Project: Ghana Emergency Medicine Collaborative

Document Title: Toxicology of Analgesic Agents

Author(s): Hernan Gomez (Hurley Medical Center)

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Toxicology of:
Analgesic Agents
Core Toxicology Review

- Acetaminophen
- Salicylates
- NSAIDS
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° F, O₂ sat 97% on 2L NC

Non focal neuro exam; pt is “agitated, but arousable;” head contusion noted

Labs = pH 7.33, pO₂ 94, pCO₂ 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
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

Pt developed 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”
## Salicylates

### Salicylate Preparations

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active Ingredient</th>
<th>Salicylate Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil of Wintergreen</td>
<td>Acetylsalicylic acid</td>
<td>Salicylate 7000 mg/tsp</td>
</tr>
<tr>
<td>Bayer Aspirin</td>
<td>Acetylsalicylic acid</td>
<td>Salicylate 325 mg/tab</td>
</tr>
<tr>
<td>St. Joseph Children</td>
<td>Acetylsalicylic acid</td>
<td>Salicylate 81 mg/tab</td>
</tr>
<tr>
<td>Pepto-Bismol</td>
<td>Bismuth Subsalicylate</td>
<td>Salicylate 131 mg/tsp</td>
</tr>
<tr>
<td>Excedrin Migraine</td>
<td>Acetylsalicylic acid</td>
<td>Salicylate 300 mg/tab</td>
</tr>
</tbody>
</table>

### Minimum Lethal Exposure

#### 7.3 CASE REPORTS

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHRONIC</td>
<td>A 52-year-old man ingested an estimated 96 grams of aspirin over nine days and died despite emergency treatment (Kearney, 1989).&lt;br&gt;b) An 18-month-old boy died after receiving one baby aspirin every 4 to 6 hours for two days (Snodgrass et al, 1981).&lt;br&gt;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).</td>
</tr>
<tr>
<td>ACUTE</td>
<td>1) OIL OF WINTERGREEN&lt;br&gt;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).&lt;br&gt;2) A 2-year-old boy ingested approximately 7.5 milliliters of wintergreen oil, was not treated, and subsequently died (MacCready, 1943).&lt;br&gt;3) A 21-year-old man died after ingesting 6 mL of oil of wintergreen (Davis, 2007).&lt;br&gt;4) A 44-year-old man died after accidentally ingesting 30 milliliters of wintergreen oil (Cauthen &amp; Hester, 1989).</td>
</tr>
<tr>
<td></td>
<td>PEPTO-BISMOL&lt;br&gt;1) A 4-year-old girl died after ingesting 3 ounces of Pepto-Bismol(R) (Fisher et al, 1985).</td>
</tr>
</tbody>
</table>

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
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
Salicylates
Treatment

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

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

What is the definition of pKa?

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

\[ \text{HA} \rightleftharpoons \text{H}^+ + \text{A}^- \]

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

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
Acetaminophen

The Pain Reliever Hospitals Use Most.

For Night Time Pain And Sleeplessness Rest Easy...It's Tylenol PM.

Strong All Day Arthritis Relief.

Tylenol Allergy Sinus Takes Care Of It All.

The Strength You Need From The Name You Trust.

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 2\textsuperscript{nd} ED visit, Pt died within 48 hours

▲ 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

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
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!

Source undetermined
## 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
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 dysrhythmias)

▲ Nomogram proposed historically, but without available labs, and no specific antidote – not used

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 arteriosus)

▲ 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