UNUSUAL ACETAMINOPHEN TOXICITY SCENARIOS
Objectives

• Management of acetaminophen ingestions when the Rumack-Matthew doesn’t apply

Staggered ingestions
Repeated supratherapeutic ingestions
Mitochondrial acetaminophen toxicity
Acetaminophen

- Easy access, perceived as benign
- Combination products with other medications
- Well-known antidote: N-acetylcysteine
What is the toxic dose of acetaminophen?

A. Adults 150 mg/kg
B. Adults 200 mg/kg
C. Adults 100 mg/kg
D. It depends
E. I don’t remember
Acetaminophen Toxicity

- Single ingestion time
- Toxic dose
- 150-200 mg/kg (country specific)

- Phase 1 asymptomatic or mild GI (< 12h)
- Phase 2 Hepatotoxicity AST/ALT >1000 IU/L (12h-24h)
- Phase 3 FHF, encephalopathy (24-72h)
- Phase 4 Resolution, death or transplant

Rumack BH Acetaminophen misconceptions. Hepatology 40:1 2004
Acetaminophen Toxicity

- Single ingestion time
- > 4h; < 16h
- Rumack-Matthews nomogram
Acetaminophen Toxicity

Glucuronide moiety (Non-toxic) → Acetaminophen → Sulfate moiety (Non-toxic)

Acetaminophen is metabolized by P450 (2E1) to form N-acetyl-p-benzo-quinone imine (NAPQI) (TOXIC), which is detoxified by glutathione to form cysteine and mercapturic acid conjugates (non-toxic). Glutathione (GSH) is often used to treat acetaminophen toxicity.
Risk Assessment

• 28 year old male, intractable migraines
• Took 4 tablets of acetaminophen 500 mg every 2 hours from 8 AM until 6 PM
• Presents 2 hours after the last dose (because no pain relief)
Risk Assessment

• 8 AM 2 g
• 10 AM 2 g
• Noon 2 g
• 2 PM 2 g
• 4 PM 2 g
• 6 PM triage
• Weight 80 kg
• Total 10 grams = 125 mg/kg
Is this toxic?

A. Yes
B. No
C. Not sure
Management Staggered Ingestions

- Poorly studied, risk of HT uncertain (higher?)
- Options
  1. transform them mathematically in single ingestion with the earliest time of ingestion as T0
     • [APAP] now; if above threshold → treat
     • [APAP] 4h after last dose; if above threshold → treat
  2. Treat all
- Same NAC protocol as single acute ingestion

Craig et al. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. BJCP 2012. 73:3; 385-294.
A patient took APAP with diphenhydramine (cold remedy) in unknown quantity. 4h APAP is 840 umol/L below the nomogram.

A. You send him to psychiatry
B. You start treatment with NAC
C. You call your Poison Control
D. You wait and you repeat the level
Extended release APAP ingestion

- Prolonged absorption
- Diphenhydramine, Opiates
- Peak delayed
- Might be after 4 hours

- If 4h concentration non-toxic, repeat 2 hours later
- Peak should occur by 8h unless significant ileus, bezoar or other situation decreasing absorption
Supratherapeutic / Chronic

- Definitions change according to authors.
  - Staggered $\geq 8h \ (\leq 24h)$ vs. RSTI/ Chronic $\geq 24h$
- Multiple ingestion times
- Over more than 24 hours
- Cannot use the Rumack-Matthews nomogram
- Treat all
  - With any detectable [APAP]
  - Abnormal aminotransferases $\geq 50$ IU/L
  - Time of sampling to ingestion not specified...

Risk Assessment

- 18 years old female
- Brought to ER 90 minutes post ingestion
- 200 tablets of 500 mg acetaminophen
- Weight 80 kg
- Toxic load = 1250 mg/kg
1250 mg/kg ingestion 90 minutes ago

A. I start NAC right away
B. I give activated charcoal
C. I call my poison centre
D. Follow procedure as usual
Acetaminophen?

- 90 minutes PI = [APAP] 6499 umol/L
- Becoming lethargic and tachypneic
- Lactate 8
- Bicarbonate 16
- pH 7.20
- Normal INR and LFT’s
- No other medication ingested
- How would you manage this result?
Will NAC be enough for this patient?

Rumack-Matthews Nomogram
Comparison of the 20-Hour Intravenous and 72-Hour Oral Acetylcysteine Protocols for the Treatment of Acute Acetaminophen Poisoning

Mark C. Yarema, MD
From the Division of Emergency Medicine and Department of Family Medicine (Yarema, Berlin), the Acetylcysteine for Acetaminophen Poisoning

Yarema et al

Table 1. Patient characteristics by study group.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>20-Hour Intravenous (n=2,086)</th>
<th>72-Hour Oral (n=1,962)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (IQR)</td>
<td>21.0 (15.0)</td>
<td>20.0 (11.0)</td>
<td>1.0 (1.0 to 4.0)</td>
</tr>
<tr>
<td>Sex, female, No. (%)</td>
<td>1,497 (71.8)</td>
<td>1,365 (69.6)</td>
<td>2.2 (0.7 to 5.1)</td>
</tr>
<tr>
<td>Acute ethanol ingestion, No. (%)</td>
<td>525 (25.2)</td>
<td>31 (1.6)</td>
<td>23.6 (21.6 to 25.6)</td>
</tr>
<tr>
<td>Chronic ethanol ingestion, No. (%)</td>
<td>339 (16.1)</td>
<td>81 (4.1)</td>
<td>12.0 (10.2 to 13.9)</td>
</tr>
<tr>
<td>Reported acetaminophen dose ingested, g, median (IQR)</td>
<td>20.0 (22.5)</td>
<td>22.5 (15.0)</td>
<td>-2.5 (-4.0 to -1.0)</td>
</tr>
<tr>
<td>Median extrapolated 4-h acetaminophen concentration, µg/mL (IQR)</td>
<td>280.3 (217.1)</td>
<td>260 (198.7)</td>
<td>20.3 (12.1 to 31.7)</td>
</tr>
<tr>
<td>Patients in categories based on extrapolated 4-h acetaminophen concentration, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150-200 µg/mL</td>
<td>497 (23.8)</td>
<td>538 (27.4)</td>
<td>-3.6% (-6.3% to 0.9%)</td>
</tr>
<tr>
<td>200-300 µg/mL</td>
<td>653 (31.3)</td>
<td>659 (33.6)</td>
<td>-2.3% (-5.2% to 0.7%)</td>
</tr>
<tr>
<td>300-400 µg/mL</td>
<td>371 (17.8)</td>
<td>289 (14.7)</td>
<td>3.1% (0.7% to 5.4%)</td>
</tr>
<tr>
<td>400-500 µg/mL</td>
<td>182 (8.7)</td>
<td>155 (7.9)</td>
<td>0.8% (-0.9% to 2.6%)</td>
</tr>
<tr>
<td>&gt; 500 µg/mL</td>
<td>383 (18.4)</td>
<td>321 (16.4)</td>
<td>2.0% (-0.4% to 4.4%)</td>
</tr>
<tr>
<td>Median time from ingestion to start of acetylcysteine therapy, h (IQR)</td>
<td>8.8 (6.8)</td>
<td>11.5 (7.5)</td>
<td>-2.7 (-3.4 to -2.5)</td>
</tr>
<tr>
<td>Received 20 h of intravenous acetylcysteine, No. (%)</td>
<td>1,632 (78.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received &lt;20 h, No. (%)</td>
<td>44 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received &gt;20 h, No. (%)</td>
<td>410 (20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received 72 h of oral acetylcysteine, No. (%)</td>
<td></td>
<td>1,744 (88.9)</td>
<td></td>
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<tr>
<td>Received &lt;72 h, No. (%)</td>
<td></td>
<td>175 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Received &gt;72 h, No. (%)</td>
<td></td>
<td>43 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Median duration of acetylcysteine therapy, h (IQR)</td>
<td>20 (0)</td>
<td>72 (0)</td>
<td></td>
</tr>
<tr>
<td>Range, h</td>
<td>1 to 220</td>
<td>68 to 124</td>
<td></td>
</tr>
</tbody>
</table>
APAP Mitochondrial Toxicity

- Rarer presentation
- Massive ingestion > 350-500 mg/kg
- Efficacy of NAC imprecise ([APAP] ≥ 3300umol/k at 4h)
- Amount of NAC to give?
- Coma, metabolic acidosis < 12h post-ingestion
- Before evidence of hepatotoxicity
- Toxicity from APAP, NAPQI, both?
- Genetic susceptibility?

Shah et al. Understanding lactic acidosis in paracetamol poisoning. BJCP 2010. 71:1
Jaeschke & Bajt. Mechanisms of Acetaminophen Hepatotoxicity in Comprehensive Toxicology Ed McQueen CA. Elsevier Science;2010
Figure 1  Basic metabolism of acetaminophen (APAP) in hepatocytes and initiation of toxicity (see text for details). Bcrp1, breast cancer resistance protein 1; GSH, glutathione; mrp, multidrug resistance-associated protein; NAPQI, N-acetyl-p-benzoquinone imine.
Acetaminophen

• Animal studies
• NAPQI is detoxified by GSH
• No glutathione
  – Binding to hepatocellular AND mitochondrial protein
• Inhibition of mitochondrial respiration (cytochrome B)
  – Doses > 500-600 mg/kg
    • Peroxynitrite formation
    • DNA damage
    • Oxidative stress,
    • Opening of transition pore with membrane potential collapse

• Animal study
• With N-AC 500 mg/kg
• Important % death
• APAP > 500 mg/kg
Treatment Options

• NAC same dose protocol
  – 150 mg/kg bolus
  – 50 mg/kg over 4h (12.5 mg/kg)
  – 100 mg/kg over 16h (6.25 mg/kg)
• NAC “double dose” 3rd infusion (200 mg/kg in 16h)
  – Empirical- always get advice from PCC.
  – Based on molar NAPQI to molar NAC estimation
• Hemodialysis
• 4-MP (fomepizole)
Fomepizole?

• Inhibition of alcohol dehydrogenase
• Also inhibition of cytochrome P-450
• 4-MP prevented hepatotoxicity in rats after 2000 mg/kg APAP
• 4-MP vs NAC both prevented hepatotoxicity
• Theoretical and rat studies no human report

Evidence for Hemodialysis

- Acetaminophen
  - Molecular weight 151.2 D
  - Volume of distribution 0.7-1 L/kg
  - Protein binding 25%
  - Half life 1-2 hours

- Toxicokinetic
  - No major change in volume of distribution
  - Half life increases > 4 hours

- NAC also hemodialysed
  - 50% of dose with IHD
Conclusions

☠ Different acetaminophen scenarios
☠ Rumack-Matthew not always applicable
☠ Delayed presentations carry worse prognosis
  — Supratherapeutic (staggered and chronic)
☠ Early acidosis with mental status changes
  — Will NAC be enough??
☠ Risk assessment with toxic load in mg/kg
☠ Call your Poison Control for help
Questions?