ETHYLENE GLYCOL AND METHANOL POISONING
January 2, 2004

I. INTRODUCTION

A. Physical Characteristics

Methanol (MeOH) - clear, colorless, flammable, faintly pleasant odor
Ethylene Glycol (EG) - colorless, odorless, sweet taste

B. Sources/names

MeOH
- wood alcohol
- paint removers
- ink solvents
- solid canned fluid
- embalming fluid
- windshield wiper fluid
- bootlegged whiskey
- duplicator fluid
- model airplane fluid
- deicers
- carbinol
- HEET

EG
- Antifreeze, solvent in paints, brake fluid, glass cleaners, cellosolves

II. PHARMACOKINETICS

A. Absorption

MeOH
- Absorption is rapid via GI (peak levels in 30 -60 min), lung (60 % retention), skin

EG
- Rapid and complete with peak levels in 1-4 hours; little absorption via skin or lung
- Therefore, gastric decontamination is of limited benefit in most patients unless the time of ingestion is very recent.

B. Metabolism

MeOH
- Hepatically metabolized via oxidation by alcohol dehydrogenase to formaldehyde and then formic acid.
EG
- Also metabolized by alcohol dehydrogenase to glycoaldehyde. This is then metabolized to glycocolate and glyoxalate.
- Glyoxalate is converted to oxalic acid which can lead to chelation of calcium

III. PATHOPHYSIOLOGY

MeOH
- MeOH is converted to the toxic metabolite formic acid which inhibits the cytochrome oxidase complex results in the severe acidosis and multiple organ system dysfunction seen in patients. Although formaldehyde is a metabolite, it has never been measured in the blood in individuals which means that its conversion to formic acid is quite rapid and complete. Because of the accumulation of metabolite, there is a often a delay of 12-30 hours before the onset of symptoms. Ocular toxicity is one of the most specific signs of poisoning and is thought to result from production of formaldehyde by the retina leading to retinal edema and blindness.

EG
- Ethylene glycol has a stronger affinity to alcohol dehydrogenase therefore symptoms typically appear sooner. The main toxic metabolite of EG is glycolic acid which is the major contributor to the anion gap metabolic acidosis and multiple organ system dysfunction exhibited. Toxicity can be characterized into 3 distinct phases. Phase I (30 min-12 hours) is associated with the CNS effects of the parent compound. The patient may appear intoxicated but will not have an odor of alcohol on their breath. Phase II (12-24 hours) can be described as a metabolic stage where cardiopulmonary symptoms are predominant. Phase III (> 24 hours) is related to excretion of the toxic metabolites. Oxalic acid formed via metabolism of the glycolic acid binds Ca2+ which can result in hypocalcemia and renal failure. Oxidation of ethylene glycol to glyoxylate (which does not remain very long in the body) and eventually to oxalate requires conversion of NAD to NADH. The altered NAD/NADH ratio shifts pyruvate to lactate which can augment the acidosis exhibited to a limited extent.

IV. RANGE OF TOXICITY

MeOH
- Lethal dose: - Variable (30-240 ml)
- Minimum toxic dose: - approx. 100 mg/kg
- Serum concentrations: > 20 mg/dL considered toxic; 40 mg/dL reported in one fatality
EG
Lethal dose: - 1-1.5 mL/kg (30-60 mL in children, ~ 100 mL in adults)
- adults with 1-2 L ingestions treated within 1 hour have survived
Serum concentrations: - > 20 mg/dL considered toxic; 98-775 mg/dL reported in fatalities

V. CLINICAL EFFECTS

MeOH
A. Initial
- CNS depression
- Inebriation to a lesser degree than ethanol
- + Osmol gap; + anion gap (can see anion gap metabolic acidosis; may appear late
  - not usually before 6 hours)

B. Delayed (12-24 hours):
  1. Visual
     - "stepping out into a snowfield"
     - restricted visual field
     - dilated/sluggish pupils
     - change in color perception
     - photophobia
     - diplopia
     - blurring
     - misty

  2. Metabolic
     - anion gap metabolic acidosis (often very severe at <7.0) which can lead to
       cardiovascular collapse, respiratory failure, coma and death.
     - Formic acid is toxic on a cellular level to all tissues.

  3. CNS
     - Headache, dizziness, amnesia, confusion, agitation
     - CNS depression, convulsions, coma

  4. GI
     - severe epigastric pain/pancreatitis
     - N/V

  5. OTHER
     - HA, weakness
### EG

<table>
<thead>
<tr>
<th></th>
<th><strong>Early (&lt;4 hours)</strong></th>
<th><strong>Late (&gt;4 hours)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CV</td>
<td>mild increase in HR, BP</td>
<td>CHF, tachycardia, mild HTN, shock</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dysrhythmias</td>
</tr>
<tr>
<td>CNS</td>
<td>stupor, coma, decreased DTRs, seizures, ataxia</td>
<td>bilateral facial paralysis, ataxia, hyperreflexia, seizures, coma</td>
</tr>
<tr>
<td>HEENT</td>
<td>diploplia, blurred vision, nystagmus</td>
<td></td>
</tr>
<tr>
<td>RESP</td>
<td></td>
<td>tachypnea, pulmonary edema</td>
</tr>
<tr>
<td>METAB</td>
<td>osmol gap, mild fever</td>
<td>anion gap metabolic acidosis (often severe at &lt;7.0), hypocalcemia, hypothermia</td>
</tr>
<tr>
<td>GI</td>
<td>N/V</td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td></td>
<td>oxaluria, renal failure</td>
</tr>
</tbody>
</table>

### VI. DECONTAMINATION

Rapid absorption limits efficacy

- Gastric lavage may be useful in large ingestions presenting early (less than 1 hour)
- Syrup of ipecac may be beneficial in accidental ingestions if administered very early
- Activated charcoal does bind both alcohols but their rapid GI absorption makes efficacy limited. However, since these are adsorbed, activated charcoal should be recommended in recent, significant ingestions (occurring within 1 hour).

### VII. TREATMENT

Treatments below are for both MeOH and EG unless otherwise specified

#### A. Laboratory

These should be obtained on admit:
1. Blood alcohol level
2. MeOH/EG level (only run at Regions Hospital, HCMC, Mayo, Medtox)
3. Serum osmolality (should be measured by freezing point depression)
   - calculate osmolar gap (measured osmolality - calculated osmolarity):
     - Calculated osmoles = \([2(\text{Na}) + \text{Glucose}/18 + \text{BUN}/2.8 + \text{Ethanol level}/4.6]\)
A gap of > 10 mOsmol/kg MAY indicate presence of low molecular weight substance in serum (e.g. MeOH, EG). As time increases post ingestion the gap will decrease due to the lower alcohol levels.

The gap may remain elevated due to accumulation of glycolate.

An absence of a gap DOES NOT rule out an ingestion of a toxic alcohol. Remember that as the parent compound is metabolized, its effect on the osmol gap decreases (the gap will decrease). The other factor to consider is that the patient’s normal gap is unknown and because of this even gaps of 10 or less can be indicators of significantly high EG or MeOH levels.

Differential for Osmol Gap = MEDIE: Methanol, Ethanol, Diuretics, Isopropanol, Ethylene Glycol

4. Electrolytes - can be used to determine presence of anion gap
Anion gap = Na - (Cl + HCO3); normal gap = 8-12 mEqs

- An elevated gap is often associated with the presence of lactate or an unmeasured acidic anion such as formate or oxalate

5. ABGs - typically patients present with a profound metabolic acidosis

AT MUDPILES
This mnemonic represents various causes of an anion gap metabolic acidosis
A Acetone, Acetaminophen
T Toluene
M Methanol
U Uremia
D Diabetic/starvation/alcoholic ketoacidosis
P Paraldehyde, Propylene glycol
I Iron, INH, ibuprofen, Isopropanol (rare)
L Lactate
E Ethylene glycol
S Salicylates
6. Urinalysis - can check for oxalate crystals; also can use Wood's lamp to look for fluorescein if EG suspected (though this later technique is really more for academic amusement and not typically helpful)

- There are 2 types of calcium oxalate crystals. The dihydrate which is octahedral or tent shaped and the monohydrate which is dumbbell shaped. The dihydrate typically only forms during high urinary concentrations of calcium and oxalate, and it is not very sensitive at predicting toxicity.

B. Therapies

- The preferred method of treating serious ethylene glycol or methanol poisonings is the correction of metabolic acidosis and the use of hemodialysis along with the administration of fomepazole to inhibit further metabolism of the alcohol to its toxic metabolites. However, access to fomepizole especially in the rural setting is questionable. If it cannot be obtained quickly, ethanol should be substituted.

4- METHYLPYRAZOLE (fomepizole; tradename: Antizol)
Advantages over ethanol:
- Slower rate of elimination
- Longer duration of action
- More practical dosing regimen
- No need for frequent monitoring of drug levels
- Less adverse effects (no CNS depression, hypoglycemia)

Mechanism: Competitive inhibition of alcohol dehydrogenase
Indications:  
- Suspicion of ingestion of a toxic alcohol based on history
- MeOH or EG level greater than 20 mg/dl
- Unexplained anion gap metabolic acidosis with osmol gap

Dose: Loading dose of 15 mg/kg followed by 10 mg/kg q 12hours x 4 doses then 15 mg/kg q 12h until toxic alcohol level below 20 mg/dl. Doses should be given slowly IV

ADR: Dizziness, HA, mild rash, mild LFT elevations
Dosing Antizol in patients requiring hemodialysis:

<table>
<thead>
<tr>
<th>Dose at the beginning of dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>If &lt; 6 hours since last Antizol dose:</td>
</tr>
<tr>
<td>Do not administer dose</td>
</tr>
<tr>
<td>If ≥ 6 hours since last Antizol dose:</td>
</tr>
<tr>
<td>Administer next scheduled dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose during dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose every 4 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing at the time dialysis is complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>The time between last dose and the end of hemodialysis</td>
</tr>
<tr>
<td>&lt; 1 hour</td>
</tr>
<tr>
<td>Do not administer dose at the end of dialysis</td>
</tr>
<tr>
<td>1-3 hours</td>
</tr>
<tr>
<td>Administer 1/2 of next scheduled dose</td>
</tr>
<tr>
<td>&gt; 3 hours</td>
</tr>
<tr>
<td>Administer next scheduled dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance dosing off hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Give next scheduled dose 12 hours from last dose administered</td>
</tr>
</tbody>
</table>

ETHANOL:
Mechanism: Preferred substrate of alcohol dehydrogenase thereby decreasing conversion of parent compounds to toxic metabolites
Indications: - MeOH or EG level > 20 mg/dl
- Hx of more than accidental "sip"
- Metabolic acidosis and/or osmol gap
Dose: - please see table below
- higher doses will be required in alcoholics
Route: PO or IV (IV should be used in all potentially serious cases)
Monitoring: - glucose (esp. in peds patients)
- Blood alcohol level target =100-150 mg/dl
  Should be checked 1 hour after load and hourly thereafter
Duration: Until levels are below 5-10 mg/dL and acidosis has resolved
  - May require 2-3 days of therapy
  - If levels are unavailable, a minimum of 24-48 hours needed
  - Typically, ethanol is continued for 12 to 24 hours after dialysis as some rebound effect can be seen
ADR: Decreased CNS/respiratory system, intoxicated and possibly agitated/aggressive patient, decreased glucose (pediatric patients mainly)
SODIUM BICARBONATE
Mechanism: Treatment of acidosis, enhances elimination of toxic EG metabolite, decreases CNS penetration of formic acid
Dose: 1-2 mEq/kg IV- may require large quantities
Monitoring: Fluid status, ABGs
Duration: Until acidosis has resolved

HEMODIALYSIS:
Indications: - MeOH/EG level > 20 mg/dl
- Acidosis resistant to treatment/serious s/sx; renal compromise
Remember: Need to adjust ETOH dosing (see below)
End Point: MeOH/EG level <10 mg/dl
Monitoring: Obtain MeOH/EG level before, 1-2 times during, and after dialysis

C. Toxin Specific Therapies

MeOH
FOLINIC ACID (Leucovorin)
Mechanism: Cofactor in metabolism of formic acid to carbon dioxide
Indications: Theoretical, folate deficient people but typically given in all seriously poisoned patients
Dose: If pt. is symptomatic give leucovorin 1mg/kg IV (up to 50 mg) q4-6h.

EG
PYRIDOXINE
Mechanism: May shunt metabolism away from production of oxalic acid to glycine since it is a cofactor in conversion of glyoxylic acid to nonoxalate compounds
Indication: All patients with serious EG exposure
Dose: 100 mg IV q 6 hours until intoxication resolves

THIAMINE 100 mg IV or IM q6h for two days or until intoxication resolves (works similarly to pyridoxine)

CALCIUM GLUCONATE 10%, 10-20 mL IV (0.2-0.3 mL/kg in children) or 10% calcium chloride 5-10 mL (0.1-0.2 mL/kg in children) for symptomatic hypocalcemia.
**ETHANOL DOSING**

**LOADING DOSE:**

<table>
<thead>
<tr>
<th>IV</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5-10 ml/kg over 30-60 min</td>
<td>0.8-1 ml/kg over 30 min of a</td>
</tr>
<tr>
<td>of a 10% solution</td>
<td>95% solution in 6 oz of OJ</td>
</tr>
</tbody>
</table>

**MAINTENANCE DOSE:**

<table>
<thead>
<tr>
<th>IV or PO</th>
<th>ON DIALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average 110 mg/kg/hr</td>
<td>+150 mg/kg/hr</td>
</tr>
<tr>
<td>Chronic  154 mg/kg/hr</td>
<td>+150 mg/kg/hr</td>
</tr>
<tr>
<td>Nondrinker 66 mg/kg/hr</td>
<td>+150 mg/kg/hr</td>
</tr>
</tbody>
</table>

10% Etoh IV

| Average 1.4 ml/kg/hr | 3.3 ml/kg/hr |
| Chronic  2 ml/kg/hr | 3.9 ml/kg/hr |
| Nondrinker 0.83 ml/kg/hr | 2.7 ml/kg/hr |

40% Etoh PO

| Average 0.3 ml/kg/hr | 0.7 ml/kg/hr |
| Chronic  0.4 ml/kg/hr | 0.8 ml/kg/hr |
| Nondrinker 0.2 ml/kg/hr | 0.6 ml/kg/hr |

95% Etoh PO

| Average 0.15 ml/kg/hr | 0.35 ml/kg/hr |
| Chronic  0.2 ml/kg/hr | 0.4 ml/kg/hr |
| Nondrinker 0.1 ml/kg/hr | 0.3 ml/kg/hr |

Begin Maintenance dose with Loading dose

754 mg/ml x 95/100.

10% Etoh: ml/kg = mg/kg divided by 790 mg/ml x 10/100.

If the patient already has ethanol on board:

Cp x Vd = dose in mg

Cp = difference between desired and actual blood alcohol level

Vd = for calculation use 6 dl/kg (0.6 L/kg)

doase in ml of 10% solution = dose in mg/[754 mg/ml x 95/100]

**VIII. MONITORING**

- **ABG's** - metabolic acidosis
- **Electrolytes** - Ca and Mg should be obtained in EG exposure
- **SCr/BUN** - esp. EG
- **CBC**
- **Microscopic U/A** - calcium oxalate crystals, proteinuria, hematuria
- **ECG** - can see prolonged QTc if hypocalcemia present
- **Vitals**
References

1. Antizol package insert, Orphan Medical
2. Ellenhorn's Medical Toxicology, Mathew J. Ellenhorn, 1997