ACETAMINOPHEN TOXICITY
Myths and Realities

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Acetaminophen Toxicity

- Introduction
- Toxicology
- Pharmacokinetics
- Clinical and Pathological Features
- Management
- Prevention

Terms

- **APAP** = N-acetyl-para-aminophenol also called acetaminophen and paracetamol.
- **NAC** = N-acetyl cysteine (repletes hepatic glutathione directly and secondarily by producing cysteine)
- **NAPQI** = N-acetyl-para-benzo-quinoneimine (a reactive intermediate alkylating metabolite of acetaminophen believed to be the primary toxic metabolite formed by the P450-dependent mixed function oxidases (CYP2E1)).
ACETAMINOPHEN (APAP) AND ALF

- The most common cause of phone calls to the PCC (> 100,000/year).
- 56,000 emergency room visits
- 2600 hospital admissions
- 458 deaths due to ALF
- 50% of the causes of ALF
- Represents more than 1 billion dollars in Tylenol sales


INTRODUCTION

- von Merin introduced APAP into medicine as an antipyretic/analgesic in 1893.
  - It attracted little attention until it was found to be the basic metabolite of both acetanilide and phenacetin (Brodie 1948, Axelrod 1949)**.
- Since it is safer than aspirin and NSAIs and doesn’t have any relationship with Reye’s syndrome, it became the analgesic of choice in many countries of the world.
- Proper preclinical toxicity studies were never carried out with APAP.
- Severe and fatal liver damage in humans was first reported from Scotland by Davison & Eastham and Thompson & Prescott in 1966+.
- Hepatotoxicity leading to liver failure was not recognized in US until 1980. At that time APAP was thought to be a negligible hepatotoxin in the US.

INTRODUCTION

- Acute Liver Failure study group reported retrospectively in the US in 1995 that 20% of cases of ALF were due to APAP*.
- U of Pittsburgh reported from 1983-1995 that 20% of FHF were APAP related+.
- More recently in 2001, 2003 the Acute Liver Failure group reported 39% and 49% of FHF associated to APAP toxicity**.

Liver Transpl Surg 1999;5:29-34
Liver Transplant 2000;6:163-169
Ann Intern Med 2002;137:945-954

Acute Liver Failure Study Group
Funded by NIH R03, FDA Orphan Grant,
Now R01 (‘00-‘05)

- 14 sites initially 1998, now 25
- Also 25 pediatric sites, since 2000
- 820 cases in adult, 320 in pediatric registry
- N-acetylcysteine trial for non-APAP ALF
- Numerous (38) ancillary studies in progress
- Provides a surveillance network for DILI cases
Acetaminophen cases as % of all ALF per year

<table>
<thead>
<tr>
<th>YEAR</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
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</thead>
<tbody>
<tr>
<td>Cases</td>
<td>85</td>
<td>94</td>
<td>99</td>
<td>123</td>
<td>133</td>
<td>128</td>
</tr>
<tr>
<td>Percent of ALF Cases</td>
<td>28%</td>
<td>38%</td>
<td>44%</td>
<td>38%</td>
<td>47%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Etiology of ALF in the USA (1998-2005)
Adult Registry (n = 684)

TOXICOLOGY

Animal Toxicity Studies
• APAP cause acute centrilobular necrosis in rats, mice, guinees-pigs, hamsters, rabbits, cats, dogs and pigs. (Boyd and Bereczky 1966; Davis 1974; Finco 1975; Gazzard 1975.
• There are marked species differences in susceptiblity. Mice and hamsters very sensitive while the rat is very resistant. (Davis 1974).
Human Studies

- The dose required to produce hepatic damage cannot accurately be estimated from the history of patients taking overdoses, as the dose taken is often not accurate.
- Although death has been reported after as little as 2.0 gm (Patel 1992), hepatotoxicity is not expected to develop unless at least 10-15 gm has been taken.

Dose related toxicity in low risk patients:
- <125 mg/kg: rare liver toxicity (8.75 g in a 70 kg person)
- >250 mg/kg is considered “minimum hepatotoxic dose” (17.5 g in a 70 kg person)
- >350 mg/kg: inevitable severe liver damage (AST > 1000 IU/L) (24.5 g or 38 double-strength tablets)

High risk patients:
- Depleted Hepatic Glutathione: chronic alcohol abuse, malnutrition, HIV infection, taking enzyme-inducing drugs: anticonvulsivants, rifampin, INH, phenobarbital.
- Drugs that compete for standard pathways for APAP metabolism (glucuronidation: Bactrim and Zidovudine).
- Genetic differences in cytochrome P450 enzymes and Gilbert’s Syndrome associated to increased risk.
- Also correlation between stated dose and measured plasma APAP level
- Frequent problems with inaccurate reporting of the time of ingestion.
Cytochrome p450 lead to unstable compounds!

Cytochromes P450 lead to unstable compounds!

Cytochrome p450 (phase I)

\[ \text{HN} \text{C} \text{CH}_3 \text{O} \]

\[ \text{HN} \text{C} \text{CH}_3 \text{O} \]

OH

Nontoxic Metabolites

OH

Nontoxic Metabolites

NAPQI (highly reactive intermediate)

Hepatocyte Damage

- Covalent binding to cell proteins, including enzyme itself
- ADDUCTS
- Derangement of apoptosis?
- Arylation, oxidation

Acetaminophen (APAP) adducts assay*

- HPLC-EC detects APAP-cysteine residues
- Highly sensitive and specific
- Remains positive up to 9 days after ingestion
- Present in 20% of indeterminate cases, pediatrics and adults

*Daveen TJ et al: Gastroenterology 2006;130:687-694

ALT and APAP adducts in 4 patients with acetaminophen OD
### Clinical Stages of APAP Toxicity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Time Post Ingestion</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.5 to 24 hours</td>
<td>Anorexia, nausea, vomiting, malaise, palor, diaphoresis</td>
</tr>
<tr>
<td>II</td>
<td>24 to 24 hours</td>
<td>Resolution of anorexia, right upper quadrant pain and tenderness, elevated bilirubin, INR, ALT, AST, and oliguria</td>
</tr>
<tr>
<td>III</td>
<td>72 to 96 hours</td>
<td>Peak aminotransferases, anorexia, nausea, vomiting</td>
</tr>
<tr>
<td>IV</td>
<td>4 days to 2 weeks</td>
<td>Resolution of hepatic dysfunction</td>
</tr>
</tbody>
</table>


### APAP/Narcotic Compounds (n=98; 43%)

<table>
<thead>
<tr>
<th>Brands most commonly reported</th>
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</thead>
<tbody>
<tr>
<td>Vicodin 72</td>
</tr>
<tr>
<td>Tylenol #3 7</td>
</tr>
</tbody>
</table>

*Compound users were more likely to receive NAC, had higher coma grades but similar survival to others*

### Suicidal vs. Accidental APAP Cases

<table>
<thead>
<tr>
<th></th>
<th>Suicidal (n=101)</th>
<th>Unintentional (n=109)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>75</td>
<td>76</td>
<td>NS</td>
</tr>
<tr>
<td>ACM dose (g)</td>
<td>28</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Dose per day</td>
<td>28</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>Coma (%&gt;3)</td>
<td>39</td>
<td>55</td>
<td>0.026</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>6118</td>
<td>3975</td>
<td>0.001</td>
</tr>
<tr>
<td>Spont surv (%)</td>
<td>67</td>
<td>66</td>
<td>NS</td>
</tr>
<tr>
<td>Antidepress’t</td>
<td>35</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Narcotic cpd (%)</td>
<td>19</td>
<td>62</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### ACM/Narcotic vs. ACM alone

<table>
<thead>
<tr>
<th></th>
<th>ACM/Narc (n=98)</th>
<th>ACM (n=120)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>85</td>
<td>70</td>
<td>0.03</td>
</tr>
<tr>
<td>Suicidal OD (%)</td>
<td>19</td>
<td>63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coma (%&gt;3)</td>
<td>60</td>
<td>38</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelets</td>
<td>158</td>
<td>121</td>
<td>0.001</td>
</tr>
<tr>
<td>Spont surv (%)</td>
<td>67</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>Mean alcohol (g)</td>
<td>58</td>
<td>16</td>
<td>0.01</td>
</tr>
<tr>
<td>Alcohol abuse (%)</td>
<td>44</td>
<td>22</td>
<td>0.01</td>
</tr>
</tbody>
</table>
OTHER CLINICAL MANIFESTATIONS

• Altered Consciousness
  - At the onset usually indicates co-ingestion of sedatives or narcotics
  - If Hepatic Failure develops, hepatic encephalopathy and brain edema are common
• Renal Failure
  - ATN develops in approximate 3% of all APAP overdoses and 11% of severely poisoned patients.
  - Clinical course is an increase Cr on day 2, peak increase on day 3 to 6 and recovery within 10 days.
OTHER CLINICAL MANIFESTATIONS

- Hypoglycemia
  Occur 12-72 hours after overdose due to impaired hepatic gluconeogenesis, inability to mobilize hepatic glycogen stores and hyperinsulinemia.
- Lactic Acidosis
  Presents early in severe cases and is due to diminished lactate removal by the failing liver. Bad prognostic indicator if persists after volume repletion.
- Infections
  Bacterial and fungal infections occurs in 80% of patients with hepatic failure.
  - Acute Pancreatitis
  - Myocardial Injury

TREATMENT*

1. Detectable APAP with normal aminotransferases:
   - Begin oral NAC
   - If by 36 hours, aminotransferases remain normal, therapy can be stopped.
2. History of APAP overdose and two-fold increase in aminotransferases without detectable acetaminophen levels:
   - Full course of oral NAC
3. Hepatic failure after a history of APAP overdose:
   - Full course of intravenous NAC


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**TREATMENT**

1. Gastric lavage and activated charcoal don’t reduce the effectiveness of NAC.
2. N-acetyl cysteine (NAC)*:
   - Oral load: 140 mg/kg as a load, followed by 70 mg/kg every 4 hours orally for 17 doses. (total dose 1350 mg/kg over 72 hours).
   - Side effects: vomiting, diarrhea, rotten egg smell
   - Intravenous: 150 mg/kg as a load over 15 minutes, followed by 50 mg/kg over 4 hours and then 100 mg/kg over the next 16 hours. (total dose 300 mg/kg over 24 hours).
   - Side effects: anaphylactic reaction (less than 5%), urticaria, rash, bronchospasm, tachycardia and hypotension.

*Prescott LF, Mathew H. Lancet 1974;1:998

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Fig. 2: Outcome Nomogram with the original nomogram line and the 25% safety line added during the nationwide NAC study. Patients were plotted at the point of their initial APAP level. Percent is the number of cases with AST greater than 1,000 IU/L at any time during their course.
50 consecutive patients with liver failure after APAP overdose
IV NAC vs glucose IV were randomized until clinical improvement
Time from overdose: mean of 53 to 56 hours and a range of 33 to 96 hours.

IV NAC group have:
- Better survival (48% vs 20%, p<0.04)
- Less brain edema (40% vs 68%, p<0.05)
- Less use of vasopressors (48% vs 80%, p<0.02)
- Lower frequency of renal replacement (40% vs 60%, NS)

EFFECTIVENESS OF THERAPY

Of 11,195 cases reported, 2,540 were treated with oral NAC:

HEPATOTOXICITY:
- In 6% in those treated within 10 hours
- In 34% in those between 10 and 24 hours
- In high risk patients treated between 16 and 24 hours, 116/283 (41%) developed severe liver necrosis. (Standard controls 89%)

Mortality:
- 11/2540 (0.43%)
- No patient treated within 16 hours died

INDICATIONS FOR LIVER TRANSPLANTATION

- pH < 7.3 (if present after 24 hours despite volume and support (90% mortality)
- If pH is normal, transplantation should be considered only if all three of the following occurs concomitantly (81% mortality):
  - PT > 100 sec (INR 6.7)
  - Creatinine > 3.4 mg/dL
  - Grade III/IV encephalopathy


Acute Liver Failure in US:
3 Week-Survival
Without Liver Transplantation (132/308 : 43%)*

*Acute Liver Failure Study Group, Annals of Internal Medicine 2002;137: 947-954
**MYTHS**

1. APAP outcome normogram is essential for management
2. Therapeutic doses of APAP cause hepatotoxicity in alcoholics
3. Fasting increase the risk of hepatotoxicity of APAP
4. Charcoal administration diminished the absorption of NAC
5. Cimetidine prevents hepatotoxicity in humans
6. NAC is not indicated after 24 hours of ingestion
7. Once liver failure develops, NAC should be discontinued
8. APAP is contraindicated in patients with liver disease
9. Most of the patients with FHF due to APAP will need OLT

**REALITIES**

- APAP toxicity is the first cause of acute liver failure in US
- Survival is excellent (> 80%) if patients are treated early with APAP
- The mayor determinant of toxicity is the dose of APAP and not alcohol intake
- With early NAC and good ICU treatment, OLT is exceptional
- IV NAC is the antidote of choice in liver failure patients
- Combination of APAP + NAC or Methionine needs to be explored as an interesting preventive measure: new analgesic for liver disease patients
- APAP can be used in liver patients in therapeutic doses (2.0 to 4.0 gm/24h)
- It is a preventable problem with better education of the public and package size