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  Dermal absorption
• Uses: Solvents
  Household cleaning products (windows)
  Humectant and plasticizer
  Semiconductor industry
  Brake fluid Diluent
  Decers
  Paints and Coatings
Alcohols and Glycols: Glycol Ethers

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

**Ethers: R₁-O-R₂**

- Propylene Glycol Ethers
  - Many
  - Example

EG Monoalkyl Ethers base:

R₁OCH₂CH₂OR₂

R₁ = Alkyl gp; R₂ = H or Acetate

Ethylene Glycol

Methyl Ether (EGME)

Ethylene Glycol

Butyl Ether (EGBE)

Propylene Glycol Monomethyl Ether

Is a 2° alcohol
(On the 2nd Carbon)

Alcohols and Glycols: Glycol Ethers Metabolism

- ADH is key one ➔ Alkoxyacetic acids
- Toxic Metabolite ➔ Reproductive Problems
- Gap Acidity
- 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

Not/Less With PGE

Clinical

- Reproductive

- Animal studies ➔ Reproduction Injury (Spont. abortions, testicular damage, altered sperm motility)
- Length of substituted alkyl group α / Toxicity

- Acute Ingestion ➔
  - CNS...(acute encephalopathy; agitation, coma)
  - Heme... (Hemolysis, Anemia, Bone Marrow cells)
  - Renal & Metabolic... (ARF, Metabolic Acidosis)
- Chronic (Inhalation or Dermal)
  - Non-descript toxic encephalopathy neurobehavioral changes, dizzy, headache
  - Bone marrow depression
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

\[
\text{HO} \quad \text{O} \quad \text{OH}
\]

Alcohols and Glycols
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/ initial neuro findings, ↑CSF protein w/ 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.
**Hemoglobin**

- 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.

**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)

**Diglycerolic Acid**

- CH₃-CH-OH
- CH₃-CH-OH

**Propylene Glycol**

- CH₂-CH-CH₂
- OH OH

**Propylene Glycol**

- Alcohol & Aldehyde Dehydrogenase
- Lactic Acid
- NAD⁺
- NADH
- CH₃-C-C-OH
- Pyruvic Acid

**Propylene Glycol**

- Found: Med Diluent
- Silver sulfadiazine
- Most Common
- Mild lactic acidosis
- Hyperammonemia
- Rare Serious
- Hypotension (acute)
- Renal (chronic)
- Cardiac conduction changes (Wide QRS; ↑ wave)
NADH:NAD⁺ Ratio and Alcohols

Alcohol Metabolism ➔ NADH
Ethylene Glycol 4 Oxidative steps
Isopropanol 1 Oxidative step

CH₂-CH-C-OH
Lactic Acid

NAD⁺
NADH

Glycolysis ➔ CH₃-CH-C-OH ➔ Krebs Cycle

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

Glycolysis ➔ Pyruvic Acid ➔ Krebs Cycle

CH₂-OH
Benzyl Alcohol

COOH
Benzoic Acid

H₂N
Glycine

C-NH-COOH
Hippuric Acid

• 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 (?)

Benzyl Alcohol

Usualy not done due to repetitive dosing exposure
Methanol & Ethylene Glycol Poisoning

Toxic Alcohols Defined

- All Alcohols ➔ CNS Depression (Intoxication)
- Toxic Alcohols ➔ 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 α # of carbons
- Lack of inebriation does not exclude toxicity
- All alcohols may ➔ Vasodilation & BP ↓
  ➔ Gastritis
- Acidosis
  - Ethylene Glycol: (1) Glycolate (2) Other acids (3) Renal failure
  - Methanol: (1) Formate (2) Formate ➔ TCA cycle ➔ Lactate
Metabolism

Methanol

\[
\begin{align*}
\text{H}_2\text{C}=&\text{OH} \\
\text{ADH} \\
\rightarrow \text{H}_2\text{C} = \text{CO} \\
\rightarrow \text{HC} = \text{O} \\
&\text{Folate} \\
&\text{CO}_2 + \text{H}_2\text{O}
\end{align*}
\]

(+ Osmoles'
(+ Acidosis
No Ketones

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)
  • \( \text{PK}_a \) 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$$\downarrow$
    (1) Lactate / Pyruvate Ratio &
    (2) TCA Cycle activity

Ethylene Glycol
Pathophysiology and Clinical (Con’t)

- If severe...
  - Cardiac Dysrhythmias and Depression $\rightarrow$ to
    Met acidosis & $\downarrow$ Ca$^{++}$
  - Ca$^{++}$ $\downarrow$$\rightarrow$ (1) myoclonus, tetany, Seizures
    (2) $\uparrow$QT interval
  - Multisystem organ failure; ARDS
- Late and unusual:
  - Cranial nerve palsies
  - Bone Marrow suppression

Metabolism of Ethylene Glycol

![Metabolism Diagram]

** 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>Pl. 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 ⅓ (Alone)</td>
<td>3-9 hrs</td>
<td>1–9 hrs</td>
<td>3-16 hrs</td>
</tr>
<tr>
<td>T ⅓ (EtOH or Fomep)</td>
<td>14-20 hrs</td>
<td>43-54 hrs</td>
<td></td>
</tr>
<tr>
<td>T ⅓ (Dialysis)</td>
<td>2-4</td>
<td>2-4</td>
<td></td>
</tr>
</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</th>
<th>Eth Glycol</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intoxicated ?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>End Organ Damage?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Osmole Gap ?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Anion Gap ?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Application of “New math”...

**Diagnosis: Osmol Gap**

- **Gap** = Measured osmolality - calculated osmolarity
- Measure by “Freezing point depression”
- 2 [Na] + Glucose/18 + BUN/2.8 + EtOH/4.6
- Parent alcohols → (+) Gap
- Toxic metabolites → No gap

Sensitivity is poor
Specificity is poor

My Doctor said "Only 1 glass of alcohol a day", I can live with that.
Osmoles
What is Normal?

300 "Normal" people
-2 ± 6

2.5% 68% 95%
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 Fluorescense
  - Due to fluorescein in anti-freeze
  - Tried and NOT true
  - Oxalate crystals in the urine

Sensitivity is poor
Specificity is poor
Management
Stop Alcohol Dehydrogenase

- Ethylene Glycol
- Methanol
- Alcohol Dehydrogenase
- Glycoaldehyde
- Formaldehyde
- Ethanol
- Fomepizole

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

Treat before End Organ Damage

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

• Preferred substrate for Alcohol dehydrogenase
  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 X > affinity than ethanol
  • 80,000 X > 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 X 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...

**Management**
**Cofactors**

<table>
<thead>
<tr>
<th>Ethylene Glycol</th>
<th>Pyridoxine</th>
<th>Glycine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyoxylate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine</td>
<td>α-Hydroxy-β-Ketoacidate</td>
<td></td>
</tr>
<tr>
<td>Formate</td>
<td>Folate</td>
<td>CO₂ + H₂O</td>
</tr>
</tbody>
</table>

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

**Chlorobutanol**

- Preservative
- Structure like trichloroethanol
- Mild sedative
- Like chloral hydrate (slurred speech, myoclonus, sedation)
- Local anesthetic
- Found IV thiamine; Anti-bacterial/fungal; 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) \( \rightarrow \) hydroxyacid and diacid metabolites (excreted unchanged in urine)
  - diethylene and triethylene glycol
  - In: Lorazepam, Decadron, ophthalmic ointments
  - Toxicity
    - Nephrotoxicity (ATN)
    - Hyperosmolality 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 dithiophosphate
  - Zn/Fe dimethylthiocarbamate

**Disulfiram**

![Disulfiram Reaction](image)

(A chelator for Nickel Carbonyl)

Xenobiotics with Disulfiram-like Reaction with Ethanol

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

**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