ACETAMINOPHEN TOXICITY

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Objectives

1. Recognize what medications contain acetaminophen and the percentage of acute liver failure cases observed in the United States caused by its misuse
2. Describe the pathogenesis of acetaminophen toxicity and the classic signs and symptoms indicating toxicity and need for treatment
3. Recognize what medications are used to treat acetaminophen toxicity and when they are indicated
4. State the number for Poison Control Center from memory
Poison Prevention Hotline

1-800-222-1222

Names

- Generic: Acetaminophen, paracetamol
- Brand: Tylenol, Ofirmev (IV product)
- Abbreviation: APAP
- Available in over 200 combination products

N-Acetyl-Para-Amino-Phenol
## History of Acetaminophen

- Derived from a pharmacy error in 1852
  - Acetanilide filled instead of naphthalene for a patient with intestinal parasites
  - Noted marked fever reductions as well as analgesia
- 1899 discovered that acetanilide metabolized to acetaminophen
  - First synthesized in 1909

- 1949 renewed interest in acetaminophen
- First FDA patent issued in 1951
- Brand name Tylenol released in 1955 by McNeil Labs
- First OTC alternative to aspirin that was safe for children
Which of the following contain Acetaminophen?

ALL OF THEM!
Signs something contains Acetaminophen

- Has “-cet” at end of name
  - Ultracet, Percocet, Fioricet
- Has “APAP” in the name
  - Hydrocodone/APAP, Oxycodone/APAP
- OTC medication labeled as “non-aspirin pain reliever” or “fever reducer”
- Combination cough and cold product

What is Acetaminophen?

- Analgesic, antipyretic
  - Mechanism not fully known. Believed to inhibit synthesis of pain signalers in the brain and works peripherally to block pain impulse generation
  - Decreases fever through inhibition of the heat-regulating center in the brain
- Not an anti-inflammatory, does not alter platelet aggregation
Indications

- Pain Management
  - IV: mild to moderate pain; moderate to severe pain when combined with opioids
  - Oral/Rectal: temporary relief of minor aches, pains, and headaches
- Fever
  - Temporary reduction of fever

Poison Prevention Hotline

1-800-222-1222
Acetaminophen Dosing (pain/fever)

**ADULT**
- Regular Strength (325mg)
  - 650mg every 4 to 6 hours
- Extra Strength (500mg)
  - 1000mg every 6 hours

**Infants, Children, Adolescents**
- 10-15mg/kg/dose every 4 to 6 hours
  - do NOT exceed 5 doses in 24H
  - Max: 75mg/kg/day

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Case study

- Your first born son, now 23 months old, has developed a mild fever (100.5°F). It’s the middle of the night and he’s crying incessantly. Your spouse (who does not have your medical background) wants to give some acetaminophen. WHAT DOSE DO YOU GIVE?

He weighs 22 pounds (~10 kg)
Case study

Now how many mL’s do you actually administer?

INFANT DROP  CHILDREN’S TYLENOL
- Concentration: 80mg/0.8mL  - Concentration: 160mg/5mL

(not available anymore, but why?)

ANSWER: 3.125mL (ROUND TO 3.5-4mL)

Acetaminophen Dosing

SPECIAL POPULATIONS
- Chronic alcoholism
  - May increase risk for hepatotoxicity with multiple ingestions of excessive acetaminophen doses
  - Data conflicting regarding a single overdose
- Usually lower total daily doses of APAP are recommended for those who drink more than recommended amounts chronically
  - ~2,000mg/day

https://www.youtube.com/watch?v=T3ybmcnEJDE
HOW MUCH BEER, WINE, OR LIQUOR IS CONSIDERED “1 DRINK”?

12 OZ BEER
5 OZ WINE
1.5 OZ OF 80 PROOF LIQUOR

HISTORY OF FDA’S OPINION ON APAP

- Late 1990’s, research demonstrated APAP as leading cause of acute liver failure, majority resulting from accidental overdoses.
- 1998, FDA issued warning that people that drink >3 alcoholic beverages/day consult a physician before using APAP.
- 2002, FDA added a warning for potential of hepatotoxicity to ALL acetaminophen-containing product labeling.

HISTORY OF FDA’S OPINION ON APAP

2009: new labeling developed to help patients easily identify which products contain acetaminophen
  ▪ Black box warning was placed for potential of severe liver injury (and anaphylaxis)

2013: alerted consumers of rare but serious and potentially fatal skin reactions

1/14/2014 recommendation:
“FDA is recommending health care professionals discontinue prescribing and dispensing prescription combination drug products that contain more than 325 milligrams (mg) of acetaminophen per tablet, capsule or other dosage unit.”

No evidence that taking a higher dose provides additional benefit
HISTORY OF FDA’S OPINION ON APAP

- Maximum recommended dose per FDA is 4000mg/day
  - *Some experts recommend no more than 3,250mg/day

HOW MANY REGULAR STRENGTH TABLETS WOULD THAT BE?

10!

Incidence of APAP Toxicity

- Accounts for:
  - 56,000 ED visits
  - 26,000 hospitalizations
  - 450 deaths annually
- Most common cause of:
  - Acute liver failure
- Second most common cause of:
  - Liver failure requiring transplantation
  - Approx. 50% of cases are intentional, approx. 50% are unintentional chronic overdoses

Nourjah 2006
Steps to Understanding the Mechanism of APAP Toxicity

1. Understand the metabolism of Tylenol
2. Recognize the body’s limitations
3. Recognize what happens during both ACUTE and CHRONIC ingestion of high doses
4. Use imagery to make connections
5. Briefly review how alcohol ingestion can affect Tylenol metabolism and elevate risk for toxicity

Metabolism of Acetaminophen

http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882B1_13_McNeil-Acetaminophen.htm
Metabolism of Acetaminophen

Acetaminophen

- Glucuronide (47 - 62%)
- Sulfate (25 - 36%)
- Glutathione
  - Reactive Intermediate (NAPQI)
  - Cysteine & Mercapturic Acid Conjugates (5 - 9%)

Active Repletion Process

Cytochrome P450 2E1

Saturable Metabolism

http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882B1_13_McNeil-Acetaminophen.htm
Metabolism of Acetaminophen

Acetaminophen

[Chemical structure]

47 - 62% Glucuronide
25 - 36% Sulfate

Cysteine & Mercapturic Acid Conjugates 5 - 8%

Cytotoxic Intermediate (NAPQI)

Cytochrome P450 2E1

[Diagram showing the metabolism process]

http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882B1_13_McNeil-Acetaminophen.htm
Alcohol’s Effect on APAP Metabolism

![Chemical diagram illustrating the metabolism of acetaminophen (APAP) with reactions involving glucuronide, sulfate, and glutathione conjugates.]

Signs and Symptoms of Acute Toxicity

- **Asymptomatic**
- **Nausea & vomiting**
- **Unwell**
- **Sweating**  
  - **0.5-24 hrs**

- **Right upper quadrant pain**
- **Nausea & vomiting**
- **Liver enzymes elevate**
  - **18-72 hrs**

- **Nausea & vomiting**
- **Abdominal pain**
- **Jaundice**
- **Bleeding & bruising**
- **Confusion**
- **Renal Failure**
  - **72-96 hrs**

- **Recovery**
  - **4d-3wk**
The Phases of Acetaminophen Poisoning

1. 0-24 HOURS
   Patient may exhibit sweating, nausea and vomiting, after taking the overdose. Blood levels of enzymes, associated with liver damage, begin to rise.
   Later on, the symptoms often subside and the patient may feel better. However, the enzyme levels continue to rise along with possible liver damage.

2. 18-72 HOURS
   The symptoms of abdominal pain, nausea and vomiting return. Blood tests confirm very high levels of enzymes associated with liver damage.

3. 72-96 HOURS
   As the liver fails, jaundice sets in, turning the skin and eyes yellow. Poisons accumulate in the blood, and the kidneys fail.
   Doctors must decide whether to attempt a liver transplant.

4. 96 HOURS+
   Lucky patients survive with a fully recovered liver. Others survive after a liver transplant.
   However, some patients die from liver failure.

Poison Prevention Hotline

1-800-222-1222
Treatment of Toxicity

- Activated charcoal if present within 1 hour after ingestion

Based on blood levels, not symptoms
- Rumack-Matthew nomogram
- For acute ingestions
Treatment of Toxicity

- Most important: N-acetylcysteine (NAC)
  - Brand names: Mucomyst (oral) or Acetadote (IV)
- Ideally within 8-10 hours post ingestion
- Oral or IV

NAC

- Oral
  - 140mg/kg loading dose, then 70mg/kg x 17 doses q4h (total 72hr course)
  - Tastes bad. Can be given chilled on ice, diluted with soda/juice, in a cup with a lid and straw
- IV
  - 150mg/kg loading dose, then 50mg/kg over 4hrs, then 100mg/kg over 16hrs

72 hours for oral, 21 hours for IV
Both require loading dose
Why it works

- NAC restores glutathione stores allowing for nontoxic metabolism of acetaminophen

http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882B1_13_McNeil-Acetaminophen.htm

Prognosis After Prompt Treatment

- If given N-acetylcysteine (NAC) within 10 hours of ingestion
  - NO deaths, regardless of APAP levels in most large retrospective studies
  - Hepatotoxicity occurred in <4% of patients
  - Mortality occurred in <1% of patients

http://pixgood.com/thumbs-up-happy-face.html
Prognosis After Delayed Treatment

- If patient presents AFTER onset of hepatic failure (~3-5 days post ingestion) the mortality rate is 20-40%.

Prevention

- EDUCATION!
  - Maximum daily dose of acetaminophen
  - Recognition that it is MANY OTC products

HOW MANY PRODUCTS DO YOU THINK CONTAIN APAP?

DO YOU STILL REMEMBER THE POISON PREVENTION HOTLINE???

Poison Prevention hotline:
1-800-222-1222
Case

GF is a 67 year old woman with chronic back pain who recently ruptured her Achilles tendon trying to impress her grandkids.

- Currently takes Norco (hydrocodone/acetaminophen) 5/325 2 tablets every 8 hours for back pain and two Tylenol PM ES at night to help sleep.

How much acetaminophen/day is she currently taking?

Now how much acetaminophen/day will she be taking?

Case

- GF has continued her pain medication at 2 tablets every 6 hours and is still having pain.
- A friend told her acetaminophen can help opioid pain medications work better, so she has started taking 2 extra strength acetaminophen 3 times/day.
  - How much acetaminophen now?
Case

- As if that wasn’t enough, GF has come down with a cold and has started taking an over the counter cold medication to help

Potentially up to 9000mg APAP each day!

References

References

9. Lexi-comp 2015