Toxicology

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Overview

- Discuss toxicology of acute adult ingestions
- Discussing cases without confounding co-ingestants
- Will review toxidromes that are unlikely to cause harm and several that have the potential for significant morbidity and mortality
- Poison control (24hrs): 1-800-222-1222

Father of Toxicology - Paracelsus

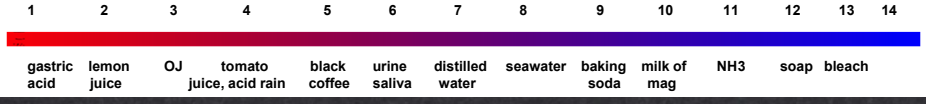
All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison.

Things That Will Probably Not Kill You!

Author: 1ur1 (CC BY 2.0)

Caustic Ingestions

- Alkali ingestions (drain cleaners) with pH of 12+
  - damage the esophagus through liquefactive necrosis
- Acid ingestions (toilet bowl or swimming pool cleaners, antirust compounds, battery fluid)
  - damage the stomach (intrinsic pH 4-5; drops to 1.5-2.5 for protein digestion)
  - Ingestion usually limited due to oropharyngeal pain.
  - Bad taste: choking, gagging.
  - Pylorospasm → stagnation → coagulation necrosis to form a protective eschar



Caustic Ingestions

- Household bleach: 5% sodium hypochlorite, pH 11
  - Hypochlorite used to clean root canals
    - Periapical extrusion: pain, swelling, hemorrhage

Author: Stikeseff (CC BY-SA 4.0)

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Author: Stikeseff (CC BY-SA 4.0)

Author: Vaoverland (CC BY-SA 3.0)

Diphenhydramine

- First generation H1 antihistamine with antimuscarinic properties
- Can bind and interact with cardiac fast sodium channels, and at higher concentrations, repolarizing potassium channels
  - wide complex tachycardia, intraventricular conduction delay, QTc prolongation, Brugada pattern
- The estimated fatal oral dose of diphenhydramine for adults is 20–40 mg/kg = 56 tabs in a 70kg adult.

Author: ParentingPatch (CC BY-SA 3.0)

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NSAIDs (excluding aspirin)

- Over 20 different types
- Reversibly inhibits cyclooxygenase (prostaglandin synthase) to cause a downstream decrease in prostaglandins
- Nonselective and COX-2 selective (eg celecoxib/Celebrex)
  - COX-2 selective have less GI side effects such as peptic ulceration but promote thrombosis (MI)

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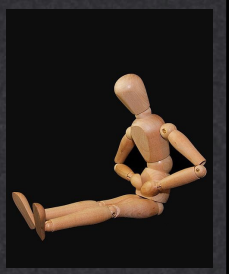
Author: Vaoverland (CC BY-SA 3.0)

Clinical presentation: largely GI symptoms

Treatment: supportive care

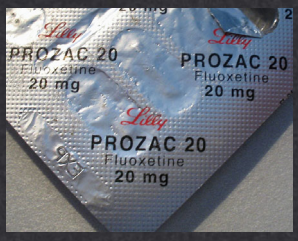


Author: Wolfgang Claussen

Image courtesy of Colin Kaide, MD

SSRIs

- Most widely prescribed antidepressant class
- First SSRI on the US market was fluoxetine (Prozac®); FDA approved in 1987
- Limits reabsorption of serotonin in presynaptic cells, increasing serotonin levels in the synaptic cleft



Author:Maksim (CC BY-SA 3.0)

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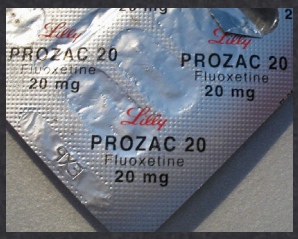
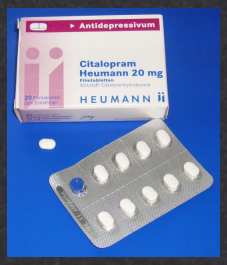


Author:Maksim (CC BY-SA 3.0)

Author: Vaoverland (CC BY-SA 3.0)

- SSRIs generally have a wide therapeutic index: ingestion 10x therapeutic dose rarely causes toxicity
- Clinical presentation
  - Central nervous system depression
  - Seizures can occur occasionally after overdose with SSRIs, particularly citalopram
- citalopram also causes QT-interval prolongation
- Patients with SSRI overdose have a 10 to 14 percent incidence of serotonin syndrome, but many of these are mild presentations



Author: Fimpelman (CC BY 3.0)

Now for…..

Author: Debivort (CC BY-SA 3.0)

Recurrent Questions

- Would they benefit from activated charcoal?
- Would they benefit from Go-Lytely®?
- Would they benefit from hemodialysis?
- Is there a specific antibody therapy (Praxbind®, DigFab®)?
- Antidote?

Ccb/bb overdose – Grim Reaper/kitchen sink

- Dihydropyridines versus non-dihydropyridines
- Beta blockers with high lipid solubility (eg, propranolol) rapidly cross the blood brain barrier
- Sotalol also has class III antidysrhythmic properties → blocks delayed potassium channels → QTc prolongation, torsades
- CCB toxicity: hyperglycemia from inhibition of calcium-mediated insulin release; rarely clinically significant except for diagnostic purposes

Author: W.carter (CC BY-SA 4.0)

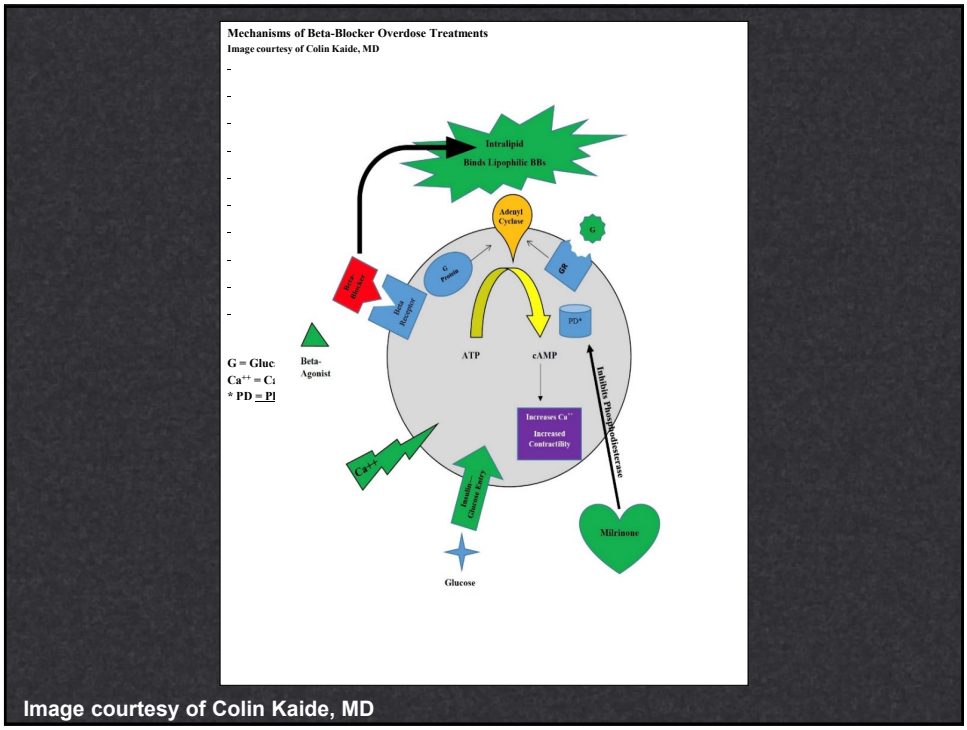


Image courtesy of Colin Kaide, MD

Drugs for Treatment of Beta Blocker Overdose		
Drug	Dosage	Comment
Glucagon	**Bolus:** 3-5 mg intravenously (0.03 – 0.15 mg/kg in pediatric patients). Repeat dose in 10 minutes if needed. **Infusion:** 2-5 mg/hr (or at bolus dose where it was effective per hr) In pediatric patients 0.07 mg/kg/hr	Can escalate the drip to 15 mg/hr if needed.
Insulin (Regular)	**Bolus:** 1 unit/kg intravenous bolus **Infusion:** 1 unit/kg/hr and titrate to blood pressure goals.	Dextrose as a 25g bolus followed by continuous infusion of 0.5 g/kg/hr with frequent blood glucose monitoring may be needed.
Calcium	**Bolus:** Calcium chloride—1 g (20 mg/kg up to 1 g in pediatric patients) OR Calcium gluconate—3 g (50-100 mg/kg up to 2 g in pediatric patients)	Calcium chloride has more calcium per gram than the gluconate form necessitating a higher dose.
Epinephrine	**Infusion:** Start at 1 mcg/minute with and titrate quickly to MAP goal of 60	Higher doses than normal may be required.
Milrinone	**Bolus:** 50 mcg/kg IV **Infusion:** 0.375-0.75 mcg/kg/min	Should be used as an adjunctive to primary catecholamine infusion.
Sodium Bicarbonate	**Bolus:** 1-2 mEq/kg IV bolus every 3-5 minutes until QTc has decreased to less than 120 ms	Useful in propranolol and sotalol overdoses.
Atropine	**Bolus:** 0.5-1 mg IV (0.02 mg/kg in pediatric patients). Repeat as needed	May not be effective.
Lipid Emulsion	**Bolus:** 1.5 mL/kg of 20% lipid emulsion IV push **Infusion:** 0.5 mL/kg/min for 30 – 60 min up to a maximum of 10-12 mL/kg for the first 30 – 60 mins.	May be effective in lipid soluble beta blockers. (propranolol, labetalol)

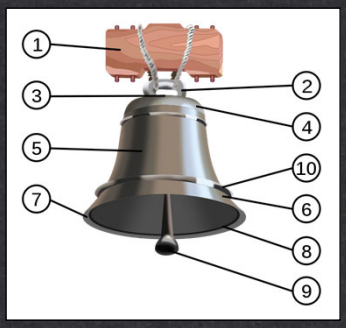
Salicylate toxicity

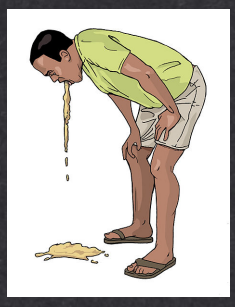
- Not just aspirin!
- One teaspoon (5 mL) of Oil of Wintergreen contains approximately 7 g of salicylate, the equivalent of almost 22 adult aspirin tablets
- Bismuth subsalicylate (eg, Pepto-Bismol®) contains 8.7 mg of salicylic acid per mL

Author: ParentingPatch (CC BY-SA 3.0)

Author: 1ur1 (CC BY 2.0)

Salicylate Toxicity





Images provided by Colin Kaide, MD

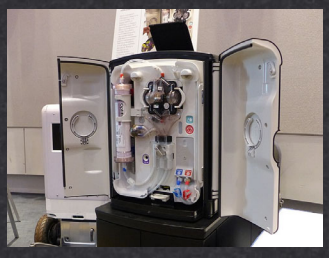
Images courtesy of Colin Kaide, MD

Salicylate toxicity

- Therapeutic serum salicylate concentrations: 10 to 30 mg/dL (0.7 to 2.2 mmol/L);
- Done nomogram fails to predict toxicity based upon the serum concentration alone
- Aggressive volume resuscitation is warranted in such patients, unless cerebral edema or pulmonary edema is present.
- Activated charcoal
- may decrease cerebral glucose concentrations despite a normal serum glucose.
- Alkalinization with sodium bicarbonate
  - Supplement with potassium
  - The usual initial dose of sodium bicarbonate is 1 to 2 mEq (or mmol)/kg bolus
  - sodium bicarbonate infusion of 100 to 150 mEq (or mmol) in one liter of D5W
- Titrate infusion rate to a urine pH of 7.5 to 8
- Consider HD

Author: OneUpOnUs (CC BY-SA 4.0)

Author: davidjmclare89 (CC BY 2.0)



Author: Stilfehler (CC BY-SA 4.0)

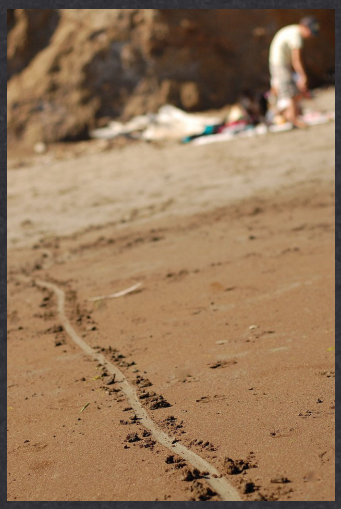
Salicylates

- Intubation: worsens acidosis
- Somnolent → worsens acidosis → more somnolent
- Normal serum glucose
- IV fluid deficits
- Bezoars breaking up, increasing surface area (sudden spike in measured levels)
- Must consider dialysis

Toxic alcohols

- History of alcohol proof: 1500s England, spirits were taxed based on alcohol content. An early way to test proof?
- Gunpowder
  - 75% potassium nitrate (a source of oxygen for the reaction)
  - 15% charcoal (fuel for the combustion reaction),
  - 10% sulfur (which lowers the reaction's ignition temperature and acts as a fuel).
  - potassium nitrate is soluble in water.
  - if exposed to enough water, the potassium nitrate in gunpowder will dissolve, making the gunpowder harder or impossible to ignite.
  - If the spirit had a higher alcohol content, the gunpowder should ignite

Toxic Alcohols



Author: Egan Snow (CC BY-SA 2.0)

Less toxic
- Ethanol
- Isopropyl alcohol

Toxic and LETHAL
- Methanol
- Ethylene glycol

Ethanol

↓ Alcohol Dehydrogenase

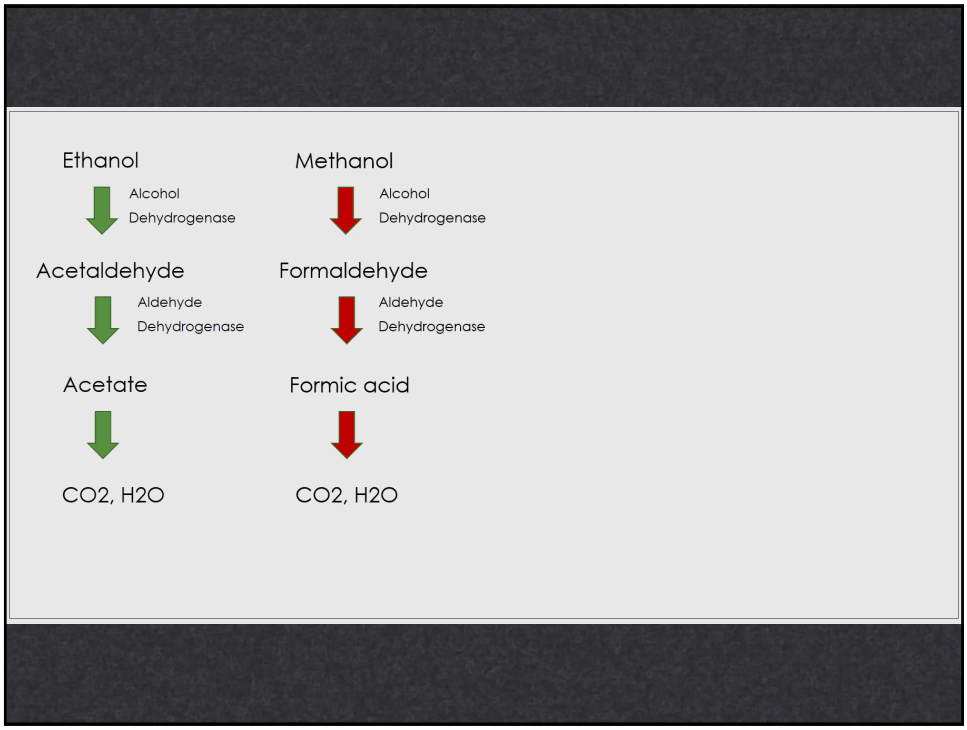
Acetaldehyde

↓ Aldehyde Dehydrogenase

Acetate

↓

CO_2, H_2O


Ethanol
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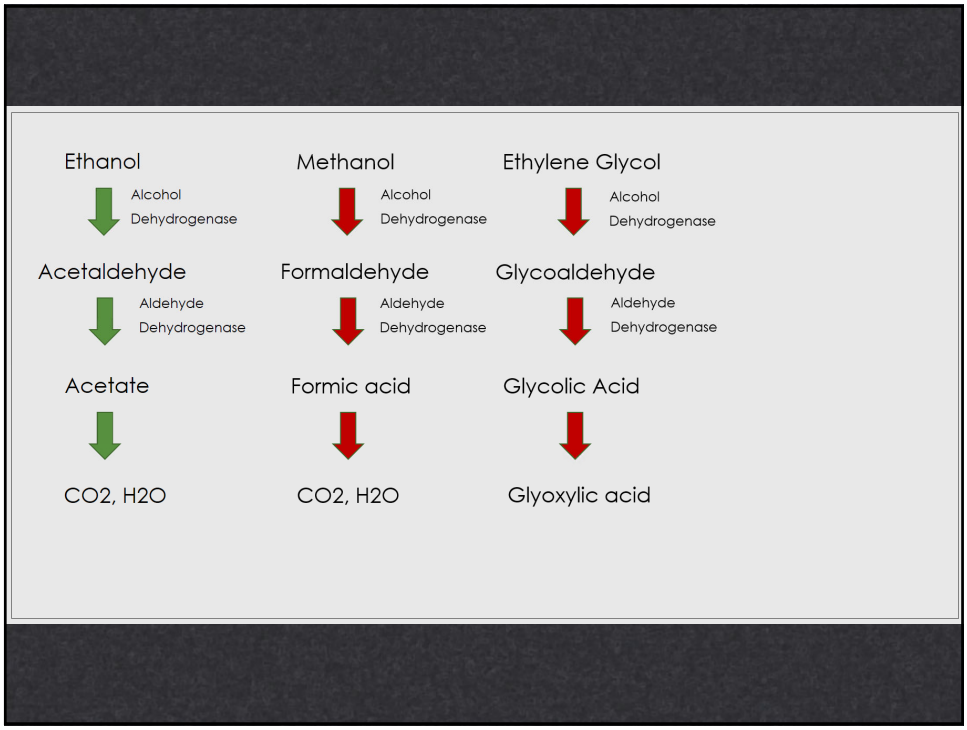
Acetaldehyde
Aldehyde Dehydrogenase
Acetate
CO2, H2O
Methanol
Alcohol Dehydrogenase
Formaldehyde
Aldehyde Dehydrogenase
Formic acid
CO2, H2O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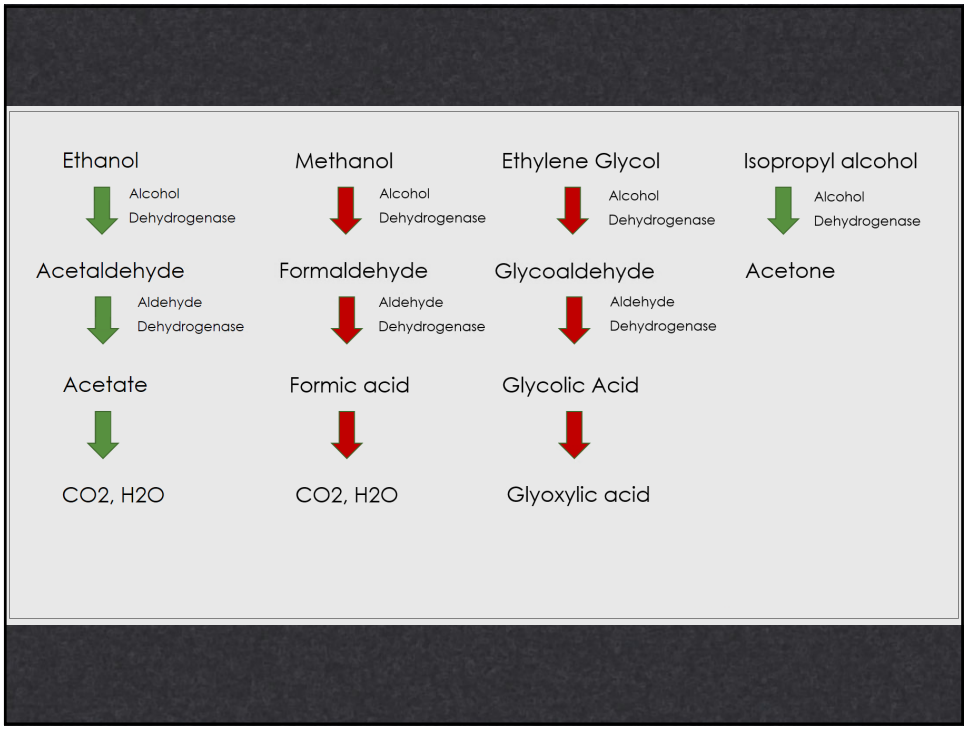
Glycolic Acid
Glyoxylic acid



Toxic alcohols - methanol

- Methanol → formaldehyde → formic acid
- An afferent pupillary defect, fixed mydriasis, retinal sheen, blindness (classic "snow field vision")
- Can cause basal ganglia infarction and hemorrhage
  - Methanol toxicity is known to cause **necrosis of the putamen (?heparin during HD or hemodynamic changes during HD)**
- Osmolar gap (parent compound), than anion gap (metabolites)

Author: gargantuan
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Toxic alcohols - methanol

Osmolar gap: higher osmolality reduces freezing point, elevates boiling point

= Measured osm – calculated osm

Measured osm = $2Na^+$ + (BUN/2.8) + (glucose/18) + (ethanol/4.6)

Anion gap: Sodium – (chloride + bicarb)

$[Na^+]$ - ($[Cl^-]$ + $[HCO^-]$)

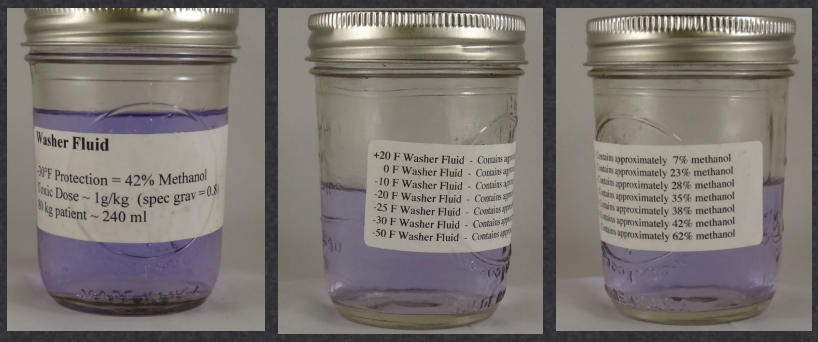
looks for unmeasured anions → MUDPILES

Toxic alcohols - methanol

Fomepizole (blocks alcohol dehydrogenase), HD, folate

- Fomepizole:
  - alcohol dehydrogenase inhibitor. Easy to dose, minimal side effects, but $$$.
  - Shifts elimination to pulmonary and renal
  - loaded at 15 mg/kg IV, followed by 10 mg/kg every 12 hours
- Folic acid helps with formate elimination pathways

Author: Stilfehler (CC BY-SA 4.0)



Images courtesy of Colin Kaide, MD

Ethylene glycol - palatable

- Ethylene glycol → glycoaldehyde → glycolate → oxalate → calcium oxalate
- Flank pain, hematuria, and oliguria
- nephrotoxicity: Hypocalcemia from chelation by oxalate, renal failure because calcium oxalate is deposited in renal tubules
- 1-2 weeks post ingestion: cranial neuropathies (CN VII) from oxalate-induced hypocalcemia

Author: 1ur1 (CC BY 2.0)

Ethylene glycol - palatable

- Osmolar gap (parent compound), than anion gap (metabolites)
- The formation of oxalate crystals in the urine is a late and nonspecific finding following ethylene glycol ingestion
- Urine fluorescence lacks sensitivity and specificity. not all ethylene glycol preparations contain fluorescein, fluorescein (when present) appears only transiently in the urine, normal urine can appear to fluoresce, and other substances can cause fluorescence

Author: 1ur1 (CC BY 2.0)

Bitrex®

- Denatonium benzoate
- The bitterest known substance known
- Completely harmless if consumed…It just tastes really, really horrible.
- Interestingly, also used in N95/N100 mask fit testing!

Image courtesy of Colin Kaide, MD

Toxic alcohols - Ethylene Glycol

Fomepizole (blocks alcohol dehydrogenase), HD, folate

- Fomepizole:
  - alcohol dehydrogenase inhibitor. Easy to dose, minimal side effects, but $$$.
  - loaded at 15 mg/kg IV, followed by 10 mg/kg every 12 hours
- pyridoxine and thiamine are involved in minor elimination pathways, but significance is uncertain

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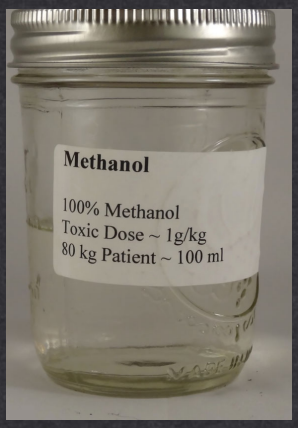

Images courtesy of Colin Kaide, MD

Toxic alcohols – isopropyl alcohol.

- a disinfectant, hand sanitizer, antifreeze, and solvent, and 70% content of "rubbing alcohol.“
- Bad tasting, but very inebriating and works quickly
- Isopropyl alcohol → acetone via alcohol dehydrogenase

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Toxic alcohols – isopropyl alcohol.

- (urine) ketosis without acidosis!
- There will still be an osmolar gap, but no high anion gap
- Ketosis is from acetone. Ketones cannot be oxidized to carboxylic acids
  - Positive urine ketones = tests for acetone. (nitroprusside reaction)
  - Beta-hydroxybutyrate will NOT be elevated
- Treatment: supportive
  - DO NOT TX WITH FOMEPIZOLE: Fomepizole therapy will prolong the patient's severe intoxication by preventing the appropriate metabolism of the isopropanol.

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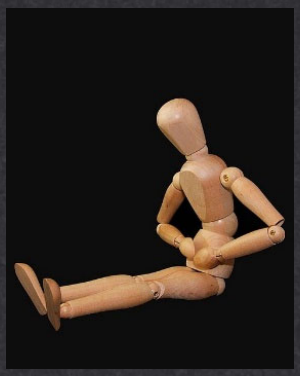
Acetaminophen toxicity

- The most common cause of acute liver failure in the US
- 90% of acetaminophen is metabolized in the liver & metabolites are excreted in urine
- 5% of acetaminophen is excreted unchanged into urine
- 5% is metabolized via oxidation by hepatic cytochrome P450 to the toxic, highly-reactive NAPQI. Normally, NAPQI is rapidly conjugated to glutathione to form metabolites excreted in the urine
  - This pathway is increasingly used in overdose. Once glutathione stores are depleted, NAPQI accumulates

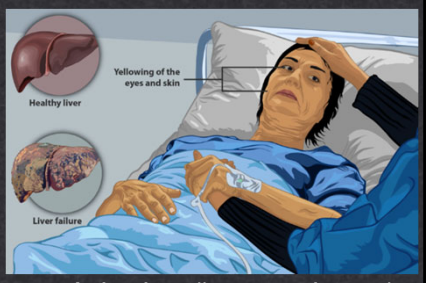
Author: 1ur1 (CC BY 2.0)

Acetaminophen toxicity



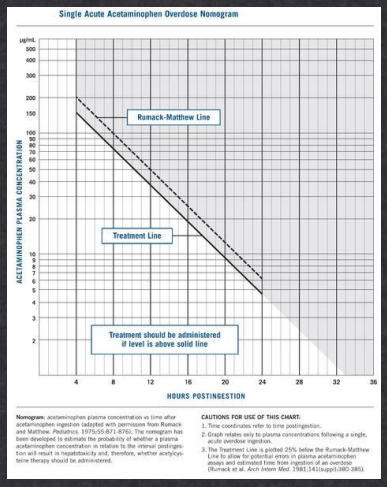
Author: Wolfgang Claussen

Author: ХЕРАЛДИКА СССС (CC BY-SA 4.0)



Author: https://www.myupchar.com/en (CC BY-SA 4.0)

Image courtesy of Colin Kaide, MD

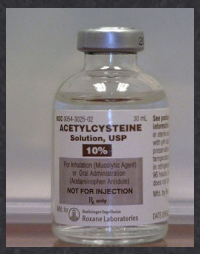


Author: Merlin Cyrstal (CC BY-SA 3.0)

Acetaminophen toxicity

- Activated charcoal
- N-Acetylcysteine: restores hepatic glutathione stores (some controversy regarding mechanism persists). Ideally start within 8 hrs of ingestion/before onset of liver injury
  - IV versus PO
    - IV: Non-IgE mediated anaphylaxis (anaphylactoid reactions).
    - PO: causes vomiting and tastes terrible

Author: OneUpOnUs (CC BY-SA 4.0)



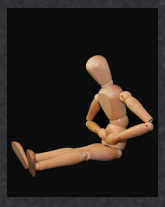
Author: The U.S. Food and Drug Administration

Iron toxicity

- Absorbed in the duodenum, where it is stored as ferritin in the intestinal cells. It is then disposed of or released to transferrin (serum Fe-binding protein)
- Toxicity occurs when transferrin is overwhelmed – increased free iron
- Toxicity is determined by the amount of elemental iron ingested
  - ferrous gluconate has the least (12%) and ferrous fumarate has the most (33%)
  - Calculate the amount of elemental Fe ingested/kg
- Iron takes hours to reach from the GI tract to the intracellular space, giving a window of opportunity to prevent further absorption via decontamination and chelation

Author: 1ur1 (CC BY 2.0)

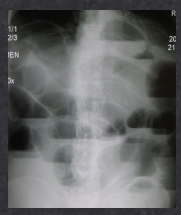
Iron toxicity



Author: Wolfgang Claussen

Author: ХЕРАЛДИКА СССС (CC BY-SA 4.0)

Author: https://www.myupchar.com/en (CC BY-SA 4.0)



Author: James Heilman, MD (CC BY-SA 3.0)

The lack of vomiting 6 hrs after an ingestion has important clinical significance; likely did not ingest a toxic dose and can be medically cleared.

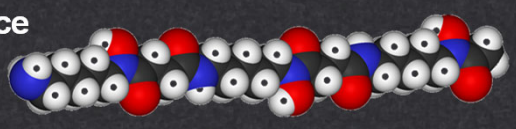
Iron toxicity

- Lab workup
  - For most preparations, a peak Fe level occurs 2–6 hours post-ingestion, then falls due to intracellular shift. The peak level predicts severity of iron toxicity
  - Start to see risk of serious toxicity increase at 500 mcg/dL or 60 mg/kg (= consider deferoxamine!)
  - The radiopacity of Fe varies with the preparation, time since ingestion, and amount of ingestion.
    - a normal KUB does not exclude ingestion.
  - Anion gap metabolic acidosis, elevated lactate indicate systemic toxicity

Images courtesy of Colin Kaide, MD

Iron toxicity

- Isotonic fluids:
  - Toxicity causes GI fluid losses
  - May prophylactically prevent hypotension from defuroxime
- Whole bowel irrigation: consider when Fe tablets are visualized on the KUB film.
- Deferoxamine
  - General indications include ANY of the following:
    - Fe level > 500 mcg/dl
    - Presence of metabolic acidosis
    - Lethargy/coma
    - Shock
    - Toxic appearance



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