semiconductor industry
  - Brake fluid Diluent
  - Deicers
  - Paints and Coatings
Alcohols and Glycols: Glycol Ethers

- Two groups:
  - Ethylene glycol ethers
  - Propylene glycol ethers
- Ethylene Glycol Ethers
  - Many exist
  - 2 examples
- Propylene Glycol Ethers
  - Many
  - Example

\[ R_1\text{OCH}_2\text{CH}_2\text{OR}_2 \]

- EG Monoalkyl Ethers base:
  \( R_1 = \text{Alkyl gp}; R_2 = \text{H or Acetate} \)

- Propylene Glycol Monomethyl Ether
  - Is a 2° alcohol (On the 2\textsuperscript{nd} Carbon)

- Ethylene Glycol Methyl Ether (EGME)
- Ethylene Glycol Butyl Ether (EGBE)
Alcohols and Glycols: Glycol Ethers Metabolism

- ADH is key one: Alkoxyacetic acids
- Toxic Metabolite Reproductive Problems
- Gap Acidosis
- Minor route & Debatable ethylene glycol
  - Oxaluria seen after some methoxyethanol & butoxyethanol ingestions
- But... Ether linkage is fairly stable
  Is No direct evidence to support

- Its 2° –OH ADH does NOT metabolize
- CYP Metabolism CO₂ (Non-Toxic)
- Replacing the ethylene glycol ethers
## Alcohols and Glycols

### Glycol Ethers

**Clinical**

- **Reproductive**
  - Animal studies ➔ Reproduction Injury (Spont. abortions, testicular damage, altered sperm motility)
  - Length of substituted alkyl group \( \alpha \)
- **Acute Ingestion ➔**
  - CNS... (acute encephalopathy; agitation, coma)
  - Heme... (Hemolysis, Anemia, Bone Marrow \( \downarrow \) cells)
  - Renal & Metabolic... (ARF, Metabolic Acidosis)
- **Chronic (Inhalation or Dermal)**
  - Non-descript toxic encephalopathy neurobehavioral changes, dizzy, headache
  - Bone marrow depression

<table>
<thead>
<tr>
<th>Not/Less With PGE</th>
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Alcohols and Glycols
Diethylene glycol – A Glycol Ether

- Clear; Colorless; Syrupy liquid; Water soluble
- Uses: Solvent, Antifreeze, humectant and plasticizer.
- History: DEG substituted for propylene glycol or glycerin in oral elixirs has been a classic and too common problem:
  - Elixir Sulfanilamide Disaster of 1937:
    - DEG used as diluent in this elixir by the Massengil company ➔ 105 Deaths
    - Resulted in the 1938 Food, Drug, and Cosmetic Act - regulated the formulation and safety of medicinal products
  - Liquid paracetamol 1996 (Haiti) ➔ Renal ↓↓; 85 kids died
Diethylene glycol

Clinical
• Stage 1
  • GI sx (NV + abd pain), intoxication, and acidosis.
  • Onset is delayed 1-2 days!!
• Stage 2 (ARF)
  • Renal failure #1 consistent problem after 2-6 days.
  • Acidosis is worse now. Severe acidosis uncommon until ARF present (Unlike EG or methanol)
• Stage 3 (Neuro)
  • If pt survives the ARF, then Neuro - CNS, ↓, CN VII neuropathy, extremity weakness

Treatment
• Hemodialysis recommended for symptomatic pts
• ADH inhibitors seem to make sense but folks have done poorly despite the use
DEG - Contaminated cough syrup distributed in Panama during 2006

- 46 pts. Median age was 67 years
- All with AKI or CRF exacerbation (median creatinine 10.0 mg/dL) at median of 5 days after symptom onset.
- 40 (87%) had neurologic signs
  - Limb weakness in 31 (77%)
  - Facial Motor weakness in 27 (68%)
  - EMGs in 21 pts w/ objective weakness - severe sensorimotor peripheral neuropathy in 19 (90%)
  - 14 pts w/o initial neuro findings, ↑CSF protein w/o pleocytosis → 13 (93%) → overt neurologic illness.
- Despite ICU care and hemodialysis, 27 (59%) died a median of 19 days (range 2 to 50 days) after presentation.
DEG Metabolism

Mammals don’t have the enzymes to break an ether bond and end up with ethylene glycol.

Renal Elimination

Enters Renal Cells and accumulates
(Little is renally eliminated)
Diglycolic Acid

- DGA results in time dependent ATP decrease; see this before see pathophysiology…see necrotic cell death only later.
- DGA looks very similar to succinic acid and fumaric acid; and in the lab DGA – decreases the activity of these tca intermediates.
- DGA - inhibits oxygen consumption of proximal tubular cells.
- Likely uses certain transporters to get into the cell but this disrupts the inner cell metabolism – can’t get it out and it stops activity.
- 5HEAA – better correlates with the acidosis (vs DGA causes the kidney injury)
- Think DGA can - CNS and can cause toxicity at this area.
Propylene Glycol

\[
\begin{align*}
&\text{CH}_3-\text{CH}-\text{CH}_2 \\
\text{Propylene Glycol} \\
\text{Alcohol & Aldehyde Dehydrogenase} \\
&\text{CH}_3-\text{CH}-\text{C}-\text{OH} \\
&\text{Lactic Acid} \\
&\text{NAD}\,^+ \\
&\text{NADH} \\
&\text{Ch}_3-\text{C}-\text{C}-\text{OH} \\
&\text{Pyruvic Acid} \\
&\text{Krebs Cycle}
\end{align*}
\]

Propylene Glycol

Found:
- Med Diluent
- Silver sulfadiazine

Most Common
- Mild lactic acidosis
- Hyperosmolarity

Rare Serious
- Hypotension (acute)
- Renal (chronic)
- Cardiac conduction changes
  (Wide QRS; ↑ wave)
NADH:NAD\textsuperscript{+} Ratio and Alcohols

Alcohol Metabolism $\rightarrow$ NADH
Ethylene Glycol 4 Oxidative steps
Isopropanol 1 Oxidative step

\[
\begin{align*}
\text{CH}_3-\text{CH}-\text{C}-\text{OH} & \quad \text{Glycolysis} \\
\text{CH}_3-\text{CH}-\text{C}-\text{OH} & \quad \text{Pyruvic Acid} \\
\text{CH}_3-\text{CH}-\text{C}-\text{OH} & \quad \text{Krebs Cycle}
\end{align*}
\]

Lactic Acid

NAD\textsuperscript{+} (LDH)

NADH
Benzyl Alcohol

- Common IV preservative at 0.0-2.0%
- Toxicity usually due to repeated dosing
- Saline / Heparin use in pre-term neonates

** Premature infants have decreased ability to make Hippurate

** "Gasping" syndrome
Benzyl Alcohol

- Severe anion gap acidosis
- Clinical
  - Hypotension
  - Hepatic and renal failure
  - Kernicterus
  - Intracranial hemorrhage
  - Hemolysis
  - Death
- Bronchitis ass with inhalation
- Treatment
  - Hemodialysis consideration (?)
  - ADH blocking agent (?)

Usually not done due to repetitive dosing exposure
Methanol & Ethylene Glycol Poisoning
Toxic Alcohols Defined

- All Alcohols $\Rightarrow$ CNS Depression (Intoxication)
- Toxic Alcohols $\Rightarrow$ Acute, Specific End Organ Damage

Toxic Alcohols
- Ethylene Glycol
- Methanol

NOT Toxic Alcohols
- Isopropanol
- Ethanol
Toxic Alcohols

- May initially be asymptomatic after exposure
- Inebriation severity $\alpha$ # of carbons
- Lack of inebriation does not exclude toxicity
- All alcohols may $\Rightarrow$ Vasodilation & BP ↓
  $\Rightarrow$ Gastritis

- Acidosis
  - Ethylene Glycol: (1) Glycolate (2) Other acids (3) Renal failure

- Methanol:
  (1) Formate
  (2) Formate $\Rightarrow$ TCA cycle $\Rightarrow$ Lactate
**Metabolism Methanol**

- **(+)** Osmoles
- **(+)** Acidosis
- No Ketones

Chemical reactions:

- Methanol ($\text{H}_3\text{C-OH}$) is metabolized by ADH to formaldehyde ($\text{H}_2\text{C}=\text{O}$).
- Formaldehyde is then converted to formate ($\text{HC-OH}$) using folic acid.
- Formate is further metabolized to CO$_2$ and H$_2$O.

**Key Terms**:
- **ADH**: Alcohol Dehydrogenase
- **Folate**: Vitamin B9
- **CO$_2$**: Carbon Dioxide
- **H$_2$O**: Water
Methanol

- **Presentation**
  - **Visual**: Blurred, dimmed, “flashes”, blind Hyperemia & edema of disks & retina
  - **CNS**: Intoxication -to- Coma
  - **GI**: N&V, abdominal pain, Pancreatitis

- **Beware of delays:**
  - End organ Sxs may not appear for 24 hrs
  - Acidosis may not appear for hours
Methanol

- Formate is directly toxic (Not the acidosis)
  - $PK_a$ 3.75 … mostly ionized at normal pH
  - Acidosis $\rightarrow$ Non-ionized form $\rightarrow$ into Eye
- Treatment Consideration
  - Sodium Bicarb $\rightarrow$ Ion Trapping (?)
Ethylene Glycol
Pathophysiology and Clinical

- CNS Depression
- Renal Damage (ATN)
  - Due to (1) Direct toxicity
    (2) Oxalate crystals in tubules
  - Early as 16 hours; Failure by 48 hours
- Metabolic acidosis due to
  (1) Glycolate (#1) & Oxalate & other metab.
  (2) EG oxidation $\Rightarrow$ NADH / NAD$^+$ ratio $\uparrow\Rightarrow$
    (1) Lactate / Pyruvate Ratio &
    (2) TCA Cycle activity
Ethylene Glycol
Pathophysiology and Clinical (Con’t)

- If severe...
  - Cardiac Dysrhythmias and Depression 2° to Met acidosis & ↓ Ca++
  - Ca++ ↓⇒ (1) myoclonus, tetany, Seizures
  (2) ↑QT interval
  - Multisystem organ failure, ARDS
- Late and unusual:
  - Cranial nerve palsies
  - Bone Marrow suppression
Metabolism of Ethylene Glycol

Ethylene glycol → Alcohol Dehydrogenase → Glycoaldehyde → Aldehyde Dehydrogenase → Glycolate

Glyoxylate → Oxalate, Formate, Glycine, α-Hydroxy-β-Ketoadipate

** Rate Limiting Step
Isopropanol

- **CNS**
  - 2-3 times more depression than EtOH
  - Acetone also a CNS depressant
- **Gastrointestinal**: Gastritis, Abdominal pain, N&V
- If Severe: Hypotension and coma (Rare)
- Blue Heaven
- Generally not a problem except for the CNS sedation and GI upset
- Could treat with alcohol dehydrogenase blocking agents, but is not generally worthwhile
# Toxic Alcohols & Isopropanol

<table>
<thead>
<tr>
<th></th>
<th>EG</th>
<th>Meth</th>
<th>Isopropanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation tox</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Derm tox</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pk Serum (Parent)</td>
<td>1-4 hrs</td>
<td>½-1 hr</td>
<td>½-1 hr</td>
</tr>
<tr>
<td>Metab Delay</td>
<td>No</td>
<td>to 24 hrs</td>
<td>No</td>
</tr>
<tr>
<td>Unchanged Elim</td>
<td>No</td>
<td>10-20%</td>
<td>No</td>
</tr>
<tr>
<td>T ½ (Alone)</td>
<td>3-9 hrs</td>
<td>1– 9</td>
<td>3-16 hrs</td>
</tr>
<tr>
<td>T ½ (EtOH or Fomep)</td>
<td>14-20 hrs</td>
<td>43-54 hrs</td>
<td></td>
</tr>
<tr>
<td>T ½ (Dialysis)</td>
<td>2-4</td>
<td>2-4</td>
<td></td>
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</tbody>
</table>
# Differential Diagnosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Odor</th>
<th>A. Gap</th>
<th>Ketosis</th>
<th>Glc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eth Glycol</td>
<td>No</td>
<td>++</td>
<td>-</td>
<td>➡</td>
</tr>
<tr>
<td>Methanol</td>
<td>No</td>
<td>++</td>
<td>-</td>
<td>➡</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>Ketone</td>
<td>-</td>
<td>++</td>
<td>➡</td>
</tr>
<tr>
<td>D. Ketoacid.</td>
<td>Ketone</td>
<td>++</td>
<td>++</td>
<td>➡</td>
</tr>
<tr>
<td>A. Ketoacid.</td>
<td>Ketone</td>
<td>++</td>
<td>++</td>
<td>➡</td>
</tr>
</tbody>
</table>
## Diagnostic Considerations

<table>
<thead>
<tr>
<th>Metabolism Status</th>
<th>Methanol Eth Glycol</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intoxicated ?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>End Organ Damage?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Osmole Gap ↑</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Anion Gap ↑</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
My Doctor said "Only 1 glass of alcohol a day". I can live with that.

Application of “New math” ...
Diagnosis: Osmol Gap

- Gap = Measured osmolality - calculated osmolarity
- Measure by “Freezing point depression”
- $2 \ [\text{Na}] + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8} + \frac{\text{EtOH}}{4.6}$
- Parent alcohols $\rightarrow$ (+) Gap
  Toxic metabolites $\rightarrow$ No gap

Sensitivity is poor
Specificity is poor
Osmoles
What is Normal?

300 “Normal” people
-2 ± 6

97.5% population
gap < 10
Diagnosis: Osmol Gap

- Ethylene glycol at 50 mg/dL will add only ~ 8 mOsm
- Not surprising: Case of a patient with a gap of 7.2 who eventually needed dialysis

- A normal gap does **not** rule-out a toxic ingestion
- A really big gap (> 40) likely is a toxic alcohol
- An osmole gap is a substitute for a toxic alcohol level. **Do NOT use a gap if you can get timely levels**
Diagnosis

- Urine Fluorescence
  - Due to fluorescein in anti-freeze
  - Tried and NOT true
- Oxalate crystals in the urine

Sensitivity is poor
Specificity is poor
It could be that the purpose of your life is only to serve as a warning to others
Management
Stop Alcohol Dehydrogenase

Ethylene Glycol → Glycoaldehyde → Ethanol
Methanol → Formaldehyde → Ethanol

Alcohol Dehydrogenase
Fomepizole
Management
Ethanol or Fomepizole

Indications

- History suggests it
- Osmole gap
- Elevated toxic alcohol levels
- End organ Damage
- Anion Gap Metabolic Acidosis

A first dose provides 12 hours to sort things out...
Management

Ethanol

- Preferred substrate for Alcohol dehydrogenase (100 Xs > affinity than for ethylene glycol)
- Intravenous infusion or oral
- Adverse effects:
  - CNS sedation ↑
  - Hypoglycemia
  - Vein irritant
  - Ethanol elimination is erratic

Need an ICU bed
Management
Fomepizole

- Affinity for ADH is:
  - $8000 \times > \text{affinity than ethanol}$
  - $80,000 \times > \text{affinity than methanol}$
- FDA approved for Eth glycol and Methanol
- Rapidly distributed
- Induces own P-450 metabolism w/i 30-40 hrs
- Renal elimination
- Adverse effects: Minimal
Management

Fomepizole

• Cost:
  • ~ $1000 per gram
  • ICU stay **not** required

• Dosing
  • Load 15 mg/kg, then
    10 mg/kg every 12 hours × 4 doses, then
    15 mg/kg every 12 hours until
    ethylene glycol level is < 20 mg/dL
  • Every four hours if dialyzing

Note the increase
Management
Hemodialysis

**Indications:**

End organ Damage
- Metabolic acidosis that can’t easily correct
- Renal compromise
- Vision changes

Ethylene glycol or methanol levels
- > 25 mg/dL...very doubtful...
- > 50 mg/dL...but not absolute...

Dialysis
- NOW
- Maybe
Management
Cofactors

Suggested by (1) animal models, (2) Rx in primary oxaluria, & (3) case studies of elimination. No proven role in toxicity.

- Glyoxylate
- Formate
- Glycine
- α-Hydroxy-β-Ketoadipate
- CO₂ + H₂O

Cofactors:
- Ethylene Glycol
- Methanol
- Pyridoxine
- Thiamine
- Folate
Chlorobutanol

- Preservative
- Structure like trichloroethanol
- Mild sedative.
- Like chloral hydrate (slurred speech, myoclonus, sedation)
- Local anesthetic
- Found: IV thiamine; Anti-bacterial / fungals; Injectable, ophthalmic, otic, and cosmetic preps.
- Found as 0.25-0.5% in procaine, epinephrine.
Polyethylene glycols

- Various compounds with wide range molecular weights.
- The “number” is the avg. MW (Range 200-40,000).
- < 600 are clear, viscous liquids; Absorbable, can be toxic
  - Partially metabolized (ADH) → hydroxyacid and diacid metabolites (excreted unchanged in urine)
  - diethylene and triethylene glycol
  - In: Lorazepam, Decadron, ophth ointments
- Toxicity
  - Nephrotoxicity (ATN)
  - Hyperosmolarity and metabolic acidosis
- > 1000 are solid (pastes to flakes) but soluble.
  - Not absorbed and are Non-Toxic
  - Ex - PEG 3350 - PEG-ELS (WBI agent)
Disulfiram Reactions
Antifungals and More

- Carbon Disulfide
- Dimethylformamide
- Tetraethylthiuram disulfide (Disulfiram)
- Tetramethylthiuram disulfide (Thiram)
- Thiram Analogs (fungicides)
  - Cu/Hg/Na diethyldithiocarbamate
  - Zn/Fe dimethyldithiocarbamate

Disulfiram

A chelator for Nickel Carbonyl

Dithiocarbamate

Carbon Disulfide
Xenobiotics with Disulfiram-like Reaction with Ethanol

- Carbon Disulfide
- Dimethylformamide
- Tetraethylthiuram disulfide (Disulfiram)
- Tetramethylthiuram disulfide (Thiram)
- Thiram Analogs (fungicides)
  - Cu/Hg/Na diethyldithiocarbamate
  - Zn/Fe dimethyldithiocarbamate

**Halogenated HCs**
- Carbon Tetrachloride
- Chloral Hydrate
- Trichloroethylene
Sorbitol

- Intestinal Evacuant as hyperosmotic agent (like lactulose). Are sugars that are NOT absorbed; preventing water from being absorbed.
- The most cramping among cathartics and the most nausea and vomiting.
- Electrolyte abnormalities
  - Hypernatremia