The Swill that can Kill – Toxic Alcohol Poisoning

Adam Mah – LMPS Resident
Emergency Medicine rotation
January 23rd, 2018
Learning objectives

• Understand the pathophysiology behind negative clinical outcomes from toxic alcohol ingestion

• Describe the clinical presentation of a toxic alcohol ingestion

• Be able to recommend antidotes (where applicable), supportive care measures, and monitoring parameters for toxic alcohol ingestion
**Case**

<table>
<thead>
<tr>
<th>ID</th>
<th>Mr. C, 58 yo male, 71.5 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/C</td>
<td>Nausea.</td>
</tr>
<tr>
<td>HPI</td>
<td>Last evening friend bet him he “couldn’t finish a litre of antifreeze over the next month”. Ingested <strong>unknown amount</strong> of antifreeze approx. 4 hours prior to admission. Has Hx of previous ingestion of antifreeze 4 years ago requiring dialysis.</td>
</tr>
<tr>
<td>PMHx</td>
<td>Hypertension, previous rib fractures</td>
</tr>
<tr>
<td>MPTA</td>
<td>Nil</td>
</tr>
<tr>
<td>Allergies</td>
<td>NKDA</td>
</tr>
</tbody>
</table>
## Vitals and ROS

<table>
<thead>
<tr>
<th>Vitals</th>
<th>AVSS. BP &lt;140/&lt;90.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Nausea, no vomiting prior to arrival. Bowel sounds present, no guarding or tenderness.</td>
</tr>
<tr>
<td>Rest of systems</td>
<td>Unremarkable.</td>
</tr>
</tbody>
</table>
Labs and investigations

• **Measured serum osmolality** = 364 mOsm/kg

• **Lytes**: Na 142, K 3.8, Cl 107, HCO₃ 26, gluc 10
  – Calculated osmolality = 317. **Osmolal gap (OG) = 47**
  – Anion gap (AG) = 9

• **Renal**: BUN 2.4, SCr 67, eGFR 100

• **Toxic alcohol panel**
  – Methanol, acetone, isopropyl-OH <2. **Ethanol 21 (↑)**
  – Ethylene glycol 51 (↑↑) (normal <3)
  – Rest of general tox panel (ASA, APAP) unremarkable
DTP and initial course

• Mr. C is at risk of anion gap metabolic acidosis, renal failure, and death secondary to not receiving antidote therapy for toxic alcohol ingestion
• Patient to undergo hemodialysis within the next couple of hours
• Clinical Pharmacy and DPIC consulted – fomepizole? What dose to give?
What are toxic alcohols?

- Compounds with alcohol (-OH) moiety
- Converted to toxic acid metabolites by alcohol dehydrogenase
- Cause metabolic derangements
- Absorbed PO, TD, and inhaled

Approach to the toxic-OH poisoned patient

- Stabilization (ABCs) +/- intubation
- Toxicological history – which alcohol?
- Gastric decontamination – usually too late
- Antidote – Fomepizole? Ethanol?
- Enhanced elimination – Hemodialysis?
- Supportive care throughout
- Monitoring and disposition
Clinical presentation

• Quick onset (<0.5-1 hour)
• **CNS/Neuro**: Decreased LOC, weakness
• **HEENT**: Blindness (methanol)
• **Resp**: Tachypnea, Kussmaul respirations
• **GI**: N/V
• **GU**: AKI, renal failure
• **Lytes/fluids**: Hyper-K, hypo-Ca
• **MSK**: Rhabdomyolysis
Which alcohol is important

• Propylene glycol and isopropyl alcohol ingestion may be managed more conservatively – monitor, oral dilution

• Others are metabolized via ADH to toxic acids – metabolic acidoses, renal failure, crystallization of acid salts in the renal tubules

• Two antidotes available
Mind the gap

- A normal anion gap is not reassuring
- Depends on timecourse to admission
- With time, ↑anion gap, ↓osmolal gap
  - Toxic alcohols osmotically active
  - As toxic metabolites form, they appear as unaccounted-for acid in anion gap

Fomepizole

- Competitive inhibition of alcohol dehydrogenase (ADH)
- Non-HD = 15 mg/kg IV load, then 10 mg/kg IV q12h
- HD = Dose maintenance q4h
- DPIC usually consulted to direct dosing
- Common ADRs = Headache, nausea, taste perversion, dizziness, drowsiness

Lexicomp
Ethanol

- Also competitive inhibitor of ADH
- Caution in alcoholic cirrhosis
- Dosing dependent on route, concentration of solution, whether pt is undergoing HD, and whether pt is chronic drinker
- 750 mg/kg load, then 100-300 mg/kg/hr
- Target serum EtOH of 22-32 mmol/L

Lexicomp,
www.dpic.org
When is antidote indicated?

- Ethylene glycol >3, or methanol >6
- Osmole gap >10 corrected for EtOH
- Hx or strong clinical suspicion plus ≥2 of:
  - HCO$_3$ <20
  - Anion gap >16
  - Arterial pH <7.3
  - Osmole gap >10
  - Oxalate crystalluria

Borron SW et al, 1999
Brent J et al, 1999
**Which antidote to use?**

<table>
<thead>
<tr>
<th>P</th>
<th>Patients who have ingested a toxic alcohol that is receptive to antidote treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fomepizole IV</td>
</tr>
<tr>
<td>C</td>
<td>IV or PO ethanol</td>
</tr>
<tr>
<td>O</td>
<td>Mortality, progression to hemodialysis, permanent blindness, prolonged renal insufficiency</td>
</tr>
</tbody>
</table>
Search strategy

• PubMed, Embase
• [Fomepizole] AND [Ethanol] (in Title/Abstract)
• Clinical trials, observational studies, SRs, MAs, English
• 1 retrospective observational study, 1 cross-sectional case series, 1 SR
## Predictors of death and prolonged renal insufficiency

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Retrospective observational study, n = 171</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>Patients poisoned with ethylene glycol</td>
</tr>
<tr>
<td><strong>Comparator 1</strong></td>
<td>Patients who died or had prolonged renal insufficiency (D/RI)</td>
</tr>
<tr>
<td><strong>Comparator 2</strong></td>
<td>Patients who had uncomplicated recovery (REC)</td>
</tr>
<tr>
<td><strong>Predictors</strong></td>
<td>Time to antidote, time to dialysis</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>D/RI group more likely to present comatose, seize, require intubation, <em>time to dialysis &lt;6 hours, and time to antidote &gt;6 hours.</em></td>
</tr>
</tbody>
</table>
## Analysis of a mass methanol poisoning

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Cross-sectional case series, n = 93 in Czech Republic after outbreak of mass methanol poisonings</td>
</tr>
<tr>
<td>Patients</td>
<td>Patients with diagnosis of methanol poisoning</td>
</tr>
<tr>
<td>Intervention</td>
<td>Fomepizole (n = 25)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Ethanol (n = 68)</td>
</tr>
<tr>
<td>Results</td>
<td>NSS in terms of survival and length of hospital stay. <strong>Positive serum ethanol</strong> and arterial blood pH &gt;7.3 were independent predictors of survival.</td>
</tr>
</tbody>
</table>
Comparing fomepizole and EtOH

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Systematic review of Embase and Medline</td>
</tr>
<tr>
<td>Studies included</td>
<td>Ethanol or fomepizole use in adults presenting &lt;72 hrs post-methanol or eth glycol ingestion, n = 145 trials. No RCTs, no head to head trials. Total 897 patients.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Fomepizole (FOM) (n = 146)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Ethanol (ETH) (n = 720)</td>
</tr>
<tr>
<td>Of note</td>
<td>33 patients treated with both antidotes.</td>
</tr>
</tbody>
</table>
| Results | Mortality for methanol: FOM 17.1%, ETH 21.8% 
Mortality for ethylene glycol: FOM 4.1%, ETH 18.1% |
Summary

• No head-to-head or placebo-controlled trials
• Must consider patient factors, safety profile, and cost
• **Ethanol**: Cumbersome dosing, pt is enebriated, adverse event profile unfavourable. $
• **Fomepizole**: Requires IV access, easy dosing, safety profile favourable. $$$
MR. C'S COURSE IN HOSPITAL

- 0750h: ED started fomepizole 1075 mg IV stat, DPIC and Pharmacy consulted
- 0930h: Renal consult – given ethylene glycol level of 51 mmol/L, decision made to dialyze within next 2 hrs for 6 hr HD run
- 0930h: I communicated with DPIC on best dosing strategy, suggested 1st maintenance dose given 4 hours post-start of HD
Mr. C’s course in hospital

• Fomepizole removed by dialysis
• Suggested to give 2\textsuperscript{nd} maintenance dose 4 hours after 1\textsuperscript{st} maintenance (2 hours after HD run complete)
• DPIC: Give 2\textsuperscript{nd} maintenance immediately after HD run concludes, then dose q12h as per normal

The Dialysis of Drugs, 2013
Lexicomp
Mr. C’s course in hospital

• 1200h: Pt admitted under CTU, Renal following, HD run under way
• 1600h: Pt receives second dose (700 mg IV – 10 mg/kg)
• When to dialyze? Give antidote with dialysis?
• When to stop treatment?
Hemodialysis for toxic alcohol poisoning

• Adjunct for antidote – should give fomepizole/ethanol concurrently with dialysis

• Indicated if
  – Pt worsens clinically on antidote alone
  – Arterial pH <7.25 unresponsive to treatment
  – Coma, seizure, severe electrolyte imbalances
  – Ethylene glycol >15, methanol >6
When to stop fomepizole?

• Monitoring (q6h or more often)
  – Lytes, BUN, SCr, glucose, EtOH
  – Arterial (or venous) blood gases
  – Serum osmolality
  – Ethylene glycol (or methanol) level

• Stop treatment when
  – Metabolic acidosis is corrected, AND
  – Osmole gap <10 x 2
Mr. C’s course in hospital

• 1800h: HD run complete, received 2\textsuperscript{nd} maintenance dose of fomepizole
• Labs drawn 2230h: EtOH <2, AG 7, OG 3
• Decision made to D/C fomepizole
• Held overnight for observation, no longer nauseous.
• 0715h next day: eGFR 130, serum osmolality 292 (normal)
Questions?