Dialysis of Poisons

• Case presentation
  • Ethylene glycol overdose / intoxication

• Review of extracorporeal techniques for overdoses

• Newer uses for hemodialysis in overdoses
  • Baclofen
  • Dabigatran
Case presentation

HPI:

• 38 y/o Caucasian male with PMH notable for schizoaffective D/O, EtOH abuse, history of lithium use (? CKD), AKI in 9/2012 at an OSH complicated by hyponatremia, history SVT, alcoholic pancreatitis, low EF (40-45%) due to unclear etiology, and prior seizures, who presented with a 1 day history of severe gait instability, dysarthria, seizure activity, and 2 wks of progressively worsening AMS and behaviors which have been attributed to his psychiatric disease.

• He reportedly had headaches, increased agitation 2 wks ago, and may have accidentally drank bleach (? chlorine vs. peroxide based).

• Evaluated by multiple different psychiatrists in the weeks prior and was just started on Lithium & Valproic acid 2 days prior to presentation at UCLA. He was taking Zyprexa & Lexapro prior.
Case presentation

• The night PTA he was noted to be more altered, was fixated on obtaining cigarettes. He reportedly has very pronounced addictive & compulsive behaviors including smoking cigarettes (tobacco + electronic) and coffee (decaf) up to 50 cups/day.
• At dinnertime, he was incontinent of urine without noticing.
• At 2-3 AM, he tried to get cigarettes, went through the house, garage, and car in an attempt to find these. He locked himself outside and was found around 6AM under the house in the crawlspace, clearly soiled clothing but not incontinent.
• His gait at this time was noticeably worse, unable to walk without assistance. He showered, and then vomited "coffee" without blood. He could not remain upright, either standing or sitting.
• At this time, 911 was called.
Case presentation

ED course:
- Diffuse nystagmus, peri-orbital twiching, then some arm jerking movements concerning for seizure.
- His initial labs showed severe metabolic acidosis, and concern for toxic ingestion was entertained, and he was subsequently intubated for airway protection.

ALL: Ampicillin

Meds: Unknown doses of Zyprexa, Lexapro, Lithium and Valproic acid

FH: Notable for father with ESRD

Case presentation

Physical Exam:
- Vitals: T 98.3, P 103 reg, BP 138/95, R 18, O2 sat 97% RA
- GEN: Intubated, sedated, thin adult male
- Head: Limited ROM exam due to intubation.
- Eyes: PERRL, Sclera anicteric, EOMI
- Mouth: Intubated, MMM, OP clear
- Neck: Supple, no thyromegaly or palpable lymphadenopathy
- CV: RRR S1 S2 no m/r/g
- Pulm: CTA b/l, fair air movement
- Abd: Soft, NT/ND, + BS, no palpable organomegaly. Palpable aortic pulse in midline, approx. 2 cm.
- Ext: No c/c/e. +2 radial/DP bilaterally.
- Neuro: Limited exam, sedated, no nystagmus noted
- Skin: No rashes, jaundice, bruising.
Case presentation

ABG (post-intubation): 7.05 / 21 / 265 / 5.6 / 100%

UDS = negative for amphetamines, barbituates, BZD, THC, cocaine, methadone, opiates, ethanol

UA = SG 1.005, pH < 5, trace protein, 0 RBC, 0 WBC, 0 squam. cells.
(Repeat UA post-foley = 1+ blood, 1+ protein, 20 RBC, 11 WBC, 4 squam. cells, + calcium oxalate crystals)
Case presentation

Serum EtOH < 10
Acetaminophen < 10
Salicylate < 4
Lithium < 0.3
Valproic acid 15 (50-100 therapeutic)

Na 143, K 5.1, Cl 111, tCO2 11, BUN 8, Cr 1.0, Glu 89, Ca 10.4,
  Mg 1.9, Phos 4.2
→ Anion Gap 21 (Lactate 12 = normal)

Measured Osm 324 (Calculated Osm 294) → Osmolar gap 30

WBC 10.8, Hgb 15.6 (MCV 101), Plts 279
Case presentation

Assessment & Plan:
38 y/o Caucasian male with the following acute medical problems:
   Metabolic acidosis, severe, + AG, +OG, concerning for overdose from
   methanol, isopropyl alcohol, ethylene glycol, other volatile chemicals.
   Electronic cigarettes are often nicotine based in propylene glycol.
   Patient may have had access to "rubbing alcohol" (usually 70% isopropyl),
   "windshield cleaner" (methanol), unlikely "antifreeze" (ethylene glycol).

Recommendations:
- Emergent HD, fomepizole.
- Close monitoring of BMP, anion gap, osmolar gap.
- Follow up toxic levels (sent).
- Check CPK.
- Thiamine, B6 (pyridoxine), folic acid.
Case presentation

HD #2:
• Post-HD x1 with improvement in pH, tCO2.
• Remained intubated, agitated. No evidence of seizure activity
• Low BPs overnight, s/p IVF, no pressors.
• Fomepizole ongoing.
• Patient's mother went home after ED visit, and found bottle of "Antifreeze" (ethylene glycol) and insect deterrent (paraffinic oil) near entryway to crawlspace beneath house.
• Anion gap 19, Osmolar gap 10.
• UA (repeat) with calcium oxalate crystals.
Case presentation

Revised recommendations:

- Cont. HD today (#2) for ongoing osmolar gap, anion gap acidosis, with known ethylene glycol intoxication.

- Cont. fomepizole. Please note: fomepizole is dialyzable, and the frequency of its dosing should be increased to every four hours during hemodialysis. An additional dose should be given at the beginning of hemodialysis if six or more hours have elapsed since the prior dose.
Case presentation

HD #3:
- Anion gap 10, Osmolar gap 10. AKI ongoing.
- Clarification, isopropyl alcohol unlikely given + anion gap.
- Finished fomepizole.

HD #4: Anion gap 8, AKI ongoing.

  Psych evaluation = suicide attempt, patient admitted to drinking antifreeze.
Case presentation

HD #6-7:
• Pulled out HD catheter, agitated. Dilantin ppx for seizures, transfer to neuro service for AMS. DC seroquel, Rx Zyprexa prn.

Notable Meds:
• Pyridoxine 50 mg daily
• Thiamine 100 mg daily
• Folic acid 1 mg daily
• Multivitamin daily
• Phenytoin 300 mg IV daily
• Quetiapine 25 mg q8hrs
• Famotidine 40 mg daily
• Chlordiazepoxide 25 mg TID
Case presentation

HD #8:
• MICU for volume overload (+20L by I+O), febrile.
• ? PNA vs. CHF. NS IVF dc’d, Bicitra cont. for NAGMA.Lasix added.

HD #10: Floor. Respiratory status, acidosis, AKI improving.
HD #13: Inpatient psych. AKI resolving to Cr 0.8-1 (baseline) at one month. Required HD x 2 total.

Renal function remains stable as of March 2013.
Background

- Only 3% toxic exposures were treated in ICU setting
- Only 0.05% required extracorporeal treatment (2004)
- Extracorporeal therapy is indicated if severe toxicity exists, and total body elimination can be increased by 30% or more
- Whether removal of a substance is possible is highly dependent (characteristics of toxin, technique used)
- Majority of reported toxic exposures occur in kids (< 6 y/o), therefore understanding the importance of which substances are lethal even in low doses is key
Background

Pharmacokinetics:

- Absorption & bioavailability (% drug -> systemic circulation)
- Volume of distribution (Vd) is the theoretical dispersion of the substance in the body.
  - Amount of drug in the body / concentration of the drug in plasma.
  - Affected by obesity, ECF volume, CO, renal function, age, gender, etc.
  - Low Vd is < 1 L/kg
- Clearance is the theoretical volume of blood from which the substance is removed per unit time.
  - Native clearance depends on the ability of a molecule to pass across the GBM into the urine, a function of molecular size, charge, urine flow rate (ml / min). Solute removal is via convection (filtration) & modified by tubules.
Background

Indications of severe toxicity

1) Ingested quantity associated with severe toxicity
2) Ingestion of a toxin with serious delayed effects
3) Natural removal mechanism impaired
4) Clinical condition deteriorating
5) Clinical evidence of severe toxicity: hypotension, coma, metabolic acidosis, respiratory depression, dysrhythmias or cardiac decompensation
Background

Substances able to kill children at low doses

- Calcium antagonists
- Camphor
- Clonidine & other imidazolines
- Lomotil
- Opiates
- Salicylates
- Toxic alcohols
- Tricyclic antidepressants
Osmolar Gap

Calculated Osm - Measured Osm = Osmolar gap
Measures Osm = 2 (Na) + Glu / 18 + BUN / 2.8
Significant OG if > 15 mOsm/L
Can correct for ethanol: EtOH level / 4.5
  • Then an OG > 10 significant

Estimate alcohol level from OG:

<table>
<thead>
<tr>
<th>Drug (MW)</th>
<th>Toxic level</th>
<th>Corr. Factor</th>
<th>Toxic ΔOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol (32)</td>
<td>&gt;50</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Ethanol (44)</td>
<td>&gt;400</td>
<td>4.5</td>
<td>88</td>
</tr>
<tr>
<td>Ethylene glycol (62)</td>
<td>&gt;25</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Isopropanol (100)</td>
<td>&gt;350</td>
<td>5</td>
<td>75</td>
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</table>
Extracorporeal techniques

- Hemodialysis
- Continuous hemofiltration
- Hemoperfusion
- MARS (molecular adsorbent recirculating system)
## Extracorporeal properties

<table>
<thead>
<tr>
<th></th>
<th>Hemo-dialysis</th>
<th>Hemo-filtration</th>
<th>Hemo-perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solubility</strong></td>
<td>Water</td>
<td>Water</td>
<td>Water or lipid</td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
<td>&lt; 500 Da</td>
<td>&lt; 40 kDa</td>
<td>&lt; 40 kDa</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>Low (&lt; 80%)</td>
<td>Low</td>
<td>Low or high</td>
</tr>
<tr>
<td><strong>Volume of distribution (Vd)</strong></td>
<td>&lt; 1 L/kg</td>
<td>&lt; 1 L/kg</td>
<td>&lt; 1 L/kg</td>
</tr>
<tr>
<td><strong>Endogenous clearance</strong></td>
<td>&lt; 4 ml/min/kg</td>
<td>&lt; 4 ml/min/kg</td>
<td>&lt; 4 ml/min/kg</td>
</tr>
<tr>
<td><strong>Distribution time</strong></td>
<td>Short</td>
<td>Longer</td>
<td>Short</td>
</tr>
</tbody>
</table>
Hemodialysis (HD)

- Toxins & other substances are cleared from the blood by diffusion across a semi-permeable membrane down a concentration gradient from blood to dialysate.
- Toxic substance must be water soluble, have low MW, low protein binding, and low volume of distribution.
- Clearance of the toxin depends on membrane surface area (& type), blood and dialysate flow rated.
- High-flux membranes can also remove higher MW toxins.
- Risk for post-HD “rebound” due to redistribution of toxin.
Continuous techniques

Continuous hemofiltration (CVVH, CVVHD)

• Blood passes through large hollow pore fibers, allowing convective removal of molecules up to 40kDa.
• Useful in unstable patients
• Prolonged duration of therapy, minimizes rebound effects
• Disadvantages however include lower clearance vs. HD
  • CVVH with post-dilution, clearance is equal to UF flow rate (usually not > 4L / hr or 67 ml/min (vs. 500 ml/min in HD)
Hemoperfusion

- Blood passes through a cartridge with sorbent material able to absorb the toxin
- Charcoal based, synthetic resins, anion exchange
- Toxic substance must have binding affinity to the sorbent & have a low volume of distribution
- Charcoal efficiently removes molecules in 1000-1500 kDa range, but doesn’t remove protein-bound molecules
- Resins more effective with protein/lipid-bound toxins
- Generally declining modality due to limited use, poor life of cartridges (change q2-3hrs), more technically difficult to perform, unable to correct acid-base, fluid, electrolytes
- Could combine with HD however (in series)
MARS

Molecular adsorbent recirculating system (MARS)
• Blood purification system aimed at removing albumin-bound toxins
• Three serial extracorporeal circuits: blood, albumin detoxification, hemodialysis
MARS

blood pump
MARS-Flux

adsorption columns

low-flux dialyzer
bicarbonate buffered dialysate

albumin pump

blood circuit
albumin circuit

single pass dialysis
MARS

Blood from patient

MARS membrane

Albumin dialysate

Dialysis membrane

Haemofiltration/ Haemodialysis circuit

To patient

Anion Exchange Resin

Activated Charcoal

MARS membrane

Blood Plasma

Albumin with toxins bound

Toxin

Binding sites on MARS membrane

Albumin Dialysate
Intoxications for EC Therapies

- Barbituates (HP)
- Lithium (HD) – 74 Da
- Metformin (HD) – 166 Da
- Salicylates (HD)
- Theophylline (HP) - > 50% protein bound
- Toxic alcohols (HD) – EG, Methanol, Isopropanol
- Valproic acid (HD) – 144 Da
- Carbamazepine (HD)

- Possibly: Diltiazem (MARS), Phenytoin (MARS), Mushrooms (MARS)
# List of Drugs, Toxins by Modality

<table>
<thead>
<tr>
<th>HD</th>
<th>CRRT</th>
<th>Hemoperfusion</th>
<th>Plasmapharesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Lithium</td>
<td>Carbamazepine</td>
<td>Phalloids</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td></td>
<td>Paraquat</td>
<td></td>
</tr>
<tr>
<td>Methanol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Valproic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Theophylline</td>
<td>Theophylline</td>
<td></td>
</tr>
</tbody>
</table>
Lithium

Dialysis indications:
• Serum Li level > 3.5
• Serum Li level > 2.5 with symptoms & decreased GFR
• Moderate intoxication with expectation that lithium levels will increase (or not decline) to therapeutic range in 36hrs
• Continue HD until Li level < 1
• Expect rebound 6-8 hrs after HD session

Pharmacokinetics
• Vd = 0.7-0.9 L/kg
• Mild & moderate intoxication = 1.5-2.5, 2.5-3.5 mmol/L
  • Neuromuscular irritability, nausea, diarrhea
• Severe intoxication > 3.5 mmol/L
  • Seizures, stupor, permanent neurologic damage
• Therapeutic < 0.6 mmol/L
Toxic alcohols

Fomepizole (4-methyl-pyrazole)

- Blocks metabolism of alcohols to their toxic metabolites (alcohol dehydrogenase = AD) just like ethanol does
- Has > 8000 fold higher affinity for AD than EG, > 800 than EtOH
- Recommended use:
  - Ingestion of alcohol, concentration > 20 mg/dl
  - Recent ingestion with osmolar gap > 10 mOsm/L
  - Strong clinical suspicion of ingestion of alcohol and 2 of the following: arterial pH < 7.3, tCO2 < 20, osmolar gap > 20 mOsm/L (or urinary oxalate crystals if ethylene glycol)
  - Loading dose (10-15 mg/kg), 10 mg/kg q12hrs x 4 doses, then 15 mg/kg q12hrs until EG < 20, asymptomatic, normal pH
  - Most effective prior to onset of AG metabolic acidosis
Toxic alcohols

Metabolism of the Alcohols

- Ethylene glycol
  - “antifreeze”
  - Glycoaldehyde
  - Glycolic acid
  - Glyoxylic acid
  - Oxalic acid

- Methanol
  - “wood alcohol”
  - Formaldehyde
  - Acetaldehyde
  - Acetate

- Ethanol
  - “rubbing alcohol”, “antifreeze”, windshield, de-icing
  - Acetone

- Isopropanol
  - “rubbing alcohol”, “antifreeze”, windshield, de-icing

Toxic alcohols & toxic metabolites.
AD = alcohol dehydrogenase)
Toxic alcohols

Dialysis indications:

- Severe metabolic acidosis, pH < 7.2
- AKI or electrolyte imbalances, medically refractory
- Deteriorating VS despite intensive care
- Alcohol level > 50 mg/dL unless fomepizole is administered, patient is asymptomatic, and pH is normal.

Can also help metabolism of toxic metabolites to nontoxic byproducts with pyridoxine (B6) and thiamine (B1) in ethylene glycol poisoning, folate in methanol poisoning.
Toxic alcohols

Ethylene glycol

- HD until the level is < 20 mg/dl or without a level, recommend HD x 8+ hrs repeated BID
- Glycolic acid has long half-life, slow elimination rate, but also low MW (76 Da), water-soluble, low Vd (0.55 L/kg)
- Therefore, a low EG level with increased AG = glycolic acid levels, and should perform HD

Methanol

- If very high levels may need HD x 18-21 hours, repeated q24hrs if there is rebound toxicity.
- Avoid heparin given risk of ICH, particularly basal ganglia.
- Folate (folinic acid) helps increase the metabolism of formic acid to CO2 + H2O.
Ethylene Glycol – chronic OD

Case report (Oslo, Norway)

• 26 year-old female with dissociative disorder.
• Admitted with EG poisoning 154 times.
  • Fomepizole = 99
  • Ethanol = 60
  • Fomepizole + ethanol = 6
  • Dialysis = 73
• Long-term lab review correlated EG level with OG
• Eventually expired with EG level 506 mg/L (!)
• Autopsy: Calcium oxalate crystals in kidneys, slight liver steatosis, pulmonary edema
Salicylates

Overdose in adults:
• Characterized by respiratory alkalosis (stimulate the respiratory center in medulla) and then metabolic acidosis (lactic acid from interruption of mitochondrial electron transport chain).
• CNS symptoms = severe poisoning
• Immediate goal of Rx -> reverse acidosis & alkalosis to prevent respiratory collapse, as vent management is difficult to maintain high RR and concern for respiratory dys-synchronization

Alkalization of urine is paramount (if UOP ok)
• Prevents reabsorption of salicylates
• K administration prevents hypokalemia & acidification of urine
• Low pH allows more salicylate to cross BBB, increased CNS tox.
• Goal urine pH > 5
Salicylates

Dialysis indications:

- CNS depression at level > 50 mg/dl
- Salicylate level > 80 mg/dl
- Salicylate-induced pulmonary edema
- Continue HD until level < 10 mg/dl

Pharmacokinetics

- MW = 38-180 Da
- Vd = 0.17 L/kg (? Enteric coated ASA)
- At therapeutic levels, 90% salicylates are protein-bound, but unbound % increases as the total concentration increases
- 50% protein-bound drug is removed with IHD
Theophylline

- Phosphodiesterase inhibitor
- Toxicity even at levels > 15 mcg/ml (in therapeutic range), mostly toxic > 25 mcg/ml.
- Overdose can occur with acute or chronic ingestion.
- Seizures at > 40 mcg/ml (chronic) vs. > 120 (acute).
- Neuropsych symptoms, GI hypermotility, increased cardiac excitation. Fevers, hypotension, hypoK/Phos/Ca.
- Treatment: IVF, electrolyte Rx, alkalanization, charcoal
- Pharmacokinetics: Vd 0.4-0.6 L/kg, ~ 60% Alb bound.
- HD is safer than HP, although could use in series.
  - Initiate at > 100 (acute) or > 60 (chronic)
  - Continue until level < 20
TCAs (Tricyclic Antidepressants)

- Maybe in ~ 25% adult intoxications.
- Lactic acidosis, hypotension, seizures, conduction delays & ventricular arrhythmias.
- Serum level less helpful than clinical picture
- Rapidly but erratically absorbed via GI tract
- High Vd (20-50 L/kg), highly protein bound (>90%), large molecules generally
- Case reports suggest HD or HP may be helpful
Baclofen

- Eliminated mostly by kidney, encephalopathy usually found with renal failure patients.
- Case report:
  - 55 y/o male with 420 mg baclofen -> intubated for resp. depression.
  - Consciousness returned 9 hrs later after HD, extubated.
  - Half-life pre-HD = 15.7 hrs, post-HD = 3.1 hrs.
  - Initial level = 1167 ng/ml → 424 ng/ml post-HD
  - Therapeutic level is 80-400 ng/ml
Dabigatran

• Oral direct thrombin inhibitor
• Approved in USA 2010, and since drug-associated hemorrhage has garnered much attention (lawyers too).
• Small (471 Da), lipophilic molecule (large Vd), 35% protein bound, > 80% renally cleared.
• Methods to reverse Coumadin are ineffective
• Case reports:
  • NYU: 80 y/o male, hemoptysis, s/p 2 units FFP, INR 7-8. HD x 1, and level went from 1100 -> 18 ng/ml over 4 hrs, rebounded to 100ng/ml 20 minutes after HD. No further bleeding.
  • UC-Davis: 94 y/o male, fall, large SDH with midline shift, alert but hesitant for invasive NSx procedure. INR 1.5. Level 312 ng/ml. HD x 1, level fell to 29, rebounded to 43.
Sources