Surgical Critical Care: Poisoning and Toxicology

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Toxicology

• “All substances are poisons, there is none which is not a poison. The right dose differentiates a poison from a remedy” Paracelsus, 1493-1541

• Dosis facit venenum
  The dose makes the poison

• Study of the effects of drugs, poisons, toxic substances on the physiology of living organisms
Poisoning

- 5-14% of adult ICU admissions
- Second leading method of suicide (behind firearms)
- 50% of intentional ingestion misreported
- Toxico-kinetic stages
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
# Deaths from Poisoning

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>410</td>
</tr>
<tr>
<td>- Alone</td>
<td>170</td>
</tr>
<tr>
<td>- Combination</td>
<td>240</td>
</tr>
<tr>
<td>Sedative/hypnotic/antipsychotic</td>
<td>395</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>280</td>
</tr>
<tr>
<td>Opioids</td>
<td>266</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>260</td>
</tr>
<tr>
<td>Alcohols</td>
<td>169</td>
</tr>
<tr>
<td>Stimulants/street drugs</td>
<td>133</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>81</td>
</tr>
</tbody>
</table>

Mechanism of Action

• Usually functional reversible
  o Support organ function until toxin elimination

• Exceptions – fatal cellular damage
  o Acetaminophen
  o Carbon monoxide
  o Corrosives
  o Toxic alcohols
  o Heavy metals
  o Neurotoxic hydrocarbons
# Physiologic Assessment

<table>
<thead>
<tr>
<th>Excited</th>
<th>Depressed</th>
<th>Discordant</th>
<th>Normal</th>
</tr>
</thead>
</table>
| **Sympathomimetics**  
  - Amphetamines  
  - Cocaine  
  - MAO-I   | **Sympatholytics**  
  - ACE-I  
  - B-blockers, CCB  
  - TCA  
  - Digitalis   | **Asphyxiants**  
  - CO, cyanide  
  - Hydrogen sulfide  
  - Herbicides   | **Nontoxic exposure** |
| **Anticholinergics**  
  - Antihistamines  
  - Atropine  
  - TCA   | **Cholinergics**  
  - Insecticides  
  - Nicotine  
  - Pilocarpine   | **AGMA inducers**  
  - Ethylene glycol, methanol  
  - Salicylate, Valproic   | **Toxic time bombs**  
  - Acetaminophen  
  - Mushrooms  
  - Anticholinergics   |
| **Hallucinogens**  
  - LSD  
  - Amphetamine  
  - PCP   | **Opioids**  
  - Analgesics  
  - Heroin   | **CNS syndromes**  
  - INH  
  - Solvents  
  - Strychnine   | **- Carbamazepine**  
  **- Digitalis**  
  **- Ethylene glycol**  
  **- Heavy metals**   |
| **Withdrawal**  
  - B-blockers, TCA  
  - Clonidine  
  - EtOH, opioids   | **Sedative-Hypnotics**  
  - EtOH, benzos  
  - Anticonvulsants  
  - Barbituates   | **Membrane active**  
  - Antiarrhythmics  
  - TCA, heavy metals  
  - Local anesthetics   | **- Methanol**  
  **- MAO-I**  
  **- Salicylates**   |
Toxidromes

- **Anticholinergic**
  - Tachycardia
  - Hyperthermia
  - Hallucination
  - Dry mouth
  - Mydriasis
  - Ileus
  - Urinary retention
  - Dry, flushed skin

- **Narcotic**
  - ↓RR, miosis, ↓LOC, ↓BP

- **Sedative/hypnotic**
  - ↓RR, ↓LOC, ↓BP

- **Sympathomimetic**
  - Mydriasis
  - Agitation
  - Diaphoresis
  - Hypertension
  - Hyperthermia
  - Tachycardia

- **Cholinergic**
  - Salivation
  - Lacrimation
  - Urination
  - Defecation
  - GI cramps
  - Emesis
  - Bradycardia, miosis, confusion
Treatment Objectives

- Resuscitation
- Prevention of further exposure
- Enhanced elimination
- Antidotal therapy
Resuscitation

- Airway
- Breathing
- Circulation
- Depressed level of consciousness
  - Naloxone 0.2-4+ mg
  - Thiamine 100mg
  - 50% glucose 25-50g
Prevention of absorption

- Body cavity exposure
- Eye and skin exposure
- Inhalational exposure
- Ingestion
  - Activated charcoal – 1g/kg, most effective if 1-2h after ingestion
    - Not indicated for acids, alkali, hydrocarbons, Fe, lithium, cyanide
  - Gastric lavage – left lateral decubitus
  - Whole bowel irrigation
  - Surgery – cocaine packets with toxicity
  - Dilution – corrosive ingestion
  - Ipecac/cathartecis – NO evidence
Enhanced Elimination

• Diuresis, manipulation of urinary pH
  o Sulfonamides, salicylates, barbituates
  o 3-8cc/kg, urine pH > 7.5

• Multiple-Dose Activated Charcoal
  o Binds toxins:
    • excreted in bile
    • secreted by intestinal cells
    • passively diffuse into gut

• Extracorporeal Methods
  o PD, HD, hemoperfusion, hemofiltration, plasmapheresis, exchange transfusion
  o Hemodialysis
    • Barbituate, bromide, chloral hydrate, EtOH, ethylene glycol, isopropyl alcohol, lithium, methanol, procainamide, acetaminophen, theophylline, salicylate, heavy metals
<table>
<thead>
<tr>
<th>Agent</th>
<th>Antidotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Physostigmine</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Vitamin K, protamine, PCC</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Flumazenil</td>
</tr>
<tr>
<td>B-antagonists</td>
<td>Glucagon, calcium salts</td>
</tr>
<tr>
<td>CCB</td>
<td>Calcium salts, glucagons</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Cholinergics</td>
<td>Atropine, pralidoxime</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Nitrites, thiosulfate, hydroxycobal</td>
</tr>
<tr>
<td>Digoxin (digitalis)</td>
<td>Fab Antibody fragments, magnesium</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Ethanol, 4-methylpyrazole, pyridoxine, thiamine</td>
</tr>
<tr>
<td>Envenomations</td>
<td>Antivenins</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Calcium and magnesium salts</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Dimercaprol, D-penicillamine, calcium disodium, EDTA</td>
</tr>
<tr>
<td>Hydrogen sulfide</td>
<td>Oxygen, nitrites</td>
</tr>
<tr>
<td>Iron</td>
<td>Deferoxamine</td>
</tr>
<tr>
<td>INH</td>
<td>GABA agonists, pyridoxine</td>
</tr>
<tr>
<td>Methanol</td>
<td>Ethanol, 4-methylpyrazole, folate</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Methylene blue</td>
</tr>
<tr>
<td>Opiods</td>
<td>Naloxone, nalmefene, naltrexone</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Adrenergic blockers</td>
</tr>
</tbody>
</table>
Acetaminophen

• Consider co-ingestion
• Early charcoal use
• Assess level 4h after ingestion
• Rumack-Matthew nomogram for single ingestion
• Additional level 4h later for extended-release
• Antidote: N-acetylcysteine
  o Best in 8h, works up to 24h later
IV N-acetylcysteine

- Preferred especially if:
  - > 8-10h after ingestion
  - encephalopathy

- Dose:
  - 150mg/kg over 15 min
  - 50mg/kg over 4h
  - 100mg/kg over 16h

- Dosing regimen 20h, but if given late continue

- Anaphylactoid reactions in 14-18%
  - Hypotension, bronchospasm, rash, death
  - Caution with asthma
  - Treat with diphenhydramine
Oral N-acetylcysteine

- Dose: 140mg/kg, then 70mg/kg every 4h for 17 doses (72h)
- NG tube for administration
- Antiemetics
- No dosage adjustment needed with charcoal
- Redose within 1h if vomiting
Alcohols and Glycol

Alcohol Dehydrogenase

- Ethanol
- Methanol
- Ethylene Glycol
- Methanol

Subproducts:

- Glycoaldehyde
- Glycolic acid
- Glyoxylic acid
- Oxalic acid
- Acetaldehyde
- Acetate
- Acetyl CoA
- Formaldehyde
- Formic acid
Ethylene Glycol and Methanol

• Early
  o CNS, GI (methanol), cardiopulmonary symptoms
  o Osmol gap
    • $2 \times \text{Na} + (\text{glucose} / 18) + (\text{BUN} / 2.8) + \text{EtOH}/4.6$
  o Oxalate crystals (ethylene glycol)

• Late
  o Visual disturbances/ophthalmologic findings (methanol)
  o Renal failure, myositis, seizures (ethylene glycol)
  o Anion gap metabolic acidosis
Ethylene Glycol and Methanol

- **Treatment**
  - IV sodium bicarbonate to pH \( \geq 7.3 \)
  - Inhibition of alcohol metabolism
    - Ethanol (PO or IV)
    - Fomepizole
  - Hemodialysis
    - Renal failure
    - Severe metabolic acidosis pH \(< 7.25\)
      - End organ toxicity
        - Kidneys (ethylene glycol)
        - Visual (methanol)
    - Concentration > 25-50 mg/dL
Ethanol Therapy

- Preferred substrate for ADH – competitive inhibitor
- Oral (20-30%) or IV (5-10%)
- Loading dose: 0.8g/kg of 100% EtOH
- Goal serum level of 100-150mg/dL
- Side effects
  - Sedation/agitation
  - Hemodynamic instability
  - Respiratory depression
  - Hypoglycemia
  - Gastritis
Fomepizole Therapy

• More potent competitive inhibitor of ADH

• Advantages
  o no CNS/behavior issues
  o no concentration monitoring
  o Wide therapeutic margin, fixed dosing

• Disadvantage - Expense

• Loading dose: 15mg/kg

• Maintenance (12h after loading)
  o 10mg/kg q 12h x 48h then
  o 15mg/kg q 12h

• Higher frequency during dialysis
Additional Therapies

- Ethylene glycol
  - IV pyridoxine (100mg) qDay
  - IV thiamine (100mg) qDay
  - Ethylene glycol undetectable, metabolic acidosis resolved

- Methanol
  - IV Folinic acid (leucovorin) or folate
  - 1-2mg/kg q4-6h
  - Methanol undetectable, metabolic acidosis resolved
Propylene Glycol

- Solvent, antifreeze, used in pharmaceuticals
  - IV lorazepam (Ativan), diazepam (Valium), etomidate, phenobarbital, pentobarbital, phenytoin (Dilantin), procainamide, nitroglycerin, theophylline
  - Topical silver sulfadiazine (silvadene)
- Rapid IV infusion (Dilantin load)
  - Prolonged PR and QRS duration
  - Idioventricular rhythms
  - Cardiorespiratory depression/arrest
- Prolonged use, > 3 days of high doses
- Seizures, renal dysfunction, CNS depression, arrhythmias
- Osmolar gap with anion gap acidosis, ↑ lactate
- Stop therapy, support
B-Blocker, CCB Toxicity

- Atropine, IVF, vasopressor
- Hyperinsulinemic euglycemia
  - Insulin bolus – 1 U/kg with 25-50ml of D50W IV
  - Infusion at 1 U/kg/h and dextrose at 0.5 g/kg/h
- Calcium chloride (1g) over 5 min, repeat q10-20 min for 3-4 doses
- Glucagon (5-10mg) IV bolus, repeat q1 min or drip
- Ventricular pacing
- Sodium bicarbonate
- Milrinone (phosphodiesterase inhibitor)
- Lipid emulsion - maybe
Antidepressants

- SSRI
  - Serotonin syndrome
    - Altered mental status
    - Autonomic dysfunction
    - Neuromuscular irritability
  - Supportive
    - Sedation
    - Paralysis
    - Intubation
    - Anticonvulsants
    - Active cooling
  - Cyproheptadine (serotonin antagonist) 4-12 mg PO q8h
Antidepressants

• Cyclic antidepressants
  o CNS depression, seizures, hypotension, dysrhythmias, cardiac conduction abnormalities
  o Activated charcoal (some enterohepatic circulation), intubation (prevent respiratory acidosis), treat seizures, sodium bicarb (for acidosis and cardiac conduction abnormalities)

• MAO-I
  o Initial neuromuscular excitation (hyperadrenergic state) then
  o Catecholamine depletion
  o High dose benzodiazepine
  o Cooling, possible RSI and paralysis
  o Alkalization until cardiac conduction improves
  o Nitroprusside, nitroglycerin, esmolol -> epi, norepi
Cocaine

- **Sympathomimetic overdrive**
  - Tachycardia, hypertension, dilated pupils, agitation, hyperthermia, rhabdomyolysis

- **Cardiovascular effects**
  - Chest pain common, 6% have AMI
  - 18-45 y/o 25% of AMI are due to cocaine
  - Cardiac conduction
    - Prolonged QRS and QTc
  - Dyrhythmias
    - Sinus tachycardia, a.fib/flutter, SVT, V.Tach, V.fib, Torsade de pointes
  - Acute intestinal infarction
Cocaine

- No specific antidote
- Benzodiazepine
- Haldol
- Aggressive cooling
- Beta-blockers contra-indicated
  - Unopposed alpha stimulation
  - Paradoxic exacerbation of HTN
  - Worsening coronary vasoconstriction
- Acute Coronary Syndrom
  - ASA, benzo, NTG
  - Phentolamine (alpha-blocker) or CCB
  - False-positive ST-segment elevations – up to 43%
Amphetamines

• Ingestion, inhalation, intranasal, rectal, SC, IM, IV
• Catecholamine release
• Complications
  o AMI – Benzo, Beta-blocker ok, after r/o cocaine, CCB
  o Dysrhythmias
  o Cardiomyopathy
  o Intracranial bleed
  o Hyperthermia, rhabdomyolysis
  o Bronchospasm, pulmonary edema, ARDS – treat as normal
  o Pneumomediastinum, pneumothorax
Phencyclidine

- PCP – related to ketamine
- Ingested, inhaled or injected
- Delirium
- Violent or agitated behavior, rigid extremities
- Rhabdomyolysis
- Treatment
  - Benzos
  - Haldol
Narcotics/Opioid

- Miosis, respiratory failure, coma

- Naloxone
  - IV, IM, endotracheal, SL
  - 0.1-10 mg
  - 2mg frequent starting dose
  - t½ of 60-90min

- Fentanyl not detected on screening
Sedative/Hypnotic

• Benzodiazepines
  o GABA receptor binding
  o Flumazenil may precipitate withdrawal syndrome with seizures
    • Contra-indicated in TCA or chronic benzo use

• Barbiturates
  o Multi-dose activated charcoal
  o Hemodialysis or hemofiltration if cardiovascular instability

• Muscle relaxants, other sedatives
  o Soma, baclofen
  o Gamma hydroxybutyrate (GHB) or “pine needle oil”
Lithium

- Bipolar, depression, schizophrenia
- Induces neutrophilia 1.5-2x normal leukocyte counts
- Toxic if > 2.5-5 mmol/L
  - CNS
  - Renal (95% renal excretion)
    - Nephrogenic DI, Na wasting nephritis
  - Non-specific cardiac abnormalities
- Whole bowel irrigation
- IVF resuscitation to improve renal clearance
- +/- Kayexalate
- CRRT or HD if severe
Hydrofluoric Acid

- Industrial reagent 6-90%
  - High concentration – tissue injury
  - Low concentration – life-threatening hypocalcemia and hypomagnesemia
- Irrigation for > 15 min
- Calcium gluconate 2.3-2.5% water-soluble gel
  - At least 30 minutes
- Intra-arterial (or IV with Bier block) calcium perfusion
  - 50 mL of 2.5% calcium gluconate in saline over 4h, may repeat
- Inhalation
  - Supportive
  - Possible role for nebulized calcium gluconate solution
Salicylate

- N/V
- CNS disturbances
- Vasodilation/sweating, fever
- Dehydration, osmotic diuresis, HCO3 loss
- ↓Na, K, HCO3, iCa
- Respiratory alkalosis
  - Direct stimulation of medullary respiratory center
- Anion gap metabolic acidosis
- Coagulopathy
- Pulmonary edema
- Hepatotoxicity
Salicylate

- **Hydration**
  - Underappreciate a possible 5-6L volume deficit
- **If intubation, ensure hyperventilation to prevent life-threatening acidosis, give HCO3 prior to intubation**
- **Urine alkalization (pH 7.5)** UOP 1-2 cc/kg/h, replete K
- **Multi-dose activated charcoal, gastric lavage, whole bowel irrigation**
- **Hemodialysis**
  - 100 mg/dL salicylate level common threshold
  - Seizure, AMS, cerebral/pulmonary edema, renal failure
  - Refractory acidosis, T > 38
  - HCO3 rich bath, ensure adequate hydration
Hospital Acquired

• Gabapentin – AMS, coma
• Propylene glycol (Ativan)
• Topical anesthetics (methemoglobinemia)
  o 50mg IV methylene blue
• Propofol infusion syndrome
  o Sepsis, CHI, poor oxygen delivery
  o ICU patients (4 mg/kg/hr, 48h)
  o Surgical patients with lower dose
    • Myocardial failure, arrhythmias, bradycardia
    • Lactic acidosis
    • Hyperkalemia
    • Rhabdomyolysis
    • ARF
    • Hyperlipidemia
Questions

1. CHI trauma patient intubated and on lorazepam infusion for withdrawal, receiving 12mg/h. On PTD#4 he develops a new anion gap acidosis and osmolar gap. Which intervention is best?
   - A) Stop lorazepam, start midazolam infusion
   - B) Stop lorazepam, start diazepam infusion
   - C) Stop lorazepam, start fentanyl infusion
   - D) Initiate hemodialysis
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Propylene glycol toxicity
Questions

2. A 30 y/o M s/p self-inflicted radial artery injury from suicide attempt and history of depression, presents with altered mental status and EKG changes:

- A) Amiodarone
- B) Cardioversion
- C) Magnesium sulfate
- D) Sodium Bicarbonate
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- C) Magnesium sulfate
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Antidepressant toxicity
Wide complex tachycardia
Questions

3. A 40 y/o M s/p auto-pedestrian accident with pulmonary contusion and rib fractures, toxicology screen positive for cannaboids and cocaine has chest pain & the following EKG changes:

Which is not appropriate:

A) Phentolamine
B) Aspirin
C) Metoprolol
D) Nitroglycerin
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B) Aspirin  
C) Metoprolol  
D) Nitroglycerin

No B-blockers in cocaine toxicity
Thank you