Project: Ghana Emergency Medicine Collaborative

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Toxicology of: Analgesic Agents

Sarah_Ackerman, flickr

Core Toxicology Review

- ☑ Acetaminophen
- ☑ Salicylates
- ☑ NSAIDS

Analgesics

- 22 y/o male arrives by EMS after found lying next to bed lethargic
- Parents note he had taken a benadryl containing med the night before
- VS: BP 120/70, RR 28, Temp 100^{o} F, 0_2 sat 97% on 2L NC
- Non focal neuro exam; pt is "agitated, but arousable;" head contusion noted
- Labs = pH 7.33, pO_2 94, pCO_2 25, CPK 19. 4 K, Na 140, K^+ 4.1, Cl 107, HCO3 18, SGOT 426, SGPT 100, BUN 18, Cr 2.0, WBC 27 K, ASA 44.6, Acet 10.4, ETOHNeg, UDS Neg, CXR & Head CT nL
- Placed on Bicarb drip in ED – and admitted to ICU
- Diagnosis = Salicylate toxicity

Analgesics

- Pt arrives to ICU and noted to be increasingly tachypneic and agitated
- Multiple doses of ativan and haldol given …
- Intubated for respiratory depression
- Temps in ICU over next 4 hours = 101.2, 102.3, 105
- Decorticate posturing noted
- Decision made approx 6 hours after ED presentation to transfer to facility with higher level of care
- Ptdeveloped asystole in ambulance
- Autopsy findings showed moderate cerebral edema
- Postmortem ASA conc = 67 mg/dL, Diphenhydramine = 3.9 mg/dL

Salicylates

Salicylate Bezoar

Source undetermined

Salicylates

- 18 month old female found playing with an open bottle of “oil of wintergreen”
- Parents note child’s shirt has a strong “wintergreen” odor
- Upon examination you find a well appearing child with “wintergreen breath”

 Omer Wazir, flickr

Salicylates

Salicylate Preparations

7.3 MINIMUM LETHAL EXPOSURE

A) CASE REPORTS

1) CHRONIC

a) A 52-year-old man ingested an estimated 96 grams of aspirin over nine days and died despite emergency treatment (Kearney, 1989).

b) An 18-month-old boy died after receiving one baby aspirin every 4 to 6 hours for two days (Snodgrass et al, 1981).

c) A 64-year-old woman died after inadvertently receiving 7,100 milligrams of enteric coated aspirin daily for 10 days (Shkrum et al, 1989).

2) ACUTE

a) OIL OF WINTERGREEN

1) 5 milliliters of oil of wintergreen is equivalent to approximately 7000 milligrams of salicylate (Botma et al, 2001). Fatalities have been reported in children following methyl salicylate exposure with the lowest reported dose being 4 mL in 2 children (17 months and a 2-year-old) (Davis, 2007)

2) A 2-year-old boy ingested approximately 7.5 milliliters of wintergreen oil, was not treated, and subsequently died (MacCready, 1943).

3) A 21-year-old man died after ingesting 6 mL of oil of wintergreen (Davis, 2007).

4) A 44-year-old man died after accidentally ingesting 30 milliliters of wintergreen oil (Cauthen & Hester, 1989).

b) PEPTO-BISMOL

1) A 4-year-old girl died after ingesting 3 ounces of Pepto-Bismol(R) (Fisher et al, 1985).

 Source undetermined

Salicylism

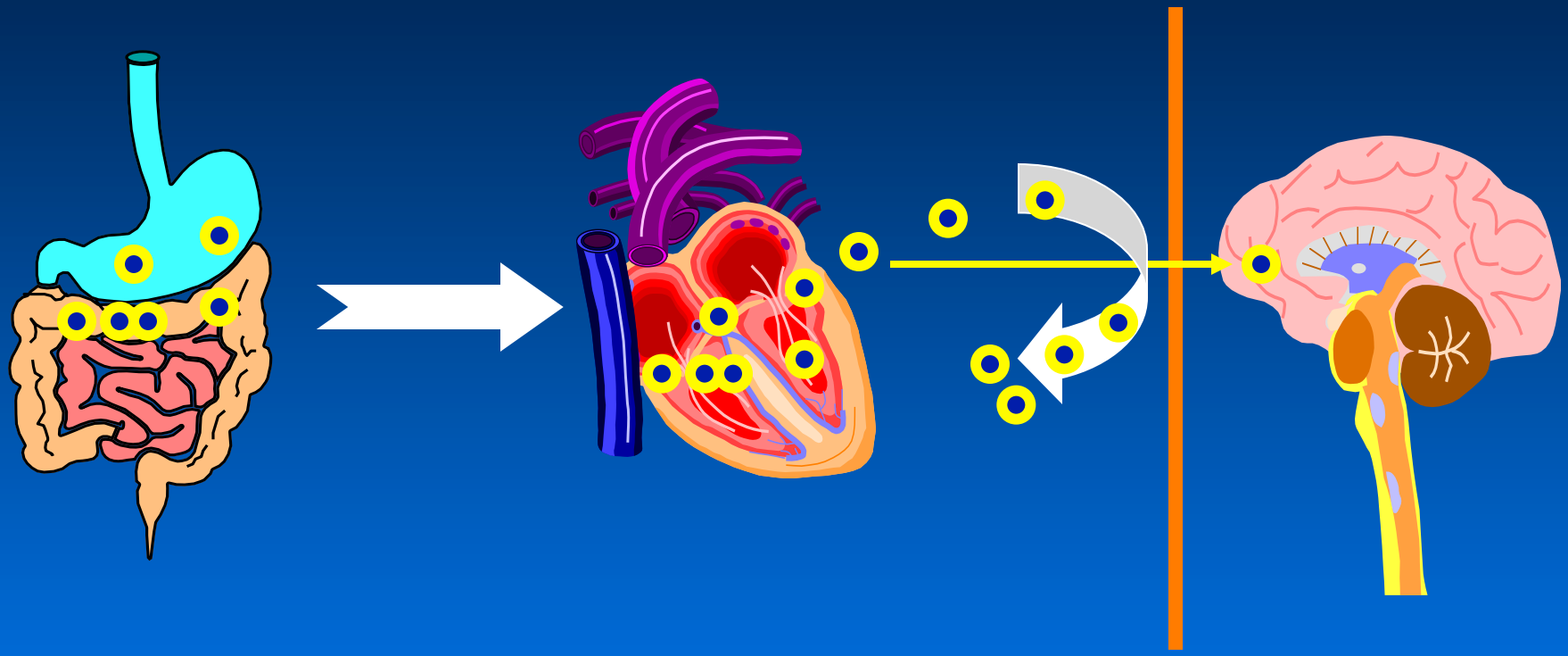
Acute

- Mild: tinnitus, deafness
- Moderate: hyperventilation, N/V, hyperthermia, acidosis, hyper or hypoglycemia
- Severe: Severe acidosis, fever, cerebral/ pulmonary edema, renal failure, Sz

Chronic

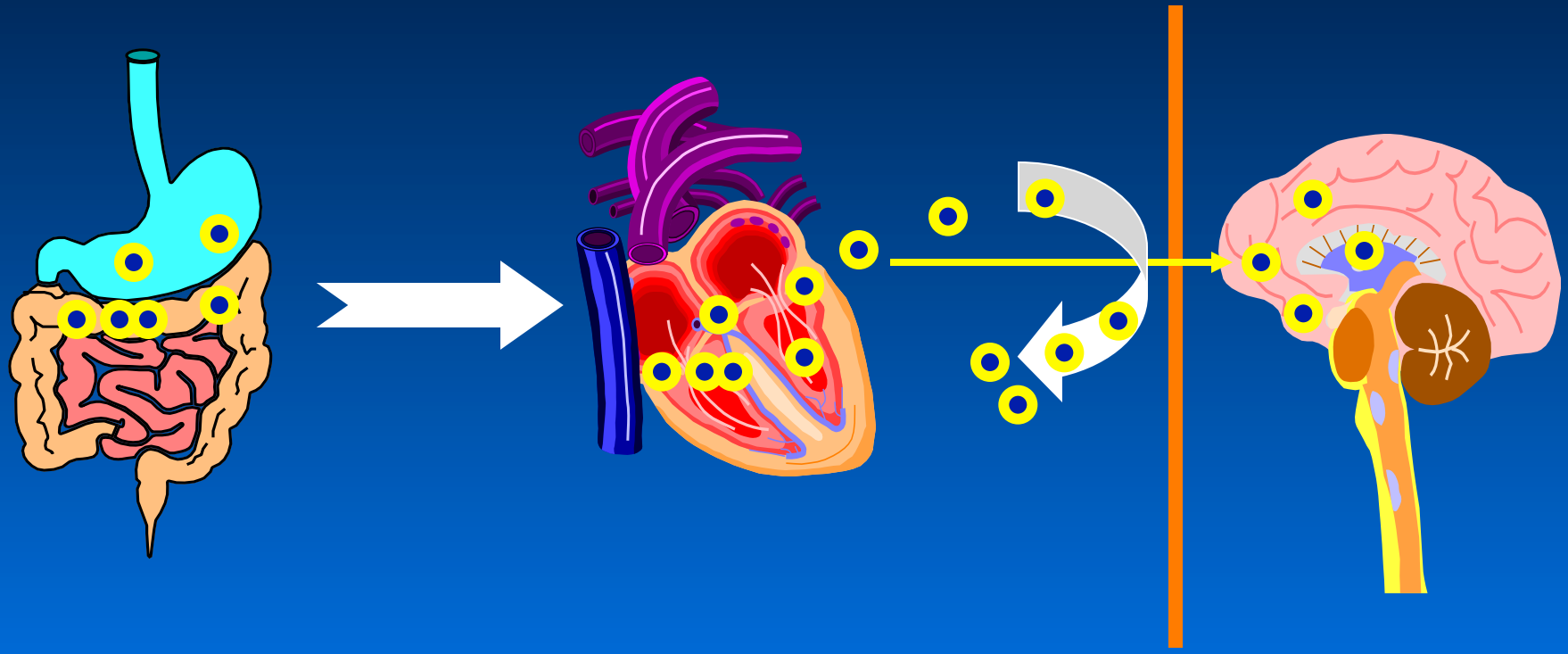
- Adult with DJD, child with Kawasaki's with diarrhea, tinnitus, tachypnea
- Higher mortality rates than acute intoxication
- ↑ Incidence of cerebral and pulmonary edema

Compartmental Concepts



Acute ASA 50 mg/dL with mild symptoms

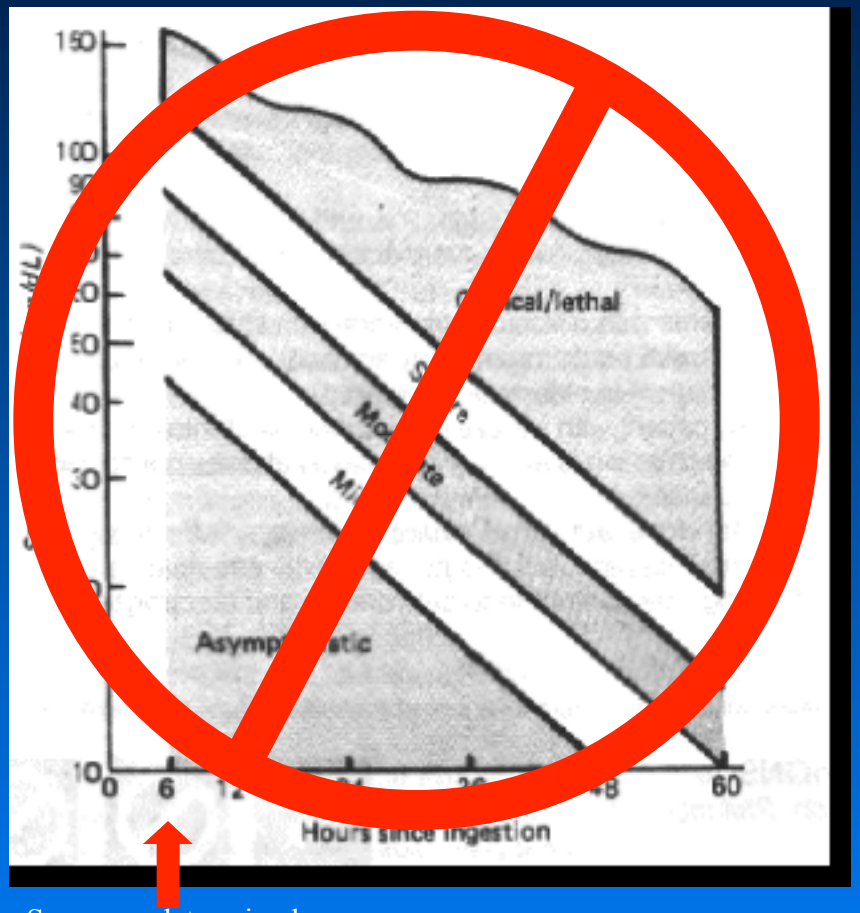
Compartmental Concepts



Chronic ASA 50 mg/dL, yet very ill

Salicylates
Laboratory Studies

- Lytes (K^+), serial salicylate levels until ASA levels fall
- Hypoxic? ABG, CXR
- MS changes? CT scan
- Done nomogram now largely historical



Source undetermined

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Done Nomogram

Salicylates
Treatment

- Lavage, multi-dose activated charcoal
- Urinary alkalinization
- IV hydration, K^+ supp
- Hemodialysis
  - acute > 80-100 mg/dL
  - chronic > 50-60 mg/dL
  - Acidosis, MS changes, cerebral or pulmonary edema, renal failure

soccerkrys, flickr

Whole Bowel Irrigation

- Polyethylene glycol
- First described in the Pediatric literature*
- History of expulsion of button batteries
- Very safe track record

PD-INEL Source undetermined

*Tenenbein M: Whole bowel irrigation for iron poisoning. J Pediatr 1987;111:142-145.

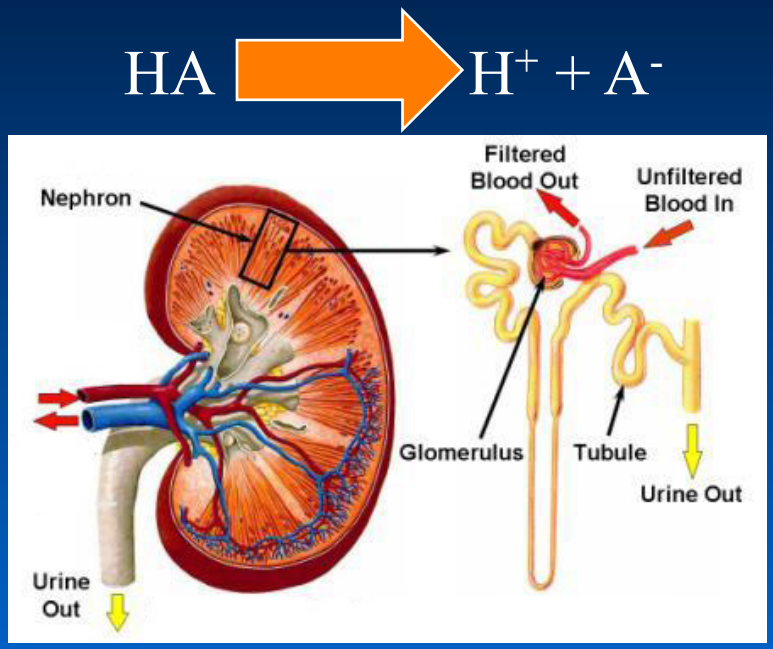
What is the definition of pKa?

The pH of a solution in which the concentrations of ionized and non-ionized drug are equal.

Cell membranes are more permeable to substances that are in the non-ionized form (lipid soluble)

Urine Alkalinization
Rationale

- Some toxins are weak acids –As they pass through glomeruli non ionized forms are reabsorbed back into circulation
- Alkaline urine causes disassociation of H+ in weak acids
- Polar forms remain in the renal tubules and are excreted in urine



PD-INEL Source undetermined

Acetaminophen

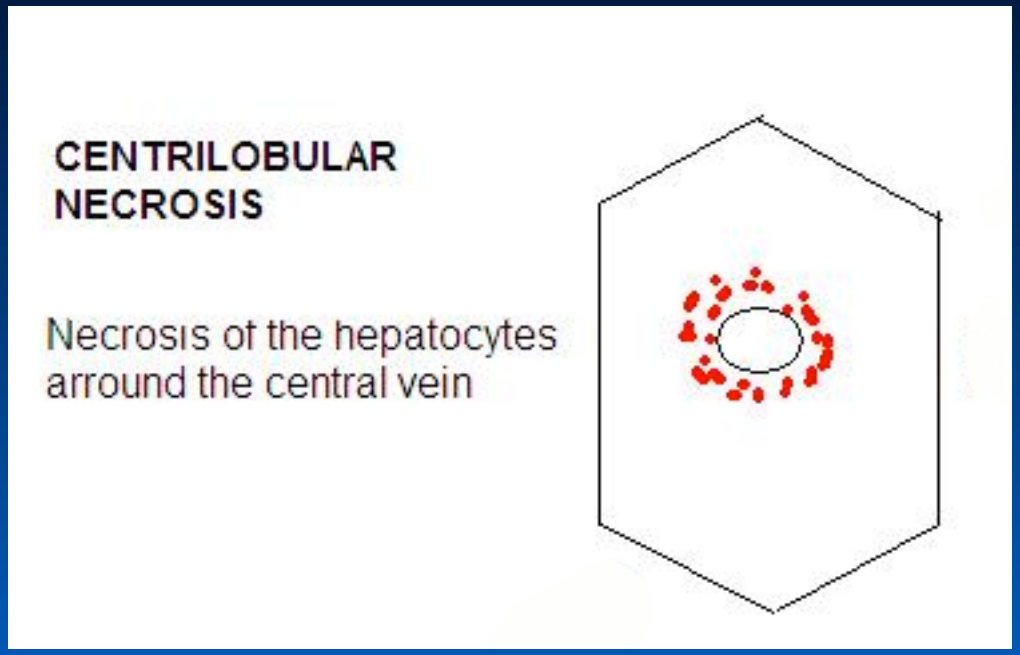
Source undetermined

Acetaminophen

- 15 yo female with derangement Lt knee while skiing at Vale
- She presents to the ED 4 days later with persistent vomiting and myalgias
- GI labs were obtained with mildly elevated BUN/CR, SGOT 650, SPGT 525, Total bili = 2.1, direct bili 1.9, BUN 28, Cr 1.5
- Dx of viral syndrome with dehydration made
- Supportive care with IVF and antiemetics given in ED
- Hepatitis panel was drawn and patient was asked to follow up with PMD in 1-2 days
- Discharge instructions advised Tylenol as needed for muscle aches and pains

Acetaminophen

- Pt sees PMD 1 day later with no change in symptoms
- Returns to the ED with continued emesis, and RUQ pain
- Labs = SGOT 8350, SGPT 7960, Total bili = 12.2, PT = 20, Acet conc = 25 µg/mL
- NAC started in 2nd ED visit, Pt died within 48 hours



PD-INEL Source undetermined

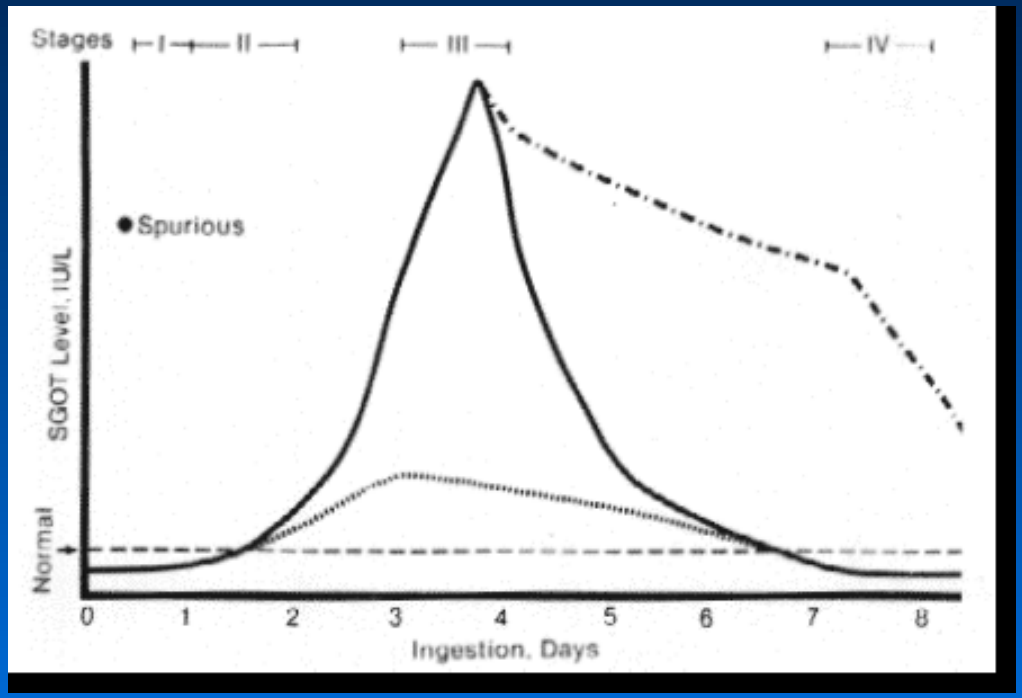
- Plaintiff's attorney wrote: "physician treated the poisoned patient with more poison"

Acetaminophen
Toxicity Result of Metabolism

- Sulfation, glucuronidation >>> P-450 system
- NAPQI: Product of P-450 is hepatotoxic
- NAPQI is detoxified by glutathione, overdose may exceed glutathione stores
- Accumulated NAPQI reacts directly with macromolecules causing hepatic cell death

Acetaminophen
Clinical Presentation

- Phase I(1/2-24 hrs): Anorexia, nausea, vomiting
- Phase II(24-72 hrs): RUQ pain, PT & liver transaminases begin to rise
- Phase III(72-96 hrs): Centrilobular necrosis
- Phase IV(4d to 2 wks): Complete resolution



PD-INEL Source undetermined

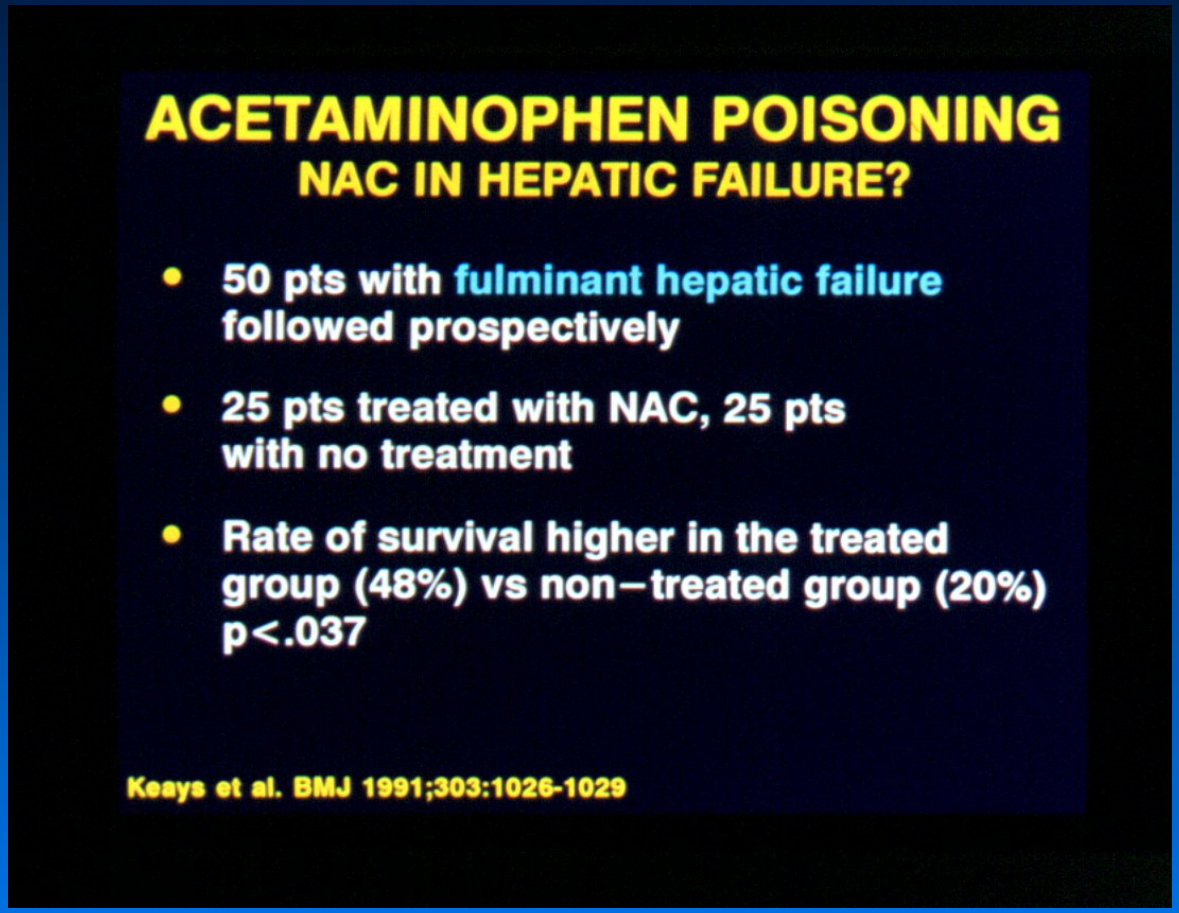
Acetaminophen
N-acetylcysteine

- May act as glutathione substitute
- May stimulate glutathione synthesis
- May act as free radical scavenger (oxygen-free radicals are liberated by necrotic hepatic tissue)
- NAC may optimize tissue oxygen delivery and utilization

N-acetylcysteine

Acetaminophen

- 4 hrs conc ≥ 150 ug/ml potentially toxic
- Toxic levels receive oral NAC 140 mg/kg
- Maximal benefit if started within 8-10 hrs
- Treatment should not be withheld if delay over 24 hrs!



Nonsteriodal Anti-inflammatory Drugs

Acetic Acids
Diclofenac = Voltaren
Etodolac = Lodine
Indomethacin = Indocin
Ketorolac = Toradol
Sulindac = Clinoril
Tolmetin = Tolectin

Fenamates (Anthralic acids)
Meclofenamate = Meclomen
Mefenamic acid = Ponstel

Proprionic Acid
Ibuprofen = Motrin
Ketoprofen = Actron
Naproxen = Naprosyn

Oxicams
Piroxicam = Feldene

Pyrazolones
Phenylbutazone = Butazolidine

Combination Products
Diclofenac/ misoprostol
Hydrocodone/ ibuprofen

Selective Cox-2 Inhibitors
Celecoxib = Celebrex
Meloxicam = Mobic
Rofecoxib = Vioxx
Valdecoxib = Bextra

NSAIDS

- Acetyl salicylic acid developed by Felix Hoffman in 1897
- Search for drug with less GI adverse affects led to development of Ibuprofen in 1961 – marketed in US 1974
- 1984 Ibuprofen available without prescription
- 1999 First selective Cox-2 inhibitor Rofecoxib introduced; 2004 withdrawn after increased risk for MI and CVAs associated with use

NSAIDS Pharmacology

- Cyclooxygenase (Cox 1& 2) system induces prostaglandins and prostinoids via arachidonic acid
- Cox 2 induced Prostanoids are part of bodies inflammatory response (cytokines, leukotrienes)
- Cox 1 produces PGE2 – vasodilator effect in gastric mucosa (promotes perfusion and healing), PGE2 renal sodium regulation and induces renal vasodilation

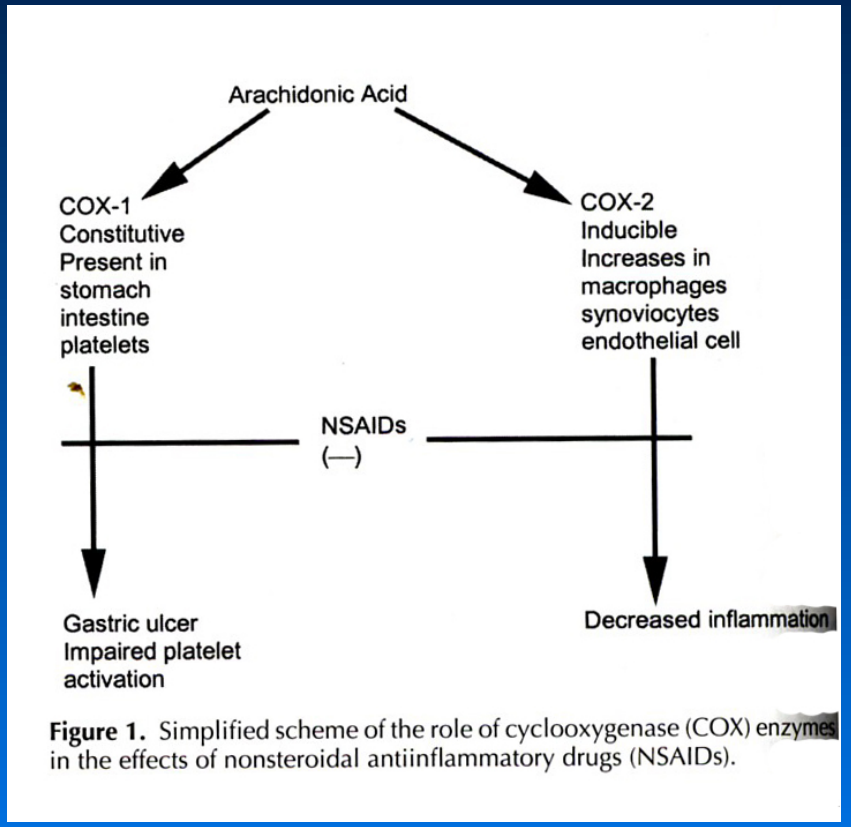


Figure 1. Simplified scheme of the role of cyclooxygenase (COX) enzymes in the effects of nonsteroidal antiinflammatory drugs (NSAIDs).

NSAIDS Pharmacology

- Cox 1: Produces thromboxane (TXA2) – a potent platelet stimulator
- Cox 2: Produces PGI2 which inhibits platelet function and promotes blood flow
- Thus inhibiting PGI2, without inhibition of TXA2 may explain increased thrombotic events noted by selective Cox 2 NSAIDS

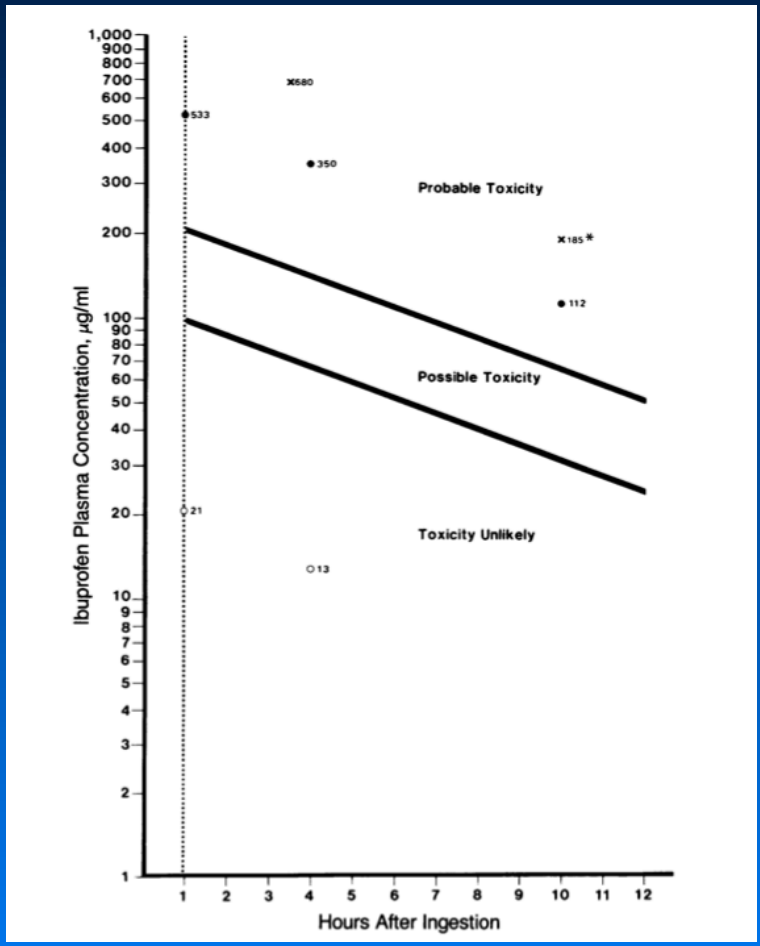
NSAIDS Overdose

- Cox 2 selective agents (i.e. celecoxib/ celebrex) overdose information is limited
- Case series of 92 OD patients had drowsiness, agitation, vomiting in only 2% of cases (and no deaths)*
- Overdose of NSAIDS in general result in no symptoms to altered mental status, seizures
- Seizure esp common with Mefenamic acid

Suggested Reading: Forrester MB. Hum Exp Toxicol 2009; 28: 194-4

NSAIDS Overdose

- Rise in hepatic transaminases and acute renal insufficiency published in case reports – but uncommon
- Massive acute NSAID OD (usually ibuprofen over 400 mg/kg) may result in death from multisystem organ failure (coma, seizures, hypotension, cardiac dysrthymias)
- Nomogram proposed historically, but without available labs, and no specific antidote – not used



Hall et al. West J Med 1988; 148: 653-656

NSAIDS Overdose

- Emergency Department Care
  - Activated charcoal
    - Consider whole bowel irrigation
    - Monitor vital signs
    - Manage symptoms
- Since NSAIDS are protein bound there is no role for hemodialysis, hemoperfusion, or hemofiltration
- *Apply the "Science of supportive care"

Suggested Reading: Alvin Bronstein 3rd Edition Medical Toxicology, Chapter 127B, p. 754

NSAIDS Pitfalls*

- Avoid use in pregnancies (esp. 3rd trimester) due to Cox 1 inhibition of PGE2 (potential for premature closure of ductus arteriosis)
- In OD – most symptoms appear within 4 hours, though few case reports of delayed symptoms

Suggested Reading: Alvin Bronstein 3rd Edition Medical Toxicology, Chapter 127B