Clinical Correlation: Clinical Management of Acetaminophen Toxicity

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Overview

- Describe the pharmacokinetics, pharmacological activity, and mechanism of action of acetaminophen.
- List the major side effects of acetaminophen, the signs and symptoms of acetaminophen overdose, and the mechanism of its toxicity in overdose.
- Describe the treatment of acetaminophen overdose and the value of the Rumack nomogram in treatment decisions.
Epidemiology

- Most widely used analgesic and antipyretic worldwide
  - Available in 100 plus OTC preparations
  - Tablets, capsules, gelcaps, infant drops, suspensions, chewable tablets, suppositories, extended release formulation, IV (Ofirmev; 2011).
  - Commonly combined with antihistamines, decongestants, etc in “cold formulations”
  - Widespread availability: “unintentional overdose”
- Strong record of safety in therapeutic doses
Estimates of Annual APAP Overdoses in US

- 100,000 phone calls to poison control centers annually
- 56,000 ER visits
- 26,000 hospitalizations
- 458 deaths
- PCC - Doubling of fatality rates from 1997 (98) to 2001 (173)

Sources: Emergency Department data bases, hospital discharge databases, National mortality data, TESS

Nourjah et al, 2005, *Pharmacoepidemiology and Drug Safety*
Etiology of ALF in the US
Adult ALFSG Registry (n=1321)

- APAP: 605 (46%)
- Drug: 156 (12%)
- Hep B: 102
- Hep A: 34
- Autoimm: 78
- Ischemic: 61
- Wilson's: 19
- Budd-chiari: 12
- Pregnancy: 11
- Other: 63
- Indeterminate: 180 (15%)

Will Lee, PI, ALFSG
Poisonings and Terminology

- **Intentional**
  - Single ingestion
  - Usually suicide or attention seeking

- **Unintentional** (accidental)
  - May occur during “therapeutic setting”
  - Wrong dose, multiple APAP containing medications, misreading of label, wrong formulation
  - Acute overdose in a child (toddler)
Therapeutic Use in a Controlled Setting

Serum ALT vs Time on Study

ALT (IU/L)

Placebo

APAP

APAP + Opioid

Acetaminophen + Opioids

- Percocet (oxycodone), Lortab/Vicodin (hydrocodone), etc
- ½ of cases of acetaminophen related acute liver failure
- Vicodin = Very common prescription drug in US
- Addictive drug + Dose dependant hepatotoxin = TROUBLE
The FDA and Acetaminophen

2011 Ruling – increased regulation

- Change in upper dose limit for APAP in APAP opioid combinations (500 to 325 mg/tablet)
- Limitation to one liquid APAP (160 mg/5 mL)
- Reduction in daily adult dosing from 4 grams to 3 grams
- New warning labels on some products (use of > 4 grams/24 h can cause liver injury)
Pharmacokinetics

- **Therapeutic dose:** absorption is rapid; complete within 1 hour
- **Overdose:** absorption complete by 4 hours; “extended release” may have prolonged absorption
- Not highly protein bound
- **Metabolism** is by first order kinetics (level declines over time at predictable rate) unless significant hepatotoxicity present
- **Elimination half-life** is around 2.5 hours for therapeutic doses; longer in severe overdose
Mechanism of Effects

- Metabolite of phenacetin
- Marketed as an analgesic and antipyretic
- *However* - weak anti-inflammatory, weak inhibitor of cyclo-oxygenase
- Mechanism of effect – poorly understood

- No effect on neutrophil activation
- Not a gastric irritant
- No effect on platelets, bleeding time
- Role in patients for whom aspirin or NSAID’s contraindicated
Mechanisms of Toxicity

- **Metabolism is basis of toxicity**
- “Toxification” by the liver
- **Therapeutic doses:**
  - > 90% parent compound undergoes glucuronidation or sulfation and eliminated by kidneys
  - 2% direct renal elimination
  - Remainder metabolized by CYP P450 enzymes to NAPQI (N-acetyl-p-benzoquinone imine)
  - Glutathione (GSH) “detoxifies” NAPQI
Acetaminophen (APAP) undergoes metabolism primarily by the CYP P450 2E1 enzyme, resulting in a non-toxic sulfated metabolite (60%) and an unchanged APAP (2%). A small fraction (5%) is metabolized by CYP P450 2E1 to NAPQI, which is then detoxified by glutathione to a non-toxic mercapturic acid (30%). CYP 3A4 and 2A1 play minor roles in the metabolism of APAP.

Therapeutic doses of acetaminophen (APAP) are safe when taken as directed.
Mechanisms of Toxicity

- **Overdose:**
  - “Normal pathways” overwhelmed (Figure 1)
  - “Build up” of NAPQI
  - Glutathione depleted
  - NAPQI binds to proteins, forming adducts

*Reactive oxygen species; mitochondrial injury; inflammation cytokines*
OVERDOSES OF ACETAMINOPHEN (APAP)

APAP

- Non-toxic sulfated metabolite – 60% saturated
- Unchanged APAP – 2%
- Glucuronide metabolite – 30% saturated

CYP P450

NAPQI

- GLUTATHIONE depleted
- ADDUCT FORMATION
- CELL DEATH
Variables Affecting Toxicity

- **Age:** Children “relatively protected” (most deaths in adults)
  - ? Increased sulfation
  - ? Earlier recognition
  - ? Smaller doses
  - ? “Self decontamination”

- **Induction of CYP P450’s**
  - **CYP2E1:** primary P450 for APAP metabolism
    - Induced by isoniazid, **ethanol** (inhib/induction)
  - **CYP1A2:** induced by cigarette smoke, charbroiled foods
  - **CYP3A4**
Variables Effecting Toxicity

- Ethanol: complicated mechanism
  - Long term use induces CYP 2E1 by 2-3 fold
  - Binge use at time of overdose may decrease NAPQI formation
  - Case reports of toxicity with “therapeutic intent”
    - anecdotal in nature
    - no evidence of toxicity in well-controlled, “short-term” dosing studies
  - Alcoholics have decreased glutathione stores
Toxic dose

- 150 mg/kg in a child
- 10 grams in an adult

- Therapeutic dosing: 75 mg/kg/day for children; 4 grams per day for adults, lowering to 3 grams per day per manufacturer

- Low therapeutic index (ratio of lethal/therapeutic dose)
# Phases of Toxicity

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>0.5 – 24 hours after overdose</th>
<th>Nausea, vomiting, may have elevation of hepatic transaminases, or asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>24 – 72 hours after overdose</td>
<td>Abdominal tenderness in RUQ. Elevated hepatic transaminases. Clotting factors impaired.</td>
</tr>
</tbody>
</table>

**ALT**, alanine aminotransferase  
**AST**, aspartate aminotransferase  
**PT**, prothrombin time
Centrilobular Necrosis

(A) Acetaminophen

(B) Control
## Phases of Toxicity

<table>
<thead>
<tr>
<th>Phase 3</th>
<th>72 - 96 hours after overdose</th>
<th>Sequelae of hepatic injury: jaundice, coagulation defects, hepatic encephalopathy, renal failure, death.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 4</td>
<td>4 – 14 days after overdose</td>
<td>Death or resolution of liver failure</td>
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</tbody>
</table>
Treatment

- N-acetylcysteine (NAC)
  - Sulfhydryl tripeptide that acts as glutathione substitute
  - Increases glutathione synthesis
  - Enhances sulfation of acetaminophen
OVERDOSES OF ACETAMINOPHEN (APAP)

APAP

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- Unchanged APAP - 2%
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Glutathione
- Depleted

NAPQI
- Adduct formation
- Cell death
NAC

- Traditional treatment protocol is 72 hour protocol with intermittent dosing of NAC (18 oral doses)
- FDA approval since 1980’s
- IV NAC used widely in Europe
- IV NAC approved in US in 2004
  - Increased risk of anaphylaxis with IV; some evidence that it is less effective for late presenting patients
- Use varies by center
NAC

- Efficacy is highly dependent on the time of NAC relative to the overdose
- “Glutathione substitute”
- Risk of toxicity for treatment within 10 hours of overdose = 6%
- Risk of toxicity for treatment 10-24 hours of overdose = 26.4% (4 fold elevation)
- Possibly of benefit “late” due to antioxidant effects
Efficacy of Oral NAC vs Treatment Delay

2540 patients requiring NAC, % of patients with peak ALT > 1000 IU/L, Kulig, NEJM, 1988
NAC: Adverse effects

- Vomiting, vomiting, vomiting
- Sulfur smell
- Anaphylaxis associated with IV dosing
  - Pre-medication with antihistamines and steroids
Who do you treat?

- History of “toxic ingestion”
- Rumack nomogram
  - Time vs. concentration plot of “risk of toxicity” in adults
  - Toxicity = ALT > 1000 IU/L (Normal < 40 IU/L in adults)
Rumack Treatment Nomogram

Estimation of Risk of Toxicity

Serum APAP (mg/dL)

Possible
Probable (60%)
High

Hours from Overdose

200
100
50
10
Limitations of Nomogram

- Applies only to single, acute ingestions
- Not “validated” in children, but generally utilized
- Limited to 24 hours of overdose
- “Extended release” ingestions
  - 325 mg immediate release with 325 of extended release
- Concurrent therapy with CYP 2E1 inducing drugs - Alcoholics
- No role in “Therapeutic misadventures” (chronic overdose)
Other Aspects of Treatment

- Activated charcoal if patient presents within 2 hours of the overdose
- Treat nausea/vomiting
  - Nasogastric tube if severe
  - Anti-emetics
- Close monitoring of hepatic transaminases
- Referral for liver transplant if patient develops encephalopathy; hepatic transaminases continue to rise
“Therapeutic misadventures”

- Excess dosing of acetaminophen in “therapeutic setting”
- Maximum daily dose: adult, 4 grams/day; children, 90 mg/kg/day

- Scenarios:
  - Multiple dosing by multiple care-givers
  - Dispensing errors
  - Non-English speaking populations
  - Adult formulations used in children
Case #1

- 2 year old who “drinks” 4 ounces of Tylenol suspension
Case #1: Calculation of Dose

2 year old (weight = 15 kg) who “drinks” 4 oz of Tylenol suspension

- $160 \text{ mg}/5 \text{ mL} = 32 \text{ mg}/1 \text{ mL}$
- 4 oz = 120 mL
- $120 \text{ mL} \times 32 \text{ mg} = 3840 \text{ mg}$
- $3840 \text{ mg} / 15 \text{ kg} = 256 \text{ mg/kg} = \text{toxic dose}$
  by history
Case #1

- Acetaminophen level obtained by hospital 4 hours after overdose
- Level = 80 mg/dL
- Treat?
Rumack Treatment Nomogram

Serum APAP (mg/dL) vs Hours from Overdose

- High
- Probable
- Possible
Case #1

- Level is “non-toxic”
- No need for treatment with NAC
Case #2

- 15 year old male presents to ACH for acetaminophen overdose
- History: ingested 29 grams of acetaminophen 8 hours ago
- Multiple episodes of vomiting at home
- Treat?
Case #2

- Laboratory: acetaminophen level = 270 mg/dL at 8 hours
- He is on no medications and has no past medical history
- AST 81 IU/L; ALT 64 IU/L
- Treat?
Rumack Treatment Nomogram

**Serum APAP (mg/dL)**

- **Hours from Overdose**
  - 4
  - 8
  - 12
  - 16
  - 20
  - 24

- **Possible**
- **Probable**
- **High**
Case #2

- “Toxic” by Nomogram and by history
- Has symptoms (vomiting)
-Admitted to hospital for 72 hour treatment with NAC
- Liver function monitored daily; full recovery
Case #3

- 16 year old presents to hospital after ingesting unknown amount of acetaminophen 2 hours ago
- He has no other past medical history
- ?
Case #3

- Acetaminophen level 4 hours after overdose = 160 mg/dL
- Treat?
Rumack Treatment Nomogram

Serum APAP (mg/dL)

Hours from Overdose

Possible
Probable
High