Management of Acetaminophen Toxicity

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Pharmacokinetics

• Absorption

  – Rapidly absorbed from the GI tract
  – Peak concentration usually occurs between 60 and 120 minutes
  – Peak plasma levels almost always occur within 4 hours
Distribution

- Vd 1.0 - 2.0 L/Kg
- Approximately 20% plasma protein bound may increase to 50% in overdose
- Has been reported to cross the placenta
Acetaminophen → Sulfation → Glucuronidation → Oxidation → Remaining 5-15% → NAPQI → Glutathione → Acetaminophen – mercaptate compound

NORMAL METABOLISM
**Acetaminophen**

- **Sulfation**
- **Glucuronidation**
- **Oxidation**
  - \( \text{Cyt P450} \)
  - \( \gg \gg \gg 5-15\% \)
  - **NAPQI**
  - **Glutathione**

**METABOLISM IN OVERDOSE**

- \( \text{Acetaminophen} \)
  - \(-\text{mercaptate compound}\)
  - \( \text{metabolized}\)
Half life

- Average 2 hours
  - range 0.9 to 3.25 hours
- No age related differences
- No change in patients with renal disease
- With liver dysfunction, may increase to 17 hours
Extracorporeal elimination

- Hemodialysis
  - Not proven effective in reducing or preventing liver damage in overdose

- Peritoneal dialysis
  - Not effective
Toxicity

- Factors involved in predicting hepatotoxicity
  - total quantity ingested
  - time from ingestion to treatment
  - age of the patient
  - alcoholism
  - enzyme inducing medications

- serum concentration in relation to Rumack nomogram
• **Toxic dose**

  – In adults, threshold for liver damage is 150 to 250 mg/kg

  – Children under 10 appear to be more resistant
• Potential liver damage

  – Adults: > 150 mg/kg in acute dose

  – Adults: > 7.5 Grams in 24 hours (chronic)

  – Children (<10 yrs): > 200 mg/kg
4 Stages of Acetaminophen Poisoning

- Phase I (30 minutes to 24 hours)
  - Within a few hours after ingestion, patients experience anorexia, nausea, pallor, vomiting, and diaphoresis. Malaise may be present.

Patient may appear normal
Phase II (24 to 48 hours)

- clinical signs of hepatotoxicity.
- Right upper quadrant pain due to hepatic damage
- hepatomegaly, AST/ALT/bili/lipase elevation.
- Prothrombin times may be prolonged
- Renal function may begin to deteriorate.
Phase III (3 to 5 days)

- Fulminant hepatic failure +/- death
- Associated lactic acidosis, coag-ulopathy, encephalopathy; possible pancreatitis, hypoglycemia, jaundice, and renal failure.
- Marked elevation of liver enzymes (with AST typically >3,000),
- Elevation of NH3, coags, lactate Characterized by symptoms of hepatic necrosis.
Phase IV (4 days to 2 weeks)

- Complete resolution or death
<table>
<thead>
<tr>
<th>Stage</th>
<th>Time</th>
<th>Labs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>½ –24 hrs</td>
<td>Usually normal</td>
<td>N/V, pallor, lethargy</td>
</tr>
<tr>
<td>II</td>
<td>24-72 hrs</td>
<td>Coags out, AST/ALT up by 36 hrs, incr Cr</td>
<td>Initially improve, then RUQ pain, HM</td>
</tr>
<tr>
<td>III</td>
<td>72-96 hrs</td>
<td>Abnormalities peak</td>
<td>Jaundice, confusion, bleeding, N/V</td>
</tr>
<tr>
<td>IV</td>
<td>4 d - 2 wks</td>
<td>Slow return to normal (if pt survives)</td>
<td>recovery</td>
</tr>
</tbody>
</table>
Treatment

- GI decontamination
  - Syrup of Ipecac
    - return usually 30-40% at best
    - best if used early (first 1-2 hours)

- Gastric lavage
  - effectiveness diminishes with time
• Activated charcoal
  - Should not be withheld
  - dose 50-100 Grams

• Cathartic
  - utilized to speed transit time
• Hemodialysis
  – Limited benefit
  – Damage occurs quickly

• Hemoperfusion
  – No benefit

• Peritoneal dialysis
  – No benefit
Blood Sample

• **4 hour post ingestion**
  
  Acetaminophen level
  
  – levels drawn earlier may be erroneous
  
  – levels may be accurate out to 18 hours
• Plot level on Rumack-Matthews nomogram

- **150 mg/dl at 4 hours is possibly toxic**

- Do not use therapeutic “normal” values to determine potential toxicity!
Rumack and Matthew Nomogram

Not valid after 24 hours

Late

Hours After Acetaminophen Ingestion

mcg/ml

500
150
100
50
10
5
- Baseline CBC
- creatinine, BUN, blood sugar, electrolytes
- prothrombin times
- AST, ALT
  - repeat q 24 hours
  - elevations typically seen 24-36 hours post ingestion
• If APAP level plots above the possible risk line administer N-acetylcysteine (NAC).

• If NAC is indicated, full regimen should be followed. Do not stop NAC early if nomogram indicates toxic possibility.
**N-acetylcysteine (NAC)**

- **Mechanism of action**
  - glutathione substitute
  - may supply inorganic sulfur, altering metabolism

- **Route of administration**
  - Orally or IV
    - IV not approved in the U.S.
• NAC dosing

  - Oral 72 hour protocol
    • Loading dose is 140 mg/kg
    • Maintenance doses: 70 mg/kg
      - Given every 4 hours x 17 doses starting 4 hours after loading dose
NAC supplied as 10 or 20% oral solution
- dilute to 5% final concentration with juice or soft drink
- May be administered via NG tube
- If emesis occurs within 1 hour of administration, repeat the dose
• If emesis persists, antiemetics may be used
  
  – (metoclopramide)
    • 0.1 to 1.0 mg/kg iv is often effective

  – If emesis is refractory, may consider (ondansetron) or ® (granisetron)
    • Expensive, but very effective
**Pediatric overdoses**

- More resistant to toxicity vs. adults
  - if a child plots in the possible risk category on the Rumack nomogram, do not resist using NAC because of this greater tolerance to APAP
  - Administer full course of NAC if nomogram indicates that it is needed
Special considerations with NAC

- NAC administered on basis of nomogram plot
- if initial level indicates need for NAC do not discontinue
NAC side effects

• Relatively free of side effects when given orally

• Emesis may occur
  – extremely offensive sulfur odor
ED Admission

Estimate time of ingestion

Less than 4 hours since overdose

Less than 2 hours since overdose

Gastric emptying

Activated charcoal

Draw blood plasma 4 hours after overdose for plasma acetaminophen assay

Acetaminophen concentration available within 8 hours of overdose

Wait for acetaminophen assay result

APAP level below risk line on nomogram

DC NAC if started

No further medical management needed

Treat other med or psychiatric problems

More than 2 hours since overdose

Activated charcoal

4 or more hours since overdose

Draw blood ASAP for plasma acetaminophen assay

Acetaminophen concentration not available within 8 hours of overdose

Start NAC pending assay result

Loading does: 140 mg/kg

APAP level on or above risk line

Treat with full course of NAC

Daily LiverFT’s, prothrombin times

Provide supportive care
Thanks for attention